3rd Edition

Radiation Oncology

A Question-Based Review

Boris Hristov
Steven H. Lin
John P. Christodouleas

Wolters Kluwer

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Preface

It is with great excitement that we introduce the third edition of *Radiation Oncology: A Question-Based Review*. As a result of many favorable responses to the first two editions, we have again updated this text to ensure that it continues to provide both trainees and practicing radiation oncologists with the most current and salient information in our field. This edition has been thoroughly reviewed and updated to include the latest AJCC 8th edition staging, seminal new studies, and practice-changing trials published since the last edition, and a new primer section/chapter on immunotherapies.

In spite of these changes and additions, the book's core format and objectives have essentially remained the same, namely to provide medical students, residents, and radiation oncologists with a succinct briefing on the clinical management of all the major cancer types and conditions that are currently treated with radiation. An enduring goal of this edition is to serve as a user-friendly means for self-assessment and, with this objective in mind, we continue to include popular mnemonics and tie in useful facts from other relevant disciplines such as radiology, anatomy, and medical oncology. The most challenging goal of this edition was to keep the overall length of the book similar to that of past editions by deleting older and less relevant data when incorporating newer studies and techniques. By tasking experienced section editors specializing in particular areas of radiation oncology (e.g., pediatrics, breast, GI, etc.) and by empowering them to distill each chapter to its most salient points and evidence-based principles,
we strongly feel that we have met this goal.

We hope that our third edition of *Radiation Oncology: A Question-Based Review* continues to serve as a proven high-yield study-aid and that it grants both students and practitioners alike a somewhat firmer footing in the ever-shifting and evolving field of radiation oncology.

The Editors

Abbreviation Key

Abbrev	*Full Spell-Out*
2D	two-dimensional
3D	three-dimensional
3D-CRT	three-dimensional conformal radiation therapy
5-FU	5-fluorouracil
ABMT	autologous bone marrow transplant
abnl	abnormal
APBI	accelerated partial breast irradiation
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
adj	adjuvant
Adr	Adriamycin
AFP	alpha-fetoprotein
AI	aromatase inhibitor
AIDS	acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
aka	also known as
alk phos	alkaline phosphatase
Alt	alternated with

am	morning (ante meridian)
ANC	absolute neutrophil count (lab)
ant	anterior
anterolat	anterolateral
AP	anterior–posterior
APC	adenomatous polyposis coli (gene mutation)
appx	approximately
APR	abdominoperineal resection
ARUBA	A Randomized Trial of Unruptured Brain Arteriovenous Malformations
ASCO	American Society of Clinical Oncology
ASCUS	atypical squamous cells of unknown significance
ASTRO	American Society for Therapeutic Radiation and Oncology
AUC	area under the curve
avg	average
BAT	B-mode acquisition and targeting
b/c	because
b/t	between
BCT	breast conserving treatment
BED	biologically equivalent dose
BED	biologically effective dose
bFFP	biochemical freedom from progression
β-HCG	beta-human chorionic gonadotropin

bid	twice daily
bilat	bilateral
BM	bone marrow
BMI	body mass index
BMP	basic metabolic panel
BMT	bone marrow transplant
BTSG	Brain Tumor Study Group
BWS	Beckwith–Wiedemann Syndrome
Bx	biopsy/biopsies
C	cervical (spine level)
c/w	compared with
CA19-9	cancer antigen 19-9
CA125	cancer antigen 125
CALGB	Cancer and Leukemia Group B
C/A/P	chest/abdomen/pelvis
CBC	complete blood count (lab)
CBCT	cone beam computed tomography
CCCG	Colorectal Cancer Collaborative Group
cCR	clinical complete response
CD	cone-down
CD4	cluster of differentiation 4 (for immune cells)
CEA	carcinoembryonic antigen

CESS	Cooperative Ewing Sarcoma Study
CHART	Continuous Hyperfractionated Accelerated Radiotherapy Trial
chemo	chemotherapy
CHF	congestive heart failure
CIN	cervical intraepithelial neoplasia
CIS	carcinoma in situ
cm	centimeter/centimeters
CMP	complete metabolic panel (lab)
c-myc	(gene)
cN0	clinically node-negative
CN	cranial nerve
CNS	central nervous system
Co-60	cobalt-60
COG	Children’s Oncology Group
COPD	chronic obstructive pulmonary disease
contralat	contralateral
CPT	common procedural terminology
Cr	creatinine
CR	complete response
CRT	chemoradiation
CSF	cerebrospinal fluid
CSI	craniospinal irradiation

CSM	cancer-specific mortality
CSS	cause-specific survival
CT	computed tomography
cT	clinical T-stage
CTV	clinical target volume
CW	chest wall
Cx	cervical (spine level)
CXR	chest x-ray
D/C	discontinue/discontinued
D&C	dilation and curettage
DCC	deleted in colorectal cancer (gene)
DDx	differential diagnosis
DFS	disease-free survival
DI	diabetes insipidus
DLBCL	diffuse large-B cell lymphoma
DLCO	lung diffusion capacity testing
DM	distant metastasis
DMFS	distant metastasis-free survival
DOI	depth of invasion
DRE	digital rectal examination
DSS	disease-specific survival
d/t	due to

DVH	dose volume histogram
DVT	deep venous thrombosis
Dx	diagnosis/diagnoses
Dz	disease/diseases
EB	external beam
EBRT	external beam radiation therapy
EBUS	endobronchial ultrasound
EBV	Epstein–Barr virus
ECE	extracapsular extension
ECOG	Eastern Cooperative Oncology Group
EFRT	extended field radiotherapy
EFS	event-free survival
e.g.	for example
EGFR	epidermal growth factor receptor
EM	electron microscopy
ENE	extranodal extension
ENI	elective nodal irradiation
EORTC	European Organisation for Research and Treatment of Cancer
Epo	erythropoietin
ER	estrogen receptor
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate (lab)

et al.	and others
EUA	exam under anesthesia
EUS	endoscopic ultrasound
EWS	Ewing sarcoma
exam	examination
f/b	followed by
f/u	follow up
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
FDG	fluorine-18 2-fluoro-2-deoxy-D-glucose
FEV	forced expiratory volume
FFS	failure-free survival
FFTF	freedom from treatment failure
FIGO	International Federation of Gynecology and Obstetrics
FH	favorable histology
FHIT	fragile histidine triad
FISH	fluorescence in situ hybridization
FKHR	forkhead (drosophilia) homolog 1 (rhabdomyosarcoma) (gene)
FLAIR	fluid attenuation inversion recovery
F:M	female to male ratio
FN rate	false-negative rate
FNA	fine needle aspiration

FOLFOX	5-FU/leucovorin/oxaliplatin
FPR	false-positive rate
FSH	follicle-stimulating hormone
FSR	fractionated stereotactic radiotherapy
fx	fraction/fractions
GBM	glioblastoma multiforme
GERD	gastroesophgeal reflux disease
GH	growth hormone
GI	gastrointestinal
GK	gamma knife
GN-CSF	granulocyte-macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
GS	gleason score
GTR	gross total resection
GTV	gross target volume
GU	genitourinary
Gy	gray
gyn	gynecologic
H&N	head and neck
H&P	history and physical
HA	headache
HAART	highly active antiretroviral therapy

HCG	human chorionic gonadotropin (lab test)
HDC+SCT	high-dose chemotherapy with stem cell transplant
HDR	high dose rate
HER2	avian erythroblastic leukemia viral oncogene homolog 2/human epidermal growth factor receptor 2
Hgb	hemoglobin
HGG	high-grade glioma
HGSIL	high-grad squamous intraepithelial lesion
HIV	human immunodeficiency virus
HNPCC	hereditary nonpolyposis colon cancer
HPV	human papilloma virus
hr/hrs	hour/hours
HR	hazard ratio
HRT	hormone replacement therapy
HSV	herpes simplex virus
HTN	hypertension
HVA	homovanillic acid
Hx	history/histories
Hyperfx	hyperfractionation
IBCSG	International Breast Cancer Study Group
IC	internal carotid
ICP	intracranial pressure
IDL	isodose line

i.e.	that is
IELCAP	International Early Lung Cancer Action Project
IFN	interferon
IgA	immunoglobulin A
IGF	insulin-like growth factor
IgG	immunoglobulin G
IGRT	image-guided radiation therapy
IJROBP	*International Journal of Radiation Oncology, Biology, and Physics*
IM	internal mammary
IMA	inferior mesenteric artery
IMRT	intensity-modulated radiation therapy
inf	inferior
INR	international normalized ratio
intraop	intraoperative
IORT	intraoperative radiation therapy
ipsi	ipsilateral
IQ	intelligence quotient
ITV	internal target volume
IVC	inferior vena cava
JAMA	*Journal of the American Medical Association*
JCO	*Journal of Clinical Oncology*
JCOG	Japan Clinical Oncology Group

JCRT	Joint Center for Radiation Therapy
JHH	Johns Hopkins Hospital
JNCI	Journal of the National Cancer Institute
JPA	juvenile pilocytic astrocytoma
KPS	Karnofsky performance status
L	lumbar (spine level)
LA	lymphadenopathy
lab	laboratory/laboratory test
LAD	lymphadenopathy
LAMP	Locally Advanced Multimodality Protocol
LAO	left anterior oblique
lat	lateral
LC	local control
LDCT	low dose computed tomography
LDH	lactate dehydrogenase
LDR	low dose rate
LE	lower extremity
LEEP	loop electrosurgical excision procedure
LF	local failure
LFT	liver function test
LGSIL	low-grade squamous intraepithelial lesion
LH	luteinizing hormone

LINAC	linear accelerator
LLL	left lower lobe
LML	left middle lobe
LN	lymph node
LND	lymph node dissection
LOH	loss of heterozygosity
LP	lumbar puncture
LPO	left posterior oblique
LR	local recurrence
LRC	locoregional control
LRF	locoregional failure
LRFS	local recurrence-free survival
LRR	locoregional recurrence
LUL	left upper lobe
LVI	lymphovascular invasion
LVSI	lymphovascular stromal invasion
MALT	mucosa-associated lymphoid tissue
max	maximal/maximum
MB	medulloblastoma
MDACC	MD Anderson Cancer Center
med	medication
MEN	multiple endocrine neoplasia
mets	metastasis/metastases

M:F	male to female ratio
MFS	metastases-free survival
MGMT	O^6-methylguanine DNA-methyltransferase
MI	myocardial infarction
MIBG	metaiodobenzylguanidine
min	minimal/minimum
MLC	multileaf collimator
MLD	mean lung dose
MN	mediastinal node
mo/mos	month/months
MRC	Medical Research Council
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MS	median survival
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated/tolerable dose
Mtx	methotrexate
MVA	multivariate analysis
NB	neuroblastoma
N/C	nuclear to cytoplasm ratio
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group

NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NED	no evidence of disease
NEJM	*New England Journal of Medicine*
neoadj	neoadjuvant
NF	neurofibromatosis
NGGCT	nongerminomatous germ cell tumor
NHL	non-Hodgkin lymphoma
NPCR	National Program of Cancer Registries
NPV	negative predictive value
NPX	nasopharynx
NR	no response
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSS	not statistically significant
NTR	near-total resection
n/v	nausea/vomiting
NWTS	National Wilms Tumor Study
NZ	New Zealand
OAR	organ at risk
OPX	oropharynx

OR	odds ratio
ORN	osteoradionecrosis
ORR	overall response rate
OS	overall survival
PA	posterior-anterior
PAND	periarotic lymph node dissection
PAP	Papanicolau
PCI	prophylactic cranial irradiation
PCNSL	primary CNS lymphoma
PCP	pneumocystic pneumonia
pCR	pathologic complete response
PCR	polymerase chain reaction
PDGFR	platelet-derived growth factor receptor
PEG (tube)	percutaneous endoscopic gastrostomy tube
periop	perioperative
PET	positron emission tomography
PF	posterior fossa
PFS	progression-free survival
PFT	pulmonary function test
PgR	progesterone receptor
Plt	platelets
pm	afternoon (post meridian)

PM	parameningeal (for rhabdomyosarcoma)
PMH	Princess Margaret Hospital
PMRT	post-mastectomy radiotherapy
pN0	pathologically node negative
PNET	primitive neuroectodermal tumor
PNI	perineural invasion
PNS	paranasal sinuses
PORT	postoperative radiation therapy
post	posterior
posterolat	posterolateral
postop	postoperative
PPV	positive predictive value
PR	partial response
P-A	para-aortic (for lymph nodes)
PrT	paratesticular (for rhabdomyosarcoma)
preop	preoperative
PS	performance status
PSA	prostate-specific antigen
pt/pts	patient/patients
PTHr	parathyroid hormone–related peptide
PT	prothrombin time
pT	pathologic tumor stage
PTV	planning target volume

PUVA	psoralen and long-wave ultraviolet radiation
q	every
qd	daily
QOL	quality of life
QUANTEC	quantitative analysis of normal tissue effect in the clinic
RAO	right anterior oblique
RASSFIA	Ras Association (RalGDS/AF-6) domain family member 1A
RB	retinoblastoma
RBE	relative biologic effectiveness
RCC	renal cell carcinoma
RCT	randomized controlled trial
rcv	receive/received
RFS	relapse-free survival
RLL	right lower lobe
RML	right middle lobe
RMS	rhabdomyosarcoma
r/o	rule out
ROM	range of motion
RPLND	retroperitoneal lymph node dissection
RPO	right posterior oblique
RR	relative risk
RT	radiation or radiation therapy

RTOG	Radiation Therapy Oncology Group
RUL	right upper lobe
RUQ	right upper quadrant
Rx	prescription/prescriptions
S	sacral (spine level)
SABR	stereotactic ablative radiotherapy
SAD	source-axis distance
SBO	small bowel obstruction
SBRT	stereotactic body radiation therapy
SCs	spinal cord
SCC	squamous cell carcinoma
SCV	supraclavicular
SEER	surveillance epidemiology and end results (data)
SFOP	French Society of Pediatric Oncology
Sg	surgery
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SIB	simultaneous integrated boost
SIL	squamous intraepithelial lesion
SLNB	sentinel lymph node biopsy
SMA	superior mesenteric artery
SQ	subcutaneous
s/p	status post

SPECT	single photon emission computed tomography
SRS	stereotactic radiosurgery
SS	statistically significant
SSD	source to skin distance
ST	soft tissue (as in sarcoma)
STD	sexually transmitted disease
STR	subtotal resection
STS	soft-tissue sarcoma
sup	superior
SUV	standard uptake value
SVC	superior vena cava
Sx	symptom/symptoms
T	thoracic (spine level)
TBI	total body irradiation
TD	tolerance dose
TFT	thyroid function test
tid	three times a day
TKI	tyrosine kinase inhibitor
TMZ	temozolomide
TNM	tumor/node/metastasis
trilat	trilateral
TRUS	transrectal ultrasound
TSH	thyroid-stimulating hormone

Tx	treatment/treatments
UA	urinalysis
UCSF	University of California at San Francisco
UE	upper extremity
UH	unfavorable histology
UK	United Kingdom
unilat	unilateral
US	ultrasound
U.S.	United States
USPSTF	United States Preventive Services Task Force
UV	ultraviolet
VALCSG	Veterans Administration Lung Cancer Study Group
VCE	vincristine, carboplatin, etoposide (chemo regimen)
VMA	vanillylmandelic acid
vs.	versus
WBC	white blood cell
WBI	whole breast irradiation
WBRT	whole brain radiation therapy
WHO	World Health Organization
wk/wks	week/weeks
WLE	wide local excision
yo	year old/years old

yr/yrs	year/years

Symbols

+	meaning *with* or *and* (as in Surgery + RT)
→	meaning *followed by*
↑	meaning *increasing, high(er),* or *elevated*
↓	meaning *decreasing* or *low(er)*

Contents

1

Rhabdomyosarcoma

Updated by Shane R. Stecklein

BACKGROUND

What are the 2 incidence age peaks of RMS and their associated histologies?

Show Answer

2–6 yo (embryonal) and **15–19 yo (alveolar)**

What is the estimated overall annual incidence of RMS in the United States?

Show Answer

350 cases/yr of RMS in the United States, 3% of all childhood cancers (#1 STS)

What are the most common sites of RMS? List them in order of approximate frequency in %.

Show Answer

Most common sites of RMS:

. H&N 40% (PM 25%, orbit 9%, non-PM 6%)
. GU 30%
. Extremity 15%
. Trunk 15%

What are the most common sites of mets?

Show Answer

Bone, BM, and lung
What % of pts present with mets? What types are prone to have hematogenous mets?

Show Answer

15% of pts present with mets. The prostate, trunk, and extremities are prone to hematogenous mets.
What is the most common origin of RMS?

Show Answer

Mesenchymal stem cells. Sporadic RMS is the most common.
What genetic syndromes are associated with RMS?

Show Answer

Genetic syndromes: Beckwith–Wiedemann syndrome (BWS), Li Fraumeni, NF-1, Costello syndrome, and Noonan syndrome
What are the 4 major histologies of RMS and their associated subtypes (if any)? Which is most common?

Show Answer

Major histologies of RMS and subtypes:

- Embryonal (classic, spindle cell, and botryoid) (Most common: 60%)
- Alveolar
- Pleomorphic
- Undifferentiated

What genetic change is associated with embryonal RMS?

Show Answer

LOH 11p15.5 (embryonal) is associated with IGF2 **gene deletion,** seen in BWS; also, abnormalities in chromosomes 2, 8, 12, and 13 are associated with MYCN, MDM2, CDK4, CDKN2A (p16), CDKN2B ($p15^{INK4b}$), and TP53 genes.
What translocations are associated with alveolar RMS? What are the genes involved in the fusion?

Show Answer

Alveolar RMS is associated with **t(2;13)** (70%) and **t(1;13)** (20%). Genes involved are PAX3 **or** PAX7 **with** FOXO1 **(aka** FKHR**).**
Which is the most common histology of RMS in infants? Young children? Adolescents? Adults?

Show Answer

Most common RMS histology **(by age group):**

Infants: botryoid
Young children: embryonal
Adolescents: alveolar
Adults: pleomorphic
Which histologies are most commonly associated with each organ site (H&N, GU, extremities/trunk)?

Show Answer

Most common RMS histologies **(by site):**

H&N: embryonal
GU: botryoid
Extremities/Trunk: alveolar
What is the most important histologic tumor marker for RMS?

Show Answer

MyoD (and other myogenic proteins: actin, myosin, desmin, myoglobin)

What is the DDx for small round blue cell tumors of childhood?

Show Answer

Small round blue cell tumors of childhood:

Lymphoma
EWS
Acute lymphoblastic leukemia
RMS
NB
Neuroepithelioma
MB
Retinoblastoma

(Mnemonic: **LEARN NMR**)
List the histologies of RMS in terms of prognosis from best to worst.

Show Answer

. Spindle cell and botryoid
. Classic embryonal
. Alveolar
. Undifferentiated

What are the 5-yr OS rates for each of the histologic subtypes?

Show Answer

5-yr OS **(by histology):**

Botryoid: 95%
Spindle cell: 88%
Embryonal: 66%
Alveolar: 54%
Undifferentiated: 40%
Which sites require LND b/c of a high propensity for LN mets? What is

the risk of LN mets for these sites?

Show Answer

The following sites are associated with **>20%** LN mets rate and thus require LND:

PrT: (only if >10 yo)
Bladder: pelvic
H&N: NPX, LND typically not done for NPX
Extremities: UE (axillary) and LE (inguinal/femoral) (La TH et al., IJROBP 2011)

Which sarcoma histologies are at high risk for LN mets?

Show Answer

Sarcomas with significant risk of LN mets are:

Synovial cell sarcoma
Clear cell sarcoma
Angiosarcoma
RMS
Epithelioid sarcoma

(Mnemonic: **SCARE**)

Which International Rhabdomyosarcoma Study (IRS) called for routine LN sampling in RMS of the extremity?

Show Answer

IRS-IV (Neville HL et al., J Pediatr Surg 2000): 139 extremity pts, 76 pts had surgical LN evaluation; of the 10% who were clinically node positive (cN+), 50% were Pathologically node positive (pN+); **of those cN0, 17% were pN+.**

What are considered nonregional mets/LNs for various sites (UE, LE, pelvic organs [PrT, vagina, uterus])?

Show Answer

Nonregional LN stations by primary site:

UE: scalene node
Pelvic (PrT/vagina/uterus): inguinal
Retroperitoneal (RP): P-A (except if immediately adjacent)
LE: iliacs/P-A
What are the 4 favorable organ sites and their estimated 3-yr OS rate?

Show Answer

Favorable organ sites:

- Orbit
- Non-PM H&N
- Nonprostate/bladder GU
- Biliary

The estimated 3-yr OS is **94%.**
What is the estimated 3-yr OS for RMS arising from unfavorable sites (PM H&N, prostate, bladder, extremities/trunk)?

Show Answer

For unfavorable sites, estimated 3-yr OS is **70%.**
What are the PM H&N sites?

Show Answer

PM H&N sites:

Middle ear
Mastoid
Nasal cavity
NPX
Infratemporal f**O**ssa

Pterygopalatine f**O**ssa
PNS
Parapharyngeal space

(Mnemonic: **MMNNOOPP**)
What are the non-PM H&N sites?

Show Answer

Scalp, cheek, parotid, oral cavity, oropharynx, and larynx

WORKUP/STAGING

List the general workup for RMS.

Show Answer

RMS workup: H&P, basic labs (CMP, CBC, LDH), EUA, CT/MRI primary, CT chest/abdomen, bone scan, bilat BM Bx, and primary site core Bx/incisional Bx; PET/CT may be useful in determining extent of Dz
What specific workup studies are needed for PM RMS?

Show Answer

PM RMS workup: MRI brain, CSF cytology (neuroaxial MRI if +)
What specific workup studies are needed for bladder RMS?

Show Answer

Bladder RMS workup: EUA and cystoscopy
Summarize the TNM criteria for RMS.

Show Answer

T1: confined to anatomic site of origin
T1a: ≤5 cm
T1b: >5 cm
T2: extension or fixed to adjacent tissue
T2a: ≤5 cm

T2b: >5 cm
N0: no regional LN involvement
N1: regional node involvement
M0: no DM
M1: DM
Summarize the preop staging of RMS.

Show Answer

Stage 1: favorable site (any T, any N, M0)
Stage 2: unfavorable site, T1a or T2a (≤5 cm), N0, M0
Stage 3: unfavorable site, T1b or T2b (>5 cm), and/or N1, M0
Stage 4: M1
Summarize the postop grouping for RMS.

Show Answer

Group I: R0 resected, localized Dz
Group II: R1 resected and/or resected +LN
Group III: R2 (residual primary Dz or LN) or Bx only
Group IV: M1
What proportion of RMS pts end up with Group III Dz?

Show Answer

Most (~50%) RMS end up with **group III** Dz.
Define the risk groups for RMS (based on IRS-VI).

Show Answer

Low risk: all favorable embryonal and Group I–II unfavorable embryonal
Intermediate risk: any alveolar and Group III unfavorable embryonal
High risk: all metastatic Dz

TREATMENT/PROGNOSIS

What is the Tx paradigm for RMS?

Show Answer

The Tx for RMS in the IRS studies varies based on site, histology, and tumor size.

RMS Tx paradigm: **generally, max safe resection (or Bx alone) → chemo +/- RT (timing of CRT depends on risk groupings)**

What chemo regimens are commonly used in RMS?

Show Answer

Vincristine/Actinomycin D/Cytoxan (VAC) and vincristine/actinomycin D (VA) are commonly used.

Ifosfamide/Etoposide (IE) is also used in subsets of RMS.

How does age factor into the prognosis of metastatic embryonal RMS?

Show Answer

>10 yo is worse than <10 yo (EFS 14% vs. 47%).

What factors drive poor prognosis in PM RMS?

Show Answer

Subarachnoid space involvement with skull base erosion, CN palsy, intracranial extension; DFS 51% vs. 81% (without risk factors)

What is the seminal trial that 1st supported the use of chemo for RMS?

Show Answer

Heyn RM et al. (Cancer 1974): VA chemo vs. nothing after Sg associated with improved OS.

IRS-I: What did it answer?

Show Answer

Group I: favorable histology (FH); **RT not needed**

Group II: RT + VA × 1 yr (no need for Cytoxan)

Groups III–IV: RT + VAC × 2 yr (no Adr needed) DM is more common than

LF.

No dose response for RT; no difference in RT field size (large = involved field):

PM RMS ↑ CNS relapse if certain high-risk features are present.

IRS-II: What did it answer?

Show Answer

Group I: VA × 1 yr same as VAC × 2 yrs (except in UH)

Group II: RT + VA × 1 yr same as RT + VAC + 1 yr (except in UH, use VAC + RT).

Groups III–IV: no benefit adding Adr to VAC + RT (except in UH).

Better PM outcomes than **IRS-I** with prophylactic WBRT for high-risk pts.

Chemo alone for special pelvic sites with VAC is not adequate (bladder preservation only 22% b/c of inadequate response).

According to IRS I–II analysis, which RMS site was shown to carry the highest risk for LN mets?

Show Answer

The **prostate** was shown to have the highest risk for LN mets (~40% with LN+ Dz).

IRS-III: What did it answer?

Show Answer

Groups I–II UH: better with vincristine/Adriamycin/cyclophosphamide (VAdrC) alternating with VAC + RT, than RT + VA or VAC.

Groups II–III favorable site: VA + RT adequate

Groups II–III unfavorable site and group IV FH/UH: VAC + RT; no benefit adding Adr

WBRT prophylaxis did not reduce CNS relapse.

There was an improved bladder preservation rate and OS in the multimodality Tx of special pelvic sites.

Who did not get RT in IRS-III?

Show Answer

Group I FH and group III special pelvic sites (if CR after chemo) did not get RT.

In IRS-III, the OS was mainly driven by what groups of pts?

Show Answer

Groups I–II UH getting VAdrC alternating with VAC and group III FH special pelvic sites

What did IRS-III demonstrate about the Tx of special pelvic sites?

Show Answer

Pelvic site I (bladder dome, vagina, uterus): VAdrC alternating with VAC × 2 yrs → Second-look surgery (SLS) at 20 wks → if PR, then RT at wk 20 + Adr/etoposide × 2 cycles; if CR, no RT and continue chemo.

Pelvic site II (bladder neck/trigone, prostate): VAdrC alternating with VAC × 2 yrs → RT (wk 6) → SLS at 20 wks.

Bladder preservation rate 60% vs. 25% (IRS-I–II) and better OS rate (83% vs. 72%).

IRS-IV: What did it answer?

Show Answer

IRS-IV focused on improving outcome for group III: utility of adding IE to VAC, and bid RT (1.1 Gy bid to 59.4 Gy) vs. conventional RT (1.8–50.4 Gy).

Conventional once daily RT remains standard. VAC remains standard, even for the alveolar type.

However, **for group IV, VAC + IE is standard** (IE vs. vincristine/melphalan).

What trial utilized WBRT prophylaxis for high-risk PM RMS, and how did it differ from other IRS trials?

Show Answer

IRS-II–III, with whole brain to 30 Gy with intrathecal chemo, all started day 0. IRS-IV started day 0 but did not treat the whole brain—just to tumor + 2-cm margin on day 0.

For **IRS-IV,** RT started wk 9 except at day 0 for SC compression and wk 1 for high-risk PM (direct intracranial extension, base of skull invasion, CN palsy).

What did Wolden et al. data show about the importance of RT in clinical group (CG)-I UH RMS?

Show Answer

Wolden et al. (JCO 1999) analyzed **IRS-I–III,** RT vs. no RT in **CG-I** pts: showed only a trend to improved FFS and no OS with RT in FH; however, **in CG-I UH, RT improved FFS and OS.**

What was the purpose of COG-D9602?

Show Answer

To determine whether the lowest risk pts from IRS-III and IRS-IV (localized, grossly resected, or gross residual [orbit only]) embryonal RMS could be treated with reduced toxicity by reducing RT dose and eliminating cyclophosphamide. (Raney RB et al., JCO 2011)

What are the 2 subsets of low-risk pts on COG-D9602?

Show Answer

Subsets of low-risk pts on COG-D9602:

Subset A (treated with VA + RT on **IRS-III–IV**): stage 1, CG-I–II, orbit CG-III, stage 2, CG-I–II. Now treated with VAC × 4 cycles **(reduced chemo) → 4 cycles VA + RT.**

Subset B (treated with VAC + RT on **IRS-III–IV**): stage 1, CG-III (nonorbit), stage 3 CG-I–II. Now treated with VAC × 4 cycles **(reduced**

chemo) → 12 cycles VA + RT.

What did the results of COG-D9602 demonstrate?

Show Answer

5-yr FFS rate (88%) and OS rate (97%) were similar to comparable IRS-III pts, even with lower RT doses but were worse than comparable IRS-IV pts receiving VA + cyclophosphamide. (Raney RB et al., JCO 2011)

What RT doses were used in COG-D9602?

Show Answer

Dose depended on CG (extent of Sg) and LN positivity. After resection, pts with microscopic residual and uninvolved LN rcvd 36 Gy. Involved LN: **41.4–50.4 Gy.** Orbital primary: **45 Gy.** (Breneman J et al., IJROBP 2012)

What are the major study questions for intermediate-risk pts in COG-ARST0531?

Show Answer

VAC vs. VAC alternating with vincristine/irinotecan (VI); timing of RT (wk 4 vs. wk 10, **IRS-IV)**

What are the major study questions for high-risk pts in COG-ARST0431?

Show Answer

VAC alternating with IE using interval dose compression; ability to improve LC in metastatic RMS by using VI with RT.

What is the timing of RT in IRS-V?

Show Answer

Low risk: **wk 3**
Intermediate risk: **wk 12**
High risk: **wk 15**

What is the timing of RT in COG-D9602?

Show Answer

Low risk: **wk 13**
Intermediate risk: **wk 4**
High risk: **wk 20**
What were the secondary objective questions for RT in COG-D9602?

Show Answer

Whether 36 Gy is adequate for N0, R1 and if 45 Gy is adequate for orbital RMS.
What is the dose for CG-I with FH?

Show Answer

0 Gy. No RT is required for CG-I with FH.
What study provided the rationale for reduced RT doses of 36 Gy in IRS-V–COG-D9602?

Show Answer

MSKCC retrospective review (Mandell L et al., JCO 1990): in only 32 CG-II pts, no difference in LC b/t <40 Gy vs. >40 Gy.
All pts with initial nodal involvement, regardless of response to induction therapy or SLS, must get what?

Show Answer

RT to **41.4 Gy if R0–R1** resected; all gross or suspected **gross Dz** treated to **50.4 Gy.**
RT is NEVER omitted for node+ Dz.
Under what circumstances should RT be interrupted?

Show Answer

ANC <750 µL or Plt <75 K, and if uncontrolled infection or Hgb <10. RT is restarted after these are normalized; if a low blood count is a problem, chemo

should be withheld or modified until RT is completed.
How do you treat PA nodes (if +)?

Show Answer

AP/PA to 36 Gy → boost to 50.4 Gy with off-cord technique, IMRT, or protons (allowed on COG studies).
What is defined as a minor deviation of an RT plan?

Show Answer

95% IDL covers <90% PTV but b/t 90% and 100% CTV, or >110% PTV
What is defined as a major deviation of an RT plan?

Show Answer

95% IDL covering <90% of CTV
What % of CG-III pts get a GTR at SLS?

Show Answer

25% of **CG-III** pts get a GTR at SLS.
PT RMS arises from where?

Show Answer

PT RMS arises from the **distal spermatic duct.**
Which RMS tumors have a better prognosis: hyperdiploid or diploid?

Show Answer

Hyperdiploid (found in embryonal histologies) vs. diploid (in alveolar histologies)
Based on a review of IRS-III data, where do failures mostly occur after Tx? What is the #1 prognostic factor for LF?

Show Answer

LF > DM. LN positivity is the biggest predictor for LF.

What evidence supports the use of ≤40 Gy in the management of CG-II RMS (and therefore the rationale for a test dose of 36 Gy in COG-D9602)?

Show Answer

St. Jude data (Regine WF et al., IJROBP 1995) suggest that for the 24 CG-II pts in this study, the LC rate with <40 Gy (89%) was not statistically different from ≥40 Gy (100%).

MSKCC data (Mandell L et al., JCO 1990): 32 CG-II pts treated with various doses also found that the LC for doses <40 Gy was equivalent to doses ≥40 Gy.

What evidence is there to support IMRT for H&N RMS (as endorsed by IRS-VI)?

Show Answer

Wolden et al. reviewed 28 pts (21 PM) treated with IMRT. A 1.5-cm margin was used, with a median dose of 50.4 Gy. There was excellent LC (95%) despite reduced margins used, min late toxicity, and comparable acute toxicity. (IJROBP 2005)

In IRS-V, what additional dose must be given if Tx is delayed by 2–3 wks? How about >3 wks? If <2 wks?

Show Answer

2–3 wks: **1.8 Gy**

>3 wks: **3.6 Gy**

<2 wks: no change in dose

What 3 issues must be considered when treating an extremity site?

Show Answer

Considerations when treating an extremity site:

. Evaluate the need to radiate regional nodes.

- Include scars/drains in the field.
- Try to spare a strip of skin or portion of the joint/epiphyses.

If a CR is obtained after induction chemo with a group III, N0 embryonal tumor of the vagina, cervix, and uterus, what RT dose would you use?

Show Answer

No RT if CR! These are “special sites.”
What dose of RT would you give for a pt with stage III, group I embryonal RMS? How about alveolar RMS?

Show Answer

No RT for ALL embryonal group I pts (stages I–III). For UH group I pts, **36 Gy** RT is given.
If a pt is high risk (i.e., metastatic), should the mets be treated as well as the primary with RT?

Show Answer

At the discretion of the RT oncologist. At the JHH, the preference is to treat the primary and let the pt finish chemo; if the pt responds to chemo, then mets are treated with RT. Consider treating the mets concurrently with the primary if not too large a BM volume is irradiated.
For what 2 sites of the H&N would you not recommend primary resection?

Show Answer

The **orbit and PM** sites are not recommended for primary resection.
For what RMS tumor sites would LND be recommended?

Show Answer

LND is recommended for the following RMS tumor sites:

- GU (PrT/bladder) (pelvic and P-A)
- Extremities/Trunk (axillary, inguinal)

What are 2 favorable prognostic factors in pts with CG-IV RMS?

Show Answer

Per **IRS-IV, ≤2 metastatic sites and embryonal histology** were associated with better OS. (Breneman JC et al., JCO 2003)

FOLLOW-UP/TOXICITY

Per COG-D9602, what is the dose constraint for the whole kidney?

Show Answer

The dose constraint for the whole kidney is **19.8 Gy.**
What is the max allowed dose to the whole liver?

Show Answer

The max dose to the whole liver is **23.4 Gy.**
Per COG-D9602, what is the dose limit to the chiasm?

Show Answer

The dose limit to the chiasm is **46.8 Gy.**
What is the max allowed dose to the whole heart? Whole abdomen/pelvis?

Show Answer

The max dose to the whole heart is **30.6 Gy.** The max dose to the whole abdomen/pelvis is **24 Gy (at 1.5 Gy/fx).**
What is the dose limit to the lungs, if less than half of the combined lung volume is in the PTV?

Show Answer

In this situation, the dose limit to the lung is **15 Gy (in 1.5 Gy/fx).**
What is a major side effect of VAC besides myelosuppression?

Show Answer

Veno-occlusive Dz of the liver.

Table 1-1 Radiation Doses for Favorable Histology Tumors (per COG-ARST0331, closed)	
Stage 1, clinical group I	No radiotherapy
Stage 1, clinical group II, N0	Conventional RT: 36 Gy
Stage 1, clinical group II, N1	Conventional RT: 41.4 Gy
Stage 1, clinical group III	Conventional RT: 45 Gy (orbit only)
Stage 1, clinical group III	Conventional RT: 50.4 Gy (nonorbit)
Stage 2, clinical group I	No radiotherapy
Stage 2, clinical group II, N0	Conventional RT: 36 Gy
Stage 2, clinical group II, N1	Conventional RT: 41.4 Gy
Stage 3, clinical group I	No radiotherapy
Stage 3, clinical group II, N0	Conventional RT: 36 Gy
Stage 3, clinical group II, N1	Conventional RT: 41.4 Gy

RT, radiation therapy. For certain clinical group III pts, the radiotherapy dose may be modified by the use of 2nd-look surgery.
Source: http://members.childrensoncologygroup.org (ARST0331).

Table 1-2 Radiation Doses for Unfavorable Histology Tumors (per COG-ARST0531, completed)	
Clinical Group	Dose
Group I, alveolar only	36 Gy
Group II, node negative	36 Gy
Group II, node positive	41.4 Gy
Group III, alveolar, orbit only	45 Gy
Group III, all others	50.4 Gy

Table 1-3 Principles of Radiation Therapy (per COG-D9602, completed)
Low risk: Surgery 1st, then chemo. If group I → chemo only, no RT. All pts with initial +node must get RT regardless of response to induction chemo or SLS (at least 41.4 Gy, 50.4 Gy to gross Dz). Vincristine is given with RT

and dactinomycin is given at wk 13 prior to RT, but they are not given concurrently.

- Target volume: GTV—pre-Tx volume + involved LN; CTV = GTV + 1 cm; PTV = CTV + 0.5 cm. For CG-III to 50.4 Gy, CD at 36 Gy to pre-Tx GTV + 0.5 cm (CTV), with PTV = CTV + 0.5 cm. The planning OAR volume is based on organs at risk; GTV can be defined by exam, CT, MRI, or PET.
- Timing: RT begins wk 13 after postop chemo. The exceptions are those who get SLS and those with vaginal primaries. For those who get SLS, RT starts after surgery at wk 13 (to allow time for healing).
- All pts with initial CG-III in a favorable site (stage I, except orbit and paratesticular sites) should be considered for SLS at wk 13.

Intermediate risk: RT given at wk 4 (compare with data from wk 10 on IRS-IV). IMRT/proton/brachytherapy/electron and PET imaging are all allowed. CRT = VC or VI concurrently. Simulation occurs before wk 4 to begin on time.

- Margins: CD after 36 Gy for tumors with “pushing” rather than invasive (lung, intestine, bladder). Boost to 50.4 Gy with new GTV representing response + 1 cm (CTV) and 0.5 cm (PTV). If 36 or 41.4 Gy, there is no volume reduction. GTV is pre-Tx volume + margin, except intrathoracic or intra-abdominal tumors (GTV as pre-Tx volume excluding intrathoracic or intra-abdominal/pelvic tumor from which it was debulked, since these are “pushing” borders).
- Timing: All at wk 4. Emergency RT for symptomatic cord compression and high-risk PM (intracranial extension) can be given on wk 1 (day 1). Management of BOS erosion and CN palsy was not specified in the protocol, so it can be managed according to the discretion of the radiation oncologist.

High risk: RT given on wk 20 to primary and metastatic sites (except high-risk PM sites with IC extension and emergency RT).

- High-risk PM sites with only BOS and/or CN palsy will get RT at wk 20.

PM sites with intracranial extension will rcv RT at wk 1 (day 0) (but within 2 wks of the 1st cycle of chemo to start RT) and Tx to the metastatic site at wk 20 (unless the metastatic site is within the same Tx port as the primary). Emergency RT for cord compression is on day 0.

CRT: VI is given concurrently with RT, starting on wk 19 (day 0 if an emergency or PM with IC). Alternative: VC, if VI is not tolerable.

Margins: CD after 36 Gy for tumors with "pushing" rather than invasive (lung, intestine, bladder). Boost to 50.4 Gy with new GTV representing response + 1 cm (CTV) and 0.5 cm (PTV). If 36 or 41.4 Gy, GTV is pre-Tx volume + margin.

Bilat whole lung 15 Gy (10 fx) for pulmonary mets or pleural effusion (can boost to gross Dz) to 50.4 Gy.

IRS, International Rhabdomyosarcoma Study; chemo, chemotherapy; RT, radiation therapy; pt, patient; +node, positive node; SLS, second-look surgery; Gy, gray; Dz, disease; wk, week; GTV, gross target volume; Tx, treatment; LN, lymph node; CTV, clinical target volume; cm, centimeter; PTV, planning target volume; CG, clinical group; CD, cone down; exam, examination; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; postop, postoperative; IMRT, intensity modulated radiation therapy; CRT, chemoradiation; VC, vincristine/Cytoxan; VI, vincristine/irinotecan; PM, parameningeal; BOS, base of skull; CN, cranial nerve; IC, internal carotid; rcv, receive; bilat, bilateral; fx, fraction; met, metastasis.

Table 1-4 Principles of Surgery (per COG-D9602, completed)

1. WLE with margin preferred, no amputation for group IV setting. The rest get incisional or core Bx (orbit, PM H&N).
2. Sentinel LN Bx should be done for extremity sites.
3. Needle Bx or open Bx can be done; an aggressive LN sample is most appropriate.
4. Definitive surgery can be carried out after initial Bx or noncancer surgery. This subsequent PRE is followed by local adj therapy based on pathology from the definitive PRE.
5. A subsequent delayed resection can be done after chemo and RT (for

initial Bx only) if the tumor has diminished enough to make resection feasible. SLS takes place on wk 13 (except orbit, PT).

6. If residual tumor persists after SLS, subsequent-look procedures can be done after further therapy, if the tumor appears resectable. SLS should be done to max extent if it is cosmetically and functionally feasible.
7. H&N sites: no neck dissection unless there is clinical involvement.
8. PrT: Only ipsi RP LN dissection should be done. Do not do radical bilat regional node dissection. Regional LNs are ipsi iliac and RP nodes up to the hilum of the ipsi kidney. Orchiectomy and resection of the entire spermatic cord is via inguinal excision. Bx can take place prior to excision (but must ensure there is no spillage).
9. GU (bladder/prostate): if laparotomy is preformed, then iliac/para-aortic node sample should be done, and any other clinically involved site(s) should be biopsied. Bladder preservation rate is 50%–60%. Partial cystectomy should be done for bladder dome tumors.
10. Elective LND is not indicated except for extremities and PT lesions. Open Bx or LN sampling should be done for any gross enlarged nodes.

WLE, wide local excision; Bx, biopsy; PM, parameningeal; H&N, head and neck; LN, lymph node; PRE, pretreatment re-excision; adj, adjuvant; chemo, chemotherapy; RT, radiation therapy; SLS, second-look surgery; wk, week; PrT, paratesticular; max, maximum; ipsi, ipsilateral; RP, retroperitoneal; bilat, bilateral; GU, genitourinary; LND, lymph node dissection.

2

Ewing Sarcoma

Updated by Amy Catherine Moreno

BACKGROUND

What is the annual incidence of EWS in the United States? How common is it relative to other bone tumors?

Show Answer

200–300 cases/yr of EWS in the United States; **2nd most common bone tumor** (osteosarcoma #1)

What is the median age of presentation of EWS?

Show Answer

The median age of EWS is **14–15 yrs.**

Is EWS associated with congenital Dz?

Show Answer

No. However, it can occur as a 2nd malignant neoplasm secondary to chemo (i.e., VP16) or RT.

What is the racial and gender predilection?

Show Answer

EWS is more common in **whites** (>90% of cases) and among **males** (1.5:1).

What is the embryologic tissue and cell of origin in EWS?

Show Answer

Neuroectodermal tissue is the embryonic tissue of origin for EWS and it is derived from primordial BM mesenchymal stem cells.
What is the most common genetic change seen in EWS?

Show Answer

- **t(11;22)** in 90%, FLI1(11): EWS(22). Other minor translocations include:
- t(21;22) in 10% of cases and
- t(7;22)

What other neoplasms are associated with the EWS translocation?

Show Answer

PNET, malignant melanoma of soft parts, and desmoplastic small round cell tumor (DSRCT)
Which exon fusion in t(11,22) is most common, and why is this important?

Show Answer

The most common fusion is **exon 7** of EWS and **exon 6** of FLI1 in 60% of cases. It is **associated with a lower proliferative rate and better prognosis.**
What type of cell morphology is expected to be seen in EWS?

Show Answer

Small round blue cells are expected with EWS.
What constitutes the Ewing family of tumors?

Show Answer

EWS (osseous and extraosseous), **PNET, DSRCT,** and **Askin tumor**
What other tumors also have small round blue cells?

Show Answer

Lymphoma
Ewing

Acute lymphoblastic leukemia
RMS
NBNB
Neuroepithelioma
MB
Retinoblastoma

(Mnemonic: **LEARN NMR**)
What markers help differentiate EWS from other small round blue tumors?

Show Answer

Markers that differentiate EWS:

- Vimentin
- HBA-71
- β2-microglobulin
- ↑c-myc (vs. n-myc in NB)

How is PNET similar to and different from EWS histologically?

Show Answer

PNET and EWS have similar translocations and are both CD99 (MIC2)+ and vimentin+. However, **PNET is NSE+,** S100+, more differentiated, and has more neuroendocrine features. **EWS is NSE**−, S100 variable, and Homer Wright rosettes+.
What major factors have been classically associated with a poor prognosis in EWS?

Show Answer

Male gender
Age >15 yrs (>17 yrs in some)
Pelvic/axial **S**ite or rib origin

Size (**>8 cm** per St. Jude or >100 cc per **CESS-81** [Cooperative Ewing Sarcoma Studies])
Stage (presence/absence of metastatic Dz is strongest prognostic factor)
↑LDH
Poor **response** to chemo (>10% viable tumor)

(Mnemonic: **MASSSive LDH response**) (Jürgens H et al., Klin Padiatr 1988)
What is an Askin tumor?

Show Answer

Askin tumor is a **nonosseous PNET of the CW** (worse prognosis than other sites).
What % of EWS pts present with mets?

Show Answer

25% of EWS pts present with mets.
Where do mets typically occur?

Show Answer

Lung (25%–40%) ≥ **Bone/BM** (~25%) and LNs (<10%).
What % of pts with localized Dz vs. lung mets have BM micromets?

Show Answer

25% (localized) vs. 40% (lung mets)

WORKUP/STAGING

What is the typical clinical presentation with EWS?

Show Answer

Pain (96% of cases) and swelling (63% of cases) are most common → fever (21%) and fractures (16%).
What Sx at presentation portends a particularly poor prognosis in EWS?

Show Answer

Pts who present with **fever** tend to have a poor prognosis.
What is the most commonly involved site in EWS at presentation?

Show Answer

Extremities (53%) > **axial skeleton** (47%). The **LE** is the most common region (41%), and the **femur** is most common site (~20% of cases) f/b the pelvis (26%), CW (16%), UE (9%), spine (6%), and skull (2%).
If an EWS tumor presents centrally, what is the most common site?

Show Answer

The **pelvis** (26% of cases) is more common than the axial skeleton (12% of cases).
List the general workup for a pt who presents with an extremity mass.

Show Answer

Extremity mass workup: H&P, plain x-ray, MRI/CT primary, and core needle Bx or incisional Bx. Once a Dx of a sarcoma (EWS) is confirmed, complete the workup with CBC, BMP, LDH, ESR, LFTs, CXR, CT chest, bone scan, or PET/CT (preferred), echo, and bilat BM Bx.
What are the characteristic findings on plain x-ray in EWS? How does this compare to osteosarcoma?

Show Answer

Classically, EWS shows an **"onion skin"** reaction on plain films, whereas osteosarcoma is associated with a "sunburst" appearance. The **Codman triangle,** an area of new subperiosteal bone as a result of periosteal lifting by underlying tumor, can be seen in both EWS and osteosarcoma. However, EWS tends to have metaphyseal rather than diaphyseal involvement.
How is EWS staged?

Show Answer

No standard staging system exists. Tumors are either **localized** or **metastatic.**
In EWS, what is meant by expendable bones? Name 3.

Show Answer

Expendable bones are ones that can be resected with min morbidity, such as:

- Proximal fibula
- Ribs
- Distal four fifths of clavicle
- Body of scapula
- Iliac wings

TREATMENT/PROGNOSIS

Summarize the current Tx paradigm for EWS.

Show Answer

EWS Tx paradigm: **induction VAC-IE** (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide/etoposide) → **local therapy at wk 12** (Sg ± RT or definitive RT **with non-Adria chemo given during RT,** usually 2 cycles) → **further adj chemo to wk 48.** Sg when possible, give PORT when necessary, and whole lung irradiation (WLI) for lung mets.
Estimate the 5-yr OS for localized and metastatic EWS.

Show Answer

5-yr OS for **localized EWS** is **60%–80%** (60% for pelvic, 80% extremities) and **20%–30%** for **metastatic EWS** (bone mets 5 yrs 30%; lung mets 5 yrs 50%).
What are the RT doses given for EWS in the definitive vs. the postop setting?

Show Answer

Definitive: **55.8 Gy**/31 fx (45 Gy to prechemo volume with 1–2-cm margin

with boost to postchemo volume to 55.8 Gy).

Postop: **50.4 Gy for microscopic**/tumor spill and **55.8 Gy for gross** residual;

45 Gy for vertebral body involvement b/c of SC tolerance.

What is the LF rate for EWS after definitive RT?

Show Answer

Overall, 5%–25%; worse with pelvic sites (LF 15%–70%); worse with large (>8 cm) lesions (LF 20%).

What are considered adequate surgical margins in EWS?

Show Answer

Per COG protocol **AEWS0031,** adequate margins are **>1 cm** for bone, **>0.5 cm** for ST, and **>0.20 cm** for fascia. (Womer RB et al., JCO 2012)

What are 3 indications for adj RT after Sg in EWS?

Show Answer

+Margin, tumor spill, and >10% viable tumor after induction chemo (poor chemo response).

Is there a difference in LC b/t EWS pts who rcv preop RT vs. postop RT vs. definitive RT?

Show Answer

Yes. Schuck et al. performed a secondary analysis of 1,085 pts in **CESS-81 and -86** and **EICESS 92** (European Intergroup CESS) and found no difference in LF b/t preop and postop RT (5.3% vs. 7.5%), but LF was significantly worse in the definitive RT arm (26%). However, there was a strong negative selection bias against the definitive RT cohort. There was no difference in LF b/t RT alone and Sg + post-RT if only partial resection was achieved. Preop RT may improve LC if STR is deemed likely. (IJROBP 2003)

When is Sg preferred to RT as a local therapy in EWS?

Show Answer

Sg is preferred when expendable bones are involved, if there is a pathologic fracture, and when there is a LE lesion in a child (<10 yo).
What Tx were compared in IESS-1 (1973–78)? Summarize the study's major results (OS, RFS, and LR).

Show Answer

IESS-1 compared adj vincristine/actinomycin D/Cytoxan (**VAC**) alone vs. vincristine/actinomycin D/Cytoxan/doxorubicin **(VACAdr)** vs. **VAC + prophylactic WLI.** 5-yr OS was significantly worse in the VAC alone arm (28%) compared to VACAdr (65%) or VAC + WLI (53%). 5-yr OS was not significantly different b/t VACAdr and VAC + WLI. However, the VACAdr arm had an improved 5-yr RFS (60%) compared to VAC + WLI (44%). 5-yr LR was not significantly different b/t arms (~15%). **Conclusions:** adj chemo improved RFS and OS, WLI is effective, and nonpelvic sites respond better. (Nesbit ME et al., JCO 1990)
In IESS-1, which site had the worst prognosis?

Show Answer

In IESS-1, pts with **pelvic primaries** had significantly worse 5-yr OS (pelvic 34% vs. nonpelvic 57%). Among pelvic cases, there was no OS difference by Tx arm ($p = 0.81$) vs. in nonpelvic cases ($p < 0.001$). (Nesbit ME et al., JCO 1990)
What Tx were compared in IESS-2 (1978–82)? Summarize the study's major results.

Show Answer

IESS-2 randomized 214 pts b/t induction high-dose intermittent (HDI) VACAdr to moderate-dose continuous (MDC) VACAdr in nonpelvic localized tumors. HDI given q3wks vs. MDC given weekly. 5-yr RFS, DFS, and OS improved with HDI. **5-yr OS** HDI 77% vs. MDC 63%. Main failure

in both arms: mets-lung > bone. (Burgert EO et al., JCO 1990)
What Tx were compared in INT-0091 (IESS-3) (1988–92)? Summarize the study's major results (OS and LR).

Show Answer

INT-0091 randomized pts to induction **VACAdr vs. VACAdr alternating with IE.** The study enrolled 518 pts with EWS, PNET of bone and primitive sarcoma of bone, and pts with both localized and **metastatic Dz (23%).** In pts with **nonmetastatic Dz,** the addition of IE significantly improved **5-yr OS (72% vs. 61%),** 5-yr EFS (69% vs. 54%), 5-yr LR (5% vs. 15%). There was no 5-yr OS advantage with adding IE for pts with metastatic Dz at presentation. (Grier HE et al., NEJM 2003)
When was local therapy given in INT-0091?

Show Answer

In **INT-0091,** local therapy (Sg +/– PORT or RT alone) was given at **wk 12.**
How was RT given in INT-0091 compared to IESS-1–2?

Show Answer

INT-0091: definitive RT was given with IE to **GTV + 3-cm margin** to 45 Gy → conedown (CD) to postchemo volume to 55.8 Gy. For PORT: if R0, then no PORT; if R1, then 45 Gy (initial GTV + 1 cm); if R2, then 55.8 Gy.

IESS-1–2: definitive RT to **whole bone** to 45–50 Gy → CD to 55–60 Gy
In INT-0091, what prognostic factors were associated with worse outcomes?

Show Answer

Pts with **pelvic tumors, large tumors (≥8 cm),** or of **older age (≥18 yrs).**
In INT-0091, for pts with pelvic primaries, did LR differ b/t Sg alone, Sg + PORT, and definitive RT?

Show Answer

LR did not differ by local therapy for pts with pelvic primaries (~15%). (Yock TI et al., JCO 2006)

What RT Tx techniques were compared in POG-8346 (1983–88)? Summarize the study's major results.

Show Answer

In **POG-8346,** osseous EWS pts who rcvd definitive RT for local therapy after induction chemo were randomized to **whole bone RT (39.6 Gy → 55.8 Gy boost to GTV +2 cm) vs. involved-field RT (GTV + 2 cm to 55.8 Gy).** All pts then rcvd maintenance chemo. The RT Tx techniques had similar 5-yr EFS (~41%) and LC (~53%). (Donaldson SS et al., IJROBP 1998)

What are 2 Tx options in EWS pts with lung mets?

Show Answer

In addition to chemo, **consider WLI or surgical resection (if <5 mets).**

What 2 key retrospective studies support the use of WLI in pts with metastatic EWS?

Show Answer

EICESS secondary analyses: Paulussen et al. reviewed the outcomes of EWS pts with (a) isolated pulmonary mets or (b) combined lung + bone/BM mets who were treated +/– WLI as part of a series of protocols from the EICESS. WLI was associated with improved EFS in both subgroups. (Ann Oncol 1998)

St. Jude's retrospective study: Rodriguez-Galindo et al. reviewed outcomes in EWS pts with isolated pulmonary recurrence. Pts who rcvd WLI had improved 5-yr postrecurrence survival (30% vs. 17%). (Cancer 2002)

What doses and technique are used for WLI in EWS?

Show Answer

The WLI dose in EWS depends on age: if <14 yo, then **15 Gy (1.5 Gy/fx); if ≥14 yo, then 18 Gy (mostly in European protocols, but US protocols still use 15 Gy).**
Describe the field borders used in WLI for EWS.

Show Answer

Superior–Inferior: 1 cm above 1st rib to L2
Lateral: 1 cm lat rib cage

Block PA kidney at 7.5 Gy.
Is there a difference in prognosis for metastatic EWS pts who present with isolated lung mets, bone-only mets, or both?

Show Answer

Yes. Metastatic EWS pts who present with either isolated pulmonary mets or skeletal mets have a similar EFS. However, EFS is significantly worse in pts with both.

5-yr OS for metastatic EWS:

- Lung mets: ~35%
- Bone/BM mets: ~25%
- Lung 1 bone/BM mets: ~15%

(Paulussen M et al., Ann Oncol 2009)
What evidence supports the use of hemithorax RT in CW EWS?

Show Answer

Schuck A et al. retrospectively reviewed 138 pts with localized CW EWS treated in **CESS-86** and **EICESS 92.** 42 pts rcv hemithorax RT. If <14 yo, then 15 Gy; otherwise, 20 Gy at 1.5 Gy/fx or 1.25 Gy bid. All RT pts rcv a boost to the primary site of 45–60 Gy. Despite worse baseline prognostic factors in the hemithorax RT cohort, 7-yr EFS trended in its favor (63% vs. 46%). Improvements in EFS appeared to be d/t reductions in pulmonary

mets. A major criticism of this study is that the RT group had sup chemo. (IJROBP 2002)

Does hyperfx improve outcomes in EWS?

Show Answer

No. CESS-86 randomized localized osseous EWS pts being treated with definitive RT to conventional fractionation (60 Gy in 1.8–2.0 Gy/fx) during a chemo break or split-course hyperfractionated RT concurrently with chemo. Hyperfractionated RT was 1.6 Gy bid to 60 Gy with a 12-day break after the initial 22.4 Gy and 44.8 Gy. LC was somewhat higher in the hyperfx arm (86% vs. 76%), but the difference was not SS. Benefits of this altered fractionation may have been lost d/t the Tx breaks. (Dunst J et al., IJROBP 1995)

In EWS, how are the Tx volumes defined, and what are the margins used for the following scenarios?

- **Bone-only lesion**
- **Bone lesion with soft tissue extension**
- **Postop setting**

Show Answer

In EWS, **RT volumes depend on the chemo response.**

- **Bone only:** treat prechemo GTV + 2 cm to block margin (1-cm CTV, 0.5-cm PTV) to 55.8 Gy.
- **Bone with ST extension:** treat prechemo GTV + 2 cm to 45 Gy, then CD to initial/prechemo bone and postchemo ST extent + 2 cm to 55.8 Gy.
- **Postop setting:** treat preop, prechemo volume (except pushing borders in areas of lung or intestines) + 2 cm to 45 Gy, then CD to postop residual + 2 cm to 55.8 Gy.

In EWS pts with resected node+ Dz, what RT dose is used to treat the nodal bed?

Show Answer

In EWS pts with resected node+ Dz, treat the nodal bed to **50.4 Gy.**
Based on the SFOP (France) metastatic EWS protocol, what was the 5-yr EFS with the addition of high-dose busulfan and melphalan as consolidation?

Show Answer

High-dose oral busulfan and melphalan were used → stem cell rescue as consolidation after 5 cycles Cytoxan/Adr and 2 cycles IE → local therapy (Sg and/or RT). 5-yr EFS was 52% for lung-only mets and 36% for bone-only mets (no BM involvement). With BM involvement, survival was **4%.** (Oberlin O et al., JCO 2006)
Based on the SFOP (France) metastatic EWS protocol, how was local therapy delivered?

Show Answer

Local therapy was delivered either before or after consolidative high-dose chemo. RT was given alone or after incomplete resection (55–60 Gy).
RT after R0 resection was given if >5% viable cells were seen (40 Gy). If <5% viable cells were seen, no RT was given. (Oberlin O et al., JCO 2006)

FOLLOW-UP/TOXICITY

What is the 20-yr cumulative risk of 2nd malignancies in pts treated for EWS?

Show Answer

Kuttesch et al. retrospectively reviewed 266 EWS pts treated at St. Jude's Hospital. 20-yr cumulative incidence was **9.2% for any malignancy** and 6.5% for sarcoma. There appeared to be an **RT dose–response relationship** with a 2nd malignancy **RR of 40 if RT was >60 Gy.** (JCO 1996)
What GU side effect is of particular concern when treating pelvic EWS

tumors?

Show Answer

Since EWS pts are typically treated with ifosfamide and cyclophosphamide, **RT cystitis** is of particular concern.

What dose causes premature epiphyseal closure?

Show Answer

>20 Gy causes premature epiphyseal closure. Decreased bone growth can occur at ~10 Gy.

How can lymphedema be minimized in the extremities when treating with RT?

Show Answer

Attempt to spare a 1–2-cm strip of skin on the extremity or minimize the circumferential RT dose to 20–30 Gy.

What are some factors that influence fracture risk?

Show Answer

Total dose, extent of cortical disruption at Dx, younger age, and 2nd bone malignancy in the RT field.

3

Wilms Tumor

Updated by Jennifer Logan

BACKGROUND

What is the estimated annual incidence of Wilms tumor (WT) in the United States?

Show Answer

~500 cases/yr of WT are diagnosed in the United States.
What is the median age at Dx?

Show Answer

Median age at Dx is **3–4 yrs** (95% <10 yrs) for WT.
Is there a sex predilection?

Show Answer

Yes. Females are more commonly affected than males.
How does the age of presentation differ with Wilms when compared to neuroblastoma (NB)?

Show Answer

NB often presents at **<2 yrs. Unilat WT** presents at **3.5–4 yrs.**
What is the age of presentation for hereditary/bilat tumors?

Show Answer

Hereditary/bilat tumors often present at **2.5 yrs** (younger than sporadic

cases).
Name 3 genetic syndromes associated with Wilms.

Show Answer

. WAGR
. Denys–Drash
. Beckwith–Wiedemann

What is WAGR syndrome, and what is the associated genetic change?

Show Answer

Mnemonic: WAGR:

Wilms
Aniridia
GU anomalies
Mental **R**etardation
Associated genetic change: **del 11q13** (WT1 deletion)
What is Denys–Drash syndrome, and what is the associated genetic change?

Show Answer

Denys–Drash: Wilms, renal Dz (proteinuria during infancy, nephritic syndrome, progressive renal failure), male pseudohermaphroditism
Associated genetic change: point mutation of WT1 gene
What is Beckwith–Wiedemann syndrome, and what is the associated genetic change?

Show Answer

Beckwith–Wiedemann: macrosomia, macroglossia, omphalocele, hemihypertrophy
Associated genetic change: **11p15.5,** duplication of WT2 locus
What transcription factor is important for normal kidney/gonadal

development and is associated with Wilms?

Show Answer

WT1 (a zinc finger protein) is associated with Wilms and is important for normal kidney/gonadal development.
What is the function of WT2?

Show Answer

Function of WT2 is **unknown.** It affects IGF2, the H19 tumor suppressor, and p57 cell cycle protein.
What are the other genetic defects seen in Wilms?

Show Answer

LOH 1p16q, FWT1 (17q), and FWT2 (19q)
Name 1 paternal and 1 maternal environmental risk factor for WT.

Show Answer

Fathers who are welders/machinists (RR 5.3); mothers who use hair dyes (RR 3.6)
What are some poor prognostic factors seen in Wilms?

Show Answer

Unfavorable histology (UH), advanced **tumor stage, molecular** (+telomerase) and **genetic** (LOH 1p16q) markers, **age >24 mos**
What histology has the worst outcome in Wilms?

Show Answer

Diffuse anaplasia (DA), f/b rhabdoid and clear cell sarcoma. A review of NWTS-1 and -2 studies involving ~1,200 children, DA had the shortest survival time compared to nonanaplastic histologies. (Bonadio F et al., JCO 1985) In another study, DA was seen in 10% of cases, but accounted for 60% of the deaths. (Faria P et al., Am J Surg Pathol 1996)

What study demonstrated the prognostic importance of LOH 1p16q for Wilms?

Show Answer

NWTS-5 analysis. (Grundy PE et al., JCO 2005) For FH, LOH 1p or 16q is associated with ↑ (RR) of relapse. LOH of both ↑ RR of relapse + death.
What are the UH subtypes in Wilms?

Show Answer

Anaplastic: focal or diffuse
How is focal anaplasia (FA) defined?

Show Answer

FA is sharply localized within the primary tumor, without atypia in the rest of the tumor.
What renal tumors are not WT but are treated similarly to WTs?

Show Answer

Malignant rhabdoid tumor and clear cell sarcoma of the kidney
What are the 4 sets of criteria used to define DA?

Show Answer

Criteria to define DA:

. Nonlocalized
. Localized with severe nuclear unrest elsewhere in the tumor
. Anaplasia outside the tumor capsule or mets
. Anaplasia revealed by random Bx

What is the stage-by-stage 4-yr OS for anaplastic/UH WT?

Show Answer

4-yr OS for anaplastic/UH Wilms:

Stage I: 83%
Stage II: 81%
Stage III: 65%
Stage IV: 38% (immediate nephrectomy) vs. 56% (preop chemo)
Stage V: 55%

(Dome JS et al., JCO 2006)
How does the 4-yr OS compare b/t focal and diffuse anaplasia?

Show Answer

Overall: 82% vs. 60%
Stage I: 89% vs. 79%
Stage II: 80% vs. 82%
Stage III: 71% (FA: preop chemo) vs. 67% (DA: nephrectomy) vs. 53% (DA: preop chemo)
Stage IV: 72% (FA: preop chemo) vs. 33% (DA: nephrectomy) vs. 44% (DA: preop chemo)
Stage V: 88% vs. 42%
What are the typical presenting Sx in Wilms? How does this compare to NB?

Show Answer

Asymptomatic abdominal mass (83%) → abdominal pain (37%), HTN (25%, d/t ↑ renin), hematuria (25%), fever, anemia (d/t ↓ Epo)

NB most commonly presents with systemic Sx.
(Mnemonic: **WWNN**—**W**ilms are **W**ell**, N**euroblastomas are **N**ot well)

WORKUP/STAGING

What is the typical workup for an abdominal mass of unclear etiology in a child?

Show Answer

Abdominal mass workup: H&P (focusing on congenital defects), labs, UA (including urinary catecholamines), abdominal US, CXR, and CT C/A/P
What is the recommended 1st-line imaging modality for an abdominal mass?

Show Answer

US is the recommended 1st-line study for imaging the abdomen.
Pts with what histologic subtype(s) require bone scan?

Show Answer

Clear cell
With a Dx of Wilms, what 2 chest imaging modalities can be employed for staging purposes?

Show Answer

Both **CXR and CT** are used for chest imaging. Lesions seen on CT but not visible on CXR may be treated more conservatively than lung mets visible on CXR.
Pediatric pts with what renal tumors need BM Bx?

Show Answer

Pts with **clear cell and rhabdoid** require BM Bx.
Pediatric pts with what renal tumors require MRI of the head as part of their workup?

Show Answer

Rhabdoid: 10%–15% will have PNET in brain (atypical teratoid rhabdoid tumors)
Clear cell: to r/o brain mets
What is the typical appearance of WT on CT?

Show Answer

Large round mass with pseudocapsule usually without calcifications. Less likely to cross midline than NBs.
Under what circumstances should Bx be performed?

Show Answer

Do not Bx unless the tumor is **unresectable** or **bilat** Dz. If Bx is necessary, use a **post approach** to avoid contaminating the abdomen.
On what issues should the surgeon comment at the time of Sg?

Show Answer

Involvement of regional nodes, opposite kidney, peritoneum, liver, renal vein/IVC. Also, if there is tumor spillage and if it is confined to the ipsi flank.
What % of pts present with each of the features summarized in this table?

Show Answer

Presenting Features	**Patients (%)**
Bilat Dz	7
Multifocal Dz	12
Renal vein invasion	10
LN involvement	20
Mets	10

What are some common sites of mets?

Show Answer

Lung (80%) → liver → bone, brain (clear cell), LN (outside abdomen and pelvis)
How commonly is calcification seen in Wilms?

Show Answer

Calcification is seen in 10%–15% of cases but is seen in 85% of NB cases.
How many stages are there in Wilms?

Show Answer

There are **5 stages** in Wilms.
Summarize the staging of WT.

Show Answer

I. **(40% of pts):** limited to kidney
II. **(20%):** extension to outside capsule, vessel involvement >2 mm
II. **(20%):** R1–R2 resection, +LN, local spillage or diffuse peritoneal spillage, Bx (including FNA), +implants, +margin, transected tumor thrombus, piecemeal resection, unresectable tumor
V. **(10%):** hematogenous mets or LN+ outside the abdomen/pelvis
V. **(4%–8%):** bilat Dz; each side staged independently

Is adrenal involvement considered a met?

Show Answer

No. Adrenal involvement is considered local extension.

TREATMENT/PROGNOSIS

What is the Tx paradigm for WT in the United States?

Show Answer

WT Tx paradigm: initial surgical resection → risk-adapted adj chemo +/– RT
What is the major difference b/t the International Society of Pediatric Oncology (SIOP) Tx paradigm (European Cooperative Group) and the National Wilms Tumor Study (NWTS) paradigm (American Cooperative Group)?

Show Answer

SIOP trials incorporate **preop therapy** (CRT), whereas the NWTS/COG

trials do not.
Under what circumstance is the SIOP paradigm favored in the United States?

Show Answer

In **unresectable or bilat Wilms,** preop chemo is used.
What are the indications for postop RT in the current COG protocols (AREN0532,533)? (Table 3-1)

Show Answer

Indications for postop RT depend on **histology and stage:**

Favorable histology: stages III–IV
Unfavorable histology: stages I–IV

Table 3-1 Current Children's Oncology Group Wilms Protocol (AREN0532/533)

Goals: Reduce Tx-related toxicity in low-risk tumors and improve outcome for high-risk tumors with chemo intensification.

Tumor Risk Classification	Multimodality Treatment
Very low risk FH WT >2 yrs, stage I FH, <550 g	Surgery, no therapy if central pathology review and LN sampling
Low-risk FH WT ≥2 yrs, stage I FH, ≥550 g	Surgery, no RT, regimen EE4A
Standard-risk FH WT	Surgery, regimen DD4A
Stages I–II FH with LOH	Surgery, regimen DD4A
Stage III FH without LOH	Surgery, RT, regimen DD4A
Stages III–IV FH with LOH (AREN0533)	Surgery, RT, regimen M, WLI
Stage IV FH (slow/incomplete	

responders)	
Stage IV FH: CR of lung mets at wk 6/DD4A (rapid early responders)	Surgery, RT, regimen DD4A; no WLI
Stages I–III FA	Surgery, RT, regimen DD4A
Stage I DA	
Stage IV FA	Surgery, RT, regimen UH1
Stages II–IV DA	
Stage IV CCSK	
Stage IV RTK	
Stages I–III CCSK	Surgery, RT, regimen 1

FH, favorable histology; WT, Wilms tumor; LN, lymph node; RT, radiation therapy; LOH, loss of heterozygosity; WLI, whole lung irradiation; CR, complete response; FA, focal anaplasia; DA, diffuse anaplasia; CCSK, clear cell sarcoma of the kidney; RTK, rhabdoid tumor of the kidney.

Table 3-2 Chemotherapy Regimens on AREN0532/533 Protocols

Regimen	Agents
EE4A	VCR/AMD
DD4A	VCR/AMD/ADR
M	VCR/AMD/ADR; CY/ETOP
I	VCR/DOX/CY; CY/ETOP
UH1	CY/CARBO/ETOP; VCR/DOX/CY

VCR, vincristine; AMD, dactinomycin; ADR, Adriamycin; CY, Cytoxan; ETOP, etoposide; DOX, doxorubicin; CARBO, carboplatin.

What chemotherapeutic agents are typically used in Wilms? (Table 3-2)

Show Answer

Vincristine, actinomycin D (Adr/VP-16/Cytoxan/carboplatin added in UH)
What did the early NWTS-1 and NWTS-2 studies show?

Show Answer

. Vincristine and actinomycin D (VA) are better together than either alone.

- RT is not needed for stage I FH pts if they rcv chemo, but when RT given, it should preferably start within 9 days of Sg (but no later than postop day 14).
- There was no RT dose response from 10–40 Gy.

Which study demonstrated that whole abdomen irradiation (WAI) is not needed for local spillage?

Show Answer

NWTS-1; flank fields suffice if spillage is local.
Which study demonstrated that adding Adr to VA benefited group 2–4 pts?

Show Answer

NWTS-2; adding Adr benefited group 2–4 FH, especially group 2–4 UH pts (OS 38% vs. 78%).
Which study demonstrated that 10 wks was equal to 6 mos of chemo for stage I pts?

Show Answer

NWTS-3; 4-yr OS was 96%–97%.
Which study showed that stage II FH pts do not need RT as long as VA is given?

Show Answer

NWTS-3 (4-arm: vincristine/Actinomycin D/Adr [VAAdr] vs. VA vs. +/– RT → 4-yr OS ~90%–95%, no difference)
Which study eliminated Adr from stage II FH?

Show Answer

NWTS-3. VA alone was sufficient.
Which study demonstrated that 10 Gy was equal to 20 Gy if Adr was

added to stage III pts?

Show Answer

NWTS-3 demonstrated the noninferiority of lower RT doses with Adr.
Which study addressed the addition of Cytoxan to VAAdr for high-risk pts?

Show Answer

NWTS-3. Cytoxan improved outcome in UH stage II–IV but not FH stage IV.
Which study addressed pulse-intense (PI) chemo?

Show Answer

NWTS-4. 6 mos of PI was equal to 15 mos of conventional chemo.
What are the main advantages of PI chemo?

Show Answer

With PI chemo, there is ↓ **hematologic toxicity** and ↓ **total cost** b/c fewer drugs are used.
Which study found that local spillage (old stage II) without RT results in a ↑ LR?

Show Answer

NWTS-4; ↑ LR, but no difference in OS; so, moved to stage III for FH (need adj RT)
What question does NWTS-5 address? (Dome JS et al., JCO 2006)

Show Answer

Nonrandomized, assesses prognostic importance of LOH 1p16q
For which pts did NWTS-5 show ↑ (13.5%) rates of relapse with nephrectomy alone and without adj chemo?

Show Answer

Stage I FH, pts <2 yo, and tumors <550 g. Most (>70%) were salvaged successfully, however.
What chemo regimen in NWTS-5 improved outcomes for stages II–IV with DA?

Show Answer

Vincristine/Adr/cyclophosphamide/etoposide
Did stage I anaplastic tumors qualify for RT in NWTS-5?

Show Answer

No. Anaplastic tumors did not qualify for RT in **NWTS-5.**
What do the current protocols (COG AREN0532, 0533) address?

Show Answer

Tx intensification based on LOH 1p16q status; stage I anaplastic pts get RT + Adr (with VA).
What were the factors that determine risk groups in the COG AREN0532/0533?

Show Answer

Age (>2 yo worse), tumor weight (550 g), stage, LOH 1p16q, and chemo response
What subset of pts on the current COG protocol could get Sg alone without adj Tx?

Show Answer

Very low risk group **(stage I FH, pts <2 yo, and tumors <550 g)** and if there is central pathology review and LN sampling
What are the RT doses to the postop bed for Wilms pts ≥16 yo and/or those with rhabdoid and/or DA? How about for other pts? (Table 3-3)

Show Answer

19.8 Gy to flank for stage III DA or rhabdoid stages I–III (+10.8 Gy boost to mets/gross Dz = 30.6 Gy), **10.8 Gy** for the rest (stage III FH, stages I–III FA, stages I–II DA, stages I–III clear cell, age <16 yrs, infants with DA or rhabdoid histology)

Table 3-3 Radiation Planning and Doses on Protocols AREN0532/533

RT timing: Concurrent with VCR, surgery day 1, RT ≤ day 10 (max day 14).
Exception: Medical contraindication or delay in central pathology review.
RT field design:

I. Flank RT: GTV = preop CT/MRI (tumor and involved kidney).

CTV + PTV = ≤1 cm

Medial border across midline to include vertebral bodies + 1-cm margin but sparing contralat kidney. Other field borders placed at edge of PTV. Use AP/PA.

If + PA and surgically removed, then treat entire PA chain to 10.8 Gy.

If + residual Dz, then boost with 10.8 Gy after initial 10.8 Gy (3D-CRT, GTV = postop volume).

Dose limits: Two-thirds contralat kidney to 14.4 Gy, one-half of undiseased liver to 19.8 Gy.

II. WAI: CTV = entire peritoneal cavity from diaphragm to pelvic diaphragm.

Superior border: 1 cm above dome of diaphragm.

Inferior border: Bottom of obturator foramen.

Laterally: 1 cm beyond lat abdominal wall; block femoral heads.

Dose 10.5 Gy (1.5 Gy/fx) except for diffuse anaplasia or rhabdoid tumors (dose is 19.8 Gy, shield kidney to keep <14.4 Gy).

III. WLI: CTV includes lungs, mediastinum, and pleural recesses. PTV =

CTV + 1 cm.

Inf border at L1, sup border 1 cm above 1st rib, block humeral heads. Can boost after 12 Gy (1.5 Gy/fx) (10.5 Gy for <12 mos) for persistent Dz after 2 wks → +7.5 Gy (19.5 Gy) to residual with conformal fields.

IV. **Liver mets:** Surgery for solitary mets, excised to –margins. Whole liver RT for diffuse liver mets to 19.8 Gy (with additional 5.4–10.8 Gy at discretion).

V. **Brain:** WBRT to 21.6 Gy (30.6 Gy if >16 yo). If 21.6 Gy → conformal RT boost with additional 10.8 Gy.

VI. **Bone:** GTV + 3-cm margin, AP/PA to 25.2 Gy (30.6 Gy if >16 yo).

VII. **Unresected nodes:** Cover entire LN chain to 19.8 Gy (30.6 Gy if >16 yo), with optional 5.4–10.8 Gy boost. If removed +PA LN, use 10.8 Gy to cover.

RT, radiation therapy; VCR, vincristine; max, maximum; GTV, gross target volume; preop, preoperative; CT/MRI, computed tomography/magnetic resonance imaging; CTV, clinical target volume; PTV, planning target volume; cm, centimeter; contralat, contralateral; AP/PA, anterior-posterior/posterior-anterior; +, positive; Gy, gray; Dz, disease; 3D-CRT, three-dimensional conformal radiation therapy; postop, postoperative; WAI, whole abdomen irradiation; lat, lateral; fx, fractions; WLI, whole lung irradiation; inf, inferior; sup, superior; mos, months; wks, weeks; mets, metastasis; –, negative; WBRT, whole brain radiation therapy; yo, years old; LN, lymph node.

What are the indications and the RT doses for WAI?

Show Answer

Seeding/rupture/diffuse spill; **10.5 Gy (1.5 Gy/fx),** boost to 21 if bulky (but 19.8 Gy for DA or rhabdoid)

What are the indications for flank RT?

Show Answer

Stage III FH, localized spill, stages I–III UH, and recurrent Wilms (also done for certain stage IV pts)

What is the standard flank RT dose?

Show Answer

The standard flank RT dose is **10.8 Gy in 6 fx.**
What is the dose to unresected +LNs?

Show Answer

19.8 Gy to entire chain → boost with optional 5.4–10.8 Gy; 30.6 Gy if >16 yo
What is the preferred Tx for localized liver mets? Diffuse liver mets?

Show Answer

Sg is preferred for localized liver mets. For diffuse liver mets, **19.8 Gy** to the entire liver (with optional boost of 5.4–10.8 Gy) is an option.
What dose is given to resected +LNs?

Show Answer

Resected +LNs get a dose of **10.8 Gy.**
At what age can pts rcv greater flank doses and greater doses to mets?

Show Answer

≥16 yo (19.8 Gy to flank or WAI and 30.6 Gy to mets in bone, LNs, and brain)
When is whole lung irradiation (WLI) not required in a Wilms pt with lung mets?

Show Answer

WLI is not required in these pts **if mets are seen only on CT and not on CXR** or **if a CR is seen after VAAdr at wk 6.**
When is WLI indicated? What are the doses?

Show Answer

WLI is indicated when there is no CR seen on CT at wk 6 after 3-drug chemo (per current protocol); it is not based on # of mets, size, or detectability on CT or CXR. The dose for WLI is **12 Gy (>1 yo)** or 1**0.5 Gy (<1 yo)** in **1.5 Gy/fx.** If there is persistent Dz after WLI, consider a **7.5 Gy boost.**
What med should pts take when treated with WLI?

Show Answer

Trimethoprim/sulfamethoxazole (Bactrim) for PCP prophylaxis
How is bilat Wilms treated?

Show Answer

Initial Sg or Bx to **stage each side → chemo → 2nd-look Sg at 6 wks** for a max safe resection (spare two-thirds of 1 kidney if possible) → continuation of chemo. **RT is given after Sg based on the final local stage.**
RT should preferably start by which day and should begin no later than which day after Sg?

Show Answer

RT should preferably start by **day 9** and should begin no later than **day 14.** Secondary analyses of **NWTS-1** and **NWTS-2** showed worse outcomes when RT was delayed >10 days.
How long is the chemo regimen for stages I–II and III–IV FH?

Show Answer

18 wks (VA); **24 wks** (VAAdr)
What is the medial border of a flank field?

Show Answer

1 cm from the contralat vertebral body edge. Be aware of the intact kidney location.
What are the preferred RT margins/techniques for a flank field?

Show Answer

Preop GTV + 1 cm; AP/PA for flank; conformal for boost (residual + 2 cm)
What is the dose for brain mets?

Show Answer

The dose for brain mets is WBRT to 21.6 Gy if <16 yo (+ 10.8 Gy boost = 32.4 Gy) or 30.6 Gy (–boost) if >16 yo.
What is the dose for bone mets?

Show Answer

The dose for bone mets is **25.2 Gy** (30.6 Gy if > 16 yo).
How do you manage a pt who presents with mets and a resectable tumor?

Show Answer

These pts are treated the same way as nonmetastatic pts, except mets are treated at the same time as abdominal RT, if needed.
What is the outcome for relapsed Wilms treated with VA only for stage I or II Dz?

Show Answer

4-yr EFS/OS: 71% (stage I) vs. 82% (stage II). Pt salvaged with Sg, RT, and chemo with vincristine/Adr/Cytoxan/etoposide. Lung mets only, 4-yr EFS/OS: 68% (stage I) vs. 81% (stage II).
What about relapsed stages III–IV Dz?

Show Answer

Relapse after stages III–IV Tx is worse (4-yr EFS/OS: 42% vs. 48%, respectively), lung only mets: 4-yr EFS/OS: 49% vs. 53%, respectively. (Green DM et al., Ped Blood Cancer 2007; Malogolowkin M et al., Ped Blood Cancer 2008)

FOLLOW-UP/TOXICITY

What is the dose constraint for the kidney?

Show Answer

One-third of contralat kidney <14.4 Gy
What is the dose constraint for the liver?

Show Answer

One-half of uninvolved liver <19.8 Gy; with liver mets, 75% of liver ≤30.6 Gy
Pts are at risk for what late effects with flank RT? WLI?

Show Answer

Scoliosis of the spine, muscular hypoplasia, kyphosis, iliac wing hypoplasia, SBO, veno-occlusive Dz of the liver.
Breast hypoplasia (four-fifths of females who get WLI will have underdeveloped breasts), pneumonitis, CHF, 2nd malignancy, and renal failure
What is the risk of SBO at 15 yrs after flank/abdominal RT?

Show Answer

15%.
What is the risk of a 2nd malignancy at 15 yrs?

Show Answer

1.6%–2%.
The reirradiation tolerance of which organ decreases with time after initial RT?

Show Answer

Reirradiation tolerance of the **kidney** decreases with time.
What is the TD 5/5 for an entire kidney?

Show Answer

The TD 5/5 is **23 Gy.**
What is the cumulative max total dose (including prior RT) for WT pts?

Show Answer

30.6 Gy (if <3 yrs) or 39.5 Gy (if >3 yrs)

4

Neuroblastoma

Updated by Tommy Sheu

BACKGROUND

What are the 4 most common malignancies of childhood?

Show Answer

4 most common malignancies of childhood:

. Leukemia
. Brain tumors
. Lymphoma
. NB

What is the most common malignancy in infants?

Show Answer

NB is the most common malignancy in infants.
Estimate the annual incidence of NB in the United States.

Show Answer

There are **~650 cases/yr** of NB in the United States.
What is the median age at Dx for NB?

Show Answer

The median age at Dx is **17 mos,** with a range b/t birth and 15 yrs.
Name 5 syndromes associated with NB.

Show Answer

. NF1
. Hirschsprung Dz
. Fetal hydantoin syndrome
. Turner syndrome
. Central hypoventilation syndrome

What tests have been used to screen infants for NB?

Show Answer

Historically, infants were screened for NB using **urinary catecholamines (vanillylmandelic acid/homovanillic acid).**
What % of NB pts have detectable urinary catecholamines?

Show Answer

90%
Does screening improve survival in NB?

Show Answer

This is **controversial.** The value of catecholamine-based screening is limited by its FPR and b/c a high % of infant NBs spontaneously regress. The Quebec project increased the detection rate of NBs but failed to have an impact on mortality in the screened populations.
What are the 3 types of neuroblastic tumors?

Show Answer

These tumors differ in the degree of cellular maturation.

. NB (Schwannian stroma-poor)
. Ganglioneuroblastoma (Schwannian stroma-rich)
. Ganglioneuroma (Schwannian stroma-dominant)

What markers distinguish NB from other small round blue tumors?

Show Answer

NB-specific markers:

- NSE
- Synaptophysin
- Neurofilament

What is the cell of origin for NB?

Show Answer

Neural crest cells of the sympathetic ganglion
What are the classic histologic findings seen in NB?

Show Answer

Homer Wright pseudorosettes, hemorrhage, and calcification
What genetic changes are associated with N-myc amplification?

Show Answer

Double-minute chromatin bodies and homogeneously staining regions are associated with N-myc amplification.
What are the genetic/chromatin changes that portend a poor prognosis in NB?

Show Answer

Genetic/chromatin changes with a poor prognosis in NB:

- **N-myc amplification**
- LOH 1p or 11q
- Trisomy 17q
- diploid DNA
- ↑ telomerase activity

What germline mutations have been associated with a genetic predisposition to NB?

Show Answer

ALK gene mutation, PHOX2B gene mutation, and germline deletion of 1p36 or 11q14–23.

In which pts does DNA content not have prognostic importance?

Show Answer

DNA content does not have prognostic importance in **metastatic pts.**

What % of NB pts present with N-myc amplification?

Show Answer

30%–40% of pts present with N-myc amplification. An N-myc amplification is associated with poor prognosis.

What % of NB pts present with 1p deletions?

Show Answer

20%–40% of pts present with 1p deletions.

What is the genetic variation on 6p22 that is associated with clinically aggressive NB?

Show Answer

Homozygosity for 3 single nucleotide polymorphisms on 6p22 is associated with stage IV Dz, N-myc amplification, and Dz relapse. (Maris JM et al., NEJM 2008)

What are some presenting Sx of NB?

Show Answer

Along with the presentation of a mass, NB may be associated with **constitutional Sx** (fever, malaise, pain, and weight loss), periorbital ecchymosis **("raccoon eyes"), "blueberry muffin" sign** (nontender blue skin mets), scalp nodules, bone pain, irritable/ill appearance, diarrhea (↑ vasoactive intestinal peptide), Horner syndrome, opsomyoclonus truncal

ataxia (rare paraneoplastic syndrome of ataxia, random eye movement, and myoclonic jerking associated with early stage but persists after cure), and Kerner–Morrison syndrome (diarrhea, low K).
What are the most common sites of presentation for NB?

Show Answer

Adrenal medulla > paraspinal > post mediastinum
In what age group is thoracic presentation of NB more common?

Show Answer

Thoracic NB is more common in **infants.**
What % of NB pts present with mets overall? How does this differ by age?

Show Answer

75% of all NB pts present with mets overall. 60% of pts <1 yr present with localized Dz, while 70% of pts >1 yr present with mets.
What are the most common sites of mets for NB?

Show Answer

NB metastasizes to **bone (~50%, commonly of the skull/orbit), LNs (35%),** BM, liver, skin, and orbits. **Lung mets are rare.**
What features distinguish NB from Wilms tumor?

Show Answer

	Wilms Tumor	Neuroblastoma
Clinical Presentation:	Median age 3.5 yrs	Median age 1 yr
	Healthy appearing	Sick appearing
	Mets to lung	Rarely mets to lung
	More common in African	More common in White

	American children	children
Imaging Features:	Arises from kidney	Displaces kidney
	Does not cross midline	Crosses midline
	5%–10% with calcifications	85% with calcifications

WORKUP/STAGING

Outline the workup for pts with suspected NB.

Show Answer

Suspected NB workup:

- H&P
- Labs: CBC, BUN/Cr, LFTs, serum markers, UA, urine catecholamines
- Imaging of primary: CT C/A/P, abdominal US, or MRI abdomen/liver/spine
- Workup of mets: bone scan, I-131 metaiodobenzylguanidine [MIBG] scan, bilat BM Bx, CT/MRI as needed
- Pathology: DNA content, N-myc amplification, and cytogenetics

Why is a BM Bx important in the workup of NB?

Show Answer

BM Bx may obviate the need for primary site Sg if the testing is positive and the clinical picture is clear.

What % of NB pts have uptake on an I-131 MIBG scan?

Show Answer

~90% of NB pts have uptake on an I-131 MIBG scan.

What are the currently used NB staging systems?

Show Answer

As of 2010, most cooperative group trials use the **International Neuroblastoma Staging System (INSS),** which involves the extent of surgical resection. However, a new staging system that uses only pre-Tx factors has been developed: the **International Neuroblastoma Risk Group (INRG).** These 2 staging systems will likely be used concurrently to allow for comparisons b/t trials. (Monclair T et al., JCO 2009)
Summarize the INSS staging system.

Show Answer

Stage 1: unilat localized tumor s/p GTR +/– microscopic residual Dz; ipsi LN–, though LNs attached and removed with the primary may be involved
Stage 2A: unilat localized tumor s/p STR only; ipsi LN–, though LNs attached and removed with the primary may be involved
Stage 2B: unilat localized tumor s/p GTR or STR with involved nonadherent ipsi LNs; enlarged contralat LN– microscopically
Stage 3: unresectable localized tumor extending across the midline +/– regional LN involvement; unilat localized tumor with contralat regional LN involvement; midline tumor with bilat involvement via LN or direct extension
Stage 4: distant Dz except as defined by stage 4S
Stage 4S: localized unilat primary as defined by stage 1, 2A, or 2B; distant Dz limited to the liver, skin, and/or <10% of BM in infants <1 yo
What are the prognostic factors in NB per INRG?

Show Answer

Age, stage, histologic category, grade, N-myc amplification, 11p or 11q aberration, DNA ploidy
Summarize the INRG staging system.

Show Answer

In the **INRG system,** locoregional tumors are staged **L1** or **L2** based on the

absence or presence of 1 or more of 20 image-defined radiographic findings (IDRFs). These IDRFs generally affect whether or not a tumor is surgically resectable and to what degree, although resectability is ultimately surgeon-dependent. **Metastatic tumors** are defined as stage **M,** except for stage **Ms,** in which mets are confined to the skin, liver, and/or BM in pts <18 mos old. (Monclair T et al., JCO 2009)
What is the INRG stage of an 8-mo-old pt with metastatic Dz to bone only?

Show Answer

An 8-mo-old pt with metastatic Dz to bone only is INRG **stage M** (only BM, liver, and skin mets qualify for stage MS).
What is the INSS stage of a 14-mo-old pt with metastatic Dz to BM only?

Show Answer

A 14-mo-old pt with metastatic Dz to BM only is INSS **stage 4** (only pts <12 mos old qualify for stage 4S).
What 2 clinical factors are most predictive of cure in NB?

Show Answer

The 2 clinical factors most predictive of cure are **age** and **stage at Dx.**
In children with metastatic Dz, what is the most important prognostic factor?

Show Answer

In children with metastatic Dz, **age (<1 yo best)** is the strongest prognostic factor, even more so than N-myc.
The Shimada classification system divides NB into what 2 categories?
What 5 features are used to classify pts in this system?

Show Answer

The Shimada classification system divides NB into **favorable histology** (FH)

and **unfavorable histology** (UH). Favorable factors:

Stroma-rich
Age
Differentiation
Mitotic/karyorrhectic index
Nod**d**ularity

(Mnemonic: Dr. Shimada has a **SAD MiNd**)

Favorable tumors:

- Age <1.5 yr: Poorly differentiated or differentiating NB, low/intermediate mitosis/karyorrhexis index
- Age b/t 1.5–5 yr: Differentiating NB and low mitosis/karyorrhexis index
- Ganglioneuroblastoma, intermixed (Schwannian stroma-rich) & ganglioneuroma histologies

What 5 factors are used to classify NB pts into low-, intermediate-, and high-risk groups per the COG?

Show Answer

5 factors used to classify NB in COG low-, intermediate-, and high-risk groups:

- **S**tage, INSS
- **A**ge
- **N**-myc status
- **D**NA ploidy
- **S**himada classification

(Mnemonic: **SANDS**, see Table 4-1)
An NB pt with stage I Dz and N-myc amplification is in what risk group?

Show Answer

All stage I NB pts are **low risk.**
Can a pt with N-myc amplification be classified as intermediate risk?

Show Answer

No. All NB pts with N-myc are either low risk or high risk.

Table 4-1 Children's Oncology Group Risk Groupings

Risk Group	INSS Stage	Age (yrs)	N-myc	Shimada	DNA Index
Low	1	0–21	Any	Any	Any
	2	<1	Any	Any	Any
	2	>1	Normal	Any	Any
	2	>1	Amplified	Fav	Any
	4S	<1	Normal	Fav	>1
Intermediate	3	<1	Normal	Any	Any
	3	1–21	Normal	Fav	Any
	4	<1	Normal	Any	Any
	4S	<1	Normal	Any	= 1
	4S	<1	Normal	Unfav	Any
High	2	1–21	Amplified	Unfav	Any
	3	<1	Amplified	Any	Any
	3	1–21	Normal	Unfav	Any
	3	1–21	Amplified	Any	Any
	4	<1	Amplified	Any	Any
	4	1–21	Any	Any	Any
	4S	<1	Amplified	Any	Any

INSS, International Neuroblastoma Staging System; Fav, favorable; Unfav, unfavorable.

What makes a stage 2 or stage 3 pt high risk?

Show Answer

Stage 2 pts are high risk if they have all 3 risk factors: (1) N-myc

amplification, (2) UH, and (3) ≥1 yo.

Stage 3: either (1) N-myc amplification at any age, or (2) ≥1 yo & UH.

What feature makes NB pts with stage 4S Dz high risk?

Show Answer

NB stage 4S pts are high risk if tumors are **N-myc amplified.**

What features make NB pts with stage 4S Dz intermediate risk?

Show Answer

NB stage 4S pts are intermediate risk if tumors are **not N-myc amplified** and are **either Shimada UH or have diploid DNA.**

In which COG risk group do NB pts most commonly present?

Show Answer

NB pts are most commonly **high risk (55%).** 30% are low risk.

TREATMENT/PROGNOSIS

Estimate the 3-yr OS for low-, intermediate-, and high-risk NB.

Show Answer

NB 3-yr OS by risk group:

Low risk: 95%–100%
Intermediate risk: 75%–98%
High risk: <30%

What % of stage 4S pts experience spontaneous regression?

Show Answer

Up to 85% of pts with stage 4S NB experience spontaneous regression. Thus, low-risk stage 4S pts can be observed.

What is the Tx paradigm for low-risk NB?

Show Answer

Low-risk NB Tx paradigm: Sg alone with chemo reserved for persistent or recurrent Dz.
What is the Tx paradigm for low-risk stage 4S NB, and which study supports this approach?

Show Answer

Low-risk stage 4S NB Tx paradigm: Bx → supportive care. Chemo and/or RT are reserved for rapidly growing or symptomatic Dz. A subgroup analysis of **CCG 3881** showed that supportive care is sufficient for 57% of pts. The protocol resulted in a 5-yr EFS of 86% and an OS of 92%. (Nickerson HJ et al., JCO 2000)
Which studies support the use of observation (without resection) in infants with localized NB without N-myc amplification?

Show Answer

The use of observation (without resection) in infants with localized NB without N-myc amplification was evaluated in the German GPOH trials **NB95-S and NB97.** Of 93 pts with gross Dz, 44 had spontaneous regression. OS and DMFS were no different from outcomes of pts treated with Sg or chemo in these trials. (3-yr OS 99%, DMFS 94%). (Hero B et al., JCO 2008)
What is the role of RT in the Tx of intermediate-risk NB?

Show Answer

In intermediate-risk pts, RT is typically reserved for those who are symptomatic d/t tumor bulk and are not responding to initial chemo, such as pts with respiratory distress d/t hepatomegaly or with neurologic compromise d/t cord compression. RT is not indicated as a consolidative therapy even with persistent Dz. Indications for RT based on **A3961:** Symptomatic palliation, viable residual Dz in Tx-refractory pts, and recurrent Dz.
What is the Tx for unfavorable stage 4S (intermediate-risk) Dz?

Show Answer

The Tx is **chemo × 8 cycles.**
What is the Tx paradigm for high-risk NB?

Show Answer

High-risk NB Tx paradigm: induction chemo, resection, high-dose chemo and stem cell transplant → **consolidation RT,** then oral cis-retinoic acid and immunotherapy (anti-GD2 + IL2/GM-CSF).
Which targeted agent has recently been demonstrated as promising new adj therapy for high-risk NB?

Show Answer

Promising results have been observed **with immunotherapy targeting the surface glycolipid molecule disialoganglioside (GD2).** A recent phase III randomized trial showed a significant improvement in EFS and OS for children with high-risk NB receiving chimeric anti-GD2 (ch14.18) combined with cytokines (IL2 and GM-CSF) and isotretinoin after myeloablative consolidation therapy. (Yu AL et al., NEJM 2010)
In low-risk and intermediate-risk NB, what dose of RT is generally used?

Show Answer

In low-risk NB, RT to 21 Gy at 1.5 Gy/fx can be used for Sx that do not respond to chemo. In intermediate-risk NB, if PR to chemo and viable residual Dz after 2nd-look Sg, then RT can be given locally to the primary + 2-cm margin to 24 Gy at 1.5 Gy/fx.
In high-risk NB, what tissues are targeted during RT and to what dose?

Show Answer

Per current **COG ANBL0532,** high-risk NB pts are treated with RT to their **postchemo, preop tumor bed** to a total dose of **21.6 Gy in 1.8 Gy/fx if GTR** and 36.0 Gy (21.6 Gy to preop GTV → 14.4 Gy boost) **if gross residual.** Based on pts with residual Dz treated on CCG 3891, 21.6 Gy is also acceptable for high-risk Dz. (Haas-Kogan D et al., IJROBP 2003)

In high-risk NB, should elective nodal RT be given?

Show Answer

No. In high-risk NB, only clinically+ or pathologically+ LN regions are covered in the RT volumes.
What study indirectly demonstrated an RT dose–response in high-risk NB?

Show Answer

A secondary analysis of **CCG 3891** found that high-risk NB pts who rcvd 10 Gy local EBRT + 10 Gy TBI as part of a transplant preparation regimen had better LC than pts who did not get TBI (or a transplant) (5-yr LR rate was 22% vs. 52%). These results support the current use of 21.6 Gy in high-risk protocols. (Haas-Kogan D et al., IJROBP 2003)
What study demonstrated the benefits of high-dose chemo → BMT as well as adj cis-retinoic acid in high-risk NB?

Show Answer

In **CCG 3891,** 379 high-risk NB pts were treated with induction chemo → Sg and 10 Gy to gross residual. Pts were then randomized to 3 cycles of nonmyeloablative chemo vs. myeloablative chemo, TBI, and BMT. Pts underwent secondary randomization to observation vs. cis-retinoic acid × 6 mos. Both the myeloablative chemo and cis-retinoic acid improved OS. 5-yr OS for pts who rcvd both was 59%. (Matthay KK et al., JCO 2009)
What is the appropriate Tx for NB pts with cord compression?

Show Answer

Consider chemo initially for NB-related cord compression. Unresponsive Dz can be treated with Sg or RT.
What is the RT dose and dose/fx used for NB pts being treated for symptomatic cord compression?

Show Answer

For symptomatic cord compression:

- If pt is <3 yo, treat to **9 Gy** (1.8 Gy/fx)
- If pt is ≥3 yo, treat to **21.6 Gy** (1.8 Gy/fx)

What is the RT dose and dose/fx used for NB pts being treated for symptomatic hepatomegaly?

Show Answer

Symptomatic hepatomegaly is treated to **4.5 Gy** (1.5 Gy × 3).
Can the vertebral body be split during RT planning?

Show Answer

No. It is necessary to always cover the full width of the vertebrae to avoid scoliosis.
What chemo drugs are typically used in NB?

Show Answer

Chemo drugs typically used in NB:

- Cisplatin
- Etoposide
- Vincristine
- Cyclophosphamide
- Doxorubicin

What is the role of I-131 MIBG in NB?

Show Answer

I-131 MIBG can be used for refractory NB, based on a promising phase II study showing a 36% response rate. (Matthay KK et al., JCO 2007)

FOLLOW-UP/TOXICITY

In NB, what dose constraint is used for the contralat kidney per COG ANBL0532?

Show Answer

Limit the dose to V12 <20%, V8 <50%.
In NB, what dose constraint is used for the liver per COG ANBL0532?

Show Answer

Limit liver V9 <50%, V18 <25%.
In NB, what dose constraint is used for the lung per COG ANBL0532?

Show Answer

Limit lung V15 to <33%.
What are some complications of RT Tx in NB?

Show Answer

Disturbances of growth, infertility, neuropsychologic sequelae, endocrinopathies, cardiac effects, pulmonary effects, bladder dysfunction, secondary malignancy

5

Retinoblastoma

Updated by Vincent J. Lee

BACKGROUND

What is the incidence and median age for presentation of RB?

Show Answer

1 in 15,000 live births (250–300 cases/yr); Median age: **1 yo for bilat Dz,** and **2 yo for unilat; 95% <5 yo**

What is the most common eye tumor in infants?

Show Answer

Metastatic leukemia (1,000 cases/yr). RB is the #1 primary tumor.

What are the 3 most common ocular tumors (considering all age groups)?

Show Answer

Metastatic carcinoma, melanoma, and RB

What % of multifocal RB is heritable vs. from somatic mutations?

Show Answer

40% are heritable, and 60% are from somatic mutations in the RB1 gene. Heritable RB is associated with germline mutations which can be de novo; appx **25%** of heritable RB has a **positive family Hx.**

What % of RBs are bilat/multifocal vs. unilat at presentation?

Show Answer

25% bilat/multifocal vs. 70%–80% unilat. Bilat tumors are typically multifocal (~5 tumors on avg) and present younger (~15 mos).
To what other malignancy are RB pts particularly prone?

Show Answer

RB pts are prone to **osteosarcoma.**
What gene is mutated in RB?

Show Answer

The **RB1 tumor suppressor gene** is mutated in RB.
On what chromosome is the RB tumor suppressor gene located?

Show Answer

The RB tumor suppressor gene is located on **chromosome 13.**
What cell cycle checkpoint does RB1 affect?

Show Answer

RB1 affects the **G1/S** checkpoint.
What is the cell of origin for RB?

Show Answer

RB arises from **neuroepithelial cells** (from the nucleated photoreceptor layer of the inner retina).
What is Knudson 2-hit hypothesis for heritable RB?

Show Answer

1st hit: germline RB1 mutation
2nd hit: somatic loss of heterozygosity d/t mitotic recombination error, or allelic loss. p53 suppression with MDM2 amplification may also be involved as a 3rd hit.

What is the unique histologic feature/pattern associated with RB?

Show Answer

Flexner–Wintersteiner rosettes (also small round blue cells, $+Ca^{2+}$, necrosis)
What are the 5 patterns of spread for RB?

Show Answer

Patterns of spread for RB:

. Local extension
. Optic nerve to brain
. CSF to leptomeninges/subarachnoid
. Heme mets
. Lymphatic dissemination via conjunctiva, ciliary body, extraocular tissues

What are the most common sites of hematogenous spread in RB? What % of pts present with DMs?

Show Answer

Bone, liver, and spleen. **10%–15%** of pts present with DMs.
What are 2 tumor-related factors that correlate with an increased risk for mets?

Show Answer

Thickness (relates to invasion of optic nerve, uvea, orbit, choroid) and **size** of lesion
What is trilat RB? How common is it? What is the prognosis?

Show Answer

Trilat RB is **bilat RB + intracranial PNET** (pineal or suprasellar), representing **3%–9% of hereditary RB** (rare). It is almost **uniformly fatal.**
How do pts present with RB in the United States vs. in developing countries?

Show Answer

In the United States: **leukocoria** > strabismus > painful glaucoma, and irritability. Leukocoria refers to an abnl white reflection from the retina.
In developing countries: proptosis, orbital mass, and mets (more advanced)
What are the 3 main morphologic growth patterns of RB?

Show Answer

Endophytic mass (projects into vitreous), exophytic (associated with exudative retinal detachment), and diffuse infiltrating RB (least common)
What are the major negative prognostic factors in RB?

Show Answer

Delay in Dx of >6 mos, Hx of intraocular Sg leading to seeding, cataracts, thick tumors, Hx of RT (b/c of high risk for secondary cancers), extraocular extension

WORKUP/STAGING

What is the DDx for pts who present with leukocoria?

Show Answer

Toxocariasis, hyperplastic primary vitreous, Coat Dz, retrolental fibrodysplasia, congenital cataracts, and toxoplasmosis
Is Bx done for RB?

Show Answer

Generally not. B/c of the fear of seeding, the Dx is established clinically.
What is the typical workup for pts with an intraocular mass?

Show Answer

Intraocular mass workup: H&P (EUA, max dilated pupil, scleral indentation, ocular US), labs, US/CT, MRI of brain and orbits (most sensitive to evaluate extraocular extension)
When are bone scan, BM Bx, and LP indicated?

Show Answer

If the tumor is not confined to the globe (with deep invasion), BM Bx, LP, and bone scan are indicated.
What % of RBs are calcified?

Show Answer

90% of RBs are calcified.
What staging systems are used for RB?

Show Answer

The **International Classification for Intraocular Retinoblastoma** is used for staging in COG protocols. **Reese–Ellsworth grouping system** predicts for visual preservation after EBRT but does not predict for survival and is therefore **being phased out**. The **AJCC 8th edition** now incorporates Dz extent with germline cancer predisposition.
Summarize the International Classification for Intraocular Retinoblastoma.

Show Answer

Group A (Very Low Risk): all tumors ≤3 mm in thickness, confined to retina, and >3 mm from foveola and >1.5 mm from optic disc

Group B (Low Risk): all tumors confined to retina, clear subretinal fluid ≤3 mm from tumor with no subretinal seeding

Group C (Moderate Risk): discrete tumors, subretinal fluid without seeding involving up to one-fourth of retina, local fine vitreous seeding close to discrete tumor, local subretinal seeding ≤3 mm from tumor

Group D (High Risk): massive or diffuse tumors; subretinal fluid or diffuse vitreous seeding; retinal detachment; diffuse or massive Dz including greasy seeds or avascular tumor masses; subretinal seeding may include subretinal plaques or tumor nodules

Group E (Very High Risk): presence of any of the following features:

invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, ant chamber; tumor ant to ant vitreous surface involving ciliary body or iris; diffuse infiltrating RB; neovascular glaucoma; opaque media from hemorrhage in ant chamber, vitreous, or subretinal space; tumor necrosis with aseptic orbital cellulites; phthisis bulbi (shrunken, nonfunctional eye)

Summarize the AJCC 8th edition clinical staging for RB.

Show Answer

cT0: No evidence of intraocular tumor

cT1: Intraretinal tumor(s) with subretinal fluid ≤5 mm from the base of tumor

- **cT1a:** Tumors ≤3 mm and >1.5 mm from disc and fovea
- **cT1b:** Tumors >3 mm or <1.5 mm from disc or fovea

cT2: Intraocular tumor(s) with retinal detachment, vitreous seeding, or subretinal seeding

- **cT2a:** Subretinal fluid >5 mm from base of tumor
- **cT2b:** Vitreous seeding and/or subretinal seeding

cT3: Advanced intraocular tumor(s)

- **cT3a:** Phthisis or prephthisis bulbi
- **cT3b:** Tumor invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or ant chamber
- **cT3c:** Raised intraocular pressure with neovascularization and/or buphthalmos
- **cT3d:** Hyphema and/or massive vitreous hemorrhage
- **cT3e:** Aseptic orbital cellulitis

cT4: Extraocular tumor(s) involving orbits, including optic nerve

- **cT4a:** Radiologic evidence of retrobulbar optic nerve involvement or thickening of optic nerve or involvement of orbital tissues
- **cT4b:** Extraocular tumor clinically evident with proptosis and/or an orbital mass

cN0: No regional LN involvement

cN1: Evidence of preauricular, submandibular, and cervical LN involvement

cM0: No signs or Sx of intracranial or distant mets

cM1: DM without microscopic confirmation

- **cM1a:** Tumor(s) involving any distant site (e.g., BM, liver) on clinical or radiologic tests
- **cM1b:** Tumor involving the CNS on radiologic imaging (not including trilat RB)

H0: Normal RB1 alleles in blood tested with demonstrated high-sensitivity assays

H1: Bilat RB, RB with an intracranial PNET, Pt with FHx of RB, or molecular definition of a constitutional RB1 gene mutation

TREATMENT/PROGNOSIS

What is the Tx paradigm for very low/low risk unilat intraocular RB?

Show Answer

Unilat intraocular RB Tx paradigm: Chemoreduction for larger tumors involving macula → focal therapy

What are some focal therapies used for RB?

Show Answer

Cryotherapy, photocoagulation (laser), ophthalmic artery chemosurgery (OAC), plaque brachytherapy

When can cryotherapy/laser be used in RB?

Show Answer

Small lesions, at least 4 disc diameters from the fovea/optic disc

Which Tx modalities have significantly diminished the role of EBRT and systemic therapy in the Tx of RB over the last 10 yrs?

Show Answer

OAC and **intravitreous chemotherapy** have replaced the role for RT more and now offers hope of eye preservation for even group D tumors.

What is the current management of unilat RB based on the international RB groupings?

Show Answer

Group A: focal therapy (laser, cryotherapy, plaque brachytherapy)
Group B: focal therapy; OAC f/b focal therapy for macular tumors
Group C: OAC +/– intravitreous chemotherapy
Group D: OAC +/– intravitreous chemotherapy
Group E: enucleation, with consideration or adj Tx
When is EBRT now typically used in the management of RB?

Show Answer

Following enucleation with microscopic residua at the cut section of the optic nerve or sclera, or palliation of bulky metastatic Dz
What are indications for enucleation?

Show Answer

Painful glaucoma, buphthalmos, ant chamber seeding, diffuse infiltrating RB, phthisis bulbi
How is bilat RB managed?

Show Answer

Individualize the Tx for each eye (bilat eye preservation, if possible). In no case is EBRT used as primary therapy for bilat RB.
What is the eye preservation rate for unilat Group D tumors with OAC alone?

Show Answer

83% (Abramson D et al., JAMA Ophthalmol 2015)
How was EBRT given for RB, and what are the volumes irradiated?

Show Answer

4–6 MV IMRT/3D, proton therapy, electron therapy if available to entire globe + 5–8 mm of optic nerve (spare lens and iris for lower stages), 36–45 Gy; 0.5-cm bolus if needed.
What RT fields/setups were used for unilat vs. bilat RB?

Show Answer

Old standard for unilat Dz was 4 ant oblique fields **and for bilat** Dz opposed lat + ant oblique fields. Advanced techniques tended to use ant/ant oblique angles.
What chemo agents are employed in OAC?

Show Answer

Melphalan, carboplatin, and/or **topotecan**
What are the indications for episcleral brachytherapy? What is the dose used?

Show Answer

Solitary lesion **6–15 mm base diameter, ≤10 mm thick, >3 mm from disc/fovea; 40–45 Gy** to apex, **100–120 Gy** to base
What isotopes and plaque sizes are used in episcleral brachytherapy for RB?

Show Answer

I-125 or Ru-106 (more uniform loading, lower energy [beta] and less dose to ant ocular structures), diameter of tumor + 4 mm (**2-mm margin** around the tumor)

FOLLOW-UP/TOXICITY

What are the major complications of EBRT in the Tx of RB?

Show Answer

Induction of secondary malignancies (particularly in pts with heritable RB);

damage to retina, optic nerve, lacrimal gland, and lens; midface hypoplasia with retardation of orbital bone growth when given at age <12 mos.
What is the 2nd malignancy rate in heritable RB treated with RT vs. no RT?

Show Answer

With RT: 4% at 10 yrs, 18% at 35 yrs, **50% at 50 yrs**
Without RT: **15%–35% rate at 50 yrs,** mainly sarcomas (ST and osteosarcoma) and melanomas
Is the risk of 2nd malignancy also increased in sporadic RB treated with RT?

Show Answer

Yes, but minimally—**5% at 50 yrs** (Wong FL, JAMA 1997)
What are the complications from episcleral plaque therapy?

Show Answer

Retinopathy, maculopathy, glaucoma, and papillopathy
In what manner and how often should pts with bilat RB be screened for trilat RB?

Show Answer

With **biannual MRI** of the brain for at least 5 yrs.

6

Langerhans Cell Histiocytosis

Updated by Harvey B. Wilds

BACKGROUND

What is Langerhans cell histiocytosis (LCH)?

Show Answer

A rare disorder characterized by single or multiple osteolytic bone lesions demonstrating infiltration with histiocytes. These histiocytes (which is an antiquated term referring to WBCs that reside in tissue throughout the body), along with lymphocytes, macrophages, and eosinophils may infiltrate nearly every organ. LCH is characterized by an uncontrolled clonal proliferation of Langerhans cells which belong to the normal human mononuclear-phagocytic system.

Is there a sex predilection in LCH? What is the estimated annual incidence in the United States?

Show Answer

Yes. Males are more commonly affected than females (3:2). **~1,200 cases/yr** of LCH in the United States. It is likely underdiagnosed in the general population. It is most common in children 1–3 yrs.

What is the cell of origin of LCH?

Show Answer

LCH results from dysregulated differentiation program of **myeloid dendritic**

cell precursors (and not from epidermal dendritic cells called Langerhans cells). As a result, it has been suggested that LCH (along with juvenile xanthogranuloma and Erdheim–Chester Dz) be reclassified as inflammatory myeloid neoplasms. (Berres M et al., Adv Immunol 2013)
What are the diagnostic histopathologic characteristics of LCH?

Show Answer

Pathologic findings vary depending on the site of the Bx, but is confirmed by immunohistochemistry demonstrating the presence of dendritic cell markers such as **CD1a, S100, and CD207 (Langerin).**
What is the normal function of Langerhans cells? Where are they normally found?

Show Answer

Langerhans cells serve as **antigen presenting cells to lymphocytes** and are typically found in **skin, mucosa, spleen, and lymphatics.**
What organs are typically involved in LCH?

Show Answer

Bones (children) and lungs (adults), but LCH can present in any organ (e.g., liver, skin, etc.). LCH is limited to 1 organ system (e.g., bone) in 55% of cases and skin involvement is seen in 40% of cases.
How does LCH relate to other histiocytosis entities like eosinophilic granuloma, Letterer–Siwe Dz, Hand–Schuller–Christian Dz, and histiocytosis X?

Show Answer

All are antiquated terms. Eosinophilic granuloma is an older term for focal LCH, while the eponyms represent multifocal Dz. Histiocytosis X is the older term for LCH in general.
In what age group are widespread seborrheic rashes in the scalp/groin, +LAD, and liver involvement seen with LCH?

Show Answer

These Sx are seen in LCH pts **<2 yo.**
For what age group is DI a common presentation of LCH?

Show Answer

>2 yo (20%–50%). In this group, bone (pain +/– ST mass), lung, oral mucous membrane, and cerebral involvement by LCH can be seen.

WORKUP/STAGING

What type of workup is necessary?

Show Answer

LCH workup: H&P, labs, skeletal survey (lucency in the medullary cavity), and **Bx**
What is the appearance of LCH lesions on plain radiograph?

Show Answer

LCH lesions appear **lytic** or **"punched-out"** on plain radiograph.
What other radiographic studies are useful?

Show Answer

PET scan has been found to be the most sensitive test. Bone can be used in conjunction with skeletal survey if PET is not available.
What staging system is used for LCH?

Show Answer

A staging system was proposed by Greenberg et al. in 1981, but is not universally accepted. The Histiocyte Society guidelines describe a 2-system stratification. **Single system:** 1 organ or system involved or **Multisystem:** 2 or more organs/systems involved.

TREATMENT

What is the recommended initial Tx for LCH?

Show Answer

Pts with multisystem LCH should initially be treated with a combination of prednisone and vinblastine for 6 wks f/b re-evaluation and maintenance therapy if they have responded to therapy.
What are the indications for RT in LCH?

Show Answer

Painful or unstable unifocal or multifocal bone lesions and Tx of extraosseous ST or organ involvement.
When is RT not indicated in LCH?

Show Answer

RT is not indicated for **sclerotic LCH lesions and collapsed vertebral lesions** (only indicated if such lesions are painful).
What data support the use of RT for localized osseous LCH lesions?

Show Answer

German meta-analysis (Olschwski T et al., Strahlenther Onkol 2006): LC was 96% and CR was 93% for single-system Dz with RT.
What are the commonly used doses and volumes for LCH?

Show Answer

DI: **15 Gy** to pituitary/hypothalamus
Bone (small margin): **5–10 Gy**
Adults: **15–24 Gy** (in 2 Gy/fx)
When is chemo used in LCH?

Show Answer

Multisystem Dz (e.g., if fever, pain, severe skin involvement, failure to thrive, and organ dysfunction)

What systemic agents are used for LCH?

Show Answer

Prednisone (1st-line), then vinblastine. Single-agent chemo is as good as multiagent chemo. Vincristine can also be used.

How are asymptomatic, organ-confined LCH lesions managed?

Show Answer

Asymptomatic LCH lesions are typically **observed.**

How is a symptomatic bony LCH lesion managed?

Show Answer

A symptomatic bony LCH lesion is typically managed by Sg **(curettage, excision) and/or local injection of steroids.**

How are symptomatic LCH skin lesions managed?

Show Answer

Symptomatic LCH skin lesions are managed by **topical therapy with nitrogen mustard, steroids, or systemic therapy.**

How is LCH of the eye, ear, spine, or weight-bearing bones managed?

Show Answer

LCH of these areas is managed by s**ystemic steroids or local RT.**

How is asymptomatic multifocal LCH Dz with organ dysfunction managed?

Show Answer

Such asymptomatic LCH Dz is typically **observed.**

How is symptomatic multifocal LCH Dz with organ dysfunction managed?

Show Answer

Symptomatic multifocal LCH Dz with organ dysfunction is managed by **systemic therapy** (as described above). If the pt is symptomatic due to organ failure, consider transplant (liver, lung).

What is the long-term OS for solitary LCH lesions?

Show Answer

The OS for solitary LCH lesions is **~100%.**

What is the long-term OS for multisystem LCH with organ dysfunction?

Show Answer

The long-term OS for multisystem LCH with organ dysfunction is **33%–54%.**

What is the long-term OS for multisystem LCH without organ dysfunction?

Show Answer

The long-term OS for multisystem LCH without organ dysfunction is **82%–96%.**

FOLLOW-UP/TOXICITY

What is the RT TD 5/5 dose threshold for developing hypopituitarism?

Show Answer

The TD 5/5 for hypopituitarism is **40–45 Gy** (GH levels decrease first with doses as low as 18 Gy, then LH/FSH, then TSH/ACTH).

7

Medulloblastoma

Updated by Shane R. Stecklein

BACKGROUND

Estimate the annual incidence of medulloblastoma (MB) in the United States. What is its frequency relative to other CNS tumors in children?

Show Answer

~500 cases/yr of MB in the United States. It is the **2nd most common** pediatric CNS tumor (20% of cases; #1 is low-grade glioma at 35%–50%). It is the most common malignant brain tumor in the PF in children and adolescents, comprising 40% of all PF tumors.

What is the median age of MB at Dx?

Show Answer

MB has a bimodal age distribution, with a median age of **7 yrs in children (peak incidence b/t 5 and 9 yrs)** and **25 yrs in adults.**

Is there a sex predilection to MB?

Show Answer

Yes. Males are more commonly affected than females (2:1).

What is the cell of origin?

Show Answer

Neuroectodermal cells from the sup medullary velum (germinal matrix of

cerebellum) or cerebellar vermis.
MB is a subtype of what class of tumors?

Show Answer

MB is a subtype of **embryonal tumor** (along with PNET and atypical teratoid rhabdoid tumor [ATRT]).
Mutation of which gene distinguishes ATRT from MB?

Show Answer

Loss of INI1 distinguishes ATRT from MB. INI1 is found on chromosome 22 and functions as a tumor suppressor gene.
What % of pts present with CSF spread at Dx?

Show Answer

30%–40% of MB cases present with CSF spread at Dx.
For what MB age group is CSF spread more common?

Show Answer

This is more common in **younger pts.**
Does extra-axial spread occur in MB? If so, where?

Show Answer

Extra-axial spread is **rare,** but when it does occur it is typically to **bone.**
What are the characteristic histologic features and markers for MB?

Show Answer

MB appears as **small round blue cells.** 40% have **Homer Wright rosettes,** and most stain + for NSE, synaptophysin, and nestin.
What are some other types of small round blue cell tumors?

Show Answer

Small round blue cell tumors of childhood:

Lymphoma
EWS
Acute lymphoblastic leukemia
RMS
NB
Neuroepithelioma
MB
Retinoblastoma

(Mnemonic: **LEARN NMR**)
What are the 3 histologic variants of MB?

Show Answer

Histologic variants of MB:

. Classic
. Nodular/Desmoplastic (better prognosis)
. Large cell/Anaplastic (worse prognosis)

The desmoplastic histologic variant of MB is associated with what clinical features?

Show Answer

The desmoplastic variant is associated with:

. LOH 9q
. Older age at Dx
. Better prognosis

What is the most aggressive histologic variant that also has a particularly high rate of CSF dissemination?

Show Answer

Large cell/Anaplastic is the most aggressive MB variant.

What % of MBs are familial, and what are some associated genetic syndromes?

Show Answer

2%–5% of MBs are familial. Associated genetic syndromes include **Gorlin syndrome** (PTCH1 mutation, associated with nevoid basal cell carcinoma syndrome) and **Turcot syndrome** (APC mutation, associated with FAP).
What are the common cytogenetic abnormalities in MB?

Show Answer

Common cytogenetic abnormalities in MB include:

- **Deletion of 17p** (40%–50%)
- **Isochromosome 17q**
- **Deletion of 16q**
- **LOH 9q** (desmoplastic variant)

Where does MB most commonly arise?

Show Answer

Midline cerebellar vermis (75%), with the rest in cerebellar hemispheres.
What is the DDx for a PF mass?

Show Answer

DDx for a PF mass includes:

- MB
- Ependymoma
- ATRT
- Astrocytoma
- Brainstem glioma
- Juvenile pilocytic astrocytoma
- Hemangioblastoma

. Mets

What are the 4 genetic MB subgroups and what mutations tend to occur in each subgroup?

Show Answer

. Wingless homolog (WNT) group: CTNNB1 mutation. Associated with Turcot syndrome. Least common (10%) subgroup.
. Sonic hedgehog (SHH) group: PTCH1, GLI3, MYCN. 30% of MB, often desmoplastic. Overrepresented in infants and adults (bimodal).
. Group 3: MYC amplification, GABAergic expression. Enrich for large cell histology and are frequent mets at Dx. Worst prognosis.
. Group 4: MYCN, CDK6 amplification

(Northcott PA et al., JCO 2011)
Describe the prognosis for each subgroup.

Show Answer

Good prognosis: WNT group and **infants** in SHH group
Intermediate prognosis: Group 4 and SHH group
Poor prognosis: Group 3

WORKUP/STAGING

What are some common presenting Sx for MB?

Show Answer

HA (nocturnal or morning), n/v, altered mentation d/t hydrocephalus, truncal ataxia, head bob, and diplopia (CN VI)
What causes the common presenting Sx in MB?

Show Answer

Obstructive hydrocephalus/↑ ICP (HA and vomiting) and cerebellar dysfunction

What Sx would be expected with midline vs. lat cerebellar tumors?

Show Answer

Midline tumors may cause gait ataxia or truncal instability (i.e., broad-based gate, difficulty with heel-to-toe), whereas tumors in the lat hemispheres (more common in adults) may cause limb ataxia (i.e., dysmetria, intention tremor, difficulty with heel-to-shin). ATRT more likely to involve lat hemispheres.

What is the “setting-sun” sign?

Show Answer

Downward deviation of gaze from ↑ ICP (CNs III, IV, and VI)

List the general workup for a PF mass at presentation.

Show Answer

PF mass workup: H&P (funduscopic exam, CN exam), CBC/CMP, MRI brain/spine, CSF cytology (may not be possible d/t herniation risk), and baseline ancillary tests. Consider bone scan and CXR depending on presentation and risk factors.

What are some important ancillary tests to obtain prior to starting Tx?

Show Answer

Baseline audiometry, IQ testing, TSH, and growth measures

Is a tumor Bx necessary for Dx? Is a BM Bx necessary?

Show Answer

Per current COG MB protocol **ACNS0331,** a **tumor Bx is unnecessary;** pts often go straight to Sg. **BM Bx is not part of the standard workup.**

Is there any risk of CSF dissemination with shunt placement for MB?

Show Answer

No. There is no risk of CSF dissemination.

What tests should be obtained on days 10–14 postop?

Show Answer

MRI spine, CSF cytology. (Delay until day 10 to avoid a false+ result from surgical debris.)

When is MRI of the brain done? Of the spine?

Show Answer

MRI brain: preop and 24–48 hrs postop

MRI spine: preop or 10–14 days postop

What can be done before Tx to reduce ICP?

Show Answer

Ventricular drain or shunt, steroids, acetazolamide (Diamox)

List the T staging according to the modified Chang staging system for MB.

Show Answer

T1: <3 cm

T2: ≥3 cm

T3a: >3 cm, with extension into aqueduct of Sylvius or foramen of Luschka

T3b: >3 cm, with unequivocal extension into brainstem

T4: >3 cm, extends beyond aqueduct of Sylvius and/or foramen magnum

List the M staging according to the modified Chang staging system for MB.

Show Answer

M0: no subarachnoid or hematogenous mets

M1: +CSF

M2: nodular intracranial seeding

M3: nodular seeding in spinal subarachnoid space

M4: extraneural spread (bone, BM most common in MB)

Define standard-risk and high-risk MB.

Show Answer

Standard risk (two-thirds): >3 yo, GTR/NTR <1.5 cm^2 residual, and M0
High risk (one-third): <3 yo, or STR ≥1.5 cm^2 residual, or M+
What may contribute to the poor prognosis of <3 yo?

Show Answer

Reduction in volume and/or dose or elimination of RT in very young children d/t concerns of toxicity may contribute to the poor prognosis in this age group.

TREATMENT/PROGNOSIS

What is the most important prognostic factor at Dx for MB? What are other poor prognostic factors for MB?

Show Answer

M stage is the most important prognostic factor. Other poor prognostic factors include male sex, age <3 yrs, and unresectable Dz/STR.
What is the management paradigm for standard-risk MB?

Show Answer

COG approach: Standard-risk MB management: max safe resection → RT with concurrent weekly vincristine → adj chemo (eight 6-wk cycles of cisplatin/CCNU/vincristine). **RT is CSI to 23.4 Gy → cone down 1 (CD1) to PF to 36 Gy, then cone down 2 (CD2) to cavity/residual or PF to 54–55.8 Gy; or CSI to 23.4 Gy → CD to cavity/residual to 54–55.8 Gy (MDACC).**
What chemo regimens are typically used for MB?

Show Answer

Initial studies that established the efficacy of reduced-dose CSI (23.4 Gy)

with chemo in standard-risk MB used **concurrent vincristine with RT → adj cisplatin/CCNU/vincristine.** The **CCG A9961** trial recently found similar outcomes when cyclophosphamide was substituted for CCNU. (Packer R et al., JCO 2006)
What is the management paradigm for high-risk MB?

Show Answer

High-risk MB management paradigm for pts >3 yo: same as standard risk, but the **CSI dose is 36 Gy;** also, nodular intracranial or spinal mets may to be boosted to 45–50.4 Gy depending on location (whether lesion is above or below SC terminus).
For high-risk MB pts, what is the total boost dose for pts with intracranial (M2) vs. spinal (M3) mets?

Show Answer

Per COG **ACNS0332,** boost intracranial mets to 50.4 Gy, focal spinal mets below the cord terminus to 50.4 Gy, focal spinal mets above the cord terminus to 45 Gy, and diffuse spinal Dz to 39.6 Gy.
Estimate the 5-yr EFS for standard- and high-risk MB.

Show Answer

The 5-yr EFS for standard risk is **80%** and for high risk is **50%–60%.**
What is the management paradigm for MB pts <3 yo?

Show Answer

MB pts <3 yo management paradigm: max safe resection → chemo until pt reaches 3 yo. At 3 yo, consider standard therapy with CSI → more chemo. If desmoplastic histology, consider omitting RT altogether. New protocols use surgical bed RT alone after induction chemo in 18- to 36-mo pts.
What are the potential risks of aggressive Sg in the PF?

Show Answer

The major risk of aggressive Sg in the PF is **PF syndrome (10%–15% of cases):** mutism, ataxia, dysphagia, hypotonia, respiratory failure, and mood lability caused by disruption of the dentatorubrothalamic pathway to the supplemental motor cortex. PF syndrome typically presents 12–24 hrs postop and improves over several mos. Other potential complications include aseptic meningitis and CSF leakage. **Do not delay RT b/c of PF syndrome.**
In MB, how are NTR, STR, and "Bx only" defined?

Show Answer

NTR: <1.5 cm^2 residual on postop MRI
STR: ≥1.5 cm^2 residual on postop MRI
Bx only: No attempt at definitive resection
In MB, is there a difference b/t NTR vs. GTR in terms of EFS? How about STR and GTR?

Show Answer

Retrospective studies suggest that pts who obtain an **NTR and GTR have similar outcomes.** (Gajjar A et al., Ped Neurosurg 1996) However, 5-yr EFS is worse in STR pts (54%) compared to GTR/NTR pts (78%). (Zeltzer PM et al., JCO 1999)
What chemo agent improved DFS and OS according to MB studies in the 1990s?

Show Answer

Cisplatin. Prior to the introduction of cisplatin, several studies **(SIOP I** and **CCG 942)** failed to show improved OS with the addition of adj chemo.
What 2 studies demonstrated the need for chemo with reduced-dose CSI (23.4 Gy) for standard-risk MB?

Show Answer

There has been no RCT comparing reduced-dose CSI +/– cisplatin-based chemo. The need for cisplatin-based chemo is inferred from the following 2

studies:

- **POG 8631/CCG 923:** randomized standard-risk MB to 36 Gy vs. 23.4 Gy CSI alone (no chemo). There was a trend toward ↓ EFS and OS in the 23.4-Gy arm. (Thomas PR et al., JCO 2000)
- **CCG 9892 (phase II):** standard-risk MB treated with 23.4 CSI with concurrent weekly vincristine → 55.8-Gy boost to PF → adj cisplatin/CCNU/vincristine. 5-yr PFS was 79%, which was similar to historical controls treated with 36 Gy CSI and similar chemo. (Packer R et al., JCO 1999) Basis for POG A9961 reduced dose CSI.

Can RT be delayed for MB pts <3 yo by using chemo alone? What studies support this?

Show Answer

Yes. Given the toxicity of RT in pts <3 yo, it is reasonable to delay RT until 3 yo, **especially with desmoplastic histology.**

Baby POG (Duffner PK et al., Neurooncol 1999, NEJM 1993): <3 yo, 206 pts, high-/low-risk MB + other PNET, chemo alone (Cytoxan + Vincristine (VCR) × 2→ cisplatin + etoposide) × 2 yrs if <2 yo, × 1 yr if 2–3 yo. 5-yr OS was 40%, and PFS was 32%.

German BTSG data (Rutkowski S et al., NEJM 2005): <3 yo, 43 pts, high-/low-risk MB, chemo (Cytoxan, vincristine, Mtx, carboplatin, VP-16, intrathecal Mtx). 5-yr PFS was 58%, and OS was 66%. The majority of pts had a desmoplastic variant histology. The benefit was best in M0 pts (5-yr PFS of 68% and OS of 77%)

SFOP data (Grill J et al., Lancet Oncol 2005): <5 yo, 79 pts. 5-yr OS was best in R0M0 (73%) vs. 13% with M+.

What was the Tx regimen on COG A9934 for MB pts <3 yo?

Show Answer

Initial Sg → induction chemo × 4 mos with Cytoxan, vincristine, cisplatin,

etoposide → 2nd Sg for identifiable or residual Dz → age/risk group/response-adapted conformal RT to PF + primary site (no CSI) → maintenance chemo × 8 mos. Enrolled children were older than 8 mos but younger than 3 yrs, all M0 MB.

Age/risk/response-adapted RT:

(Ashlet DM et al., JCO 2012)
If <24 mos and CR: 18 Gy to PF → tumor bed boost to 50.4 Gy, or 54 Gy if PR/Stable disease/+ residual
If >24 mos and CR or PR: 23.4 Gy to PF → tumor bed boost to 54 Gy
What evidence supports the use of >50 Gy total doses in MB?

Show Answer

Retrospective data suggest that LC in the PF varies with dose above and below 50 Gy. In 60 MB cases, if the PF dose was >50 Gy, the LC was 79%. However, if the PF dose was <50 Gy, the LC was 33%. (Hughes EN et al., Cancer 1988)
In MB pts, does the entire PF need to be boosted to >50 Gy?

Show Answer

Retrospective evidence suggests that **few failures occur in the PF outside the tumor bed (<5%).**

Fukunaga-Johnson et al. reviewed 114 pts treated with CSI → boost to the entire PF. The solitary site of the 1st failure within the PF but outside the tumor bed occurred in 1 of 27 failures. (IJROBP 1998)
Wolden et al. reviewed 32 pts treated with tumor bed boost only. There were 6 total failures: 5 outside the PF and 1 within the PF but outside the boost volume. (JCO 2003)
Merchant et al. conducted a prospective phase II trial of 23.4 Gy CSI + PF boost to 36 Gy and primary site to 55.8 Gy with dose-intensive chemo. 5-yr EFS was 83%, and PF failure was 5%. Reduced doses to temporal lobes,

cochlea, hypothalamus. (IJROBP 2008)

What are the RT technique questions being addressed in COG ACNS0331?

Show Answer

In **ACNS0331, standard-risk pts 3–7 yo** are randomized to **CSI to 18 Gy vs. 23.4 Gy.** For the **18 Gy arm, all pts got a PF boost to 23.4 Gy.** All standard-risk pts 3–7 yo underwent a 2nd randomization: CD to **54 Gy to whole PF vs. tumor bed only.** Standard-risk pts 8–22 yo: 23.4 Gy CSI → randomization to CD to 54 Gy to PF vs. tumor bed only.

What was the rationale for 18-Gy CSI in ACNS0331?

Show Answer

CSI doses in excess of 20 Gy still pose a significant risk for cognitive and growth outcomes, particularly in young children. Pilot study in 10 children with PNET of the PF showed comparable outcomes to higher doses. (Goldwein J et al., IJROBP 1996)

What do the preliminary results of ACNS0331 show?

Show Answer

For pts with standard-risk MB, boosting the tumor bed alone is sufficient, but decreasing the CSI dose to 18 Gy is associated with higher risk of recurrence and is not recommended. (Michalski JM et al., IJROBP 2016)

What question does ACNS0334 attempt to address?

Show Answer

Phase III trial in children **<3 yrs with high-risk MB or PNET.** Trial addresses the addition of high-dose Mtx to the 4-drug induction chemo regimen of VCR, etoposide, Cytoxan, cisplatin → 2nd Sg, consolidation, and peripheral blood stem cell rescue. RT is at the discretion of the institution.

What study is examining molecular risk-adapted Tx?

Show Answer

SJMB12 is a St. Jude trial examining risk-adapted escalation and de-escalation of radiotherapy and chemo based on molecular subtype (WNT, SHH, and Non-WNT/SHH [Group 3/4]), cytogenetics, histology, and extent of resection.

Is there a role for pre-RT chemo in MB pts >3 yo?

Show Answer

No. In MB pts >3 yo, intensive chemo prior to RT (vs. RT then chemo) is associated with ↑ RT toxicity, RT Tx delays, and worsened RFS. (German **HIT 91:** Kortmann RD et al., IJROBP 2000)

What benefit does proton therapy have in the Tx of MB?

Show Answer

Retrospective data suggest that proton plans have ↓ **dose to the cochlea/temporal lobe compared to IMRT** (0.1%–2% vs. 20%–30%), and virtually no exit dose to the abdomen, chest, heart, and pelvis. Recent study suggests less morbidity, including GI and heme toxicity (although this is in adults). (Brown AP et al., IJROBP 2013)

Is there a role for hyperfractionated RT to reduce cognitive sequelae of MB Tx?

Show Answer

MSFOP 98, a phase II trial, evaluated hyperfractionated RT in MB and showed promising results. 48 standard-risk pts were treated with CSI 1 Gy bid to 36 Gy → tumor bed boost 1 Gy bid to 68 Gy. **6-yr OS was 78%, and EFS was 75%. Decline in IQ appeared less pronounced than in historical controls.** (Carrie C et al., JCO 2009)

How are MB pts simulated?

Show Answer

MB simulation: supine or **prone, neck extended** (so PA spine field does not exit through the mouth), head mask, **shoulders positioned inferiorly** (to allow for lat cranial fields). Depending on institutional experience, can simulate supine, which allows better airway access during anesthesia, most places are now doing supine technique.
What modalities of RT have been used for CSI?

Show Answer

Photons, electrons (at MDACC in yrs past), and protons are the more commonly used RT modalities for CSI therapy.
In CSI, which fields are placed 1st?

Show Answer

Spinal fields are placed 1st (to allow calculation of collimator angle for the cranial field based on spinal field beam divergence).
Cranial fields are placed 2nd (down to C5–6 or as low as possible but need to ensure lats do not go through shoulder).
By what angle are the cranial field collimators rotated?

Show Answer

Arctan (one-half length of sup spine field/SSD), which matches the cranial field to the spine field divergence
What are the borders of the spine field(s)?

Show Answer

Superior: matched to cranial field
Inferior: end of thecal sac (near S2–3, check on sagittal spine MRI)
Lateral: 1 cm past pedicles (some centers plan with wider margins in sacrum to cover neural foramina)
By what angle is the couch kicked and in which direction?

Show Answer

Couch kick for CSI: **arctan (one-half length of cranial field/SAD);** couch kicked **toward** side treated to match cranial field divergence (for breast, kick is **away**)
What is a potential problem with a couch kick?

Show Answer

Couch could be rotated in the opposite direction than intended. At MDACC, Tx are usually planned without a couch kick to eliminate moving table in wrong direction. A small amount of overlap occurs lat to cord, but doses used are relatively low and amount of overlap is decreased by feathering the junction.
If multiple spinal fields are used, what is the skin gap? At what depth is the match?

Show Answer

With multiple spine fields, the **skin gap = ([0.5 × Length$_1$** × d**]/SSD$_1$) + ([0.5 × Length$_2$** × d**]/SSD$_2$)** where d is the depth of the match, which is typically at the ant cord edge.
How is “feathering” done? Why is it used?

Show Answer

There are several techniques, and feathering is dependent upon institutional experience. Feathering helps reduce hot and cold spots in a plan. At MDACC, several techniques are used, including inter- and intrafractional junctioning for photons, electron junction technique, and proton junction technique.

Interfractional junctioning may be modulated with field-in-field technique and consists of moving junction superiorly 0.5 cm on 7th and 13th fx. This creates 12 fields with junctions.

Intrafractional junctioning may be modulated with step-and-shoot technology. 3 junction control points at 1-cm gaps (i.e., 0, 1, and 2 cm with

the use of MLCs) are created, and each control point delivers one-third of the fractional dose. MLC leaves remain outside the field to ensure min interleaf leakage.

Where should the isocenter be placed in the cranial field for CSI? What cranial structure should be assessed for adequate coverage?

Show Answer

For the half-beam block technique, the isocenter should be placed **behind the lenses** to minimize divergence of beams into the opposite lens; the **cribriform plate** is not optimally visualized on conventional simulation films. A generous margin must be given in this area, or CT contours of the cribriform plate can be outlined to ensure coverage.

What CSI techniques can be employed if the entire spine cannot be included in 1 field?

Show Answer

The practitioner can **increase the SSD (i.e., 100 cm → 120 cm) or rotate the collimator** using a single field, but if the length is >36–38 cm, then **2 spinal fields** are needed, with the inf field's isocenter placed at the junction (using half-beam block to minimize the cold spot). Match at L1–2, as this is the area where the depth of cord changes the most.

FOLLOW-UP/TOXICITY

What is Collins law as it pertains to the max length of f/u needed for pediatric tumors?

Show Answer

Defines period of risk for recurrence (**age at Dx + 9 mos** [gestational period]). If tumor was present in utero, then **age at Dx + 9 mos** determines rate of growth for it to become clinically evident. Residual Dz should become evident in same timeframe. (Sure U, Clin Neurol Neurosurg 1997)

What factors predict for greater decline in IQ after CSI?

Show Answer

Factors for decline in IQ after CSI:

Age <7 yrs (most important)
Higher dose (36 Gy vs. 23.4 Gy)
Higher IQ at baseline
Female sex

(Ris MD et al., JCO 2001)
For how long can the pt's IQ decline after CSI?

Show Answer

>5 yrs. Hoppe-Hirsch et al. reviewed 120 MB pts treated with CSI to 36 Gy. At 5 yrs, 58% had an IQ >80. At 10 yrs, only 1% had an IQ >80. (Childs Nerv Syst 1990)
What are some important factors influencing IQ scores/neurotoxicity after RT?

Show Answer

Age at Tx with RT (most important), volume and dose of RT, and sex (female > male)
What is the dose constraint to the cochlea?

Show Answer

V30 <50% is the dose constraint to the cochlea (max is 35 Gy with chemo).
What is the most common hormone deficiency after RT to the brain? What is the dose threshold?

Show Answer

GH. The threshold dose for GH deficiency is ~10 Gy.
What is the annual IQ drop after full PF boost in MB pts younger and older than 7 yrs? What structure is most important?

Show Answer

IQ drop of **5 points/yr if <7 yo and 1 point/yr if >7 yo.** The dose to the **supratentorial brain** (temporal lobes) is most important.

8

Ependymoma

Updated by Penny Fang

BACKGROUND

In children and adults, what % of brain tumors are ependymomas?

Show Answer

Children: 5% (3rd most common childhood CNS tumor)
Adults: 2%
What is the median age of Dx for ependymomas?

Show Answer

Bimodal peak distribution, with peaks at **5 yrs** and **35 yrs**
What % of ependymomas arise intracranially, and how does this differ in children vs. adults? What are the most common locations?

Show Answer

Children: 90% intracranial (10% cord). If intracranial, the PF is the most common site (60% infratentorial [floor of 4th ventricle], 40% supratentorial [lat ventricle]).

Adults: 75% arise in spinal canal. Of intracranial tumors, two-thirds are supratentorial and one-third is infratentorial.

What is the cell of origin for ependymomas?

Show Answer

Ependymomas arise from the **ependymal cells lining the ventricles.**
What % of primary spinal tumors is ependymoma?

Show Answer

~20% (meningiomas comprise 33%, spinal nerve tumors 27%)
What genetic syndrome is associated with SC ependymoma?

Show Answer

SC ependymoma is associated with **NF-2.**
What % of ependymoma pts present with CSF seeding? What features predispose to seeding?

Show Answer

5%–10%; infratentorial location, high-grade tumors, and LF predispose to CSF seeding.
What is the WHO classification of ependymoma?

Show Answer

Grade I: myxopapillary and subependymoma
Grade II: classic ependymoma
Grade III: anaplastic
Grade IV: ependymoblastoma
Where do grade IV ependymomas generally arise?

Show Answer

Grade IV ependymomas usually arise in the **supratentorium.**
What is the classical pathologic feature of ependymomas?

Show Answer

Perivascular pseudorosettes are a classical pathologic feature of ependymomas.
What defines malignant ependymomas on pathology?

Show Answer

Greater number of mitoses, cellular atypia, and more necrosis
Which histopathologic subtype is most commonly found in the lumbosacral SC?

Show Answer

Myxopapillary ependymomas usually arise in the conus/filum region of the SC.
What is the typical presentation of ependymomas?

Show Answer

Depends on location. If infratentorial: CN deficits, ↑ ICP; if supratentorial: seizures, focal deficits
With what neurologic deficits are SC ependymoma pts likely to present?

Show Answer

Sensory deficits (vs. cord astrocytomas, which present with pain/motor deficits)

WORKUP/STAGING

What is the workup for ependymoma?

Show Answer

Ependymoma workup: H&P, basic labs, CSF cytology/sampling, and MRI brain/SC
When is LP contraindicated?

Show Answer

LP is contraindicated with a **PF tumor with surrounding mass effect.**
When should spinal MRI or CSF cytology be obtained after resection?

Show Answer

2 wks (10–14 days) postop to avoid false+.

TREATMENT/PROGNOSIS

What is the Tx paradigm for ependymoma?

Show Answer

Traditional ependymoma Tx paradigm: max safe resection with adj RT for children >3 yo (adj chemo if <3 yo)

Under what circumstances should CSI be done for ependymomas?

Show Answer

CSI should be done if **+CSF, +MRI neuroaxis, and ependymoblastoma** histology. For all others, local RT is sufficient.

What evidence supports the omission of CSI for anaplastic ependymomas after resection if there is no evidence of neuroaxial involvement?

Show Answer

Multiple retrospective reviews reveal the following: LR is the primary pattern of failure (>90%) regardless of field size; spinal seeding is uncommon without LR; and prophylaxis with CSI or WBRT does not affect survival when compared to local RT.

What is the role of chemo in ependymoma? What is the response rate?

Show Answer

Traditionally, chemo is utilized for <3 yo to delay RT and for salvage (cisplatin, VP-16, TMZ, and nitrosoureas). The response rate typically is 5%–15%. However, a prospective study from St. Jude's Children's Hospital (Merchant TE et al., Lancet Oncol 2009), which included many pts <3 yo (78%) treated with max safe resection and postop conformal RT to 59.4 Gy with 10-mm margin around postop bed, suggests that RT can be given safely and effectively for pts <3 yo. The 7-yr OS was 81%, EFS was 69%, and LC rate was 87.3% (cumulative LF rate is 16.3%). Therefore, young age should

not preclude pts from receiving high-dose RT after Sg, except for infants <1 yo. Current protocols require postop RT in completely resected infratentorial ependymoma starting at age 18 mos. If STR, chemo may be used to see if GTR is possible with 2nd-look Sg after 2 cycles of chemo.
What is the single most important favorable prognostic factor in ependymoma?

Show Answer

Completeness of surgical resection (correlates closely with LC for ependymomas)
What is the difference in 5-yr OS b/t GTR and STR for ependymomas?

Show Answer

75% vs. 35% (similar for low-grade vs. high-grade ependymomas)
What ependymoma locations are most amenable to GTR? Least?

Show Answer

Spinal (GTR ~100%) > supratentorial (80%) > infratentorial
What is given to children <3 yo after STR for ependymoma?

Show Answer

2 cycles of chemo can be used as a bridge Tx to see if GTR can be achieved. RT can be deferred with chemo until >18 mos, based on the St. Jude's trial (Merchant TE et al., Lancet Oncol 2009) and SEER analysis. (Koshy M et al., J Neurooncol 2011) Both suggest that postop RT in children <3 yo improves survival.
What types of chemo are typically used for ependymoma?

Show Answer

Cisplatin, cyclophosphamide, and etoposide are typical chemo agents for ependymoma.
What is the dose and volume of RT to be used if no CSI is given for

ependymomas?

Show Answer

Preop GTV + 1–2-cm margin to **54–59.4 Gy** (54 Gy for children <18 mos and >18 mos with GTR)
How is ependymoblastoma treated? What is the total dose to spine lesions vs. cranial lesions?

Show Answer

Treat like high-risk MB/PNET: **CSI 36 Gy + vincristine** +/– carboplatin, boost to cavity/gross Dz. 45–50.4 Gy if spine and 54–59.4 Gy if cranial → vincristine/Cytoxan/prednisolone 6 wks after RT.
How is infratentorial ependymoma managed?

Show Answer

Max safe resection f/b **involved field postop RT** to a dose of **54–59.4 Gy.**
How is supratentorial ependymoma managed?

Show Answer

If not anaplastic (i.e., if grades I–II), observation after max GTR is acceptable.
How is recurrent ependymoma managed?

Show Answer

If no prior RT: Sg → RT
If prior RT: Sg → stereotactic RT or chemo
Which phase II study showed min neurocognitive decrement with conformal/small RT fields?

Show Answer

St. Jude's study ACNS0121 (Merchant TE et al., JCO 2004): 88 pts, 33 pts with grade 3. 3-yr PFS was 74%. IQ testing was stable after 2 yrs.

What is a major reason infratentorial lesions should get adj RT, regardless of histologic grade?

Show Answer

Difficulty with complete resection d/t proximity to floor of 4th ventricle, or laterally protrusion through foramen of Luschka and involvement of CN nerves or CNS vessels → higher LR if infratentorial without RT

Which recent studies showed a benefit with adj RT after GTR for PF ependymomas?

Show Answer

Rogers L et al.: 10-yr LC GTR/RT 100% vs. 50% GTR alone. Nonsignificant benefit in 10-yr OS GTR (67%), GTR/RT (83%). (J Neurosurg 2005)

Merchant TE et al.: 5.3-yr median f/u update from the phase II study **ACNS0121**. All rcvd conformal RT to 59.4 Gy for NTR/all sites and grade, and for R0 infratentorial lesions of all histologies. Well-differentiated lesions after GTR were observed. Chemo for STR, then evaluated for Sg and RT. 7-yr OS was 81%, LC was 87.3%, and EFS was 69.1%. Median age 2.9 yrs, with 78% of the pts <3 yo. (Lancet Oncol 2009)

When is RT used in spinal ependymomas?

Show Answer

When resection is incomplete or anaplastic histology (Kaiser data: Volpp PB et al., IJROBP 2007)

What fields/doses are used for spinal ependymomas?

Show Answer

Primary tumor plus a 3–5 cm margin to 45 Gy (boost if below cord to 50.4–59.4 Gy)

What molecular subgrouping is associated with poor outcomes in ependymoma?

Show Answer

PF-EPN-A (Posterior Fossa, EPeNdymoma-A) subtype, the most common PF ependymoma subtype, is characterized by presentation in young children with gain of chromosome 1q in 25% of cases and associated with higher Dz recurrence and lower survival rates. (Pajtler KW et al., Cancer Cell 2015)
Do young children or young adults with ependymoma have a worse prognosis?

Show Answer

Children. Age <4 yrs is a poor prognostic factor.
Which ependymoma lesions have a poorer prognosis: supratentorial or infratentorial?

Show Answer

Supratentorial (↑ high grade and more STR) (Mansur DB et al., IJROBP 2005)
What are the 5- and 10-yr OS rates for pts with grades II–III ependymomas?

Show Answer

70% and 55%, respectively (Mansur DB et al., IJROBP 2005); no difference b/t grade II and grade III tumors (p = 0.71)
What % of ependymoma pts eventually die of their Dz?

Show Answer

50% of ependymoma pts eventually die of their Dz.

FOLLOW-UP/TOXICITY

How long of a f/u is required for pts with ependymoma?

Show Answer

At least **10 yrs,** b/c late recurrences of >12 yrs after Sg can occur.

What imaging is required during the f/u for ependymoma pts?

Show Answer

Craniospinal MRI q3 mos for yr 1–2, then q6 mos for the next 3 yrs.
What is a commonly used dose constraint for the SC?

Show Answer

45 Gy is the usual dose constraint for the SC.
What is a commonly used dose constraint for the chiasm?

Show Answer

50.4–54 Gy is the usual max point dose constraint for the chiasm.

9

Intracranial Germ Cell and Pineal Tumors

Updated by Harvey B. Wilds

BACKGROUND

What are the 2 broad categories of germ cell tumors?

Show Answer

Gonadal and extragonadal

Pineal tumors represent what % of adult and children's tumors?

Show Answer

Pediatric: 5%

Adult: 1%

Germ cell tumors represent what % of pediatric and adult brain tumors?

Show Answer

Pediatric: 0.5%–3% (more frequent in Japan and other Asian countries—up to 11%)

Adult: 1%

How would a "germinoma" of the testicles or ovaries be described?

Show Answer

Germinoma is referred to as seminoma in the testicles and dysgerminoma in the ovaries.

What are the most common sites of extragonadal germ cell tumors in adults? In children?

Show Answer

In adults: ant mediastinum, retroperitoneum, pineal/suprasellar regions
In children: sacrococcygeal and intracranial
What are the 2 subtypes of intracranial germ cell tumors? Which has a more favorable prognosis? Which is more common?

Show Answer

Germinoma and nongerminomatous germ cell tumor (NGGCT). Germinoma has a more favorable prognosis and requires less intensive therapy.
Germinomas are more common (two-thirds of all intracranial germ cell tumors).
What are 4 subtypes of intracranial NGGCTs?

Show Answer

Endodermal sinus tumor (yolk sac, elevated AFP), choriocarcinoma (elevated β-HCG), teratoma (immature and mature), embryonal (elevated placental alkaline phosphatase [PLAP]), and mixed (25% of NGGCT).
What are the median age at Dx and the sex/race predilection for intracranial germinomas?

Show Answer

10–12 yrs, males > females (2–3:1), **Asian** > white (4% vs. 1% pediatric CNS tumors in Asia vs. the United States)
Where do the majority of intracranial germinomas and NGGCTs arise?

Show Answer

Midline proximal 3rd ventricular structures: two-thirds pineal and one-third suprasellar. Other sites include basal ganglia, thalamus, cerebral hemisphere, and cerebellum. 5%–10% present with both pineal and

suprasellar tumors, may be bifocal rather than metastatic, and are usually pure germinomas.
What % of germinomas have CSF dissemination at Dx?

Show Answer

10%–15%
What is the probability of spinal failure in pts with various types of pineal-based tumors without evidence of spinal seeding at Dx?

Show Answer

- Mature and immature teratoma: 0%
- Mixed NGGCT: 4%
- Other NGGCT: 39% (teratomas with malignant transformation and yolk sac tumors)
- Germinoma: 17%
- Pineocytoma: 0%
- Pineal parenchymal tumor (PPT), pineoblastoma, or PPT of intermediate differentiation: 57%
- Pineoblastoma and NGGCT have the highest propensity for CSF dissemination. (Schild SE et al., Cancer 1996)

What is the typical presentation of a tumor in the pineal region?

Show Answer

↑ ICP (d/t obstructive hydrocephalus, causing, n/v, papilledema, lethargy, somnolence); Parinaud syndrome (decreased upward gaze, accommodates but abnl light response); endocrinopathies rare but DI sometimes observed.
Pressure/mass effect on what anatomic structure causes Parinaud syndrome?

Show Answer

Pressure/mass effect on the **sup colliculus** causes Parinaud syndrome.
How do pts with suprasellar masses present?

Show Answer

Triad of **visual** difficulties (bitemporal hemianopsia), **DI,** and precocious or delayed/**abnl sexual development.** Other aspects of hypothalamic/pituitary dysfunction possible, including GH deficiency, hypothyroidism, and adrenal insufficiency.

WORKUP/STAGING

What is the DDx for a pediatric brain tumor in the pineal region?

Show Answer

Pineoblastoma, pineocytoma, PPT of intermediate differentiation, germinoma, NGGCT, glioma, meningioma, lymphoma, benign cyst, Langerhans cell histiocytosis, hamartoma; most are germ cell tumors.

What is the DDx for a pediatric brain tumor in the suprasellar region?

Show Answer

Germinoma, NGGCT, craniopharyngioma, pituitary adenoma, meningioma, glioma, aneurysm, infection, mets

What is the workup for a suspected germ cell tumor?

Show Answer

Suspected germ cell tumor workup: H&P (esp CNs, funduscopic exam), MRI brain/spine, basic labs, serum AFP/β-HCG, CSF AFP/β-HCG (more sensitive than serum), and CSF cytology

What AFP levels exclude the Dx of a germinoma?

Show Answer

An **AFP >10 ng/mL** excludes the Dx of pure germinoma.

What a-HCG levels exclude the Dx of germinoma?

Show Answer

None are truly exclusive, but if the β-HCG is >50 ng/mL, then it probably is

not a germinoma. Very high levels are consistent with choriocarcinoma.
What stain definitively confirms the Dx of a germinoma?

Show Answer

PLAP staining confirms the Dx of germinoma.
What is the role of Sg in Dx of GCT?

Show Answer

If AFP and β-HCG are normal, Sg can distinguish pure germinoma or mature teratoma from other benign or malignant lesions. If β-HCG is elevated but normal AFP, Sg can distinguish β-HCG secreting germinoma from immature teratoma or choriocarcinoma (i.e., NGGCT).
What are the typical MRI findings of pure germinoma? Are there any distinctions on imaging from NGGCTs?

Show Answer

Homogeneous or heterogeneous pattern, hypointense T1, hyperintense T2, +Ca, cysts. These are indistinguishable from NGGCTs on imaging.
Historically, how was RT used in the Dx of intracranial germinomas?

Show Answer

Tumors were irradiated with a diagnostic dose of 10–20 Gy. If there was a response, then the Dx was germinoma and RT was continued to a definitive dose of 40–56 Gy. This is no longer done.
What staging system is used for intracranial GCTs M staging?

Show Answer

The **medulloblastoma staging** (modified Chang) system is used for staging of intracranial GCTs M staging, but usually M0 or M+ (disseminated) is adequate.

TREATMENT/PROGNOSIS

What is the most important prognostic factor in germ cell tumors?

Show Answer

Histology is the most important prognostic factor in germ cell tumors.
What is the prognosis of pure germinomas vs. NGGCTs?

Show Answer

The prognosis is **better for germinomas** (5-yr PFS >90% vs. 40%–70%, respectively).
Describe 2 Tx paradigms for localized pure germinomas.

Show Answer

Tx paradigms for localized germinoma:

1. Definitive RT
   or
2. Neoadj chemo → lower-dose RT

Describe the definitive RT technique for localized germinoma.

Show Answer

Whole ventricular radiation therapy (WVRT) to **21–24 Gy,** boost to primary tumor to 40–45 Gy
For which pineal tumor type is Sg generally not done?

Show Answer

Sg is generally not done for **germinomas,** since they are radiosensitive tumors and Sg can lead to morbidity. However, extent of resection is important for NGGCT.
What is the RT technique for disseminated germinoma?

Show Answer

CSI to 24 Gy, gross Dz **boost to 45 Gy**
Can chemo replace RT in the Tx of pure germinomas?

Show Answer

No. In a large CNS GCT study (Balmaceda C et al., JCO 1996), 45 germinomas were treated with carboplatin/etoposide/bleomycin. 84% had CR, but 48% recurred in 13 mos and 10% of pts died d/t Tx toxicity. >90% were salvaged by RT (ifosfamide/carboplatin/etoposide [ICE] × 3 → involved-field radiation therapy [IFRT] of 24 Gy).
What hypothesis is being tested in the current germinoma study ACNS1123?

Show Answer

ACNS1123 is attempting to determine **if neoadj chemo can help reduce RT doses and volumes in** localized **germinoma and NGGCT.**
Describe the RT technique with neoadj chemo for localized germinoma.

Show Answer

Reduced RT doses: CR to chemo: WVRT to **18 Gy;** boost to **30 Gy in 1.5 Gy/day in pts who achieve a CR on chemo on current COG protocol. PR/stable Dz to chemo, WVRT to 24 Gy +12 Gy boost**
In germinoma protocols, what does “occult multifocal germinoma” refer to? What is the boost volume?

Show Answer

Pineal-region tumor and DI. Boost volume is the enhancing tumor (pineal region), infundibular region, and the 3rd ventricle after WVRT.
In ACNS1123, what chemo agents are being tested?

Show Answer

Carboplatin, etoposide and ifosfamide are being tested in **ACNS1123.**
With pre-RT chemo, what are the RT doses in the experimental arm of ACNS1123 for germinoma?

Show Answer

In **ACNS1123,** the RT doses depend on the chemo response.

Induction chemo, carbo/etoposide × 3 cycles + alternating ifosfamide × 3 cycles—for a total 6 cycles of chemo.
If CR, WVRT to 18 Gy + boost to 30 Gy with IFRT alone.
If <CR, 24 Gy whole ventricular irradiation + 12-Gy boost.
What studies showed that even with CR to chemo, IFRT (without WVRT) may not be sufficient for localized germinoma?

Show Answer

SIOP CNS GCT96 (Calaminus G et al., Neurooncol 2013): M0 pts treated with CSI 24 Gy + 16-Gy boost (RT alone) vs. 2 × ICE → IFRT 40 Gy (CRT). 5-yr PFS was 88% for CRT vs. 97% with RT alone (p = 0.04); 5-yr OS was 92% vs. 94% (NS). All CRT failures were within the ventricular system. Conclusion: Suggest inclusion of ventricles in RT fields. In M+ Dz, they found reduced-dose CSI to 24 Gy was effective (98% EFS and OS).
What other evidence demonstrates that IFRT may not be sufficient for germinomas?

Show Answer

(Rogers SJ et al., Lancet Oncol 2005): literature review of 788 pts. There was a greater failure rate in focal RT vs. WBRT or WVRT + boost or CSI + boost (23% vs. 4%–8%). The pattern of relapse was mostly isolated spinal (11%), but there was no difference in WVRT vs. CSI in spinal relapse (3% vs. 1%). Conclusion: WVRT + boost should replace CSI. Similar findings were found in a **Seoul study.** (Eom KY et al., IJROBP 2008)
What early studies established the feasibility of RT dose reduction?

Show Answer

German MAKEI 83/86/89 studies (from 50 Gy to 34 Gy)
Describe 2 Tx paradigms for NGGCT.

Show Answer

NGGCT Tx paradigms:

- **Induction** platinum-based **chemo** 4–6 cycles → **CSI RT 30–36 Gy** (lower dose for CR) → **boost primary to 50.4–54 Gy;** Sg for residual or recurrent Dz
- Max surgical resection → adj platinum-based chemo; restage; if no neuroaxial involvement, consolidate with IFRT; if +neuroaxial Dz, CSI to 30–36 Gy, boost to 50.4 Gy

When is chemo indicated in the Tx of NGGCTs?

Show Answer

Chemo is **always** indicated for NGGCTs (influences survival).
What is the Tx paradigm for pineoblastoma?

Show Answer

Pineoblastoma Tx paradigm: treat as **high-risk** MB (CSI 36 Gy + local boost to 54 Gy)
What is the Tx paradigm for pineocytoma?

Show Answer

Pineocytoma Tx paradigm: treat like a low-grade glioma (GTR → observation; STR → consideration of adj RT or observation with Tx at the time of progression [50–54 Gy])
Which study showed that bifocal germinoma can be treated as localized Dz?

Show Answer

Canadian data (Lafay-Cousin L et al., IJROBP 2006): chemo and then limited-field RT (WVRT + boost) resulted in a CR.

FOLLOW-UP/TOXICITY

Which recent study showed better QOL with CRT (dose/field reduction)

than with RT alone?

Show Answer

Seoul study (Eom KY et al., IJROBP 2008), need for hormonal therapy: RT alone 69% vs. CRT 38% (however, all RT alone pts rcvd CSI)
What is the long-term rate of RT-induced 2nd CNS malignancies? What type is most common?

Show Answer

5%–10%; usually **glioblastoma multiforme**
What chemo agent should be avoided with brain RT? Why?

Show Answer

6-mercaptopurine. It is associated with **high rates of secondary HGGs.**

10

Craniopharyngioma

Updated by Amy Catherine Moreno

BACKGROUND

What is the origin of craniopharyngioma?

Show Answer

Epithelial tumor derived from **Rathke pouch,** the embryonic precursor to the ant pituitary

In what region of the brain does it usually arise?

Show Answer

Suprasellar region (most common), sella proper (less common)

Are craniopharyngiomas malignant?

Show Answer

No. They are histologically benign but behave aggressively with frequent LRs and **high risk of morbidity** d/t the location of Dz.

Appx how many cases of craniopharyngioma occur annually in the United States?

Show Answer

~300–350 cases/yr of craniopharyngioma in the United States, accounting for 1%–3% of all pediatric brain tumors.

At what ages does craniopharyngioma occur?

Show Answer

Commonly occur b/t ages 5–10 yrs. There is a bimodal distribution (5–15 yrs and 45–60 yrs); one-third of cases occur in pts aged 0–14 yrs.
What are the 2 histologic subtypes of craniopharyngioma?

Show Answer

Adamantinomatous and **papillary;** thought of as WHO grade 1 tumors.
Which subtype is characterized by a solid and cystic pattern?

Show Answer

Adamantinomatous craniopharyngioma has a solid and cystic pattern. A recent study suggests this histology has more frequent LR. (Pekmezci M et al., Neurosurgery 2010)
Historically, how has the cyst fluid consistency been described?

Show Answer

"Crankcase (machine) oil"–like (very **proteinaceous fluid** with cholesterol crystals)
What structures do cysts usually abut superiorly?

Show Answer

Tumors/cysts usually abut the **3rd ventricle and the hypothalamus** superiorly.
Name the most common presenting signs/Sx of craniopharyngioma.

Show Answer

- HA, n/v (i.e., ↑ **ICP**)
- Visual change (bitemporal hemianopsia)
- Endocrinopathies (TSH, GH, LH/FSH).

What is the most common hormone deficiency at presentation?

Show Answer

At presentation, **GH** is the most common hormone deficiency.
Do craniopharyngioma tumors respond rapidly or slowly to RT?

Show Answer

Craniopharyngioma tumors respond **slowly** to RT.

WORKUP/STAGING

What is the workup for a craniopharyngioma?

Show Answer

H&P, basic labs, endocrine/pituitary panel (ACTH, FH/LSH, IGF-1, TSH, T4, prolactin, AFP, β-HCG), and MRI of brain.
What ancillary studies need to be done before Tx?

Show Answer

Endocrine, audiology, vision, and neuropsychiatric studies
What is the classic appearance of craniopharyngiomas on CT/MRI?

Show Answer

Heterogenous partially **calcified** nodular suprasellar mass with associated cysts on CT/MRI.
What is the staging of craniopharyngioma?

Show Answer

There is **no formal staging.**

TREATMENT/PROGNOSIS

What is the Tx paradigm for craniopharyngioma?

Show Answer

Tx paradigm: **max safe resection**
While controversial, what is the favored Tx approach?

Show Answer

Conservative/STR + RT. The morbidity of a GTR can be detrimental. An STR spares some morbidity and has better QOL (e.g., St. Jude's data [2002] showed that the Sg group lost an avg of 9.8 IQ points; the more limited Sg + RT group lost an avg of 1.25 points).
What surgical approach is typically employed for craniopharyngioma resection?

Show Answer

Lat pterional approach (temporal craniotomy). Approach depends on location of tumor relative to 3rd ventricle and optic nerves.
What is the rate of GTR?

Show Answer

Large referral centers report GTR rates in **50%–79%** of pts.
What % of attempted craniopharyngioma GTRs result in STR?

Show Answer

Depends on location, but overall, **20%–30%.** (Tomita T et al., Childs Nerv Syst 2005)
Is observation ever appropriate after incomplete resection for craniopharyngioma?

Show Answer

Yes. Observation is especially appropriate in young pts. Adj and salvage therapy may have similar LC in closely followed pts. However, more surgical procedures often lead to higher morbidity.
What are the RT doses used for craniopharyngioma?

Show Answer

50.4–54 Gy with EBRT in 1.8 Gy/fx
What volumes are typically irradiated for craniopharyngioma?

Show Answer

GTV is residual tumor and cyst volume. CTV includes GTV + 0.5–1-cm margin and postop tumor bed. PTV is 3–5 mm expansion on CTV. **Be aware of cyst(s) and monitor during RT for possible adaptive RT planning.**
Estimate the 10-yr LC with Sg alone vs. Sg + postop RT for craniopharyngioma.

Show Answer

Sg (GTR + STR) alone **~42%;** Sg + RT **~84%.** (Stripp DC et al., IJROBP 2004)
Estimate the 10-yr LC with adj RT vs. salvage RT.

Show Answer

Similar rates. **Both ~83%–84%.** (Stripp DC et al., IJROBP 2004) RT can be deferred for children <5–7 yo after Sg.
With what methods can craniopharyngioma cysts be managed?

Show Answer

Aspiration of fluid; injection of radioactive isotope, bleomycin, or IFN. (Cavalheiro S et al., Neurosurg Focus 2010)
What isotopes have been used for intracystic RT and what do they deliver?

Show Answer

a-emitting isotopes (**yttrium-90, P-32**, Rh-186); **200–250 Gy** to the cyst wall, be aware of location of chiasm relative to cyst wall.
What is the energy and half-life of P-32 and to what depth is it effective?

Show Answer

0.7 MeV, 2 wks. The effective depth is **3–4 mm.**
What are the indications for intralesional cyst Tx (vs. cyst aspiration)?

Show Answer

Intralesional Tx is an option if the cyst is >50% of total tumor bulk and the number of cysts is ≤3 (ideal if there is a **solitary cyst**) or for those with **recurrent cysts** after prior resection.
What intracystic chemo has been used?

Show Answer

Bleomycin typically has been used for intralesional cyst management.
What is the typical response rate to intralesional bleomycin?

Show Answer

Limited data, **~65% ORR** (29% CR). Median PFS is 1.8 yrs. (Hukin J et al., Cancer 2007)
If a pt has worsening visual Sx while getting adj RT, is this likely d/t an acute side effect from RT?

Show Answer

No. Acute Sx during RT are likely d/t a **rapidly enlarging cystic component**; therefore, **urgent surgical intervention for decompression** should be considered. Radiographic cyst monitoring during RT is recommended to allow for smaller PTV. **15%** of cysts increase in size during RT.
Is there a dosimetric advantage to protons vs. photon therapy?

Show Answer

Yes. Compared to IMRT, proton therapy reduces integral dose to the brain and body. (Beltran C et al., IJROBP 2012; Boehling NS, IJROBP 2012)
What important Tx consideration is needed when treating with protons for craniopharyngioma?

Show Answer

Cyst dynamics. Frequent imaging is necessary when treating with protons (or any conformal techniques) to ensure adequate coverage of the cysts.

(Winkfield KM et al., IJROBP 2009) Merchant et al. showed that pts with more frequent cyst surveillance during RT had a lower rate of progression. (IJROBP 2013)
What factors have been shown to correlate with inf LC in craniopharyngioma?

Show Answer

Size > 5 cm (Joint Center data: Hetelekidis S et al., IJROBP 1993) and **RT dose < 55 Gy** (Pittsburgh data: Varlotto JM et al., IJROBP 2002)
What is the significance of cyst regrowth after RT?

Show Answer

Cyst regrowth may occur after definitive Tx (does not mean failure, as RT can take a long time to exert its ablative effects). Repeat aspirations are in order if the pt is symptomatic.
What study proposed a risk-stratification scheme to guide the aggressiveness/extent of Sg for craniopharyngioma?

Show Answer

A **French study by** Puget et al. showed significant reductions in endocrine and hypothalamic dysfunction if pts were stratified prospectively before Sg based on the degree of hypothalamic involvement: grades 0–1, attempt GTR; grade 2, STR (+ RT if >5 yo, observe if <5 yo). (J Neurosurg 2007)
What is the 10-yr OS of pts with craniopharyngioma?

Show Answer

10-yr OS is **70%–92%.**
What is the 20-yr OS of pts with craniopharyngioma?

Show Answer

The 20-yr OS is **76%.**
What are the 10-yr LC rates for pts with craniopharyngioma (by Tx)?

Show Answer

GTR/STR alone is about 42%.
Sg + RT is ~85%.
Adj RT vs. Salvage RT both 83%–84%.

FOLLOW-UP/TOXICITY

What is the mortality and morbidity rate from Sg for craniopharyngioma?

Show Answer

In modern series, mortality is **<4%.** Morbidity ranges b/t **8% and 14%.**
What are the most common/serious side effects of Sg?

Show Answer

DI, hypothalamic obesity, vision loss (<2%), and other hypothalamic injury (defective short-term memory, sleep disturbances)
What are the potential long-term side effects of RT?

Show Answer

Hypopituitarism (short stature, delayed puberty in 14%–50% depending on age), cognitive dysfunction or ↓IQ (10%), 2nd malignancy, and vasculopathy
The hypothalamus should be kept at or below what total RT dose?

Show Answer

If possible, the hypothalamus dose should not exceed **45 Gy.**
How long does it usually take for tumors to regrow? What f/u is needed?

Show Answer

2 yrs on avg. However, there is a wide range, and regrowth can take up to 9 yrs. Thus, the pt requires **long-term f/u** with serial MRIs and neuro-ophthalmology or endocrinology exams.

11

Hemangioblastoma

Updated by Harvey B. Wilds

BACKGROUND

What is the typical age of presentation for hemangioblastoma?

Show Answer

20–50 yrs is the typical age of presentation for hemangioblastoma (primarily in young adults).

Where do most hemangioblastomas arise anatomically?

Show Answer

Most hemangioblastomas arise in the **cerebellum.** They account for 7%–10% of tumors arising in the PF in adults. Other areas include the brainstem and SC.

What genetic disorder is associated with hemangioblastomas?

Show Answer

Von Hippel–Lindau (VHL; hemangioblastomas, pancreatic/renal cysts, RCC). Hemangioblastomas occur either sporadically (75%) or as a manifestation of VHL (25%).

Are hemangioblastomas benign/low grade or malignant/high grade?

Show Answer

Benign/low grade (WHO grade I)

What is the cell of origin or hemangioblastomas, and what is the associated pathology?

Show Answer

Endothelial stem cells; closely packed vascular lesions with a stroma of large oval “foamy” cells that result in a “clear cell” morphology.
The # of lesions seen in hemangioblastomas correlates with what in terms of etiology?

Show Answer

Single lesion (sporadic, older pts) **vs. multiple lesions** (VHL, younger pts)
What characteristics are common in hemangioblastomas associated with VHL?

Show Answer

Diagnosed at **younger age,** mean of 29 yrs.
Distribution is 50% in SC, 40% in cerebellum, and 10% brainstem. Usually, multiple lesions.
What hematologic abnormality is present in pts with hemangioblastomas? Why?

Show Answer

Polycythemia is present b/c of Epo production by the tumor.
How do hemangioblastomas cause morbidity if not treated?

Show Answer

Local compression and hemorrhage
What are common Sx of hemangioblastoma at presentation?

Show Answer

HA, hydrocephalus, and imbalance depending on location at presentation

WORKUP/STAGING

What steps are critical during the workup of a hemangioblastoma?

Show Answer

Thorough **neurologic exam and MRI** (craniospinal); **angiography** to aid in embolization before Sg

How do hemangioblastomas appear on MRI?

Show Answer

On MRI, hemangioblastomas can present as a **cyst with an enhancing mural nodule, or as a solid mass with or without a cystic component.**

TREATMENT/PROGNOSIS

What are the 2 main Tx approaches for hemangioblastoma?

Show Answer

Sg (max safe resection is curative and preferred) **and SRS**

What are the LC rates of Sg vs. SRS for hemangioblastomas?

Show Answer

Surgery: 50%–80%

SRS: 82%–92% at 2 yrs, 75% at 5 yrs

What is the SRS dose range used for the Tx of hemangioblastomas?

Show Answer

15–21 Gy to 50% IDL (dose ranged from 15–40 Gy with median dose of 22 Gy in Moss JM et al., Neurosurgery 2009)

What does the older dose–response data show for fractionated EBRT for the Tx of hemangioblastomas?

Show Answer

It showed **better results with higher doses.** (Smalley SR et al., IJROBP 1990: better OS with dose >50 Gy; Sung DI et al., Cancer 1982: better survival with 40–55 Gy vs. 20–36 Gy)

What are the traditionally employed EBRT doses for hemangioblastomas?

Show Answer

50–55 Gy at 1.8 or 2 Gy/fx

For cystic hemangioblastoma lesions, what component does not have to be removed during Sg?

Show Answer

If there is a negative margin, there is no need to remove the **entire cyst.** In this case, only the mural nodule/tumor should be removed.

When has RT (either SRS or EBRT) been traditionally used in the management of hemangioblastomas?

Show Answer

After recurrence (i.e., after definitive Sg or after STR for recurrence), for surgically inaccessible locations, or for pts with multiple lesions (i.e., VHL Dz)

For what type of hemangioblastoma lesions is fractionated EBRT a better choice than SRS?

Show Answer

Multiple tumors, larger lesions (>3 cm), and lesions in eloquent regions of the brain

Which hemangioblastoma pts have a better prognosis after EBRT: VHL+ or VHL- pts?

Show Answer

VHL+ pts have a better prognosis after EBRT. (PMH data: Koh ES et al., IJROBP 2007)

What is the prognostic significance of a cyst component after SRS for hemangioblastoma?

Show Answer

LC is worse if the tumor is cystic. (Japan data: Matsunaga S et al., Acta Neurochir 2007)

What is the median time to recurrence after EBRT or SRS for hemangioblastoma?

Show Answer

Hemangioblastomas tend to recur **2–4 yrs** after RT.

What is the pattern of failure after EBRT for pts with hemangioblastoma?

Show Answer

Failure is **predominantly local.**

FOLLOW-UP/TOXICITY

What is the surgical mortality rate of pts treated for hemangioblastoma?

Show Answer

The surgical mortality can be as high as **10%–20%** in pts treated for hemangioblastoma depending on location.

12

Brainstem Glioma

Updated by Harvey B. Wilds

BACKGROUND

What is the prevalence of brainstem gliomas (BSGs) in relation to pediatric CNS tumors overall?

Show Answer

BSGs comprise **10%–20% of pediatric primary CNS tumors** (<2% of adult CNS tumors).

What is the peak age of presentation for BSGs in children? What is the sex predilection?

Show Answer

The peak age of BSG presentation in children is **5–9 yrs. Males** are more commonly affected than females.

What are the 2 classes of BSGs? Where are they most commonly located, and what is the prognosis?

Show Answer

The 2 classes of BSGs are **focal and diffuse:**

Focal (20%): in the **upper midbrain/lower medulla;** best prognosis

Diffuse (80%): in the **pons and upper medulla;** infiltrative and worst prognosis

What are the anatomical subdivisions of BSGs?

Show Answer

Diffuse intrinsic pontine glioma (DIPG), exophytic medullary glioma, and midbrain or tectal glioma

What BSG histology most commonly involves the medulla? The pons? The midbrain?

Show Answer

BSG that arise from midbrain, medulla, and cervicomedullary junction are typically low grade (grade 1 or 2) and are focal, discrete, well-circumscribed tumors without local invasive growth or edema. Pontine gliomas are predominantly diffuse, high-grade, and locally infiltrative.

What mutation is present in most DIPGs?

Show Answer

Up to 85% of DIPGs have a **K27M** mutation in a **gene coding for histone 3.** (Cohen et al., Neuro-Oncology 2017)

Is grade prognostic for outcome in DIPG?

Show Answer

No. Although most DIPGs are high-grade, up to one-quarter are low grade and have a similarly dismal prognosis.

What is the median OS for DIPG?

Show Answer

9–11 mos

What is the median OS for focal BSGs?

Show Answer

- Tectal gliomas: more than 10 yrs
- Other than tectal gliomas, focal BSGs tend to behave like gliomas elsewhere in the brain and have OS reflecting the underlying histology

WORKUP/STAGING

What are some typical clinical findings with DIPG?

Show Answer

Typical findings with DIPG:

- CN palsy (CNs VI–VII)
- Ataxia
- Long tract signs (hyperreflexia, etc.)

What is the typical workup for a child with DIPG?

Show Answer

H&P, labs, MRI, typically no **Bx**

When should Bx be done for DIPG?

Show Answer

When mass lesions have an **unusual MRI appearance or** there is an **atypical clinical course.**

How is BSG staged?

Show Answer

There is **no formal staging** of BSG.

TREATMENT/PROGNOSIS

What is the typical Tx paradigm for DIPG?

Show Answer

Steroids/shunts → RT

Is there a role for concurrent and adj TMZ in DIPG?

Show Answer

No. Despite glioblastoma being the most common histology of DIPG, a COG study did not find a benefit of concurrent/adj TMZ. (Cohen KJ et al., Neuro

Oncol 2011)
Is there any benefit with other chemos in DIPG?

Show Answer

No. Although multiple chemo regimens have been tried, RT is the only modality that alters the course of DIPG.
What type of BSG is amenable to surgical resection?

Show Answer

Dorsally exophytic BSGs have a 75% 10-yr OS with Sg. These are usually pilocytic astrocytomas with a good prognosis.
What is the typical RT volume for DIPG?

Show Answer

Tumor as defined by MRI + a margin of 1–2 cm
What is the typical RT dose for DIPG?

Show Answer

The typical RT dose for DIPG is **54 Gy** in 1.8–2 Gy/fx.
What proportion of DIPG pts will have stabilization or improvement of Sx after RT?

Show Answer

After RT, **two-thirds** of pts will have stabilization or improvement of Sx.
Is there a role for hyperfx or dose escalation in DIPG?

Show Answer

No. Both did not improve survival in multiple POG/CCG trials (only better radiographic response at higher doses with greater radionecrosis and steroid dependence).
Is there a role for hypofx in BSG?

Show Answer

Yes. For pts with DIPG, RT over 3–4 wks offers equal OS and PFS as conventional RT with less Tx burden. (Janssens et al., IJROBP 2013; Zaghloul et al., Radiotherapy & Oncology 2014)

Is there a role for brachytherapy or GK boost after RT in BSG?

Show Answer

No. There is no role for brachytherapy or gamma knife boost after RT.

How are midbrain tectal plate tumors managed? What is their histology?

Show Answer

Tectal plate tumors are typically managed with **observation and a ventriculoperitoneal shunt** to relieve obstruction. They are typically **pilocytic astrocytomas** (indolent).

What are the major prognostic factors dictating outcome in pts with BSGs?

Show Answer

- Diffuse vs. focal
- Adult vs. child
- Histology (for BSGs other than DIPG)

What usually causes death in pts with BSGs?

Show Answer

Local expansion usually causes death in pts with BSGs.

FOLLOW-UP/TOXICITY

What is the RT dose tolerance of the brainstem?

Show Answer

The dose tolerance of the brainstem is **54 Gy** (if fractionated EBRT) and **12 Gy** (if SRS).

13

General Central Nervous System

Updated by Jennifer Logan

BACKGROUND

What is the estimated annual incidence of primary CNS tumors in the United States?

Show Answer

~80,000 cases/yr of CNS tumors (~1/3 of cases are malignant, 2/3 are nonmalignant tumors)

What is the most common intracranial tumor?

Show Answer

Brain mets (20%–40% of all cancer pts develop brain mets)

What are the most common primary histologies associated with brain mets?

Show Answer

Most common: lung, breast, melanoma

Which primary histologies are associated with hemorrhagic mets?

Show Answer

RCC, melanoma, and choriocarcinoma are associated with hemorrhagic mets.

Which primaries tend to metastasize to the PF?

Show Answer

GU/Pelvic primaries tend to go to the PF, where they are more likely to have a mass effect.
What is the most common type of primary CNS tumor in adults?

Show Answer

Meningioma (36%) > Glioma (25% of all primary cases, 80% of all malignant tumors)
What % of CNS tumors are mets vs. glioma vs. other?

Show Answer

Of all CNS tumors, roughly one-third are mets, one-third are gliomas, and one-third are other (meningioma, schwannoma, pituitary, lymphoma, etc.)
What % of adult astrocytomas are low grade vs. high grade?

Show Answer

25% low grade vs. 75% high grade
What is the most common histologic type of malignant CNS tumor in children? In adults?

Show Answer

Children: juvenile pilocytic astrocytoma (JPA) (20% <14 yo vs. 12% >14 yo)
Adults: GBM
What is the most common benign intracranial tumor in adults?

Show Answer

Meningioma
What is the strongest risk factor for developing CNS tumors?

Show Answer

Ionizing RT in children (no threshold—glioma, meningioma, nerve sheath)
What CNS tumors are linked to the following?

1. **NF-1**

2. **NF-2**
3. **Tuberous sclerosis**
4. **Von Hippel–Lindau**
5. **Li-Fraumeni**
6. **Cowden**
7. **Gorlin**
8. **Turcot**
9. **RB**
0. **Ataxia telangiectasia**
1. **MEN-1**

Show Answer

. Optic glioma, JPA
. Bilat acoustic neuroma, spinal ependymoma
. Subependymal giant cell astrocytoma, retinal hamartoma
. Hemangioblastoma
. Glioma
. Meningioma
. MB
. MB, GBM
. Pineoblastoma
. CNS lymphoma
. Pituitary adenoma

What are the 4 factors used for grading in the WHO brain tumor grading system?

Show Answer

Nuclear **A**typia
Cellularity and **M**itosis
Endothelial proliferation
Necrosis

(Mnemonic: **AMEN**)

WHO grade I = no factors present
WHO grade II = atypia
WHO grade III = atypia, mitoses
WHO grade IV = endothelial proliferation or necrosis
Which CNS entities/pathologies are known to cross midline?

Show Answer

GBM, RT necrosis, meningioma (extra-axial can spread along meninges to contralat side), epidermoid cyst, multiple sclerosis
What CNS tumors tend to have CSF spread?

Show Answer

MBs and other blastomas (except astroblastoma/GBM), CNS lymphoma, choroid plexus carcinomas, germ cell tumors, and mets
What is the pathway in which CSF flows?

Show Answer

CSF is produced by the choroid plexus → lat ventricles → foramen of Monroe → 3rd ventricle → cerebral aqueduct of Sylvius → 4th ventricle → foramen of Magendie, and 2 lat foramina of Lushka
What CNS tumors have Flexner–Wintersteiner rosettes?

Show Answer

Pineoblastoma and RB (any PNET)
What CNS tumors have psammoma bodies?

Show Answer

Meningioma and pituitary tumors (uncommon)
What CNS tumor type exhibits Verocay bodies? Schiller–Duval bodies?

Show Answer

Schwannomas exhibit Verocay bodies, and **yolk sac tumors** exhibit Schiller–Duval bodies.
Which CNS tumors have Homer Wright rosettes?

Show Answer

NB, MB, pinealoblastoma, and PNET
What CNS tumor has pseudorosettes?

Show Answer

Ependymoma
What receptors are commonly overexpressed in gliomas?

Show Answer

EGFR (30%–50% in GBM tumors) **and PDGFR** (non-GBM tumors)
Neural stem cells express which marker? Why are they important?

Show Answer

CD133. Neural stem cells are thought to be **precursors for astrocytomas.**
What gene on chromosome 17 is frequently lost in both low- and high-grade gliomas?

Show Answer

The **p53** gene is frequently lost in low- and high-grade gliomas.
What is the genetic mutation in NF-1, and for which sites does it predispose to gliomas?

Show Answer

In NF-1, the genetic mutation is **17q11.2/neurofibromin.** It predisposes to **optic/intracranial gliomas.**

WORKUP/STAGING

Which structures enhance on the MRI sequences, T_1, T_2, and FLAIR?

Show Answer

T_1 enhances fat and ST, does not enhance fluid. **T_1 with contrast** is generally the best way to visualize intracranial tumors. **T_2** enhances fluid (CSF, edema) and does not enhance fat. **FLAIR** removes the increased CSF signal on T2 and shows abnl fluid (masses and edema).
Which structures enhance with contrast?

Show Answer

Mets, **A**bscess, **G**BM, **L**ymphoma, +/– **A**A or **A**O [anaplastic astrocytoma/anaplastic oligodendroglioma]) (Mnemonic: **MAGLA**), meningioma, pilocytic astrocytoma, gliosis, cerebritis
Which structures do not enhance with contrast?

Show Answer

Grade 2 low-grade gliomas, +/– AA or AO, rare for GBM to not enhance.
Which gyri contain the sensory and motor area?

Show Answer

The precentral gyrus contains the motor area, and the postcentral gyrus contains the somatosensory area. Medial = body, LEs, feet. Lat = trunk, arms, head.
What brain region is associated with expressive aphasia?

Show Answer

The **Broca motor area** (dominant/left frontal lobe) is associated with expressive aphasia.
What brain region is associated with receptive aphasia?

Show Answer

The dominant/left temporal lobe at the post end of the lat sulcus **(Wernicke area)** is associated with receptive aphasia.

Which CN exits on the dorsal side of the brain (midbrain)?

Show Answer

CN IV exits on the dorsal side of the brain.
What structures are in the cavernous sinus?

Show Answer

CNs III, IV, VI, V1, and V2; internal carotid artery
What common defect does tumor involving the cavernous sinus produce?

Show Answer

CN VI palsy (no abduction of the lat rectus)
What components traverse the sup orbital fissure?

Show Answer

CNs III, IV, VI, and V1
What nerve passes through the foramen rotundum?

Show Answer

V2 passes through the foramen rotundum.
What nerve passes through the foramen ovale?

Show Answer

V3 passes through the foramen ovale.
What structures pass through the foramen spinosum?

Show Answer

The **middle meningeal artery and vein** as well as the **nervus spinosus** (branch of CN V3), pass through the foramen spinosum.
Through what structure do CNs VII–VIII traverse?

Show Answer

CNs VII–VIII traverse through the **internal auditory meatus.**

Through which foramen does CN VII traverse the skull base?

Show Answer

CN VII emerges through the **stylomastoid foramen.**
What passes through the jugular foramen?

Show Answer

CNs IX–XI pass through the jugular foramen.
How many spinal nerves are there in the SC?

Show Answer

There are **31 spinal nerves** in the SC (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal).
Where does the cord end? Where does the thecal sac end?

Show Answer

The cord ends at **L3–4 in children** and **L1–2 in adults.** The thecal sac ends at **S2–3 in both children and adults.**
What tumors present with a dural tail sign?

Show Answer

Meningioma (60%), also chloroma, lymphoma, and sarcoidosis

FOLLOW-UP/TOXICITY

Name some acute RT complications in pts receiving RT for CNS tumors.

Show Answer

Alopecia, dermatitis, fatigue, transient worsening of neurologic Sx, n/v, otitis externa, seizures, and edema
What is the timing and mechanism of somnolence syndrome?

Show Answer

6–12 wks post-RT, due to transient **demyelination** of axons

What are some common late complications of RT to the CNS? What is the timing for these?

Show Answer

Radionecrosis, leukoencephalopathy, retinopathy, cataracts, endocrine deficits, memory loss, learning deficits, and hearing loss; **3 mos to 3 yrs**

14

Low-Grade Glioma

Updated by Tommy Sheu

BACKGROUND

Low-grade gliomas (LGGs) account for what % of all primary brain tumors?

Show Answer

~10% of all primary brain tumors are LGGs.

Is there a racial predilection for LGG?

Show Answer

Yes. Whites are more commonly affected than blacks (2:1).

What are the histologic subtypes of LGGs?

Show Answer

Histologic subtypes of LGG (WHO 2016 update):

Grade I: pilocytic astrocytoma, subependymal giant cell tumor
Grade II: diffuse astrocytoma (fibrillary, protoplasmic, gemistocytic) including isocitrate dehydrogenase (IDH) mutant/wildtype; oligodendroglioma, IDH mutant/1p19q co-deleted; and oligoastrocytoma

What 4 pathologic features determine glioma grading?

Show Answer

Necrosis

Atypia
Mitotic figures
Endothelial proliferation

(Mnemonic: **NAME** or AMEN)
Which subtype of diffuse astrocytoma has the worst prognosis?

Show Answer

The **gemistocytic subtype** tends to de-differentiate and has the worst prognosis. Some prefer to treat it like a HGG.
Where anatomically does pilocytic astrocytoma most commonly present?

Show Answer

Most commonly presents in the **PF** (80% cerebellar, 20% supratentorial).
What pathologic feature is characteristic of pilocytic astrocytoma?

Show Answer

Rosenthal fibers are characteristic of pilocytic astrocytoma.
Where do grade II LGGs most commonly present?

Show Answer

Grade II LGGs most commonly present in the **supratentorium.**
What is the median age of Dx for pilocytic astrocytoma vs. other LGG?

Show Answer

The median age for **pilocytic astrocytoma is 10–20 yrs** and for grade II **LGG is 30–40 yrs.**
What genetic changes are important prognostic factors in LGG?

Show Answer

In LGG, **LOH 1p19q and IDH mutations** portend a better survival. **p53 mutation** indicates poorer survival and time to malignant transformation. IDH1 and IDH2 mutations are strongly associated with better prognosis.

What genetic change is prognostic in oligodendroglioma?

Show Answer

LOH 1p19q is prognostic in oligodendroglioma and is present in over 50% of cases. Associated with sup OS (MS 10 yrs in del 1p/19q vs. 3 yrs in intact) and PFS. (Jenkins RB et al., Cancer Res 2006)

What is the characteristic pathologic appearance of oligodendroglioma?

Show Answer

"Fried egg" appearance (round cells with nuclear halo) is characteristic of oligodendroglioma.

Where do most oligodendrogliomas occur in the brain?

Show Answer

Most oligodendrogliomas occur in the **hemispheres** (80%).

Anaplastic transformation from LGG to HGG occurs in what % of pts?

Show Answer

~70%–80% of pts with LGG will undergo anaplastic transformation (based on **EORTC 22845**).

What chromosome is affected in NF-1, and with what type of gliomas is it associated?

Show Answer

NF-1 is a result of a mutation on the long arm of **chromosome 17** (NF1/neurofibromin tumor suppressor gene) and is associated with **optic/intracranial gliomas**.

What chromosome is affected in tuberous sclerosis, and with what glioma is it associated?

Show Answer

Tuberous sclerosis is a result of a mutation on **chromosome 9** (TSC1 tumor

suppressor gene) or chromosome 16 (TSC2 tumor suppressor gene)and is associated with **subependymal giant cell astrocytoma**.
What syndrome is associated with gliomas and GI polyposis?

Show Answer

Turcot syndrome is associated with gliomas and polyposis.
With what Sx do LGGs most commonly present?

Show Answer

Seizures (60%–70%, better prognosis) > HA, focal neurologic Sx
What is the 5-yr OS of LGG?

Show Answer

The 5-yr OS is **60%–70%.**

WORKUP/STAGING

What is the workup for suspected glioma?

Show Answer

Suspected glioma workup: H&P, basic labs, and MRI brain
How should tissue be acquired for Dx?

Show Answer

Tissue should be acquired by **max safe resection** (per the NCCN), otherwise by stereotactic Bx.
What is the typical MRI characteristic seen in LGG?

Show Answer

On MRI, LGGs appear hypointense on T1, are **nonenhancing with gadolinium,** and show T2 prolongation.
What is the typical MRI appearance of pilocytic astrocytoma?

Show Answer

Well-circumscribed, cystic mass, intensely enhancing solid mural nodule
What % of nonenhancing lesions are grade III gliomas?

Show Answer

~**30%** are grade III gliomas (65% are LGG).
What feature has been associated with oligodendrogliomas on imaging?

Show Answer

Calcifications are a prominent feature on imaging of oligodendrogliomas.
What is suggestive of a malignant tumor on MR spectroscopy?

Show Answer

Increased choline (cell membrane marker), **low creatine** (energy metabolite), and **low** N-**acetyl-aspartate** (a neuronal marker) are suggestive of malignancy on MR spectroscopy.
What is the staging of LGG?

Show Answer

There is **no formal staging** for LGG.

TREATMENT/PROGNOSIS

What are the 5 negative prognostic factors for LGG as determined by EORTC 22844 and 22845?

Show Answer

Negative prognostic factors per the EORTC index:

. Age >40 yrs
. Astrocytoma histology
. Tumors ≥6 cm
. Tumors crossing midline
. Preop neurologic deficits

(Pignatti F et al., JCO 2002)

What is the general Tx paradigm used for LGGs?

Show Answer

LGG Tx paradigm: max safe resection → observation if low risk (≤40 yo and GTR) or adj RT +/– PCV chemo if high risk (>40 yo or STR).
What prospective data support initial observation over adj RT in LGG (early vs. delayed)?

Show Answer

EORTC 22845 ("Non-Believers Trial") randomized 314 LGG pts to early RT vs. delayed RT until time of progression. Concluded early RT lengthens PFS (5.3 yrs vs. 3.4 yrs) and seizure control (25% vs. 41%) but does not impact OS. (Van den Bent MJ et al., Lancet 2005)
What adj and salvage chemo regimens are typically used in LGG?

Show Answer

Chemo agents used in LGG:

- TMZ
- BCNU/CCNU (carmustine/lomustine)
- PCV (procarbazine/CCNU/vincristine)

What RT dose is typically used for LGG?

Show Answer

LGG is commonly treated to **50.4–54 Gy (1.8 Gy/fx)**
A complete resection can be achieved in what proportion of pts with LGGs?

Show Answer

Appx one-third of pts with LGGs have a GTR.
Within what timeframe should postop MRI be obtained for pts with LGGs? Why is it needed?

Show Answer

Postop MRI should be done within 48–72 hrs of Sg to assess for residual Dz/extent of resection.

In LGG, how are the RT Tx volumes defined, and what margins are typically used?

Show Answer

Per RTOG1072/ECOG E3F05:

GTV = cavity + T2/FLAIR + enhancement
CTV = GTV + 1 cm
PTV = CTV + 0.5 cm

In what clinical circumstances can adj RT be considered for LGGs?

Show Answer

- For pts >40 yo or with STR per RTOG 9802
- For pts with 3 of 5 high-risk features per the EORTC index (above). No LOH 1p19q or IDH mutation are also adverse features that may be considered.

What % of LGG pts undergoing initial observation in EORTC 22845 eventually required salvage RT?

Show Answer

In **EORTC 22845, 65% of pts** in the observation arm rcvd subsequent salvage RT.

What proportion of pts do not need salvage RT when observed after surgical resection for LGG?

Show Answer

Per EORTC 22845, appx **one-third** of pts will not require salvage RT.

In EORTC 22845, how did the OS after progression compare in the adj vs.

observation arms?

Show Answer

Survival after progression was better in initially observed pts, most of whom rcvd salvage RT. OS after 1st recurrence was **3.4 yrs vs. 1 yr** (SS).
Is there prospective evidence to support dose escalation with adj RT for LGG?

Show Answer

No. Dose escalation in LGG has been evaluated in 2 RCTs, neither of which showed a benefit:

- **EORTC 22844** randomized 343 pts to adj RT 45 Gy vs. 59.4 Gy. **There was no difference in 5-yr OS (58%–59%) or PFS (47%–50%).** (Karim AB et al., IJROBP 1996)
- INT/NCCTG randomized 203 pts to adj RT 50.4 Gy vs. 64.8 Gy. **There was no difference in 5-yr OS (65%–72%). 92% of failures were in-field.** (Shaw EG et al., JCO 2002)

Is adj therapy needed after GTR or STR for pilocytic astrocytoma in adults?

Show Answer

No. Brown et al. prospectively followed 20 young (<47 yo) adult pilocytic astrocytoma pts s/p GTR, STR (6 pts), or Bx (3 pts). **20-yr OS and PFS in GTR pts was 100%.** 20-yr OS and PFS for STR was 100% and 83%. (Neurooncol Pract 2015)
Is there a benefit of chemo with RT for LGGs with high-risk features?

Show Answer

RTOG 9802 stratified pts into low risk (age <40 yrs s/p GTR) and high risk (age >40 yrs or STR/Bx only). **High-risk pts were randomized to adj RT alone (54 Gy) vs. RT + PCV.** Outcomes were better in the chemo arm and

were SS after long-term f/u (10-yr OS: 40% vs. 60%; PFS: 21% vs. 51%). Benefit to actuarial PFS and OS were apparent after 2 and 4 yrs, respectively. (Buckner et al., NEJM 2016)

In RTOG 9802, what were the 5-yr OS and PFS for low-risk pts observed after GTR?

Show Answer

In **RTOG 9802,** low-risk pts (<40 yo s/p GTR) were observed and had **5-yr OS of 93% and PFS of 48%.** (Shaw et al., J Neurosurg 2008)

Is there a role for TMZ in the initial Tx of LGG?

Show Answer

Results of 2 trials are **preliminary:**

- **Intergroup EORTC 22033–26033** randomized 477 high-risk LGG pts (>1 of: age >40, progressive Dz, tumor ≥5 cm, tumor crossing midline, neurologic Sx) to adj RT vs. adj TMZ. Overall there was no difference in PFS or OS at 4 yrs. In exploratory analyses, pts with IDH mutations/1p19q noncodel had better PFS with RT compared to TMZ. IDH-wt and IDH-mt/codel pts saw no PFS difference b/t the 2 arms. (Baumert BG et al., Lancet Oncol 2016)
- **RTOG 0424** is a phase II study that enrolled high-risk LGG pts (3 of 5 EORTC features) and treated with RT (54 Gy) + concurrent TMZ then adj TMZ. Preliminary results show a 3-yr OS rate of 73%, which is higher than historic controls. The 3-yr PFS was 59.2%, however, 43% of pts had G3 adverse events. (Fisher BJ et al., IJROBP 2015)

For pilocytic astrocytoma, what is the estimated 10-yr and 20-yr RFS in pts treated with GTR alone?

Show Answer

10-yr and 20-yr RFS is **100%** in pilocytic astrocytoma pts treated with GTR alone. (Brown et al., Neurooncol Pract 2015)

In pts with oligodendroglioma/mixed oligodendroglioma, what is the median OS for those +/- LOH for 1p19q?

Show Answer

With LOH 1p19q: median OS ~13 yrs
Without LOH 1p19p: median OS ~9 yrs

(Jenkins RB et al., Cancer Res 2006)

FOLLOW-UP/SURVEILLANCE

How does RT affect QOL in the Tx of LGG?

Show Answer

QOL in LGG is impacted by **Sg, RT, chemo, and seizure meds.** Based on the **EORTC 22844** dose-escalation study, higher-dose RT was significantly associated with fatigue/malaise and insomnia and ↓ emotional functioning. (Kiebert GM et al., Eur J Cancer 1998)

Does RT predispose LGG lesions to malignant transformation?

Show Answer

No. RT is not associated with an ↑ rate of malignant transformation. In **EORTC 22845,** there was a 70% transformation rate in both the adj and observation arms.

What is the NCCN recommended radiographic surveillance frequency for LGG post Tx?

Show Answer

The recommended imaging frequency post Tx is MRI q3–6mos for 1st 5 yrs, then annually. (NCCN 2018) Chiasm is commonly constrained to **54 Gy** in 1.8–2 Gy/fx and **8 Gy** in a single fx.

What is the cause of somnolence syndrome after brain RT?

Show Answer

Somnolence syndrome is thought to be caused by **demyelination.**

15

High-Grade Glioma

Updated by Penny Fang

BACKGROUND

What % of primary CNS tumors are malignant?

Show Answer

~35% of primary brain tumors are considered malignant.
In adults, what is the most common malignant CNS neoplasm?

Show Answer

~80% of CNS neoplasms in adults are **glioblastoma** (GBM), which constitutes 20% of all primary tumors. ~26,000 new malignant primary brain tumors are diagnosed annually in the United States.
What are the WHO classifications for high-grade CNS tumors?

Show Answer

WHO III: anaplastic astrocytoma (AA)/anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA)
WHO IV: GBM
What are some common genetic changes seen in malignant brain tumors?

Show Answer

↑ EGFR (50%) and phosphatase and tensin homolog (PTEN) mutation (30%–40%)

What are the initial genetic changes associated with primary vs. secondary GBM?

Show Answer

Primary: ↑ EGFR/MDM2 amplification/LOH 10/p16 loss
Secondary: p53 mutation → LGG → LOH 19q/p16 loss → AA → LOH 10, DCC → 2nd GBM; IDH mutation is also very common in secondary GBM

What % of GBMs are multicentric?

Show Answer

<**5%** of GBMs are multicentric.

What are the 4 pathologic characteristics used for astrocytoma grading?

Show Answer

Nuclear **A**typia, **M**itoses, **E**ndothelial proliferation, and **N**ecrosis

(Mnemonic: **AMEN**)

What is the defining pathologic characteristic of GBM?

Show Answer

Necrosis

WORKUP/STAGING

What is the Cushing triad, and what does it represent in brain tumors?

Show Answer

HTN, bradycardia, respiratory irregularity. It represents ↑ ICP.

With what Sx do high-grade gliomas (HGGs) most commonly present?

Show Answer

HA (especially in the morning, 50%), seizures (20%), focal neurologic dysfunction, and mental status change

What are the common imaging characteristics of HGGs on MRI?

Show Answer

Hypodense on T1, **gadolinium enhancing,** T2 enhancing, and + T2 FLAIR (edema)

TREATMENT/PROGNOSIS

What is the MS for LGG vs. HGG?

Show Answer

Low grade: pure oligodendroglioma: 10 yrs; oligoastrocytoma: 7 yrs; AO: 5 yrs

High grade: AA: 3 yrs; GBM: 14 mos

What are the most important factors used for the recursive partitioning analysis (RPA) stratification?

Show Answer

Age 50 yrs, histology (AA or GBM), KPS of 70, MS changes, and Sx ≥3 mos

(Curran WJ et al., J Natl Cancer Inst 1993)

What is the MS of a pt with RPA classes I–II, III–IV vs. V–VI?

Show Answer

MS by RPA class:

Classes I–II: 40–60 mos (3–5 yrs)
Classes III–IV: 11–18 mos (1–1.5 yrs)
Classes V–VI: 5–9 mos

Under what RPA classes can GBM fall?

Show Answer

GBMs fall under **classes III–VI:**

Class III: <50 yo, KPS 90–100
Class IV: <50 yo, KPS <90 or >50 yo, good KPS

Class V: >50 yo, KPS <70 but no change in MS
Class VI: KPS <70 and MS change
On what is the current modified RPA based?

Show Answer

Outcomes with TMZ (Mirimanoff RO, JCO 2006)
What is the 4-yr OS and MS for RT + TMZ vs. RT alone for the adapted RPA groups for malignant gliomas (per Mirimanoff RO, ASTRO 2007 update)?

Show Answer

Overall survival: class III (<50 yo, PS 0): **28.4%** vs. 6.4%; class IV: **11.3%** vs. 3.3%; class V (>50 yo, Mini-Mental State Examination <27, Bx only): **6%** vs. 1%
Median survival: class III: 21 mos vs. 15 mos; class IV: 16 mos vs. 13 mos; class V: 10 mos vs. 9 mos
What additional factors did the European Nomogram (European GBM Calculator) investigate for stratification purposes?

Show Answer

MGMT methylation status and extent of resection; only MGMT, age, PS, and MS were prognostic (Gorlia T et al., Lancet Oncol 2008).
What is MGMT, and why is it important?

Show Answer

MGMT is a **DNA repair enzyme that removes alkyl groups from the O^6 position of guanine.** When methylated the MGMT gene is inactive and therefore, there is no ability to repair the damage caused by TMZ = chemosensitive. Methylated MGMT leads to increased OS regardless of the type of Tx.
What is the mechanism of action of TMZ?

Show Answer

Oral agent that crosslinks DNA (alkylating).
When should anticonvulsants be started?

Show Answer

Anticonvulsants should be started **only if the pt is symptomatic or has a Hx of seizures.**
What is the impact of resection extent in HGGs?

Show Answer

Data suggest that the extent of resection correlates with **improved outcomes.** (Sanai N et al., Neurosurgery 2008; Stummer W, Lancet Oncol 2006)
What is the Tx paradigm for AA and GBM?

Show Answer

AA Tx paradigm: Sg → RT to 56–59.4 Gy + TMZ or procarbazine, CCNU/lomustine, vincristine (PCV)
GBM Tx paradigm: Sg → RT to 60 Gy + TMZ → TMZ × 6 mos
What is the dose of TMZ, and how is it administered/scheduled?

Show Answer

Oral pill; 7 days/wk at **75 mg/m^2** concurrent with RT → 1-mo break → 6 cycles of adj TMZ at **150–200 mg/m^2** given 5 days of every 28 days
With the current Tx paradigm, what additional pharmacologic therapies are often necessary?

Show Answer

Steroids, proton pump inhibitors, and PCP prophylaxis
Which early GBM studies demonstrated significant (doubled) survival with RT vs. supportive care and helped RT become a standard component of Tx?

Show Answer

GBM studies showing significant survival benefit:

BTSG 69–01 (Walker MD et al.): randomized to observation, BCNU (carmustine), WBRT, and BCNU + WBRT. There was no difference b/t WBRT vs. WBRT + BCNU, but RT was better than no RT. (J Neurosurg 1978)

BTSG 72–01 (Walker MD et al.): Randomized to MeCCNU (semustine), RT alone, BCNU + RT, and semustine + RT. MS 3–6 mos without RT, 9–12 mos with RT. (NEJM 1980)

Scandinavian Glioblastoma Study Group (SGSG) (Kristiansen K et al.): 45 Gy + bleomycin vs. 45 Gy vs. observation: MS 10.8 mos vs. 10.8 mos vs. 5.2 mos (SS). (Cancer 1981)

Which randomized study supports the use of RT vs. best supportive care for the elderly with GBM?

Show Answer

French data (Keime-Guibert F et al.): pts >70 yo, KPS ≥70, to 50.4 Gy vs. observation. **MS improved with RT:** 6.7 mos vs. 3.9 mos. There was no difference in QOL or cognition. (NEJM 2007)

What studies support the use of hypofx in elderly GBM pts with a poor KPS?

Show Answer

Roa W et al. (JCO 2004), Bauman GS et al. (IJROBP 1994), Malmström A et al. (Lancet Oncol 2012), and Roa W et al. (JCO 2015) suggest feasibility of hypofx. The 1st 3 trials looked at hypofractionated courses vs. standard fractionation in pts >60–65 yrs or with poor KPS and showed hypofx was as good as or better than standard fractionation in terms of OS. Dose fractionation schemes included 40 Gy in 15 fx (Roa), 30 Gy in 10 fx (Bauman), and 34 Gy in 10 fx (Malmström). The 4th trial compared 25 Gy in

5 fx with 40 Gy in 15 fx, demonstrating noninferiority.
Which study suggested that WBRT is not required (i.e., that limited-field RT is sufficient) in the Tx of HGGs?

Show Answer

BTCG 80–01 (Shapiro WR et al., J Neurosurg 1989): prospective RCT, 510 pts, WBRT to 60 Gy vs. WBRT to 43 Gy → CD to 60 Gy. There was no difference in survival in the RT arms. This study also demonstrates that BCNU single agent is equivalent to a multiagent regimen.
What evidence supports current RT volumes being used in the Tx of HGGs?

Show Answer

Hochberg FH: CT correlation with postmortem tissue, CT abnl + 2-cm margin encompassed tumor extent by 83%. Recurrence by imaging also occurred within 2 cm of the margin in primary Dz in 90% of cases. (Neurology 1980)

Kelly PJ: correlated imaging (MRI + CT) with stereotactic Bx in untreated gliomas. The study found that isolated tumor cells extended at least as far as T2, suggesting that T1 enhancement is equivalent to GTV and a +T2 is equivalent to subclinical Dz. (J Neurosurg 1987)

What evidence supports the current RT dose of 60 Gy used for HGGs?

Show Answer

Combined analysis of 3 BTSG trials (Walker MD, IJROBP 1979): 4 doses (<45 Gy, 50 Gy, 55 Gy, and 60 Gy). MS was 4 mos, 7 mos, 9 mos, and 10 mos, respectively. MRC data (Bleehen NM et al., Br J Cancer 1991): RCT, 474 pts, 45 Gy vs. 60 Gy (no chemo). MS was 9 mos vs. 12 mos.
Is there evidence for a dose-escalation benefit beyond 60 Gy in HGGs?

Show Answer

No. There is no evidence for a dose-escalation benefit.

In **RTOG 7401,** there was no benefit for 70 Gy vs. 60 Gy in >600 pts. (Chang CH, Cancer 1983)

Chan JL et al. escalated the dose to 90 Gy without survival benefit. Of those who failed at 90 Gy, 91% failed in-field. (JCO 2002)

Is there evidence supporting RT hyperfx for GBM?

Show Answer

No. RTOG 8302: >700 pts, randomized phase I, 64.8 vs. 81 Gy bid. There was no benefit. **RTOG 9006** also showed no benefit.

Is there a benefit to radiosurgery boost for HGGs?

Show Answer

No. RTOG 9305 showed no benefit and higher toxicity. (Souhami L et al., IJROBP 2004)

Before the TMZ data, was there any benefit to CRT for HGGs?

Show Answer

Yes. This was shown by evidence from 2 large meta-analyses: The MRC Glioma Meta-analysis Trialist Group showed a small improved median PFS (7.5 mos vs. 6 mos) with chemo, reduced risk of death by 15%, and ↑ 1-yr OS by 6%. There was no RT dose–response with less or more than 60 Gy. (Stewart LA et al., Lancet 2002)

What is the evidence that supports the current gold standard in GBM Tx with TMZ?

Show Answer

EORTC/NCIC data (Stupp R et al., NEJM 2005 and 5-yr update Stupp R et al., Lancet Oncol 2009): 5-yr OS 10% (+ TMZ) vs. 2% (– TMZ), **MS 14.6 mos (+ TMZ) vs. 12 mos (– TMZ).** Benefit in all groups including ages 60–70. In pts with methylated MGMT there is a PFS benefit to TMZ + RT vs. RT alone.

Which modified RPA class did TMZ + RT not benefit significantly (per

Mirimanoff RO et al., JCO 2006)?

Show Answer

Class V. MS per RPA: class III, 17 mos; class IV, 15 mos; and class V, 10 mos. The only significant benefit of TMZ + RT vs. RT alone was in classes III–IV.
What is the role of MGMT methylation in terms of response to Tx with HGGs?

Show Answer

Greater response to TMZ + RT in those with methylated MGMT (Hegi ME et al., NEJM 2005; Mirimanoff RO, ASTRO 2007): 4-yr OS unmethylated (RT alone vs. RT + TMZ): **0% vs. 11%** and methylated **5% vs. 22%,** all SS
What data supports the use of TTFs as maintenance therapy in GBM?

Show Answer

Stupp et al., JAMA 2015 compared adj TMZ and TTFs vs. TMZ alone in pts receiving the Stupp regimen for newly diagnosed GBM. Median OS was improved in the TTF group (20.5 mos vs. 15.6 mos).
How are TTFs achieved and what is the proposed mechanism of action?

Show Answer

They are achieved via **transducer arrays on scalp** (worn >18 hrs/day) and are thought to interfere with **organelle assembly**/cell division.
What are the options for recurrent GBM?

Show Answer

TMZ, bevacizumab, reirradiation to ~35(10) Gy (Fogh SE et al., JCO 2010), radiosurgery, brachytherapy (GliaSite), Gliadel, TTFs or clinical trial
What are the approved uses of Gliadel?

Show Answer

FDA approval: recurrent Dz with re-resection improved survival advantage 31 vs. 23 wks. (Brem H et al., Lancet 1995)

In newly diagnosed adj setting: MS was 13.9 mos vs. 11.6 mos. (Westphal M, Neurooncol 2003)

What are the general guidelines for RT target volume delineation in GBMs?

Show Answer

RTOG:

Initial volume (46 Gy): GTV1 = T1/tumor bed + T2/FLAIR, CTV1 = GTV1 + 2 cm

Boost volume (14 Gy): GTV2 = T1/tumor bed, CTV2 = GTV2 + 2 cm. PTV adds 0.5 cm to all CTVs. Postop imaging (with MRI fusion) should be used for target delineation.

Alternative MDACC technique with SIB (Chang et al., IRJOBP 2007): GTV = T1/tumor bed, CTV = GTV + 2 cm. PTV 50 = CTV + 5-mm dose to 50 Gy in 30 fx, PTV 60 = GTV + 5-mm dose 60 Gy in 30 fx

Which study showed similar survival outcomes with adj RT vs. adj chemo with PCV or TMZ in WHO III gliomas (AA)?

Show Answer

German **NOA-04** study (Wick W et al., JCO 2009): same PFS/OS for all arms (RT alone or 2 chemo agents alone). Good predictors: extent of resection, oligo component (oligodendroglioma or oligoastrocytoma), IDH1 mutation, MGMT promoter hypermethylation, 1p19q codeletion. Toxicity: grades 3–4 hematologic toxicity was significantly higher for PCV than for TMZ.

Which study investigated sequential PCV → RT vs. RT alone in oligodendroglial tumors?

Show Answer

RTOG 9402/INT-0149 (Cairncross G et al., JCO 2006; Cairncross G et al., JCO 2013): AO or AOA s/p resection randomized to PCV × 4 → RT 59.4 Gy vs. RT alone. No median OS benefit. There was improved median PFS (8.4 yrs vs. 2.9 yrs) with chemo. Pt with 1p19q codeletion (unplanned subgroup analysis) had improved median OS with PCV vs. RT alone (14.7 vs. 7.3 yrs). PCV increased toxicity.
Which recent study investigated sequential RT → BCNU vs. RT alone in AA? What did it find?

Show Answer

EORTC 26882 (Hildebrand J et al., Eur J Cancer 2008): no OS or PFS difference
What study tested the role of adj PCV after RT in oligodendroglial tumors?

Show Answer

EORTC 26951 (Van den Bent MJ et al., JCO 2006; Van den Bent MJ et al., JCO 2013): With long-term f/u OS better with RT + PCV (24.3 mos vs. 13.2 mos). 1p19q deleted pts did better. There was no long-term difference in QOL after PCV.
What phase III study investigated the efficacy of combining RT with either TMZ or nitrosourea in anaplastic gliomas?

Show Answer

RTOG 9813 (Chang S, Neurooncol 2008): Study closed early with 201 pts enrolled. Showed increased toxicity with BCNU vs. TMZ.
What studies are investigating the role of TMZ in AO/AOA?

Show Answer

NCCTG N0577 (CODEL): pts **with** 1p19q codeletion randomized to RT + PCV vs. RT + TMZ → TMZ vs. TMZ × 12 cycles.
EORTC 26053 (CATNON): anaplastic gliomas **without** 1p19q del 2 × 2

randomization RT vs. RT + TMZ then observation vs. adj TMZ. Interim results presented at ASCO 2016 showed sup 5-yr OS with RT + TMZ (56%) vs. RT alone (44%).

What is the Tx paradigm for gliosarcoma?

Show Answer

Gliosarcoma Tx paradigm: treat like GBM (Sg → RT + TMZ → TMZ)

Which study tested dose-intensified TMZ after TMZ + RT?

Show Answer

RTOG 0525 (Gilbert M et al., ASCO 2011). This study randomized pts after TMZ + RT (after a 1-mo break) to TMZ on days 1–21 vs. standard days 1–5 for up to 12 cycles (max) depending on the response. Prelim results showed more toxicity in dose-dense arm and no difference in OS or PFS. Final data are pending as are neurocognitive and QOL results.

What ongoing phase III studies looked at bevacizumab in the upfront setting for GBM?

Show Answer

RTOG 0825 (Gilbert M et al., ASCO 2013): all treated with RT + TMZ then randomized to concurrent bevacizumab vs. placebo. Preliminary results show no OS or PFS benefit, but bevacizumab arm had worse QOL, cognitive function, and Sx burden.

AVAglio (Gilbert MR et al., NEJM 2014): all treated with RT + TMZ then randomized to bevacizumab vs. placebo. No OS benefit. Longer PFS 10.7 mos with bevacizumab vs. 7.3 mos with placebo.

FOLLOW-UP/SURVEILLANCE

What is the radiographic appearance of radionecrosis?

Show Answer

Central hypodensity, ring enhancement, edema, and low PET avidity (occurs

>6 mos post-RT)
What was the grade 3–4 toxicity rate from the Stupp R et al. trial (NEJM 2005) for the RT + TMZ arm? What main toxicity was noted?

Show Answer

7%; mostly hematologic from TMZ (thrombocytopenia and lymphocytopenia)
What does the f/u entail after RT for HGGs?

Show Answer

MRI 2–6-wks post-RT, then q2–4mos for yrs, then q6mos; weekly labs (blood counts) while on TMZ (NCCN 2018)
What % of HGG recurrences are local?

Show Answer

80%–90% of HGG recurrences are local.
What % of pts may show pseudoprogression after RT + TMZ?

Show Answer

Up to **50%** (Taal W et al., Cancer 2008)
Does MGMT promoter methylation status influence the incidence of pseudoprogression in HGGs?

Show Answer

Yes. MGMT methylation status increases the incidence of pseudoprogression after TMZ + RT. (Brandes AA et al., JCO 2008)

16

Optic Pathway Glioma

Updated by Hubert Pan

BACKGROUND

What is the typical age distribution of pts diagnosed with optic pathway gliomas (OPGs)?

Show Answer

OPGs occur mainly in **children**, with 90% diagnosed before age 20 and 75% before age 10.
OPG represents what % of all CNS tumors in children?

Show Answer

OPG represents **5%** of all CNS tumors in children.
What histologic grade is typical of OPG?

Show Answer

OPGs are typically **low grade.** Pilocytic astrocytoma (grade I) is the predominant histology. However, grade II has been reported.
What genetic syndrome is associated with OPG?

Show Answer

OPG is strongly associated with **NF-1.** Anywhere from 25% to 60% of pts with OPGs have NF-1. However, only 15%–20% of NF-1 pts have OPG (typically diagnosed before age 6 yrs), and only 1%–5% become

symptomatic.
What are the subtypes of OPGs?

Show Answer

OPGs are organized by location:

- Ant visual pathway (orbital, intracanalicular, and intracranial prechiasmal optic nerve)
- Post visual pathway (chiasm, hypothalamus, ant 3rd ventricle)

Which OPG subtype is more common in children with NF-1?

Show Answer

Ant OPG is more common in children with NF-1, while post OPG is more common in NF-1 negative children.
Which subtype has the worst prognosis?

Show Answer

Post (esp hypothalamic) OPG has the worst prognosis (OS **50%–80%**/LC **40%–60%**) vs. other types (OS **90%–100%**/LC **60%–90%**).
How do pts with OPGs typically present?

Show Answer

Orbital tumors often present with **painless proptosis.** Other Sx include ↓ visual acuity, visual field defects, changes in appetite or sleep/precocious puberty (hypothalamic), and new-onset HA and n/v (obstructive hydrocephalus).
What is the typical clinical course of OPG?

Show Answer

The clinical behavior of OPG is **variable in children,** including spontaneous regression and malignant degeneration. OPGs are **aggressive in adults,** reflecting the commonly underlying malignant histology.

WORKUP/STAGING

What is the workup for pts with suspected OPG?

Show Answer

Suspected OPG workup: H&P (including a neuro-ophthalmic exam with a quantitative visual acuity assessment), MRI brain and orbits, genetic evaluation, and baseline endocrinology

What is the DDx of an optic nerve mass?

Show Answer

Optic neuritis, glioma, RB, optic nerve meningioma, lymphoma, hamartoma

How do OPGs appear on MRI?

Show Answer

On MRI, OPGs appear as **well-circumscribed, homogeneously enhancing lesions** (isointense on T1 and iso- to hyperintense on T2). Contrast enhancement and presence of cysts are more common in sporadic OPGs than in NF-1 associated.

Is Bx necessary for Dx?

Show Answer

No. Imaging and the clinical exam are sufficient for OPG Dx.

TREATMENT/PROGNOSIS

What is the preferred initial Tx for pts with OPGs?

Show Answer

OPG Tx (controversial): Initial management most commonly is **observation.** Tx is typically reserved for pts with **documented progression or declining visual acuity.**

What is the Tx paradigm once pt progresses?

Show Answer

- Chemo: 1st step d/t risks of local therapy, especially if pt <10 yo
- RT: good tumor control option for older pts (>10 yo)
- Debulking Sg: reserved for refractory or symptomatic

What chemo agents are generally used for OPG?

Show Answer

Carboplatin + vincristine or cisplatin + etoposide

What data support prolonged chemo as a way of avoiding/delaying RT without compromising OS or visual function?

Show Answer

Laithier V et al. prospectively evaluated prolonged chemo (alternating procarbazine/carboplatin, etoposide/cisplatin, and vincristine/cyclophosphamide q3wks). 2nd-line chemo was given at relapse before RT. The objective response rate was 42%, 5-yr OS was 89%, and 5-yr freedom from RT was 61%. (JCO 2003)

What data support initial RT instead of initial chemo?

Show Answer

Awdeh RM et al. from St. Jude's prospectively followed 20 pts. (IJROBP 2012) Visual acuity was better in pts treated with upfront RT compared to those treated with chemo and RT as salvage therapy.

What were the findings of the Children's Oncology Group (COG) protocol (A9952)?

Show Answer

COG A9952 compared **chemo regimens** (carboplatin/vincristine vs. thioguanine/procarbazine/lomustine/vincristine) for unresectable low-grade glioma and found **no statistical difference in 5-year EFS** (39% for CV, 52% for TPCV, p = 0.10). (JCO 2012)

When is RT indicated in OPG?

Show Answer

RT is typically used after **chemo options are exhausted,** when there are **progressive Sx,** or when there is **intracranial extension.**
OPGs are typically treated using what RT dose, fractionation, and technique?

Show Answer

OPGs are typically treated to **45–54 Gy in 1.8 Gy/fx.** Proton therapy may have dosimetric advantages, especially in children. Fractionated stereotactically guided RT has good outcomes (5-yr PFS 72%). (Combs SE et al., IJROBP 2005)
What is the estimated 5-yr OS in OPG?

Show Answer

The estimated 5-yr OS is **89%.** (Laithier V et al., JCO 2003)

FOLLOW-UP/SURVEILLANCE

What is the main risk of Sg for OPGs?

Show Answer

Visual morbidity is the main surgical risk.
What are the more common late complications of RT in the Tx of OPGs?

Show Answer

Late complications of RT include **endocrine dysfunction, vasculopathy, and possible decline in visual acuity.**
What is a major disadvantage of RT in NF-1 pts?

Show Answer

High incidence of 2nd CNS tumors (RR 5.3: Sharif S et al., JCO 2006)
What is the RT TD 5/5 dose threshold for developing hypopituitarism?

Show Answer

The hypopituitarism TD 5/5 is **40–45 Gy** (GH levels ↓ 1st, then LH/FSH, f/b TSH/ACTH).

17

Primary Central Nervous System Lymphoma

Updated by Jennifer Chen Ho

BACKGROUND

What are the incidence and median age at Dx of PCNSL?

Show Answer

1,000 cases/yr of PCNSL; median age **55 yrs (immunocompetent)** vs. **35 yrs (immunocompromised)**

What % of primary brain tumors are PCNSL?

Show Answer

~4%

What is the sex predilection, and how does it relate to immunocompetency?

Show Answer

Immunocompetent pts: males > females (2:1)
AIDS pts: 95% males

What risk factors are often associated with CNS lymphoma?

Show Answer

Immunodeficiency (congenital or acquired) and EBV infection

What type of non-NHL is most often associated with PCNSL?

Show Answer

DLBCL is most often associated with PCNSL.
What % of PCNSL has ocular involvement?

Show Answer

15% of PCNSL has ocular involvement (vitreous, retina, choroid > optic nerve) that is typically bilat.
What is the most common genetic alteration seen in PCNSL?

Show Answer

The most common genetic alteration in PCNSL is the **gain of chromosome 12** (12p12–14), which corresponds to the amplification of MDM2 to enhance p53 suppression.
If the pt presents with ocular lymphoma, what % later develop CNS involvement?

Show Answer

75% of pts who present with ocular lymphoma develop CNS involvement.
With what is orbital lymphoma often associated?

Show Answer

Systemic NHL is often associated with orbital lymphoma.
What % of pts present with isolated SC/meningeal involvement?

Show Answer

<**5%** of pts present with isolated SC/meningeal involvement.
What proportion of pts present with CSF involvement?

Show Answer

One-third of pts present with CSF involvement.
What % of pts present with PCNSL but have a negative systemic lymphoma workup?

Show Answer

Nearly all pts (>95%) who present with PCNSL have a negative lymphoma workup, so if lymphoma is found outside the CNS, it is NHL with involvement of the CNS.
What are the high-risk features of systemic NHL that increase the risk of CNS mets?

Show Answer

Burkitt, lymphoblastic lymphoma, immunocompromised pt, BM+, parameningeal presentation (NPX, PNS), and testicular relapse
What % of pts present with multifocal Dz?

Show Answer

Immunocompetent pts: 50%
AIDS pts: 100%
What % of pts with grossly unifocal Dz are actually microscopically multifocal?

Show Answer

>90% of pts with grossly unifocal Dz are microscopically multifocal.
What % of AIDS pts develop CNS lymphoma?

Show Answer

2%–13% of AIDS pts develop CNS lymphoma. Invariably all are EBV+.
What has happened to the incidence of PCNSL over the past 30 yrs?

Show Answer

There has been a dramatic **increase** (3-fold) in immunocompetent and immunocompromised PCNSL pts.
In what regions of the CNS does PCNSL arise?

Show Answer

Brain, SC, leptomeninges, and globe (retina, vitreous)
What virus has been associated with PCNSL?

Show Answer

EBV has been associated with PCNSL (60% of immunocompromised cases).
Are B cells normally found in the CNS?

Show Answer

No. They develop as part of the pathologic process.
What is the more radioresistant NHL: intracranial or extracranial?

Show Answer

Intracranial. Per RTOG 8315, pts rcvd 40 Gy WBRT + 20 Gy boost and 25 of 41 pts (61%) failed in the brain.
What % of PCNSLs are supratentorial?

Show Answer

The majority of PCNSLs **(75%)** are supratentorial.

WORKUP/STAGING

With which CNS Sx do pts present?

Show Answer

Focal neurologic deficits (70%), neuropsychiatric/personality change (frontal lobe involvement [43%]), ↑ ICP ([33%] HA, n/v, CN VI deficit, blurred vision), seizures, leg weakness, urinary incontinence/retention, and ocular Sx (blurry vision)
With which systemic Sx do pts present?

Show Answer

Fever, night sweats, and weight loss (80%)
All PCNSLs are what stage? What type of NHL?

Show Answer

All PCNSLs are **stage IE.** PCNSL is considered an **extranodal NHL.**
What brain location and specific structures are commonly involved?

Show Answer

The #1 location is the **frontal lobe, often the deep white matter and frequently periventricular** (↑ CSF spread).
What are considered deep structures of the brain according to the International Extranodal Lymphoma Study Group (IELSG)?

Show Answer

Corpus callosum, basal ganglia, brainstem, and cerebellum
How is the Dx of ocular lymphoma made?

Show Answer

The Dx of ocular lymphoma is made by slit lamp exam and **vitrectomy.**
What infectious etiology is often confused with CNS lymphoma?

Show Answer

Toxoplasmosis is the infectious etiology often confused with CNS lymphoma.
What is the DDx?

Show Answer

Secondary metastatic lymphoma, other primary brain tumors, mets, abscess, hemorrhage, multiple sclerosis, sarcoidosis, and toxoplasmosis in AIDS
What is the 1st step if a pt has a brain MRI suggestive of lymphoma?

Show Answer

Bx of brain lesion, least invasive approach. Consider LP, if safe and would not delay Tx or diagnostic process, to obtain CSF (15–20 mL to increase diagnostic yield). If the MRI and CSF show unequivocal evidence of PCNSL,

brain Bx may be deferred (per NCCN). **Do not initiate steroids, if possible, prior to diagnostic procedure.**
What do you do if the Bx is nondiagnostic?

Show Answer

If the pt rcvd steroids prior to the Bx, then D/C the steroids and re-Bx when Dz progresses. If no steroids were given, can re-Bx or workup for other Dx.
What is the workup of a pt with a new Dx of CNS lymphoma (per NCCN 2018)?

Show Answer

Ophthalmic slit lamp exam to r/o ocular involvement, LP if safe, MRI spine if symptomatic or +CSF, CBC, CMP, LDH, HIV status, PET/CT or contrast-enhanced body CT, consider BM Bx, consider testicular US (men >60 yo)
What imaging studies should be performed?

Show Answer

MRI brain (MRI spine if Sx or CSF+), contrast-enhanced body CT or PET/CT
How does CNS lymphoma appear on MRI?

Show Answer

Indistinct fluffy borders, periventricular location common, T1 enhancement with gadolinium, and ring enhancement (d/t central necrosis, often seen in AIDS), less edema than would be expected for similar-sized glioma or mets
When is PCNSL more likely to be multifocal?

Show Answer

PCNSL is more likely to be multifocal when the **pt is immunocompromised** (50%–80% of such pts).
What chemical abnormalities are seen in the CSF of pts with CNS lymphoma?

Show Answer

↑ Protein (85%), ↓ glucose (33%), ↑ LDH, ↑ β2-microglobulin
What additional tests are necessary for AIDS pts with a possible Dx of CNS lymphoma?

Show Answer

Toxoplasmosis titer (r/o this and other opportunistic infections) and BM Bx
How can the Dx of PCNSL be most definitively established?

Show Answer

Bx brain/globe or CSF sampling
What are the 5 poor prognostic factors for PCNSL according to the IELSG?

Show Answer

Poor prognostic factors for PCNSL:

. Age >60 yrs
. ECOG PS >1
. Elevated LDH
. Elevated CSF protein
. Deep brain involvement (periventricular, basal ganglia, brainstem, cerebellum)

(Fererri AJ et al., JCO 2003)
What is the 2-yr OS for pts with 0–1, 2–3, and 4–5 factors?

Show Answer

2-yr OS for these pts is **80%, 50%, and 15%, respectively.** (Fererri AJ et al., JCO 2003)
What are other prognostic factors for PCNSL?

Show Answer

Poor response to chemo, AIDS, and multifocality

Who are considered “good-risk” immunocompromised pts with PCNSL?

Show Answer

Non-HIV immunosuppression and HIV+ with CD4 >200

TREATMENT/PROGNOSIS

What is the management paradigm for an immunocompetent pt with PCNSL and KPS ≥40?

Show Answer

PCNSL management paradigm: high-dose Mtx (good CNS penetration) based regimen. If CR: consider: high-dose chemo with stem cell rescue, high-dose cytarabine +/– etoposide, or low-dose WRT.

If no CR: WBRT, or consider high-dose cytarabine +/– etoposide, or best supportive care.

What is the management paradigm for a KPS <40?

Show Answer

Give steroids. If KPS improves, chemo, otherwise WBRT (24–36 Gy WBRT then boost to 45 Gy). (NCCN 2018)

What is the 1st intervention in a symptomatic pt after Bx?

Show Answer

The use of **high-dose steroids** is the 1st intervention in a symptomatic pt after Bx.

If a pt is suspected of harboring PCNSL, why should steroids not be started right away before obtaining a Bx?

Show Answer

Tumor regression (in 90%) with subsequent Bx yielding nondiagnostic results; Bx 1st → start of steroids (upfront steroids only for unstable pts)

How does the RT response differ b/t PCNSL and other types of extranodal NHL?

Show Answer

PCNSL is **very radioresistant** (5-yr OS is 4%). Extranodal NHL response is 90%.

How did the IELSG determine the prognostic groups that may predict for better survival?

Show Answer

Fererri AJ et al.: 378 pts from 1980–1999, **HIV–** with CNS lymphoma. All were treated with various regimens (+/– chemo, +/– RT). (JCO 2003)

How do survival outcomes differ b/t CRT and RT alone?

Show Answer

MS is ~44 mos (CRT) vs. ~10–18 mos (RT alone). 5-yr OS is 30% (CRT) vs. 5% (RT alone).

What % of pts are long-term survivors?

Show Answer

~15%–20% long-term survival in contemporary clinical trials of Mtx-based chemo (+/– RT).

What is the outcome of pts with ocular lymphoma?

Show Answer

The outcome of pts with ocular lymphoma is **uniformly fatal.** MS is only 6–18 mos.

Is cyclophosphamide HCl/doxorubicin/Oncovin/prednisone (CHOP) effective against PCNSL? Is cyclophosphamide HCl/doxorubicin/Oncovin/dexamethasone (CHOD) effective?

Show Answer

No. There is ineffective blood–brain barrier penetration. 3 RCTs, including **RTOG 8806** (Schultz C et al., JCO 1996), demonstrated no benefit of CHOP or CHOD.

What pts should be considered for WBRT after chemo and to what dose?

Show Answer

This should be decided based on the response to chemo. In general should be given to younger pts, as WBRT may increase neurotoxicity especially in pts >60 yrs. The dose depends on the response. For CR after chemo, give WBRT 23.4 Gy in 1.8 Gy fx. If <CR, give WBRT 30–36 Gy then boost gross Dz to 45 Gy. (NCCN 2018)

What were the results of the phase II trial on R-MPV f/b reduced-dose consolidative WBRT and cytarabine (Morris PG et al., JCO 2013)?

Show Answer

This was a multicenter phase II study of 52 pts receiving induction rituximab (Rituxan), Mtx, procarbazine, and vincristine (R-MPV) for 5–7 cycles, f/b reduced dose WBRT (23.4 Gy) for a CR or standrad WBRT (45 Gy) for nonCR. 60% had CR and rcvd reduced dose WBRT, with 3-year OS of 87% and 2-yr PFS of 77%. There was min neurotoxicity.

Which study demonstrated that an RT boost is not beneficial for PCNSL?

Show Answer

RTOG 8315 (phase II): WBRT 40 Gy → CD to 60 Gy. MS was 11.5 mos. 80% failed in the boost field.

What does the Memorial MSKCC data demonstrate on the use of high-dose Mtx + WBRT and the relation of age to developing neurotoxicity?

Show Answer

MSKCC data: phase II, 52 pts. MS was 60 mos. High-dose Mtx × 5 cycles (3.5 g/m^2) was Alt intrathecal Mtx (12 mg) → procarbazine/vincristine + WBRT 45 Gy → high-dose cytosine arabinoside (Ara-C) (intravenous 3 mg

× 2). Of those aged >60 yrs, some did not rcv RT. Survival was the same b/t no RT vs. RT, but DFS was worse if there was no RT. Those >60 yrs who rcvd RT had ↑ risk of neurotoxicity (83%) vs. age <60 yrs (6%). With chemo alone, only 1 pt developed neurotoxicity. (Abrey LE et al., JCO 2000)
In the Abrey study, what was the response rate to pre-RT chemo?

Show Answer

CR 56% and PR 33% **(ORR 89%).** (Abrey LE et al., JCO 2000)
In RTOG 9310, did 36 Gy (1.2 Gy bid) benefit PCNSL pts when compared to 45 Gy (conventional qd) WBRT?

Show Answer

RTOG 9310 (Fisher B et al., J Neurooncol 2005): no difference in control and survival, but worse neurotoxicity (23% vs. 4%); prospective study of Abrey chemo regimen → **45 Gy vs. 36 Gy bid** (if CR to chemo) (63 pts rcvd 45 Gy, and 16 pts rcvd 36 Gy. MS was 37 mos).
What were the results of RTOG 0227?

Show Answer

RTOG 0227 (Glass J et al., JCO 2016) was a phase I/II study of induction chemo with Mtx, rituximab, and TMZ, f/b hyperfractionated WBRT (hWBRT; 36 Gy in 1.2 Gy bid) and subsequent TMZ. In phase I, 13 pts rcvd increasing doses of TMZ, and in phase II, 53 pts were treated. 2-yr OS and PFS of 81% and 64%, respectively, were significantly improved compared to historical controls from RTOG 9310 (see above). 66% had G3/4 toxicity before hWBRT, and 45% had G3/4 toxicity attributed to hWBRT. Cognitive function and QOL improved/stabilized after hWBRT.
What did the RCT of +/- consolidative WBRT by Thiel et al. show (JCO 2010)?

Show Answer

This was a multicenter, randomized phase III, noninferiority trial of 318 pts

treated with high-dose Mtx + ifosfamide +/– WBRT. There was **no OS difference** (32.4 mos WBRT vs. 37.1 mos no WBRT). There was improved PFS in the WBRT arm but neurotoxicity was more common in the WBRT arm (49% vs. 26%).

What are the CR rates with chemo and deferred RT after chemo?

Show Answer

Several phase II trials have tested this approach of chemo with deferred RT, with CR rates ranging from 42% to 61%, and OS from 14 to 55 mos. However some pts did not achieve CR and need WBRT, and even among those with CR, ~half relapse.

In pts with failure after high-dose Mtx without prior RT, what are the Tx options?

Show Answer

If the response duration >12 mos, options include: re-treating with high-dose Mtx, other systemic therapy, high-dose therapy with stem cell rescue. If the response duration <12 mos, WBRT or involved field RT with/without chemo, or consider high-dose therapy with stem cell rescue.

What is the typical response rate to salvage WBRT for pts failing initial chemo?

Show Answer

CR 37%–58% and PR 21%–37% (Nguyen PL et al., JCO 2005; Hottinger AF et al., Neurology 2007)

What critical volumes need to be covered with WBRT?

Show Answer

The **post retina and CNS down to C2** need to be covered.

What volumes are treated with RT if the pt presents with an ocular primary?

Show Answer

WBRT to C2, + bilat orbits with opposed lats to 36 Gy → CD to WBRT + post retina to 45 Gy

How should AIDS+ PCNSL be treated?

Show Answer

The optimal therapy has not been well defined. High-dose Mtx therapy with steroids and antiretroviral therapy has been shown to offer palliation for up to 12–18 mos. In very select pts, can consider rituximab plus high-dose Mtx. WBRT has historically been the standard Tx, which leads to CR rates of 20%–50%, but survival is still very poor, ~3.5 mos.

What was the Tx regimen in RTOG 93–10? What was the MS?

Show Answer

Intravenous/intrathecal Mtx/vincristine/procarbazine → WBRT to 45 Gy → intravenous cytarabine. MS was **3 yrs.** (DeAngelis LM et al., JCO 2002)

What options are there for leptomeningeal PCNSL?

Show Answer

Intrathecal Mtx or high-dose Mtx. Alternative therapies include slow release cytarabine, systemic chemo, or CSI to 36 Gy with a boost to 45–50 Gy.

What is the Tx paradigm for ocular lymphoma?

Show Answer

Ocular lymphoma Tx paradigm: **RT to 36 Gy or intraocular chemo**

What is the rationale for omitting WBRT in the elderly with PCNSL?

Show Answer

Neurotoxicity in older pts (Abrey LE et al., JCO 2000): 80% of pts >60 yo had neurocognitive defects after 45 Gy; 6% if <60 yo. Some pts >60 yo did not get WBRT and had similar OS (worse DFS with no WBRT, however).

What is the WBRT dose for PCNSL after CR to chemo?

Show Answer

24–36 Gy. Consider omitting RT altogether if the pt is >60 yo.
What is the WBRT dose for PCNSL after PR to chemo?

Show Answer

36–45 Gy WBRT; focal CD to gross Dz to 45 Gy
What is 1 additional systemic option after RT, especially after PR to initial chemo?

Show Answer

Consolidation high-dose cytarabine +/- etoposide is an additional option after RT.
What is the role of rituximab in PCNSL? How can it be incorporated, and what studies support its use?

Show Answer

Can be used with Mtx/procarbazine/vincristine) as induction regimen → dose-reduced WBRT to 23.4 Gy if CR (45 Gy if PR) → Ara-C consolidation.
MSKCC data (Shah GD et al., JCO 2007): 2-yr OS, 67%, 2/3 pts had CR
Morris PG et al., JCO 2013: 3-yr OS 87%, 60% had CR
What is another consolidative option in pts with a CR to chemo?

Show Answer

High-dose chemo with stem cell rescue, based on several single-arm phase II studies. 1 multicenter phase II study (Illerhause G et al., Blood 2012) of 79 pts (<65 yrs) rcvd induction chemo with Mtx, cytarabine, thiotepa and rituximab → high-dose carmustine/thiotepa + auto HCT (only those without CR after HCT, n = 10, had WBRT). The CR was 27% after induction chemo and 77% after HCT. The 2-year OS was 87%.

What did RTOG 8315 investigate? What did it show?

Show Answer

RTOG 8315: RT alone/dose escalation (40 Gy + 20 Gy boost). There was high LR in the brain at 61% and significant neurotoxicity with higher doses. (Nelson DF et al., IJROBP 1992)

Which recent randomized international phase II study investigated the use of induction cytarabine for PCNSL? What did it find?

Show Answer

IELSG (Ferreri AJ et al., Lancet 2009): randomized to 4 cycles of Mtx vs. Mtx/cytarabine → WBRT. CR rates were 18% vs. 46% and ORR 40% and 69%, respectively.

What regimen was used in CALGB 50202 and what were the results?

Show Answer

Mtx, TMZ, and rituximab (MT-R) f/b etoposide/cytarabine consolidation (EA), with no WBRT. CR is 66% with 2-yr PFS of 57%—comparable to previous regimens with WBRT. (Rubenstein JL et al., JCO 2013)

FOLLOW-UP/SURVEILLANCE

What is the recommended radiographic f/u?

Show Answer

MRI q3 mos for 2 yrs, q6 mos for yrs 2–5, then annually (NCCN 2018)

What was the toxicity rate in the RTOG 93–10 study?

Show Answer

RTOG 93–10: 15% had severe delayed neurotoxicity (especially if >60 yo). (DeAngelis LM et al., JCO 2002)

What was the Tx-related mortality for pts treated with chemo alone in the German trials?

Show Answer

In German trials, Tx-related mortality with chemo alone was **9%.** PCNSL: results of a pilot and phase II study of systemic and intraventricular chemo with deferred radiotherapy. (Pels H et al., JCO 2003)

18

Meningioma

Updated by Jennifer Logan

BACKGROUND

What % of all primary CNS tumors do meningiomas account for in adults?

Show Answer

36%. Meningioma is the most common benign 1st-degree CNS tumor. (Central Brain Tumor Registry of the United States, 2016 update) Autopsy studies suggest prevalence of subclinical meningiomas in up to 3% of the general population.

What are the age and sex predilection for meningiomas?

Show Answer

The incidence of meningiomas **increases with age** (mean age at Dx 62, incidence peaks in the 8th decade). **Females** are more commonly affected than males (2:1).

What are some risk factors for meningiomas?

Show Answer

Prior RT (RR 10, median interval to development 20 yrs), **NF-2** (5%–15% risk of multiple meningiomas)**,** and **HRT** in women (RR 2).

Which protein is defective in NF-2, and to what else does NF-2 predispose?

Show Answer

Merlin; bilat acoustic neuromas/ependymomas and juvenile subcapsular cataracts

What histologic features can be seen in meningiomas?

Show Answer

Psammoma bodies and calcifications

List 5 negative prognostic factors for meningiomas.

Show Answer

Negative prognostic factors for meningiomas:

1. High grade
2. Young age
3. Chromosome alterations
4. Poor PS
5. STR

What is the grade classification of meningiomas?

Show Answer

WHO **grade I** (benign), **grade II** (atypical), **and grade III** (anaplastic/malignant)

According to the 2007 WHO classification, what criterion upgrades an otherwise grade I meningioma to grade II?

Show Answer

Brain invasion

What is the prevalence of grades II–III meningiomas?

Show Answer

6% and 4%, respectively. **90% are grade I.**

Name the histologies associated with WHO grades II–III meningiomas.

Show Answer

Grade II: atypical, clear cell, chordoid
Grade III: anaplastic, rhabdoid, papillary
Of grade I meningiomas, which histologic subtype is most aggressive?

Show Answer

The **angioblastic** subtype is the most aggressive grade I meningioma.
What is the OS difference b/t atypical and anaplastic meningiomas?

Show Answer

Atypical 12 yrs vs. anaplastic 3.3 yrs (Yang SY et al., J Neurol Neurosurg Psychiatry 2008)
What are some prognostic factors identified for anaplastic meningiomas?

Show Answer

Brain invasion, adj RT, extent of resection, and p53 overexpression (Yang SY et al., J Neurol Neurosurg Psychiatry 2008)

WORKUP/STAGING

What is the most common Sx at presentation for meningiomas?

Show Answer

HA is the most common presenting Sx.
What is the appearance of meningiomas on CT/MRI?

Show Answer

Homogeneously and intensely enhancing mass, +/– dural tail
What % of meningiomas exhibit a dural tail? In what other tumors/lesions can dural tails be seen?

Show Answer

60%. Dural tails can also be seen in **chloroma, lymphoma, and sarcoidosis.**
What proportion of incidentally found meningiomas remain stable on imaging?

Show Answer

Two-thirds. The majority remain stable on imaging.
For meningiomas, with what are slower growth rates associated?

Show Answer

Slower growth rates are associated with **older pts and calcifications.**
What surgical grading system is used in meningiomas? For what does it predict?

Show Answer

Simpson grade (I/GTR–V/decompression) predicts the **likelihood of LR.**
In what anatomic regions is GTR more difficult to achieve for meningioma resection?

Show Answer

Cavernous sinus, petroclival region, postsagittal sinus, and optic nerve
How is optic sheath meningioma diagnosed?

Show Answer

Optic sheath meningioma is diagnosed clinically/radiographically by a neuro-ophthalmologist/MRI (no Bx).

TREATMENT/PROGNOSIS

What are the Tx paradigms for meningiomas?

Show Answer

Meningioma Tx paradigms:

If incidental/asymptomatic: observation
If grade I and symptomatic/progressive: Sg + RT (if STR)
If grade II (high risk) or III: Sg + RT
For which types of meningioma is RT the primary Tx modality?

Show Answer

Optic nerve sheath and cavernous sinus (inaccessible regions)
When should observation be considered?

Show Answer

Observation should be considered with **incidental/asymptomatic and stable lesions.** Consider Sg for large (≥30 mm) lesions, if accessible.
When is RT utilized after Sg for meningiomas?

Show Answer

RT should be utilized after Sg if there is **recurrent Dz or STR** or if there is **anaplastic histology or brain invasion.**
What is the avg time to recurrence after Sg for meningiomas?

Show Answer

4 yrs is the avg time to recurrence after Sg.
What are the 10-yr recurrence rates with Sg alone after either GTR or STR?

Show Answer

10-yr recurrence rates with Sg alone are **~10% after GTR** and **60% after STR.**
Is there a benefit to upfront RT after STR for grade I meningioma?

Show Answer

This is **controversial** (upfront control rates are considered equivalent to salvage rates). RTOG 0539 showed RT benefit for WHO II (post-STR) and all WHO III tumors (Rogers L et al., NeuroOncol 2017) and may address this question in its low-risk cohort.
What are the RT doses employed for meningiomas?

Show Answer

RT doses are **45–54 Gy for benign** and **60 Gy for malignant** tumors (CTV = GTV + 1–2 cm).
Is there any RT dose–response data for meningiomas?

Show Answer

Yes. Goldsmith BJ et al. showed improved PFS with doses >52 Gy. (J Neurosurg 1994)
What are typical SRS doses used for meningiomas?

Show Answer

Typical SRS doses range from **12–16 Gy** to 50% IDL at the tumor margin (depending on location/size).
What is the 5-yr LC rate for meningiomas after SRS?

Show Answer

The 5-yr LC rate is **~95% for grade I tumors.** For grades II–III, it is 68% and 0%, respectively. (Stafford SL et al., Neurosurgery 2001)
What poor prognostic factors have been identified in pts receiving SRS for meningiomas?

Show Answer

Male sex, previous Sg, tumors located in parasagittal/falx/convexity regions (Pollock BE et al., Neurosurgery 2012)
Should the dural tail be covered in the RT field?

Show Answer

In general, no; however this is controversial. Some studies have shown improved 5-yr DFS when the dural tail was included in SRS Rx isodose. (DiBiase SJ et al., IJROBP 2004)

FOLLOW-UP/SURVEILLANCE

What is the surgical complication rate after resection for meningiomas?

Show Answer

After resection, the surgical complication rate is **2%–30%** depending on the location/type; 1%–14% mortality (worse in the elderly).
If observed, pts should get MRIs at what intervals?

Show Answer

At **3 mos, 6 mos, and 12 mos, then every 6–12 mos for 5 yrs,** then every 1–3 yrs if stable (NCCN 2018)
What is the toxicity rate for SRS if doses >16 Gy are used?

Show Answer

There is **temporary toxicity in 10%** of pts and **permanent toxicity in 6%** of pts. Perilesional edema is observed in 15%. (Kullova A et al., J Neurosurg 2007)
How are optic nerve sheath/cavernous sinus meningioma pts followed?

Show Answer

These pts should be followed with **serial MRIs, neuro-ophthalmology exams, and regular endocrinology exams.**

19

Pituitary Tumor

Updated by Jason T. Hayes

BACKGROUND

What is the % of pituitary tumors in relation to all primary brain tumors?

Show Answer

~10%–15% of all diagnosed primary brain tumors are of pituitary origin with up to 25% seen on autopsy series.

What % of pituitary tumors are functional vs. nonfunctional?

Show Answer

75% of pituitary tumors are functional, while **25%** are nonfunctional.

What are the sex and age predilection for pituitary tumors with symptomatic presentations?

Show Answer

Symptomatic pituitary tumors occur mostly in **females.** 70% occur from **30–50 yrs.**

What is a heritable syndrome that predispose to pituitary tumors, and what is the inheritance pattern?

Show Answer

MEN-1 (3 “Ps”: pituitary, parathyroid, pancreas), 11q13 mutant/menin. Autosomal dominant inheritance.

What is Nelson syndrome?

Show Answer

Nelson syndrome is **ACTH-secreting adenoma that develops after adrenalectomy** (pts can develop hyperpigmentation of the skin d/t a melanocyte-stimulating hormone). These may be less responsive to RT.
What are the embryonic derivatives of the ant pituitary vs. post pituitary?

Show Answer

Anterior: Rathke pouch (oral ectoderm)
Posterior: extension of the 3rd ventricle (neuroectoderm)
What is the name for the bony structure that houses the pituitary?

Show Answer

The **sella turcica** houses the pituitary.
What are the boundaries of the sella?

Show Answer

Tuberculum sellae anteriorly, dorsum sellae posteriorly, sphenoid sinus inferiorly, dural folds superiorly, and post clinoid processes laterally.
What CN deficit is most commonly caused by pituitary adenoma?

Show Answer

CN II. Pituitary adenomas are the most common cause of optic chiasm compression. Less commonly, CN III, CN IV, and CN VI deficits can cause ocular motility Sx.
What hormones are secreted by lobes of the pituitary?

Show Answer

Anterior: prolactin (PL), GH, ACTH, TSH, LH, FSH
Intermediate: melanocyte-stimulating hormone (MSH)
Posterior: ADH, oxytocin

What is the histopathologic description of the cells of nonfunctional tumors?

Show Answer

Histopathologically, the cells of nonfunctional tumors are **chromophobic.**
What hormones are secreted by basophilic cells? Acidophilic cells?

Show Answer

Basophilic: ACTH, TSH, LH, FSH
Acidophilic: GH, PL
What is the most common functional pituitary tumor? 2nd most common? 3rd most common?

Show Answer

Prolactinoma (30%) > GH (25%) > ACTH (~15%)
Which pituitary tumors are more common in males and the elderly? Which are more common in females?

Show Answer

Males and the elderly: nonfunctioning or GH
Females: PL and ACTH secreting
Which are the more common pituitary tumors: micro- or macroadenomas?

Show Answer

Macroadenomas (≥1 cm) are the more common pituitary tumors.
Which are the most common pituitary tumors in females?

Show Answer

Microadenomas (<1 cm) are the most common pituitary tumors in females, particularly those that are PL secreting.
What is the most common cause of pituitary dysfunction in adults? Children?

Show Answer

Adults: pituitary adenoma
Children: craniopharyngioma
What histologic features are prominent in prolactinomas?

Show Answer

Calcifications and amyloid deposits are prominent in prolactinomas.
What immunohistochemical stains are positive in pituitary adenomas?

Show Answer

Synaptophysin, chromogranin, and hormone-specific stains

WORKUP/STAGING

With what signs/Sx do pts with nonsecretory pituitary tumors present?

Show Answer

Bitemporal hemianopsia (optic chiasm compression), HA (↑ ICP), oculomotor deficits: CNs III–IV, VI, V1–V2 (cavernous sinus compression), hydrocephalus (3rd ventricle compression), hyperprolactinemia (disruption of PL suppression from hypothalamus d/t compression of pituitary stalk), or panhypopituitarism (from general glandular disruption).
With what signs/Sx do pts with secretory pituitary tumors present?

Show Answer

PL secreting (50%): galactorrhea, amenorrhea, infertility, and vaginal dryness for women, loss of libido, erectile dysfunction and infertility for men
GH secreting (25%): acromegaly
ACTH secreting (20%): Cushing Dz
TSH secreting (≤1%): hyperthyroid Sx
What is the DDx of a pt with a pituitary mass?

Show Answer

Pituitary tumor, craniopharyngioma, meningioma, glioma, suprasellar germ cell, mets, and benign lesions (cyst, aneurysm, empty sella syndrome)
What is the workup of a pt with a pituitary tumor?

Show Answer

Pituitary tumor workup: H&P (physical: CNs, visual field, endocrinopathy), labs, including hormone levels, thin-slice MRI through the base of skull, and tissue Dx (transsphenoidal resection)
What lab findings are suggestive of a prolactinoma?

Show Answer

Normal prolactin is ~2–25. If >100–200, prolactinoma is suspected, particularly in the setting of a pituitary mass.
What are other causes of elevated PL?

Show Answer

Pregnancy, lactation, polycystic ovary syndrome, **hypothyroidism** (thyroid-releasing hormone from hypothalamus stimulates PL secretion), **seizures, and cirrhosis**
What lab findings are suggestive of a GH adenoma?

Show Answer

GH >10 (not suppressed by glucose) and elevated IGF-1 are findings that suggest GH adenoma.
What lab abnormalities are noted in Cushing Dz?

Show Answer

High cortisol not suppressed by low-dose dexamethasone and normal or ↑ ACTH
What is Cushing syndrome?

Show Answer

Cushing syndrome is **elevated cortisol d/t a variety of causes** (e.g., adrenal production, exogenous use). Pts have low ACTH, unlike in Cushing Dz.
What primary malignancies most commonly metastasize to the pituitary?

Show Answer

Breast and lung cancer. Usually in the setting of diffuse metastatic Dz with >4 other sites.

TREATMENT/PROGNOSIS

What are the Tx paradigms of choice for the management of pituitary adenomas?

Show Answer

Can consider external RT alone for definitive local Tx with either stereotactic radiosurgery or FSR.

- Observation if small, nonsecreting microadenomas or prolactinomas
- Medical management with bromocriptine or cabergoline for a microadenoma prolactinoma not causing local Sx. However, 30% cannot tolerate bromocriptine d/t nausea, HA, and fatigue.
- Surgical resection if hypersecreting or symptomatic (d/t mass effect for nonsecreting tumors) → observation or postop RT if fail to suppress biochemically.

How long does it take for normalization of the PL level to occur after initiating Tx?

Show Answer

Normalization of the PL level takes **1–2 mos** following the initiation of pharmacologic suppression as compared to 2–5 yrs after radiotherapy.
What pharmacologic agents are used for GH-secreting pituitary adenomas?

Show Answer

Somatostatin, octreotide, and pegvisomant (GH receptor antagonist)
What pharmacologic agents are used for ACTH-secreting pituitary adenomas?

Show Answer

Ketoconazole (best), cyproheptadine (inhibits ACTH secretion), mitotane (↓ cortisol synthesis), RU-486 (blocks glucocorticoid receptor), and metyrapone
What is the hormone normalization rate after Sg for a hyperfunctioning pituitary tumor?

Show Answer

Hormone levels normalize in 80%–90% of those with microadenoma and ~65% of those with macroadenoma.
What types of surgical resection are used for pituitary tumors, and what are the indications?

Show Answer

Transsphenoidal microsurgery: for microadenomas, decompression, debulking of large tumors, reducing hyperfunctioning tumors
Frontal craniotomy: for large tumors with invasion into cavernous sinus, frontal/temporal lobes
What are the LC rates after transsphenoidal resection? Are they better for macroadenomas or microadenomas?

Show Answer

95%. LC rates are better for **microadenomas** after surgical resection.
What are some poor prognostic factors after transsphenoidal resection of prolactinoma?

Show Answer

Size >2 cm, high preop PL level, ↑ age, and longer duration of amenorrhea
What are some poor prognostic factors after surgical resection of GH-

secreting tumors?

Show Answer

High preop GH and somatomedin-C levels, tumors >1 cm, and extrasellar extension

Which pituitary tumors have a high recurrence rate after resection?

Show Answer

TSH-secreting tumors (risk factors: Hx of thyroid ablation, Hashimoto thyroiditis, prior RT/Sg)

What are the indications for radiotherapy in the Tx of pituitary tumors?

Show Answer

Pituitary tumor indications for radiotherapy:

- Medically inoperable or otherwise not felt to be good surgical candidate d/t proximity to vessels or cavernous sinus.
- Persistence of hormone defect after Sg
- Macroadenoma with STR or decompression
- Recurrent tumor after Sg

What are the long-term control rates for hormone-secreting tumors after RT?

Show Answer

Best outcomes with RT for GH-secreting tumors (80%) > ACTH (50%–80%) > PL (30%–40%)

What should be done with medical/pharmacologic Tx before initiating RT for pituitary adenomas?

Show Answer

Medical Tx **needs to be D/C** b/c of lower RT sensitivity with concurrent medical Tx. (Landolt AM et al., J Clin Endocrinol Metab 2000)

What is the typical LC rate with RT for pituitary tumors?

Show Answer

The LC after RT is >**90%** for most pituitary tumors. (Loeffler JS et al., J Clin Endocrinol Metab 2011)

What are the typical RT volumes and doses used for pituitary tumors?

Show Answer

With IMRT or proton beam therapy: Treat operative bed + gross Dz + 0.3–0.5 cm PTV; **45–50.4 Gy in 1.8 Gy/fx if postop with no gross Dz, 54 Gy for gross Dz.**

What evidence supports at least 45 Gy as the min effective RT dose for pituitary tumor control?

Show Answer

Older Florida data (McCollough WM et al., IJROBP 1991): 10-yr LC was 95%.

What are the indications for and the benefits of SRS in the Tx of pituitary adenomas?

Show Answer

SRS is used for **microadenomas** and yields **better control of hormone secretion** (same LC as fractionated and is more convenient).

What are the typical SRS doses used for functional vs. nonfunctional tumors?

Show Answer

Functional SRS dose: **~20 Gy**

Nonfunctional SRS dose: **~14–18 Gy**

What are the differences b/t LINAC-based and GK-based SRS for pituitary tumors?

Show Answer

With GK, there is **less homogeneous dose to the tumor, more precise setup, and slightly less normal tissue treated** (similar outcomes/conformality can be achieved with LINAC-based SRS, however).
When is FSR preferred instead of SRS for pituitary adenomas?

Show Answer

FSR is preferred **when the pituitary lesion is >3 cm and/or the lesion is <3 mm from the chiasm.**
What RT doses are used with fractionated EBRT?

Show Answer

45–50 Gy (nonfunctioning), 50–54 Gy (functioning).
What form of RT can be used to reduce dose to normal tissues with fractionated EBRT?

Show Answer

Proton therapy. The Loma Linda experience showed it to be effective. (Ronson BB et al., IJROBP 2006) However, long-term results needed to determine clinical results from normal tissue sparing.

FOLLOW-UP/SURVEILLANCE

What is the most common toxicity of pituitary irradiation?

Show Answer

Hypopituitarism. Risk is ~20% at 10 yrs post Tx (Brada et al., Clin Endocrinol 2002) with FSR or SRS. (Sheehan et al., J Neurosurg 2013)
What is the RT TD 5/5 TD threshold for developing hypopituitarism?

Show Answer

The TD 5/5 is **40–45 Gy.** GH levels ↓ 1st, then LH/FSH → TSH/ACTH.
What are the main benefits of using SRS for pituitary adenomas?

Show Answer

Benefits of SRS include ↓ **neurocognitive sequelae and possible preservation of normal pituitary function** by reducing the dose to the hypothalamus (↑ risk of damage to the optic nerve/chiasm).
What is the best way to assess the response to RT in GH-secreting tumors?

Show Answer

The response to RT can be assessed by **monitoring IGF-1 levels.**
What hormone is the 1st to respond/decrease after RT?

Show Answer

GH is the 1st hormone to respond/decrease after RT.
What is the operative mortality/complication rate after Sg?

Show Answer

Mortality: 1%–2%
Complication rate: 15%–20%
What are the most common surgical complications after resection of pituitary tumors?

Show Answer

DI (6%) → hyponatremia and CSF leak
Which pituitary pts/tumor types are prone to increased rates of 2nd malignancies after Tx with RT?

Show Answer

Men with **GH-secreting pituitary adenomas** tend to have increased rates of 2nd malignancies after RT. (Norberg L et al., Clin Endocrinol 2007)

20

Primary Spinal Cord Tumor

Updated by Jennifer Chen Ho, Boris Hristov, William Kempton Jeffrey Skinner, and Timothy Chan

BACKGROUND

At what level does the SC end in adults? Newborns?

Show Answer

Adults: L1–2
Newborns: L3–4
What is the filum terminale?

Show Answer

A **filamentous process that anchors the dural sac inferiorly to the coccyx.**
What is the conus medullaris?

Show Answer

The **inf/tapering portion of the SC**
What % of all primary CNS malignancies arise in the SC?

Show Answer

2%–4%
How are spinal tumors classified?

Show Answer

By their anatomic location, intramedullary tumors originate in the SC,

intradural-extramedullary tumors originate within the dura but outside the SC parenchyma, extradural tumors are outside the nervous system and often originate in the vertebrae.
What % of primary spinal tumors are extramedullary vs. intramedullary?

Show Answer

67% extramedullary and 33% intramedullary
What are the most common intramedullary spinal tumors?

Show Answer

Gliomas (ependymomas, astrocytomas, and less commonly, oligodendrogliomas); intramedullary mets are much less common.
What grade is most common for primary SC astrocytomas?

Show Answer

~>80% are **low grade**/WHO grades I–II (pilocytic/fibrillary).
What is the most common intramedullary tumor in adults, and at what age does presentation peak?

Show Answer

Ependymoma, peaking b/t 30 and 40 yrs
What is myxopapillary ependymoma and why is it considered to be a special case of ependymoma?

Show Answer

Ependymoma typically arising from the filum terminale, a **filamentous process that anchors the dural sac inferiorly to the coccyx.** These tumors are slow growing tumors biologically different from other ependymomas with propensity for seeding neuraxis.
In what part of the spine are ependymomas most commonly located?

Show Answer

Appx 50% occur in the lumbosacral spine or filum terminale and 50% in thoracic and cervical spine.
In what part of the spine are astrocytomas most commonly located, and with what are they associated?

Show Answer

Cervical/thoracic spine; associated with cysts in ~35%
What are the most common intradural-extramedullary spinal tumors?

Show Answer

Nerve sheath tumors (schwannomas and neurofibromas) and meningiomas
From what anatomic portion of the meninges do meningiomas arise?

Show Answer

Arachnoid
What are the most common extradural spinal tumors?

Show Answer

Mets, often arising in vertebral bodies
What are primary extradural spinal tumors?

Show Answer

Chordomas, sarcomas, lymphomas, plasmacytoma, multiple myeloma, Langerhans cell histiocytosis

WORKUP/STAGING

What is the most common presenting Sx of primary SC tumors, and over what timeframe do Sx present?

Show Answer

Pain (75%), with Sx presenting over **mos to yrs** (long prodrome)
What is particularly important as part of the workup for an SC tumor?

Show Answer

Detailed neurologic exam and SC imaging (MRI with contrast)
What is the difference b/t astrocytomas and ependymomas on MRI (location/appearance)?

Show Answer

Astrocytoma: T1: iso/hypointense, T2: hyperintense, T1 C+: majority patchy enhancement, eccentric/asymmetric expansion of SC
Ependymoma: T1: iso/hypointense, mixed if cyst/hemorrhage, T2: hyperintense, peritumor edema, T1 C+: almost all enhance, central/symmetric expansion of SC
What is the MRI appearance of SC lipomas?

Show Answer

Bright on T_1 without contrast, and **signal disappears on fat suppression.**
Which primary SC tumors require imaging of the entire craniospinal axis?

Show Answer

Ependymomas, GBM, and anaplastic astrocytomas

TREATMENT/PROGNOSIS

What is the Tx paradigm for primary SC tumors?

Show Answer

Primary SC tumor Tx paradigm: max resection +/– RT pending grade, extent of resection and progression of Dz or definitive RT alone
What are the 2 main advantages of upfront surgical resection?

Show Answer

Histologic confirmation and decompression of the cord
After GTR, which meningiomas—spinal or intracranial—have higher rates of recurrence?

Show Answer

Intracranial meningiomas have a 10%–20% recurrence rate, while spinal meningiomas have ~5% recurrence rate.
What is the most important predictor of recurrence for meningiomas/ependymomas?

Show Answer

Extent of resection. There are few recurrences after GTR.
In what % of SC meningioma/ependymoma pts is GTR achievable?

Show Answer

>90% of pts. (Retrospective series: Gezen F et al., Spine 1976; Peker S et al., J Neurosurg Sci 2005)
In what proportion of SC astrocytoma pts is GTR possible?

Show Answer

<15% of pts, d/t infiltrative nature of glioma (Raco et al., Neurosurg 2005)
Why is RT controversial for most SC tumors, even after STR?

Show Answer

Many SC tumors are indolent (slow growing), and there is **potential for SC toxicity** with RT.
What RT options are available after STR for ependymoma/meningioma?

Show Answer

Involved-field EBRT to a dose of 45–50 Gy. STR meningioma can often be observed with EBRT or SRS reserved for tumor regrowth.
Does WHO grade I or grade II spinal ependymoma carry a worse prognosis?

Show Answer

WHO grade I (Tarapore PE et al., Neurosurg 2013)

What Tx options are available for SC astrocytomas?

Show Answer

Low grade: observe after GTR/consider 45–50.4 Gy after STR or definite progression
High grade: 45–54 Gy

What retrospective series support RT in pediatric pts with low-grade SC astrocytomas?

Show Answer

JHH: After surgical resection, 12 of 29 pts rcvd RT to a median dose of 47.5 Gy. Acute RT toxicity was low grade, and long-term side effects were uncommon and manageable at median f/u of ~4.3 Gy. In 7 of 8 pts with low-grade tumors who rcvd adj or salvage RT, there was no Dz progression or recurrence. (Guss ZD et al., IJROBP 2013)

What retrospective studies support use of RT in SC astrocytomas?

Show Answer

- Postop RT improved survival in more aggressive infiltrative astrocytoma. Use of RT in pilocytic astrocytoma may be overtreatment. (Minhehan, IJROBP 2009)
- PMH: PFS was significantly influenced by RT in low- and intermediate-grade tumors; however, the RT group had fewer complete resections as c/w the Sg alone group (13% vs. 53%; p = 0.01). (Rodrigues GB et al., IJROBP 2000; Abdel-Wahab M et al., IJROBP 2006)

What data support the RT dose–response for SC ependymomas?

Show Answer

Garcia DM: <40 Gy, 23% OS; >40 Gy, 83% OS (IJROBP 1985)
Mayo Clinic data: 35% LF for <50 Gy vs. 20% for >50 Gy (Shaw EG et al., IJROBP 1986)

For what type of SC tumor has adj RT been shown to be beneficial, regardless of extent of resection?

Show Answer

Adj RT has been shown to be beneficial with **myxopapillary ependymoma.**
MDACC data: +/– 50.4 Gy RT 10-yr LC GTR/STR (55%/0%) vs. GTR + RT/STR + RT (90%/67%), all SS (Akyurek S et al., J Neurooncol 2006)
What RT schedule is often used for high-grade ependymomas with CSF spread?

Show Answer

CSI to 36 Gy + boost to 50.4–54 Gy gross Dz
What anatomic region needs to be covered with RT in caudal ependymomas?

Show Answer

The **thecal sac down to S2–3** needs to be covered.
What are the typical sup–inf RT margins for SC tumors?

Show Answer

The typical sup–inf margin required for SC tumors is **3–5 cm (1 vertebral body above and below tumor mass).**

FOLLOW-UP/TOXICITY

What is the Lhermitte sign? When does it occur, and what causes it?

Show Answer

The Lhermitte sign is **shocklike sensations in the extremities on neck flexion.** It occurs within **2–6 mos of RT** from **demyelination of the nerve tracts.**
When does RT myelopathy occur, and what is the temporal sequence of onset for neurologic deficits?

Show Answer

RT myelopathy occurs **13–29 mos** after RT, with paresthesia → weakness → pain/temperature loss → loss of bowel/bladder function.
Per QUANTEC, what is the risk of myelopathy with 1.8–2.0 Gy/fx to the full thickness of the cord at 54 Gy? At 61 Gy?

Show Answer

<1% at 54 Gy, <10% at 61 Gy (Kirkpatrick JP et al., IJROBP 2010)
Per QUANTEC, what is the risk of myelopathy with SRS to the cord to 13 Gy in 1 fx? To 20 Gy in 3 fx?

Show Answer

<1% with 13 Gy/1 fx, <1% with 20 Gy/3 fx (Kirkpatrick et al., IJROBP 2010)
Within what timeframe do SC astrocytoma pts usually relapse?

Show Answer

Relapse in SC astrocytoma pts usually occurs within **2 yrs** (most in-field).
How long of a f/u is required after SC ependymoma resection?

Show Answer

>10 yrs f/u is required, as **late recurrences** (**>12 yrs) have been reported** in 5%–10% of pts.
What region of the SC has traditionally been thought to be most sensitive to RT? Least sensitive?

Show Answer

The **lumbar SC is thought to be most sensitive** to RT, while the **cervical cord is thought to be least sensitive.**

21

Choroid Plexus Carcinoma and Papilloma

Updated by Boris Hristov

BACKGROUND

What is the function of the choroid plexus (CP) and where is it found?

Show Answer

The CP is located in the brain ventricles and is the tissue that produces CSF.
What % of intracranial neoplasms do CP tumors represent in children vs. adults?

Show Answer

CP tumors are more common in children, representing up to 5% of pediatric brain tumors vs. <1% of primary intracranial neoplasms in adults.
What are the most common locations of CP tumors in children vs. adults?

Show Answer

Children: Lat ventricles
Adults: 4th ventricle
What is the name for the benign CP variant, and how frequent is it? How about the malignant variant?

Show Answer

Benign variant: choroid plexus papilloma (CPP)/WHO grade I (60%–80% of

cases)

Malignant variant: choroid plexus carcinoma (CPC)/WHO grade III (20%–40% of cases)

What are the pathologic features of WHO grade I papillomas vs. WHO grade II atypical papillomas vs. WHO grade III carcinomas?

Show Answer

WHO grade I CPPs are characterized by papillary formation and lack of mitosis. WHO grade II atypical papillomas resemble WHO grade I papillomas but have more mitoses (≥2 mitoses per high-power field). WHO grade III CPCs are characterized by nuclear atypia, pleomorphism, frequent mitoses, and invasion of brain parenchyma. (WHO Classification of Tumors of the CNS, 4th ed. 2016)

With what syndrome is CPC associated?

Show Answer

Li–Fraumeni, d/t p53 mutation (Tabori U et al., JCO 2010)

What proportion of children present with metastatic Dz at Dx?

Show Answer

One-third of children present with metastatic Dz, all typically with CPC.

What is the most common age of presentation for these tumors?

Show Answer

70% of pts are **<2 yo.**

What % of CPCs can have CSF seeding? How about CPPs?

Show Answer

Up to 40% of CPCs have CSF seeding; seeding is **very rare for CPPs.**

What are the 2 most important prognostic/predictive factors for CP tumors?

Show Answer

Histologic grade and extent of resection
How does age affect prognosis?

Show Answer

Pts >40 yrs have poorer prognosis, f/b children <10 yrs. Those in the 10–40-yo group fare the best. Sex is not a prognostic factor.

WORKUP/STAGING

What are the 2 most common Sx at presentation in pts with CP tumors?

Show Answer

Hydrocephalus and HA (d/t CSF overproduction and flow obstruction)
What studies need to be performed during the workup for CP tumors?

Show Answer

MRI of brain and spine and CSF cytology
What is the differential for an intraventricular mass?

Show Answer

Ependymoma, subependymoma, central neurocytoma, subependymal giant cell astrocytoma, CPP, CPC, meningioma, mets. (Koeller KK et al., Radiographics 2002)
What are the radiologic features of CPPs vs. CPCs?

Show Answer

CPP: lobulated, solid, well-demarcated intraventricular mass that is isodense to mildly hyperdense on CT, often with calcifications. On MRI, homogeneous with intense contrast enhancement.

CPC: usually larger than papillomas with heterogeneous signal patterns on CT and MRI; may contain calcifications, necrosis, and hemorrhage and frequently invades brain parenchyma.

TREATMENT/PROGNOSIS

What is the general Tx paradigm for CP tumors?

Show Answer

CP tumor Tx paradigm: max safe resection (after embolization/chemo, if necessary) +/− chemo (younger pts) and/or RT (if age >3 yrs)

What are the indications for RT in pts with CP tumors?

Show Answer

Age >3 yrs and any of the following: carcinoma histology, +CSF/spine Dz (CSI), or recurrent tumors

What is the role of RT in CPPs after STR?

Show Answer

No RT is necessary upfront, as only 50% of STR pts require reoperation, surgical salvage is good, and reoperation may not be needed until yrs later. Consider RT if there is an STR after recurrence. (Mayo data: Krishnan S et al., J Neurooncol 2004)

What is the recommended EB dose for CPPs?

Show Answer

Conventional RT: **>50 Gy** to localized field

Stereotactic RT: **12 Gy to 50% IDL** (Pittsburgh data: Kim IY et al., J Neurosurg 2008)

What is the strongest indication for CSI?

Show Answer

Positive neuroaxis staging. If pt >3 yo, CSI can be given to 35 Gy f/b boost to primary site and/or mets up to 54 Gy.

What makes the resection of CPCs especially challenging?

Show Answer

CPCs are **very friable and extremely vascular.**
What can be attempted preoperatively to make resection easier?

Show Answer

Embolization (reduces intraop bleeding risk) or neoadj chemo
What agents may be used neoadjuvantly (after Bx and before 2nd-look Sg) for CPCs?

Show Answer

Ifosfamide, carboplatin, and etoposide (Wrede B et al., Anticancer Res 2005)
What data support the use of adj RT in CPCs?

Show Answer

Wrede B meta-analysis (Wrede B et al., J Neurooncol 2007): 5-yr OS 47% with RT and 25% w/o RT
Wolff JE et al., Br J Cancer 2002: for STR CPCs, 2-yr OS was 50% with RT and 0% w/o RT
What do the data show with regard to RT after GTR for CPC?

Show Answer

Study by Wolff JE et al., Lancet 1999 showed improved survival (5-yr OS was 68% with RT vs. 16% without) but only for older pts.
What meta-analysis supports the use of adj chemo for CPC?

Show Answer

Wrede meta-analysis (Wrede B et al., J Neurooncol 2007) of 857 pts; confirmed improved median OS rates (2.75 vs. 0.58 yrs) with adj chemo for subtotally resected CPCs.
What adj chemo arms were used in the CPT-SIOP-2000 study?

Show Answer

2 cycles of etoposide and vincristine with either carboplatin or

cyclophosphamide. (Werde B et al., J Neurooncol 2009)
What study supports delaying RT in very young children with CPCs?

Show Answer

"Baby" Pediatric Oncology Group study: 8 CPC pts treated with Sg, chemo, and delayed RT without any adverse sequelae. (Duffner PK et al., Pediatr Neurosurg 1995)
What data support CSI over smaller RT fields in CPC?

Show Answer

Mazloom A et al. reviewed the literature and found 56 pts with CPC; 5-yr PFS with CSI was 44.2% vs. 15.3% with smaller fields. (IJROBP 2010)
What is the 5-yr survival rate for CPPs?

Show Answer

The 5-yr survival rate is 80%–100% following GTR and 68% following STR.
What is the 5-yr survival rate for CPCs?

Show Answer

The 5-yr OS is only 20%–30%.

FOLLOW-UP/SURVEILLANCE

What are some prominent side effects from RT in the pediatric population with CP tumors?

Show Answer

Skull hypoplasia and neurocognitive/endocrine deficits
In pts with Li–Fraumeni syndrome, what long-term risk is of special concern after RT?

Show Answer

RT-induced 2nd malignancies

22

Arteriovenous Malformation

Updated by Jason T. Hayes

BACKGROUND

What is the avg age at presentation for arteriovenous malformations (AVMs)?

Show Answer

30 yrs (10–40 yrs)
What is the nidus of an AVM?

Show Answer

The nidus is a **tangle of abnl arteries/veins connected by at least 1 fistula.**
What is the main histologic abnormality in the vasculature of an AVM?

Show Answer

Absence of smooth muscle layer; ↑ venous pressure (fibromuscular thickening with incomplete elastic lamina)
What are the morbidity and mortality per bleed for AVMs?

Show Answer

Morbidity: 30%–50%/bleed
Mortality: 5%–10%/bleed (1%/yr)
What is the rate of hemorrhage per yr for AVMs?

Show Answer

AVMs have a 3% chance of hemorrhage/yr. After an initial hemorrhage this risk increases to 5%/yr.
Are most AVM cases familial or sporadic?

Show Answer

Most AVMs are **sporadic.**
What familial/genetic syndromes are associated with AVMs?

Show Answer

Osler–Weber–Rendu (hereditary hemorrhagic telangiectasia) **and Sturge–Weber syndromes** are associated with AVMs.
What characteristics portend an increased risk of hemorrhage from AVMs?

Show Answer

Previous hemorrhage, increased age, aneurysm, deep venous sinus drainage, deep location, single draining vein, and venous stenosis
Aneurysms are found in what % of pts with AVMs?

Show Answer

6%–8% of AVM pts harbor aneurysms.

WORKUP/STAGING

What are the common presenting signs of AVMs?

Show Answer

Intracerebral hemorrhage (42%–72%) > seizures (11%–33%) > HA > focal neurologic deficit. Children are more likely to present with hemorrhage than adults.
What imaging modality is ideal to r/o a bleed?

Show Answer

CT is ideal to r/o cerebral bleeds.

What is the gold standard imaging modality for AVMs?

Show Answer

Angiography is the gold standard modality for imaging AVMs.
What other imaging modalities can be used for AVMs? What are their advantages?

Show Answer

CT angiography (good vascular detail), MR angiography (good anatomy detail), functional MRI (eloquent areas), and diffusion tensor imaging (for white matter tracts)
What scale is used to evaluate AVM pts for Sg?

Show Answer

Spetzler–Martin scale/grading system (totals possible: I–V)
What 3 AVM characteristics in the Spetzler–Martin scale are predictive of surgical outcomes?

Show Answer

AVM characteristics that predict surgical outcome:

- **Diameter** (≤3 cm = 1, 3.1–6.0 cm = 2, >6 cm = 3)
- **Location** (noneloquent area = 0, eloquent area = 1)
- **Pattern of venous drainage** (superficial = 0, deep = 1)

How does AVM diameter/size scoring correlate with surgical outcomes?

Show Answer

The smaller the AVM diameter/size (<3 cm), the better the outcomes.
What brain areas are considered eloquent?

Show Answer

Eloquent areas include sensorimotor, language, visual, thalamus,

hypothalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.

TREATMENT/PROGNOSIS

What are the 3 Tx options for AVMs?

Show Answer

Sg, radiosurgery, and endovascular embolization
When is Tx indicated?

Show Answer

An Hx of previous rupture is the most important consideration; other factors include pts with an estimated elevated risk of future hemorrhage d/t younger age, AVM location, size, or other vascular features.
What is a simple way to approximate the risk of recurrence?

Show Answer

Lifetime risk of hemorrhage = 105 – pt age in yrs.
What is the goal of Tx with AVMs? Why?

Show Answer

Complete obliteration is the goal, there is **no benefit or decreased risk of bleed** if the obliteration is partial.
Is Tx of unruptured AVMs beneficial?

Show Answer

Possibly. The ARUBA trial is the only RCT to address this issue and compared medical management alone to medical management +interventional therapy (neurosurgery, SRS, or embolization). It was stopped early when the risk of death or stroke was found to be significantly lower in the medical management group (HR 0.27; 95% CI 0.14–0.54). (Mohr JP et al., Lancet 2014) However, in those pts who had imaging evidence of

obliteration, an 85% risk reduction of stroke was noted (HR 0.15; CI 0.02–0.53; p = 0.002). (Hanakita S et al., Stroke 2016)
Which lesions are most amenable to Sg?

Show Answer

Those with **low (I–III) Spetzler–Martin scores** are most amenable to Sg.
What is frequently done for grade III lesions before Sg?

Show Answer

Embolization can be performed for grade III lesions before Sg.
What is the main advantage of Sg?

Show Answer

Immediate cure and reduction in the risk of hemorrhage
For what AVM lesions is SRS preferred?

Show Answer

Radiosurgery is preferred for **lesions <3 cm that are located in deep or eloquent regions of the brain.**
What is the main disadvantage of SRS for AVMs?

Show Answer

The main disadvantage of SRS is the **lag time of 1–3 yrs to complete obliteration** (i.e., continued bleeding risk).
How does RT lead to AVM obliteration?

Show Answer

Vascular wall thickening (fibrointimal hyperplasia) **and luminal thrombosis** from RT effect result in obliteration of the AVM.
Is the bleeding risk completely eliminated after SRS?

Show Answer

No. It is reduced by ~54% during latency period and 88% after obliteration but not eliminated. (Maruyama K et al., NEJM 2005; Yen CP et al., Stroke 2011)

On what do SRS cure rates for AVMs primarily depend?

Show Answer

Size of AVM: 81%–91% if <3 cm, lower if >3 cm (Maruyama K et al., NEJM 2005)

What can be done for high-grade AVMs (IV–V) not amenable for Sg?

Show Answer

Staged SRS (different components targeted at separate sessions) (Sirin S et al., Neurosurg 2006)

For which AVMs can embolization be curative?

Show Answer

AVMs <1 cm that are fed by a single artery can be cured by embolization alone.

How are AVMs with feeding artery aneurysms managed?

Show Answer

If the aneurysm is >7 mm in diameter, clip or coil the aneurysm 1st, then treat the AVM. The aneurysm is at greater risk for rupture if the AVM is treated 1st.

What SRS doses are commonly used for AVMs?

Show Answer

Lesions <3 cm: **21–22 Gy** to 50% IDL. If the lesion is in the brainstem, lower the dose to ≤16 Gy.

Lesions >3 cm: **16–18 Gy** to 50% IDL.

FOLLOW-UP/SURVEILLANCE

What are the reported rates of permanent weakness or paralysis, aphasia, and hemianopsia for grades I–III AVM pts treated with Sg?

Show Answer

The rate of serious postsurgical complications is **0%–15%.**
What are the common early and delayed complications after SRS for AVMs?

Show Answer

Overall, there is about an 8% risk of RT-related complications.

Early: seizures (up to 10%), n/v, HA
Delayed: seizures, hemorrhage, radionecrosis (1%–3% risk), new neurologic deficits, edema, venous congestion, cyst formation

What is the incidence of transient vs. permanent neurologic complications after SRS for AVMs?

Show Answer

Complications after SRS for AVMs are as follows: **transient (5%) vs. permanent (1.4%).**
On what 2 factors do complication rates after SRS for AVMs primarily depend?

Show Answer

Size of AVM and RT dose
What does the f/u entail after Tx for AVMs?

Show Answer

Adequate f/u includes routine H&P + MRI q6 mos for 1–3 yrs, then annually.
What study needs to be performed once the MRI shows evidence of AVM obliteration?

Show Answer

An **angiogram** needs to be performed (in addition to MRI) to confirm complete AVM obliteration.

23

Vestibular Schwannoma/Acoustic Neuroma

Updated by Jennifer Logan

BACKGROUND

What is the cell of origin for vestibular schwannomas and acoustic neuromas (ANs)?

Show Answer

The **Schwann cell** of the myelin sheath is the cell of origin for ANs.
Which CN do ANs affect?

Show Answer

ANs affect **CN VIII.** Most affect the vestibular portion of the nerve.
In which anatomic region do ANs arise?

Show Answer

Most ANs are found in the **cerebellopontine angle** (CPA).
What are the most common presenting Sx, incidence, and what CNs are they associated with?

Show Answer

Hearing loss (95% of pts) and **tinnitus** (63%) → CN VIII; cochlear nerve unsteadiness/veering/tilting (61%) → CN VIII; vestibular nerve, facial paresthesia, or pain (17%) → CN V; facial paresis (6%) → CN VII.

(Matthies C and Samii M, Neurosurg 1997)
What is the median age at Dx?

Show Answer

50 yrs
Most people with symptomatic ANs will present b/t what ages?

Show Answer

Most symptomatic pts are **30–50 yo.**
What proportion of ANs are sporadic?

Show Answer

The **majority (90%)** are sporadic as well as unilat.
What % of ANs are bilat, and with what genetic abnormality are they associated?

Show Answer

10% are bilat and associated with **NF-2,** the tumor suppressor gene on chromosome 22.
What protein is abnl in NF-2 pts?

Show Answer

Merlin or schwannomin (involved in actin cytoskeleton organization)
What is the name of the anatomic layer of CN VIII that gives rise to most ANs?

Show Answer

The **Obersteiner–Redlich zone** (the junction b/t the central and peripheral myelin) gives rise to most ANs.
Subclinical ANs are present in what % of the general population?

Show Answer

Up to 1% (autopsy series) of the general population harbor subclinical ANs.
ANs account for what % of intracranial tumors?

Show Answer

5%–8% of intracranial tumors are ANs. Overall incidence is ~1/100,000 person-yrs.
Apart from NF-2, what are 2 other risk factors that predispose to the development of ANs?

Show Answer

Loud noise exposure (ORR 13) and parathyroid adenoma (ORR 3.4), childhood exposure to low-dose RT (RR per Gy 1.14).
What are the Antoni A and Antoni B areas on histopathology?

Show Answer

Antoni A and B are **zones of dense and sparse cellularity,** respectively.
For what do ANs stain on immunohistochemistry?

Show Answer

Most ANs stain for **S100.**
How do bilat ANs fare after Tx when compared to unilat ANs?

Show Answer

Bilat ANs have **similar failure rates** to unilat lesions if treated adequately.

WORKUP/STAGING

What tests are performed on physical exam for pts with CPA lesions?

Show Answer

Rinne test (mastoid bone, air conduction > bone conduction) and Weber test (occiput, vibratory sound louder on good side) to confirm sensorineural hearing loss; also need to check for other CN deficits (CN VII, hypesthesia, corneal twitching)

What CN is being tested when a pt is asked to tighten the ant neck muscles?

Show Answer

CN VII (innervates platysma muscle) can often be affected with large AN lesions.

Why are pts with CPA lesions often asked to march in place with their eyes closed on physical exam?

Show Answer

When the vestibular nerve is affected, **pts will often veer to the side of the lesion.**

What is the best initial screening test for ANs, and what does it usually show?

Show Answer

Audiometry (**asymmetric sensorineural loss,** more prominent at ↑ frequencies) is the best screening tool for ANs.

What is the avg growth rate per yr for ANs?

Show Answer

~1 mm/yr. Growth rates range from 0.5–2.5 mm/yr (slow-growing lesions) to ≥2.5 mm/yr (fast-growing lesions).

What % of ANs are stable (shrink/do not grow)?

Show Answer

~20%–40% of ANs are considered stable.

Is the size of the tumor at presentation predictive of the tumor's growth rate?

Show Answer

No. Tumor size is generally not predictive of the tumor's growth rate.

Does AN tumor size correlate with hearing loss?

Show Answer

Usually not. The location of the tumor (i.e., intracanalicular vs. not intracanalicular) is more predictive. Pts with tumor growth rate ≤2.5 mm/yr have higher hearing preservation than those with higher tumor growth. (Sughrue ME et al., J Neurosurg 2010)

What do brainstem auditory evoked potentials typically show in pts with ANs?

Show Answer

A **delay of conduction time on the affected side** is seen with auditory evoked potentials.

What imaging study is typically performed for ANs?

Show Answer

Thin-slice (1–1.5 mm) MRI with gadolinium. MRI can detect tumors as small as 1–2 mm in diameter. If NF is suspected, neuraxis MRI is performed. If pt cannot undergo MRI, high-resolution CT scan +/− contrast is the alternative.

To what is the "ice cream cone" appearance of ANs on MRI due?

Show Answer

This AN appearance is d/t **enhancing lesions in the canal (cone) and CPA (ice cream).**

TREATMENT/PROGNOSIS

What options are available for AN pts?

Show Answer

Observation, Sg, or RT

When is observation appropriate for ANs?

Show Answer

Observation is appropriate with small tumors (<2 cm) or no/slow growth without Sx progression. 43% with growth, **51% stable,** and 6% regressed without Tx. (Smouha EE et al., Laryngoscope 2005)
What f/u is required for AN pts opting for observation?

Show Answer

Audiometry and MRI scans q6–12 mo
What are the 4 surgical approaches available for ANs, and what are the prominent disadvantages/advantages of each?

Show Answer

Retromastoid: may not be able to achieve GTR/good facial nerve preservation, good **hearing preservation,** can be used for any size tumor
Middle cranial fossa: GTR, facial nerve preservation moderate-**hearing preservation** better, good for small <1.5-cm tumors
Translabyrinthine: sacrifices hearing/good facial nerve preservation, recommended if tumor >3 cm
Retrolabyrinthine: sacrifices hearing
When is Sg the preferred Tx option for ANs?

Show Answer

Sg is preferred for **large (>4 cm) symptomatic tumors or recurrence/progression after RT.**
What are the recurrence rates after GTR for ANs?

Show Answer

<1% (Samii M et al., J Neurosurg 2001; Guerin C et al., Ann Acad Med Singapore 1999; Gormley WB et al., Neurosurgery 1997)
What are the overall facial nerve and hearing preservation rates after Sg for ANs?

Show Answer

After Sg for ANs, there is an **80%–90% facial nerve preservation rate** and a **50% hearing preservation rate.**
What are the overall facial nerve and hearing preservation rates after RT for ANs?

Show Answer

With SRS: facial nerve preservation rate >95%, hearing preservation 70%–90%
With FSR: **~95% facial nerve preservation rate** and **~55%–65% hearing preservation rate**
What are the long-term LC rates after RT for ANs?

Show Answer

Long-term LC after RT for ANs is **90%–97%.** (Lunsford LD et al., J Neurosurg 2005; Combs SE et al., IJROBP 2006; Litre F et al., Radiother Oncol 2013; Hasegawa T et al., J Neurosurg 2013; Maniakas A et al., Otol Neurotol 2012)
What are some commonly employed doses when SRS/GK SRS is used for ANs?

Show Answer

12–13 Gy to 50% IDL is a commonly employed SRS regimen for ANs.
What has the dose trend been for the Tx of ANs with SRS?

Show Answer

The dose was **lowered from 16 Gy to 12–13 Gy.** Pittsburgh and Japanese data showed similar LC rates but less facial weakness and hearing loss with lower doses.
What doses are used with FSR?

Show Answer

50–55 Gy (in 25–30 fx at 1.8 Gy/fx) if larger (>2–3 cm) lesions. Alternative approach: **25 Gy (5 Gy × 5 fx)** with smaller lesions

What are the hearing preservation rates with FSR?

Show Answer

This is **controversial,** but hearing preservation rates are thought to be slightly better with FSR than with SRS or Sg (**94%** in Combs SE et al., IJROBP 2005; **81%** in Andrews DW et al., IJROBP 2001). Other studies suggest outcomes are equivalent if SRS dose <13 Gy. (Combs SW et al., IJROBP 2011)

What recent data suggest better hearing preservation and similar LC rates with lower-dose FSR?

Show Answer

Thomas Jefferson data: a lower dose of 46.8 Gy (vs. 50.4 Gy) had 100% LC at 5 yrs with a better hearing preservation rate. (Andrews DW et al., IJROBP 2009)

What other RT modalities have been successfully employed in AN?

Show Answer

CyberKnife (Chang SD et al., J Neurosurg 2005) and protons (Weber DC et al., Neurosurg 2003; Vernimmen FJ, Radiother Oncol 2009): worse hearing preservation (not used with tumors >2 cm and if pt can hear well)

What important AN studies prospectively compared Sg to SRS? What did they show?

Show Answer

Mayo Clinic data: <3-cm tumors, same tumor control rates but worse pt QOL after Sg. (Pollock BE et al., J Neurosurg 2006)

French data: largest prospective study. GK pts had better function overall. (Regis J et al., Neurochirurgie 2002)

Meta-analysis: included 16 studies showed SRS better long-term hearing

preservation (70% vs. 50%) but no difference in tumor outcome. (Maniakas A and Saliba I, Otol Neurotol 2012)

What AN study prospectively evaluated SRS vs. FSR?

Show Answer

Dutch data: dentate pts rcvd FSR (20–25 Gy in 5 fx) and edentate SRS (10–12.5 Gy), with similar LC and functional outcomes. (Meijer OW et al., IJROBP 2003)

What agent has recently been shown to be effective in NF-2 pts with refractory ANs?

Show Answer

Bevacizumab (Avastin) was recently shown to be effective in NF-2 pts with refractory ANs. (Plotkin SR et al., NEJM 2009)

FOLLOW-UP/TOXICITY

The dose falloff to which structures needs to be carefully evaluated with GK SRS for ANs?

Show Answer

Cochlea and brainstem doses need to be carefully evaluated with GK SRS.

What IDL is prescribed in GK? Why? How about for LINAC-based SRS?

Show Answer

GK: **50%** (sharpest drop-off in dose is at 50% IDL)

LINAC: **80%**

What is the difference in the onset of side effects after Sg vs. RT for ANs?

Show Answer

Side effects present **upfront/immediately after Sg vs. in a delayed/gradual (mos to yrs) fashion after RT.**

What is the dose threshold above which hearing preservation rates

decrease with RT?

Show Answer

Preservation rates decrease at doses **>13 Gy.** (Japanese data: Hasegawa T et al., J Neurosurg 2005)
What mean cochlea dose is the threshold for hearing preservation with SRS?

Show Answer

Mean cochlea 3 Gy. 2-yr hearing preservation 91% if mean cochlea <3 Gy vs. 59% if >3 Gy (Baschnagel J et al., Neurosurg 2013)
What are some toxicities and rates of toxicities after SRS for ANs?

Show Answer

Trigeminal neuropathy/hyperesthesia: 0%–5%
Facial nerve neuropathy/palsy: 0%–5%
Hearing deficit: useful hearing preserved in 40%–60%
What are the main toxicity differences b/t RT and Sg?

Show Answer

RT carries a lower risk of facial nerve/trigeminal nerve injury.

24

Ocular Melanoma

Updated by Vincent Lee and Gopal K. Bajaj

BACKGROUND

What is the incidence of intraocular melanoma in the United States, and how does it rank in terms of incidence among the various eye malignancies? Is there a race of gender predilection?

Show Answer

Appx 5 in 1 million (~2,500 cases/yr of ocular melanoma). Intraocular melanoma is the #1 primary adult intraocular malignancy (#1 overall is ocular mets). 98% of pts are Caucasian, and the incidence is slightly higher in males than females.

What are some of the risk factors for developing ocular melanoma?

Show Answer

Occupational UV exposure, fair skin, light eye color, family Hx of ocular melanoma, and personal Hx of cutaneous melanoma or cutaneous nevi.

What is the most common site in the eye where ocular melanomas arise?

Show Answer

Uvea, mostly choroidal (85%) > adnexa (10%) > conjunctiva (5%)

What is the cell of origin for ocular melanoma?

Show Answer

Ocular melanoma arises from **melanocytes of the uveal stroma** (neural crest origin).
What are the components of the uveal tract?

Show Answer

The **choroid, ciliary body, and iris** comprise the uveal tract.
What is the association b/t uveal melanoma location and metastatic risk?

Show Answer

Ciliary body involvement carries the highest risk of death from mets, f/b choroidal tumors. Iris tumors carry the most favorable prognosis.
Name the layers of the choroid from outer to inner.

Show Answer

Layers of the choroid (outer to inner):

- Haller layer
- Sattler layer
- Choriocapillaris
- Bruch membrane

What are the basic layers of the globe?

Show Answer

Outer fibrous layer (sclera), middle vascular layer (choroid), and inner nerve layer (retina)
What region in the retina is particularly important for color vision?

Show Answer

The **macula** is important for color vision.
Where is the optic disc relative to the macula?

Show Answer

The optic disc is **2 mm medial** to the macula (~1.5 mm in diameter).
What are the histologic subtypes of ocular melanoma, and which carry the best and worst prognosis?

Show Answer

Spindle cell (best), epithelioid (worst), and mixed (if <50% epithelioid histology)
What % of pts with ocular melanoma present with DM at Dx? What is the most common location?

Show Answer

1%–2% present with DM. The **liver** is the most common site (89% in COMS).
What are the different ways melanoma can spread within the globe?

Show Answer

Melanoma can spread intraocularly (through the vitreous, aqueous, or along ciliary vessels/nerves); extraocularly (through the optic nerve, transsclerally, vascular tracking), and through extrascleral extension (10%–15%).
What tumor characteristics predict for DM in ocular melanoma? What is the 5-yr mortality rate in these pts?

Show Answer

Epithelioid histology, large tumors, ant location (ciliary body invasion), monosomy 3 often combined with gain in chromosome 8q, scleral penetration, ↑ mitotic rate, ↑ Ki-67, pleomorphic nucleoli, optic nerve invasion, ↑ MIB-1 index, vascular networks of closed vascular loops, extraocular extension. The 5-yr mortality rate is **55%.**
How has Gene Expression Profiling (GEP) been used to predict DM? What genetic mutation has also been discovered to be associated with DM?

Show Answer

GEP has been used to differentiate tumors with high-risk class 2 associated with ↑ DM. Mutations in the BAP1 **gene** on chromosome 3 have been associated with ↑ DM. PRAME expression has also been associated with DM risk as well.

What is the 10-yr DM rate from choroidal/ciliary body melanoma?

Show Answer

10-yr DM rate has been reported at **19**% (AJCC Task Force, Finger PT et al., JAMA Ophthalmol 2015) and **34**%. (COMS Report No. 26, Arch Ophthalmol 2005) High-risk features ↑ DM rate to ≥50%.

WORKUP/STAGING

How do pts with ocular melanoma normally present?

Show Answer

Appx one-third of pts present with **blurred vision,** and about 30% are **asymptomatic.** Other presenting Sx include photopsia, scotoma, or pain (rare).

What is the workup for a pt with suspected ocular melanoma?

Show Answer

H&P, CBC, LFTs, ophthalmic/funduscopic/slit lamp exam, visual acuity/visual field testing, US (Kretz A-scan, immersion B-scan), fluorescein angiography, MRI, CT C/A/P or PET/CT to r/o mets

Is Bx necessary for Dx of ocular melanoma?

Show Answer

Not required; it is a clinical Dx made by exam and imaging. There has been historical concern for tumor seeding from Bx, but it has not been associated with the development of DM. The role for Bx has been increasing for molecular analysis and risk stratification.

What are simulation lesions?

Show Answer

Simulation lesions are **lesions that may look like melanoma,** such as nevi, hemangiomas, retinal detachment, age-related disciform lesions, and mets.
What feature does ocular melanoma manifest on standard A-scan US?

Show Answer

An **acoustic "quiet" zone** (central hypoechoic area) vs. mets or hemangiomas (have higher internal reflectivity)
What features do ocular melanomas exhibit on fluorescein angiography?

Show Answer

On fluorescein angiography, ocular melanomas exhibit a **double circulation pattern and fluorescein leakage** (appearing as hot spots).
What is the T staging of choroidal/ciliary body melanoma based on the latest AJCC (8^{th} edition, 2017) staging guidelines?

Show Answer

AJCC staging is based on 4 tumor size categories that depend on tumor diameter and height as follows (Fig. 24.1):

T1: tumor size category 1
T2: tumor size category 2
T3: tumor size category 3
T4: tumor size category 4
For the T staging of choroidal/ciliary body melanomas, what do the designations a–e represent?

Show Answer

a. no ciliary body involvement/extraocular extension
b. with ciliary body involvement

. no ciliary body/with extraocular extension ≤5 mm in largest diameter
. with ciliary body/with extraocular extension ≤5 mm
. with extraocular extension >5 mm

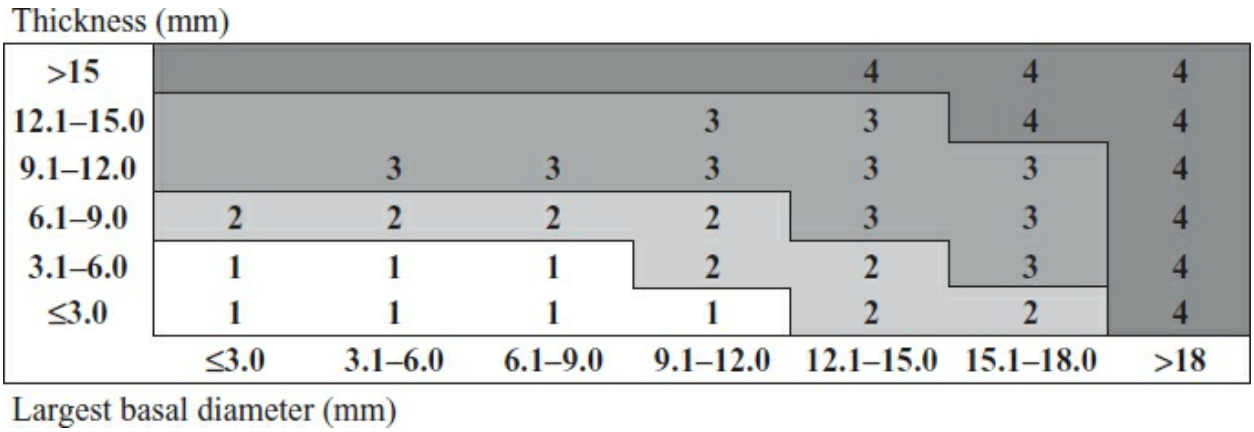

FIGURE 24.1 Primary ciliary body and choroidal melanomas are

Describe the AJCC staging for choroidal/ciliary body melanomas.

Show Answer

Stage I: T1aN0M0
Stage IIA: T1b–dN0M0 or T2aN0M0
Stage IIB: T2bN0M0 or T3aN0M0
Stage IIIA: T2c–d, T3b–c, T4aN0M0
Stage IIIB: T3d, T4b–cN0M0
Stage IIIC: T4d–eN0M0
Stage IV: T1–4N1M0; T1–4N0–1 M1a–c
For the M staging of choroidal/ciliary body melanomas, what do the designations a–c represent?

Show Answer

M1a: largest diameter of mets ≤3 cm
M1b: largest diameter of mets 3.1–8 cm
M1c: largest diameter of mets >8 cm

In the Collaborative Ocular Melanoma Study (COMS) staging system, what are COMS small, medium, and large lesions?

Show Answer

COMS staging is based on apical height (AH) and basal diameter (BD):

Small: AH 1–3 mm, BD 5–16 mm
Medium: AH 3.1–8 mm, BD 5–16 mm
Large: AH >8 mm and/or BD ≥16 mm
What are the 10-yr OS rates of COMS small, medium, and large tumors? Pts with DM?

Show Answer

10-yr OS for COMS tumors:

Small: 80%
Medium: 60%
Large: 30%–40%
DM pts: <7 mos

TREATMENT/PROGNOSIS

In order of importance, what are the 3 main goals of Tx in the management of ocular melanoma?

Show Answer

Main goals of ocular melanoma Tx (in order of importance):

. Preserve life
. Preserve eye
. Preserve vision

What is the preferred management approach for COMS category small uveal melanomas?

Show Answer

Observation or local therapy (transpupillary thermotherapy, photodynamic laser photocoagulation, local resection)
When is RT employed in the management of COMS category small uveal melanomas?

Show Answer

RT is employed when there is **progression after conservative management** (i.e., observation or other local Tx).
As per ABS 2014 guidelines, what are the eligibility criteria for observing uveal melanomas?

Show Answer

AJCC T1 tumor in the absence of: thickness ≥2 mm, subretinal exudative fluid, and superficial orange pigment lipofuscin. Tx should be initiated when growth is detected.
If resection is employed for small melanomas, for what ocular location is it generally reserved?

Show Answer

Resection is utilized for **lesions of the iris or ciliary body.** It is not usually recommended for uveal lesions d/t impact on vision.
In the COMS trials, pts with small uveal melanomas were observed with close f/u. What % of pts progressed after 5 yrs?

Show Answer

~33% of pts with small melanomas progressed. (COMS No. 4, JAMA Ophthalmol 1997)
What features of small uveal melanomas were found to be associated with growth after observation?

Show Answer

Orange pigmentation (6.4 times), no drusen and no adjacent retinal

pigmentary changes (4.2 times), >2 mm thickness (4.4 times), >12-mm BD (5.2 times)
What are the Tx options for COMS medium melanomas?

Show Answer

Enucleation, plaque brachytherapy, or charged particle/proton RT
When is enucleation a preferred approach for the management of uveal melanoma?

Show Answer

Pt choice, as salvage therapy, tumor involving >40% of intraocular volume, tumor in a nonfunctional eye, symptomatic pt (pain), eye with marked neovascularization, and extrascleral extension
What are the indications for the use of plaque brachytherapy?

Show Answer

Plaque brachytherapy is used for **organ preservation** for COMS medium lesions and **small progressive tumors** after observation.
What are the max AH and BD sizes allowed for plaque brachytherapy?

Show Answer

For plaque brachytherapy, max allowed sizes are **≤10-mm (3–8 mm optimal) AH and 16-mm BD.**
What tumor features are deemed unsuitable for plaque brachytherapy as per the ABS 2014 guidelines?

Show Answer

Tumors with T4e extraocular extension, BDs that exceed the limits of brachytherapy, blind painful eyes, and those with no light perception vision are not suitable for plaque therapy.
Under what circumstances should notched plaques be used?

Show Answer

Notched plaques are typically used for **peripapillary tumors.**
What is the most common isotope used in plaque brachytherapy? What is the dose rate?

Show Answer

I-125, at a dose rate of **0.7–1 Gy/hr** (Tx times vary from 4–7 days)
What other isotope can be used for small-to medium-sized tumors? Why might it be preferred over I-125?

Show Answer

Ruthenium-106 (β-emitter). Ru-106 has limited dose penetration relative to I-125, so it results in less toxicity and is also easier to insert.
How is the dose prescribed with plaque brachytherapy?

Show Answer

85 Gy to the tumor apex (or 5 mm from the internal surface of the sclera if the height is <5 mm), with a 2-mm margin around the tumor (or a plaque size equal to 4 mm + greatest BD)
What advantages do proton/charged particle therapy confer over brachytherapy in the Tx of uveal melanoma?

Show Answer

Proton/charged particle therapy beam is preferable for larger tumor thickness, tumors near the optic nerve/disc or macula, and tumors under the orbital muscles.
How is proton beam RT prescribed in the Tx of uveal melanoma?

Show Answer

70 cobalt gray equivalents (CGE) in 5 fx over 7–10 days
What is the long-term LC rate of proton beam compared to plaque

brachytherapy?

Show Answer

Proton beam: 95%
Plaque brachytherapy: 92%–94%
What is the 5-yr DM rate of ocular melanoma after Tx with either protons or brachytherapy?

Show Answer

The 5-yr DM rate after local RT is **16%–20%.**
Which randomized phase III study compared the efficacy of enucleation vs. plaque brachytherapy for medium-sized uveal melanomas?

Show Answer

COMS study (Report No. 28, Arch Ophthalmol 2006): 1,317 pts. There was no difference in all-cause mortality and melanoma-specific mortality. 12-yr OS was 17%–21%.
In the COMS medium trial, what is the 5-yr secondary enucleation rate after plaque brachytherapy? What were the most common reasons?

Show Answer

The 5-yr secondary enucleation rate is **12.5%** d/t **Tx failure or ocular pain** from brachytherapy complications. (COMS No. 19, Ophthalmol 2002)
What is the standard management for large uveal melanomas?

Show Answer

Enucleation. Heavy particle/proton therapy can also be used.
What % of pts present with large uveal melanomas?

Show Answer

30% of pts present with large uveal melanomas.
Per the COMS trial, does preop EBRT improve outcomes over enucleation

alone for COMS large tumors?

Show Answer

No. In the COMS trial, there was no OS or DFS difference b/t the 2 groups. (COMS No. 24, Am J Ophthalmol 2004)
Per the Ophthalmic Oncology Task Force, how does LR affect the risk of developing mets?

Show Answer

LR increased risk of DM by an HR of 6.28; LR detected up to 9.8 yrs after Tx and associated with extrascleral extension but not T-stage. (Ophthalmic Oncology Task Force, Ophthalmol 2016)

FOLLOW-UP/TOXICITY

What are some early and late complications associated with plaque brachytherapy?

Show Answer

Early: pain, bleeding, diplopia, infection, edema
Late: **retinopathy (42% at 5 yrs, increasing to 80%–90% thereafter)**, decreased visual acuity, cataracts, keratitis, optic neuropathy
The use of what agent has recently been associated with a lower incidence of macular edema after plaque brachytherapy?

Show Answer

Triamcinolone (periocular injections). In an RCT, macular edema rates were 58% in the control group vs. 36% in the triamcinolone arm. (Horgan N, Ophthalmology 2009)
What % of pts have loss of ≥6 lines of vision 3 yrs after plaque brachytherapy?

Show Answer

~50% of pts have significant vision loss after plaque brachytherapy.
What % of pts have cataracts 5 yrs after plaque brachytherapy?

Show Answer

83% of pts develop cataracts after plaque brachytherapy.
How should pts treated with plaque brachytherapy be followed?

Show Answer

Plaque brachytherapy f/u: H&P, ocular US q3 mos × 1 yr, q4 mos in 2nd yr, q6 mos in 3rd and 4th yrs, then annually; CT C/A/P or liver US q6 mos with LFTs (can detect >95% of mets)
Are periodic LFTs alone adequate to r/o liver mets?

Show Answer

No. There is very poor sensitivity (15%), PPV (46%), and NPV (71%), with a specificity of 92%. Adding liver US to LFTs increases the detection rate to 95%. (Eskelin S et al., Cancer 1999)
What imaging modalities are useful in detecting liver mets? What is the main disadvantage of these modalities?

Show Answer

MRI, CT C/A/P or PET/CT are useful for the detection of liver mets. The **cost and availability** of such testing are the main disadvantages.

25

Orbital and Intraocular Primary Eye Lymphomas

Updated by Tommy Sheu and Gopal K. Bajaj

BACKGROUND

Under what type of lymphomas are intraocular/orbital lymphomas classified?

Show Answer

Intraocular/orbital lymphomas are classified as **NHLs** (B-cell histology > T-cell histology).

What is the median age of onset? What are the 2 main types of eye lymphoma?

Show Answer

The median age of onset is **50–60 yrs** (females > males). The 2 main types are **intraocular (bimodal age distribution at 31 and 60 yrs) and orbital/ocular adnexal lymphoma (median age at 65 yrs).**

What are the most common histologies?

Show Answer

Intraocular: usually diffuse large B-cell lymphoma

Orbital: extranodal marginal zone B-cell lymphoma or MALT lymphoma

Which structures are involved in intraocular vs. orbital lymphomas?

Show Answer

Intraocular lymphomas involve the neural structures.
Orbital lymphomas can involve the conjunctiva, ocular adnexa, lacrimal apparatus, uvea, and retrobulbar areas.
What % of pts with primary intraocular lymphomas develop CNS Dz within 3 yrs?

Show Answer

60%–80% of pts with intraocular lymphomas develop CNS Dz.
What % of pts with primary CNS lymphomas develop intraocular involvement?

Show Answer

25% of pts with primary CNS lymphoma develop intraocular involvement.
What is the recurrence rate after Tx of intraocular lymphomas?

Show Answer

The recurrence rate after Tx is **~50%.**
Intraocular lymphoma is bilat in what % of pts? How about orbital/adnexa lymphoma?

Show Answer

Intraocular: 80%
Orbital: 20%
What is a common chromosomal translocation in intraocular lymphoma? What % of pts have this translocation?

Show Answer

t(14;18) is a common translocation in intraocular lymphoma. **56%** of pts have this translocation.
Ocular lymphoma cells are usually positive for which important

immunohistochemical markers?

Show Answer

Ocular lymphomas usually stain positive for **CD20** and **bcl-2, bcl-6, and MUM1.**

What type of lymphoma accounts for most lymphomas of the ocular adnexa?

Show Answer

MALT lymphoma accounts for most lymphomas of the ocular adnexa.

Which ocular lymphoma has a male predominance and is associated with mycosis fungoides?

Show Answer

Ocular lymphoma of T-cell histology occurs predominantly in males and is associated with mycosis fungoides.

With what infectious agent has orbital MALT been associated? What site is often involved?

Show Answer

Chlamydia psittaci has been associated with orbital MALT lymphomas. The **lacrimal gland** is often involved. Tx with doxycycline alone in a phase II trial of 47 pts (89% with biopsy + Chlamydia DNA) resulted in a 5-yr PFS of 55% and lymphoma regression in 65% of pts. (Ferreri AJ et al., JCO 2012)

Lymphoma of what orbital structure has a high propensity for LN spread?

Show Answer

Lacrimal gland lymphoma has a high propensity for LN spread (>40% are LN+).

Which lymphomas have a better prognosis: orbital or intraocular?

Show Answer

Orbital lymphomas tend to be indolent, whereas intraocular lymphomas are aggressive with a high propensity for CNS involvement.

WORKUP/STAGING

What are the common presenting Sx of ocular/orbital lymphomas?

Show Answer

Blurred vision, floaters, pain (uveitis/vitreitis), proptosis (if retro-orbital), and orbital lesion (e.g., salmon-colored conjunctival mass).

What must the physical exam portion of the workup include?

Show Answer

The physical exam portion must include an **ophthalmologic exam** (fundoscopy, slit-lamp exam) as part of the workup.

What lab/pathology tests are required during the workup?

Show Answer

CSF/vitrectomy, BM Bx, CBC, LFTs, ESR

What imaging is recommended for ocular/orbital lesions?

Show Answer

MRI brain/orbits, ocular US, CT C/A/P (PET/CT if MALT: Perry C et al., Eur J Haematol 2007)

What staging system is used for eye lymphomas?

Show Answer

Ann Arbor staging system:

Stage IE: localized eye lymphomas
Stage II: cancer located in 2 separate regions
Stage III: cancer on both sides of diaphragm, including 1 organ or area near LNs or spleen
Stage IV: diffuse or disseminated involvement of ≥1 extralymphatic organs

(e.g., liver, BM, or nodular involvement of lungs)

What is the most widely used classification system for lymphomas of the eye?

Show Answer

REAL (Revised European-American Classification of Lymphoid Neoplasms): 3 classes—indolent, aggressive, and highly aggressive

TREATMENT/PROGNOSIS

What is the Tx paradigm for orbital lymphoma?

Show Answer

Orbital lymphoma Tx paradigm: **RT alone** (low grade) **or CRT** (if intermediate/high grade)

What RT doses are used for orbital lymphoma?

Show Answer

19.5–24 Gy at 1.5 or 2 Gy (MALT, low grade) or even **4 Gy in 2 fx ("boom-boom") can be used as a palliative dose,** and **30–36 Gy** (high grade, based on chemo response).

Does RT alone offer high rates of LC for low-grade orbital lymphoma? What rates have been reported?

Show Answer

Yes. A retrospective series of 31 orbital MALT lymphoma pts at Stanford treated with 30–40 Gy achieved a 10-yr LC of 100% and freedom from relapse of 71%; no dose response was observed as there was no difference in pts treated with >34 Gy vs. ≤34 Gy. (Le Q et al., IJROBP 2002)

What is the Tx paradigm for intraocular lymphoma?

Show Answer

Intraocular lymphoma Tx paradigm: **chemo +/- RT.** These are treated more

like primary CNS lymphomas.
What area is irradiated in intraocular lymphoma?

Show Answer

The **orbits (+/- whole brain)** are irradiated in intraocular lymphoma.
Which chemo agent is typically used for intraocular lymphomas?

Show Answer

High-dose **methotrexate** (Mtx). Intraocular/intravitreal Mtx and rituximab (Rituxan) are usually employed.
What chemo regimens are typically used for high-grade orbital/ocular adnexa lymphomas?

Show Answer

Cyclophosphamide HCl/doxorubicin/Oncovin/prednisone + Rituxan **(R-CHOP) or** cyclophosphamide/vincristine/Adr/dexamethasone **(CVAD)** are typically used for high-grade orbital lymphomas.
What is 1 additional option for refractory/relapsed Dz?

Show Answer

Radioimmunotherapy with I-131 or yttrium-90 is another option for refractory/relapsed Dz. (Esmaelli et al., Ann Oncol 2009)
What RT technique can be utilized for ant (eyelid, conjunctival) lesions?

Show Answer

Ant orthovoltage or electron fields can be employed for ant eye lesions.
How is lens shielding accomplished with an ant orthovoltage field?

Show Answer

A lead shield is **suspended in the beam** to shield the lens (limits lens dose to 5%–10%).
What are some poor prognostic factors for ocular/orbital lymphomas?

Show Answer

High-grade Dz, advanced Dz (stage IVE), elevated LDH, age > 60, lacrimal gland involvement, and symptomatic Dz

FOLLOW-UP/TOXICITY

Above what cumulative dose (standard fractionation) is lens opacification seen?

Show Answer

Lens opacification is seen with doses **>13–16 Gy.**
What toxicities are associated with radioimmunotherapy?

Show Answer

Myelosuppression, myelodysplastic syndrome, and acute myeloid leukemia
What is the min dose to induce cataracts with a single fx vs. multiple fx of RT?

Show Answer

Doses of **2 Gy** (single fx) and **4–5 Gy** (multiple fx) can induce cataracts.
Is cataract induction a stochastic or deterministic late effect? Explain.

Show Answer

Deterministic. There is a threshold and the severity/latency is dose related.
Which region of the lens is affected most by RT?

Show Answer

The **postsubcapsular region of the lens** is affected most by RT.
What are the side effects associated with intravitreal chemo?

Show Answer

Cataracts, glaucoma, corneal epitheliopathy, maculopathy, vitreous hemorrhage, optic atrophy, and sterile endophthalmitis

What is the dose tolerance of the lacrimal glands?

Show Answer

The mean dose tolerance of the lacrimal apparatus is **26–30 Gy.**
Above what dose can painful keratitis be seen?

Show Answer

Doses **>60 Gy** can cause painful keratitis. (Kwok et al., Ophthalmology 1998)

26

Thyroid Ophthalmopathy

Updated by Boris Hristov

BACKGROUND

What causes thyroid ophthalmopathy (TO)?

Show Answer

T-cell infiltration of orbital and periorbital tissues (secondary to autoimmune antibody–mediated reaction against the TSH receptor); this thyroid-mediated inflammation then leads to fibroblast proliferation and hypersecretion of glycosaminoglycans causing swelling

Name 2 conditions associated with TO.

Show Answer

Graves Dz and **Hashimoto thyroiditis** are both associated with TO.

What is the end result of untreated TO?

Show Answer

Untreated TO will lead to **fibrosis,** which develops over the course of 3–5 yrs.

What are the signs/Sx of TO?

Show Answer

Exophthalmos, impaired extraocular movements/diplopia, periorbital edema, and lid retraction. In severe cases, compression of the optic nerves and

decreased visual acuity can occur.

WORKUP/STAGING

What does the general workup of TO include?

Show Answer

TO workup: H&P (Hertel exophthalmometer to measure proptosis), CBC, CMP, TFTs, and CT/MRI orbit

What is a commonly used risk stratification system?

Show Answer

The **VISA stratification** developed by Dolman PG and Rootman J (Opthal Plast Reconstr Surg 2006); assesses 4 severity parameters: V (vision); I (inflammation/congestion); S (strabismus/motility restriction); and A (appearance/exposure).

TREATMENT/PROGNOSIS

What is the general Tx paradigm for TO?

Show Answer

TO Tx paradigm: first, restore euthyroidism and smoking cessation. For mild Dz, consider observation vs. RT; for moderately severe Dz, consider high-dose steroids (generally 1st-line Tx with response in up to 60% of pts) vs. RT; and for severe Dz unresponsive to steroids, perform orbital decompression Sg (e.g., for acute visual acuity or color perception changes as these are Sx of optic nerve compression).

RT should be initiated within how many mos from onset of TO?

Show Answer

RT should be initiated **within 7 mos** of TO onset for pts who fail or have contraindications to high-dose steroids. Delayed RT is not as effective based on retrospective data.

What are 2 common contraindications to high-dose steroids in pts with

TO?

Show Answer

Optic neuropathy and corneal ulceration are 2 contraindications to steroids in pts with TO.
What are the typical RT dose/fractionations for TO? What evidence supports these doses?

Show Answer

Typical RT dose/fractionations for TO: Kahaly et al. prospectively compared the 3 regimens below and found that all were equally effective (the latter 2 were better tolerated). (J Clin Endocrinol Metab 2000)

- **20 Gy in 2 Gy/fx** (most common)
- **10 Gy in 1 Gy/fx**
- **20 Gy in 1 Gy/fx/wk × 20 wks**

What beam arrangement is used for TO?

Show Answer

Opposed lat fields.
What RT technique is used to minimize the dose to the contralat lens?

Show Answer

Place the isocenter post to lenses and the half-beam block anteriorly (limits divergence to contralat lens).
What structures define the post, sup, and ant borders of the RT fields?

Show Answer

Post: ant clinoids
Sup/Ant: bony orbit
In pts with moderately severe active Dz, what evidence supports adding RT to steroid therapy?

Show Answer

Retrospective **Canadian data** of 351 pts (Shams PN et al., Am J of Opthalmol 2014); at 3.2 yrs, addition of RT to steroids reduced rate of compressive optic neuropathy from 17% to 0%.

What evidence is there to support RT for mild TO?

Show Answer

Prummel MF et al.: A double-blind RCT of 88 pts with Graves: 44 rcvd RT vs. 44 sham RT. RT improved clinical Sx (response rate 52% for RT vs. 27% for sham RT). There was no improvement in the QOL survey and no reduction in overall Tx costs. (J Clin Endocrinol Metab 2004)

What evidence is there against RT for mild TO?

Show Answer

Gorman CA et al.: In an RCT with crossover, RT was administered to 1 orbit and then the opposite orbit after 6 mos. At 6 mos, there was no difference in results for either eye. At 12 mos, there was minor improvement in the 1st treated eye. The authors concluded that RT was not justified. (Ophthalmology 2001)

What evidence is there to support RT for moderately severe TO?

Show Answer

Premmel MF et al.: In an RCT, all pts with Graves rcvd RT vs. 3 mos of prednisone. RT and prednisone were equally effective, but RT was better tolerated. (Lancet 1993)

Mourits MP et al.: In an RCT, all pts with Graves rcvd RT vs. sham RT. RT improved diplopia and elevation but not proptosis or eyelid swelling. It was concluded that RT should be used to treat motility impairment only. (Lancet 2000)

Would a pt with diplopia or proptosis be more likely to see an improvement in Sx after RT?

Show Answer

A patient with **diplopia** would be more likely to see improvement after RT (Mourits MP et al., Lancet 2000); also supported by recent meta-analysis (Stiebel-Kalish H et al., J Clin Endocrinol Metab 2009)
Estimate the response rate of TO pts to RT.

Show Answer

Response rates to RT are **50%–70%** in pts with TO. (Prummel MF et al., J Clin Endocrinol Metab 2004; Kahaly GJ et al., J Clin Endocrinol Metab 2000)
What % of TO pts will require further therapy after RT?

Show Answer

50%–75% of TO pts will require further therapy. (Mourits MP et al., Lancet 2000; Gorman CA et al., Ophthalmology 2001)

FOLLOW-UP/TOXICITY

What are the late side effects of orbital RT?

Show Answer

Cataracts, permanent dry eye, retinopathy, and optic neuropathy
In what pts should orbital RT generally be avoided?

Show Answer

Pts with uncontrolled/severe **diabetes and/or HTN;** very **young pts** (<35–40 yo)
What is the RT dose limit of the lenses?

Show Answer

Try to limit the dose to <8–10 Gy to prevent cataracts.
What other disciplines/specialists should be actively involved in the f/u of pts with TO?

Show Answer

The ophthalmologist and the endocrinologist should be actively involved in the f/u of pts with TO.

27

Orbital Pseudotumor

Updated by David Eastham and Gopal K. Bajaj

BACKGROUND

What is an orbital pseudotumor (OP) and how does it most commonly present?

Show Answer

OP is an idiopathic benign lymphocytic inflammatory process causing a mass lesion in the orbit.

OP most commonly presents with sudden unilat proptosis and diplopia.

What is the eponym given to OP with cavernous sinus involvement?

Show Answer

Tolosa–Hunt syndrome is OP with cavernous sinus involvement. It manifests with painful ophthalmoplegia d/t CN involvement.

What % of pts with OP will subsequently develop a malignant lymphoma?

Show Answer

5%–25% will subsequently develop a malignant lymphoma. (Orcutt JC et al., Br J Ophthalmol 1983; Mittal BB et al., Radiology 1986)

Does OP affect children, adults, or both?

Show Answer

OP affects **both children and adults.** 5%–15% are pediatric cases. (Smitt

MC et al., Semin Radiat Oncol 1999)
Name 5 signs/Sx associated with OP.

Show Answer

Signs/Sx associated with OP:

. Orbital mass
. Orbital pain
. Proptosis
. Abnl extraocular movements (e.g., diplopia)
. Decreased visual acuity

WORKUP/STAGING

What is the DDx for an orbital mass?

Show Answer

RMS, malignant orbital lymphoma, thyroid ophthalmopathy, and nodular fasciitis. OP is a Dx of exclusion.
What is the workup for an orbital mass?

Show Answer

The workup is the same as for a suspected orbital lymphoma, including CT/MRI brain/orbit and biopsy if necessary.
How is OP subclassified?

Show Answer

There is **no formal staging system** for OP. OP is subclassified by the orbital anatomy involved with the inflammation.

TREATMENT/PROGNOSIS

What is the initial Tx for OP?

Show Answer

Steroids are the mainstay initial Tx for OP. (Smitt MC et al., Semin Radiat Oncol 1999)
What are the response rate and long-term control rate with a single steroid course?

Show Answer

Response rate: 80%
Long-term control rate: 33%

(Mombaerts I et al., Ophthalmology 1996)
What is the 2nd-line therapy for OP?

Show Answer

RT is the 2nd-line therapy for OP for pts with contraindications, unacceptable toxicity, or inadequate response to steroid therapy.
What is the most common RT dose/fx schedule for OP?

Show Answer

20 Gy in 10 fx is the most commonly employed schedule for OP.
What are the estimated control rates for OP with RT?

Show Answer

Control rates with RT range from **66%–100%.** (Smitt MC et al., Semin Radiat Oncol 1999)
What is the standard RT setup for OP?

Show Answer

There is no standard RT setup, as the process may involve any aspect of the orbit. Tx must be individualized.
Can RT be repeated for OP?

Show Answer

Yes. RT can be repeated, if necessary.

FOLLOW-UP/TOXICITY

What are the potential late toxicities of orbital RT?

Show Answer

Cataracts, permanent eye dryness, retinopathy, and optic neuropathy

What is the RT dose limit of the lens?

Show Answer

Try to limit the lens to **<8–10 Gy** depending on the clinical situation.

Diabetic pts are at an increased risk for what complication after orbital RT?

Show Answer

After orbital RT, diabetic pts are at an increased risk for **RT retinopathy.** (Wakelkamp IM et al., Ophthalmology 2004)

28

Nasopharyngeal Cancer

Updated by Brian Deegan

BACKGROUND

What is the incidence of nasopharyngeal cancer (NPC) in the United States vs. in Asian countries?

Show Answer

NPC is rare in the United States (0.2–0.5 in 100,000) but endemic in Asia (25–50 in 100,000).

What are the environmental risk factors associated with NPC?

Show Answer

Consumption of salted fish and preserved meats, EBV infection, and smoking for keratinizing squamous cell type (no alcohol association)

What is the median age at Dx for NPC?

Show Answer

~50 yrs

Is there a sex predilection for NPC?

Show Answer

Yes. **Males > Females** (3:1)

What are the anatomic boundaries that make up the nasopharynx (NPX)?

Show Answer

Superior: sphenoid bone
Inferior: soft palate
Posterior: clivus/C1–2
Anterior: post edge of choanae
From what anatomic location do most NPCs arise?

Show Answer

Fossa of Rosenmuller (pharyngeal recess)
What is the local pattern of spread for NPC superiorly, inferiorly, posteriorly, laterally, and anteriorly?

Show Answer

Superiorly: invades (via the **foramen lacerum**) the cavernous sinus with initial CN VI involvement
Inferiorly/posteriorly: OPX
Laterally: parapharyngeal space
Anteriorly: nasal cavity
What 2 CN syndromes are commonly associated with NPC, and what CNs are involved in each?

Show Answer

Petrosphenoidal syndrome: CNs III–IV and VI involvement (oculomotor signs/Sx)
Retroparotidian syndrome: CN IX–XII involvement
What CNs or structures traverse through the base of skull sinuses/foramina (e.g., cavernous sinus, foramen rotundum, ovale, lacerum, jugular, hypoglossal)?

Show Answer

Cavernous sinus: CNs III–IV, V1 and V2, and VI
Foramen rotundum: V2
Foramen ovale: V3

Foramen lacerum: cartilage of the eustachian tube
Jugular foramen: CNs IX–XI
Hypoglossal canal: CN XII
What are the histologic subtypes of NPC and corresponding WHO classifications?

Show Answer

Keratinizing SCC (WHO type I, 25%). Sporadic form
Nonkeratinizing carcinoma: Differentiated (WHO type II, 12%).
Undifferentiated (WHO type III 63% vs. 95% in Asia)
Which type of NPC is endemic and prone to distant recurrence?

Show Answer

Nonkeratinizing undifferentiated (WHO type III) is endemic (better LC but higher metastatic risk).
Which type of NPC is associated with smoking and has poor LC but a lower propensity for DM?

Show Answer

Keratinizing SCC (WHO type I) is associated with smoking, poorer LC, and less distant spread.
Which type of NPC is most strongly associated with EBV exposure?

Show Answer

Nonkeratinizing undifferentiated (WHO type III)
With what autoimmune condition can NPC be associated?

Show Answer

Dermatomyositis
What histologic feature of NPC is an adverse prognostic factor in terms of LC and OS?

Show Answer

Presence of keratin (WHO type I)
What role does p53 play in the pathogenesis of NPC?

Show Answer

Little. p53 alteration is seen in the minority of cases (unlike other H&N cancers).
What is a commonality b/t NPX and OPX cancers?

Show Answer

Viral-associated tumors (EBV-NPX: HPV-OPX) have better LC but higher propensity for distant spread compared to nonviral-associated tumors in these regions.

WORKUP/STAGING

What are some common presenting Sx in pts with NPC?

Show Answer

Neck mass (>60%); epistaxis, headache, diplopia, facial numbness, otalgia, and nasal congestion. Trismus and/or CN deficits are seen with more advanced Dz.
What is the workup for a pt who presents with a neck node and a suspicious mass in the NPX according to the NCCN guidelines?

Show Answer

H&P, nasopharyngolaryngoscopy and Bx of the lesion, MRI with gadolinium of base of skull, NPX, and neck to clavicles, CT of skull base/neck with contrast as indicated; dental, speech and swallow, and audiology evaluations as indicated, and PET scan or other imaging to evaluate for DM
What is the DDx for a pt with a nasopharyngeal mass?

Show Answer

Carcinoma, lymphoma, melanoma, plasmacytoma, angiofibroma, RMS (children), and mets
What % of NPC pts present with palpable LAD?

Show Answer

60%–90%
What % of NPC pts present with bilat LAD?

Show Answer

Up to **50%**
Adenopathy near the mastoid tip is indicative of involvement of which nodal group?

Show Answer

Retropharyngeal nodes (node of Rouviere)
Pts with upper-level V LAD are most likely to have what kind of H&N primary?

Show Answer

NPC
What factors predict for DM in pts with NPC?

Show Answer

Lower neck nodal involvement, advanced nodal stage, and nonkeratinizing undifferentiated (WHO type III) **histology**
What are the common DM sites for NPC?

Show Answer

Bones, lungs, and liver
What correlates better with DM spread in NPC: N stage or T stage?

Show Answer

N stage

How does the latest AJCC 8th edition staging of NPC differ from the previous version?

Show Answer

T Stage	Description
T0	No primary identified with EBV+ cervical node(s)
T1	NPX ± OPX ± nasal cavity without parapharyngeal involvement
T2	Parapharyngeal extension ± adjacent ST involvement (medial or lat pterygoid, prevertebral muscles)
T3	Base of skull bones ± PNS ± cervical vertebra, pterygoid structures
T4	intracranial extension, CNs, hypopharynx, orbit, parotid, beyond lat pterygoid muscle
N Stage	**Description**
N1	Unilat cervical ≤6 cm ± retropharyngeal LN ≤6 cm (unilat or bilat), above caudal border of cricoid
N2	Bilat cervical ≤6 cm above the caudal border of the cricoid
N3	>6 cm and/or extension or involvement below the caudal border of the cricoid

Masticator space extension (to the lat pterygoid) is now T2 vs. T4 previously.

SCV involvement is no longer formally recognized (previously N3b) and is consolidated with any Dz present below the cricoid as N3.

Stage grouping:

	N0	N1	N2	N3
T1	I	II	III	IVA
T2	II	II	III	IVA
T3	III	III	III	IVA
T4	IVA	IVA	IVA	IVA

M1: stage group IVB

TREATMENT/PROGNOSIS

What is the typical Tx paradigm for pts with NPC?

Show Answer

RT alone for stage I, CRT for stages II–IVA, chemo (with RT reserved for focal palliation) for stage IVB

What must be done before planning the NPC pt for RT?

Show Answer

Nutrition consult, dental evaluation are recommended before RT.

When is Sg indicated in the management of NPC?

Show Answer

To Bx the lesion and in cases of selective neck dissection for persistent Dz after CRT.

For early-stage NPC, what are the typical survival and control rates with RT alone?

Show Answer

With RT alone, the 3-yr OS is **70%–100% for stage I–II NPC** and LC rates are **70%–80% for T1–T2 lesions.**

What stages of NPC should be treated with concurrent chemoradiotherapy (CRT)?

Show Answer

Per the **Intergroup 0099 study** (Al Sarraf M et al., JCO 1998), all T3–T4 or N+ pts should be considered for CRT. Per **RTOG 0225** (Lee N et al., JCO 2009), pts with T2 and N+ Dz should be considered (AJCC 8th edition staging).

What was the CRT regimen used for locally advanced NPC in the Intergroup 0099 (Al-Sarraf et al.) study?

Show Answer

Concurrent chemo with **cisplatin (100 mg/m^2) q3 wks** and **RT to 70 Gy** → adj chemo with cisplatin/5-FU × 3 cycles

What were the PFS and OS outcomes in the Intergroup 0099 (Al-Sarraf et al.) trial?

Show Answer

In **Intergroup 0099,** 3-yr PFS was 24% vs. 69%, and **3-yr OS was 46% vs. 76%** in favor of CRT over RT alone. B/c of this striking difference, the study was closed early. This was 1 of the 1st studies to demonstrate a survival benefit with CRT.

What are the main criticisms of the Intergroup 0099 (Al-Sarraf et al.) study?

Show Answer

Major criticisms of **Intergroup 0099** include the large number of pts (25%) with WHO type I NPC (not typically seen in endemic areas) and the poor results of the RT-alone arm. Single-institution studies with RT alone (PMH: Chow E et al., Radiother Oncol 2002) for locally advanced NPC had better **5-yr** DFS (48%) and OS (62%). Other groups (NYU: Cooper JS et al., IJROBP 2000) also demonstrated better outcomes with RT alone (3-yr DFS was 43%, and 3-yr OS was 61%).

What are the 3 key confirmatory randomized trials from Asia that

demonstrated a benefit with CRT vs. RT alone for locoregionally advanced NPC?

Show Answer

- **Hong Kong** (**NPC-9901:** Lee AWM et al., Cancer 2017): 348 pts, RCT, median f/u 10.7 yrs; concurrent cisplatin + RT + adj chemo vs. RT alone, no adj chemo; CRT improved PFS (56% vs. 42%), LRC (87% vs. 74%), and OS (62% vs. 49%, p = .047) but not DM rate; toxicities similar @10 yrs (52% vs. 47%)
- **Singapore** (**SQNP01:** Wee J et al., JCO 2005): 221 pts, RCT, median f/u 3.2 yrs; used Al-Sarraf regimen: better DFS (72% vs. 53%), OS (80% vs. 65%), and DM rate (13% vs. 30%); greater toxicity with CRT; **confirmed results** of Intergroup 0099 for endemic NPC
- **Taiwan** (Lin JC et al., JCO 2003): 284 pts, median f/u 5.4 yrs; cisplatin/5-FU + RT vs. RT alone: better PFS (72% vs. 53%) and OS (72% vs. 54%). The subgroup reanalysis (Lin JC et al., IJROBP 2004) showed that CRT benefited low-risk "advanced" NPC (LN <6 cm, no SCV) but not high-risk "advanced" pts

Is there a benefit to the addition of induction chemo followed CRT in locally advanced NPC?

Show Answer

Yes. Sun Trial (Sun et al., Lancet Oncol 2016). 480 pts. RCT of **induction TPF** f/b CRT vs. CRT alone. Median follow-up 3.75 yrs. Improved 3-yr: FFS (80% vs. 72%), OS (92% vs. 86%), DMFS (90% vs. 83%). No significant difference in LRF.

Is there a benefit with the use of adj chemo after definitive CRT in locally advanced NPC?

Show Answer

Maybe. Network Meta-analysis (Ribassin-Majed et al., JCO 2017) found the

addition of adj chemo ranked sup to CRT alone for PFS, LRC and OS. However, only PFS was statistically significant.
Estimate the LC of NPC treated with IMRT to 70 Gy in standard fx.

Show Answer

UCSF data (Lee N, IJROBP 2004) suggests LC rates as high as 97% for NPC pts treated with IMRT.
What is the typical IMRT dose painting technique, and what are the corresponding IMRT doses used in the Tx of NPC?

Show Answer

Many institutions (MSKCC/RTOG) employ the SIB technique: **2.12 Gy × 33 = 69.96 Gy** to GTV, **1.8 Gy × 33 = 59.4 Gy** to intermediate-risk areas, and **1.64 Gy × 33 = 54 Gy** to low-risk areas.
How would you support the use of IMRT in NPC?

Show Answer

Better salivary outcomes with IMRT were demonstrated in data from Queen Mary Hospital (Pow EH et al., IJROBP 2006): 51 pts, stage II NPC, 2D vs. IMRT. At 2 mos, there was no difference in xerostomia; however, over time, QOL and objective salivary function improved for the IMRT group.

FOLLOW-UP/TOXICITY

What are the RTOG 0225 dose constraints for the chiasm/optic nerves when using IMRT for NPC?

Show Answer

Per **RTOG 0225,** the dose constraints for the chiasm/optic nerves are **54 Gy** or 1% of the PTV not >60 Gy.
What are the accepted RTOG 0225 dose constraints for the parotids?

Show Answer

Per **RTOG 0225,** the dose constraints for the parotids are as follows: mean dose <**26 Gy** (should be achieved in at least 1 gland) or at least 20 cc of the combined volume of both parotid glands <20 Gy or at least 50% of 1 gland <30 Gy.

Why might sparing of the parotid glands not be sufficient to prevent xerostomia?

Show Answer

Sparing of the parotids alone may not be sufficient b/c **mucus production by minor salivary glands may be necessary for subjective improvement,** according to data from Prince of Wales Hospital (Kam MK et al., JCO 2007): 60 pts randomized to IMRT or 2D-RT. Objective improvement in both stimulated and unstimulated salivary flow was found, but not in the subjective improvement of xerostomia.

What is the NCCN-recommended f/u schedule for NPC pts?

Show Answer

H&P with nasopharyngolaryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, and q12 mos if >5 yrs), imaging (for signs/Sx or smoking Hx/surveillance), TSH q6–12 mos (if neck irradiated), speech/hearing/dental evaluation, and smoking cessation

29

Sinonasal/Paranasal Sinus

Updated by Courtney Pollard, III and Gopal K. Bajaj

BACKGROUND

What is the incidence of sinonasal/paranasal sinus (PNS) tumors in the United States?

Show Answer

~2,000 cases/yr (<1% of all tumors). 3% of H&N cancers.

Is there a sex predilection for sinonasal/PNS tumors?

Show Answer

Yes. Males are more commonly affected than females (2:1).

Sinonasal/PNS tumors are more common in what continents?

Show Answer

PNS tumors are more prevalent in **Asia and Africa.**

What histologies are typically seen with sinonasal/PNS tumors?

Show Answer

Squamous (50%), adenocarcinoma, adenoid cystic, melanoma, esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), small cell, sarcoma (RMS), lymphoma, plasmacytoma, and mets.

What nonmalignant entities present as a mass in the PNS or the nasal cavity?

Show Answer

Sinonasal polyposis, choanal polyps, and juvenile angiofibromas.
What sinuses make up the PNS?

Show Answer

The **frontal, ethmoid, sphenoid, and maxillary** sinuses make up the PNS.
What structures border the maxillary sinus?

Show Answer

Anterior: facial bone
Anterolateral: zygomatic arch
Posterolateral: infratemporal fossa
Posterior: pterygopalatine fossa
Superior: orbital floor
Inferior: hard palate
Medial: nasal cavity
What is the name for the thin bone in the medial wall of the orbit that is prone to erosion/breakthrough by ethmoid tumors?

Show Answer

The thin bone of the medial orbital wall is called the **lamina papyracea.**
What is the local invasion pattern of ethmoid tumors?

Show Answer

Superiorly through the cribriform plate to the ant cranial fossa or **medially** through the lamina papyracea into the orbit.
Which is the most common sinus/site of origin for PNS tumors?

Show Answer

The **maxillary sinus** is the most commonly involved sinus/site for PNS tumors (70%–80%).

What is the most common site for ENB?

Show Answer

The **nasal cavity**.

What environmental exposures are associated with the development of sinonasal/PNS tumors?

Show Answer

Industrial fumes, wood dust, nickel, chromium, hydrocarbons, formaldehyde, nitrogen mustard, air pollution. They have also been linked to HPV and EBV.

WORKUP/STAGING

What are some presenting Sx of sinonasal/PNS tumors?

Show Answer

Facial pain, nasal obstruction, nasal discharge, epistaxis, sinus obstruction, trismus (pterygoid involvement), ocular deficits (diplopia, blurry vision), facial pain d/t trigeminal neuralgia, midfacial hypesthesia from impingement of the infraorbital branch of CN V2, palatal mass/erosion, and otalgia.

What is the basic workup for sinonasal/PNS tumors?

Show Answer

PNS tumor workup: H&P w/ nasal endoscopy and Bx, labs, CT/MRI head/neck, CT chest, PET if stage III/IV, dental consult if required (per NCCN, 2018).

Describe the T staging of maxillary and nasal cavity/ethmoid tumors per the latest AJCC (8^{th} edition, 2017) classification.

Show Answer

Maxillary

T1: confined to sinus, no bone erosion

T2: bone erosion w/o involvement of post wall of max sinus or pterygoid

plates

T3: invades post wall of max sinus, SQ tissues, **pterygoid fossa,** floor/medial wall of orbit, or ethmoid sinus

T4a: invades ant orbital structures, skin of cheek, **pterygoid plate,** infratemporal fossa, cribriform plate, sphenoid or frontal sinus

T4b: invades orbital apex, NPX, clivus, intracranial extension, CN involvement (except V2), dura, brain

Nasal Cavity/Ethmoid

T1: confined to 1 subsite, w/ or w/o bone invasion

T2: invades 2 subsites in a single region or extending to involve an adjacent region w/ in the nasoethmoidal complex, w/ or w/o bone invasion

T3: invades medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate

T4a: invades ant orbital contents, skin of nose or cheek, min extension to ant cranial fossa, pterygoid plates, sphenoid, or frontal sinuses

T4b: invades orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, NPX, or clivus

There is no formal T staging for frontal or sphenoid tumors!

How are the nodes staged for sinonasal/PNS tumors?

Show Answer

N1: single ipsi ≤3 cm and ENE–

N2a: single ipsi >3 and ≤6 cm and ENE– or single ipsi/contralat node ≤3 cm and ECE+

N2b: multiple ipsi nodes ≤6 cm and ENE–

N2c: bilat or contralat ≤6 cm and ENE–

N3a: node >6 cm and ENE–

N3b: single ipsi node >3 cm and ENE+ or multiple ipsi/contra/bilat nodes, any with ENE+

How are the overall sinonasal/PNS stage groups broken down (based on

TNM)?

Show Answer

Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or T1–3N1
Stage IVA: T4aN0–1 or T1–4aN2
Stage IVB: T4b or N3
Stage IVC: M1

What is Ohngren line, and why is it important?

Show Answer

The Ohngren line is a theoretic plane that extends **from the medial canthus of the eye to the angle of the mandible.** Tumors superoposterior to this line have deeper invasion, with many being unresectable (d/t invasion of the orbit, ethmoids, and pterygopalatine fossa). The relationship of a tumor to Ohngren line was an important prognostic factor, but with CT, MRI, and PET for imaging tumors, the significance of this line is principally historic.

For sinonasal/PNS tumors, what factors predict for nodal mets?

Show Answer

Neck nodal involvement is uncommon at Dx except **when tumors have progressed to involve the mucosal surfaces** (i.e., oral cavity, maxillary gingiva, or gingivobuccal sulcus). Histology is also predictive; squamous and undifferentiated tumors most commonly present with nodes, while nodal Dz is very uncommon with adenoid cystic and adenocarcinomas.

What neck node groups are generally involved with sinonasal/PNS tumors?

Show Answer

Retropharyngeal (1st echelon), Level Ib, II, and periparotid nodes are most commonly involved.

What subsite of PNS tumors has the highest rate of nodal mets?

Show Answer

Maxillary sinus tumors have the highest rate of nodal mets (10%–15%) of all PNS tumors.

What is the 5-yr OS rate for maxillary/ethmoid sinus tumors (all stages)?

Show Answer

~45%

What is the 5-yr OS rate for N+ maxillary and ethmoid sinus tumors?

Show Answer

Maxillary: ~15%, Ethmoid: 0%

What is the overall LC rate for sinonasal/PNS tumors?

Show Answer

50%–60%

TREATMENT/PROGNOSIS

How are sinonasal/PNS tumors typically managed?

Show Answer

Surgical resection and adj RT +/- chemo. Consider induction chemo in SNUCs, small cell, sinonasal neuroendocrine tumors, very advanced primary squamous carcinomas.

Are there any RCTs that define Tx for sinonasal/PNS tumors?

Show Answer

No. Dz is rare and presents at multiple sites with varying histologies. It would be difficult to appropriately power an RCT.

What type of Sg is necessary to manage a maxillary sinus tumor?

Show Answer

Partial (2 walls of maxilla removed) **or total maxillectomy to –margins.**
For smaller tumors, endoscopic sinus surgery, with or without robotic assistance, is replacing open procedures. For larger medial tumors, a medial maxillectomy with a midfacial degloving technique is performed with an incision made under the lip (Caldwell–Luc). For tumors that are mainly inf, an infrastructure maxillectomy is often performed. For larger tumors, access through the nasal crease/upper lip may be necessary. Tumors involving the orbital floor or orbit often require orbital exenteration. Reconstruction is done with skin grafting and obturator placement. Larger defects are filled with free flaps.
How are ethmoid sinus tumors managed surgically?

Show Answer

Ethmoid sinus tumors are surgically managed by either endoscopic sinus surgery for small tumors or **craniofacial resection,** requiring access both anteriorly through the sphenoethmoid area (through the nose) and superiorly with a craniotomy (neurosurgery) to address the skull base/dura.
When is orbital exenteration necessary in sinonasal/PNS tumors, and when is it not absolutely necessary?

Show Answer

It is necessary if extraocular muscles, optic nerve, bulb, or eyelid are involved. It is not necessary if there is only bone erosion or periorbital fat involvement.
What are some indications for definitive radiotherapy in the management of sinonasal/PNS tumors?

Show Answer

Inoperable tumors (medically and technically).
What are the indications for adj radiotherapy after resection of sinonasal/PNS tumors?

Show Answer

Maxillary sinus T3–T4 lesions or T1–2 adenoid cystic above Ohngren line, ethmoid sinus T2–T4 lesions (can consider omission of adj RT in T1 ethmoid per NCCN 2018), N+, + or close margins, +PNI, +LVSI, high-grade histology.

How is radiotherapy delivered and to what dose?

Show Answer

IMRT, volumetric modulated arc therapy, IGRT, proton beam therapy approaches, to **70 Gy (definitively) or 60–66 Gy (adj), to the tumor bed and margins; 50–56 Gy to low-risk areas.** Use image fusion (MRI/PET) for planning purposes.

Per the NCCN (2018), what altered RT fractionation regimens can be employed for maxillary sinus tumors when definitive RT is delivered without chemo?

Show Answer

Per **NCCN 2018:**

Accelerated (6 fx/wk during wks 2–6): 66–70 Gy for gross Dz and >50 Gy for subclinical Dz

Concomitant boost (bid last 2 wks): 72 Gy over 6 wks (1.8 Gy/fx large field and 1.5 Gy/fx same-day boost over last 2 wks)

Hyperfractionated: 1.2 Gy/fx bid to 81.6 Gy over 7 wks

Is concurrent chemo a standard approach in the definitive management of sinonasal/PNS tumors with RT?

Show Answer

No. Prospective trials are evaluating CRT, and it can certainly be considered based on principles for other H&N cancers for which concurrent chemo is recommended (stages 3–4 treated definitively, or +margins or nodes with

ECE in the adj setting).
For which tumors should elective neck management be considered (with Sg or RT)?

Show Answer

Elective neck management should be strongly considered for **tumors with squamous or undifferentiated histology and for T3 or T4 tumors of other histologies.** It is controversial for ENB, though recommended by many centers. It may be left out for other subsites with N0 Dz.
What studies/data support the use of ENI for maxillary sinus tumors?

Show Answer

Stanford data (Le QT et al., IJROBP 2000): 97 pts (36 RT alone, 61 Sg + RT), 12% nodal failure overall in levels I–II; 5-yr nodal failure risk 20% – ENI, 0% +ENI; 5-yr distant relapse rate 29% with neck control, 81% if neck failure.

MDACC data (Bristol I et al., IJROBP 2007): SCC/undifferentiated histologies nodal failure 36% in 36 pts without ENI vs. 7% in 45 pts with ENI.

What have recent studies demonstrated regarding the use of adj IMRT for sinonasal/PNS tumors?

Show Answer

There was **no significant improvement in terms of LC or OS;** however, there was a lower incidence of complications with IMRT. (Madani I et al., IJROBP 2009; Dirix P et al., IJROBP 2010)
What did the 2017 NCDB analysis (Robin TP et al., Cancer 2017) show regarding the multimodality management of sinonasal/PNS tumors?

Show Answer

Sup OS with multimodality therapies vs. Sg alone; adj RT (HR 0.658, $p < 0.001$), adj CRT (HR 0.696, $p = 0.002$), or neoadj therapy (HR 0.656, p =

0.007); neoadj CRT associated with greater likelihood of achieving –margins (OR 2.641, p = 0.045).

FOLLOW-UP/TOXICITY

Describe the recommended f/u schedule for pts treated for PNS tumors.

Show Answer

PNS tumor f/u (per NCCN 2018): H&P (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, and q12 mos thereafter), imaging as clinically indicated (consider baseline imaging post Tx), TSH q6–12 mos if neck RT.

30

Oral Cavity Cancer

Updated by Brian Deegan

BACKGROUND

What is the incidence of oral cavity cancer (OCC) in the United States?

Show Answer

~24,000 cases/yr of OCC in the United States

What % of H&N cancers are OCCs?

Show Answer

OCCs comprise **25%–30%** of all H&N cancers.

What are the anatomical borders and of what structures does the OC consist?

Show Answer

Lips, gingiva, upper/lower alveolar ridge, buccal mucosa, retromolar trigone (RMT), hard palate, floor of mouth (FOM), oral tongue.

What is the most and least commonly involved site in OCC?

Show Answer

The lower **lip is the most common site** (38%), and the **buccal mucosa is the least common site** (2%). The tongue is involved 22% of the time. (Krolls SO et al., J Am Dent Assn 1976)

What CNs provide motor and sensory innervation to the oral tongue?

Show Answer

Motor: CN XII
Sensory: CN V3 (lingual branch)
What CNs provide the tongue with taste sensation?

Show Answer

Ant two-thirds of tongue: CN VII (chorda tympani)
Post one-third of tongue: CN IX
Which nerve provides motor innervation to the lips?

Show Answer

The **facial nerve** (CN VII) provides motor innervation to the lips.
Where is the ant-most border of the OC?

Show Answer

The **vermilion border of the lips** is the ant-most border of the OC.
Where is the post-most border of the OC?

Show Answer

The **hard/soft palate junction superiorly and the circumvallate papillae inferiorly.**
What are some premalignant lesions of the OC, and which type has the greatest propensity to progress to invasive cancer?

Show Answer

Erythroplakia (~30% progression rate) **and leukoplakia** (4%–18% progression rate)
What are some risk factors that predispose to OCC?

Show Answer

Tobacco and alcohol. Also, betel nut consumption, periodontal Dz, sun exposure (lip).

What are the sup and inf spans of levels II–IV LN chains/levels?

Show Answer

Level II: skull base to bottom of hyoid
Level III: infrahyoid to bottom of cricoid
Level IV: infra-cricoid to clavicles
Where are the levels IA–IB nodes located?

Show Answer

Level IA nodes are **submental** (space b/t the ant belly of the digastric muscles), and level IB nodes are **submandibular** (space lat the digastric muscle and mandible).
Where are the levels V–VI nodes located?

Show Answer

Level V nodes are in the **post triangle.** Level VI nodes are in the central compartment **paratracheal/prelaryngeal region.**
What is the Delphian node?

Show Answer

The Delphian node is a **midline prelaryngeal level VI node.**
What is the estimated risk of LN involvement with a T1–T2 primary of the lip, FOM, oral tongue, and buccal mucosa?

Show Answer

The risk of LN involvement is **~5% for the lip, 20% for the oral tongue, and 10%–20% for the other OC T1–T2 primaries.**
What is the estimated risk of LN involvement with a T3–T4 primary of the lip, FOM, oral tongue, and buccal mucosa?

Show Answer

The risk of LN involvement is **~33% for the lip and 33%–67% for the**

other OC T3–T4 primaries.
What is the nodal met rate for a T1 vs. T2 lesion of the oral tongue?

Show Answer

The nodal met rate is **14% for T1 tongue lesions and 30% for T2 tongue lesions.** (Lindberg R et al., Cancer 1972)
What is the overall and stage-by-stage nodal met rate for FOM lesions?

Show Answer

Overall: 20%–30%

T1: 10%
T2: 30%
T3: 45%
T4: >50%

(Lindberg R et al., Cancer 1972)
Lesions located where in the OC predispose to bilat LN mets?

Show Answer

Midline and anterolat OC lesions (tongue, FOM) predispose to bilat LN mets.
Which OC cancer has the greatest propensity for LN spread?

Show Answer

Oral tongue cancer has the greatest propensity for LN spread.
What OC subsite is 2nd only to the oral tongue in propensity for nodal spread?

Show Answer

The **alveolar ridge/RMT** has the 2nd highest propensity for LN spread (3rd highest is FOM).
Can ant oral tongue lesions involve other LN levels without involving

level I LNs?

Show Answer

Yes. ~13% of ant tongue lesions skip the level I LNs. (Byers RM et al., Head Neck 1997)
Which anatomic structure divides the oral tongue from the base of tongue (BOT)?

Show Answer

The **circumvallate papillae** divide the oral tongue from the BOT.
What is the most common site of minor salivary cancers?

Show Answer

Hard palate
What are common sites of DM for cancers of the OC?

Show Answer

Lungs, bones, and liver
What anatomic structure divides the FOM anteriorly into 2 halves?

Show Answer

The **lingual frenulum** divides the FOM anteriorly.
Where is the Wharton duct located, and what gland does it drain?

Show Answer

The Wharton duct **opens at the ant FOM** (midline) and **drains the submandibular gland.**
From where in the OC do most gingival cancers arise?

Show Answer

Most (80%) gingival cancers arise from the **lower gingiva.**
Do most lip cancers arise from the upper or lower lip?

Show Answer

Most (~90%) lip cancers arise from the **lower lip.**
What are some benign lesions that arise from the lip?

Show Answer

Benign lip lesions include **keratoacanthoma, actinic keratosis, hemangiomas, fibromas, HSV, and chancre.**
What nodal groups drain the tip of the tongue, the ant tongue, and the post tongue?

Show Answer

Tip of tongue: level IA
Ant tongue: level IB and level III (midjugular)
Post tongue: level IB and level II
Which OC site lesions are notorious for skipped nodal mets?

Show Answer

Ant oral tongue lesions can skip levels II–III and involve only level IV (so a full neck dissection is typically needed).
What features of lip cancer predict for nodal spread?

Show Answer

DOI, high grade, large size, invasion of buccal mucosa/dermis, or recurrent Dz after resection
What nodal stations are involved with upper vs. lower lip lesions?

Show Answer

Upper lip lesions spread to preauricular, facial, parotid, and IA–IB LNs; lower lip lesions spread to levels IA–IB and level II LNs.

WORKUP/STAGING

A pt presents with tongue deviation to the left. What CN is involved?

Show Answer

The **left CN XII** (hypoglossal) is involved with left tongue deviation (deviation is toward the involved nerve).
A pt presents with an OC lesion and ipsi ear pain. What nerve is responsible?

Show Answer

The **auriculotemporal nerve** (branch of **CN V3**) causes ear pain in OCC.
Which lesions in the OC are most and least likely to present with +LNs?

Show Answer

Most likely: tongue, FOM
Least likely: lips, buccal mucosa, gingiva
What are some common presenting signs with OC lesions?

Show Answer

Asymptomatic red/raised lesion, ill-fitting dentures, bleeding mass, pain, dysphagia (d/t tongue fixation), trismus (pterygoid/masticator space involvement), and otalgia
What does the typical workup of OC lesions entail?

Show Answer

OC lesion workup: H&P with palpation, mirror/fiber optic exam, Bx, CBC, CMP, CT/MRI H&N, chest imaging, consider PET/CT for stage III or greater.
What is the DDx for lesions of the OC?

Show Answer

SCC, minor salivary gland tumors, lymphoma, melanoma, sarcoma, plasmacytoma, and ameloblastoma
What defines T categories of the OC (AJCC 8th edition)?

Show Answer

T1: ≤2 cm, ≤5 mm DOI (DOI is NOT tumor thickness)
T2: ≤2 cm, DOI >5 mm and ≤10 mm, **or** >2 cm but ≤4 cm and DOI ≤10 mm
T3: >4 cm **or** DOI >10 mm
T4a: LIP: invasion of bone or involved inf alveolar nerve, FOM, skin of face
OC: invasion of adjacent structures (bone, deep tongue muscles, maxillary sinus, skin)
T4b: very advanced (invasion of masticator space, pterygoid plates, skull base, carotid artery), typically unresectable

What is the clinical nodal staging OCC (AJCC 8th edition)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi >3 cm and ≤6 cm ENE(–)
N2b: multiple ipsi, ≤6 cm and ENE(–)
N2c: bilat or contralat, ≤6 cm and ENE(–)
N3a: >6 cm and ENE(–)
N3b: clinically overt ENE(+)

What is the pathologic nodal staging OCC (AJCC 8th edition)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi ≤3 cm and ENE(+) **or** single ipsi >3 cm and ≤6 cm ENE(–)
N2b: multiple ipsi, ≤6 cm and ENE(–)
N2c: bilat or contralat, ≤6 cm and ENE(–)
N3a: >6 cm and ENE(–)
N3b: single ipsi >3 cm ENE(+) **or** multiple ipsi/contra/bilat nodes any with ENE(+)

Are radiographic findings alone sufficient for ENE?

Show Answer

No. Radiographic evidence alone is insufficient. Exam findings are required (e.g., skin involvement, tethering to adjacent structures, CN findings, etc.), though radiographic evidence should be in support of the physical exam.
What is the OCC group staging?

Show Answer

Stage I: T1 N0
Stage II: T2 N0
Stage III: T3 N0 **or** N1 (T1–T3)
Stage IVA: T4a **or** N2
Stage IVB: T4b **or** N3
Stage IVC: M1
If RT is anticipated for OCC, what should be done and when should it be done before starting Tx?

Show Answer

Dental evaluation (teeth extractions, fluoride trays) should be done 10–14 days before RT.
What is the most common location involved in oral tongue cancers?

Show Answer

The **lat undersurface of the tongue in the middle to post 3rd** is most commonly involved.
What is the overall bilat nodal involvement rate for oral tongue cancers?

Show Answer

5% of oral tongue cancers present with bilat neck Dz (most nodal Dz is ipsi).
If N+, there is an ~30% risk for bilat Dz.
What 2 factors are most predictive of nodal involvement in oral tongue cancers?

Show Answer

DOI and tumor thickness are most predictive of LN mets in oral tongue cancers.
What are the 2 most important prognostic factors after Sg alone for buccal mucosa cancers?

Show Answer

DOI ≥3 mm or tumor thickness ≥6 mm are the most important prognostic factors for buccal mucosa cancers. (Urist MM et al., Am J Surg 1987)

TREATMENT/PROGNOSIS

In general, what is the Tx paradigm for OCC?

Show Answer

OCC Tx paradigm: **Sg +/- PORT (+/- chemo)**
What pathologic features of the OCC primary lesion call for prophylactic/elective neck management?

Show Answer

Tumor thickness >2 mm, grade III Dz, +LVI, lower alveolar ridge and RMT, and a recurrent lesion are features that increase the need for prophylactic neck management.
What are the indications for PORT?

Show Answer

N2 or N3, low neck nodes or >2 LN levels, T3/T4, +/close margins, no neck dissection in high-risk pts, and LVI, PNI are indications for PORT.
In what circumstances should chemo be added to PORT?

Show Answer

Chemo should be administered with RT if there is a **+margin, +ECE** (per Bernier and Cooper adj RCT of PORT vs. PORT + chemo). (Bernier J et al., NEJM 2004; Bernier J et al., J Head Neck 2005; Cooper JS et al., IJROBP

2012)
When is bilat neck dissection recommended for lesions of the OC?

Show Answer

Bilat neck dissection is recommended with ≥**N2c Dz** (bilat or bulky LNs).
For what OC sites is definitive RT preferred?

Show Answer

Definitive RT is preferred (over Sg) for **lip commissure and RMT lesions with tonsillar pillar involvement.**
What is generally considered a close margin?

Show Answer

<5 mm
What are the indications for PORT to the primary site for OC lesions?

Show Answer

+ or close margin, PNI/perivascular invasion, and T3–T4 Dz are indications for PORT.
What RT doses are typically used in OCC?

Show Answer

PORT: **60 Gy** (–margins) to **66 Gy** (+margins) in 2 Gy/fx
Definitive RT: **70 Gy** to gross Dz +/– chemo
When is brachytherapy indicated for OCC?

Show Answer

Definitive: early (T1–T2) lip/early oral tongue/FOM lesions—LDR to **66–70 Gy** in 1 Gy/hr
As a supplement: T4 tongue/FOM lesions, 40% of total dose or **~30 Gy**
For oral tongue lesions, which modality is associated with better LC: LDR or HDR?

Show Answer

Both modalities yield similar results. 5-yr LC was 76%–77% for both HDR and LDR techniques in a phase III comparison. (Inoue T et al., IJROBP 2001)

What are the common LDR and HDR doses used with an interstitial implant for OCC?

Show Answer

LDR: 60–70 Gy (0.4–0.6 Gy/hr)
HDR: 60 Gy (5 Gy bid × 12 fx)

What alternate teletherapy modalities can be employed for superficial OC lesions?

Show Answer

An **intraoral cone** can be employed for superficial OC lesions: orthovoltage (100–250 keV) or electrons (6–12 MeV).

Why is a tongue depressor/bite block used when irradiating the OC?

Show Answer

A tongue depressor is used to **spare the sup OC/palate and to surround the lat oral tongue lesion with other mucosa** to minimize air tissue interfaces and maximize dose buildup.

What kind of surgical resection is typically performed for leukoplakia or CIS of the lip?

Show Answer

Vermilionectomy with advancement of the mucosal flap (“lip shave”), which involves simple excision from the vermilion to the orbicularis muscle.

When is Sg an option for cancers of the lip?

Show Answer

Sg is an option **if the lesion involves <30% of the lip, if it is a T1 lesion, or the lesion does** not **involve the oral commissure;** otherwise, use RT. Sg is typically WLE with primary closure (W-shaped excision) and with a 0.5-cm gross margin.

When is definitive RT used for cancers of the lip?

Show Answer

Definitive RT is used for lip tumors **>2 cm, large lesions** (**>50% of the lip), upper lip lesions, or if the lesion involves the oral commissure.**

Is elective nodal RT of the neck required for T1–T2 cancers of the lip?

Show Answer

No. Elective nodal RT is not needed b/c the occult nodal positivity rate is only ~5%.

What are the doses used for the Tx of T1–T2 cancers of the lip?

Show Answer

T1: 50 Gy (2.5 Gy × 20)
T2: 60 Gy (2.5 Gy × 24) with 100–250 keV photons or 6–9 MeV electrons + 1-cm bolus

When is PORT indicated for lip cancers?

Show Answer

PORT is indicated for lip cancers in case of **T4 Dz (bone invasion), +margin, extensive PNI, +ECE, ≥2 nodes+, or T3–T4 Dz without dissection of the neck.**

What randomized evidence supports PORT over Sg alone for stages III–IV SCC of the buccal mucosa?

Show Answer

Indian data. Mishra RC et al. showed improved 3-yr DFS with PORT (68% vs. 38%). (Eur J Surg Oncol 1996)

Is bilat neck RT required for stage III–IV buccal mucosa lesions?

Show Answer

No. Ipsi RT may be sufficient for stages III–IV buccal mucosa lesions. (Lin CY et al., IJROBP 2008)
What must the PORT field include for gingival lesions with PNI?

Show Answer

PORT fields for gingival lesions with PNI must include the **entire hemimandible** (from the mental foramen to the temporomandibular joint).
What randomized data support the need for PORT for OC lesions based on specific risk factors?

Show Answer

MDACC series (Ang KK et al., IJROBP 2001): pts with a +margin, PNI, and ECE had higher failure rates.
For RMT/alveolar ridge tumors, in what circumstances is RT preferred over Sg and vice versa?

Show Answer

Definitive RT preferred if there is no bone erosion or if the lesion extends to the ant tonsillar pillar, soft palate, or buccal mucosa. If there is bone erosion, then Sg is preferred → PORT.
What is the preferred management approach for hard palate lesions?

Show Answer

Generally, initial Sg is preferred for all cases, except if there is extension to the soft palate or RMT, in which case definitive RT can be considered.
Per NCCN guidelines, what is the recommended time interval b/t Sg and PORT for OCC?

Show Answer

Per **NCCN** guidelines, the recommended time interval b/t Sg and PORT for OCC is **6 wks.**

FOLLOW-UP/TOXICITY

Why is brachytherapy generally avoided for gingival lesions?

Show Answer

There is a **high risk of osteoradionecrosis** with brachytherapy for gingival lesions.

To avoid malnutrition during a course of RT or CRT, pts need at least how many calories/day?

Show Answer

To avoid malnutrition during a course of RT or CRT, pts need at least **2,000 calories/day.**

The mandible should be kept at or below what RT dose?

Show Answer

The max mandibular RT dose should be **≤70 Gy.**

What does the f/u for OCC pts entail (NCCN 2018)?

Show Answer

OCC follow-up: H&P + laryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, and q12 mos if >5 yrs), imaging (for signs/Sx), annual TSH (if the neck is irradiated), speech/hearing/dental evaluation, and smoking cessation

31

Oropharyngeal Cancer

Updated by Hubert Pan and Gopal K. Bajaj

BACKGROUND

What is the incidence of oropharyngeal cancer (OPC) in the United States?

Show Answer

~36,000 cases/yr of OPC in the United States with 6,850 deaths (2013 data)

How does the incidence of OPC compare to that of other H&N sites?

Show Answer

The incidence of **OPC is increasing,** whereas **cancer of other H&N sites is decreasing.**

Is there a sex predilection for OPC?

Show Answer

Yes. Males are more commonly affected than females (3:1).

What are the 4 subsites of the OPX?

Show Answer

Soft palate, tonsils, base of tongue (BOT), and pharyngeal wall

From which subsite do most OPCs arise?

Show Answer

The **tonsil** (ant tonsil pillar and fossa) is the most common primary site.

What are the borders of the OPX?

Show Answer

Anterior: oral tongue/circumvallate papillae
Superior: hard palate/soft palate junction
Inferior: valleculae
Posterior: pharyngeal wall
Lateral: tonsil

What 3 structures make up the walls of the tonsillar fossa?

Show Answer

Walls of the tonsillar fossa:

- Ant tonsillar pillar (palatoglossus muscle)
- Post tonsillar pillar (palatopharyngeus muscle)
- Inf glossotonsillar sulcus

What are the 4 most important risk factors for the development of OPC?

Show Answer

Risk factors for developing OPC:

- Smoking
- Alcohol
- HPV infection (up to 80% of cases now)
- Betel nut consumption

What is the 1st-echelon drainage region for most OPCs?

Show Answer

The 1st-echelon drainage site for most OPCs is the **level II (upper jugulodigastric) nodes.**

Are skip mets common for OPC?

Show Answer

No. Skip mets are **extremely rare** in OPC (<1%).
What are the 2 most common histologies encountered in the OPX? Rare histologies?

Show Answer

Most common histologies: squamous cell carcinoma (SCC) (90%), non-Hodgkin lymphoma (10% tonsil, 2% BOT)
Rare histologies: lymphoepithelioma, adenoid cystic carcinoma, plasmacytoma, melanoma, small cell carcinoma, mets
What proportion of pts with OPC fail locoregionally vs. distantly?

Show Answer

1:1 proportion of locoregional:distant failures
How prevalent is HPV infection in OPC?

Show Answer

Depending on the series, **40%–80%** of OPCs are associated with HPV infection.
Which HPV serotype is most commonly associated with OPC?

Show Answer

HPV 16 is the most common serotype in OPC (80%–90%).
What is a surrogate marker of HPV infection in OPC that can be used as an indirect indication of HPV seropositivity?

Show Answer

The surrogate marker for HPV infection is **p16 staining;** E7 protein inactivates Rb, which upregulates p16.
Which pt population is most likely to present with HPV-related OPC?

Show Answer

Nonsmokers and nondrinkers are most likely to have HPV+ SCC of the

OPX.
Do HPV+ or HPV– OPC pts have a better prognosis?

Show Answer

HPV+ OPC pts have a better prognosis. Data from **RTOG 0129** (Ang KK et al., NEJM 2010) showed better 3-yr OS (82.4% vs. 57.1%) and risk of death (HR 0.42) for HPV+ pts. Smoking was an independent poor prognostic factor.
What is the hypothesis behind why HPV+ OPC pts have a better prognosis?

Show Answer

HPV+ H&N cancers are **usually in nonsmokers and nondrinkers, so p53 status is usually nonmutated;** p53 mutation (which is common in non–HPV-related H&N cancers) predicts for a poor response to Tx.

WORKUP/STAGING

What nerves are responsible for otalgia in cancers of the oral tongue, BOT, and larynx/hypopharynx (HPX)?

Show Answer

Oral tongue: CN V (auriculotemporal) → preauricular area
BOT: CN IX (Jacobson nerve) → tympanic cavity
Larynx/HPX: CN X (Arnold nerve) → postauricular area
What are the 4 extrinsic tongue muscles, and what are their anatomic spans?

Show Answer

Extrinsic tongue muscles (-glossus) and anatomic spans:

- Genioglossus (ant mandible to tongue)
- Styloglossus (styloid process to tongue)
- Palatoglossus (palate to tongue; also forms ant tonsillar pillar)

. Hyoglossus (hyoid bone to tongue)

What is the most common presentation of OPC?

Show Answer

The most common presentation is a **neck mass,** especially with HPV+ OPC.
What are additional common presenting Sx by OPX subsite?

Show Answer

Base of tongue: sore throat, dysphagia, otalgia, neck mass
Tonsils: sore throat, trismus (T4b), otalgia, neck mass
Soft palate: leukoplakia, sore throat with swallowing, trismus/perforation, phonation defect with advanced lesions
Pharyngeal wall: pain/odynophagia, bleeding
Describe the workup for a pt with an OPX mass (per NCCN 2018).

Show Answer

OPX mass workup: H&P (bimanual exam of the floor of mouth), labs, laryngoscopy, CT/MRI with contrast H&N, tissue Bx with HPV testing (EUA if necessary), CT chest, consider PET/CT for stages III–IV Dz, nutrition, speech/swallow, audiogram
If the neck mass Bx is positive, is an additional Bx of the primary lesion necessary?

Show Answer

Yes. A Bx of the primary (or suspected primary) should also be done.
What % of OPC pts have clinically +nodes? Clinically occult nodes? Bilat nodes?

Show Answer

~75% of OPC pts have clinically+ nodes at presentation, **30%–50%** have clinically occult nodes, and **~30%** have bilat nodes (especially BOT/midline).

What is the T staging of p16(-) OPC? How is it different for p16(+) OPC?

Show Answer

T staging of p16(–) OPC is as follows:

T1: ≤2 cm
T2: >2 cm, ≤4 cm
T3: >4 cm or extension to lingual surface of epiglottis
T4a (moderately advanced): invades larynx, deep/extrinsic tongue muscles, medial pterygoid, hard palate, mandible
T4b (very advanced): invades lat pterygoid muscle, pterygoid plate, lat NPX, skull base, carotid encasement

For p16+ OPC, T4a and T4b are combined into a single T4 designation.

What are the N and summary staging of p16(-) OPC?

Show Answer

N and summary staging for p16(–) OPC are the same as other H&N sites (except for NPX).

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi, >3 cm, ≤6 cm, ENE(–)
N2b: multiple ipsi, ≤6 cm, ENE(–)
N2c: any bilat or contralat, ≤6 cm, ENE(–)
N3a: any >6 cm, ENE(–)
N3b: any clinically overt ENE(+)
Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or T1–3N1
Stage IVA: T4aN0–1 or T1–4aN2
Stage IVB: T4b any N or any T N3
Stage IVC: any T any N M1

What is the N staging of p16(+) OPC?

Show Answer

Clinical

N1: any ipsi, ≤6 cm
N2: any contra or bilat LNs, ≤6 cm
N3: any >6 cm

Pathologic

N1: ≤4 LN positive
N2: >4 LN positive
What is the overall stage grouping for p16(+) OPC?

Show Answer

Clinical

Stage I: T1–2 N0–1
Stage II: T1–2 N2 or T3 N0–2
Stage III: any T N3 or T4 any N
Stage IV: M1

Pathologic

Stage I: T1–2 N0–1
Stage II: T1–2 N2 or T3–T4 N0–1
Stage III: T3–4 N2
Stage IV: M1

TREATMENT/PROGNOSIS

Broadly speaking, what OPC pts/stage groups are deemed early, intermediate, and advanced?

Show Answer

Based on RTOG 0129 and AJCC 8th edition staging:
Early: stages I–II (cT1–2N0) and select III (T2N1)

Intermediate/favorable: HPV(+) stages III–IV (without T2N1) in nonsmokers/drinkers, T3N0 (exophytic) regardless of HPV/smoking status
Advanced/unfavorable: HPV(–) smokers with stages III–IV Dz, T4 Dz regardless of HPV/smoking status
What are the Tx paradigms for early oropharyngeal tumors?

Show Answer

Early oropharyngeal tumor Tx paradigm: **surgical resection with selective neck dissection +/- PORT or definitive RT alone**
What are the Tx paradigms for intermediate oropharyngeal tumors?

Show Answer

Intermediate-group oropharyngeal tumor Tx paradigms: **Sg +/- postop CRT, altered fractionation RT, and CRT** (conventional fractionation)
What are the Tx paradigms for advanced/unfavorable oropharyngeal tumors?

Show Answer

Advanced/unfavorable oropharyngeal tumor Tx paradigm: **CRT (conventional)**
When is WLE alone appropriate for OPC?

Show Answer

Rarely. WLE may suffice in the rare instance of a small (<1 cm), ant tonsillar pillar lesion.
Is tonsillectomy ever adequate as a definitive Tx for tonsillar cancers?

Show Answer

Generally, **no.** Simple tonsillectomy is considered an excisional Bx and thus needs further definitive Tx. Radical tonsillectomy may be adequate in select cases but results in worse functional outcomes than RT.
What type of Sg is required for the surgical management of OPC?

Show Answer

Historically, labiotomy and mandibulotomy were required to gain access to the OPX, but there is growing experience with transoral approaches with transoral laser microsurgery (TLM) and **transoral robotic surgery (TORS).**
When is PORT indicated for OPC? When is postop CRT indicated for OPC?

Show Answer

Similar to other H&N sites, PORT is generally for intermediate-risk factors such as **T3–T4, LN+, LVSI, and PNI,** while postop CRT is indicated for **+margin or +ENE.**
When can unilat neck Tx be considered for OPC pts?

Show Answer

Unilat neck Tx can be considered **if the lesion is well lateralized** (T1–T2, <1 cm soft palate extension, no BOT involvement) **and 1 or few regional ipsi nodes <6 cm** based on multiple retrospective reviews showing a very low contralat failure rate (<3%).
Which LN regions/levels should be irradiated in pts with an early T stage but N+ OPC?

Show Answer

Levels II–IV should always be included/irradiated; however, some data (Sanguineti G et al., IJROBP 2009) suggest that levels I and V may be omitted d/t a significantly lower incidence of nodal spread.
What is the main indication for a neck dissection after definitive CRT for OPC?

Show Answer

The main indication for a neck dissection after CRT is **persistent nodal Dz** that can be documented by fine-needle sampling, CT (at 4–6 wks), or

PET/CT (at 10–12 wks).
What is the recommended timing for a neck dissection after CRT?

Show Answer

Neck dissection should typically occur at **6–8 wks** (**12–15 wks** if evaluated by PET/CT).
How should OPC pts be set up for simulation?

Show Answer

OPC pts should be simulated **supine, with arms pulled inferiorly and the head extended with a bite block or stent.** Contrast is recommended with CT.
What type of custom stent can be used?

Show Answer

Mouth opening, tongue depressing stent
What should the pre-RT evaluation/preparation include?

Show Answer

Dental evaluation/fluoride prophylaxis, speech and swallow evaluation/exercises, and nutrition evaluation with a PEG tube if the pre-Tx weight loss is >10% over 3 mos
What are the typical CTVs for IMRT planning?

Show Answer

CTV high dose (CTVHD): primary tumor and nodal GTV with 0.5–1-cm margin
CTV intermediate dose (CTVID): soft palate, adjacent parapharyngeal space, sup tonsillar pillars for lat tumors, and nodal levels adjoining involved nodes
CTV elective dose (CTVED): levels II–IV, RP nodes. If node+, most include ipsi IB and V.

What are the typical RT doses and volumes used for OPC?

Show Answer

T1 and superficial T2N0: **66–70 Gy to CTVHD, 60 Gy to CTVID, and 54 Gy to CTVED, given in 30–35 fx over 6–7 wks**

>T2+ without chemo: (1) 70 Gy to CTVHD, 63 Gy to CTVID, and 56 Gy to CTVED given in 35 fx over 6 wks (per Danish Head and Neck Cancer Group [DAHANCA]); (2) 70 Gy to CTVHD, 60 Gy to CTVID, and 57 Gy to CTVED given in 33 fx

>T3 or >N2 with chemo: 70 Gy to CTVHD, 63 Gy to CTVID, and 59.5 Gy to CTVED in 35 fx

What is the 2-yr LF rate after IMRT alone for early (T1–2N0–1) OPC?

Show Answer

RTOG 00–22 (Eisbruch A et al., IJROBP 2010) demonstrated excellent results with accelerated hypofractionated IMRT for early OPC: **2-yr LF rate was 9%** (if major deviations, 50%; otherwise, 6%, SS).

What were the RT techniques and doses employed in RTOG 00–22? How was the N stage established?

Show Answer

In **RTOG 00–22** (Eisbruch A et al., IJROBP 2010), RT was delivered with **accelerated hypofractionated IMRT** as follows: 66 Gy in 30 fx (2.2 Gy/fx) to the primary PTV and 54–60 Gy in 30 fx (1.8–2 Gy/fx) to the secondary PTV. **Neck staging was clinical** (not from CT); however, pts "upstaged" by CT (e.g., cN1 but N2 after CT) were also eligible.

What did the RTOG 90–03 study demonstrate about the use of altered fractionation in H&N cancers?

Show Answer

RTOG 90–03 (Fu KK et al., IJROBP 2000): 1,073 pts with H&N cancers (10% OC, 60% OPX, 13% HPX) with stage III (28%) or stage IV (68%) Dz

randomized to (a) conventional 70 Gy qd, (b) 81.6 Gy in 1.2 Gy/fx bid, (c) accelerated with split, and (d) concomitant boost (1.8 Gy/fx qd × 17, with last 12 fx bid with 1.8 Gy AM, 1.5 Gy PM to 72 Gy). There was better LC with altered fx (54% vs. 46%) but no OS/DFS benefit. There was worse acute toxicity but no difference in late toxicity.

What randomized studies demonstrated better outcomes with hyperfractionated RT over conventional RT for OPC?

Show Answer

RTOG 90–03 (Fu KK et al., IJROBP 2000): see above.

EORTC 22791 (Horiot JC et al., Radiother Oncol 1992): 325 pts (all OPX, but no BOT): 70 Gy vs. 80.5 Gy at 1.15 Gy bid. There was better LC (60% vs. 40%) but no OS benefit. LC was best for T3 Dz.

What data showed good LC rates with RT alone for select advanced (stages III–IV) OPCs?

Show Answer

MDACC data (Garden AS et al., Cancer 2004): pts with small primaries but stages III–IV Dz by virtue of +LNs; treated with RT alone. There were acceptable 5-yr LF (15%), DM (19%), and OS (64%) rates.

What are 2 important randomized trials that demonstrated the importance of adding chemo to conventionally fractionated RT in OPC?

Show Answer

GORTEC 94–01 (Calais G et al., JNCI 1999): 222 pts with stages III–IV OPC randomized to conventional RT alone vs. conventional RT + carboplatin/5-FU, no planned neck dissection for N2–3 Dz. The CRT arm had better 3-yr OS (51% vs. 31%), DFS (30% vs. 15%), and LC (66% vs. 42%); however, there was significantly worse grades 3–4 mucositis and weight loss/feeding tube use in the CRT arm.

Head and Neck Intergroup Study (Adelstein DJ et al., JCO 2003): 295 pts

with unresectable stages III–IV H&N cancers (15% OC, 55% OPX, 20% HPX), RT alone vs. CRT with cisplatin 100 mg q3 wks × 3. 3-yr OS was better in the CRT arm (37% vs. 23%). There also was improved DFS (51% vs. 33%) in the CRT arm.

Pooled analysis from which 2 important RCTs support adding chemo to PORT in H&N cancers for +margin and ECE?

Show Answer

EORTC 22931 (Bernier J et al., NEJM 2004): 334 pts randomized to PORT 66 Gy vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: ECE, +margin, PNI, LVI, and levels 4–5 +N from OCC/OPC. There was better OS, DFS, and 5-yr LC with CRT but ↑ grades 3–4 toxicity.

RTOG 95–01 (Cooper JS et al., NEJM 2004): 459 pts randomized to 60–66 Gy PORT vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: >2 LN, ECE, +margin. There was better DFS (43% vs. 54%) and 2-yr LRC (72% vs. 82%) but only a trend to improvement in OS (57% vs. 63%).

What study demonstrated improvement in OS with the addition of cetuximab (C225) to RT in H&N cancers?

Show Answer

Bonner JA et al. (NEJM 2006): 424 pts with stages III–IV SCC of the OPX, laryngeal cancer, or HPX randomized to RT vs. RT + C225. RT options were conventional to 70 Gy, 1.2 bid to 72–76.8 Gy, or concomitant boost to 72 Gy. There was better 3-yr LRC (47% vs. 34%) and OS (55% vs. 45%) with C225 + RT. Subset analysis showed improvement mostly in OPC and in the altered fractionation RT arms (~50% treated with altered fractionation).

What studies are looking at Tx deintensification for HPV+ OPX?

Show Answer

1. **E1308:** Phase II, stages III/IV, induction chemo (paclitaxel, cisplatin,

cetuximab) f/b 54 Gy in 27 fx if CR or 69.3 Gy in 33 fx if PR, both with concurrent cetuximab. Although the study (Marur S et al., J Clin Oncol 2017) met its 2-yr PFS target based on historical control, other phase III trials indicate induction chemo adds toxicity without survival benefit (PARADIGM, DeCIDE).

2. **RTOG 1016:** Phase III, stages III/IV, treated with accelerated IMRT to 70 Gy/6 wks randomized to concurrent cisplatin vs. cetuximab.
3. **NRG HN002:** Phase II, stages III/IV, randomized to dose-reduced cisplatin CRT (60 Gy in 6 wks) vs. accelerated RT alone (60 Gy in 5 wks).

What 2 randomized studies demonstrated a benefit with induction taxane/platinum/5-FU (TPF) chemo over PF in pts with unresectable H&N cancers?

Show Answer

TAX 324 study (induction chemo → CRT) (Posner MR et al., NEJM 2007): 501 pts, unresectable stages III–IV H&N cancers (52% OPX, 13%–18% OC, larynx, HPX) randomized to induction platinum + 5-FU or TPF → CRT with carboplatin. There was better 3-yr OS (62% vs. 48%), MS (71 mos vs. 30 mos), and LRC (70% vs. 62%) in the TPF arm. Pts in the TPF arm had fewer Tx delays than in the platinum/5-FU arm despite higher myelotoxicity in the TPF arm (98% rcvd planned Tx in the TPF arm vs. 90% in the PF arm).

TAX 323 study (induction chemo → RT) (Vermorken JB et al., NEJM 2007): 358 pts, unresectable stages III–IV H&N cancers (46% OPX, 18% OC, 29% HPX, 7% larynx) randomized to induction platinum + 5-FU or TPF → RT alone. TPF resulted in better median PFS (11 mos vs. 8.2 mos), MS (18.8 mos vs. 14.5 mos), and HR 0.73. The rate of toxic deaths was greater in the platinum/5-FU group (5.5% vs. 2.3%). Also, there was more grades 3–4 thrombocytopenia, anemia, stomatitis, n/v, diarrhea, and hearing loss in the platinum/5-FU arm. Neutropenia, leukopenia, and alopecia were more common in the TPF arm.

What study compared induction chemo vs. upfront CRT?

Show Answer

PARADIGM study (induction TPF → CRT vs. CRT) (Haddad H et al., Lancet Oncol 2013): 145 pts, stages III–IV (55% OPX), randomized to induction TPF → CRT vs. CRT. At a median follow-up of 49 mos, there was no difference in 3-yr OS (73% for induction vs. 78% for CRT), with a higher rate of febrile neutropenia observed in the induction arm.

What are some advantages and disadvantages of split-field IMRT (vs. whole-field IMRT) in the Tx of H&N cancers?

Show Answer

There is potentially **better laryngeal sparing with split-field IMRT techniques;** however, the drawback is that the **practitioner may have to junction the RT dose through involved nodes.**

What are the advantages and disadvantages of IMRT "dose painting" (vs. sequential plans) in the Tx of H&N cancers?

Show Answer

The main advantage of IMRT dose painting is that **better conformality can be achieved** in a single plan. The drawback, however, is that **nonstandard doses/fx are required.**

How do unplanned RT interruptions in H&N cancer affect LC rates and why?

Show Answer

Each wk of Tx-time prolongation **reduces the LC rate by ~10%–12%** in H&N cancer pts b/c of **accelerated repopulation.**

What is the best way to compensate for several/few missed RT sessions and avoid Tx-time prolongation in H&N cancer pts?

Show Answer

According to Bese NS et al. the best way to compensate is by preserving total time, dose, and dose/fx (i.e., can treat bid on Fridays or extra fx on Saturdays). Alternatively, dose/fx can be increased (e.g., by 0.5–0.7 Gy/day). (IJROBP 2007)

FOLLOW-UP/TOXICITY

What is the approximate long-term PEG tube dependency rate after CRT for OPC?

Show Answer

The long-term PEG tube dependency rate after CRT can be as high as **15%–20%,** which is reduced with efforts on sparing swallowing structures (pharyngeal constrictors, larynx) with swallowing exercises and the use of PEG on demand.

What are some typical RT dose constraints for the parotid glands?

Show Answer

Typical RT dose constraints for the parotid glands are (a) mean dose to either parotid **<26 Gy** or (b) at least 50% of either parotid gland **<30 Gy.**

What is the typical RT dose constraint for the inner ears?

Show Answer

The mean dose to the inner ears should be **≤35 Gy.**

Appx what % of pts receiving cisplatin-based chemo will experience hearing loss as a result of ototoxicity?

Show Answer

~30% of pts will experience hearing loss.

What were the xerostomia rates for OPC pts treated with IMRT in RTOG 00–22?

Show Answer

Xerostomia rates in **RTOG 00–22** (Eisbruch A et al., IJROBP 2010) were **55% at 6 mos, 25% at 1 yr, and 16% at 2 yrs.** Salivary output did not recover over time.

What was the observed rate of osteoradionecrosis with accelerated hypofractionated IMRT in RTOG 00–22?

Show Answer

The observed rate of osteoradionecrosis was **6%** in **RTOG 00–22** (Eisbruch A et al., IJROBP 2010), which is higher than expected for IMRT (potentially b/c of the accelerated hypofractionated approach). Other toxicities were acceptable (grade 2+ for mucosa [24%], salivary [67%], esophagus [19%]).

What oral care do all pts need to be instructed on?

Show Answer

Fluoride trays. Consult a dental oncologist before any dental procedures.

What is the follow-up paradigm for OPC pts?

Show Answer

OPC follow-up paradigm: H&P + pharyngolaryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, q12 mos if >5 yrs), imaging (for signs/Sx), annual TSH, speech/hearing/dental evaluation, and smoking cessation.

32

Salivary Gland Cancer

Updated by Hubert Pan

BACKGROUND

What is the incidence of salivary cancers in the United States?

Show Answer

~2,500 cases/yr of salivary cancers (~5% of all H&N cancers)

What is the sex predilection and median age at presentation for benign vs. malignant tumors?

Show Answer

Benign: female > male, 40 yo
Malignant: female = male, 55 yo

What is the most common type of benign tumor of the salivary gland, and where is it most commonly found?

Show Answer

Pleomorphic adenoma (65%). It is most commonly found in the **parotid glands.**

In addition to pleomorphic adenoma, what are some other benign salivary gland tumors?

Show Answer

Warthin tumor (papillary cystadenoma lymphomatosum), Godwin tumor

(benign lymphoepithelial lesion, associated with Sjögren), and monomorphic adenoma (oncocytoma, basal cell)
What is the most common malignant salivary gland tumor, and where is it most commonly found?

Show Answer

Mucoepidermoid carcinoma. It most commonly arises in the **parotid** (most are low grade, but if the tumor is high grade, it needs to be managed with Sg + LND + adj RT).
How are tumors of the salivary gland separated into low vs. intermediate vs. high grade by histology?

Show Answer

Tumors should be assigned a grade by the pathologist. Some tumors are assumed a grade unless specified, though it should always be verified. Acinic cell carcinoma is typically a low-grade tumor. Carcinoma ex-pleomorphic adenoma (CexPA), and salivary ductal carcinomas are almost always high grade. Mucoepidermoid carcinoma must be graded. Adenoid cystic carcinoma (ACC) is often low grade, but rather than grading, pathologists will describe ACC as either tubular, cribriform (low), or solid (high). ACC is often grouped with high-grade tumors as its propensity for poorly defined borders and neurotropism almost always requires multimodal therapy. The nomenclature for salivary gland tumors is also evolving. Thus, mixed malignant tumors are rarely seen as the majority are CexPA, and most adenocarcinomas seen are aggressive salivary duct carcinoma or low-grade polymorphous adenocarcinoma (most commonly seen in the hard palate).
What is the relationship b/t the gland size and malignant nature of the salivary tumor?

Show Answer

Typically, **the smaller the gland, the more malignant the tumor.**

What is the approximate incidence ratio of benign to malignant tumors in the various salivary glands?

Show Answer

Approximate incidence ratios of benign to malignant tumors:

- Parotid, ~75:25
- Submandibular gland, ~50:50
- Sublingual gland, ~10:90
- Minor salivary, ~20:80

What is the most common malignant histology arising in the submandibular gland?

Show Answer

ACC is the most common malignant histology of the submandibular gland.
What is the most common malignant histology arising in the minor salivary glands?

Show Answer

ACC is the most common malignant histology of the minor salivary glands.
Where are the minor salivary glands found in the H&N?

Show Answer

Minor salivary glands are found in the **mucosal lining of the aerodigestive tract.** Most are in the OC (85%–90%), with the palate (especially the hard palate) being the #1 site. They can be found in all sites of the OC, nasal cavity, PNS, OPX, and larynx.
What are the risk factors for developing salivary gland tumors?

Show Answer

Ionizing RT, personal Hx of tumor, and family Hx
What is the lymphatic drainage predilection of the parotid,

submandibular/sublingual, and minor salivary glands?

Show Answer

Lymphatic drainage predilection:

Parotid: preauricular, periparotid, and intraparotid, with deep intraparotid nodes draining sequentially along the jugular nodes (levels II–IV)
Submandibular/sublingual: levels I–II nodes, less often levels III and IV
Minor salivary: depends on site of involvement and histology
How does the propensity for LN mets relate to the site of origin of the salivary tumor?

Show Answer

The propensity for LN spread is **greatest for the minor salivary gland > submandibular/sublingual > parotid gland malignancies.**
What is the natural Hx of ACC?

Show Answer

ACC is often low grade (cribriform or tubular), but **is very locally infiltrative. PNI with skipped lesions and involvement of large nerves is common, as is DM. Recurrence can be very late,** though high-grade tumors (solid type) tend to have a more aggressive course. **Nodal mets are uncommon** (5%–8%).
What % of pts with ACC ultimately go on to develop lung mets?

Show Answer

~**40%** of pts with ACC ultimately develop lung mets.

WORKUP/STAGING

What is the most common presentation of parotid gland tumors?

Show Answer

A **painless, solitary mass** is the most common presentation of parotid gland

tumors.
For what does a painful growth/mass in the salivary gland predict?

Show Answer

It predicts for **malignancy or an inflammatory etiology/condition.**
What are some other presenting Sx in pts with salivary gland tumors?

Show Answer

Pain, facial weakness from CN VII involvement, rapid growth of mass, skin involvement, neck nodes. Sensory changes of the face can occur from involvement of the trigeminal nerve branches (CN V), and dysarthria/dysphagia can occur from CN XII being affected.
What is the DDx for a parotid mass?

Show Answer

Primary tumor, mets, lymphoma, parotitis, sarcoid, cyst, Sjögren syndrome, stone, lipoma, hemangioma
What are the 2 most important factors that predict for nodal mets in salivary gland malignancies?

Show Answer

Grade and size are the 2 most important factors that predict for nodal mets: high grade (50%) vs. intermediate/low grade (<10%) and size (>4 cm: 20% vs. <4 cm: 4%).
What is the typical workup performed for salivary gland tumors?

Show Answer

Salivary gland tumor workup: H&P (CNs/nodes), CBC, CMP, CXR, CT/MRI H&N, and FNA Bx
How should Bx be obtained for pts who present with a salivary gland mass?

Show Answer

Some argue that a salivary gland mass should be removed regardless, so do not Bx. However, FNA should be done (despite an FN rate of 20%), as knowledge of the histology may impact the type of Sg.

What is the T-staging breakdown for major salivary gland tumors (AJCC 8th edition)?

Show Answer

T1: ≤2 cm no extraparenchymal extension (ST invasion, clinical/macroscopic)
T2: >2 cm, ≤4 cm, no extraparenchymal extension
T3: >4 cm and/or extraparenchymal extension
T4(a–b): local invasion of adjacent structures (see below)

What is the distinction b/t T4a vs. T4b major salivary gland tumors?

Show Answer

T4a: usually still resectable; skin, mandible, ear, facial nerve invasion
T4b: usually unresectable; skull base, pterygoid plate, carotid artery encasement

What is the clinical nodal staging system used for major salivary gland tumors?

Show Answer

The same as most H&N sites (except for NPX and p16+ OPX):

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi, >3 cm, ≤6 cm, ENE(–)
N2b: multiple ipsi, ≤6 cm, ENE(–)
N2c: any bilat or contralat, ≤6 cm, ENE(–)
N3a: any >6 cm, ENE(–)
N3b: any clinically overt ENE(+)

What is the pathologic nodal staging system used for major salivary gland tumors?

Show Answer

The same as most H&N sites (except for NPX and p16+ OPX):

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi/contra ≤3 cm, ENE(+) OR single ipsi >3 cm, ≤6 cm, ENE(–)
N2b: multiple ipsi, ≤6 cm, ENE(–)
N2c: any bilat or contralat, ≤6 cm, ENE(–)
N3a: any >6 cm, ENE(–)
N3b: any ENE(+) besides N2a
Per the latest AJCC 8th (2017) edition classification, what are the stage groupings for major salivary gland tumors?

Show Answer

Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or T1–3N1
Stage IVA: T4aN0–1 or T1–4aN2
Stage IVB: T4b any N or any T N3
Stage IVC: M1
On what is the staging system for the minor salivary gland tumors based?

Show Answer

Staging of the minor salivary gland tumors is based on the **site of origin.**
What are some important prognostic factors in salivary gland tumors?

Show Answer

Size, grade, histology, nodal status, and "named" nerve involvement are important prognostic factors.
What is the 5-yr OS for stages I–IV cancers of the salivary gland?

Show Answer

Stage I: 80%
Stage II: 60%
Stage III: 50%
Stage IV: 30%
What is the 5-yr OS of pts who present with facial nerve involvement?

Show Answer

The 5-yr OS is **65% with simple invasion and 10% if pts have nerve dysfunction** (i.e., if symptomatic).

TREATMENT/PROGNOSIS

What is the general management paradigm for benign mixed/pleomorphic adenoma of the parotid?

Show Answer

Benign mixed/pleomorphic adenoma management paradigm: **WLE, or superficial parotid lobectomy → observation** (even if +margin or with extraglandular extension)
What is the management paradigm for low- to intermediate-grade tumors of the salivary gland?

Show Answer

Low- to intermediate-grade salivary gland tumor management paradigm: **surgical resection with PORT** for close (<2 mm) or +margin, unresectable Dz, pT3–4, PNI, capsule rupture, +nodes, or recurrent Dz
What is the management paradigm for high-grade tumors of the salivary gland?

Show Answer

High-grade salivary gland tumor management paradigm: **surgical resection** (facial nerve sparing if possible for parotid tumors), **including LND if node+**

→ **PORT**

What is the role of concurrent CRT?

Show Answer

The level of evidence for CRT is weak. NCCN guidelines (2018) recommend **consideration** of definitive CRT for T4b Dz or PORT + chemo for pathologic adverse features including intermediate or high grade, inadequate margins, PNI, +LN, and LVI.

What is the management paradigm for ACC with pulmonary mets?

Show Answer

ACC (cribriform or tubular) with pulmonary mets (typically asymptomatic with low tumor burden) management paradigm: **same local therapy as in pts without mets** b/c pulmonary mets have a long natural Hx

What is the difference b/t superficial, total, and radical parotidectomy?

Show Answer

Superficial: en bloc resection of gland superficial to CN VII
Total: en bloc resection of entire gland with nerve sparing
Radical: en bloc resection of entire gland + CN VII + skin + fascia +/– muscle

What are the indications for LND with salivary gland tumors?

Show Answer

A clinically+ neck. LND is often done for high-grade and large tumors, but in the clinically negative neck, if the pt is to get PORT, the role of LND is questionable.

What are the indications for PORT in the management of salivary gland cancers?

Show Answer

Adj RT is indicated for the following: **high grade (regardless of margin),**

close/+ margin, pT3–T4 Dz, PNI, capsule rupture, tumor spillage, ECE, N2–N3 Dz, unresectable tumor/gross residual Dz, and recurrent tumor
For which cN0 salivary gland tumors, by histology, does elective nodal RT significantly reduce the incidence of nodal relapse?

Show Answer

Elective nodal RT is more likely to reduce the incidence of nodal relapse in **pts with squamous, undifferentiated, or adenocarcinoma histologies.** (Chen AM et al., IJROBP 2007)
When should bilat neck coverage with RT be considered for salivary gland neoplasms?

Show Answer

Tx of the ipsi neck should be adequate for major salivary gland cancers. Bilat nodal Tx is considered for high-grade minor salivary gland cancers affecting midline structures.
What are some ways to deliver RT/set up the RT fields in the Tx of parotid gland tumors?

Show Answer

RT delivery and set up of RT fields:

- **AP/PA wedge pairs** (120-degree hinge angle) but difficult setup, exit through OC
- **Sup/Inf wedge pair** (with 90-degree couch kick), avoids exit through OC but exits through brain
- **Single direct field with mixed energy beam** (80% 15 MeV electron: 20% 6 MV photon) with bolus, electron portal 1 cm larger than the photon field b/c of IDL constriction with depth, higher dose to bone, keep contralat parotid at <30 Gy
- **IMRT** (most commonly utilized nowadays)

What are the PORT doses used in the management of salivary gland

tumors?

Show Answer

60 Gy for –margin, **66 Gy** for close/+margin, **70 Gy** for gross residual, and **50–56 Gy** to a low-risk neck

What RT techniques can be used in the management of the ipsi neck?

Show Answer

RT techniques for the ipsi neck:

1. Single lat appositional electron field
2. Mixed electron–photon beam technique
3. Half beam block technique
4. IMRT (most commonly utilized nowadays)

What key retrospective data demonstrated the importance of adding PORT for stages III–IV and high-grade salivary gland tumors?

Show Answer

MSKCC data (Armstrong JG et al., Arch Otolaryngol Head Neck Surg 1990; Harrison L et al., J Surg Oncol 1990) showed improved LC and survival. **SEER data** (Mahmood U et al., Arch Otolaryngol Head Neck Surg 2011) also showed improved survival.

What is the largest retrospective study demonstrating the benefit of adj RT for malignant salivary gland neoplasms?

Show Answer

Dutch NWHHT study (Terhaard CHJ et al., IJROBP 2005): 498 pts. Adj RT significantly improved LC in pts with T3–T4 Dz, a close margin, incomplete resection, bony invasion, and PNI.

What is the best RT modality for managing unresectable salivary gland tumors?

Show Answer

Neutrons (sup LC, with photons showing LC of 25% for inoperable cases). If no access to neutrons, some advocate concurrent CRT.
When is surgical resection alone adequate in the management of recurrent salivary gland tumors?

Show Answer

If tumors are of low/intermediate grade, <3 cm, and there are no other risk features, then Sg alone may suffice.

FOLLOW-UP/TOXICITY

What is Frey syndrome, and from what does it result?

Show Answer

Auriculotemporal nerve syndrome (gustatory sweating or redness and sweating on the cheek area when the pt eats, sees, or thinks about or talks about certain kinds of food). It is a **postop complication of parotidectomy.**
What is 1st bite syndrome, and from what does it result?

Show Answer

First bite syndrome is a rare complication of Sg involving the infratemporal fossa, parapharyngeal space or removal of the deep lobe of the parotid gland. It is characterized by facial pain after the 1st bite of each meal which usually subsides after subsequent bites. It is believed to be caused by autonomic dysfunction of salivary myoepithelial cells.
What are some possible Tx sequelae from RT for parotid cancers?

Show Answer

The main concerning sequelae are related to the ear. Acute effects include otitis externa or media with mild hearing loss. Late effects include dry cerumen, otitis media, and hearing loss. ORN of the temporal bone (parotid cancer) is uncommon as is mandibular ORN. Since Tx is mostly unilat, xerostomia is mild.

Above which RT doses can salivary gland function be compromised, resulting in xerostomia?

Show Answer

The parotid is the most sensitive gland d/t a large component of serous glands which are highly radiosensitive. There is no dose threshold. Min doses to effect parotid function start at ~14 Gy. Based on older data, mean doses of 26–30 Gy are still used as planning goals with IMRT, although doses as high as 40 Gy can still allow some recovery. The doses that result in damage to other salivary glands have not been well studied.

What is the general follow-up for pts with salivary gland neoplasms?

Show Answer

Per 2018 NCCN guidelines, H&P (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, and q12 mos thereafter), chest imaging if clinically indicated, and TSH q6–12 mos if neck RT

33

Laryngeal and Hypopharyngeal Cancers

Updated by Brian Deegan

BACKGROUND

What is the incidence of laryngeal cancer (LCX) in the United States?

Show Answer

~12,000 cases/yr of LCX (~20% of all H&N)

What are the risk factors for developing LCX?

Show Answer

Smoking, alcohol use, and voice abuse

What are the subsites of the larynx?

Show Answer

Supraglottic, glottic, and subglottic

What is the incidence/distribution of LCX according to subsite?

Show Answer

Glottic: 69%

Supraglottic: 30%

Subglottic: 1%

What % of premalignant lesions (leukoplakia/erythroplakia) progress to invasive laryngeal lesions?

Show Answer

20% of premalignant laryngeal lesions ultimately progress to invasive cancer (higher for erythroplakia than leukoplakia).
What is the most common LCX histology?

Show Answer

Squamous cell carcinoma (SCC) makes up >95% of LCX. Other histologies include verrucous carcinoma (1%–2%), adenocarcinoma, lymphoma, chondrosarcoma, melanoma, carcinoid tumor, and adenoid cystic carcinoma.
What are the subdivisions of the supraglottic larynx?

Show Answer

Supraglottic larynx: **Epiglottis (suprahyoid and infrahyoid), AE folds, arytenoids, ventricles, and false vocal cords** (FVCs)
What are the subdivisions of the glottic larynx?

Show Answer

Glottis: **Ant/Post commissures, true vocal cords** (TVCs)
What are the anatomic borders of the subglottic larynx?

Show Answer

Subglottis: **0.5 cm below the TVCs to the 1st tracheal ring**
What are the nodal drainage pathways of the various laryngeal subsites?

Show Answer

Supraglottic: levels II–IV
Glottic: virtually no drainage
Subglottic: pretracheal and Delphian (level VI)
What is the incidence of hypopharyngeal cancer (HPxC) in the United States?

Show Answer

There are **~2,500 cases/yr.**
What is the median age at Dx for HPxC?

Show Answer

The median age at Dx is **60–65 yrs** for HPxC.
What are the subsites of the hypopharynx (HPX)?

Show Answer

Pyriform sinus
Postcricoid area
Posterior pharyngeal wall

(Mnemonic: **“3 Ps”**)
What are the anatomic boundaries of the HPX?

Show Answer

The HPX spans from **C4–6 or from the hyoid bone to the inf edge of the cricoid cartilage.**
What is the sex predilection for HPxC based on the different subsites?

Show Answer

The sex predilection is **predominantly male for pyriform sinus and post pharynx primaries,** but **predominantly female for postcricoid area tumors.**
What are the classic risk factors for the development of HPxC?

Show Answer

Smoking, alcohol, betel nut consumption, nutritional deficiency (vitamin C, Fe [Fe deficiency is associated with 70% of postcricoid cancers in northern European women]), and prior Hx of H&N cancer
Is nodal involvement common with HPxC?

Show Answer

Yes. Nodal involvement is common due to abundant submucosal lymphatic plexus drainage to the retropharyngeal nodes, cervical LNs, paratracheal LNs, paraesophageal nodes, and SCV nodes.
What are the most commonly involved nodal stations in HPxC?

Show Answer

Levels II, III, and the retropharyngeal nodes are most commonly involved in HPxC. **Level VI** can also be involved and therefore should be covered when planning these cases for RT.
What is the name for the most sup of the lat retropharyngeal nodes?

Show Answer

The most sup of the lat retropharyngeal nodes is the **Node of Rouviere.**
What % of HPxC pts have nodal involvement at Dx?

Show Answer

~75% overall have nodal involvement at Dx (~60% for T1).
What is the typical histology seen in HPxC?

Show Answer

The predominant histology is **SCC** (>95%) → adenoid cystic, lymphoma, and sarcoma.
What are the most common subsites of origin for HPxC?

Show Answer

The **pyriform sinus (70%–80%), post pharyngeal wall (15%–20%), and postcricoid (5%)** are the most common subsites of origin.
At what cervical spine levels are the hyoid bone and the TVCs located?

Show Answer

The **hyoid bone is at C3,** whereas the **TVCs are located near C5–6.**

WORKUP/STAGING

How do pts with LCX typically present?

Show Answer

Hoarseness, odynophagia/sore throat, otalgia (via the Arnold nerve/CN X), aspiration/choking, and neck mass

What is the typical workup for pts presenting with a possible laryngeal mass?

Show Answer

Possible laryngeal mass workup: H&P (voice change, habits, indirect/direct laryngoscopy), CXR, CT/MRI, PET, basic labs, EUA + triple endoscopy, and Bx of the primary +/– FNA of the neck mass

What does the loss of the laryngeal click on palpation of the thyroid cartilage indicate?

Show Answer

Loss of the laryngeal click on exam indicates **postcricoid extension (or postcricoid tumor).**

What does pain in the thyroid cartilage indicate on exam?

Show Answer

Pain on palpation of the thyroid cartilage indicates **tumor invasion into the thyroid cartilage.**

What imaging modality is best to assess for bony or cartilage erosion in pts with LCX?

Show Answer

CT scan is best for assessing bony/cartilage erosion (bone window).

What is the incidence of nodal involvement for T1, T2, and T3–T4 glottic cancer?

Show Answer

T1: 0%–2%
T2: 2%–7%
T3–T4: 15%–30%
What is the incidence of nodal involvement for supraglottic lesions according to T stage?

Show Answer

T1–T2: 27%–40%
T3–T4: 55%–65% (Wang CC, Radiation therapy for head and neck neoplasms 1996)
What proportion of pts with supraglottic cancer present with unilat vs. bilat nodal Dz?

Show Answer

~55% of supraglottic cancer pts present with unilat nodal Dz, and **16%** present with bilat nodal involvement. (Lindberg R et al., Cancer 1972)
What % of pts with subglottic cancer present with nodal involvement?

Show Answer

20%–50% of subglottic pts present with nodal Dz (generally the prelaryngeal/Delphian, lower jugular, pretracheal or upper mediastinal nodes).
Describe the T staging for cancers of the supraglottic larynx (AJCC 8th edition, 2017).

Show Answer

T1: 1 subsite with normal VC mobility
T2: more than 1 adjacent subsite of supraglottis or glottis or region outside supraglottis (base of tongue, vallecula, medial wall of pyriform sinus) without fixation of larynx
T3: Larynx-confined with cord fixation and/or invasion of postcricoid area, pre-epiglottic space, paraglottic space and/or inner cortex thyroid cartilage

T4a (resectable): through outer cortex thyroid cartilage and/or beyond larynx (trachea, ST of neck, extrinsic muscles of tongue, strap muscles, thyroid, esophagus)

T4b: invasion of prevertebral space, encased carotid, mediastinum

Describe the T staging for cancers of the glottic larynx (AJCC 8th edition, 2017).

Show Answer

T1: limited to TVCs (+/– commissure involvement), normal mobility (T1a: 1 cord, T1b: both)

T2: extends to supra- or subglottis or impaired vocal cord mobility

T3: fixed vocal cords, confined to larynx and/or paraglottic space invasion and/or inner cortex thyroid cartilage

T4a–b: same as above/for supraglottic lesions

What is the T-staging breakdown for cancers of the subglottic larynx (AJCC 8th edition, 2017)?

Show Answer

T1: tumor limited to subglottis

T2: extension to vocal cords, with normal or impaired mobility

T3: limited to larynx with vocal cord fixation or paraglottic space extension, invasion of inner cortex thyroid cartilage

T4a–b: same as above

What is the clinical nodal staging for LCX (AJCC 8th edition, 2017)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)

N2a: single ipsi >3 cm and ≤6 cm ENE(–)

N2b: multiple ipsi, ≤6 cm and ENE(–)

N2c: bilat or contralat, ≤6 cm and ENE(–)

N3a: >6 cm and ENE(–)

N3b: clinically overt ENE(+)

What is the pathologic nodal staging for LCX (AJCC 8th edition, 2017)?

Show Answer

N1: single ipsi, ≤3 cm, ENE(–)

N2a: single ipsi or contralat ≤3 cm and ENE(+) **or** single ipsi >3 cm and ≤ 6 cm ENE(–)

N2b: multiple ipsi, ≤6 cm and ENE(–)

N2c: bilat or contralat, ≤6 cm and ENE(–)

N3a: >6 cm and ENE(–)

N3b: single ipsi >3 cm ENE(+) **or** multiple ipsi/contralat/bilat nodes any with ENE(+)

Describe the overall stage groupings for LCX (AJCC 8th edition, 2017).

Show Answer

Stages I: T1N0

Stage II: T2N0

Stage III: T3N0 or N1

Stage IVA: T4a or N2

Stage IVB: T4b or N3

Stage IVC: M1

With what stage of Dz do most pts with HPxC present?

Show Answer

Most pts (>80%) present with **stage III or IV Dz** (lesions often remain asymptomatic until advanced Dz).

What % of pts with HPxC present with DMs?

Show Answer

~2%–4% of HPxC pts present with DMs. ~20%–30% develop DMs within 2 yrs despite Tx.

With what Sx do most HPxC pts present?

Show Answer

Neck mass, sore throat, dysphagia, hoarseness (**direct vocalis or cricoarytenoid joint invasion**), and otalgia (Arnold nerve/CN X involvement)

What is the typical workup for pts who present with hoarseness?

Show Answer

Hoarseness workup: H&P (check for thyroid click), labs, CT/MRI, PET, neck FNA, EUA + triple endoscopy, and Bx of the primary mass

Describe the T staging of HPxC (AJCC 8th edition, 2017).

Show Answer

T1: 1 site of HPX and/or ≤2 cm
T2: more than 1 subsite or 2–4 cm without hemilarynx fixation
T3: >4 cm or fixation of hemilarynx or esophageal extension
T4a: invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, central STs (prelaryngeal strap muscles and SQ fat)
T4b: invades prevertebral fascia, encases carotid artery, or mediastinal structures

What is the nodal staging breakdown for HPxC (AJCC 8th edition, 2017)?

Show Answer

Same system as used for p16 negative OPX

N1: single ipsi, ≤3 cm, ENE(–)
N2a: single ipsi, >3 cm, ≤6 cm, ENE(–)
N2b: multiple ipsi, ≤6 cm, ENE(–)
N2c: any bilat or contralat, ≤6 cm, ENE(–)
N3a: any >6 cm, ENE(–)
N3b: any clinically overt ENE(+)

Describe the overall stage groupings for HPxC.

Show Answer

Stage I: T1N0
Stage II: T2N0
Stage III: T3N0 or N1
Stage IVA: T4a or N2
Stage IVB: T4b or N3
Stage IVC: M1

TREATMENT/PROGNOSIS

What does total laryngectomy entail?

Show Answer

It entails the **removal of the hyoid, thyroid and cricoid cartilage, epiglottis, and strap muscle with reconstruction of the pharynx as well as a permanent tracheostomy.**
What structures are removed with a supraglottic laryngectomy?

Show Answer

A supraglottic laryngectomy sacrifices the **FVCs, epiglottis, and aryepiglottic folds.**
What is the preferred surgical option for dysplastic lesions on the glottic larynx?

Show Answer

Mucosal stripping is typically curative for dysplastic lesions. Close follow-up is needed.
What are the Tx options for Tis lesions of the glottic larynx?

Show Answer

1. **Cord stripping/laser excision** (need close follow-up; cannot r/o microinvasive Dz) **or definitive RT**

What are the ~5-yr LC rates for glottic CIS with the use of stripping vs. laser vs. RT?

Show Answer

Stripping: 72%
Laser: 83%
RT: 88%–92% (all >95% after salvage)
What are the Tx options for T1–T2 glottic cancer?

Show Answer

Cordectomy (CO2 laser)/partial laryngectomy, or definitive RT
What are the 5-yr control and survival rates after hemilaryngectomy for T1–T2 glottic cancer?

Show Answer

After hemilaryngectomy, the **~5-yr LC is 83%** and the **DFS is 88%** for T1–T2 glottic cancer. (Scola B et al., Laryngology 1999)
What is the salvage Tx of choice for glottic lesions after RT failure?

Show Answer

The salvage Tx of choice is **total laryngectomy +/- neck dissection.**
What is the ~5-yr CSS rate for T1 glottic cancers treated with definitive RT?

Show Answer

The 5-yr CSS rate with RT is **>90%** (95% with salvage; organ preservation rate is >90%).
What are the advantages and disadvantages of using RT for early glottic cancer?

Show Answer

Advantages: better voice quality, noninvasive, organ preservation

Disadvantages: long Tx duration, RT changes could obscure post-Tx surveillance

What is the voice quality preservation rate for early glottic tumors/pts treated with laser vs. RT?

Show Answer

The JHH data (Epstein BE et al., Radiology 1990) suggest **better voice quality after RT** (laser: 31%, RT: 74%, p = 0.012). More recent RCT from Finland (Aaltonen L et al., IJROBP 2014) also suggest better voice quality with RT.

What are the initial and ultimate (after salvage) LC rates for T2 glottic lesions?

Show Answer

Initial LC is 70%–90% and **50%–70% after salvage** for T2 glottic lesions.

What are the currently accepted dose fractionation and total dose Rx for CIS and T1 glottic lesions?

Show Answer

The currently accepted RT doses are **60.75 Gy for CIS** and **63 Gy for T1,** at **2.25 Gy/fx.**

What is the typical RT dose used for T2 glottic lesions?

Show Answer

The typical RT dose for T2 lesions is **70 Gy at 2 Gy/fx** or **65.25 Gy at 2.25 Gy/fx.**

What randomized data/trial highlighted the importance of hypofractionation for early glottic cancers?

Show Answer

Japanese data (Yamazaki H et al., IJROBP 2006): 180 pts, 2 fractionations: 2 Gy/fx (60–66 Gy) vs. 2.25 Gy/fx (56.25–63 Gy). 5-yr LC rate was better

with 2.25 Gy/fx (92% vs. 72%). The greater toxicity for the hypofractionation regimen was acute skin erythema (83% vs. 63%).
What RT field sizes/spans are employed for Tis/T1 glottic cancers?

Show Answer

5 × 5 cm opposed lat fields—from the upper thyroid notch to the lower border of the cricoid, post border at the ant edge of the vertebral body, and flash skin at the ant border.
What RT planning technique can be used when treating T1 glottic lesions with ant commissure involvement?

Show Answer

Generally, for T1 glottic lesions, **wedges** are used (heel ant, usually 15 degrees) to reduce ant hotspots due to curvature of the neck. However, if there is ant commissure Dz, the wedges can be removed, or wedge angle reduced, to add hotspots to this region. Bolus/beam spoiler can be added for additional coverage anteriorly.
What structures must be encompassed by the 95% IDL when irradiating T1 glottic cancer?

Show Answer

The 95% IDL must encompass the **TVCs, FVCs, and the sup subglottis.**
What RT fields are used for T2 glottic lesions?

Show Answer

This is **controversial** and may depend on the degree of supraglottic/subglottic extension. Most advocate using 6 × 6 cm opposed lat fields; others advocate covering levels II–III nodes (2 cm above the angle of the mandible, splitting vertebral body, down to the bottom of the cricoid) to **50–54 Gy,** with CD to the 5 × 5 cm box covering the larynx to **70 Gy.**
What are the Tx options for early-stage supraglottic LCX?

Show Answer

Supraglottic laryngectomy, transoral laser resection, or definitive RT
What are the 5-yr LC and OS rates for early supraglottic cancers treated with Sg and LND?

Show Answer

The **5-yr LC rate is ~85%,** whereas the **5-yr OS is ~100% for T1 and ~80% for T2** supraglottic lesions.
What are the LC rates for early-stage supraglottic cancers after definitive RT alone?

Show Answer

Retrospective series demonstrate LC rates of **73%–100% for T1 and 60%–89% for T2 lesions** (e.g., University of Florida and Italian data).
Describe the standard RT fields used in treating supraglottic cancers.

Show Answer

B/c 20%–50% of T1–T2 supraglottic cancers have +LNs (occult), necks need to be covered for all pts (levels II–IV). This required an off-cord CD after 45 Gy and a boost to the post neck to 50 Gy with electron fields. Most of these are currently treated with IMRT.
What definitive RT doses are typically recommended for early-stage supraglottic cancers?

Show Answer

T1 dose: **70 Gy** in 2 Gy/fx
T2–3 dose: hyperfractionated dosing to **79.2–81.6 Gy** in 1.2 Gy/fx bid or with concomitant boost techniques to **72 Gy** (1.8 Gy in AM × 30 fx to 54 Gy to areas of subclinical Dz, and 1.5 Gy in PM for the last 12 days of Tx to boost GTV + 1.5–2 cm to 72 Gy)
What early data showed feasibility/effectiveness of reirradiation for

previously treated early-stage LCX pts?

Show Answer

Massachusetts General Hospital data (Wang CC et al., IJROBP 1993): 20 pts treated with 1.6 Gy bid to 65 Gy. 5-yr OS was 93%, and LC was 61% after reirradiation.
What are the Tx options for pts with advanced LCX?

Show Answer

Total laryngectomy (with adj RT or CRT for +margin, +ECE) or organ preservation with definitive CRT **(RTOG 91–11)** or RT alone (altered fractionation)
What are the Tx options for pts with advanced HPxC?

Show Answer

Induction chemo → RT or Sg depending on response for T1–3N+ Dz; total laryngectomy/laryngoesophagectomy (with CRT for +margin, +ECE) for T4 Dz
What are the typical RT doses used to treat advanced LCX/HPxC?

Show Answer

Subclinical Dz (2^{nd}-echelon nodal regions) to **50–54 Gy; high-risk regions (1^{st}-echelon or involved nodal regions) to 60–63 Gy,** primary tumor to **70 Gy** (in 2 Gy/fx)
What are the 3 indications for boosting the stoma with PORT?

Show Answer

Indications for boosting the stoma with PORT:

- Emergency tracheostomy
- Subglottic extension
- Ant ST extension

What are some indications for performing an elective neck dissection after definitive RT?

Show Answer

This is controversial, but elective neck dissection should be done for persistent Dz and can be considered with >N2 Dz, although it is now common to observe if clinical and radiographic CR is obtained after RT.
What randomized data/study compared preop RT to PORT for (predominantly) HPxC?

Show Answer

RTOG 73–03 (Tupchong L et al., IJROBP 1991): 354 pts, 50 Gy preop vs. 60 Gy postop; 69% of pts had advanced supraglottic or HPxC. LC was better with PORT but not OS.
What are the 2 randomized phase III trials that demonstrated a benefit with postop CRT vs. PORT alone for high-risk H&N pts?

Show Answer

EORTC 22931 (Bernier J et al., NEJM 2004): 334 pts randomized to PORT 66 Gy vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: ECE, +margin, PNI, LVI, and levels 4–5 +N from oral cavity cancer/oropharyngeal cancer. There was better OS, DFS, and 5-yr LC with CRT but ↑ grades 3–4 toxicity.

RTOG 95–01 (Cooper JS et al., NEJM 2004): 459 pts randomized to 60–66 PORT vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: >2 LNs, ECE, +margin. There was better DFS (43% vs. 54%) and 2-yr LRC (72% vs. 82%) with CRT but only a trend to improvement in OS (57% vs. 63%).

What are the presumed reasons why EORTC 22931 showed an OS benefit while RTOG 9501 did not?

Show Answer

The EORTC trial included more margin+ pts (28% vs. 18%), pts with worse tumor differentiation (19% vs. 7%), more HPX cases (20% vs. 10%), and more pts who started RT 6 wks or later after Sg (32%).

Which randomized trials demonstrated a benefit with altered fractionation RT in advanced H&N cancer?

Show Answer

EORTC 22851 (Horiot JC et al., Radiother Oncol 1997): 512 pts (all H&N except the HPX) randomized to conventional RT to 70 Gy (7 wks) or 1.6 Gy tid to 72 Gy (5 wks). There was better 5-yr LRC with tid RT (59% vs. 46%) but not OS.

RTOG 9003 (Fu KK et al., IJROBP 2000): 1,073 pts (all H&N sites) randomized to (1) standard fx 70 Gy/2 qd; (2) 81.6 Gy/1.2 bid; (3) accelerated with split 67.2 Gy/1.6 bid; and (4) accelerated with concomitant boost 72 Gy/1.8 qd × 17 → 1.8 Gy AM + 1.5 Gy PM × 33 fx. All altered fx schemes were better than conventional RT in terms of LRC (54% vs. 46%) but not OS.

Which studies investigated induction CRT for organ preservation in pts with advanced LCX?

Show Answer

Department of Veterans Affairs (VA) larynx study (Wolf GT et al., NEJM 1991): stages III–IV resectable LCX; 332 pts randomized to 3 cycles induction PF f/b definitive RT (if Dz response, else TL) vs. upfront Sg + PORT. 2-yr larynx preservation rate was 64%. There was no OS difference (68%). There were more LRs with CRT and less mets.

GETTEC (Richard JM et al., Oral Oncol 1998): early closure due to poor accrual; only 68 pts, mostly T3N0, design similar to the VA study. There was poorer 2-yr survival for the chemo group (69% vs. 84%). 3-yr laryngectomy-free survival was 20%.

What is the only randomized study that investigated organ preservation for

advanced HPxC with induction CRT?

Show Answer

EORTC 24891 (Lefebvre JL et al., JNCI 1996 and Ann Oncol 2012): 194 pts randomized to Sg + PORT vs. induction chemo (5-FU/cisplatin) + RT; if NR to chemo → Sg + PORT. 5-yr larynx preservation rate was 35%. At 3 yrs, OS was better with induction therapy, but there was no difference at 5 and 10 yrs (DMs were less in the chemo arm; no difference in LRF).
Which study established concurrent CRT over both RT alone and induction approaches for larynx preservation?

Show Answer

RTOG 91–11 (Forastiere AA et al., NEJM 2003): 547 pts, T2–T4 (T4 with thyroid cartilage invasion or >1-cm base of tongue invasion excluded) randomized to (1) CRT (platinum 100 mg/m^2 q3wks), (2) induction PF chemo → RT (like the VA study), and (3) RT alone (all to 70 Gy). There was a better rate of laryngeal preservation at 3.8 yrs with concurrent CRT (84% vs. 72% vs. 67%); better 2-yr LRC (78% vs. 61% vs. 56%); and better DM rate with any chemo arm than with RT alone. There was no OS benefit. There was ↑ acute grades 3–4 toxicity but no ↑ late toxicity with concurrent CRT.
What are the survival/LC numbers based on the latest update of RTOG 91–11?

Show Answer

Long-term Results **RTOG 91–11** (Forastiere AA et al., JCO 2013) median follow-up 10.8 yrs. CRT improved larynx preservation over chemo → RT (HR, 0.58; $p = 0.005$) and over RT alone ($p < 0.001$), while chemo → RT and RT were equivalent (HR = 1.26; $p = 0.35$). Late effects were not different. The 10-yr OS was the same (27.5% CRT, 38.8% chemo → RT, and 31.5% RT). Deaths not attributed to larynx cancer or Tx were higher with CRT.
What is the only randomized study that compared Sg + RT to concurrent

CRT in advanced H&N SCC (Non-NPX)?

Show Answer

Singapore study (Soo KC et al., Br J Cancer 2005): 119 pts, most bulky T4 (56%) or stage IVA (78%) Dz; closed early d/t poor accrual; nonstandard PF chemo, nonstandard RT (66 Gy). 44% pts larynx/HPX (majority supraglottis). No difference in 3-yr DFS, primary larynx/HPX organ preservation 62% vs. nonlaryngeal sites 30%.
What study demonstrated an OS and DFS benefit with CRT over RT alone for unresectable H&N cancers?

Show Answer

Cleveland Clinic (Adelstein DJ et al., JCO 2003): 295 pts with unresectable stages III–IV H&N cancers (15% OC, 55% OPX, 20% HPX), RT alone vs. CRT with cisplatin 100 mg q3wks × 3. 3-yr OS (37% vs. 23%) and DFS (51% vs. 33%) were better with CRT.
What study demonstrated improvement in OS with the addition of cetuximab (C225) to RT in H&N cancers?

Show Answer

Bonner et al. (NEJM 2006): 424 pts with stages III–IV SCC of the OPX, larynx, or HPX randomized to RT vs. RT + C225; RT options were conventional to 70 Gy, 1.2 bid to 72–76.8 Gy, or concomitant boost to 72 Gy. There was better 3-yr LRC (47% vs. 34%) and OS (55% vs. 45%) with RT + C225. Subset analysis showed improvement mostly in OPC and in the altered fractionation RT arms (~50% with altered fractionation).
What 2 randomized studies demonstrated a benefit with induction taxane/platinum/5-FU (TPF) chemo over PF → in pts with unresectable H&N cancers?

Show Answer

TAX 324 study (induction chemo → CRT) (Posner MR et al., NEJM

2007): 501 pts, unresectable stages III–IV H&N cancers (52% OPX; 13%–18% OC, larynx, HPX) randomized to induction platinum + 5-FU or TPF → CRT with carboplatin. There was better 3-yr OS (62% vs. 48%), MS (71 mos vs. 30 mos), and LRC (70% vs. 62%) in the TPF arm. Pts in the TPF arm had fewer Tx delays than those who rcvd platinum/5-FU despite higher myelotoxicity in the TPF arm (98% rcvd planned Tx in TPF vs. 90% in the platinum/5-FU arm).

TAX 323 study (induction chemo → RT) (Vermorken JB et al., NEJM 2007): 358 pts, unresectable stages III–IV H&N cancers (46% OPX, 18% OC, 29% HPX, 7% larynx) randomized to induction platinum + 5-FU or TPF → RT alone. TPF resulted in better median PFS (11 mos vs. 8.2 mos), MS (18.8 mos vs. 14.5 mos), with an HR of 0.73. The rate of toxic deaths was greater in the platinum/5-FU group (5.5% vs. 2.3%). There was also more grades 3–4 thrombocytopenia, anemia, stomatitis, n/v, diarrhea, and hearing loss in the platinum/5-FU arm. Neutropenia, leukopenia, and alopecia were more common in the TPF arm.

Which studies compared induction chemo vs. upfront CRT?

Show Answer

1. **PARADIGM study (induction TPF → CRT vs. CRT)** (Haddad H et al., Lancet Oncology 2013): 145 pts, stages III–IV (25% larynx and HPX), randomized to induction TPF → CRT vs. CRT. At a median f/u of 49 mos, there was no difference in 3-yr OS (73% for induction vs. 78% for CRT), with a higher rate of febrile neutropenia observed in the induction arm.

2. **DeCIDE study (induction TPF(×2) → CRT vs. CRT)** (Cohen E et al., JCO 2014): 285 pts, N2–N3 Dz, docetaxel-based concurrent CRT regimen (Docetaxel, 5-FU, hydroxyurea “DFHX”). Randomized to induction TPF → CRT vs. CRT. At a min f/u of 30 mos, there was no difference in OS (median not reached), DFS, LRC or DMFS. HPV status did not impact findings, nor did OPX vs. Non-OPX primary. Toxicity higher with

induction (heme).

FOLLOW-UP/TOXICITY

What are some acute and late toxicities with RT in the Tx of LCX?

Show Answer

Acute: hoarseness, sore throat, odynophagia, skin irritation

Late: laryngeal edema, glottic stenosis, hypothyroidism, xerostomia, L'hermitte syndrome, myelitis, laryngeal necrosis

What are the main late toxicities after organ preservation with concurrent CRT for LCX?

Show Answer

Moderate speech impairment, dysphagia (25% of pts; <5% cannot swallow), and xerostomia (advanced/bilat cases)

What are some approximate RT dose constraints for laryngeal edema?

Show Answer

Some data suggest that the incidence of laryngeal edema ↑ significantly with mean doses **≥44 Gy.** (Sanguineti G et al., IJROBP 2007)

What is the QOL impact of larynx preservation when compared to laryngectomy in the Tx of LCX?

Show Answer

VA data demonstrated better social, emotional, and mental health function with larynx preservation (swallowing and speech function were similar), which suggests that better QOL is not d/t preservation of speech but d/t freedom from pain, emotional well-being, and less depression.

Hanna et al. demonstrated that pts had worse social functioning, greater sensory disturbance, more use of pain meds, and coughing after total laryngectomy than those treated with CRT. (Arch Otolaryngol H&N Surg 2004)

What is the follow-up paradigm for LCX pts?

Show Answer

LCX f/u paradigm: H&P + laryngoscopy (q1–3 mos for yr 1, q2–6 mos for yr 2, q4–8 mos for yrs 3–5, q12 mos if >5 yrs), imaging (for signs/Sx), TSH (if neck is irradiated), speech/hearing evaluation, and smoking cessation.

34

Thyroid Cancer

Updated by Boris Hristov

BACKGROUND

Name the anatomic subdivisions/lobes of the thyroid.

Show Answer

Subdivisions/lobes of the thyroid:

- Right lobe
- Left lobe
- Isthmus
- Pyramidal lobe (in 50% of individuals is remnant of thyroglossal duct)

In the thyroid follicle, what are the normal functions of the epithelial follicular cells and the parafollicular cells?

Show Answer

Epithelial follicular cells: remove iodide from the blood and use it to **form T_3 and T_4** thyroid hormones

Parafollicular cells (C cells): lie just outside of the follicle cells and **produce calcitonin**

What is the most common endocrine malignancy?

Show Answer

Thyroid cancer (TCa) is the most common endocrine malignancy, but is

only 1% of all diagnosed malignancies.
What is the estimated incidence of new TCa Dx and deaths in the United States?

Show Answer

There are an estimated 57,000 new Dx (3/4 women) and 2,000 deaths in 2017.
What are the 3 main TCa histologies in decreasing order of frequency?

Show Answer

Differentiated (follicular-derived) thyroid carcinoma (DTCa) (~94%) > **medullary** (2%–4%) > **anaplastic** (2%)
What are the 3 subtypes of DTCa in decreasing order of frequency?

Show Answer

Papillary (90% of all TCa) > **follicular** > **Hürthle cell carcinoma**
What is happening to the incidence of diagnosed papillary TCa?

Show Answer

The incidence of papillary TCa is **increasing** (by ~20% over the past 50 yrs, largely driven by better surveillance/detection of smaller lesions).
What is the typical age at Dx for follicular vs. papillary TCa?

Show Answer

Follicular incidence peaks at 40–60 yrs of age, whereas **papillary peaks at 30–50 yrs of age.**
Is there a sex predilection for papillary or follicular TCa?

Show Answer

Yes. Both papillary and follicular TCa more commonly affect **females** than males (3:1).
What is the strongest risk factor for papillary TCa?

Show Answer

RT exposure to the H&N as a child is the strongest risk factor for papillary TCa. There is no increased risk if exposure is after age 20 yrs. Most papillary cases are sporadic.
Name 4 genetic disorders associated with papillary TCa.

Show Answer

Genetic disorders associated with papillary TCa:

- Familial polyposis
- Gardner syndrome
- Turcot syndrome
- Familial papillary carcinoma

Name a genetic disorder associated with follicular TCa.

Show Answer

Cowden syndrome (PTEN gene mutation) is associated with follicular TCa.
Medullary TCa arises from what precursor cell?

Show Answer

Medullary TCa arises from the calcitonin-producing **parafollicular C cells.**
Name 2 genetic syndromes associated with medullary TCa.

Show Answer

MEN 2a and **MEN 2b** (RET gene mutation) are associated with medullary TCa.
What % of medullary TCa is related to a genetic syndrome?

Show Answer

~25% of medullary TCa is related to a genetic syndrome.
Name the nerve that lies in the tracheoesophageal (TE) groove, post to the right/left thyroid lobes.

Show Answer

The **recurrent laryngeal nerve** lies in the TE groove.
What are the primary, secondary, and tertiary lymphatic drainage regions of the thyroid?

Show Answer

Primary: central compartment **(level VI or paralaryngeal and paratracheal), Delphian** (prelaryngeal) LNs
Secondary: cervical, SCV, and upper mediastinal LNs (levels III–IV, VII)
Tertiary: upper cervical (level II)/retropharyngeal LNs

WORKUP/STAGING

What % of palpable thyroid nodules are malignant?

Show Answer

Only **5%** of palpable thyroid nodules are malignant.
In a pt with low TSH and a nodule that shows uptake on I-123 or Tc-99 scan, what is the likely Dx?

Show Answer

Adenomas commonly present with low TSH and increased uptake on I-123 or Tc-99 scans.
Which TCa subtypes are difficult to distinguish from adenomas on FNA?

Show Answer

Follicular and Hürthle subtypes are difficult to distinguish from adenomas. Histologically, they show only follicular structures. Papillary TCa shows both papillary and follicular structures, which helps to distinguish it from adenomas.
What pathologic criteria must be met to make the Dx of Hürthle cell TCa?

Show Answer

The Dx requires **hypercellularity with >75% Hürthle cells** (also referred to as oncocytic cells), which are characterized by abundant eosinophilic granular content.
Which TCa subtype is more likely to present with N+ Dz: papillary or follicular?

Show Answer

Papillary TCa (**~30%** node+) is more likely to spread to LNs than follicular (~10% node+).
Name the 2 major and 3 minor prognostic factors for DTCa.

Show Answer

Major: age and tumor size (<55 yo, ≤4 cm, respectively, have better prognosis)
Minor: histology, local tumor extension, LN status
What variables constitute the mnemonic AMES risk group system?

Show Answer

Age, **M**etastasis, **E**xtent, **S**ize
Which pts are low risk?

Show Answer

. Young (<55 yo), no DMs
. Older with minor tumor capsule involvement and tumor <4 cm and no DMs

For TCa, what sizes distinguish AJCC 8th edition T1, T2, and T3 tumors?

Show Answer

T1: ≤2 cm (T1a if ≤1 cm; T1b if >1 cm)
T2: 2–4 cm (limited to thyroid)
T3: >4 cm (T3a if in thyroid; T3b if any size and extension into strap muscles only)

What is the difference b/t T4a and T4b TCa lesions?

Show Answer

T4a: gross extension but still technically resectable (invasion of larynx, trachea, esophagus, SQ tissues, recurrent laryngeal nerve)

T4b: unresectable Dz (invasion of prevertebral fascia/spine, carotid artery encasement, mediastinal vessels)

What is the difference b/t N1a and N1b in TCa?

Show Answer

N1a: mets to any **level VI** (pre-/paratracheal, prelaryngeal) or **VII** (cervical neck, upper mediastinal) LNs; unilat or bilat

N1b: mets to **levels I–V,** or retropharyngeal LNs

List the latest AJCC 8th edition (2018) stage groupings for papillary and follicular TCa.

Show Answer

Stage I: M0 and age <55 yrs or T1–2N0M0 and age ≥55 yrs

Stage II: M1 and age < 55 yrs or T1–2N1, T3N(any) and age ≥55 yrs

Stage III: T4aN(any)M0 and age ≥55 yrs

Stage IVA: T4bN(any)M0 and age ≥55 yrs

Stage IVB: T(any)N(any)M1 and age ≥55 yrs

What is unique about the staging of nonmedullary TCa?

Show Answer

It is **age dependent;** it differs for pts > or <55 yo.

Can a pt <55 yo with follicular or papillary TCa have stage III or IV Dz?

Show Answer

No. A pt <55 yo with follicular or papillary TCa cannot have stage III or IV Dz.

What is the stage of a 37-yo pt with Hurthle TCa and a solitary bone met?

Show Answer

Stage II. If the pt were 56 yo, he or she would be stage IVB.
What is the stage of a 56-yo pt with an unresectable primary DTCa and no mets?

Show Answer

Stage IVA. If pt was 44 yo, he or she would be stage I.
What must be done prior to an I-123 or I-131 scan?

Show Answer

TSH stimulation must be done prior to an iodine scan.
What are 2 ways to do TSH stimulation?

Show Answer

TSH stimulation can be accomplished through **thyroid hormone withdrawal or by using recombinant TSH.**
What are some advantages of recombinant TSH stimulation?

Show Answer

Fewer side effects and a shorter period of elevated TSH (theoretically, a lower risk of tumor progression)
What are the approved indications for recombinant TSH stimulation?

Show Answer

Recombinant TSH is approved for **f/u iodide scans and** for the **I-131 Tx of low-risk pts.**
What sites of the body show a physiologic uptake of iodide?

Show Answer

The **salivary glands and the GI tract** show physiologic uptake d/t the presence of iodide transporters.
What is the 10-yr OS for papillary vs. follicular TCa?

Show Answer

Similar when matched for stage, **85%–95%**
Is the presentation and Tx of Hürthle cell carcinoma more similar to that of papillary or follicular TCa?

Show Answer

It is more similar to **follicular TCa;** however, Hürthle cell carcinoma has a slightly higher DM rate and worse prognosis (10-yr OS ~70%–80%).
Estimate the 10-yr OS for pts with localized vs. N+ medullary TCa.

Show Answer

For localized medullary TCa, the 10-yr OS is **~90%.** If N+, the 10-yr OS is **~70%.**
What are the stage groupings for anaplastic TCa?

Show Answer

All anaplastic TCa is **stage IV.** Stage IVA is T1–3aN0 (resectable), stage IVB is N1 or T3b–4 (unresectable), and stage IVC is metastatic.
Estimate the MS and the 1-yr OS for pts with anaplastic TCa.

Show Answer

MS is ~6 mos and the 1-yr **OS is ~20%** for all pts with anaplastic TCa.
Does the tall cell variant have a more favorable or unfavorable prognosis when compared to classic papillary TCa?

Show Answer

The tall cell variant has an **unfavorable prognosis** (10-yr OS ~75%) when compared to classic papillary carcinomas.
What is the most frequent site of DM in papillary and follicular TCa?

Show Answer

Lung (~50%), f/b bone, CNS

TREATMENT/PROGNOSIS

Generally, what is the Tx paradigm for TCa?

Show Answer

DTCa Tx paradigm: **primary Sg** (even in M1 Dz) → **observation vs. adj Tx**

What are the 3 surgical options in TCa?

Show Answer

Surgical options in TCa are:

- Lobectomy + isthmusectomy
- Near-total thyroidectomy
- Total thyroidectomy

What is the difference b/t near-total and total thyroidectomy?

Show Answer

Near-total is less aggressive around the recurrent laryngeal nerve.

For which pts with papillary TCa is a lobectomy + isthmusectomy adequate?

Show Answer

Controversial. It is a good option for pts with none of the following risk factors: age >55 yrs, tumor >4 cm, aggressive histology variant, prior Hx of RT, N+, extrathyroid extension.

In addition to improved LC, what is another reason to advocate for a total thyroidectomy even in low-risk pts?

Show Answer

It allows for **easier f/u** with whole-body iodide scans and serum thyroglobulin (Tg).

Per NCCN guidelines (2018), what are 3 indications for recommending adj Tx after GTR in DTCa?

Show Answer

Indications for adj Tx after GTR in DTCa are (if any present):

. >4-cm tumor
. Extrathyroidal extension
. Postop unstimulated Tg >5–10 ng/mL

What are the 5 aggressive histologic subtypes of DTCa that merit consideration of adj Tx?

Show Answer

Aggressive histologic subtypes that merit consideration of adj Tx are:

. Tall cell
. Columnar cell
. Hobnail
. Poorly differentiated

Generally, what is the adj Tx paradigm for DTCa?

Show Answer

DTCa adj Tx paradigm: **long-term TSH suppression alone or with I-131 +/- EBRT**
What are the indications for adj I-131 in addition to TSH suppression for DTCa?

Show Answer

Suspected or proven residual normal thyroid tissue or residual tumor, are indications for adj I-131.
What is the mCi dose range to ablate residual normal thyroid tissue?

Show Answer

30 mCi is as effective as 100 mCi to ablate residual normal thyroid tissue in low-risk DTCa. (Mallick U et al., NEJM 2012)

What is the mCi dose range to ablate a residual TCa Dz?

Show Answer

The dose to ablate a residual TCa lesion is **100–200 mCi.**
What are the 4 indications for adj EBRT in addition to TSH suppression and I-131 in TCa?

Show Answer

Indications for adj EBRT in addition to TSH suppression and I-131 are:

- pT4 papillary and ≥55 yo
- Gross residual Dz in the neck after I-131
- Bulky mets after I-131
- Lesions with inadequate iodide uptake

What 3 regions should be irradiated with EBRT in a pt ≥55 yo with pT4 papillary TCa?

Show Answer

Thyroid bed, bilat neck, and the upper mediastinal nodes
What is the prognosis for pts with locoregional vs. distant recurrence of DTCa?

Show Answer

The prognosis is **excellent if recurrence is locoregional** (long-term OS is 80%–90%). It is much **worse with distant recurrences.**
What are the typical EBRT doses for DTCa?

Show Answer

Gross Dz: **66–70 Gy,** positive margins: 63–66 Gy
Microscopic Dz: **60 Gy**
Nodal basins: **50–54 Gy**
What is a systemic salvage option for I-131 refractory DTCa?

Show Answer

Kinase inhibitors significantly improve PFS. (Schlumberger M et al., NEJM 2015)
Generally, what is the Tx paradigm for medullary TCa?

Show Answer

Medullary TCa Tx paradigm: **definitive Sg; EBRT for palliation/unresectable Dz**
Generally, what is the Tx paradigm for anaplastic TCa?

Show Answer

Anaplastic TCa Tx paradigm: **max safe resection → adj CRT;** taxane, and/or doxorubicin with conventional or hyperfractionated EBRT (Smallridge RC et al., Thyroid 2012)
For which group of anaplastic TCa pts does PORT improve survival?

Show Answer

Per recent SEER analysis (Chen J et al., Am J Clin Oncol 2008), PORT improved survival in pts with **extrathyroid extension of Dz** but not for those with thyroid-confined or metastatic Dz.

FOLLOW-UP/TOXICITY

What are the acute side effects of >100 mCi of I-131?

Show Answer

GI irritation, sialadenitis, and cystitis
What are the 3 most important long-term side effects of >100 mCi of I-131?

Show Answer

Pulmonary fibrosis, oligospermia, and leukemia
What does the f/u of TCa pts entail?

Show Answer

TCa f/u: H&P + TSH/Tg levels at 6 and 12 mos, then annually if no Dz; neck US; TSH-stimulated iodine scans if clinically indicated (NCCN 2018)
What kind of additional imaging can be considered if the I-131 scan is negative but the stimulated Tg level is elevated?

Show Answer

If the I-131 scan is negative but the stimulated Tg level is elevated, **neck US or CT with contrast** can be considered.
What is the max recommended lifetime dose for I-131?

Show Answer

The max recommended lifetime dose is **800–1,000 mCi.**

35

sHead and Neck Cancer of Unknown Primary

Updated by Amy Catherine Moreno

BACKGROUND

H&N cancers of an unknown primary represent what % of H&N cancers?

Show Answer

~3%–5% of all H&N cancers are of an unknown primary.
What is the most commonly presumed general site of origin for H&N cancers of an unknown primary?

Show Answer

The OPX is the presumed site of origin for most cases (less common are the NPX, hypopharynx [HPX], and larynx).
What are the 2 most common originating sites/primary locations if the cancer is presumed to be of oropharyngeal origin?

Show Answer

Tonsils and base of tongue (BOT). Up to 80% of presumed oropharyngeal tumors are thought to originate from these 2 sites.
Appx what % of pts with tonsillar primaries harbor Dz in both tonsils?

Show Answer

~5%–10% of pts with tonsillar primaries harbor Dz in both tonsils.

A primary can be identified in what % of H&N cancers of unknown primary?

Show Answer

A primary site of origin can be identified in **~20%–40%** of pts.

WORKUP/STAGING

What is the most common presentation for H&N cancers of an unknown primary?

Show Answer

Painless upper neck LAD (IB–III) is the most common presentation.
What is the T staging if no primary H&N site is found after workup?

Show Answer

T0 (not TX) is the assigned T stage if no primary is found.
On what are the overall stage groupings based if the primary is not known?

Show Answer

LN involvement and p16 status determine stage groupings, with p16(+) denoting more favorable prognostic stage groups than p16(-). (Please see AJCC staging, 8th edition).
What % of pts with an unknown primary present with bilat LAD (N2c)?

Show Answer

~10% of pts present with bilat neck Dz.
What does the workup include for pts with an unknown H&N primary (NCCN 2018)?

Show Answer

Unknown H&N primary workup: H&P including skin exam, EUA/panendoscopy + directed Bx with HPV testing, FNA of involved node,

CT/MRI, PET/CT (before EUA), thyroglobulin, calcitonin, PAX8, and TTF staining if adenoCa and/or anaplastic/undifferentiated, consider bilat tonsillectomy (bronchoscopy, esophagoscopy)
If FNA is negative in H&N pts with an unknown primary, what other kind of nodal Bx can be attempted?

Show Answer

If FNA is negative, a **core Bx** can be attempted next. Avoid incisional/excisional Bx, b/c this would result in "neck violation."
What does cystic appearance of the involved LNs suggest in pts with H&N cancers?

Show Answer

Cystic appearance on imaging suggests **HPV positivity/etiology.**
What is the significance of nodal location in terms of likely primary sites?

Show Answer

If upper neck nodes are involved, they are more likely to be d/t a H&N primary (e.g., if level I LNs, OC; if upper level V, NPX primary). If lower neck or SCV nodes are involved, they are more likely to be d/t a chest or abdominal primary (below the clavicle). Bilat nodes suggest midline structures. Intraparotid LN involvement suggests a cutaneous primary.
What is the significance of histology in terms of likely primary sites?

Show Answer

Squamous cell: more likely to be a H&N primary (upper aerodigestive mucosal axis)
Adenocarcinoma: more likely to be a chest or abdominal primary
What sites are traditionally biopsied for level II nodal involvement?

Show Answer

The **BOT, NPX, pyriform sinus, and tonsils** are typically biopsied with

level II LN involvement.
Why is it problematic to obtain the PET scan after endoscopy and Bx in pts with an unknown H&N primary?

Show Answer

Post-Bx inflammation may lead to false+ results. This is why some advocate that if used, PET scans should be done initially.
When is triple endoscopy indicated in pts with neck Dz and an unknown primary?

Show Answer

Triple endoscopy is generally **done in pts with levels IV–V LAD** (more likely to be lung/abdominal primary). Also, PET/CT C/A/P should be considered in such cases.
Site-directed Bx will reveal the primary in roughly what % of unknown primary cases?

Show Answer

Site-directed Bx will reveal the H&N primary in **~50%** of cases.
Unilat tonsillectomy will reveal the primary in appx what % of cases?

Show Answer

Unilat tonsillectomy will reveal the primary in **~20%–25%** of cases.
PET/CT will reveal the primary in appx what % of unknown H&N primary cases?

Show Answer

PET/CT will reveal the primary in **~15%–20%** of cases.
What do the data show in regard to bilat tonsillectomy for pts with an unknown H&N primary?

Show Answer

Data from the **JHH** (McQuone S et al., Laryngoscope 1998) showed **improved diagnostic yields with bilat tonsillectomy.** Additionally, it **may render f/u with PET/CT easier.**
When should tonsillectomy be performed in pts being worked up for an unknown primary?

Show Answer

Tonsillectomy is generally performed **at the time of direct laryngoscopy.**
What are the approximate predictive values of PET for pts with an unknown primary?

Show Answer

The **PPV is ~90%** and the **NPV is ~75%** for pts with an unknown primary.
What % of pts with an unknown H&N primary have metastatic Dz on PET/CT?

Show Answer

~10% have metastatic Dz on PET/CT—yet another reason to consider upfront PET.

TREATMENT/PROGNOSIS

What is the general Tx paradigm for H&N cancers if a primary is found vs. if there is an unknown primary?

Show Answer

H&N cancer Tx paradigm:

If primary found: treat according to the primary location
If no primary found: Sg +/– RT, RT alone, or chemo/RT +/– neck dissection
Which unknown primary pts can be treated with neck dissection alone?

Show Answer

Generally, **N1 (<3 cm) without ECE.** B/c of this, some advocate upfront

neck dissection at the time of direct laryngoscopy. (Coster JR et al., IJROBP 1992)
For which H&N pts is upfront neck dissection a reasonable approach?

Show Answer

Upfront neck dissection is reasonable **if better staging is desired** (e.g., if the path is unclear), **if the neck has been "violated"** (i.e., after incisional Bx), and **with a small, unilat, single +node** (N1).
What % of pts with N1 Dz fail at the primary site after neck dissection alone?

Show Answer

~25% of N1 pts ultimately fail at the primary site after neck dissection alone. However, this can vary from 10%–50%.
What is the approximate overall neck failure rate after neck dissection alone?

Show Answer

The overall neck failure rate is **~15%** after neck dissection alone. (Coster JR et al., IJROBP 1992)
What pathologic factor is associated with the highest risk of Tx failure for pts with an unknown primary?

Show Answer

ECE is associated with the highest risk of Tx failure in these pts.
What is the approximate neck failure rate after neck dissection if there is evidence of ECE?

Show Answer

The approximate neck failure rate after neck dissection alone is **~60% with ECE.** (Coster JR et al., IJROBP 1992)
What are the indications for PORT in pts with an unknown H&N primary?

Show Answer

≥N2 Dz, ECE/+margin, or neck violation (e.g., after open/excisional Bx)
What do the standard RT fields include in pts with an unknown H&N primary?

Show Answer

The fields generally include **both neck and the mucosal sites at risk** (NPX, OPX, HPX, larynx). Some advocate omission of the HPX/larynx from the RT fields, especially if HPV+.
What are the historical 5-yr LC and OS rates after definitive RT for pts with an unknown H&N primary?

Show Answer

University of Florida data (Erkal HS et al., IJROBP 2001): LC 78% and OS 47%
Danish data (Grau C et al., Radiother Oncol 2000): OS 37%
What factors have been traditionally associated with inf OS after definitive RT for H&N tumors of an unknown primary?

Show Answer

More advanced N stage, ECE, and lower RT doses have been associated with inf outcomes. (Erkal HS et al., IJROBP 2001)
What standard RT fields have been traditionally used for H&N tumors of an unknown primary?

Show Answer

Opposed lats matched with an ant low neck/SCV field (with post neck electron fields after 40–44 Gy). However, conformal techniques such as IMRT should be now used as standard of care.
What were the anatomical borders of the traditional setup for the 2D lat fields used for H&N tumors of an unknown primary?

Show Answer

Anterior: behind OC/hard palate
Superior: to base of skull to include NPX
Posterior: below tragus to post edge of spinous processes
Inferior: sup edge of thyroid cartilage; if level III or IV, inf edge of cricoid to cover larynx

What definitive RT doses are generally employed?

Show Answer

- **CTV1: 66 (2.2. Gy/fx) or 70 Gy (2 Gy/fx)** to gross Dz with margin (5–8 mm)
- **CTV2: 50–66 Gy (2 Gy/fx)** to intermediate-risk areas 1 nodal station above and below in ipsi side and putative primary mucosal sites (NPX, OPX, HPX)
- **CTV3: 50–54 Gy** to low-risk areas and uninvolved neck

What evidence supports the omission of the larynx/HPX from the standard RT fields?

Show Answer

University of Florida data (Baker CA et al., Am J Clin Oncol 2005): larynx-sparing RT is just as effective with less toxicity.

What is the evidence in favor of bilat neck irradiation for H&N tumors of an unknown primary?

Show Answer

Loyola data (Reddy SP et al., IJROBP 1997): contralat nodal failure is higher (**44%**) in pts receiving unilat nodal RT (vs. **14%** for bilat nodal RT). Also, there is a higher primary emergence rate with unilat RT (**44% vs. 8%**). No difference in 5-yr OS.

What are a few of the advantages of IMRT for H&N tumors of an unknown primary?

Show Answer

Greater parotid sparing, can consider concurrent chemo (Klem ML et al., IJROBP 2008), dose painting to avoid sequential CDs, **can use SIB dosing** (e.g., 212 × 33 = 69.96 Gy, 180 × 33 = 59.4 Gy, and 170 × 33 = 56.1 Gy).
When is neck dissection entertained after definitive RT for H&N tumors of an unknown primary?

Show Answer

Post-RT neck dissection is considered with **persistence of Dz** (e.g., on PET or clinically; LN >1 cm and/or PET+). Some still consider it standard for all pts with ≥N2 Dz, although more commonly, elective neck dissection after RT is not performed if there is no clinical evidence of Dz on clinical exam and radiographic restaging.
Within what timeframe after RT should neck dissection be performed if decided upon upfront (i.e., regardless of response to RT)?

Show Answer

Neck dissection should occur **~3–4 mos** (and no later than 6 mos) after RT.

FOLLOW-UP/TOXICITY

What are common acute side effects from RT to the H&N region?

Show Answer

Pain, mucositis, hoarseness, and malnutrition (weight loss).
What are common long-term complications from RT to the H&N region?

Show Answer

Xerostomia, dysphagia, neck scarring and edema (especially if combined with neck dissection), hypothyroidism, and laryngeal dysfunction (aspiration, hoarseness, etc.).
After RT, when should PET be performed to assess for nodal response?

Show Answer

PET should be performed no sooner than **3 mos** after RT. (NCCN 2018)

36

Neck Management and Postoperative Radiation Therapy for Head and Neck Cancers

Updated by Lauren Colbert and Gopal K. Bajaj

BACKGROUND

What is a radical neck dissection?

Show Answer

Radical neck dissection is a **procedure that removes all LN levels ("comprehensive") from levels I–V and other structures** (the sternocleidomastoid, jugular vein, and spinal accessory nerve).

What is a modified radical neck dissection?

Show Answer

Modified radical neck dissection is a **comprehensive nodal dissection** that spares at least 1 of the following structures: sternocleidomastoid, jugular vein, or spinal accessory nerve.

What is considered a selective neck dissection?

Show Answer

Selective neck dissection is **dissection of selective neck areas** based on the understanding of the common pathways of spread according to the H&N site.

What is a supraomohyoid neck dissection?

Show Answer

Supraomohyoid neck dissection is **removal of nodes above the omohyoid muscle** (levels I–III and sup V), common for cancers of the OC.
What is a lat neck dissection?

Show Answer

Lat neck dissection is s**elective dissection of levels II–IV,** traditionally for cancers of the larynx and pharynx.
What is an anterolat neck dissection, and when should it be done?

Show Answer

Anterolat neck dissection is a s**elective neck dissection of levels I–IV,** typically **done for cN0 oropharyngeal cancer** (OPC).
What is an ant neck dissection, and when should it be done?

Show Answer

Ant neck dissection is a **selective neck dissection of levels II–IV,** typically **done for cN0 laryngeal/hypopharyngeal cancers.**
What is a posterolat neck dissection, and when is it done?

Show Answer

Posterolat neck dissection is a **selective neck dissection of the retroauricular, suboccipital, upper jugular, and post cervical nodes.** It is commonly **used for skin cancers** (SCC, melanoma) **located post to the ear canal.**
What is an ant compartment dissection, and when is it done?

Show Answer

Ant compartment dissection is a **selective level VI dissection,** traditionally **performed for thyroid cancers.**

WORKUP/STAGING

Which 3 H&N sites have the highest rates of clinical nodal positivity?

Show Answer

The **NPX** (87%), **base of tongue** (78%), **and tonsil** (76%) have the highest rates of clinical nodal positivity. (Lindberg R et al., Cancer 1972)
Which 2 H&N sites have the highest rates of radiographic retropharyngeal nodal positivity?

Show Answer

On CT/MRI, **nasopharyngeal and pharyngeal wall primaries** have the highest rates of retropharyngeal involvement (74% and 20%, respectively). (McLaughlin MP et al., Head Neck 1995)
Which tumor sites have the highest rates of bilat lymphatic drainage?

Show Answer

Base of tongue, floor of mouth, soft palate, supraglottic larynx, any tumors at or approaching midline.
Which tumor sites should undergo contralat submandibular dissection?

Show Answer

Ant tongue, floor of mouth, or lip that crosses or approaches midline.

TREATMENT/PROGNOSIS

When is a selective neck dissection appropriate?

Show Answer

When there is a **clinically negative neck with an estimated ≥10% risk of subclinical Dz;** otherwise, a (therapeutic) modified radical neck dissection is indicated. Rarely is a radical neck dissection done anymore).
What is the role of SLNB in the management of oral cavity (OC) tumors?

Show Answer

It is an alternative to elective neck dissection for T1 or T2 OC tumors (per

NCCN 2018).

Per NCCN 2018, what type of neck dissection should N0, N1–N2c and N3 necks undergo?

Show Answer

N0: Selective neck dissection (OC at least levels I–III, OPX at least levels II–IV, hypopharynx at least levels II–IV and level VI, when appropriate)
N1–N2c: Selective or comprehensive neck dissection (controversial)
N3: comprehensive or radical neck dissection.

When is an elective neck dissection necessary after definitive RT?

Show Answer

Elective neck dissection is necessary whenever there is a **PR/residual Dz after RT (any nodal stage).**

When can an elective neck dissection be omitted for a pt with N2–N3 Dz?

Show Answer

This is **controversial.** The decision may be guided by PET response 12 wks after RT. If a metabolic CR and node <1 cm, elective neck dissection may be omitted. However, at some institutions, any pt with ≥N2 Dz undergoes an elective neck dissection regardless of the response to RT. The utilization of elective neck dissection in the absence of evidence for residual Dz after RT is increasingly less common.

What are the indications for adj RT after a neck dissection?

Show Answer

After a neck dissection, adj RT should be offered to pts with **≥3 cm +nodes, ≥2 +nodes, if ≥2 nodal levels are involved, with +ECE, or if there is an undissected high-risk nodal area.**

When should chemo be added to PORT in the management of H&N cancers?

Show Answer

Absolute indications: +margin, +ECE (category 1 per the NCCN)
Relative (weaker) indications: multiple +nodes, PNI/LVI, T4a primary, or OC primary with level IV nodes

How should cisplatin be dosed when given with RT for H&N cancers?

Show Answer

The cisplatin dosing with RT is **100 mg/m^2 intravenously on days 1, 22, and 43.**

How did the 2 seminal H&N trials supporting the addition of chemo to RT in the adj setting differ, and what did they show?

Show Answer

EORTC 22931 (Bernier J et al., NEJM 2004): 334 pts randomized to PORT 66 Gy vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: ECE, +margin, PNI, LVI, and levels 4–5 +N from OC cancer/OPC. There was better OS, DFS, and 5-yr LC with CRT but ↑ grades 3–4 toxicity.

RTOG 95–01 (Cooper JS et al., NEJM 2004): 459 pts randomized to 60–66 PORT vs. PORT + cisplatin 100 mg/m^2 on days 1, 22, and 43. Eligibility: >2 LNs, ECE, +margin. There was better DFS (43% vs. 54%) and 2-yr LRC (72% vs. 82%) but only a trend to improvement in OS (57% vs. 63%).

What are the presumed reasons why EORTC 22931 showed an OS benefit while RTOG 9501 did not?

Show Answer

The EORTC trial included more margin+ pts (28% vs. 18%), more pts with worse tumor differentiation (19% vs. 7%), more hypopharynx cases (20% vs. 10%), and more pts that started RT ≥6 wks after Sg (32%).

What important study compared preop RT to PORT for advanced H&N (mostly hypopharyngeal) cancers?

Show Answer

RTOG 73–03 (Tupchong L et al., IJROBP 1991): 354 pts, 50 Gy preop vs. 50–60 Gy postop. LC improved with PORT but not OS. Both LC and OS improved with PORT in OPC pts.

What are the indications for boosting the tracheostomy stoma with PORT?

Show Answer

Indications for boosting the stoma with PORT are:

- Emergency tracheostomy/tracheostomy prior to definitive Sg if close to tumor
- Subglottic extension
- Ant ST extension
- T4 laryngeal tumors

What are the dose recommendations for PORT to the neck and primary?

Show Answer

In 2 Gy/fx: **50–54 Gy:** undissected clinically negative area, **60 Gy:** postop (–margin) and dissected neck, **66 Gy:** postop (+margin, +ECE), **70 Gy:** gross residual

When should the retropharyngeal nodes be covered/irradiated?

Show Answer

Nasopharyngeal, hypopharyngeal, and pharyngeal wall primaries or N2 or greater Dz all merit prophylactic irradiation of the lat retropharyngeal nodes (anything with “pharynx”).

What are the indications for treating the sup mediastinal nodes in H&N cancer?

Show Answer

T3–T4, hypopharyngeal/thyroid primaries, and involvement of the SCV

nodes are indications for treating the sup mediastinal nodes.
What is the inf extent of the RT fields if sup mediastinal nodes are to be treated?

Show Answer

The inf extent encompasses **nodes to the level of the carina or 5 cm below the clavicular heads.**
What are some contraindications to neck dissection as the primary management of the neck in pts with H&N cancers?

Show Answer

Base of skull invasion, satellite skin nodules/dermal invasion, and medically unstable/inoperable pts. Relative contraindications include internal carotid invasion, bone invasion, and skin ulceration.
What did the TROG 98.02 study suggest regarding the utility of planned neck dissections after definitive CRT for H&N cancer?

Show Answer

TROG 98.02 determined that neck dissection may not be needed for N2–N3 pts who have a CR on PET 12 wks post-CRT. These pts have low rates (4%–6%) of LRF despite the omission of neck dissection. (Corry J et al., Head Neck 2008)

FOLLOW-UP/TOXICITY

What are some common late sequelae of RT (+/- neck dissection) in H&N cancer?

Show Answer

Neck fibrosis/scarring, submental edema, hypothyroidism, and xerostomia
According to the RTOG combinatorial analysis, what factors were associated with severe late toxicity after CRT in advanced H&N cancer pts?

Show Answer

Per the RTOG combinatorial analysis, advanced age, advanced T stage, laryngeal/hypopharyngeal primaries, and neck dissection were all associated with severe late sequelae after CRT. (Machtay M et al., JCO 2008)

37

Early-Stage (I–II) Non–Small Cell Lung Cancer

Updated by Lauren Colbert and Steven H. Lin

BACKGROUND

What are the estimated annual # of new lung cancer cases diagnosed in the United States and the # of deaths from lung cancers?

Show Answer

In 2017, the American Cancer Society estimates there will be 222,500 new cases of lung cancer and 155,870 deaths. This accounts for more deaths than all colon, breast, and prostate cancers combined, although it is the 2nd most common cancer (prostate cancer is more common in men, while breast cancer is more common in women).

What is the lifetime risk of developing lung cancer—in men and women? Is there a difference by race?

Show Answer

The risk of a man developing lung cancer is currently 1 in 14, and the risk of a woman developing lung cancer is currently 1 in 17; however, the rate in men has decreased more rapidly than the rate in women, most likely in response to later adoption of smoking. Black men have a 20% higher incidence of lung cancer than white men, while black women have a 10% lower incidence than white women.

Overall, what is the 5-yr survival rate for lung cancer pts by stage?

Show Answer

The overall 5-yr survival rate for NSCLC is: stage IA 49%, stage IB 45%, stage IIA 30%, stage IIB 31%, stage IIIA 14%, stage IIIB 5%.
How many lobes are there in the lung? How many segments are there per lobe?

Show Answer

There are **5 lobes in the lung**—3 on the right and 2 on the left: RUL, RML, RLL, LUL, and LLL. Lingula is the anatomic equivalent of LML and is part of the LUL. There are **5 segments per lobe, except for the RUL and RML, which are divided in 3 and 2 segments,** respectively, supplied by tertiary bronchi.
Name the 9 N2 nodal stations.

Show Answer

N2 nodal stations:

Station 1: highest mediastinal
Station 2: upper paratracheal
Station 3: prevascular (3A) and retrotracheal/prevertebral (3P)
Station 4: lower paratracheal
Station 5: subaortic (AP window)
Station 6: P-A
Station 7: subcarinal
Station 8: paraesophageal
Station 9: pulmonary ligament
Where are the intrapulmonary and hilar nodes located?

Show Answer

Intrapulmonary nodes are nodes **along the secondary bronchi,** whereas hilar

nodes are those **along the main stem bronchi.** These are all considered N1 nodes.
Name the 5 N1 nodal stations.

Show Answer

N1 nodal stations (Note: N1 nodes are all **double digits**):

Station 10: hilar
Station 11: interlobar
Station 12: lobar
Station 13: segmental
Station 14: subsegmental

What are the 3 histologic subtypes of NSCLC in decreasing order of frequency?

Show Answer

Histologic subtypes of NSCLC are: adenocarcinoma (50%) > SCC (35%) > **large cell** (15%)
In addition to tobacco smoke, what are 3 other environmental exposure risk factors for developing lung cancers?

Show Answer

Environmental exposure risk factors for lung cancer:

- Radon
- Asbestos (Note: Smoking and asbestos exposures are synergistic in early reports, but more recent studies suggest less than a multiplicative effect.)
- Occupational exposure (arsenic, bis-chloromethyl ether, hexavalent chromium, mustard gas, nickel, polycyclic aromatic hydrocarbon)

What is the estimated RR for lung cancer in heavy smokers vs. nonsmokers?

Show Answer

Heavy smokers have a 20-fold excess of lung cancer (ACS cohort study). There is also a 2%–3% per yr risk of tobacco-induced 2nd primary cancer.
What is the risk of lung cancer in former smokers compared to current smokers?

Show Answer

The risk of developing lung cancer in former smokers is **around half** (9 times vs. 20 times) that of current smokers. (ACS cohort study)
What is the risk of lung cancer from passive smoke exposure?

Show Answer

There is a RR of 1.24 for developing lung cancer from passive smoke exposure. (NCCN 2018)
Appx what % of smokers develop lung cancer?

Show Answer

<20% of smokers actually develop lung cancer (in the Carotene and Retinol Efficacy Trial, 10-yr cancer risk was 1%–15%).
What histology subtype of NSCLC is least associated with smoking?

Show Answer

Adenocarcinoma is the histologic subtype that is least associated with smoking.
Name 3 histologic variants of adenocarcinoma of the lung.

Show Answer

Adenocarcinoma in situ (previously bronchoalveolar), acinar, and papillary
Discuss the natural Hx and Tx response of adenocarcinoma in situ (formerly bronchoalveolar) carcinoma.

Show Answer

Adenocarcinoma in situ is typically not associated with smoking. It can

present as a solitary nodule or multifocally. The pneumonitic form may spread along alveoli without basement membrane invasion. These tumors may have a good response to TKIs.
Name 2 variants of large cell cancer of the lung.

Show Answer

Giant cell and clear cell
What is the most common stage at initial presentation?

Show Answer

The most common stage of presentation for lung cancer is **stage IV (30%).**
What are the most common sites of DMs for lung cancer?

Show Answer

Bone, adrenals, and brain
What are the paraneoplastic syndromes associated with lung cancers?

Show Answer

Hypercalcemia of malignancy d/t PTHrP, SIADH → ↓ Na, Cushing (d/t ↑ ACTH), Lambert–Eaton syndrome, other neurologic disorders, hypercoagulability (adenocarcinoma), gynecomastia (large cell), carcinoid (including vasoactive intestinal peptide → diarrhea), and hypertrophic osteoarthropathy (adenocarcinoma).
What is the cause of Lambert–Eaton syndrome? Clinically, how can Lambert–Eaton is distinguished from myasthenia gravis?

Show Answer

Lambert–Eaton syndrome is caused by **circulating autoantibodies against presynaptic P/Q calcium channel. Lambert–Eaton strength improves with serial effort** but not myasthenia gravis.
Which histologic subtypes of lung cancer are associated with peripheral and central locations?

Show Answer

Peripheral: adenocarcinoma, large cell
Central: SCC
With which histologic subtypes of lung cancer is Thyroid Transcription Factor-1 (TTF-1) staining associated?

Show Answer

Adenocarcinoma, nonmucinous bronchioalveolar carcinoma (adenocarcinoma in situ), and neuroendocrine tumors (i.e., small cell lung cancer, carcinoid). TTF-1 is rare in SCC. A thyroid cancer primary must be excluded.
In NSCLC, what is the role of CXR or CT screening for high-risk pts?

Show Answer

CXR is NOT recommended for screening. The USPSTF recommends annual screening with LDCT in people b/t the ages of 55 and 80 with a greater than 30 pack-yr smoking Hx in current smokers or former smokers who quit <15 yrs ago.
What RCT have reported on low-dose CT screening for lung cancer among high-risk groups?

Show Answer

The National Lung Cancer Screening Trial (NLST, N Engl J Med 2011) was a prospective, RCT of lung ca screening comparing LDCT vs. annual CXR for 3 yrs in pts at high risk for lung cancer. Results suggested that LDCT decreased the RR of lung cancer death by 20%. To prevent 1 death from lung cancer, 320 high-risk individuals needed to be screened with LDCT.
What factors define the high-risk group for lung cancer according to the NCCN guidelines?

Show Answer

Per **NCCN 2018:** Age 55–74 yrs and ≥30 pack-yr smoking Hx and smoking cessation <15 yrs (category 1) OR age ≥50 and ≥20 pack-yr Hx of smoking and additional risk factors that increase the risk of lung cancer to ≥1.3% using the Tammem↑gi lung cancer risk calculator (Tammem↑gi MC et al., PLOS Med 2014). Additional risk factors used in the risk calculation include Hx of COPD/emphysema/bronchitis, cancer Hx, family Hx of lung cancer, and ethnicity. Exposure to 2nd-hand smoking is not an independent risk factor.
What is lead-time bias and how could it affect the results of a screening trial?

Show Answer

The lead time in Dx is the length of time b/t detecting the cancer from screening and when the Dx would have otherwise have occurred (i.e., through Sx or imaging studies). This could lead to an apparent increase in survival.
What is length-time bias and how could it affect the results of a screening trial?

Show Answer

Length-time bias occurs when a screening test detects cancers that take **longer** to become symptomatic (i.e., d/t the detection of slower-growing or indolent cancers). This too could lead to an apparent increase in survival.
What is the single most clinically significant acquired genetic abnormality in NSCLC?

Show Answer

EGFR mutation in exon 19 (45% of EGFR mutants, an in-frame deletion of 4 amino acid, LREA [leucine, arginine, glutamate, alanine]) **and exon 21** (40%, L858R point mutation); results in a constitutively active receptor. Others include exon 21 (L861Q) and exon 18 (G719X).
Among pts with NSCLC, in what particular groups are the EGFR

mutations common, and for what do these mutations predict?

Show Answer

In the overall lung cancer population, EGFR mutations are **seen in only ~10%,** but this occurs at high rates (30%–70%) in nonsmokers, adenocarcinomas, and Asians. These mutations **predict for a high response rate of >80% to TKIs;** gefitinib, erlotinib, afatinib, and most recently, osimertinib based on the phase 3 FLAURA trial compared to erlotinib or gefitinib. (Ramalingam SS, ESMO 2017)

Is EGFR overexpression more common in SCC or adenocarcinoma?

Show Answer

EGFR may be overexpressed in 80%–90% of SCCs vs. 30% of adenocarcinomas.

What are some common mechanisms associated with TKI resistance?

Show Answer

T790M is the point mutation in the exon 20 of the EGFR gene that occurs in 60% of primary TKI resistance. Most pts develop T790M mutation after about 9–13 mos of therapy with oral TKIs (erlotinib, gefitinib, or afatinib). Other resistance mechanisms include KRAS mutation, ALK or ROS1 gene rearrangements, exon 20 insertion mutations, small cell transformation, and epithelial–mesenchymal transition phenotype.

WORKUP/STAGING

What is the initial workup for a pt suspected of having lung cancer?

Show Answer

Lung cancer initial workup: H&P + focus on weight loss >5% over prior 3 mos, KPS, tobacco Hx, neck exam for N3 Dz, CBC, CMP, CT chest to include adrenals, PET/CT scan, MRI brain for presumed stages II–III, MRI for paraspinal/sup sulcus tumors, Dx of lung cancer rendered by Bx via

transbronchial endoscopic or transthoracic FNA (intraop preferred), mediastinoscopy or EBUS for suspected hilar or N2 nodes, PFTs prior to Tx, and smoking cessation counseling

What is the most cost effective 1st step in a pt presenting with a new lung lesion on CXR or CT?

Show Answer

Obtain prior imaging for comparison.

What are the 3 most common presenting Sx of NSCLC?

Show Answer

Dyspnea, cough, and weight loss (others include chest pain and hemoptysis)

What is the sensitivity and specificity of sputum cytology for Dx of lung cancer?

Show Answer

Sensitivity <70%, specificity >90%. Accuracy increases with increasing # of specimens analyzed. At least 3 sputum specimens are recommended for the best accuracy.

What is the sensitivity and specificity of FDG-PET compared to CT for the staging of lung cancers?

Show Answer

PET: sensitivity 83%, specificity 91%

CT: sensitivity 64%, specificity 74%

What is the estimated % of pts who will have false+ N2 nodes based on PET/CT?

Show Answer

10%–20%. PPV >80%. +N2 nodes by PET/CT need pathologic confirmation before deferring to potentially curative Sg.

What is the estimated % of pts who will have false– N2 nodes based on

PET/CT?

Show Answer

5%–16%. NPV >95%. –N2 nodes by PET/CT for clinical T1 lesions may not need mediastinoscopic evaluation (this is controversial).
What is the rate of occult mets from lung cancer detected by FDG-PET?

Show Answer

In many series, the range is **~6%–18%.**
If a PET scan is being ordered, should a bone scan be obtained to evaluate for bone mets as well?

Show Answer

No. In NSCLC, PET is just as sensitive as bone scan but more specific. However, consider pathologic confirmation for solitary PET+ lesions given the risk of a false+.
What clinical characteristics are important to focus on to determine the nature of a solitary pulmonary nodule?

Show Answer

Nodule size (and whether there are changes in size in the past 2 yrs), **Hx of smoking, age,** and **nodule margin on CT** (i.e., spiculation)
Stage for stage, does adenocarcinoma or SCC has a worse prognosis? Why?

Show Answer

Adenocarcinoma. It has a **greater propensity to metastasize,** particularly to the brain.
Does large cell carcinoma have a natural Hx and prognosis more similar to SCC or adenocarcinoma?

Show Answer

Large cell carcinoma has a natural Hx and prognosis more similar to **adenocarcinoma.**

Describe the T staging of NSCLC using the AJCC 8th edition (2017).

Show Answer

T1: ≤3 cm, surrounded by lung parenchyma (T1a ≤1 cm; T1b 1.1–1.9 cm; T1c 2.0–2.9 cm)

T2: >3 but ≤5 cm, + visceral pleura, main bronchus (not carina), +atelectasis of lobe (T2a 3.1–3.9 cm; T2b 4.0–4.9 cm)

T3: >5 but ≤7 cm, tumor invading invasion to CW, pericardium, phrenic nerve or separate tumor nodule in same lobe

T4: >7 cm any size, invading mediastinum, diaphragm, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsi lung lobe

Describe the N staging of NSCLC using AJCC 8th edition (2017).

Show Answer

N1: ipsi hilar or pulmonary nodes

N2: ipsi mediastinal or subcarinal nodes

N3: any SCV/scalene nodes or contralat mediastinal/hilar nodes

What is the AJCC 8th edition (2017) of the TNM stage for malignant pleural/pericardial nodules/effusion or opposite lung tumor nodules in NSCLC?

Show Answer

Malignant pleural/pericardial nodules/effusion or opposite lung tumor nodules in NSCLC is characterized as **M1a.**

According to AJCC 8th edition (2017), is a single brain mets to the brain stage the same as a brain mets and a bone mets? What about 2 brain mets?

Show Answer

A single extrathoracic mets (1 brain met) is **M1b**, while multiple

extrathoracic mets (in 1 organ or >1 organ) is **M1c.** A brain and bone met or 2 brain mets would both be **M1c.**
According to AJCC 8th edition (2017), what is the nodal subclassification?

Show Answer

N1: **N1a**-Single station N1 involvement, **N1b**-Multiple station N1 involvement; **N2a1**-single station N2 without N1 involvement (skip), **N2a2**-single station N2 with N1 involvement, **N2b**-multiple station N2 involvement; N3-**N3** LN involvement
What is considered early-stage NSCLC? Categorize the appropriate TNM stratification according to AJCC 8th edition.

Show Answer

Stages I and II are considered early-stage NSCLC.
Stage IA1: T1aN0
Stage IA2: T1bN0
Stage IA3: T1cN0
Stage IB: T2aN0
Stage IIA: T2bN0
Stage IIB: T1N1, T2N1 or T3N0
What procedures prior to thoracotomy can be used to evaluate the following nodal stations: (1) left and right stations 2, 4, and 7; (2) stations 5–6?

Show Answer

. **Mediastinoscopy** to evaluate left and right stations 2, 4, and 7 **or EBUS** to evaluate left and right stations 2, 3, 4, 7, and 10
. **VATS or ant mediastinotomy** (Chamberlain procedure) for stations 5–6

When should pre-Tx mediastinal nodal assessment be done?

Show Answer

As per NCCN 2018, bronchoscopy and pathologic mediastinal staging should be done for stage IB (peripheral T2a, N0), stage I (central T1ab–2a, N0), stage II (T1ab–2ab, N1; T2b, N0) or T3N0.

. To confirm PET or CT + nodes
. All sup sulcus tumors
. If T3 or central T1–T2 lesions

What routine PFT results (FEV1 and DLCO) indicate that the pt needs further testing prior to undergoing resection?

Show Answer

If the **FEV1 is <80%** predicted for the age and size of the pt **or the DLCO is <80%** predicted, then the pt may need quantitative lung scans/exercise testing to carefully predict postop pulmonary function.
What is the min absolute FEV1 necessary for pneumonectomy and lobectomy?

Show Answer

Pneumonectomy: >2 L
Lobectomy: Postop >1.0 L
Any patient with <1.5L capacity may be a candidate for wedge resection. The marginal % FEV1 for Sg is 40% of the predicted value.
Which subsets of lung cancer pts are at high risk for surgical morbidity?

Show Answer

Subsets at high risk for surgical morbidity:

. pCO2 >45 mm Hg (hypercapnia controversial)
. pO2 <50 mm Hg
. Preop FEV1 <40% of predicted value
. Poor exercise tolerance
. DLCO <40% of predicted value (desired >60%)

- Postop FEV1 <0.71 or <30% of predicted value
- Cardiac problems (left ventricle ejection fx <40%, MI within 6 mos, arrhythmias)
- Obesity

What are some factors that predict for postop complications (i.e., mortality, infection)?

Show Answer

Active smoking (6 times higher), poor nutrition, advanced age, and poor lung function. It is advised that pts should quit smoking for at least 4 wks prior to resection and have a nutrition evaluation.
What % of lung cancer pts clinically at stage I are upstaged at Sg?

Show Answer

5%–25% of stage I lung cancer pts are upstaged at Sg.
In addition to stage, name 3 other poor prognostic factors in lung cancer pts.

Show Answer

Poor prognostic factors in lung cancer:

- KPS <80%
- Weight loss >5% in 3 mos (10% in 6 mos)
- Age >60 yrs

TREATMENT/PROGNOSIS

Generally, what is a Tx paradigm for a stage I–II medically operable NSCLC pt?

Show Answer

Stages I–II medically operable NSCLC Tx paradigm: surgical resection (lobectomy) + mediastinal LND → adj chemo for everybody except stage IA,

margin-negative resection. Stage IB and IIA with negative margins warrant chemo depending on other high-risk factors (grade, LVSI, >4 cm size, visceral pleural involvement, incomplete LN staging). (NCCN 2018)
What should be the 1st step for a stage I–II medically operable NSCLC pt with a +margin resection?

Show Answer

Re-resection, if possible +/– chemo depending on other clinical factors. (NCCN 2018)
If re-resection is not possible, what RT dose is used for a +margin after Sg?

Show Answer

Microscopic +margin: **54–60 Gy**
Gross +margin: **60–70 Gy**
Generally, what is the Tx paradigm for a stage I–II medically inoperable NSCLC pt?

Show Answer

Stages I–II medically inoperable NSCLC Tx paradigm: if T1–2N0, consider definitive hypofractionated SBRT or SABR. If T1–T2N1 or T3N0, use definitive CRT. (NCCN 2018)
Name 3 surgical options to resect a T1–T2 tumor.

Show Answer

Surgical options to resect a T1–T2 tumor:

- Wedge or segmental resection
- Lobectomy
- Pneumonectomy

For a T1N0 NSCLC, what is the estimated LC for wedge/segmental resection vs. lobectomy?

Show Answer

Wedge/segmental LC is **82%** vs. lobectomy LC is **94%** (LF 18% vs. 6%) based on RCT **LCSG 821** (Ginsberg RJ et al., NEJM 1995). Lobectomy is preferred when feasible. However, CALGB 140503 is a currently ongoing phase III trial of lobectomy vs. sublobar resection for ≤2 cm peripheral NSCLC (smaller tumors than those treated in LCSG 821).

What % of stage I NSCLC pts will develop a 2nd primary after definitive surgical resection?

Show Answer

Up to 30% of pts develop a 2nd primary.

What is the estimated 5-yr OS of completely resected T1–2N0 NSCLC with no adj chemo?

Show Answer

T1N0 ~80%; T2N0 ~68% (Martini N et al., J Thorac Cardiovasc Surg 1999)

What is the 5-yr OS, CSS, and MS for pts who refuse any Tx for T1–2N0 NSCLC?

Show Answer

5-yr OS is 6%, CSS is 22%, and MS is 13 mos (Raz DJ et al., Chest 2007). Tumor size is a prognostic factor, independent of T stage.

What are the indications for adj chemo after definitive resection for stages I–II NSCLC?

Show Answer

Indications for adj chemo after definitive resection for stages I–II NSCLC:

- High-risk stages IB–IIB
- N1 Dz (category 1)
- T2N0 (stage IB), if the tumor is >4 cm as per unplanned analysis of **CALGB 9633** (Sg +/– carboplatin/paclitaxel). (Strauss GM et al., JCO

2008)

Other risk factors include poorly differentiated tumor, LVSI, wedge resection, visceral pleural involvement, and incomplete nodal sampling.
What is the estimated 5-yr OS benefit with adj chemo for pts with completely resected stage I or II NSCLC?

Show Answer

~5% at 5 yrs for adj cisplatin-based chemo based on **LACE meta-analysis** of recent trials (Pignon JP et al., JCO 2008). However, HR for stages IA and IB were not significant. Adj chemo for stage IA may even be detrimental.
What are possible chemo regimens in the adj or neoadj setting per NCCN 2018?

Show Answer

Cisplatin 50 mg/m^2 days 1 and 8; vinorelbine 25 mg/m^2 days 1, 8, 15, 22, q28 days for 4 cycles
Cisplatin 100 mg/m^2 day 1; vinorelbine 30 mg/m^2 days 1, 8, 15, 22, q28 days for 4 cycles
Cisplatin 75–80 mg/m^2 day 1; vinorelbine 25–30 mg/m^2 days 1 + 8, q21 days for 4 cycles
Cisplatin 100 mg/m^2 day 1; etoposide 100 mg/m^2 days 1–3, q28 days for 4 cycles
Cisplatin 75 mg/m^2 day 1; gemcitabine 1250 mg/m^2 days 1, 8, q21 days for 4 cycles
Cisplatin 75 mg/m^2 day 1; docetaxel 75 mg/m^2 day 1 q21 days for 4 cycles
Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 for nonsquamous q21 days for 4 cycles
Is there a role for preop chemo in early-stage lung cancer pts?

Show Answer

No. Based on a meta-analysis, the survival gain is the same as for adj chemo

(5%). The largest randomized trial (**MRC LU22/EORTC 08012**) for 519 pts randomized to preop chemo vs. Sg alone found good RR (49%) and downstaging (31%) but no survival benefit to preop chemo (Gilligan D et al., Lancet 2007). **The CHEST Trial** tested preop gemcitabine + cisplatin and found no significant benefit for stages IB/IIA but improved OS for stages IIB and IIIA (Scagliotti DV et al., JCO 2012). The **NATCH Spanish Trial** tested Sg vs. preop chemo + Sg vs. Sg + adj chemo and found no significant differences. However, more pts were able to rcv chemo in the neoadj setting. (Felip E et al., JCO 2010)

Is there a benefit of full mediastinal dissection vs. nodal sampling in early-stage pts undergoing surgical resection?

Show Answer

Possibly. A recent pooled analysis of 3 trials demonstrated a 4-yr OS benefit in stages I–IIIA NSCLC pts (HR 0.78). Mediastinal dissection involves removal of the right 2R, 4R, 7, 8R, and 9R and the left 5, 6, 7, 8L, and 9L. (Manser R et al., Cochrane Database Syst Rev 2005)

What are the indications for PORT after definitive resection for stages I–II NSCLC?

Show Answer

+Margins, +ECE, and unexpected N2 Dz. Per NCCN 2014, give concurrent CRT for an R2+ margin and sequential for R1 Dz (chemo → RT). Although not specified in NCCN, chemo → RT may also be considered for ECE.

Which randomized study demonstrated improved LC and survival with PORT after surgical resection for early-stage (stages IA and IB) NSCLC?

Show Answer

Italian study: 104 pts, stage I, resected with LND (pN0), randomized to PORT vs. observation; PORT encompassed the bronchial stump + ipsi hilum

(mean area, 50 cm^2) to 50.4 Gy. There were better LF rates (2% vs. 23%) with a trend to improved 5-yr survival (67% vs. 58%, p = 0.048). There was min toxicity and no worsened pulmonary function. (Trodella L et al., Radiother Oncol 2002)
What is the max RT dose that has been used for definitive RT alone in stages I–II NSCLC?

Show Answer

Up to 84 Gy in standard fractionation if lung dose–volume constraints are respected. RTOG 9311 dose-escalation study found that 90.3 Gy dose level was too toxic. (Bradley J et al., IJROBP 2005)
What is the 2-yr LR rate for RT alone using standard fractionation?

Show Answer

50%–78% 2-yr LR is based on **RTOG 9311,** but this study included stage III pts as well.
In stages I–II NSCLC pts being treated with definitive RT alone, should elective nodal regions be treated? What is the estimated elective nodal failure rate if untreated?

Show Answer

No. Elective nodal failure rate was <10% in **RTOG 9311.** In most series with stage I lung cancer treated with hypofractionated SBRT, the regional nodal failure rate ranged from 5%–10%. From the Indiana University dose-escalation study using SBRT for stage I lung cancer, regional nodal failure as the site of 1^{st} failure was 10%. (Hoopes DJ et al., Lung Cancer 2007)
Multiple retrospective reviews have also shown low elective nodal failure rates.
What are the estimated 3- to 5-yr LC and OS for medically inoperable stage I pts treated with definitive hypofractionated SBRT?

Show Answer

In most series using hypofractionated SBRT for stage I lung cancer pts, the **3-yr LC ranged from 85%–95%** and the **3-yr OS was 55%–91%.**
How does SBRT compare to lobectomy for operable stage I NSCLC?

Show Answer

In the Chang et al. pooled analysis of the STARS and ROSEL trials (Lancet Onc 2015), OS at 3 yrs was 95% in the SBRT group compared to 79% for the Sg group (HR 0.14; log rank p = 0.037). This remains controversial. In a recent SEER analysis (Shirvani S et al., JAMA Surg 2014), a propensity score matched analysis showed no difference b/t SBRT and Sg.

However, recent NCDB analysis of early stage NSCLC, in a propensity matched cohort of surgery vs. SBRT in 27,200 pts, surgery had significantly higher 30 and 90 days mortality, and highest in those >70 years old and with more extensive surgery. (Stokes WA et al., J Clin Oncol 2018)
What BED should be achieved to attain max LC and survival in pts with stage I lung cancer treated with SBRT?

Show Answer

According to Japanese data, if the **BED is ≥100 Gy,** then the 5-yr LC rate is 92% and the 5-yr OS is 71%. However, if the BED is <100 Gy, then the 5-yr LC rate is 57% and the 5-yr OS is 30%. (Onishi H et al., JTO 2007)
What is the estimated 5-yr rate of nodal failure, LF, and DM in early-stage NSCLC after definitive SBRT?

Show Answer

LRR (nodal) tends to be higher in SBRT pts than surgical pts and appears to increase with time. In RTOG 0236, 5-yr LR was 7%, involved lobar recurrence was 20% and regional recurrence was 38%. Distant recurrence rate was 31% (RTOG 0236; ASTRO 2014)
What is the SBRT technique that was evaluated in RTOG 0236? What is the 2-yr LC and OS rate for this group of inoperable pts?

Show Answer

SBRT using **20 Gy × 3** (without heterogeneity correction [HC]), or 18 Gy × 3 with HC) given in 1.5–2 wks. 3-yr primary tumor control is 97.6%, but the 3-yr primary tumor and involved lobe control is 90.6%, DFS was 48.3%, and OS was 55.8%. (Timmerman R et al., JAMA 2010)

How should the SBRT dose be modified for centrally located tumors?

Show Answer

Lesions located **centrally** (i.e., **within 2 cm** of the central bronchial tree) are not good hypofractionated RT candidates using 20 Gy × 3 fx d/t the risk of grades 3–5 toxicity (Timmerman R et al., JCO 2006). **MDACC** (Chang JY et al., IJROBP 2008) proposed 12.5 Gy × 4, with LC at 17 mos of 100%. There were grades 2–3 dermatitis and CW pain in 11%. There was no pneumonitis for newly diagnosed stage I pts. **RTOG 0813** has demonstrated that 10–11 Gy × 5 fx may be safe for centrally located lesions. Other options include 70 Gy in 10 fx (MDACC).

What CTV and PTV margins are used for SBRT?

Show Answer

At **MDACC,** there is no GTV to CTV expansion. ITV (around GTV) + 5 mm → PTV when four dimensional computed tomography (4D-CT) simulation and daily CBCT are used. According to RTOG 0915, GTV + 5 mm in axial plane and GTV + 1 cm in longitudinal plane if no 4D-CT used.

What studies have attempted to address the role of SBRT in both operable and inoperable early-stage lung cancer pts?

Show Answer

Operable:

RTOG 0618: phase II, operable stages I–II NSCLC, accrued 33 pts using 18 Gy × 3 (with HC) (Timmerman R et al., ASCO 2013): Median f/u 25 mos, 2-yr LF (primary tumor + involved lobe) 19.2%, PFS 65.4%, and OS

84.4%.

ROSEL (Dutch): phase III SBRT vs. Sg for operable stage I pts. RT 20 Gy × 3 for T1, 12 Gy × 5 for T2, and 7.5 Gy × 8 for central tumors. Primary endpoint is 2- and 5-yr LC, QOL, and cost. Trial closed to lack of accrual.

STARS (Accuray/MDACC): phase III SBRT (CyberKnife) vs. Sg in operable stage I pts. RT 12.5 Gy × 4 for central lesions and 16.7 Gy × 3 fx for peripheral tumors. Primary endpoint is OS, DFS, and toxicity at 3 yrs but closed to poor accrual. Now a single arm phase II trial in operable pts. Now a single arm phase II trial in operable pts which has completed accrual in 2017.

JCOG 0403: phase II study for stage IA medically inoperable or operable pts. 48 Gy in 4 fx over 4–8 days with HC. Primary endpoint: 3-yr OS and target size of 165 pts.

Inoperable:

TROG 09.02: phase III. T1/T2aN0 for pts who are medically inoperable/refuse Sg. 54 Gy in 3 fx over 2 wks vs. conventional RT 60–66 Gy in 30–33 fx +/– concomitant carboplatin/paclitaxel. Primary endpoint: time to LF.

RTOG 0915: phase II study in inoperable stage T1/T2 (<5 cm) NSCLC and peripherally located lesions. 34 Gy single fx vs. the Japanese regimen of 12 Gy × 4 fx. The winning arm will be compared to the current RTOG reference 20 Gy × 3 fx in a future phase III trial. Early results in ASTRO 2013 showed trial met prespecified 1-yr toxicity endpoint. Longer f/u needed.

SPACE (Scandinavian): phase II randomized trial of 3D-CRT 70 Gy in 35 fx vs. SBRT 45 Gy in 3 fx.

RTOG 0813: trial has completed accrual to the phase I/II study of dose-escalated SBRT (9, 10, 11, and 12 Gy × 5 fx over 2 wks) for centrally located tumors. 1 pt developed grade 3 RP in the 12 Gy group. No Tx-related grade 3 or greater toxicity from 9–11 Gy. Phase II completed at 11

Gy × 5 fx. No LFs presented at ASTRO 2011. Final results pending.

FOLLOW-UP/TOXICITY

What is the typical f/u schedule of pts treated for lung cancer?

Show Answer

Typical lung cancer f/u: H&P + CT chest with contrast q6–12 mos for 2 yrs, then noncontrast CT chest annually; continued smoking cessation counseling. PET or brain MRI is not routinely indicated. (per NCCN 2018)

What are the toxicities seen with SBRT for early-stage lung cancer?

Show Answer

Pneumonitis, lung fibrosis/consolidation, cough, dermatitis, CW pain, esophagitis, and hemoptysis

What is the total lung V20 dose–volume constraint for RT alone?

Show Answer

The total lung V20 dose–volume constraint is **<35%.** (per NCCN 2018)

What is the MLD constraint for definitive RT to lung cancer?

Show Answer

The MLD constraint is **≤20 Gy.** (NCCN 2018)

What is the distinction b/t grade 2 and 3 RTOG pneumonitis?

Show Answer

Grade 2 pneumonitis: symptomatic with the need for steroids

Grade 3 pneumonitis: dyspnea at rest and oxygen supplementation needed

Other grades of pneumonitis include grade 1: asymptomatic, seen only on CT; grade 4: hospitalized and intubated; grade 5: death

What are the heart dose–volume constraints for conventionally fractionated RT?

Show Answer

Heart V40 ≤80%, V45 ≤60% and V60 ≤30%, mean ≤35 Gy. (NCCN 2018)
What is the dose constraint for the brachial plexus with conventional fractionation?

Show Answer

The max dose to the brachial plexus should be kept at **≤66 Gy.** (NCCN 2018)
What is the rate of brachial plexopathy seen for pts treated with SBRT for early-stage lung cancer?

Show Answer

The recommended max dose to the brachial plexus is **<26 Gy in 3–4 fx** (Forquer JA et al., Radiother Oncol 2009). Of the 37 apical tumors for the 253 pts treated, 19% of pts developed grades 2–4 plexopathy. A dose >26 Gy resulted in 46% risk vs. 8% risk if the dose was <26 Gy.

At MDACC, for 70 Gy in 10 fx, max dose to the brachial plexus should be <60 Gy, ≤1 cc reaching 50 Gy and ≤10 cc 40 Gy. For 50 Gy in 4 fx, max dose to the brachial plexus should be <40 Gy, ≤1 cc, reaching 35 Gy and ≤5 cc 30 Gy.

At a min, what other normal tissue constraints should be closely examined during SBRT?

Show Answer

Location and size are important factors when considering normal tissue toxicity and constraints. Other tissues to monitor closely include esophagus, brachial plexus, trachea, main bronchus and bronchial tree, heart, total lung, major vessels, skin, CW, and SC.
What is the esophageal dose constraint for conventionally fractionated RT?

Show Answer

Ideally, the mean dose of RT to the esophagus should be ≤34 Gy and max ≤105% of Rx dose (per NCCN 2014). Try to minimize the V60 as much as

possible (V60 <33%, V55 <66%, ≤45 Gy to the entire esophagus).
What is the max BED for SBRT resulting in significant complications when centrally located tumors were treated?

Show Answer

180–210 Gy with grade 3 pulmonary complications (Timmerman R et al., JCO 2006). Keeping the BED ≥100 Gy may be sufficient for LC and may avert toxicities for central lesions. (Onishi H et al., J Thorac Oncol 2007)
Is a normal SUVmax of FDG-PET required to be considered a good clinical response in the f/u of stage I NSCLC pts treated with SBRT?

Show Answer

No. Prospective and retrospective reviews suggest that the SUVmax remains elevated for an extended period after SBRT d/t an inflammatory response, but there is no evidence of correlation with recurrence. (Timmerman R et al., IJROBP 2009; Henderson MA et al., IJROBP 2009)
What % of pts treated with SBRT for early-stage lung cancer have grades 3–5 toxicities?

Show Answer

15% of pts have grades 3–5 toxicities in a review of 15 studies (683 pts). (Sampson JH et al., Semin Radiat Oncol 2006)
In **RTOG 0236,** 16.3% of pts experienced grades 3–4 toxicity but no grade 5 toxicity. (Timmerman R et al., JAMA 2010)
What factors predict for grades 3–5 toxicities after SBRT for early lung cancer seen on the Indiana University phase II study?

Show Answer

Location (46% hilar/pericentral vs. 17% peripheral) and **tumor size** (GTV >10 cc had 8 times the risk of grades 3–5 toxicity). (Timmerman R et al., JCO 2006)
What are the PFT changes before and after SBRT for early-stage lung

cancer?

Show Answer

Very min based on an institutional review of 92 pts (Stephans KL et al., JTO 2009): mean FEV1 –0.05 (–1.88%), DLCO –2.59% of predicted value; no association with central vs. peripheral location or the dose administered.

38

Advanced-Stage (III–IV) Non–Small Cell Lung Cancer

Updated by Jennifer Chen Ho and Steven H. Lin

BACKGROUND

What is the most common hallmark of locally advanced Dz?

Show Answer

Mediastinal or SCV nodal involvement

What % of pts present with stage IIIA non–small cell lung cancer (NSCLC)?

Show Answer

~30% of all NSCLC pts have stage IIIA Dz at presentation.

What % of pts will have occult N2 Dz found at the time of Sg?

Show Answer

25% of pts will have occult N2 Dz found at Sg.

After definitive Tx of a primary lung tumor, what is the time period after which it is considered a 2nd primary tumor?

Show Answer

A tumor that develops **≥2 yrs** after definitive Tx of primary lung cancer is likely a 2nd primary. Whenever a recurrence with identical histology occurs at <2 yrs, it is considered a met. 5-yr survival after Dx of a 2nd primary can be

as high as 40% if early stage.
What % of pts with locally advanced NSCLC develop brain mets as a 1st site of relapse?

Show Answer

~15%–30% of NSCLC pts develop brain mets as a site of 1st relapse.
What is Pancoast syndrome?

Show Answer

Pancoast syndrome is a **result of apical tumors (aka, sup sulcus tumors) invading the thoracic inlet,** with compression on structures such as the sympathetic ganglion, brachial plexus, recurrent laryngeal nerve and vasculature causing shoulder/arm pain, Horner syndrome, paresthesias of the hand in ulnar nerve distribution, hoarseness, and SVC syndrome. Tumors that cause these Sx are referred to as Pancoast tumors.
What is Horner syndrome?

Show Answer

Horner syndrome is a result of tumor compression on the sympathetic ganglion, resulting in a triad of Sx: **ipsi miosis, ptosis, and anhidrosis.**
How prevalent are sup sulcus tumors?

Show Answer

Sup sulcus tumors account for **~3% of NSCLC.**

WORKUP/STAGING

What are the types of M+ Dz in the AJCC 8th edition?

Show Answer

M1a: Separate tumor nodule(s) in a contralat lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b: Single extrathoracic mets

M1c: Multiple extrathoracic mets in 1 or more organs
What is the TNM staging (AJCC 8th edition) that defines advanced NSCLC?

Show Answer

Stage IIIA: T3N1, T1–T3N2, T4N0–1
Stage IIIB: T1–T2N3, T4N2
Stage IIIC: T3–T4N3
Stage IVA: TXNXM1a/b
Stage IVB: TXNXM1c
What is the MS of pts who present with malignant pleural effusion with NSCLC?

Show Answer

MS is **3–9 mos.** These pts are staged as M1a Dz in the new staging system.
What are the survival outcomes of stage IIIA Dz with T3N1 vs. TXN2 Dz?

Show Answer

Stage IIIA is a heterogeneous group, with 5-yr survival ranging from **25%–30%** for T3N1 and **15%–20%** for T1–3N2 Dz. There is a lot of heterogeneity in the prognosis of the T1–3N2 group d/t the # and bulk of LNs involved.
What is the utility of PET/CT to determine the resectability of the lung cancer pts?

Show Answer

PET/CT **may improve the staging** to spare pts from futile thoracotomies b/c of unresectable Dz that is not detectable by conventional imaging. A Danish RCT (Fischer B et al., NEJM 2009) randomized 189 pts using either conventional staging with CT + mediastinoscopy or conventional staging and PET/CT staging. PET reduced the # of futile thoracotomies and the total # of

thoracotomies (both SS). But the overall mortality did not differ b/t groups.
What is the % of occult distant metastatic Dz found on PET/CT at initial Dx?

Show Answer

PET/CT can diagnose occult mets 10%–15% at the time of initial diagnostic workup.

TREATMENT/PROGNOSIS

What are the Tx options for pts with cN2, stage IIIA Dz?

Show Answer

Tx options with cN2, stage IIIA Dz:

- Induction chemo → Sg ± PORT (Roth J et al., JNCI 1994; Rosell R et al., NEJM 1994)
- Neoadj CRT → lobectomy (**INT-0139**) (Albain KS et al., Lancet 2009)
- Definitive CRT (**RTOG 9410,** Curran W et al., JNCI 2011)

What are the Tx options for pts with cN3, stage IIIB Dz?

Show Answer

Definitive CRT is the only Tx option for cN3, stage IIIB Dz.
Which clinical trials have demonstrated a survival benefit with adding induction chemo to Sg for stages IIIA–B NSCLC pts?

Show Answer

MDACC data (Roth JA et al., JNCI 1994; Roth JA et al., Lung Cancer 1998): 60 pts randomized to Sg alone vs. cisplatin/etoposide/cyclophosphamide × 1 cycle → Sg. MS was 21 mos (induction chemo) vs. 14 mos for Sg alone.

Madrid data (Rosell R et al., NEJM 1994; Rosell R et al., Lung Cancer 1999): 60 pts randomized to Sg alone vs. cisplatin/ifosfamide/mitomycin-C

× 3 cycles → Sg. MS was 22 mos (chemo) vs. 10 mos for Sg alone.

Spanish Lung Cancer Group Trial 9901 (Garrido P et al., J Clin Oncol 2007): phase II study, 136 pts, all with stage IIIA (N2) or stage IIIB (T4N0–1) Dz. Pts underwent cisplatin/gemcitabine/docetaxel × 3 cycles → Sg. There was pCR in 13%. MS was 48.5 mos for R0 resection vs. 12.9 mos for R1–R2 resection. The overall complete resection rate was 69%. MS was 16 mos, 3-yr OS was 37%, and 5-yr OS was 21%.

Did any trial fail to demonstrate a benefit for induction chemo f/b Sg?

Show Answer

JCOG 9209 (Japan: Nagai K et al., J Thorac Cardiovasc Surg 2003): trial closed early d/t poor accrual. 62 pts with stage IIIA N2 NSCLC randomized to Sg alone vs. cisplatin/vindesine × 3 cycles → Sg. There was no difference in MS (16–17 mos) or 5-yr OS (10% with chemo vs. 22% with Sg).

Are there data to demonstrate the need for adding PORT to adj chemo in pts with completely resected stage IIIA N2 NSCLC?

Show Answer

This cannot be adequately answered at this point. CALGB 9734 attempted to address this question (adj chemo alone vs. chemo → RT), but the trial was closed d/t poor accrual. (Perry C et al., Lung Cancer 2007) There was no difference in DFS or OS. However, some evidence suggests that pts with N2 Dz should be evaluated for chemo → PORT.

What is the evidence for PORT? What subset of pts may benefit from PORT?

Show Answer

In subset analysis from randomized trials and meta-analysis, pts with N2 Dz **may benefit from PORT.** There are ongoing prospective phase III trials testing the role of PORT in pN2 pts.

LCSG 773 (Weisenburger TH et al., NEJM 1986): RCT, 210 pts, stages II–

IIIA (T3 or N2), margin– resection, randomized to PORT or observation. RT: ≥Co-60 to the mediastinum to 50 Gy on postop day 28 (turned out to be nearly all SCC). Overall LR was better in PORT (3% vs. 41%), and DFS was better in N2 pts. There was no difference in OS b/t the arms.

PORT Meta-Analysis Trialist Group, Cochrane database, 2005 (Burdett S et al., Lung Cancer 2005): meta-analysis of 10 trials of pts treated after 1965. Suggested OS was a detriment to PORT overall. Subset analysis showed a detriment in resected stages I–II Dz but no adverse effect in N2 Dz.

Criticisms: (1) 25% of pts were T1N0; (2) the staging technique is no longer used; (3) the RT technique is no longer used (large fields and fx, high total doses, Co-60 machines); (4) >30% of the meta-analysis relied on a poorly done study using poor techniques/technology (Dautzenberg B et al., Cancer 1999) that showed PORT to be detrimental d/t a high 5-yr mortality from PORT (31% vs. 8%), mostly d/t Tx-related cardiac or respiratory deaths.

SEER analysis (Lally BE et al., JCO 2006): 7,465 pts, stages II–III NSCLC from 1988–2002, PORT vs. observation, median f/u 3.5 yrs. Overall, PORT did not affect OS. However, for the N2 subset, PORT was associated with better OS (HR 0.85) but detrimental for N0–N1.

Reanalysis of the ANITA trial (Douillard JY et al., IJROBP 2008): RCT of adj cisplatin/vinorelbine vs. observation for stages IB–IIIA pts after resection. 232 pts rcvd PORT. Overall, as a group, PORT was detrimental on survival (HR 1.34). In subset analysis based on pN stage, PORT was detrimental for pN0 pts. However, there was improved survival in pN1 Dz in the observation arm but detrimental in the chemo arm. PORT improved survival for both observation and chemo arms in pN2 pts.

PORT National Cancer Data Base Review (Robinson CG et al., JCO 2015): 4,483 pts (PORT, n = 1,850; no PORT, n = 2,633), all pN2, 2006–2010 with modern techniques. PORT conferred OS benefit over adj chemo

alone (SS on MVA).

Do pts who have a complete pathologic nodal response after induction chemo + Sg still need PORT?

Show Answer

Possibly. These pts may still have high LRR (retrospective analysis of MDACC and MSKCC data, 3y LRR ~ 20%). (Amini A et al., Ann Surg Onc 2013) Therefore any pts with pN2, regardless of chemo response, have high LRR and may still benefit from PORT.

Is there an advantage of postop CRT vs. PORT alone for stage III N2 NSCLC?

Show Answer

No. INT-0115/RTOG 9105/ECOG (Keller MB et al., NEJM 2000) tested PORT vs. CRT in resected stage II or III NSCLC. There was no difference in OS (3.2 yrs) or LC.

What are the anatomic areas targeted with PORT when given for unexpected N2 NSCLC? What is the recommended dose?

Show Answer

Per the ongoing European LungART trial, the **bronchial stump, ipsi hilum, and extension to mediastinal pleura facing resected tumor bed** should always be included. In the mediastinum: level 7 and level 4 (all), level 5/6 (left-sided tumor), the upper and lower LN station to the involved LN area; all LNs in b/w 2 noncontiguous LN stations involved.

Standard doses after complete resection are 50–54 Gy but a boost can be administered to areas of positive margins or extracapsular extension (per NCCN 2018). Doses b/t 60–70 Gy are appropriate for gross residual Dz.

What should be the rate of Tx-related deaths (death from intercurrent Dz [DID]) following PORT for NSCLC?

Show Answer

Based on old data with old techniques, DID was 20%–30%, mainly d/t pulmonary or cardiovascular excess deaths from PORT. New data suggest much lower rates (2%–3%).

Penn retrospective (Machtay M et al., JCO 2001): 202 pts, Tx with Sg + PORT; 4-yr DID PORT (13.4%), vs. matched controls (10%). If <54 Gy, DID was 2%; but ≥54 Gy, DID was 17%.

ECOG 3590 reanalysis (Wakelee H et al., Lung Cancer 2005): 488 pts randomized to PORT vs. PORT + chemo; 50.4 Gy RT. Overall, 4-yr DID was 12.9% vs. matched controls at 10.1%.

Is preop chemo alone adequate as an induction regimen in stages IIIA–B lung cancer pts or is preop CRT better?

Show Answer

2 trials have attempted to address this question:

RTOG 0412/SWOG 0332: pts randomized to induction chemo +/– RT → Sg. Unfortunately, this trial was closed d/t poor accrual.

German Lung Cancer Cooperative Group Trial (Thomas M et al., Lancet Oncol 2008): 558 pts, stages IIIA–B NSCLC, randomized to induction chemo etoposide/cisplatin (EP) × 3 cycles → Sg → RT (arm 1) vs. chemo → CRT (bid RT with carboplatin/vindesine) → Sg (arm 2). If +margin/unresectable Dz, the pt rcvd more bid RT. There was greater pCR (60% vs. 20%) and mediastinal downstaging (46% vs. 29%) in the CRT group but no difference in PFS or survival. If pts required a pneumonectomy, postop mortality ↑ in the CRT group. This study has been criticized for its nonstandard RT regimen.

If CRT is given for stage IIIA NSCLC, is there a benefit of adding Sg afterward?

Show Answer

For all-comers, there may be an improvement in LC, but there is no

survival benefit. Subset analysis demonstrates that those receiving lobectomy may have an improved survival outcome.

INT-0139 (Albain KS et al., Lancet 2009): 396 technically resectable stage IIIA pts randomized to induction CRT to 45 Gy (50.4 Gy with heterogeneity correction) + Sg vs. definitive CRT (61 Gy) alone. Both therapies were proceeded with 2 additional cycles of chemo, which was cisplatin (50 mg/m^2 days 1, 8) with etoposide (50 mg/m^2 days 1–5), q28 day cycle. In the group overall, local relapse was much better for the Sg arm (10% vs. 22%, p = 0.002), but there was no difference in DM and no OS benefit. There was OS benefit in subset analysis in matched pts with lobectomy (5-yr OS 36% vs. 18%; MS 34 mos vs. 22 mos, p = 0.002) but not in pts who had pneumonectomy. 26% of pts with pneumonectomy died, but only 1% died from lobectomy.

The ESPATUE trial (Eberhardt EE et al., JCO 2015) studied 246 pts with pN2 or resectable IIIB NSCLC who rcvd 3 cycles of induction cis/etop, then CRT (cis/vinorelbine) to 45 Gy in 1.5 Gy BID, and assessed for resectability. 161 pts were deemed resectable and were randomized to complete CRT to 65–71 Gy vs. Sg. The trial was closed early d/t slow accrual but did not show any difference in OS or PFS.

What is the RT dose for neoadj CRT if consolidative Sg is planned?

Show Answer

45 Gy. >50 Gy has been shown to have complications of bronchopleural fistula, prolonged air leak with empyema, and prolonged postop ventilation.

After an objective response to induction chemo for a pt with stage IIIA Dz, is adding postinduction surgical resection more beneficial than adding sequential radiotherapy?

Show Answer

No. In this circumstance, resection is not more beneficial than radiotherapy.

EORTC 08941 (Van Meerbeeck J et al., JNCI 2007): randomized trial for

stage IIIA–N2 Dz. Pts responding to platinum-based induction chemo were randomized to RT 60 Gy in 2 Gy/fx (arm 1) vs. Sg (arm 2). Only 50% had radical resection, with only 5% pCR (42% pathologic downstaged). Operative 30-day mortality was 4%. There was only 55% compliance in the RT arm. There was no difference in OS or PFS. Conclusion from this study is that concurrent CRT should be the standard of care for stage III NSCLC.

In light of all the evidence above, does including surgical resection in therapy for stages IIIA–B lung cancers in general improve outcomes?

Show Answer

The studies above do not show a clear benefit to adding Sg to CRT for locally advanced NSCLC. Both INT-0139 and EORTC 08941 failed to find sup outcomes with Sg over definitive RT in stage III Dz (albeit in different contexts). Definitive CRT is probably preferred over trimodality therapy in most pts with stages IIIA–B lung cancers.

Is there a subset of stage IIIA NSCLC that is likely to benefit from trimodality therapy?

Show Answer

Pts with min, nonbulky N2 Dz who can get lobectomy are the best candidates based on the INT-0139 subgroup analysis.

What randomized study established the min dose of 60 Gy for definitive RT for stage III NSCLC?

Show Answer

RTOG 7301 (Perez C et al., Cancer 1980): stages IIIA–B pts, dose-escalation trial with RT alone of 40 Gy, 50 Gy, and 60 Gy vs. 40 Gy (split course), all in 2 Gy/fx. LC improved with 60 Gy. 60 Gy was established as the standard.

Is there a benefit of altered fractionation of definitive RT (without chemo)

for stage III NSCLC?

Show Answer

Yes. Several phase II–III trials have demonstrated this benefit.

- **RTOG 8311** (Cox JD et al., J Clin Oncol 1990): randomized phase I–II, 848 pts with unresectable N2, 1.2 Gy bid to 60, 64.8, 69.6, 74.4, and 79.2 Gy. Pts with good PS who rcvd ≥69.6 Gy had significantly better 3-yr OS.
- **CHART** (Saunders MI et al., Lancet 1997): phase III, 563 pts randomized to 54 Gy at 150 tid (450/day) × 12 consecutive days vs. 60 Gy for 6 wks. There was 10% improvement in 3-yr absolute survival for CHART compared to standard RT. Severe esophagitis was common (19% vs. 3%).

What were the 2 seminal studies that demonstrated the importance of adding chemo to radiotherapy compared to radiotherapy alone?

Show Answer

- **CALGB 8433** "Dillman regimen" (Dillman RO et al., NEJM 1990): 155 pts with stage IIIA Dz (T3 or N2) treated with (1) RT alone (60 Gy) or (2) sequential chemo (cisplatin [CDDP]/vinblastine). Sequential chemo → RT improved MS from 10 mos to 14 mos, 2-yr OS from 13% to 26%, and 5-yr OS from 7% to 19%.
- **RTOG 88–08** (Sause W et al., Chest 2000): 458 pts with unresectable NSCLC (stages II–IIIB) randomized to 3 arms: 2 Gy qd/60 Gy alone (arm 1); 1.2 bid/69.6 Gy alone (arm 2); or sequential chemo (CDDP/vinblastine) + 60 Gy RT (arm 3). There was improved MS in arm 3 with sequential chemo (arm 1) c/w conventional RT (11.4 mos) or bid RT (12 mos).

Which 2 randomized studies demonstrated the superiority of concurrent CRT over sequential CRT for unresectable or medically inoperable stages II–III NSCLC?

Show Answer

- **West Japan Lung Cancer Study Group** (Furuse K et al., JCO 1999): 320 stages II–III pts randomized to sequential vs. concurrent CRT. Concurrent arm: CDDP/vindesine/MMC split-course RT (28 Gy × 2). Sequential arm: same chemo RT (Gy conventional, nonsplit course). There was better OS and PFS in pts with concurrent CRT. MS was 16.5 mos vs. 13.3 mos (SS); 5-yr OS was 15.8% vs. 8.9% (SS).
- **RTOG 9410** (Curran W et al., JNCI 2011): 610 pts randomized to 3 arms: sequential (Dillman regimen with RT to 63 Gy) (arm 1); concurrent CRT (to 63 Gy) (arm 2); and concurrent hyperfractionated RT (1.2 bid/69.6 Gy) + chemo (arm 3). Chemo was CDDP/vinblastine (except EP for arm 3). Definitive concurrent CRT (arm 2) had a better outcome in MS (17 mos) vs. 14.6 mos (arm 1) or 15.6 mos (arm 3) and 5-yr OS (16% vs. 10% vs. 13%). However, there was ↑ toxicity in the concurrent CRT arm.

Which chemo regimen allows a full dose and which would need to be dose reduced during the course of concurrent CRT?

Show Answer

Cisplatin/etoposide and cisplatin/vinblastine allow a full dose to be administered with RT. **Carboplatin/paclitaxel, gemcitabine, or vinorelbine require a significant dose reduction** during RT administration.

Is there a benefit of adding induction chemo → CRT for pts with unresectable stages IIIA–B NSCLC?

Show Answer

No. 2 prospective studies (**LAMP** and **CALGB 39801** trials) demonstrated no benefit to neoadj chemo. Definitive CRT alone is the standard of care.

- **LAMP trial** (Belani CP et al., JCO 2005): randomized phase II, 276 pts with stages IIIA–B NSCLC randomized to arm 1: chemo × 2 cycles → 63 Gy RT (Dillman regimen); arm 2: induction chemo × 2 cycles → concurrent CRT (63 Gy); and arm 3: concurrent CRT → consolidation

chemo × 2 cycles. Chemo was carboplatin/paclitaxel. Arm 3 (concurrent CRT) had a better outcome, where MS was 16.3 mos vs. 13 mos (arm 1) or 12.7 mos (arm 2).

- **CALGB 39801** (Vokes E et al., JCO 2007): randomized phase III trial, enrolled 366 pts with unresectable stages IIIA–B randomized to arm 1: CRT vs. arm 2: induction chemo × 2 cycles → CRT. Chemo was carboplatin/paclitaxel. There was no difference in MS or OS. MS 12 mos (CRT) vs. 14 mos (induction) (p = NS), 2-yr OS 29% vs. 31% (p = NS). Upfront chemo ↑ grades 3–4 heme toxicity.

What is the role for consolidation chemo after definitive CRT?

Show Answer

Uncertain. Despite initial enthusiasm with the **SWOG 9504** phase II study showing ↑ MS with consolidation docetaxel in stage IIIB pts after definitive CRT with cisplatin and etoposide (26 mos), the randomized phase III trial (Hanna N et al., JCO 2008) demonstrated no benefit of consolidation chemo with docetaxel but only ↑ toxicities and Tx-related deaths. Thus, there may not be a role of consolidation with docetaxel, but there may be a role for other agents, such as pemetrexed, as maintenance therapy. When low-dose weekly carboplatin/paclitaxel is used as concurrent regimen with RT, consolidation full dose carboplatin/paclitaxel × 2 cycles is often recommended after completing CRT. The place for consolidation chemo is now even more uncertain given the recommendation for consolidation durvalumab from the PACIFIC trial. (NCCN 2018)

What are the different chemo regimens used with concurrent CRT for locally advanced NSCLC? Are there differences in clinical outcomes for these regimens?

Show Answer

- Low-dose weekly carboplatin (AUC 2.0) and paclitaxel (40–50 mg/m^2) (CP) → high-dose consolidation carboplatin (AUC 6.0)/paclitaxel (150–200

mg/m^2) q3wks × 2 cycles

- Cisplatin (50 mg/m^2) and etoposide (50 mg/m^2) (q4wks per cycle × 2) (PE) → consolidation platinum doublet chemo × 2 cycles
- Cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) (q3wks per cycle × 3) (PP) → consolidation pemetrexed q3wks × 4 cycles

No, there are essentially no differences b/t the different chemo regimen, except some differences in toxicity profiles.

- **Systematic review** of published studies comparing CP vs. PE + RT in 3,090 pts (Steuer CE et al., JAMA Oncol 2017) found no differences in PFS and OS. PE had higher grade 3–4 hematologic and n/v toxicities. No differences in RT pneumonitis or esophagitis.
- **PROCLAIM trial** was a phase III randomized trial comparing PE vs. PP CRT in 598 pts. (Senan S et al., JCO 2016) There were no differences in OS. PP had less grade 3–4 adverse events, including neutropenia.

Is there a role for ENI for the Tx of inoperable, locally advanced NSCLC?

Show Answer

No. The current recommendation is to treat with CRT only the involved areas (assessed either by imaging or pathology) to improve dose escalation and improve toxicity.

MSKCC data (Rosenzweig K et al., JCO 2007): retrospective analysis of pts treated with IFRT alone. 524 pts treated with definitive 3D-CRT to areas of gross Dz; mean dose 66 Gy. Total elective nodal failures (ENF) (initial uninvolved nodal areas that fail) were 6.1%. The 2-yr primary tumor control rate was 51%. Overall, 2-yr ENF was 7.6%. Pts with local Dz control had a 2-yr ENF of 9%. Ipsi mediastinum had ↑ nodal failures (3%).

Prospective phase III trial (Yuan et al., ASCO 2007): inoperable stage III NSCLC randomized to involved-field irradiation vs. ENI. Involved-field irradiation achieved better overall response and improved 5-yr LC of 51% vs. 36% ($p = 0.032$).

What are the volumes and Tx techniques used for RT of locally advanced NSCLC?

Show Answer

GTV is defined by +FDG uptake areas, Bx-proven LN areas, or any LN >15 mm on CT. PTV = GTV + 1–1.5 cm. 3D-CRT or IMRT technique to 60 Gy or higher in 1.8–2 Gy/fx should be given.

Is there a benefit of dose escalation in locally advanced NSCLC?

Show Answer

No, there is currently no evidence that a dose >60 Gy with concurrent chemo is beneficial based on results from RTOG 0617 (see below). The rationale for dose escalation was based on prior studies which suggested that dose escalation improves LC and possibly survival.

RTOG 73–01: RCT testing 40 Gy split vs. 40 Gy continuous vs. 50 Gy continuous vs. 60 Gy continuous. The 60 Gy continuous had the best survival. 60 Gy became standard b/c of this trial, and since then 55–66 Gy is standard.

RTOG 93–11: dose escalation without chemo to 70.9 Gy, 77.4 Gy, 83.8 Gy, and 90.3 Gy. The 90.3 Gy is too toxic, but 77.4 Gy and 83.8 Gy are safe if V20 is 25%–36% and <25%, respectively. LC 50%–78%, with LF in elective nodal areas <8%.

Michigan study (Kong FM et al., IJROBP 2005): 106 pts, stages I–III NSCLC, treated with 63–103 Gy in 2.1 Gy/fx with 3D-CRT; primary tumor + LN + ≥1 cm; no chemo in 81%. MS was 19 mos. MVA showed that the RT dose was the only predictor of better survival.

What was the design of RTOG 0617?

Show Answer

RCT phase III comparison for stages IIIA–B NSCLC treated with CRT with 2 randomizations:

- 60 Gy vs. 74 Gy
- Carboplatin/paclitaxel +/– cetuximab

What was the outcome of the dose escalation portion of the study?

Show Answer

Closed early at interim analysis. Pts receiving 74 Gy had worse grade 5 toxicity and grade 3 esophagitis, higher rate of LFs, and worse OS. Pts who rcvd 74 Gy also had worse QOL at 3 mos. (Movsas B et al., JAMA Oncol 2016)

What are some possible explanations for the counterintuitive findings in the higher-dose arm?

Show Answer

- Too tight margins in the high-dose arm → higher LFs → worse survival
- Unmeasured or underreported toxicities → more Tx deaths → worse survival
- Extended therapy duration → worse LC → worse survival
- Combination of the above

Was there a benefit of adding cetuximab to CRT in RTOG 0617?

Show Answer

No. There was no survival benefit except for worse toxicities in the cetuximab arm. In a subset analysis, there was suggestion that higher tumor H-score for EGFR predicted for better outcome with cetuximab.

What is the benefit of IMRT over 3D-CRT in RTOG 0617?

Show Answer

In RTOG 0617, 53% were treated with 3D-CRT; 47% with IMRT. In a secondary analysis (Chun S et al., JCO 2016), IMRT was associated with a **60% decrease in grade 3 RT pneumonitis** (3.5% vs. 7.9%), with similar survival and control, in spite of the fact that more pts treated with IMRT were

stage IIB and had larger Tx volumes. Lung V20 was associated with grade 3+ pneumonitis. IMRT plans also had lower heart doses, and the heart V40 was significantly associated with OS. IMRT (vs. 3D-CRT) also had **less clinically meaningful decline in QOL** measure at 12 mos (FACT-LCS, 21% vs. 46%, p = 0.003). (Movsas B et al., JAMA Oncol 2016)

What consolidation therapy is recommended after CRT for stage III NSCLC?

Show Answer

Immune checkpoint blockade for 1 yr with durvalumab based on the **PACIFIC trial**. (Antonia SJ et al., NEJM 2017) Pts in the trial were not allowed consolidation chemo and had not progressed after CRT or with pneumonitis were randomized. In the 1st interim report of this phase III randomized trial in 713 pts, adding durvalumab (engineered hIgG1 anti–PD-L1) at 10 mg/kg q2wks up to 12 mos vs. placebo after CRT **significantly improved median PFS by over 11 mos** (16.8 mos vs. 5.6 mos, HR 0.52, p < 0.001), and an 18-mo PFS time of 44.2% vs. 27.0%. The PFS benefit was seen across most pt subsets, regardless of PD-L1 status. The median time to death or DM was also significantly improved with durvalumab (23.2 mos vs. 14.6 mos, HR 0.52, p < 0.0001).

What should be done in NSCLC pts with incidental N2 Dz found at the time of Sg?

Show Answer

If technically resectable, with only an occult, single-station mediastinal nodal met at Sg, **surgical resection should proceed with lung resection + mediastinal LND → adj chemo, with consideration of PORT.**

For pts who rcv Sg upfront, what is the role of adj platinum-based chemo?

Show Answer

It should be given for pts with N+ Dz or primary tumors >4 cm in pts with

T2N0 (stage IB) tumors.

LACE meta-analysis for 5 adj trials demonstrated 5-yr OS advantage of 5.4%. (Pignon JP et al., JCO 2008)

CALGB 9633 unplanned subset analysis demonstrated a survival benefit for stage IB pts with tumors >4 cm. (Strauss GM et al., JCO 2008)

What is considered bulky, unresectable Dz in NSCLC pts?

Show Answer

Pts with a **histologically involved LN >3 cm on CT, +extranodal involvement, or multistation nodal Dz** (regardless of size)

What is the preferred Tx strategy for pts with stage IIIB T4N0 Dz?

Show Answer

Neoadj chemo or CRT, or definitive CRT. 5-yr OS may approach 25%–30%. R0 resection should be attempted if this is technically feasible.

What is the 5-yr OS of pts with satellite nodules in the same lobe?

Show Answer

5-yr OS is **33%** if pts undergo lobectomy. Careful nodal assessment to exclude N2 Dz must be done.

What are the Tx paradigms and survival outcomes for resectable T3–4N0–1 sup sulcus tumors?

Show Answer

Resectable T3–4N0–1 sup sulcus tumor Tx paradigms: (1) preop CRT → Sg → chemo × 2 (**SWOG 9416/INT-0160**), with a 5-yr OS of 44%, or (2) upfront Sg → CRT to 60 Gy (1.2 Gy BID) for negative margin, and 64.8 Gy (1.2 Gy BID) for positive margin with concurrent and adj cisplatin (50 mg/m^2) and etoposide (50 mg/m^2) × 5 cycles. (**MDACC Phase II study:** Gomez DR et al., Cancer 2012) The 5-yr and 10-yr OS for the MDACC study is 50% and 45%, respectively.

What trial established the role of induction CRT for sup sulcus NSCLC? What was the induction regimen and the primary outcome of this study?

Show Answer

SWOG 9416/INT-0160 (Rusch VW et al., JCO 2007) was a single-arm phase II trial which evaluated induction CRT + Sg for resectable T3–4N0–1 sup sulcus tumors. The induction regimen was with concurrent cisplatin, etoposide, and RT to 45 Gy → restage; if no progression, then Sg → chemo × 2 cycles. Chemo was cisplatin (50 mg/m^2 days 1 and 8) with etoposide (50 mg/m^2 days 1–5), repeated q28 days for a total of 4 cycles. 95% completed induction therapy. Of the pts who had thoracotomy (88 of 110 pts [80%]) based on preop judgment of resectability, 94% had complete resection (83 pts). The study showed a 56% pCR or near CR rate and a 5-yr OS of 44% (compared to 30% for historical controls). Survival was better with complete resection (54%). There was no difference b/t T3–T4 tumors.
What are the appropriate Tx volumes, dose, and field arrangement for a sup sulcus tumor?

Show Answer

GTV defined by PET + 2 cm and ipsi SCV region. AP/PA to 41.4 Gy, then off-cord to 45 Gy. Cord should not exceed 110% of the Rx dose.
Are all pts with stage IIIB NSCLC unresectable?

Show Answer

No. Pts with T4 Dz with invasion of vertebral bodies and multiple nodules in different ipsi lung lobes are still resectable.
What are the Tx options for pts with malignant pleural effusion?

Show Answer

Treat as a stage 4 pt: thoracentesis, chest tube + drainage, sclerotherapy with talc or bleomycin, or placement of a chronic indwelling catheter. Depending on PS, chemo can be considered.

What should be done for pts with 2 synchronous nodules of NSCLC (i.e., occurring in different lobes)?

Show Answer

If there is identical histology, consider M1. If a different histology or genetic signature, it can be considered synchronous stage I NSCLC and definitive Sg and/or SBRT can be considered after full workup for nodal/distant involvement is excluded.

Is there evidence for local consolidative therapy in pts with stage IV Dz when there is no progression to initial systemic therapy?

Show Answer

Yes, 2 small randomized trials demonstrated the benefit of local consolidative therapy after induction systemic therapy in stage IV NSCLC with limited metastatic Dz.

- A small multicenter randomized phase II trial (Gomez DR et al., Lancet Oncol 2016) enrolled pts with stage IV NSCLC with ≤3 mets and no Dz progression after 1st-line systemic therapy. 49 pts were randomized to local therapy (CRT/RT or resection) of all lesions (+/– subsequent maintenance Tx) vs. maintenance Tx alone (which included observation only). The median PFS was improved in the local consolidative therapy group (11.9 vs. 3.9 mos).
- A small single institution randomized phase II trial at UTSW (Iyengar P et al., JAMA Oncol 2017) randomized 29 pts after induction chemo to maintenance chemo alone vs. SABR up to 5 metastatic sites + hypofractionated RT to primary site) + maintenance chemo. PFS was found to be significant on interim analysis (9.7 mos vs. 3.5 mos, p = 0.01) in the RT consolidation arm, with fewer recurrence overall.

How should pts with newly diagnosed NSCLC with a solitary brain lesion be managed?

Show Answer

Surgical resection should be considered, especially if the pt is symptomatic or to exclude a possible primary brain tumor, then either SRS or WBRT. Otherwise, SRS +/– WBRT should be used (per NCCN). The primary lung tumor should be managed according to the appropriate TN stage.

Overall, what is the 5-yr OS in the group of NSCLC pts with solitary brain mets?

Show Answer

5-yr OS is 20%–40% as a group.

Is there a role for PCI after Tx for locally advanced NSCLC?

Show Answer

- **No.** 4 older randomized trials showed only improvement in brain relapse rates (9% vs. 19%) but no survival benefit in adding PCI (Cox JD et al., JAMA 1981; Umsawasdi T et al., J Neurooncol 1984; Miller TP et al., Cancer Ther 1998; Russell AH et al., IJROBP 1991). A meta-analysis summarizes these data. (Lester JF et al., IJROBP 2005)
- **RTOG 0214** is a modern phase III randomized trial testing the utility of PCI for locally advanced NSCLC. The trial was closed d/t futility after enrolling 356 pts (planned 1,058). There was a significant improvement for brain relapse with PCI (1-yr relapse 7.7% vs. 18.0%, p = 0.004) but no difference in 1-yr OS or PFS. (Gore EM et al., JCO 2011)

What molecular testing should be done in pts who present with metastatic Dz?

Show Answer

For adenocarcinoma, large cell, NSCLC NOS: EGFR mutation, ALK, ROS1, PDL-1, should be tested as part of broad molecular profiling. For SCC, EGFR mutation and ALK testing should be considered in never smokers, small Bx specimens, or mixed histology.

What type of pts are EGFR and KRAS mutations common in? What % of pts have overlapping EGFR and KRAS mutations?

Show Answer

EGFR mutations are more common in Asian pts (prevalent in ~10% of Western and ~50% of Asian pts), in nonsmokers, females, and nonmucinous adenocarinoma. KRAS mutations are more common in non-Asians, smokers, and mucinous adenocarcinoma. These 2 mutations are nearly mutually exclusive, since <1% of pts have overlapping EGFR/KRAS mutations.
How do EGFR and KRAS mutations predict for response to targeted therapy?

Show Answer

EGFR mutations predict for response to EGFR TKIs. However, pts with KRAS mutations have primary resistance to EGFR TKIs.
What type of pts are ALK rearrangements common in, and what is its prevalence? What Tx does it predict response for?

Show Answer

ALK gene rearrangements are common in the same type of pts (adeno, nonsmokers) that are likely to have EGFR mutations, but they are usually mutually exclusive. They are present in ~2%–7% of pts with NSCLC. ALK gene rearrangements predict for sensitivity to crizotinib and alectinib.
Should pts with stage IV Dz rcv chemo or targeted therapy first?

Show Answer

Chemo should be given only if pts have negative or unknown ALK or ROS1 rearrangements, sensitizing EGFR mutation, or PD-L1 expression status.
Common 1st-line chemo regimens in the United States include cisplatin or carboplatin and pemetrexed, carboplatin and paclitaxel (+/– bevacizumab), and gemcitabine/cisplatin.
How are chemo regimen efficacy and NSCLC histology types associated?

Show Answer

Cisplatin/pemetrexed has sup efficacy and decreased toxicity in non-SCC histology pts; cisplatin/gemcitabine has increased efficacy in SCC histology pts.

For metastatic Dz pts who are found to be positive for sensitizing EGFR mutation, ALK/ROS1 rearrangement, or ≥50% PD-L1, what should their 1st-line systemic therapy be?

Show Answer

- EGFR mutation pts should rcv **osimertinib** (preferred based on the FLAURA trial [Soria JC et al., NEJM 2018]), erlotinib, afatinib, or gefitinib. Osimertinib has better CNS penetration than the other oral TKIs and can improve PFS in EGFR mutant NSCLC pts with brain mets.
- ALK or ROS1 rearrangement pts should rcv **alectinib** based on the phase III randomized trial (ALEX) that compared alectinib vs. crizotinib (prior 1st-line standard). (Peters S et al., NEJM 2017) Alectinib has reduced Dz progression and death, as well as less grade 3–5 toxicities. It also has better CNS penetration, resulting in better CNS metastatic control.
- Pts with ≥50% tumor cell PD-L1 staining (using the Dako 22c3 antibody) should rcv **pembrolizumab.** (Keynote-024, Reck M et al., NEJM 2016)
- If these mutations are discovered prior to 1st-line chemo, they should rcv the targeted therapy. If discovered during 1st-line chemo, they can either complete planned chemo or interrupt and switch to the appropriate targeted therapy.

What is the FDA-approved therapy for T790M positive advanced NSCLC who have progressed on prior EGFR TKI?

Show Answer

Osimertinib is the oral TKI that specifically inhibits EGFR receptors with T790M mutation. It is recommended as 2nd-line and beyond therapy for pts

with EGFR T790M who have progressed on prior oral TKIs. Based on phase III trials which showed superiority in OS, PFS and toxicities compared to standard platinum-based chemo, it is also recommended as 1st-line therapy for T790M positive NSCLC (Mok TS et al., NEJM 2017). Based on the FLAURA phase III trial, it also has greater efficacy as 1st-line therapy compared to erlotinib or gefitinib in EGFR mutant NSCLC in general, with reduced CNS relapse and less toxicity. (Soria JC et al., NEJM 2018)

What is the role of endobronchial/intraluminal brachytherapy for palliation for lung cancer?

Show Answer

Various fractionation schemes (15 Gy × 2 or 8–10 Gy × 1, prescribed to 0.5 cm) have been used in prior irradiated pts with endobronchial Dz causing Sx. Sx relief can be seen in 80% of pts. Complications included fatal hemoptysis (5%–10%), bronchoesophageal fistula (2%), and bronchial edema (1%).

MDACC published a series of 81 previously irradiated lung cancer pts who were treated with palliative HDR endobronchial brachytherapy, 15 Gy × 2, 6-mm depth, over 2 wks. Response was seen in 84%. Pts with excellent response had better survival (MS 13.3 mos) vs. those with poor response (MS 5.4 mos) (p = 0.01). 2 fatal complications were d/t fistula and tracheomalacia. (Delclos ME et al., Radiology 1996)

What fractionation scheme is optimal for pts with lung cancers treated with palliative RT for Sx such as hemoptysis, cough, pain, and shortness of breath?

Show Answer

Conventional fractionation is probably no better than hypofractionation. In a Norwegian RCT, Sundstrom S et al. tested 30 Gy in 10 fx vs. 17 Gy in 2 fx (1 wk apart) vs. 10 Gy in 1 fx. All achieved equivalent palliation. (JCO 2007)

FOLLOW-UP/TOXICITY

What is the typical f/u schedule of pts treated for lung cancer?

Show Answer

Typical lung cancer f/u: Stage I/II treated w/ Sg: H&P, CT chest with contrast q6mos yrs 1–3, then low-dose noncontrast CT chest annually yrs 3–5. Stage III or treated with RT: CT chest with contrast q3–6 mos for yrs 1–3, then q6 mos for yrs 4–5, then low-dose noncontrast CT chest annually. Continued smoking cessation counseling for all. (per NCCN 2018)

What are the expected acute and late toxicities of RT for lung cancer?

Show Answer

- Acute: Skin reaction, fatigue, dysphagia, odynophagia, cough
- Subacute and late: RT pneumonitis, lung fibrosis, brachial plexopathy, Lhermitte syndrome, RT myelitis, esophageal fibrosis/stricture, pericarditis, 2nd cancers

What are the signs and Sx of RT pneumonitis, and how is it managed?

Show Answer

RT pneumonitis is a subacute reaction that begins as early as 3–6 mos after RT. Typically, Sx include **chest pain, shortness of breath, fever, and hypoxia.** CT scan shows ground glass changes within the RT port. Check oxygenation and supplement if necessary. **If symptomatic, treat with prednisone 1 mg/kg/day for at least 3 wks with a very slow taper. Bactrim can be used for PCP prophylaxis.**

What is the total lung V20 dose-volume constraint for RT alone and concurrent CRT in definitive lung cancer Tx?

Show Answer

- NCCN**:** V20 <37%
- MDACC: RT alone → V20: <40%; CRT → V20: <35% (based on Lee HK

et al., IJROBP 2003)

What is the mean lung dose (MLD) constraint for definitive RT to lung cancer?

Show Answer

MLD ≤**20 Gy.**
What is the heart RT dose-volume constraint?

Show Answer

- NCCN 2018**:** V40 ≤80%, V45 ≤60%, V60 ≤30%; Mean ≤35 Gy
- MDACC: RT alone → V40: <50%; CRT → V40: <40%

Lower dose exposure may also be important: RTOG 0617 also found that increased heart V5 and V30 were associated with inf OS on MVA.
What is the dose constraint for the brachial plexus?

Show Answer

The dose constraint is **1 cc below 60 Gy;** the max dose point should be <66 Gy. 2 retrospective studies showed that the dose could be higher. (MDACC, Amini A et al., IJROBP 2012; median dose >69 Gy, max dose >75 Gy to 2 cc; and UPenn, Eblan MJ et al., IJROBP 2013: V76 <1 cc)
What is the max esophageal dose?

Show Answer

Ideally, **MLD <34 Gy.** Try to minimize the V60 as much as possible (V60 <33%, V50 <50%, ≤45 Gy to the entire esophagus, max dose point <70 Gy).
What is the expected grade 3–4 esophagitis rate in pts treated with sequential CRT vs. concurrent CRT in locally advanced NSCLC?

Show Answer

(Choy H, ASTRO 2003 [summary of multiple studies])

Sequential: ~4%

Concurrent: ~22%

What are the strategies for delivering external RT to lung tumors if dose constraints cannot be met?

Show Answer

. Induction chemo for debulking
. Breath-hold
. IGRT (e.g., daily CBCT to decrease PTV margins)
. Adaptive planning during Tx
. Alternative modalities (i.e., protons)
. Sequential chemo → accelerated hypofractionated RT (45 Gy in 15 fx)

39

Small Cell Lung Cancer and Bronchial Neuroendocrine Tumor

Updated by Jennifer Chen Ho and Steven H. Lin

BACKGROUND

Small cell lung cancer (SCLC) accounts for what % of new lung cancer Dx in the United States? What % of lung cancer deaths?

Show Answer

14% (31,000 cases/yr) of new lung cancer diagnosed in 2017 is SCLC, accounting for **~25% of lung cancer deaths** annually.
What % of SCLC is linked to smoking?

Show Answer

Nearly all cases of SCLC are linked to smoking.
What is the median age of Dx of SCLC? What % of pts are >70 yo at Dx?

Show Answer

The median age of SCLC Dx is **64 yrs,** with **25%** of pts presenting at age >70 yrs.
What % of pts with SCLC presents with metastatic Dz?

Show Answer

67% of SCLC pts present with mets, most commonly to the contralat lung, contralat or bilat malignant pleural effusion, liver, renal, adrenals, bone, BM,

and brain.
What are the pathologic characteristics of SCLC?

Show Answer

Small round blue cells of epithelial origin with neuroendocrine differentiation, ↑ **mitotic count,** and ↑ **N/C ratio**
What are the markers that characterize SCLC?

Show Answer

Markers that characterize SCLC include **S100, synaptophysin+, chromogranin+, and neurotensin + EGFR–.**
What pathology finding is often associated with SCLC?

Show Answer

Crush artifact
What are some common neurologic and endocrine paraneoplastic syndromes associated with SCLC?

Show Answer

Neurologic: Lambert–Eaton syndrome (antibody to presynaptic voltage-gated calcium channels), encephalomyelitis, sensory neuropathy (anti-Hu antibody)
Endocrine: Cushing Dz (↑↑ ACTH), SIADH (↑↑ ADH)
What is the most common chromosomal abnormality associated with SCLC but not seen with extrapulmonary small cell carcinomas?

Show Answer

Deletion of 3p (95% of cases, particularly 3p14–25 region, with inactivation of at least 3 tumor suppressor genes, including FHIT and RASSF1A)
What is the most common genetic alteration seen in SCLC?

Show Answer

Amplification of the bcl-2/C-myc family of oncogenes is most common but likely is not the initiating event. Other common abnormalities include loss of p16, loss of Rb, and mutation in p53.

WORKUP/STAGING

How do pts with SCLC usually present?

Show Answer

Large hilar mass with bulky mediastinal LAD that causes cough, shortness of breath, weight loss, postobstructive pneumonia, and debility. Other common presentations include paraneoplastic syndromes such as Lambert–Eaton, SIADH, or ectopic ACTH production.

Classically, does SCLC present centrally or peripherally in the lung?

Show Answer

Classically, SCLC presents **centrally** in the lung.

What histology is most commonly associated with superior vena cava obstruction (SVCO) syndrome?

Show Answer

SCLC is most commonly associated with SVCO syndrome.

Do SCLC pts present with solitary peripheral nodules without mediastinal LAD? What % have true stage I dz (T1–2, N0) after mediastinal staging?

Show Answer

This presentation is very **uncommon**; <5% of pts have true stage I dz.

How should pts be managed whose FNA results cannot clearly differentiate b/w small cell and atypical carcinoid histology?

Show Answer

Surgical staging, with mediastinoscopy → surgical resection if the MNs are negative (NCCN 2018)

Once SCLC has been diagnosed in a pt who presents with a large hilar mass, what further workup is necessary besides the basic H&P and labs?

Show Answer

LDH levels, CT C/A/P +/– PET, **MRI brain,** bone scan if PET is not done, **BM Bx** (for pts with elevated LDH), thoracentesis with cytopathologic exam for pts with pleural effusion, and smoking cessation counseling
What % of pts with SCLC at the time of Dx present with brain mets, BM involvement, and bone mets?

Show Answer

Brain mets: 10%–15% (30% are asymptomatic)
BM involvement: 5%–10%
Bone mets: 30%
What is the latest AJCC system for staging SCLC?

Show Answer

The same as for non-SCLC, but this system is not commonly used.
How SCLC is most commonly staged?

Show Answer

SCLC is commonly staged using the **International Association of Lung Cancer system,** which is a modification of the VALCSG system. There are 2 stages: limited and extensive. Tumors are staged according to whether the Dz can be encompassed within an RT port. Limited stage Dz is typically confined to the ipsi hemithorax, without malignant pleural effusion, contralat Dz, or mets; other presentations are usually extensive stage.
What % of pts present with limited-stage SCLC (LS-SCLC)?

Show Answer

~33% of pts present with LS-SCLC.
What are the most important adverse prognostic factors in SCLC? What

additional factors are assoc. w/ poor prognosis in extensive- and limited-stage dz

Show Answer

Poor PS; extensive-stage; weight loss (>5% in prior 6 mos); ↑ LDH; male gender; endocrine paraneoplastic syndromes (controversial), variant, or of mixed cell type; metastatic Dz. For extensive-stage: older age, poor PS, abnl Cr/LDH, >1 metastatic site. For limited-stage: male, age >70, abnl LDH, >stage I.

What is the MS of untreated limited- and extensive-stage SCLC?

Show Answer

~12 wks for limited stage and **~6 wks** for extensive stage, based on a VALCSG trial comparing cyclophosphamide to placebo.

What is the MS for pts with limited- vs. extensive-stage SCLC?

Show Answer

Limited stage: 20–30 mos

Extensive stage: 8–13 mos

What is the long-term survival rate in limited-stage SCLC treated with a combined modality?

Show Answer

26% long-term survival (5 yrs) (Turrisi A et al., NEJM 1999)

What additional workup should be considered for pts with carcinoid tumors of the lung?

Show Answer

Consider **octreotide scan.**

TREATMENT/PROGNOSIS

What is the Tx paradigm for pts with LS-SCLC?

Show Answer

LS-SCLC Tx paradigm: 4 cycles of EP **chemo (etoposide [120 mg/m^2, days 1–3] + cisplatin [60 mg/m^2, day 1, q3wks]) + concurrent RT (only 1 cycle is concurrent). Current standard RT regimen is based on INT-0096: 45 Gy in 1.5 Gy bid × 30 fx.**

What is the Tx paradigm for pts with T1–2N0M0 SCLC?

Show Answer

Lobectomy with mediastinal dissection and adj full course chemo.

(NCCN 2018) This situation is seen in ~5% of SCLC cases. The importance of adj chemo and PCI after complete resection for early-stage SCLC was highlighted in an NCDB analysis (Yang G et al., JCO 2016). If there are nodal involvement, consideration is made for adj mediastinal RT concurrent with chemo. PCI is also recommended. For more advanced lesions, 2 randomized studies (LCSG 832 [Lad T, Chest 1994] and the MRC [Fox W et al., Lancet 1973]) showed no benefit to Sg over definitive RT.

For **medically inoperable pts**, consideration can be made for **SBRT + consolidation full course chemo and PCI**. Mediastinal staging with EBUS should be made prior to SBRT. This is based on a multicenter case series and NCDB analysis, demonstrating comparable outcomes as surgical series. (Verma V et al., IJROBP 2017; Stahl et al., Lung Cancer 2017)

What is the OS and LC benefit of adding RT to chemo in LS-SCLC?

Show Answer

There is an **OS benefit of 5%** based on Pignon J-P et al. meta-analysis (NEJM 1992), with **LC benefit of 25%–30%.** (Warde P et al., NEJM 1992 [meta-analysis])

What is the benefit of smoking cessation prior to Tx in pts with limited-stage SCLC?

Show Answer

↓ **Toxicity and** ↑ **survival,** based on a retrospective review (Videtic GMM et al., IJROBP 2003)

What are the typical response rates seen after concurrent CRT for LS-SCLC?

Show Answer

Typical response rates are **80%–95% with** CR rates of 40%–60%.

What is the median duration of response for pts with LS-SCLC after definitive Tx?

Show Answer

6–8 mos is the median duration of response.

What is the preferred Tx approach for elderly pts (age >70 yrs) with LS-SCLC?

Show Answer

Depends on PS. In pts with good PS, combined CRT is preferred; they were shown to have 16% absolute 3-yr OS benefit with addition of RT to chemo (Corso CD et al., JCO 2015). Otherwise, standard combination chemo is better than single-agent cytotoxic agents.

What is the MS of SCLC pts after recurrence if treated with salvage chemo?

Show Answer

4–5 mos is the MS for these pts.

Why is EP the preferred regimen in concurrent CRT for LS-SCLC?

Show Answer

EP causes little mucosal toxicity, offers low risk of interstitial pneumonitis, and has lower cardiac toxicity compared to doxorubicin.

Full systemic doses can be administered with RT, and there is modest hematologic toxicity. EP has a better therapeutic ratio over the older regimen of CAV (cyclophosphamide, doxorubicin, and vincristine), but it confers no survival benefit.

What are the benefits and disadvantages of substituting carboplatin for cisplatin in EP for Tx of SCLC? Is there a difference in efficacy?

Show Answer

Carboplatin is less emetic, neuropathic, nephropathic, ototoxic, but there is **more heme toxicity.** A meta-analysis found **no difference b/w cisplatin vs. carboplatin** regimens. (Rossi A et al., JCO 2012)

Is there a benefit to maintenance chemo after the initial 4–6 cycles in the Tx of SCLC?

Show Answer

No. Maintenance chemo only produces minor prolongation of response without improving survival and increasing cumulative toxicity.

Is there a benefit of irinotecan compared to etoposide when added to cisplatin in the Tx of SCLC?

Show Answer

No. A Japanese RCT demonstrated a survival benefit with irinotecan, but this was not reproduced in 3 larger trials conducted outside Japan. However, a phase III trial found slightly improved OS with irinotecan over oral etoposide with carboplatin (Hermes A et al., JCO 2008), so irinotecan + carboplatin is an option. (NCCN 2018)

What is the optimal sequence of combining chemo with RT?

Show Answer

Concurrent is better than sequential (JCOG: Takada M et al., JCO 2002): MS 27 mos vs. 20 mos; 5-yr OS 30% vs. 20% (10% OS benefit)

What evidence supports early concurrent CRT over late RT with induction

CT → CRT?

Show Answer

NCIC data (Murray N et al., JCO 1993): phase III, 308 pts. 5-yr OS was 20% (early RT) vs. 11% (late RT).

Yugoslavia data (Jeremic B et al., JCO 1997): an early vs. late RT trial showed better MS (34 mos vs. 26 mos) and 5-yr OS (30% vs. 15%) for early.

Meta-analysis of 7 trials (Fried DB et al., JCO 2004): early (<9 wks) vs. late (>9 wks) after chemo. There was **5.2%** better 2-yr OS with early RT.

What is the recommended RT dose in CRT for LS-SCLC?

Show Answer

45 Gy in 1.5 Gy BID or 60–70 Gy in 2 Gy QD (NCCN 2018)

CONVERT (European phase III trial) comparing 66 Gy/2.0 Gy QD vs. standard 45 Gy/1.5 Gy BID showed similar OS and toxicity (Faivre-Finn C et al., Lancet Oncol 2017)

CALGB 30610 is currently testing 70 Gy/2.0 Gy QD vs. standard 45 Gy/1.5 Gy BID. Previous RTOG 0712 regimen of 61.2 Gy in 5 wks (1.8 Gy qd × 16 fx → BID**)** was d/c in CALGB trial although it was not more toxic than the 7-wk regimen.

What randomized trial demonstrated a clear superiority of altered fractionation with chemo compared to qd RT in the Tx of SCLC?

Show Answer

INT-0096 (Turrisi AT et al., NEJM 1999): phase III, 381 pts, EP × 4 cycles + RT at 1st cycle; randomization with 1.5 Gy bid × 3 wks vs. 1.8 Gy qd × 5 wks (both to 45 Gy); all rcvd prophylactic cranial irradiation (PCI) to 25 Gy. There was better 5-yr OS (26% vs. 16%) and LC (64% vs. 48%) in the bid arm. There was increased grade 3 esophagitis (27% vs. 11%) in the bid regimen, but not in the grade 4 toxicity. Criticism: 45 Gy qd is not

biologically equivalent to the accelerated hyperfx of 45 Gy in 30 fx.
Do any studies support dose escalation with conventional fractionation rather than traditional bid approach?

Show Answer

CALGB 8837 (Choi H et al., JCO 1998): phase I MTD in 50 pts of 2 RT regimens: 1.5 Gy/fx bid or 2.0 Gy/fx qd; MTD of bid was 45 Gy, whereas MTD of qd regimen was >70 Gy. Updated survival results were that 6-yr OS was better in the qd regimen compared with bid (36% vs. 20%). **CALGB 30610** is an ongoing phase III trial comparing 45 Gy in 3 wks (arm A: **INT-0096**) vs. 70 Gy in 35 fx (arm B: CALGB regimen). (Arm C, 61.2 Gy in 5 wks (1.8 Gy qd × 16 fx → bid, as in RTOG 97–12, was dropped.)
Describe classic RT targets for LS-SCLC?

Show Answer

Gross tumor, ipsi hilum, bilat MN from T inlet (1st rib) down to 5 cm below the carina. CTV = GTV + 1.5 cm (and elective hilum and MN regions + 8 mm), PTV = CTV + 1 cm.
What T RT field arrangements are classically used for treating LS-SCLC?

Show Answer

Minimize contralat lung exposure with AP/PA to 15 Gy (1.5 Gy bid × 5 days) with oblique field to 45 Gy (AP/PA in AM and obliques for PM sessions).
Should elective nodal irradiation be performed?

Show Answer

Historically, clinically uninvolved MNs were included. However, several modern studies showed that omission of ENI results in very low rates of isolated nodal recurrences of <5% **if PET staging used**. The CALGB 30610 and CONVERT trials have omitted ENI.
Should you cover the pre- or postinduction systemic therapy Dz for the

tumor and nodal volumes?

Show Answer

In pts who have systemic therapy before RT, the tumor GTV can be limited to the postchemo volume, based on 2 trials comparing pre- vs. postchemo volumes (Kies MS et al., JCO 1987; Hu X et al., Cancer 2011). The nodal GTV should include prechemo involved nodes but does not need to cover the entire extent of prechemo Dz.

Are there circumstances where IMRT may be beneficial?

Show Answer

Consider IMRT if V20 >30% or FEV1 <1 L.

What PTV margins should be used with/without 4D-CT simulation?

Show Answer

PTV is CTV + 0.5 cm if daily setup imaging is used and if **ITV** assessment is done during simulation and the planning process (either breath-hold or 4D-CT imaging). If a free-breathing non-ITV approach is used (non–4D-CT simulation), the PTV is CTV + 1.5 cm (sup–inf direction) and 1.0 cm in the axial direction. If a breath-holding non-ITV, PTV is CTV + 1.0 cm (sup–inf direction) and 0.5 cm in the axial direction.

Is IMRT associated with worse outcomes compared to 3D-CRT?

Show Answer

Retrospective review of MDACC experience demonstrated no difference in LC or OS when IMRT was compared to 3D-CRT. PEG tube placement was significantly lower in IMRT cohort. (Shirvani SM et al., Int J Radiat Oncol Biol Phys 2013)

What is the role of PCI in LS-SCLC? Is there an OS benefit with it?

Show Answer

Auperin meta-analysis of 7 RCTs (NEJM 1999) compared PCI vs. no PCI

after CR following induction chemo +/– RT and no evidence of brain mets before randomization. There was ↓ 3-yr incidence of brain mets (33% vs. 59%) and **5.4%** better 3-yr OS (20.7% vs. 15.3%) and improved DFS. There was a trend to a better outcome with ↑ doses and RT <4 mos from the start of chemo.

What PCI dose is now standard for LS-SCLC?

Show Answer

25 Gy in 10 fx is now the standard dose for PCI for LS-SCLC. (**RTOG 0212-Intergroup:** Le Pechoux C et al., Lancet Oncol 2009)

For pts with LS-SCLC what PCI doses were compared in RTOG 0212?

Show Answer

Standard doses (25 Gy in 10 fx) **vs. higher doses** (36 Gy in either 18 fx qd or 24 fx bid). There was **no difference in the 2-yr incidence of brain mets,** but there was an **OS and chest relapse advantage for the standard arm** (42% vs. 37%, p = 0.05) d/t greater cancer-related mortality in the high-dose group. There was **higher 1-yr chronic neurotoxicity in the higher-dose arm** (~85%–90% vs. 60%). (Le Pechoux C et al., Lancet Oncol 2009; Wolfson AH et al., IJROBP 2011)

What is the effect of PCI timing after the initiation of chemo for SCLC?

Show Answer

Based on **Auperin meta-analysis,** there was a ↓ in risk of brain mets with earlier PCI (<4–6 mos vs. >6 mos) without an effect on risk of death.

Are there data demonstrating greater neuropsychologic complications after PCI for SCLC?

Show Answer

No. The data actually demonstrate no difference with or without PCI in a randomized trial addressing the question of neuropsychologic changes after PCI (Arrigada et al., JNCI 1995). Most pts (97%) actually have abnl

neuropsychologic testing after chemo and before PCI, without a difference after PCI. (Komaki R et al., IJROBP 1995)
What is the recommended adj Tx for SCLC if the MNs are found to be involved after attempted surgical resection?

Show Answer

Concurrent CRT directed at the MN (per NCCN 2018); if node–, adj chemo alone
What is the Tx paradigm for pts with extensive-stage SCLC?

Show Answer

Extensive-stage SCLC Tx paradigm: **multiagent chemo regimen including EP.** Consider consolidation RT to the thorax for pts who achieve a CR to distant Dz after initial chemo (Jeremic B et al., JCO 1999). Also, PCI found to offer survival benefit even if extensive-stage Dz. (Slotman B et al., NEJM 2007)
How many cycles of chemo should be given for extensive-stage SCLC?

Show Answer

4–6. Giving >4–6 cycles only modestly prolongs response duration and does **not improve survival**, while increasing cumulative toxicity.
What additional chemo agents, when added to EP, have been shown to modestly improve the survival of pts with extensive-stage SCLC?

Show Answer

Ifosfamide or cyclophosphamide + an anthracycline have been shown to modestly improve survival.
Is there evidence to support consolidative RT to T Dz in extensive-stage SCLC?

Show Answer

Yes. 2 RCTs supported this.

A European multicenter trial (Slotman et al., Lancet 2015) randomized 498 extensive-stage SCLC pts who had any response to 4–6 cycles of platinum-based chemo (70% had PR) to T RT (30 Gy in 10 fx) + PCI or PCI alone. The primary endpoint, 1-yr OS, was not significantly improved (p = 0.07), **but the 2-yr OS was improved** in those receiving T RT (2-yr OS 13% vs. 3%, p = 0.004). There was a 50% reduction in intrathoracic recurrences, improved 6-mo PFS, but no difference in progression at any site. T RT was well tolerated with no severe toxicity. The benefit of consolidation T RT was mostly limited to the pts who had residual Dz after systemic therapy.

Jeremic et al. (JCO 1999) enrolled 210 extensive-stage pts. All rcvd EP × 3. The subset of 109 pts who achieved a CR at all distant sites was randomized to rcv consolidative RT (accelerated hyperfx to 54 Gy) with concurrent carboplatin/etoposide or not. In both arms, pts rcvd PCI and consolidative EP. Consolidative CRT improved 5-yr OS (9.1% vs. 3.7%) and MS (17 mos vs. 11 mos). There was a trend in favor of LC but not DM-free survival.

What are some salvage chemo agents used at the time of recurrence for SCLC?

Show Answer

Oral topoisomerase I inhibitors are standard for postchemo failure. (Topotecan was tested in RCTs showing doubling of survival [26 wks vs. 14 wks] compared with supportive care; irinotecan as a single agent was not tested.) Paclitaxel, docetaxel, TMZ, nivolumab +/– ipilimumab, vinorelbine, oral etoposide, gemcitabine, and CAV are some others.

What seminal study demonstrated a survival benefit with PCI in pts with extensive-stage SCLC with any response to chemo? What are some main criticisms of this study?

Show Answer

EORTC 08993 RCT (Slotman BJ et al., NEJM 2007): 286 pts with

extensive-stage SCLC treated with chemo; primary endpoint was time to symptomatic brain mets; pts randomized to +/– PCI after any response to chemo; most PCI pts given 20 Gy in 5 fx. PCI lowered the risk of symptomatic mets and improved DFS and OS (5.4 mos –PCI vs. 6.7 mos +PCI). 1-yr OS nearly doubled (13% –PCI vs. 27% +PCI).

Criticisms: Pre-Tx brain imaging is not required. The RT group was more likely to rcv chemo at the time of extracranial progression (68% vs. 45%). Only about half (59%) of pts in the control group rcvd WBRT for intracranial progression of Dz.

Is there a benefit of PCI for extensive-stage pts who have a (negative) staging brain MRI?

Show Answer

Controversial, but likely not. Although the EORTC 08993 trial showed OS benefit with PCI for extensive-stage SCLC, the trial did not require pre-Tx brain imaging. The Japanese phase III randomized trial of PCI vs. no PCI in extensive-stage SCLC pts who had a **negative staging brain MRI**, closed early d/t futility of PCI after 163 pts were enrolled. There was no improvement of OS for PCI vs. no PCI; in fact, there was a trend toward a negative impact on median OS. (10.1 mos [PCI] vs. 15.1 mos [no PCI], p = 0.09). (Takahashi T et al., Lancet Oncol 2017)

What was the greatest QOL alteration after PCI in the EORTC trial for extensive-stage SCLC?

Show Answer

3-mo QOL assessment showed that the largest negative impact of PCI was **fatigue and hair loss.** Worsening role, emotional, and cognitive function were also seen after PCI. (Slotman BJ et al., JCO 2009)

What PCI dose should be given for extensive-stage SCLC?

Show Answer

The preferred dose is still 25 Gy in 10 fx, similar to LS-SCLC, however a shorter course (e.g., (20 Gy in 5 fx) can be considered for selected pts, such as those with less than a CR (most pts rcvd 20 Gy in 5 fx in the Slotman trial)).
What is the current recommendation for PCI in pts with SCLC?

Show Answer

Indicated for limited stage and considered for extensive stage (NCCN 2018), CR/PR after chemo +/– consolidation RT, +/– MRI brain, PS of ECOG 0–2, within 3–6 wks of last cycle of chemo, 25 Gy in 10 fx. Also rcvd for pts who have had a complete resection. In pts with less than a CR, PCI is at the discretion of the treating physician.
How do you treat SCLC pts who present with a limited number brain mets?

Show Answer

Whole brain radiotherapy (30 Gy in 10 fx). SRS should not be offered outside a clinical trial since these pts tend to develop multiple CNS mets, although may be considered if pts have rcvd prior PCI in selected pts. (NCCN 2018)
In SCLC pts with SVCO, cord compression, or brain mets, what regimen is preferred as upfront palliative Tx: RT or chemo?

Show Answer

In a chemonaive pt presenting with SVCO, RCTs have shown a similar symptomatic response rate with chemo compared with RT. But in a chemorefractory pt, RT is the preferred regimen. In pts with cord compression/brain mets, RT is standard (in both chemonaive and chemorefractory pts).
How is palliative RT delivered for SVCO syndrome in pts with SCLC?

Show Answer

Generally, **a few large fx upfront** (3–4 Gy × 2–3) → **more definitive dosing in conventional fractionation** (qd or bid regimen)

What fractionation scheme is optimal for pts with lung cancers treated with palliative RT for Sx such as hemoptysis, cough, pain, and shortness of breath?

Show Answer

Conventional is probably no better than hypofractionation. In a Norwegian RCT, Sundstrom et al. tested 30 Gy in 10 fx vs. 17 Gy in 2 fx (1 wk apart) vs. 10 Gy for 1 fx. All achieved similar levels of palliation. (JCO 2007)

How should a tumor characterized as a high-grade neuroendocrine carcinoma, or as large cell neuroendocrine carcinoma, is managed?

Show Answer

Treat per non-SCLC guidelines (NCCN 2018)

How should a pt with a carcinoid tumor of the lung be managed?

Show Answer

Sg is 1st line if it is resectable. Some centers will treat atypical carcinoid per the SCLC paradigm (nonsurgical).

Per NCCN 2018:

- Stages I–IIIA typical carcinoid tumor can be observed after R0 resection.
- For unresectable or medically inoperable stage IIIA or IIB, RT +/– EP is rcvd for atypical carcinoid, and can be considered for typical carcinoid tumors.
- For atypical carcinoid tumors, resected stage I–II can be observed. However, for resected stages IIIA tumors, adj chemo (EP) +/– RT is recommended.

How should stages IIIB–IV or unresectable carcinoid of the lung be managed?

Show Answer

Systemic therapy (EP), or octreotide if octreotide scan positive or symptomatic from paraneoplastic syndrome (NCCN 2018)

FOLLOW-UP/TOXICITY

What is the recommended f/u schedule for SCLC pts?

Show Answer

SCLC f/u schedule: H&P, CT chest/liver/adrenal, and labs at each visit (visits q3–4mos for yrs 1–2, q6mos for yrs 3–5, then annually). PET scan should be considered whenever CT findings suggest recurrence or mets.

What is the total lung V20 dose–volume constraint for RT alone and concurrent CRT in definitive lung cancer Tx?

Show Answer

RT alone: V20 <40%

CRT: V20 <35%

What is the recommended MLD constraint with definitive RT for lung cancer?

Show Answer

MLD is <**15 Gy** ideally but not >20 Gy.

What is the max cord dose allowed on INT-0096 (“Turrisi regimen”)?

Show Answer

On INT-0096, the max cord dose was **36 Gy** (but max dose is **41 Gy** in ongoing CALGB 30610 trial).

What is the main toxicity associated with using bid RT as done in the Turrisi regimen?

Show Answer

Grade 3–4 acute **esophagitis:** 27% (bid) vs. 11% (qd). Other toxicities

(myelosuppression, nausea) were the same as the qd regimen. This is much less in modern era using 3D or IMRT approaches, with no difference b/t QD vs. BID Tx per CONVERT trial (19% in both arms).
What is the distinction b/t grade 2 and 3 pneumonitis (per the RTOG)?

Show Answer

Grade 3 pneumonitis: dyspnea at rest or oxygen supplementation needed
Grade 2 pneumonitis: symptomatic and not requiring oxygenation
What is the heart dose–volume constraint for RT alone vs. concurrent CRT?

Show Answer

According to **CALGB 30610,** the following limits are also acceptable: 60 Gy less than one-third, 45 Gy less than two-thirds, and 45 Gy <100%.
What is the esophageal dose–volume constraint for RT alone vs. concurrent CRT?

Show Answer

RT alone: V60 <50%
CRT: V55 <50% (ideally, keep the mean dose to <34 Gy per **RTOG 0538**)

40

Thymoma and Thymic Carcinoma

Updated by Dario Pasalic and Steven H. Lin

BACKGROUND

What is the embryonic derivation of the thymus?

Show Answer

The embryonic derivation of the thymus is the **3rd pharyngeal pouch**.

Where is the thymus located, and what is its function?

Show Answer

The thymus is in the **ant** mediastinum (ME), **involved in the processing and maturation of T lymphocytes to recognize foreign antigens from "self" antigens**.

What structures are located in the ant, middle, and post ME?

Show Answer

Ant: LNs, thymus, mesenchymal tissues
Middle: Heart and great vessels, trachea, esophagus, most mediastinal LNs, vagus and phrenic nerves
Post: Paraspinal tissues, sympathetic and peripheral nerves

What proportion of tumors of the ME are malignant?

Show Answer

One-third of mediastinal tumors are malignant.

How prevalent is thymoma relative to other mediastinal tumors?

Show Answer

Thymoma comprises **20% of all mediastinal tumors** but **50% of all ant mediastinal tumors.**

What is the sex and ethnic/racial predilection for thymomas?

Show Answer

There is **no sex predilection** (male = female). **Asian/Pacific Islanders** and **African Americans** in the United States have a higher incidence of thymomas. (Engels, J Thorac Oncol, 2010)

What age group has the highest incidence of thymomas?

Show Answer

Pts in the **7th decade** of life (Engels, J Thorac Oncol, 2010)

Are thymomas common in children?

Show Answer

No. Thymomas are extremely rare in children, but if present they are extremely aggressive with poor survival.

Do thymic malignancies usually present as a result of radiation-induced secondary malignancy?

Show Answer

No. Development of a thymic malignancy is rare after radiation therapy. There is currently no environmental or infectious risk factor associated with development of thymic malignancies.

How do thymic carcinomas differ from thymomas?

Show Answer

Thymic carcinomas are much **less prevalent** (<1% of thymic tumors), **very aggressive,** with **worse survival**. They are usually **not** associated with

paraneoplastic syndromes (e.g., myasthenia gravis [MG]). Thymic carcinomas **do not** have **immature T lymphocytes**. They **lack** the **lobulated pattern** separated by thick fibrous bands usually seen in thymoma. They also **lack** histologic features such as **Hassall corpuscles**, **medullary differentiation**, and **perivascular spaces**.

What is the LN metastatic rate of thymomas vs. thymic carcinomas?

Show Answer

Thymoma: ~1%–2%
Thymic carcinoma: ~30%
(Kondo K et al., Ann Thorac Surg 2003 [review of 1,320 pts with thymic tumors])

What is the probability of hematogenous dissemination of thymomas vs. thymic carcinomas?

Show Answer

Thymoma: ~1% (mostly to lung)
Thymic carcinoma: 12% (lung > bone, liver)

Pathologically, what is the most important defining feature of thymomas?

Show Answer

Coexistence of nonneoplastic lymphoid cells with **neoplastic epithelial cells** (spindle to polygonal types)

What are the WHO histologic classification divisions of thymomas and thymic carcinomas?

Show Answer

WHO type is **based on shape** and the **lymphocyte/epithelial ratio**

Thymoma types (frequency %)

- WHO type A (4%–7%): Spindle-oval cells with few to no lymphocytes
- WHO type AB (28%–34%): Spindle cells mixed with immature lymphocyte-poor and lymphocyte-abundant areas

- WHO type B1 (9%–20%): Immature T-cells with areas of both normal thymic cortex and medulla
- WHO type B2 (20%–36%): Large polygonal epithelial cells with even mixture of lymphocytes
- WHO type B3 (10%–14%): Sheets of polygonal epithelial cells with mild–moderate atypia and scant lymphocytes
- Micronodular thymoma with lymphoid stroma: Epithelial nodules surrounded by lymphoid stroma containing mature B- and T-cells but devoid of epithelial cells
- Metaplastic thymoma: Alternating epithelial cells and bland slender spindle cells with absence of immature T-cells

Thymic carcinomas

- Squamous cell, basaloid, mucoepidermoid, lymphoepithelioma-like, sarcomatoid, clear cell, adenocarcinomas, NUT, and undifferentiated carcinomas.

What value does the WHO histologic classification system have in clinical decision-making for thymomas?

Show Answer

Controversial d/t histologic heterogeneity, but some studies have shown that histologic subtype is an independent prognostic factor in early-stage Dz as WHO Type A, AB, and B1 thymomas purport lower-risk Dz compared to B2, B3 (Chen et al., Cancer 2002). **However, stage is still the most important clinical factor.** WHO classification assists in the ability to recognize the variable appearance as thymomas, thereby providing standardization for pathologists.

WORKUP/STAGING

What is the DDx of a mediastinal mass by location in the ant, middle, and post ME?

Show Answer

Ant: Thymoma, thymic carcinoma, thyroid (retrosternal), germ cell tumors, lymphomas, carcinoid, T aorta (Mnemonic: **TTTT**: **T**hymoma, **T**eratoma, **T**hyroid neoplasm, **T**errible lymphoma)

Middle: Cysts > lymphoma, teratomas > sarcomas (osteosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma of the heart), granuloma

Post: Neurogenic tumors (PNET, schwannoma, neurofibroma, NB, ganglioneuroma), pheochromocytoma

What clinical presentations are common for pts with mediastinal tumors?

Show Answer

About **one-half** are diagnosed **incidentally** on imaging studies. The remainder present with **local** Sx (**cough, shortness of breath, pain, stridor, phrenic nerve palsy, Horner** syndrome, **SVC** syndrome) or as an **association with MG** if thymoma.

What are some key features that help to distinguish a lymphoma, teratoma, and germ cell tumors?

Show Answer

Lymphomas can be associated with **B Sx** (fever >38°C, drenching night sweats, weight loss >10% in preceding 6 mos), elevated **LDH**, and **LA**. **Teratomas** tend to have a heterogeneous **imaging** appearance with a **fat** and **cystic** component. **Germ cell** tumors are associated with an elevated **a-HCG, AFP** and have a **sudden onset**.

How do pts with thymomas or thymic carcinomas usually present?

Show Answer

50% are **incidental** findings. If there are Sx, they reflect either **locally advanced Dz, metastatic sequelae**, or **paraneoplastic disorders** (in 50%–60% of thymomas but hardly seen in thymic carcinomas).

What paraneoplastic disorders are commonly seen in thymomas?

Show Answer

MG (35%–50% of cases), **pure red cell aplasia** (5%–15%), **immune deficiency syndromes** such as hypogammaglobulinemia (5%–10%), **autoimmune** disorders (collagen vascular, dermatologic, endocrine, renal Dz), and **other malignancies** (lymphomas, GI/breast carcinomas, Kaposi sarcoma).

What workup should be employed for a mediastinal mass?

Show Answer

Mediastinal mass workup: H&P (ask about **B Sx**, **MG Sx**, physical to assess **nodal** and **neurologic** status). Basic labs (**CBC** and **reticulocyte count** to r/o red cell aplasia**, TFTs** to r/o thyroid Dz, **AFP/a-HCG** to r/o germ cell tumor, **LDH** and **ESR** to r/o lymphoma, and **antiacetylcholine receptor** and **antinuclear antibodies**). **PFTs** to assess lung function. Imaging (**PA/Lat CXR, CT** or **MRI chest, PET** if lymphoma suspected but has limited role in detecting thymic malignancy). Bx (**FNA**, but preferably Tru-Cut **core Bx** or **incisional surgical Bx** via video-assisted thoracoscopic Sg, Chamberlain procedure).

Is an MRI sup to CT imaging of the chest for ant mediastinal masses?

Show Answer

No. Aside from cystic lesions, CT is equivalent, or even sup in some settings, to MRI for Dx of ant mediastinal masses. (Seki et al., Eur J Radiol 2014)

The Dx of thymoma is essentially established clinically if the pt presents in what way?

Show Answer

Ant mediastinal mass with Sx of **MG**, **red cell aplasia**, or **hypogammaglobulinemia**

Appx what % of pts with thymoma present with MG?

Show Answer

35%–50%. Conversely, 10%–15% of pts with MG have thymoma.
What are the pathogenesis, presentation, Dx, and Tx of MG?

Show Answer

Autoantibody to the acetylcholine receptor at the postsynaptic endplate. Pts present with **easy fatigability of skeletal muscles** (with preserved sensation, reflexes)**, dysphagia, ptosis,** and **diplopia**. Sx **worse with movement**, whereas the opposite is true for Lambert–Eaton. Dx is by the **Tensilon test** (edrophonium). Tx is by **anticholinesterase** (pyridostigmine) **or thymectomy** (reverses in 40% of pts with thymoma).
What is the Modified Masaoka system used to stage thymomas?

Show Answer

Stage I: fully encapsulated, no microscopic capsular invasion
Stage IIA: microscopic invasion into capsule
Stage IIB: macroscopic invasion into surrounding fat or mediastinal pleura
Stage III: macroscopic extension to surrounding organs (lung, pericardium), without great vessel invasion (A) or with great vessel invasion (B)
Stage IVA: pleural or pericardial dissemination.
Stage IVB: +LN or DM
Is there controversy regarding the Masaoka staging system for thymoma?

Show Answer

Yes. UCLA retrospective meta-analysis of ~2,500 pts showed no difference in DFS or OS b/t stages I and II pts. (Gupta R, Arch Pathol Lab Med 2008)
What are the 5-yr survival rates for thymomas based on the Masaoka staging?

Show Answer

5-yr survival for thymomas (Masaoka staging):

Stage I: 95%

Stage II: 90%
Stage III: 60%
Stage IV: 11%–50%
Based on modern surgical series, what are the rates of complete resection, the recurrence rate, and 5-yr OS based on Masaoka staging?

Show Answer

Based on outcomes for 1,320 pts. The % of complete resection, % of recurrence, and 5-yr OS, respectively, were as follows (Kondo et al., Ann Thorac Surg 2003):

Stage I: 100%, 1%, 100%
Stage II: 100%, 4%, 98%
Stage III: 85%, 28%, 89%
Stage IVA: 42%, 34%, 71%
According to AJCC 8th edition, is there a difference b/t encapsulated and unencapsulated thymoma?

Show Answer

No. Encapsulation does not appear to be clinically relevant. The capsule appears to be generated by a tumor-related process and not actually an anatomic structure of the thymus. This is a difference compared to the Masaoka staging system.
What is the 5-yr survival rate of invasive vs. noninvasive thymomas?

Show Answer

Invasive: 50%
Noninvasive: 70%
According to AJCC 8th edition, what is the T staging of thymic malignancies?

Show Answer

T1a: Encapsulated or unencapsulated, with or without extension into mediastinal fat
T1b: Extension to mediastinal pleura
T2: Extension to/involvement of pericardium
T3: Extension to/involvement of lung, brachiocephalic vein, SVC, CW, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4: Extension to/involvement of aorta, arch vessels, intrapericardial pulmonary artery, myocardium, trachea, or esophagus

According to AJCC 8th edition, what is the N staging of thymic malignancies?

Show Answer

N0: No nodal involvement
N1: Ant (perithymic) nodes
N2: Deep intrathoracic, pericardial, or distant sites

According to AJCC 8th edition, what is the M staging of thymic malignancies?

Show Answer

M0: No metastatic Dz
M1a: Separate pleural or pericardial nodule(s)
M1b: Pulmonary intraparenchymal nodule or distant organ mets

According to AJCC 8th edition, what is the TNM stage group of thymic malignancies?

Show Answer

Stage I: T1N0M0
Stage II: T2N0M0
Stage IIIa: T3N0M0
Stage IIIb: T4N0M0
Stage IVa: TxN1M0, TxNxM1a

Stage IVb: TxN2M0–M1a, TxNxM1b

What are the most important prognostic factors for thymomas?

Show Answer

The **completeness of resection** and **stage** are the most important prognostic factors for thymomas.

Based on AJCC 8th edition staging, what is the 5-yr OS for all thymic malignancies, thymomas, and thymic carcinomas in those pts who undergo an R0 vs. R-any resection?

Show Answer

Based on **retrospective, international outcomes for >10,000 pts** which led to the revised AJCC staging (Detterbeck et al., J Thorac Oncol 2014).

Stage + R0: All Thymic Malignancies | Thymomas | Thymic Carcinoma

Stage I: 94% | 95% | 84%

Stage II: 87% | 90% | 76%

Stage IIIa: 86% | 90% | 71%

Stage IIIb: 78% | 92% | 48%

Stage IVa: 75% | 83% | 51%

Stage IVb: 56% | 76% | 31%

Stage + R-any: All Thymic Malignancies | Thymomas | Thymic Carcinoma

Stage I: 94% | 95% | 83%

Stage II: 84% | 89% | 69%

Stage IIIa: 83% | 89% | 68%

Stage IIIb: 75% | 96% | 52%

Stage IVa: 70% | 80% | 41%

Stage IVb: 52% | 81% | 29%

Based on AJCC 8th edition staging for all thymic malignancies, what is the 5-yr vs. 10-yr recurrence rate after an R0 resection?

Show Answer

5- vs. 10-yr recurrence rate, respectively (Detterbeck et al., J Thorac Oncol 2014):

Stage I: 5.1% vs. 9.7%
Stage II: 20% vs. 27%
Stage IIIa: 32% vs. 42%
Stage IIIb: 34% vs. 43%
Stage IVa: 62% vs. 73%
Stage IVb: 51% vs. 55%

After an R0 resection, are recurrences more likely in thymomas or thymic carcinomas?

Show Answer

Thymic carcinomas. At 10 yrs, thymic carcinoma had a recurrence rate for Stage I-26%, Stage II-46%, Stage IIIa-60%, Stage IIIb-50%, Stage IVa-74%, and Stage IVb-59%.

Is the Masaoka staging useful for thymic carcinoma?

Show Answer

Controversial. Although the Masaoka staging is also applied for thymic carcinomas, an MSKCC series of 43 pts failed to find association of Masaoka staging with survival. (Blumberg et al., J Thorac Cardiovasc Surg 1998)

What are the most important prognostic factors for thymic carcinomas?

Show Answer

The **completeness of resection, invasion of innominate vessels,** and **presence of LN mets** are the most important prognostic factors for thymic carcinomas.

What is the 5-yr survival rate for thymic carcinoma?

Show Answer

The 5-yr OS for thymic carcinoma is **20%–30%** in advanced Dz.

TREATMENT/PROGNOSIS

What is the most important modality in the management of thymomas?

Show Answer

Sg is the mainstay of Tx, with complete resection being the primary goal. The outcome is fully dependent on the extent and completeness of the resection, regardless of stage or histology. Surgical clips can help identify areas difficult to resect or possible residual Dz. It may even be reasonable to resect pleural mets since prolonged survival is possible.

What is the usual approach for the surgical management of thymomas?

Show Answer

Median sternotomy, but more extensive resections may be required depending on the stage at presentation, including partial or total pneumonectomy or pericardiectomy.

In a thymoma pt with MG, what should be done preoperatively?

Show Answer

Signs + Sx should be controlled medically prior to undergoing surgical resection.

How is thymic carcinoma generally managed?

Show Answer

If possible, **max Sg → CRT postoperatively**. If inoperable, consider induction therapy with chemo, RT, or combination CRT.

When is adj radiotherapy a reasonable indication for the management of thymic malignancies?

Show Answer

Adj radiotherapy should be considered with **AJCC stages II–III (Masaoka stage III)**, ≥ **R1 resection**, or **any thymic carcinoma.**

Is adj radiotherapy necessary for an AJCC stage I (Masaoka stage I or II) thymic malignancy after complete resection?

Show Answer

Masaoka stage I thymoma pts **likely do not benefit from PORT**; however the decision making is more **controversial** for **Masaoka stage II** pts. The Tx paradigm that some institutions have adopted is to do adj radiotherapy for more aggressive histology, specifically **Masaoka stage IIA + WHO B3** histology or **Masaoka stage IIB + WHO B2–B3** histology given that these combinations purport higher risk for recurrence. (Geo et al., J Thorac Oncol 2013; Chen et al., IJROBP 2010)

A Chinese trial randomized 29 **Masaoka stage I thymoma** pts to **Sg-alone vs. Sg + PORT** and failed to show differences in outcome as pts had **92% vs. 88% survival at 10 yrs**, respectively. (Zhang et al., Chin Med J 1999)

Tx has been **historically recommended** for **Masaoka stage II** based on a classic review (Curran W et al., JCO 1988) that included 103 pts with thymomas, finding that pts without PORT had ↑ LR (6 of 19 pts for stage II) vs. no LR in PORT (0 of 1 pt for stage II, 0 of 4 pts for stage III).

However, most recently, Massachusetts General Hospital (Mangi A et al., Ann Thorac Surg 2002) and Japanese series (Haniuda M et al., Ann Surg 1996) showed that **PORT may not be necessary** after **complete resection for stage II** pts. Haniuda et al. specifically demonstrated that stage II thymoma with **macroscopic adherence to the pleura did benefit** from PORT (LR 36% vs. 0%), but PORT was **not useful for microscopic invasion** of the pleura or pericardium. (Ann Surg 1996)

Meta-analysis (Korst RJ et al., Ann Thorac Surg 2009): 1981–2008 systematic review of 13 studies, 592 pts, ~42% had Sg + PORT. The **LR rate did not benefit from PORT** for **stages II–III thymoma** (OR 0.87 for both stages II–III, p = 0.69).

SEER database (Forquer et al., IJROBP 2009): 901 pts from 1973–2005; 92% thymoma, 8% TC; localized Dz in 274 pts, regional Dz in 626 pts. **5-**

yr OS benefited from Sg + PORT for **regional Dz** (76% vs. 66%, p = 0.01); for localized Dz, Sg alone was more favorable (98% vs. 91% [PORT], p = 0.03).

JART database (Omasa M et al., Cancer 2015): A large series of 2,835 pts from 32 Japanese institutions 1991–2010 had Sg, 32% had PORT. **PORT for Masaoka stage II–III thymoma showed no benefit in RFS or OS**. PORT for **stage II–III thymic carcinoma showed better RFS but not OS**.

National Cancer Database analysis (Jackson et al., J Thorac Oncol 2017): One of the largest series included 4,056 pts of which 49% rcvd PORT. **Improved OS** seen with **PORT**, specifically for **thymoma Masaoka stage IIB** or **positive margins**. Stage I–IIA thymomas did not reach statistical significance. PORT also associated with **improved OS for thymic carcinomas**.

What should the postop target volume include?

Show Answer

The postop target volume should include the **entire bed of resection and any involved organs**. It is imperative to have a preop CT scan available to help delineate tumor bed volumes. Also, information from operative and pathology reports may help determine areas that might have had adherent, invasive Dz. For high-risk Dz, consider elective LN coverage.

What are the RT doses used for the postop management of thymic malignancies?

Show Answer

Depends on the extent of resection:

If R0: **45–54 Gy**
If R1: **55–60 Gy**
If R2: **60–70 Gy**

Is there a role for proton radiation therapy for Tx of thymic malignancies?

Show Answer

Reasonable to consider given organs at risk, though there is **very limited data**.

A small study of 4 thymoma pts in the adj setting demonstrated favorable clinical toxicity with grade 1 (n = 3) and grade 2 (n = 2) radiation dermatitis. Proton plans were associated with sparing of organs at risk, specifically lower mean lung (4.6 vs. 8.1 Gy), esophageal (5.4 vs. 20.6 Gy), and heart (6.0 vs. 10.4 Gy) doses when compared to analogous IMRT plans. (Parikh et al., Clin Lung Cancer 2016)

A prospective study of 27 thymoma and thymic carcinoma cases in the adj and definitive setting using proton radiation therapy demonstrated favorable LC (100% at 2 yrs) and OS (94% at 3 yrs). No pts experienced grade ≥3 toxicity. Acute grade 2 toxicities were limited to dermatitis (37%), fatigue (11%), esophagitis (7%), and pneumonitis (4%). (Vogel et al., Radiother Oncol 2016)

When should postop concurrent chemo be considered with RT for the management of thymic malignancies?

Show Answer

Per NCCN 2018, **thymoma** with **gross residual** Dz (**R2** resection) or **thymic carcinoma** with **R1–R2** resection.

What are some management approaches for unresectable thymic tumors?

Show Answer

Management approaches for unresectable thymic tumor:

- Induction chemo → RT only
- Induction chemo → Sg → PORT
- Induction RT/CRT → Sg → ± more RT

What are the results of definitive RT for unresectable thymic tumors?

Show Answer

RT can be used as the sole modality, with **5-yr OS 50%–87%**. Sg should be done whenever possible, however, since resectability is still the most important prognostic factor.
Given the good response rates seen with platinum-based chemo, what is the current preferred Tx paradigm for unresectable thymic malignancy?

Show Answer

Unresectable thymic malignancy Tx paradigm:

- **Chemo → RT (no Sg).** (Loehrer PJ et al., JCO 1997) Cisplatin/doxorubicin/cyclophosphamide (PAC) 2–4 cycles → RT to ≥54 Gy to primary + regional LN. 5-yr OS was 53%.
- **Chemo → Sg (if possible) → PORT.** (MDACC: Shin DM et al., Ann Int Med 1998) 3 cycles induction chemo (Cytoxan/Adriamycin/cisplatin [CAP] + prednisone) → max Sg → RT. 7-yr f/u showed 100% OS and 73% DFS.

What RT dose can be used for the neoadj management of unresectable thymomas?

Show Answer

24–30 Gy with chemo → Sg → then consideration for more RT depending on resection status.
What are the 1st-line combination chemo regimens used for the management of thymic malignancies?

Show Answer

CAP +/- prednisone; VP-16/ifosfamide/cisplatin (**VIP**); cisplatin/VP-16 (**EP**); **carboplatin/Taxol**; cisplatin/Adriamycin/vincristine/Cytoxan (**ADOC**); Cytoxan/Adriamycin/vincristine/prednisone (**CHOP**)
What are the typical response rates with induction chemo for the management of thymic malignancies?

Show Answer

Typical response rates with induction chemo are **50%–60%**.

FOLLOW-UP/TOXICITY

Per NCCN 2018, what is the f/u for pts who have had a complete resection of a thymoma and thymic carcinoma?

Show Answer

F/u includes **H&P + CT chest every 6 mos × 2 yrs** f/b annual CT scans.

Is 5 yrs of f/u sufficient for a pt treated for thymomas?

Show Answer

No. Late recurrences can occur at >10 yrs. Pts need lifelong f/u.

What are the expected early and late toxicities after adj RT for the management of thymic tumors?

Show Answer

Early: skin reaction, fatigue, dysphagia/odynophagia, cough

Late: RT pneumonitis/fibrosis, pericarditis, esophageal stricture, myelitis

What are the dose-limiting structures and dose limits when the ME is irradiated?

Show Answer

Lung: RT alone → V20 <40%; CRT → V20 <35%, V5 <65%, MLD <20 Gy

Heart: V40 <50% (V40 <40% if CRT)

SC: ≤45 Gy

Esophagus: Ideally, the mean dose of RT to the esophagus should be <34 Gy. Try to minimize the V60 as much as possible (V60 <33%, V50 <50%, ≤45 Gy to the entire esophagus, max dose point <70 Gy).

41

Pleural Mesothelioma

Updated by Penny Fang and Steven H. Lin

BACKGROUND

Appx how many cases of malignant mesothelioma are diagnosed in the United States annually?

Show Answer

2,500–3,000 cases/yr of malignant mesothelioma in the United States.

In which body sites can mesothelioma arise?

Show Answer

Mesothelioma most commonly arises in the **pleura surface** but can also arise from the mesothelial surfaces of the **peritoneum, pericardium, and tunica vaginalis testis.**

What is the most common cause of malignant pleural mesothelioma (MPM)? What are some other etiologic factors?

Show Answer

The greatest risk factor for developing MPM is occupational **asbestos exposure**, with carcinogenicity **greater for amphiboles** [rodlike] **than chrysotile** [serpentine form]. Asbestos is commonly found in insulation material, brake pads, and shipyards, 95% of which are in the chrysotile form.

Other known causes include naturally occurring asbestos within soil

(tremolite), therapeutic radiation exposure (i.e., supradiaphragmatic irradiation for childhood lymphoma or testicular germ cell tumors), and possibly genetics (familial clustering of cases), with loss of BAP1 being 1 of the implicated genes.

What is the median survival (MS) of pts with MPM?

Show Answer

The MS of pts with MPM is appx **12 mos** (MS in most series is **4–20 mos).**

What is the major difference b/t the incidence of MPM in the United States vs. the developing world?

Show Answer

B/c of early adoption of asbestos regulations, the incidence of **MPM in the United States peaked in 2004 and has subsequently declined.** The incidence **has not yet peaked in the developing world** and is not expected to for the next 10–20 yrs. However, the United States still has more cases than anywhere else in the world.

What is the estimated latency b/t asbestos exposure and MPM?

Show Answer

The estimated latency b/t asbestos exposure and MPM is **20–40 yrs.** (Lanphear BP et al., J Occup Med 1992)

What % of MPM cases are related to asbestos exposure?

Show Answer

70%–80% of cases have documented asbestos exposure.

What is lifetime risk of MPM for someone with an occupational asbestos exposure Hx?

Show Answer

The lifetime risk of developing MPM with asbestos exposure is **~10%.**

Does smoking cause MPM?

Show Answer

No. Smoking alone is not associated with MPM, but smoking increases the risk associated with asbestos exposure.

Does asbestos increase the risk for developing other cancers besides MPM?

Show Answer

Yes, along with cigarette smoking asbestos exposure acts synergistically to increase the risk of **lung cancer** by 60-fold compared to nonsmoking, nonasbestos exposed persons. Other cancer includes nonmesothelioma GI cancers. An asbestos worker has a 50% chance of dying from cancers compared to nonexposed individuals (~18%).

Is there a sex predilection for MPM?

Show Answer

Yes. Males are more commonly affected than females, likely related to occupational exposure differences.

At what age does the incidence of MPM peak?

Show Answer

The **incidence does not peak.** It continuously increases with age. The median age at Dx is 72 yrs.

What are the 3 most common histopathologic subtypes of MPM in decreasing order of frequency?

Show Answer

Histopathologic subtypes of MPM: **epithelioid (favorable,** 40%) **> mixed or biphasic** (35%) > **sarcomatoid or mesenchymal** (25%)

What are some common genetic changes seen in MPM?

Show Answer

Loss of tumor suppressor genes p16, p14, and NF-2 are common genetic changes in MPM.

WORKUP/STAGING

What are the common initial presenting Sx of MPM?

Show Answer

Dyspnea and nonpleuritic chest pain. Other common Sx include cough, pleural effusion, CW mass, weight loss, fever, and sweating.

What is the initial workup of a pleural-based mass seen on CXR?

Show Answer

Pleural-based mass initial workup: H&P, CBC, CMP, serum mesothelin-related protein (SRMP) and osteopontin levels (optional), CT chest + contrast, thoracentesis for cytology, and pleural Bx (thoracoscopic Bx [preferred], open Bx, or CT-guided core Bx). Consider talc pleurodesis or a pleural catheter for management of effusion.

What additional workup should be done with a Dx of MPM?

Show Answer

MPM workup: CT C/A/P + contrast, PET/CT, and MRI chest to determine if there is CW or diaphragmatic invasion. Consider mediastinoscopy or EBUS with FNA for suspicious nodes. Consider laparoscopy to r/o transdiaphragmatic extension if suggested by imaging. Use video-assisted thoracoscopic Sg to r/o contralat Dz, if necessary. Use PFTs to assess lung function.

How does MPM appear on chest imaging (CXR, CT)?

Show Answer

Large unilat pleural effusion and/or pleural thickening may be found on CXR. On CT of the thoracic chest, malignant MPM appears as **pleural thickening with involvement of interlobar fissures/atelectasis, with**

possible pleural plaques and calcification. Effusions and contracted ipsi hemithorax are also commonly seen.
What is the DDx of tumors of the pleura?

Show Answer

Primary tumors (benign [empyema] or malignant), thymoma, sarcoma, or more commonly, **metastatic Dz** (i.e., adenocarcinoma).
What is the diagnostic yield of MPM from the fluid cytology of the pleural effusion?

Show Answer

Fairly poor, only **~23%.** Often, cytology finds atypical mesothelial cells only.
With a needle Bx, what entity is often confused with MPM? What additional procedures may be needed for definitive pathologic Dx of MPM?

Show Answer

Adenocarcinoma (metastatic) is often confused with MPM. **Surgical intervention** using video-assisted thorascopic surgery (VATS) biopsy or open thoracotomy may be needed for definitive pathologic Dx.
What pathologic features distinguish MPM from adenocarcinoma?

Show Answer

MPM is negative for periodic acid-Schiff stain, carcinoembryonic antigen, and Leu-M1. It is positive for calretinin, vimentin, WT1, and cytokeratin 5/6. In MPM, EM reveals that cells have long microvilli, in contrast to adenocarcinomas, which have short microvilli.
What biomarker is elevated in MPM?

Show Answer

SRMP could be elevated in 80% of pts, but has limited accuracy since it is not elevated in sarcomatoid lesions, and could be elevated in other cancers.

The sensitivity of SRMPs range from 19%–68% (Hollevoet K et al., J Clin Oncol 2012). **O**ther markers under evaluation include **osteopontin and fibulin-3**.

What is the AJCC 8th edition (2017) T staging of MPM?

Show Answer

Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: limited to ipsi parietal pleura, with or without visceral, mediastinal, and diaphragmatic pleural involvement
T2: involves each of the ipsi pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with a pleural tumor, and at last (a) invasion of diaphragmatic muscle, or (b) invasion of lung parenchyma
T3: locally advanced but potentially resectable Dz and involves all ipsi pleural surfaces with at least 1 of the following: (a) involving endothoracic fascia, (b) invasion into mediastinal fat, (c) solitary focus of tumor invading soft tissues of CW, and (d) nontransmural involvement of pericardium
T4: locally advanced but technically unresectable Dz, with involvement of any ipsi pleural surfaces and at least 1 of the following: (a) diffuse or multifocal invasion of soft tissues of CW, with or without rib destruction, (b) direct transdiaphragmatic extension to peritoneum, (c) direction invasion of any mediastinal organs, (d) direct extension to contralat pleura, (e) invasion into spine, (f) extension to internal surface of pericardium, with cytology + or without pericardial effusion or invasion of myocardium

Describe the N staging of MPM according to the AJCC 8th edition (2017).

Show Answer

Nx: Regional LNs cannot be assessed
N0: No regional LN mets
N1: mets involving ipsi bronchopulmonary, hilar, or MNs (including IM,

peridiaphragmatic, pericardial fat pad, or intercostal)

N2: mets to contralat mediastinal, ipsi or contra SCV nodes

Note: N3 is no longer part of the AJCC staging

Describe the overall stage groupings for MPM according to the AJCC 8th edition (2017).

Show Answer

Stage IA: T1N0
Stage IB: T2–3N0
Stage II: T1–2N1
Stage IIIA: T3N1
Stage IIIB: T1–3N2 or T4Nx
Stage IV: TxNxM1 (any distant metastasis)

Which histologic subtype of MPM has a worse prognosis?

Show Answer

The **sarcomatoid** type has the worse prognosis.

Name the 4 EORTC prognostic factors that generated the EORTC index for MPM.

Show Answer

EORTC poor prognostic factors for MPM that formed the EORTC index:

- WBC >8.3 × 10^9/dL
- PS 1–2
- Sarcomatoid histology
- Male gender

The CALGB has also evaluated a series of pts to identify 6 prognostic factors which have been validated in other series. These include pleural (vs. peritoneal or pericardial), serum LDH >500 IU/L, poor PS, chest pain, platelet count >400 K/ul, nonepithelial histology, and age >75.

What are the estimated 1- and 2-yr OS rates for EORTC low- and high-

risk MPM?

Show Answer

Low risk: 1-yr OS 40%; 2-yr OS 14%
High risk: 1-yr OS 12%; 2-yr OS 0%
Is death from MPM usually d/t local progression or DM?

Show Answer

Death is usually d/t **local progression** resulting in respiratory failure or infection.

TREATMENT/PROGNOSIS

What is the Tx paradigm for resectable MPM?

Show Answer

For stages I–III, resectable MPM Tx paradigm, a combined modality approach is preferred:

- EPP or P/D → chemo → hemithorax radiation therapy (RT) or
- Neoadj chemo → EPP or P/D → hemithorax RT

What is removed with an EPP for MPM?

Show Answer

Parietal and visceral pleura, lung, MNs, pericardium, and ipsi diaphragm, with a graft to prevent herniation of abdominal contents through the diaphragmatic defect. Mediastinal nodal dissection should be done.
What is the Tx paradigm for unresectable MPM, clinical stage IV, or sarcomatoid histology?

Show Answer

For the unresectable scenario (or relative contraindication like for sarcomatoid histology), **combination chemo,** perhaps with cisplatin/pemetrexed (Alimta), and then re-evaluation for Sg. If remains

unresectable, continue chemo, and palliative symptomatic therapy.
What % of MPM pts are surgically resectable at Dx?

Show Answer

<5% of pts are surgically resectable at Dx.
What TNM stage of Dz determines surgical resectability using EPP for MPM?

Show Answer

T1–3N0–1. Therefore, mediastinoscopy to r/o N2–N3 Dz will be important.
What are the chemos of choice for the Tx of MPM?

Show Answer

Preferred Tx includes the combination chemo of choice incorporated into trimodality regimens utilizing antifolate agents such as pemetrexed/cisplatin or gemcitabine/cisplatin. Pemetrexed/cisplatin is based on an RCT (Vogelzang NJ et al., JCO 2003) of unresectable MPM pts to cisplatin vs. pemetrexed/cisplatin. There was improved response rate (17% vs. 41%) and survival (9 mos vs. 12 mos) with pemetrexed/cisplatin. This trial led to FDA approval for use in unresectable Dz. Cisplatin/gemcitabine use is based on several phase II studies.
When is a pleurectomy with decortication (P/D) a preferred procedure over EPP in a pt with MPM?

Show Answer

P/D has traditionally been preferred over extrapleural pneumonectomy (EPP) in pts with **more advanced Dz** (↑ nodal Dz, areas of local invasion), **nonepithelioid or mixed histology,** and **medically high-risk pts**, but since there is no evidence to support a survival benefit of EPP, and given the less morbidity of P/D, P/D is increasingly used in place of EPP. Periop mortality is 2%–5%. LF 44%–73% vs. 13%–40% for EPP. It is unclear which operation is sup oncologically and factors such as tumor histology and

distribution, pulmonary function, and availability of adj Tx may be of greater importance for the outcomes of pts.
Is there any evidence that EPP offers survival benefit over P/D?

Show Answer

No, there are no randomized comparisons of EPP vs. P/D, and most retrospective series show no significant advantage of EPP over P/D, if not with greater toxicities. A large series from MSKCC (n = 663) (Flores R et al., J Thorac Cardiovasc Surg 2008) comparing EPP (385) to P/D (278) showed greater operative mortality for EPP (7% vs. 4%), but with reduced LR (33% vs. 65%). However MS was 12 mos for EPP vs. 16 mos for P/D (HR 1.4, p <0.001).
What is the mortality rate of EPP? What is the MS for MPM after EPP?

Show Answer

The mortality rate of EPP ranges from **4%–31%** (8% at MDACC) and depends largely on the experience of the center and preop selection. MS in most series is **4–20 mos.** Rice et al. reported 10.2-mo OS. If IMRT, 14.2 mos and if LN– and epithelioid, 28 mos. (Ann Thorac Surg 2007)
What study supports adj RT after EPP for MPM?

Show Answer

MSKCC phase II trial with hemithorax RT to 54 Gy after EPP improved LC and OS compared to historical controls (Rusch V et al., IJROBP 2003). 2-yr OS was 33%. MS was 34 mos for stages I–II and 10 mos for later stages.
What study supports the role of trimodality therapy for MPM?

Show Answer

Harvard retrospective review (Sugerbaker D et al., J Thorac Cardiovasc Surg 1999) of 183 pts treated with EPP + adj chemo (Cytoxan/Adr/cisplatin [CAP] or carboplatin/Taxol) + RT → adj chemo. Overall, MS was 19 mos; 5-yr OS was 15%. 3 factors predicted for best outcomes: epithelial

histology, negative resection margin, and negative extrapleural nodes.

University of Toronto retrospective review (De Perrot M et al., J Clin Oncol 2009): Induction chemo (n = 60) → EPP (n = 45) → Hemithoracic RT to ≥ 50 Gy (n = 30): MS 14 mos, with MS 59 mos and 5-yr DFS 53% if pN0–1.

Name 2 RT techniques used for adj Tx of MPM after EPP.

Show Answer

AP/PA or IMRT to 45–54 Gy, with a boost to 60 Gy for a close/+ margin. Traditional Rx for AP/PA technique: 54 Gy in 1.8 Gy/fx, off-cord at 41.4 Gy. Electrons given concurrently. IMRT is preferred to allow for more conformal high-dose RT. Radiation initiated 3–6 wks after EPP.

Describe the conventional RT field borders for adj RT Tx of MPM after EPP.

Show Answer

Based on Yajnik S et al. (IJROBP 2003): Include scars with bolus in the field and boost if necessary.

Sup: Top of T1

Lat: Flash the skin

Medial: Contralateral edge of vertebral body if MN negative or 1.5–2.0 cm beyond contralateral edge of vertebral body if MN positive for Dz

Inf: Bottom of L2

Need to block critical structures anteriorly and posteriorly from the incidental AP/PA photon beam such as the heart, stomach, and liver and supplement blocked areas with electrons.

An **abdominal block** to shield liver (right side) or stomach (left side) is present anteriorly and posteriorly throughout Tx with electron supplementation at 1.53 Gy/fx (15% scatter from photon fields under blocks). These blocks extend 1.5 cm from ipsi border of vertebral body to within 2 cm from edge of CW. Blocks are present only where diaphragm abutted the abdominal wall anteriorly/posteriorly, but not where the

diaphragm was oblique to the abdominal wall.

For **left-sided** tumors, the kidney is blocked throughout, and the heart block is present after 19.8 Gy. The **spinal cord** is blocked after 41.4 Gy by shifting the medial border to the ipsi edge of the vertebral body.

How is IMRT delivered for the adj Tx of MPM?

Show Answer

MDACC experience (Ahamad A et al., IJROBP 2003, 2004), using 13–27 fields with 8–11 angles, with <100 segments/field. Target volume was the entire hemithorax, all surgical clips, all sites of instrumentation, and the ipsi MN; initial dose to 45–50 Gy, with a boost to 60 Gy for a close/+ margin. 2-yr survival was 62%, and 3-yr DFS was 45% for LN–, epithelioid histology. 5 pts with stage I Dz had 3-yr DFS of 100%. Updated outcomes in 86 pts who rcvd IMRT (Gomez DR et al., JTO 2013) showed MS 14.7 mos, 5 grade 5 pulm toxicities. LRR = 16%, DM = 59%.

What is sometimes recommended after a P/D procedure for MPM?

Show Answer

B/c of the high LR rate, **adj RT is advocated.** At MSKCC, 125 pts were treated with pleurectomy → interstitial RT or EBRT (Gupta V et al., IJROBP 2005). MS was 13.5 mos; 2-yr OS was 23%. Those with epithelioid or earlier-stage Dz did better. <40 Gy, left-sided Dz, use of an implant, or nonepithelioid histology did worse. LC rate was 40%. However, 12 pts developed pneumonitis, 8 pts pericarditis, and 2 pts died from grade 5 toxicity within 1 mo of Tx.

Phase II single arm study (IMPRINT) at MSKCC (Rimner A et al., J Clin Oncol 2016): chemo × 4 cycles (n = 45) → P/D (n = 21) → **pleural-based IMRT** (50.4 Gy). No grade 4–5 toxicities. MS 23.7 mos, PFS 12.4 mos. Largest prognostic factor was resectability (2-yr OS for resectable Dz 59% vs. 25% for unresectable).

What is a palliative surgical procedure to consider for the management of

poor-risk MPM?

Show Answer

Pleurodesis with talc can be considered as palliative care with poor-risk MPM.

What is the role of RT in unresectable MPM Dz?

Show Answer

Palliative RT is used only for temporary pain relief. Use either 30 Gy in 10 fx or 20 Gy in 5 fx. In retrospective studies, the 2 regimens gave similar palliation.

What RT doses are used for palliation of chest pain associated with skin nodules in the CW?

Show Answer

Daily doses ≥4 Gy appear more efficacious than fx dose <4 Gy, for a total dose of 20–40 Gy.

What is the role of RT after invasive procedures for MPM? What study evaluated the role of prophylactic RT, and what were the results?

Show Answer

Historically, RT was given to areas of invasive procedure (including thoracentesis and chest tube) to avoid needle tract seeding with tumor (which occurs 10% of the time). RT was **7 Gy × 3, for a total of 21 Gy** (Boutin C et al., Chest 1995; Di Salvo et al., Acta Oncol 2008). However, O'Rourke N et al. showed in a randomized trial that **prophylactic RT to drain sites did not statistically reduce the rate of seeding.** However, b/c recurrence is morbid, prophylaxis is still generally done (Radiother Oncol 2007).

FOLLOW-UP/TOXICITY

What is the estimated contralat lung V20 associated with the development of fatal pneumonitis in the Tx of MPM?

Show Answer

RR was 42 for fatal pneumonitis if the V20 was >7% in the contralat intact lung based on MDACC data. (Rice DC et al., Ann Thorac Surg 2007)
What are the dose–volume constraints for the contralat lung in RT for MPM?

Show Answer

In the remaining lung, with the V20 <7%, **MLD ≤8.5 Gy, V5 <50%**
What is the dose constraint for the liver? Heart? Spinal cord? Esophagus? Kidney?

Show Answer

Liver: V30 <30%
Heart: V40 <50%
SC: V45 <10%, no volume >50 Gy
Esophagus: V55 <30%, mean <34 Gy
Kidney: V15 <20%
What are 5 acute and long-term complications from Tx?

Show Answer

Acute: fatigue, n/v, dysphagia/odynophagia, skin reactions, cough, dyspnea, pneumonitis, infection, Lhermitte sign
Late: cardiac (pericarditis, cardiomyopathy, MI, CHF) and lung (fibrosis, pneumonitis)

42

General Breast Cancer

Updated by Shane R. Stecklein

BACKGROUND

What are the 3 most commonly diagnosed cancers in women in decreasing order of incidence?

Show Answer

Most commonly diagnosed cancers in women: breast > lung > colorectal
(Siegal R et al., Cancer Stats 2017)

What are the 3 most common causes of cancer death in women in decreasing order of incidence?

Show Answer

Most common causes of cancer death in women: lung > breast > colorectal
(Siegal R et al., Cancer Stats 2017)

Appx how many women in the United States are diagnosed with invasive and noninvasive breast cancer, and how many will die of breast cancer annually?

Show Answer

Incidence: ~253,000 invasive breast cancers and ~63,000 noninvasive breast cancers annually
Mortality: ~41,000
(Siegal R, Cancer Stats 2017)

What is the median age of Dx for invasive breast cancer?

Show Answer

The median age for invasive breast cancer is **61 yrs.** (Miller et al., Cancer Treatment & Survivorship Facts & Figures 2016–2017)
What race has the highest rate of breast cancer Dx? What race has the highest rate of breast cancer mortality?

Show Answer

Highest Dx: whites
Highest mortality: blacks
(DeSantis et al., Breast Cancer Statistics 2017)
What percentage of women will be diagnosed with breast cancer in their lifetimes?

Show Answer

~12% (1 in 8) of U.S. women will be diagnosed with breast cancer.
(DeSantis et al., Breast Cancer Statistics 2017)
Between 2010 and 2020, is the incidence of breast cancer in the United States expected to increase or decrease?

Show Answer

The incidence is expected to **increase.** (Weir et al., Cancer 2015)
In the United States in 2015, was the incidence of breast cancer mortality increasing or decreasing?

Show Answer

The incidence of mortality was **decreasing.** (DeSantis et al., Breast Cancer Facts & Figures 2017–2018)
What % of breast cancers are due to known hereditary mutations in single genes?

Show Answer

≤10% (Foulkes WD et al., NEJM 2008)
What are the 2 most common hereditary mutations that predispose to breast cancer?

Show Answer

BRCA1 and BRCA2 are the most common mutations. (These are most common in the Ashkenazi Jewish population, where they are found in as many as 1 in 40.) (Metcalfe KA et al., JCO 2010)
Mutations in which gene, BRCA1 or BRCA2, confers a higher risk of ovarian cancer?

Show Answer

Both BRCA1 and BRCA2 are associated with increased risk of ovarian cancer, but risks are higher with BRCA1 (45% lifetime risk) compared to BRCA2 (15% lifetime risk). (Chen S et al., JCO 2007)
What are 2 other hereditary syndromes associated with an increased risk of breast cancer and their related germ line mutations?

Show Answer

Both are a result of mutations in tumor suppressor genes:

. Li-Fraumeni syndrome: TP53
. Cowden/Bannayan–Riley–Ruvalcaba syndrome: PTEN

Is HRT with estrogen and progestin associated with an increased or decreased risk of breast cancer?

Show Answer

HRT with estrogen and progestin is associated with an **increased** RR of 1.7.
Separate the following factors into those that increase or decrease the risk of breast cancer: younger age at menarche, younger age at menopause,

nulliparity, prolonged breastfeeding, use of HRT.

Show Answer

Increase risk: younger age at menarche, nulliparity, use of HRT
Decrease risk: younger age at menopause, prolonged breastfeeding
Estimate the annual risk of a contralat breast cancer in the 10 yrs following a primary Dx.

Show Answer

Premenopausal: 1%/yr
Postmenopausal: 0.5%/yr
What is the definition of natural menopause and what is the median age at which is occurs?

Show Answer

Definition: permanent cessation of menstrual periods (12 mos of amenorrhea) without other obvious pathologic or physiologic cause.
Median age: 51 yrs
What are the United States Preventive Services Task Force (USPSTF) screening recommendations for normal-risk women age 40–49 yrs, age 50–74 yrs, and age >74 yrs?

Show Answer

For normal-risk women age 40–49 yrs: individualized decision based on potential benefits and potential harms
For normal-risk women age 50–74 yrs: biennial mammogram
For normal-risk women age ≥74 yrs: insufficient evidence to assess balance of benefits and harms (USPSTF 2016)
What are the ACS screening recommendations for normal-risk women age 40–44 yrs, age 45–54 yrs, and women ≥55 yrs?

Show Answer

For normal-risk women age 40–44 yrs: opportunity for annual mammogram
For normal-risk women 45–54 yrs: annual mammogram
For normal-risk women ≥55 yrs: biennial mammogram, with opportunity to continue annual mammogram (no age cutoff, as long as life expectancy is ≥10 yrs, whereas the USPSTF recommends biennial screening mammography beginning at age 50 and discontinuation at age 74.) (Oeffinger/ACS, JAMA 2015)

For a woman with prior thoracic RT between ages 10 and 30 yrs, when should screening begin for breast cancer and how?

Show Answer

According to NCCN guidelines (2018):

Age <25: annual clinical breast exam (CBE) beginning 8–10 yrs after RT
Age ≥25: CBE every 6–12 mos + annual mammogram and breast MRI beginning 8–10 yrs after RT

When should a woman be screened for breast cancer using MRI?

Show Answer

NCCN (2018) recommends MRI to be used as an adjunct to mammography for women with a BRCA mutation or women who are 1st-degree relatives of a BRCA carrier (but are themselves untested) beginning at age 25, women with Li-Fraumeni (TP53) syndrome and their 1st-degree relatives, women with Cowden/Bannayan–Riley–Ruvalcaba (PTEN) syndrome and their 1st-degree relatives, women with mutations in ATM, CDH1, CHEK2, PALB2, PTEN, or STK11 with an expected ≥20% lifetime risk of breast cancer, women without known genetic mutations who have a lifetime risk of ≥20% as defined by models that are highly dependent on family Hx, and women who rcvd T or CW irradiation between the ages of 10 and 30.

According to NCCN 2018, what are the potential clinical indications and applications of dedicated breast MRI testing?

Show Answer

Breast MRIs should be performed only where there is a dedicated breast coil, an experienced radiologist, and capacity for MRI-guided Bx. Since false+ findings on MRI are common, surgical decisions should not be based solely on MRI; additional tissue sampling should be performed in areas of concern identified by MRI.

- Define extent of cancer, multifocal or multicentric Dz in the ipsi breast
- Screen for contralat breast cancer in a newly diagnosed breast cancer pt
- Evaluate before and after neoadj therapy to define extent of Dz, response to Tx, and potential for breast conservation
- Detect additional Dz in women with mammographically dense breasts
- Detect primary Dz in pts with +axillary LNs or Paget Dz of the nipple when primary is not identified on mammogram, US, or physical exam

Name the 5 rare histologic types of breast cancer that have a more favorable overall prognosis than invasive ductal/lobular carcinoma.

Show Answer

Rare types of breast cancer with a more favorable prognosis:

- Tubular
- Mucinous
- Medullary (not including atypical medullary)
- Cribriform
- Invasive papillary

Name the 1 rare histologic type of breast cancer that has a less favorable overall prognosis than invasive ductal/lobular carcinoma.

Show Answer

Micropapillary carcinoma has a less favorable overall prognosis.
What is the Oncotype DX, and which breast cancer pts are eligible for its

use?

Show Answer

Oncotype DX is a 21-gene assay that quantifies the likelihood of distant recurrence in tamoxifen-treated ER+, node– breast cancer patients (Paik S et al., NEJM 2004). Evaluation of Oncotype DX in pts from NSABP B20 suggests that the recurrence score also predicts the magnitude of chemo benefit (Paik S et al., JCO 2006). NCCN currently recommends considering Oncotype DX in **patients with >0.5 cm, ER+, node–** and N1mic pts.

What are the 4 major molecular subtypes of breast cancer? Which subtype is associated with the poorest prognosis?

Show Answer

Molecular subtypes:

- Luminal A (ER+/HER2–, ↓ proliferation)
- Luminal B (ER+/HER2±, ↑ proliferation)
- HER2 overexpressing
- Basal-like (ER–/PgR–/HER2–)

The basal-like subtype carries the poorest prognosis.

What are phyllodes tumors of the breast, and what is the most important factor that determines risk of recurrence?

Show Answer

Phyllodes tumors (cystosarcoma phylloides) are rare tumors containing both stromal and epithelial elements. Although the subtypes range from benign to malignant, the most important prognostic factor for recurrence is a clear margin after resection.

WORKUP/STAGING

What view(s) comprise a screening mammogram?

Show Answer

. Mediolateral oblique: allows localization of tumor in sup–inf dimensions
. Craniocaudal: allows localization of tumor in medial–lat dimensions

What is the workup for a breast lesion detected on screening mammogram?

Show Answer

Breast lesion workup: H&P (family Hx of breast and ovarian cancer, prior abnl mammograms, Hx of atypical ductal or lobular hyperplasia), diagnostic bilat mammogram (additional views including spot compression and magnification), and Bx of lesion (if mass nonpalpable, a stereotactic Bx should be performed).
What is the rate of axillary nodal positivity by T stage for breast cancer pts undergoing axillary dissection? What if the primary tumor is palpable vs. nonpalpable on exam?

Show Answer

ALL (nonpalpable/palpable)

Overall:	30%	(8%/40%)
Tis:	0.8%	(0.7%/1.1%)
T1a:	5%	(3%/7%)
T1b:	16%	(8%/22%)
T1c:	28%	(18%/32%)
T2:	47%	(23%/50%)
T3:	68%	(46%/69%)
T4:	86%	(–/86%)

(Silverstein M et al., World J Surg 2001)
What are the 5 regional LN stations in breast cancer?

Show Answer

Regional LN stations in breast cancer:

Infraclavicular (ICV) nodes typically refer to the level III axillary nodes in radiation oncology.

Station I: nodes inf/lat to pectoralis minor muscle
Station II: nodes deep to pectoralis minor and the interpectoral Rotter nodes
Station III: nodes sup/med to pectoralis minor
Station IV: supraclavicular nodes
Station V: IM nodes

What is the T staging for invasive breast cancer according to the AJCC 8th edition (2017)?

Show Answer

(Note: T classification is the same whether it is based on clinical judgment or pathologic assessment. In general, pathologic determination should take precedence for determination of T size.)

Tis: in situ (ductal carcinoma in situ* or isolated Paget)
T1mi: microinvasion ≤1 mm
T1a: >1 mm but ≤5 mm
T1b: >5 mm but ≤1 cm
T1c: >1 cm but ≤2 cm
T2: >2 cm but ≤5 cm
T3: >5 cm
T4a: extension to CW, not including only pectoralis muscle invasion/adherence
T4b: edema (including peau d'orange) but not meeting T4d criteria and/or ulceration of skin of breast, and/or ipsi satellite nodules
T4c: both T4a and T4b
T4d: inflammatory carcinoma (erythema and edema over at least one-third of

the breast, present for less than 6 mos, in conjunction with Bx proof of invasive carcinoma)

*In AJCC 8th edition, LCIS is considered a benign process and is not classified as Tis

Does involvement of the dermis alone qualify as T4 Dz?

Show Answer

No. Involvement of the skin by breast cancer qualifies as T4 only if there is edema, ulceration, or skin nodules.

What is the clinical N staging for invasive breast cancer according to the AJCC 8th edition (2017)?

Show Answer

N1: movable ipsi level I/II axillary LN

N2a: ipsi level I/II axillary LNs fixed/matted

N2b: clinically apparent IM node in absence of clinically evident axillary nodes

N3a: ipsi ICV LNs

N3b: ipsi IM and axillary nodes

N3c: ipsi SCV nodes

What is the pathologic N staging for invasive breast cancer according to the AJCC 8th edition (2017)?

Show Answer

pN0(i-): no isolated tumor cells (ITCs) by immunohistochemistry (IHC)

pN0(i+): ITCs only, but no cluster >0.2 mm (also called ITC clusters)

pN0(mol-): negative by reverse-transcriptase polymerase chain reaction (RT-PCR)

pN0(mol+): positive by RT-PCR, but no ITCs detected on IHC

pN1mi: micrometastases (~200 cells, larger than 0.2 mm, but ≤2 mm)

pN1a: 1–3 axillary LNs involved, at least 1 mets >2 mm

pN1b: positive IM node by sentinel LND, excluding ITCs
pN1c: pN1a and pN1b
pN2a: 4–9 axillary LNs involved, at least 1 mets >2 mm
pN2b: clinically detectable IM node (± microscopic confirmation) with pN0 axilla
pN3a: ≥10 axillary LNs or mets to ICV (axillary level III) LNs
pN3b: clinically detected IM node (± microscopic confirmation) with pN1a or pN2a axilla, or positive IM node by sentinel LND and pN2a axilla
pN3c: ipsi SCV node

What is the M staging for invasive breast cancer according to the AJCC 8th edition (2017)?

Show Answer

M0: no clinical or radiographic evidence of DM
cM0(i+): no clinical or radiographic evidence of DM in the presence of tumor cells or deposits no greater than 0.2 mm detected microscopically or using molecular techniques in circulating blood, BM, or nonregional LN tissue in a patient without signs or Sx of metastatic Dz.
M1: DM detected by clinical and/or radiographic means and/or histologic demonstration of a mets larger than 0.2 mm.

Define the AJCC 8th edition (2017) breast cancer stage groupings using TNM status.

Show Answer

Stage 0: TisN0
Stage IA: T1N0
Stage IB: T0–T1, N1mic
Stage IIA: T0–T1, N1 or T2N0
Stage IIB: T2N1 or T3N0
Stage IIIA: T3N1 or T0–T3, N2
Stage IIIB: T4, N0–N2

Stage IIIC: any T, N3
Stage IV: any T, any N, M1
What factors were incorporated into AJCC 8th edition (2017) to generate a breast cancer prognostic stage grouping?

Show Answer

- Grade
- HER2 status
- ER status
- PgR status
- Oncotype DX (for patients with T1–2, N0 ER+/HER2– Dz; score <11 qualifies as most favorable prognostic stage, regardless of tumor size and grade. If score ≥11, not used in prognostication.)

What are the 5-yr relative survival rates for breast cancer?

Show Answer

The 5-yr relative survival rates (observed survival in women with breast cancer vs. expected survival in women without breast cancer) according to the ACS Cancer Facts & Figures 2017 and the NCI SEER database:

Localized (confined to primary site): 99%
Regional (spread to LNs): 85%
Distant (cancer has metastasized): 26%

FOLLOW-UP/TOXICITY

What are the acute and late toxicities of whole breast RT?

Show Answer

Acute toxicities: fatigue, dermatitis, hyperpigmentation, desquamation, pneumonitis
Late toxicities: soft tissue fibrosis, telangiectasias, rib fractures, pulmonary fibrosis, cardiovascular Dz, 2nd RT-induced malignancy

What is the rate of acute skin breakdown, and where does it typically occur with whole breast RT?

Show Answer

25%–30% of pts experience skin breakdown, most often in the **inframammary fold or axillary sulcus.**

What % of women have a less than good or excellent cosmetic result after whole breast RT and lumpectomy?

Show Answer

20%–30% of pts have a more unfavorable cosmetic result.

In a pt with breast cancer, what is the rate of lymphedema after whole breast RT é axillary LND? How does the RT technique affect risk?

Show Answer

15%–35% after RT + axillary LND; 5%–10% after RT and sentinel node Bx only. It is difficult to determine the RT effect b/c of other confounding tumor and Tx factors. However, retrospective studies suggest that tangent-only RT is associated with lower risk than directed nodal RT.

What is the RR of cardiovascular Dz death after RT to left-sided breast cancer compared to right-sided breast cancer?

Show Answer

Studies from the **pre-3D planning era** suggest that RT for left-sided breast cancer is associated with an **RR of 1.5–2 for cardiovascular Dz death** compared to RT for right-sided breast cancer. This has not been confirmed in women treated using modern RT techniques.

What is the risk of 2nd malignancy after whole breast RT?

Show Answer

The lifetime risk of 2nd malignancy after whole breast RT is **1%–2%.**

43

Ductal and Lobular Carcinoma In Situ

Updated by Penny Fang

BACKGROUND

Ductal carcinoma in situ (DCIS) represents what % of all breast malignancies?

Show Answer

DCIS represents **~20%** of all breast malignancies.
Which is more common: DCIS or lobular carcinoma in situ (LCIS)?

Show Answer

DCIS is 5 times more common than LCIS.
Name the 5 most common histologic subtypes of DCIS.

Show Answer

Most common subtypes of DCIS: (Mnemonic: **C^2PMS**)

. **C**ribriform
. **C**omedo
. **P**apillary
. **M**edullary
. **S**olid

Which histologic subtypes of DCIS have the worst and 2nd worst prognosis?

Show Answer

The DCIS subtype that has the worst prognosis is comedo, and the 2nd worst is solid. DCIS is often grouped into comedo and noncomedo subgroups.
How many pathologic grades are there for DCIS?

Show Answer

There are 3 pathologic grades for DCIS: low, intermediate, and high.
What % of DCIS are estrogen receptor-positive (ER+)?

Show Answer

75%–85% of DCIS cases are ER+.
What is the most common clinical presentation of DCIS?

Show Answer

DCIS most commonly presents with **microcalcifications** on a mammogram.
What is the most common clinical presentation of LCIS?

Show Answer

LCIS most commonly presents as an **incidental finding.** LCIS typically does not result in mammographic or clinical abnormalities.
What is the incidence of progression of DCIS to invasive Dz if left untreated?

Show Answer

Very difficult to determine; **15%–50%** of DCIS cases will progress to invasive Dz if left untreated.
For a pt with LCIS, what is the risk of the pt to be diagnosed with invasive Dz by 10 yrs?

Show Answer

A pt with LCIS has an **~7%** risk of developing invasive cancer at 10 yrs (**~1%/yr**), but the risk of subsequent invasive Dz is **equal in both breasts,**

suggesting that LCIS is primarily a predictor of invasive Dz development, rather than a precursor lesion. (Chuba PJ et al., JCO 2005)
What % of pts with LCIS who subsequently develop invasive Dz develop invasive lobular cancers?

Show Answer

25%–50% of subsequent cancers are invasive lobular cancers (i.e., though LCIS is a proliferative lesion of the lobules, it is mostly a marker for subsequent ductal proliferative lesions).
Which subtype of LCIS has the worst prognosis?

Show Answer

Of LCIS subtypes, **pleomorphic** LCIS has the worst prognosis. It is more commonly associated with invasive Dz and hormone receptor negativity. Consider complete excision with negative margins.

WORKUP/STAGING

What is the initial workup after a DCIS Dx?

Show Answer

DCIS workup: H&P (with emphasis on risk of hereditary breast cancer), diagnostic bilat mammogram, path review and assessment of ER status, genetic counseling if high risk (per NCCN 2018).
What is the T stage for DCIS as per AJCC 8th edition (2017)?

Show Answer

DCIS has its own designation: **Tis.**
What is the definition of DCIS with microinvasion, and what is the significance for workup?

Show Answer

DCIS with microinvasion refers to invasion **<1 mm** in size. If microinvasion

is present, then a sentinel **LN Bx is indicated, as the LN+ rate is 4%–8%.** (Solin LJ et al., IJROBP 1992)

For a pt with DCIS, if there is <1-mm margin at excision, what is the rate of residual Dz at the time of re-excision?

Show Answer

For a pt with DCIS and a <1-mm margin at excision, **~30% will have residual Dz at re-excision.** Notably, low- and intermediate-grade DCIS is more likely to grow in a discontinuous pattern (Faverly DR et al., Semin Diagn Pathol 1994). B/c of this, margin status may be, paradoxically, more important in these lesions. In these discontinuous type lesions, gaps of uninvolved tissue b/t DCIS are typically small (<5 mm in 80% of cases).

TREATMENT/PROGNOSIS

What is the Tx paradigm for unifocal DCIS?

Show Answer

There are 3 Tx paradigms for unifocal DCIS: RT can be delivered to the whole breast using hypofractionation, standard fractionation or could be delivered using accelerated partial breast irradiation.

- Lumpectomy + postop RT (PORT) +/− tamoxifen (if ER+)
- Lumpectomy alone +/− tamoxifen (if ER+)
- Mastectomy + SLNB

Is an axillary sentinel node Bx needed for DCIS?

Show Answer

No. Surgical axillary evaluation is not needed for DCIS. However, per NCCN 2018, consider if (1) the pt is undergoing mastectomy for Tx or (2) if the location of lumpectomy will compromise future sentinel Bx should it be necessary.

For a pt with DCIS, what is the rate of LR after mastectomy alone?

Show Answer

For a pt with DCIS, the rate of LR after mastectomy is **~1%–5% at 10 yrs.**
What are considered adequate surgical margins in pts receiving breast conservation Sg for DCIS?

Show Answer

For pts who will undergo postop RT: 2 mm. For pts who will not rcv postop RT: 3 mm. A systematic review of published trials in DCIS with BCT involving 4,660 pts found that a **2-mm margin** was sup to a margin <2 mm (ORR 0.53), without any LC benefit in margins >2 mm. (Dunne C et al., JCO 2009) RTOG 9804 (RCT of omission of RT) and ECOG 5194 (observational study of omission of RT) both required a min 3-mm margin. The 2018 NCCN guidelines accept no tumor on ink as negative margins (per Society of Surgical Oncology (SSO)/ASTRO/ASCO Consensus) but acknowledge lower rate of ipsilateral breast tumor recurrence (IBTR) with margins of at least 2 mm.
What are the contraindications for BCT for DCIS?

Show Answer

Contraindications for BCT for DCIS: multicentric Dz, persistently +margins, cosmetic limitations, and, potentially, the inability to get PORT (pregnancy or prior RT).
Is there a benefit of mastectomy over BCT for DCIS?

Show Answer

This is **undetermined.** No prospective study has directly compared mastectomy vs. BCT for DCIS. Indirect comparisons suggest that mastectomy results in lower LR than BCT. However, there is no expectation that mastectomy would improve OS compared to BCT, b/c the risk of breast cancer–related death after a Dx of DCIS is <2%.
For a pt with DCIS treated with lumpectomy, what is the impact of PORT

on ipsi breast recurrence (invasive and noninvasive) and OS?

Show Answer

For DCIS treated with lumpectomy, PORT **reduces LR by 50%–85%, but there is no evidence for OS benefit.**

Name 4 prospective studies that support the addition of RT after lumpectomy in pts with DCIS.

Show Answer

- **NSABP B-17** (Fisher B et al., Semin Oncol 2001)
- **EORTC 10853** (Bijker N et al., JCO 2006)
- **UKCCCR** (Houghton J et al., Lancet 2003)
- **SweDCIS** (Holmber L et al., JCO 2008)

Describe the Tx arms and the invasive and noninvasive LR outcomes in NSABP B-17 and EORTC 10853.

Show Answer

In **NSABP B-17,** 818 DCIS pts treated with lumpectomy with no tumor at inked margins were randomized to 50 Gy whole breast RT or no RT. At 10 yrs, the overall IBTR rate was 30.8% vs. 14.9% in favor of RT. Both the invasive and noninvasive recurrence rate was appx halved by RT.

In **EORTC 10853,** 1,010 DCIS pts treated with lumpectomy with no tumor at inked margins were randomized to 50 Gy whole breast RT or no RT. At 15 yrs, RT reduced LF from 31% to 18%. Half of all recurrences were invasive.

What is the traditional target, dose, and fractionation for PORT for DCIS?

Show Answer

Target the whole breast to 50 Gy in 25 fx.

Could hypofractionated RT to the whole breast be considered?

Show Answer

Yes. The RCTs that established the efficacy of hypofractionation excluded women with DCIS, and the ASTRO task force on hypofractionated whole breast RT (Smith BD et al., IJROBP 2011) chose not to offer recommendations for or against hypofractionation for DCIS as these pts were excluded from the randomized trials. **However, subsequent completed and ongoing trials using hypofractionation (including** Shaitelman SF et al., JAMA Onc 2015**) have included women with DCIS. Caution should be used in pts with very large volume DCIS or very large breasts.**

Could accelerated partial breast irradiation be considered?

Show Answer

Yes. The updated **ASTRO APBI consensus statement** placed low-risk (as per RTOG 9804 criteria) DCIS in the "suitable" group for APBI (Correa C et al., PRO 2017). The **NSABP B 39/RTOG 0413** trial to assess the role of APBI included pts with DCIS, as well as stage 1 or 2 breast cancer with tumors ≤3 cm and ≤3 +LNs.

For a pt with ER+ DCIS, is there a benefit to tamoxifen? What studies support this?

Show Answer

Yes. 2 trials provide evidence to support the use of tamoxifen in DCIS: NSABP B-24 and United Kingdom Coordinating Committee on Cancer Research (UKCCCR).

NSABP B-24 compared lumpectomy + RT +/– tamoxifen. Pts were enrolled without respect to estrogen receptor (ER) status. At 5 yrs, the overall incidence of breast events (ipsi and contralat, invasive and noninvasive) was decreased with tamoxifen (8.2% vs. 13.4%) (Fisher B et al., Lancet 1999). A subsequent analysis of tamoxifen effect by ER status analyzed 732 of the 1,801 pts on NSABP B24 (Allred DC et al., JCO 2012). At 10 yrs, the HR for any breast event was 0.49 for ER+ pts who rcvd tamoxifen.

The **UKCCCR** was a 2 × 2 factorial trial of RT, tamoxifen, both, or neither after lumpectomy for DCIS or microinvasive Dz, without respect to ER status. At a median f/u of 52 mos, tamoxifen marginally reduced overall DCIS events only (UKCCCR Working Group, Lancet 2003). However, on 12-yr f/u analysis, tamoxifen significantly reduced overall breast events (HR 0.71). (Cuzick J et al., Lancet 2011)

To summarize, in current practice, ER+ DCIS pts are offered adj tamoxifen.

Is there evidence supporting the use of AIs for DCIS?

Show Answer

Yes. NSABP B-35 and International Breast Cancer Intervention Study II (IBIS-II) both compared 5 yrs of either tamoxifen or anastrozole for pts with DCIS after lumpectomy and RT; NSABP B-35 (Margolese RG et al., Lancet 2016) reported a longer breast cancer–free interval with anastrozole mainly in women younger than 60. IBIS-II (Forbes JF et al., Lancet 2016) found no difference in overall recurrence rate.

AIs can be used in place of tamoxifen d/t differences in toxicity profiles.

What about trastuzumab (Herceptin)?

Show Answer

There is currently no role for trastuzumab in the Tx of DCIS. NSABP B-43 is evaluating the use of 2 cycles of concurrent trastuzumab with whole breast RT after lumpectomy for DCIS.

For a pt with DCIS, what is the effect of adj tamoxifen on contralateral breast tumor recurrence (CBTR)?

Show Answer

NSABP B-24 showed that the addition of tamoxifen to BCT in DCIS pts significantly reduced CBTR as the 1st site of recurrence from 4.9% to 2.3% at 7 yrs.

For a pt with ER– DCIS, is there benefit to adj tamoxifen after lumpectomy + RT?

Show Answer

Probably not. Retrospective subset analysis of **NSABP B-24** showed that the benefit of adj tamoxifen was limited to ER+ pts. (Allred DC et al., JCO 2012)
For a pt with ER+ DCIS, does adj tamoxifen obviate the benefit of RT after lumpectomy? What study evaluated this?

Show Answer

RT is still beneficial for pts with DCIS treated with lumpectomy even with adj tamoxifen. UKCCCR was a 2 × 2 factorial study looking at the benefit of RT and tamoxifen in DCIS pts after lumpectomy. After a median f/u >4 yrs, RT reduced IBTR in women given adj tamoxifen (6% vs. 18%). (Houghton J et al., Lancet 2003)
For a pt with DCIS, name some risk factors associated with LR and which is most important.

Show Answer

Risk factors for LR in a pt with DCIS:

- Decreased margin width (most important)
- Increased size of tumor
- High grade
- Young age (<50 yrs)
- Postmenopausal status
- Comedonecrosis
- Multifocality

What is the purpose of the Van Nuys Prognostic Classification system, and what are its limitations?

Show Answer

The Van Nuys Prognostic Classification system is meant **to identify DCIS pts who are at low risk for recurrence after RT alone** using width of margins, size, grade, and age. The system was developed retrospectively and has not been validated in prospective studies or in different retrospective datasets. (Silverstein MJ et al., Am J Surg 2003)

Do all DCIS pts require PORT?

Show Answer

Some pts with low-risk DCIS can probably be safely observed. Pts can be considered for omission of RT if they have grade 1–2 DCIS no larger than 2.5 cm, with margins at least 3 mm. 2 studies provide the main evidence for omission of RT:

ECOG 5194 (Solin LJ et al., JCO 2015): prospective single-arm observational trial. 711 pts with nonpalpable DCIS measuring at least 3 mm and conservatively resected with ≥3 mm microscopic margins (606 with G1–2 Dz measuring up to 2.5 cm, 105 with G3 DCIS measuring up to 1 cm). Pts were followed without RT; 31% declared an intent to take tamoxifen. At a median f/u of 12.3 yrs, 12-yr ipsi breast event rate was 14.6% (G1–2) and 24.6% (G3). 12-yr invasive ipsi breast event rate was 7.5% (G1–2) and 13.4% (G3).

RTOG 9804 (McCormick B et al., JCO 2015): prospective randomized trial of whole breast RT (50 Gy, no boost) vs. no RT for G1–2 DCIS conservatively resected with ≥3 mm margins. 636 eligible pts enrolled (accrual target 1,790 pts); 62% took tamoxifen. At a median f/u of 7.17 yrs, the 7-yr LF rate was 0.9% with RT vs. 6.7% without RT ($p < 0.001$).

What whole breast dose and boost dose are used for a pt with DCIS after lumpectomy?

Show Answer

For DCIS, the whole breast dose is 40–50 Gy with a 10–16 Gy lumpectomy bed boost. The role of a boost in DCIS is controversial. The practice is

extrapolated from results of the EORTC and Lyon boost trials for invasive cancers, but there have been no prospective trials of the role of boost in DCIS pts. ~44% of pts from **B-24** were given a boost, mainly for +margins.

A recent population–based analysis showed that the addition of a boost was not associated with a lower risk of local or invasive recurrence unless pts had positive margins. (Nilsson C et al., Radiother Oncol 2015)

What is the Tx paradigm for LCIS?

Show Answer

LCIS Tx paradigm: for pure LCIS after lumpectomy, pts can be observed +/– risk reduction procedures. Occurrence of invasive Dz after LCIS is low and is often in the contralat breast. In addition, invasive Dz after LCIS is generally relatively favorable, and deaths subsequently are rare. The exception may be pleomorphic LCIS, although data are limited.

For a pt with LCIS, what are 2 options to reduce the risk of development of an invasive cancer?

Show Answer

Options to reduce the risk of development of an invasive cancer:

- Antiestrogen therapy with tamoxifen or raloxifene (raloxifene only if postmenopausal) **(NSABP P1 trial)**
- Bilat mastectomy

What is the management for a woman with LCIS detected on percutaneous core needle Bx?

Show Answer

LCIS on core needle Bx should typically prompt a surgical excision to confirm pure LCIS.

Is LCIS associated with invasive cancer a contraindication for BCT?

Show Answer

No. Current literature supports the safety of BCT in the presence of coexisting LCIS in the specimen, and no special effort needs to be made to obtain –margins on LCIS.

For a pt with LCIS, what is the benefit of primary tamoxifen?

Show Answer

For a pt with LCIS, tamoxifen halves the risk of invasive recurrence in either breast. (Fisher B et al., Lancet 1999)

In a pt with DCIS or invasive Dz, what is the most common contraindication for adj tamoxifen therapy?

Show Answer

In a pt with DCIS or invasive Dz, the most common contraindication for adj tamoxifen therapy is **Hx of stroke or other coagulopathy.**

FOLLOW-UP/TOXICITY

What is the recommended f/u schedule after Tx for DCIS?

Show Answer

Recommended f/u schedule after Tx for DCIS: interval H&P exam q6–12 mos for 5 yrs, then annually. Bilat mammogram annually

For a pt with LCIS, what is the recommended observation strategy?

Show Answer

Recommended observation strategy for a pt with LCIS: H&P q6–12 mos and bilat mammogram annually

What is the role of MRI screening in a pt with previous LCIS or DCIS?

Show Answer

Per NCCN 2018, MRI should only be used for screening if there is a >20% chance of a 2nd primary breast cancer largely dependent on family Hx. In the

absence of other risk factors, Hx of DCIS or LCIS alone does not confer a 20% risk.

44

Early-Stage (I–II) Breast Cancer

Updated by Lauren Colbert

BACKGROUND

What histologic subtypes of IDC are associated with favorable outcomes?

Show Answer

Tubular, medullary, mucinous (colloid), and papillary

What is a phyllodes tumor of the breast?

Show Answer

Previously known as cystosarcoma phyllodes, phyllodes tumor ranges from benign to malignant and is a **rare tumor with leaflike, lobulated appearance on microscopic section.** Sg is the primary Tx: WLE (with at least 1-cm margins) or total mastectomy; surgical axillary evaluation is not indicated in cN0 pts. Per NCCN 2018, there is no standard role for RT after either mastectomy or wide local excision with adequate margins. The role of RT after BCS for large and/or malignant phyllodes tumors is still undefined, however.

What is Paget Dz of the breast? What is the clinical presentation?

Show Answer

Paget Dz of the breast is caused by **malignant epithelial cells (Paget cells) infiltrating the epidermis of the nipple-areolar complex.** The clinical presentation is **crusting, scaling, itching, and redness on the skin of the**

nipple that can progress to ulceration and bleeding. **80%–90%** of Paget Dz is associated with underlying DCIS or invasive breast cancer.
What % of invasive cancers are lobular carcinomas?

Show Answer

10%–15% of invasive cancers are lobular carcinomas.
According to the NSABP B04 trial, what % of women with a clinically – axilla were found to have axillary mets at LND?

Show Answer

Per **NSABP B04, 40%** of these women had axillary mets at LND.
Of the women who had a clinically – axilla and did not have a nodal dissection, what % eventually developed a clinically + axilla?

Show Answer

20% of these women developed a clinically + axilla.

WORKUP/STAGING

What is the workup for early-stage invasive breast cancer (stage I–IIB)?

Show Answer

Per NCCN 2018, H&P (inc. hormone use, ob/gyn Hx, family or personal Hx of breast/ovarian ca), diagnostic bilat mammogram +/– US, pathology review w/ determination of ER/PR and HER2 status, CBC/CMP (inc. LFTs and alk phos)
When should a bone scan or CT abdomen/pelvis be performed per NCCN 2018?

Show Answer

Bone scan should only be done for localized bone pain or elevated alk phos. CT Abd/pelvis w/ contrast should be done if elevated alk phos or LFTs, abdominal Sx, or abnl physical exam. CT chest w/ contrast should only be

done if pulmonary Sx are present.

When should breast MRI be used in screening or workup per NCCN 2018?

Show Answer

Screening MRI is indicated in women with a >20% increased lifetime breast cancer risk. Risk models are largely dependent on family Hx and including Claus BRCAPRO, BOADICRA, Tyrer–Cuzick, etc. Screening annual breast MRI is also recommended in women >25 yrs who undergo thoracic RT b/t 10 and 20 yrs.

Diagnostic MRI can be used if there is concern for multifocal/multicentric Dz, Bx is possible, and it would change management (i.e., lobectomy vs. mastectomy or concern for contralat Dz).

MRI should be done in a high quality center, with a dedicated breast coil, experienced radiologist, and the ability to perform Bx under MR guidance if a lesion is identified.

What type of counseling should be provided up front?

Show Answer

Genetic counseling if pt high risk, fertility counseling if premenopausal (NCCN 2018)

How should ER/PR and HER2 status be determined and reported?

Show Answer

ER/PR status is positive if ≥1% of tumor cell nuclei are reactive via IHC (CAP 2014; Template for Reporting Results of Biomarker Testing of Specimens From Pts With Carcinoma of the Breast)

HER2 status is positive when there is evidence of protein overexpression (IHC 3+) or gene amplification (HER2 single probe ISH, copy number ≥6.0 signals/cell or dual probe ISH assay with HERs/CEP17 ratio ≥2.0 with ≥4 signals/cell). If results for IHC are equivocal (IHC 2+), reflex testing should be performed using ISH. (CAP 2015; Wolff et al., NCCN

2018)

How should the axilla and primary be evaluated prior to Sg or preop systemic therapy?

Show Answer

If radiologically identifiable primary lesion, should have core Bx and placement of fiducial prior to systemic therapy

Axillary US w/ Bx of suspicious or clinically pos nodes

If axillary LN neg, can have SLNB prior to systemic Tx or Sg

If axillary LN pos, can have ALND if going straight to Sg, or potentially SLNB if preop systemic therapy and nodes become negative prior to Sg. If axillary LN pos and planned for preop systemic therapy, should have clip placed in +LN prior to systemic therapy.

Which major trials showed SLND Bx as an alternative to ALND for sentinel node neg pts?

Show Answer

The **NSABP B-32** trial randomized 5,611 pts undergoing mastectomy or lumpectomy to SLN Bx + immediate completion axillary LND vs. SLN Bx alone. The OS, DFS, and regional control were statistically similar b/t groups. The 10-yr OS was 87.8% vs. 88.9%, DFS 76.9% for both, and LR rate 4.3% vs. 4.0%, for SLND alone vs. SLND + ALND, respectively (Krag DN et al., Lancet Oncol 2010; 10-yr update ASCO 2013). The **ALMANAC trial** (Mansel RE et al., JNCI 2006) and **Milan trial** (Veronesi U et al., NEJM 2013; Lancet Oncol 2006; 10-yr update Ann Surg 2010) also showed comparable outcomes. Both NSABP B32 and ALMANAC showed a decreased risk of lymphedema and arm numbness with SLN Bx.

What should be done if the SLND is positive?

Show Answer

If T1 or T2 tumor, 1 or 2 + SLN, WBI is planned after lumpectomy and no

neoadj systemic therapy was given, no further Sg may be considered (NCCN 2018). ACOSOG Z0011 randomized ALND (n = 445) vs. no dissection (n = 445) for +SLND Tx with WBI (tangents) but no dedicated axillary RT. Study closed (891 of 1,900) early b/c of low accrual and no expected change in results with full accrual. SLND alone did not result in inf 5-yr OS (91.8% vs. 92.5%), DFS (83.9% vs. 82.2%), or LRR-free survival (96.7% vs. 95.7%) (Giuliano AE et al., JAMA 2011). 10-yr updated results also did not show any difference in OS (86.3% vs. 83.6%). (Giuliano et al., JAMA 2017)
What can be done in high-risk pts with 1 or 2 positive axillary SLNs who don't undergo ALND?

Show Answer

High tangents (cranial tangent border ≥2 cm from humeral head). 50% of pts in ACOSOG Z0011 assigned to SLND were treated with high tangents. Another 20% rcvd directed nodal RT using ≥3 fields (Jagsi et al., JCO 2014)
List the T staging of T1 and T2 breast cancers per the 8th edition of AJCC (2017).

Show Answer

T-stage (all greatest dimension):

(c/p)T1mi: ≤1 mm
(c/p)T1a: >1 mm but ≤5 mm
(c/p)T1b: >5 mm but ≤10 mm
(c/p)T1c: >10 mm but ≤20 mm
(c/p)T2: >20 mm but ≤50 mm
What is the clinical nodal staging for N1 Dz?

Show Answer

cN1: Mets to movable ipsi level I and level II axillary nodes
cN1mi: Micromets (>0.2 mm but ≤2.0 mm)
What is the pathologic staging for N0–N1 Dz?

Show Answer

pN0(i+): ITCs only (malignant cell clusters ≤0.2 mm)
pN0(mol+): Pos molecular findings by RT-PCR; no ITCs detected
pN1mi: Micromets (<0.2 mm but ≤2.0 mm)
pN1a: Mets in 1–3 axillary LNs, at least 1 with >2.0 mm
pN1b: Mets in ipsi IM SLNs, excluding ITCs
pN1c: pN1a and pN1b combined
What T and N groupings make up stage IA, IB, IIA, and IIB?

Show Answer

IA: T1N0
IB: T0N1mi, T1N1mi
IIA: T0N1, T1N1, T2N0
IIB: T2N1, T3N0
When is the anatomic stage groups used alone per AJCC 8th edition?

Show Answer

Only in global regions where biomarker tests are not routinely available.
What is the bioscore incorporated into the AJCC 8th edition staging system?

Show Answer

The bioscore is a multivariate model incorporating grade, ER status, HER2 status and AJCC pathologic stage (Mittendorf et al., Ann Surg Onc, 2017) to assess DSS. Points are assigned for each of these factors, ranging from 0 to 7. A bioscore of 1 is consistent with a 99.4% DSS, while a bioscore of 7 is associated with 33.3% DSS. This is consistent with data that pts with triple-negative tumors have DSS in line with 1 pathologic stage above.
Which biomarker panel has level I evidence, and what is it used for?

Show Answer

The Oncotype DX recurrence score. In the AJCC 8th edition, a low Oncotype DX score downgrades a biologically low-risk T2N0 from stage II to stage I. What % of breast cancer pts are diagnosed with stages 0–II Dz (AJCC 8th edition)?

Show Answer

80% of breast cancer pts are diagnosed with stages 0–II Dz according to the most recent SEER statistics.

TREATMENT/PROGNOSIS

What are the overall management options for early-stage breast cancers?

Show Answer

a. Lumpectomy (BCS) w/ surgical axillary staging + RT
b. Total mastectomy w/ surgical axillary staging +/– reconstruction
c. If T2 or T3 and fulfills criteria for BCS other than size, can consider preop systemic therapy with thorough staging f/b either a. or b.

When should adj chemo be utilized in the management of early-stage node-negative breast cancers?

Show Answer

a. TN or HER2/neu (H2N +): tumor >1 cm (consider for tumor 0.6–1 cm)
b. ER+ AND H2N– AND tumor >0.5 cm: consider using 21-gene assay (Oncotype DX to determine role of adj chemo).

What does the Oncotype DX score tell you?

Show Answer

Risk of distant recurrence within 10 yrs of Dx with 5 yrs endocrine therapy alone in **ER+, N0 pts** who undergo upfront Sg.

Low-recurrence score (<18) → adj endocrine Tx

Intermediate-recurrence score (18–30) → adj endocrine +/– chemo

High-recurrence score (≥31) → adj endocrine + chemo
When should adj endocrine therapy be used in early-stage breast cancer?

Show Answer

ER+ AND tumor >0.5 cm (consider for tumors ≤0.5 cm)
What are some general principles of administering adj endocrine therapy?

Show Answer

General principles for administration of adj endocrine therapy:

- If the pt is premenopausal, tamoxifen (20 mg/day) is given for 5 yrs. Consider an additional 5 yrs of tamoxifen (if pt remains premenopausal) or an AI (Aromatase inhibitor).
- If the pt is postmenopausal, AI × 5 yrs is the most common approach. For women who cannot or will not take an AI, tamoxifen × 5 yrs and consider an additional 5 yrs of tamoxifen.

What is the major contraindication to the use of AIs?

Show Answer

Premenopausal status or unknown menopausal status. AIs are not effective in women with estrogen-producing ovaries.
What are the major side effects of tamoxifen and AIs?

Show Answer

Tamoxifen: blood clots, strokes, uterine cancer, and cataracts. Gyn exam q12 mos should be performed in women with a uterus.
AI: bone loss and osteoporosis, as well as joint pain and stiffness. Bone mineral density should be assessed at baseline and monitored periodically.
What are the major chemo agents used in breast cancer?

Show Answer

A: doxorubicin

E: epirubicin
C: cyclophosphamide or carboplatin
T: paclitaxel or docetaxel
F: 5-FU
H: trastuzumab
What are the major chemo combinations used in breast cancer?

Show Answer

AC: doxorubicin + cyclophosphamide
EC: epirubicin + cyclophosphamide
FAC/FEC: 5-FU, doxorubicin/epirubicin, cyclophosphamide
AC/EC/FAC/FEC + T: the T is paclitaxel
TC: docetaxel + cyclophosphamide
TCH: docetaxel + carboplatin + trastuzumab
What chemo regimens are recommended for HER2– tumors?

Show Answer

The preferred chemo regimens are:

. Dose-dense AC (q2wk × 4 instead of q3wk × 4–6) f/b paclitaxel q2wk × 4
. Dose-dense AC f/b paclitaxel q1wk × 12
. TC q3wk × 4–6

What chemo regimens are recommended for HER2+ tumors?

Show Answer

The preferred chemo regimens are:

. AC f/b T plus concurrent trastuzumab +/– pertuzumab (various schedules), f/b single-agent trastuzumab q3wk for a total of 1 yr
. TCH q3wk × 6 +/– pertuzumab, f/b single-agent trastuzumab q3wk for a total of 1 yr

What data support the equivalence of BCT (lumpectomy + radiotherapy)

to mastectomy with regard to survival?

Show Answer

Several large randomized trials (**NSABP B06, Milan III, Ontario, Royal Marsden, EORTC 10801**) support this, but B06 has the longest (20-yr) f/u data. Recent Oxford meta-analysis summarizes the data and survival outcomes:

NSABP B06 (Fisher B et al., NEJM 2002): 1,851 stages I–II pts randomized to (a) total mastectomy, (b) lumpectomy alone, or (c) lumpectomy + RT (50 Gy). 20-yr f/u results showed that there was no difference in DFS, OS, or DM.

EBCTCG Oxford meta-analysis (EBCTCG Collaborators, Lancet 2011): 10,801 women enrolled in 17 trials for BCS +/– RT. The 10-yr 1st recurrence risk reduction was 15.7% (19.3% in RT vs. 35% in BCS alone). The 15-yr breast cancer mortality was reduced by 3.8% (21.4% vs. 25.4%) with RT. Pts with pN0 Dz had 15.4% and 3.3% absolute reduction in recurrence and breast cancer mortality. Pts with pN+ Dz had 21.2% and 8.5% absolute risk reduction in recurrence and breast cancer mortality, respectively. For all risk groups, RT halves the risk of recurrence and decreases breast cancer mortality by one-sixth. For every 4 women prevented to have LR, 1 woman is saved (4:1 ratio).

What % of pts are eligible for BCT for early-stage breast cancers?

Show Answer

In early-stage breast cancers, **75%–80%** of pts are eligible for BCT. (Morrow M et al., Cancer 2006)

What are the contraindications for BCT for pts with early-stage breast cancer?

Show Answer

Absolute contraindications for BCT in early-stage breast cancer: (NCCN

2018)

- Prior RT to the chest
- Extent of Dz that excision could not achieve –margins with an acceptable cosmetic result (note that multicentricity and multifocality are not necessarily contraindications to BCT).
- Diffuse microcalcifications
- 1st or 2nd trimester of pregnancy
- Persistently +margin
- Homozygous for ATM mutation

Is there a contraindication for BCT in pts with a positive family Hx of breast cancer?

Show Answer

No. There is no evidence that demonstrates increased ipsi or contralat breast cancers in pts with a positive family Hx after BCT. (Vlastos G et al., Ann Surg Oncol 2007)

Are BRCA mutations an absolute contraindication for BCT?

Show Answer

No. Multiple case-control studies have not established a higher IBTR rate in BRCA1/BRCA2 mutation carriers compared to wild-type individuals, particularly if oophorectomy is performed in BRCA carriers. However, contralat breast cancer development is a major risk for BRCA carriers. Contralat breast cancer risk can be reduced with tamoxifen, oophorectomy, or both, but is most effectively reduced with prophylactic total mastectomy. BRCA+ breast cancer pts who elect contralat prophylactic total mastectomy will frequently also choose an ipsi total mastectomy for Tx of their known breast cancer. Note that the NCCN guidelines do state that genetic mutations are a relative contraindication to BCT

What are the dose fractionation schedules for WBI?

Show Answer

Standard fractionation schedules:

- **50 Gy** in 2 Gy fx
- **45–50.4 Gy** in 1.8 Gy fx

Hypofractionated schedules:

- **42.56 Gy** in 2.67 Gy fx
- **40.05 Gy** in 2.67 Gy fx

What data support the use of hypofractionated WBI?

Show Answer

Per NCCN 2018, 4 randomized trials with ≥10-yr f/u suggest the same outcomes using a hypofractionated approach, with potentially better side effect profile. (Canadian, START pilot, START A/B trials)

Canadian regimen (Whelan TJ et al., JNCI 2002; Whelan TJ et al., NEJM 2010): RCT using 42.5 Gy in 16 fx (2.65 Gy/fx) vs. 50 Gy in 25 fx (2 Gy/fx) with no boost; 1,234 T1–2N0 pts, all with –SMs. **Women with >25-cm breast width were excluded** (to reduce heterogeneity of dose to the breast). 10-yr f/u: no difference in LR, DFS, or cosmesis. Good to excellent cosmesis was equivalent (71.3% standard vs. 69.8% hypofractionated).

British regimen (START A/B trials, Lancet 2008): 2,215 women with pT1–3N0–1 s/p Sg randomized to 50 Gy in 25 fx vs. 40 Gy in 15 fx (2.67 Gy/fx). Boost and adj systemic Tx were optional. After 10-yr f/u, there was no difference in IBTR (~4%–5% START B; ~6%–7% START A). Physician assessed markers of cosmetic outcome better with hypofractionation. Outcomes did not vary by age, BCS vs. mastectomy, nodal status, tumor grade, or the receipt of boost or adj chemo.

According to ASTRO guidelines, who can be offered hypofractionated WBI?

Show Answer

ASTRO guidelines (Smith BD et al., IJROBP 2011 [note new guidelines are slated to be published 2017/2018]**)** state task force consensus for pts meeting all these criteria:

- ≥50 yo
- pT1–2N0, treated with BCS
- No systemic chemo
- Good homogeneity: dose along central axis +/– 7% of Rx dose.

What data support the use of a tumor bed boost?

Show Answer

2 studies have demonstrated an improved LC rate with a 10–16 Gy boost after initial whole breast dose to 45–50 Gy. In general, a boost of 10–16 Gy should be considered particularly for pts at higher risk for LR (age <50 yrs, +LVI, or close SMs). This can be administered with brachytherapy, electrons, or photons.

EORTC boost trial (Bartelink K et al., JCO 2007; Bartelink et al., JCO 2015): 5,318 women with BCT, 10-yr update: 50 Gy vs. 50 Gy + 16 Gy boost (SM–) or + 26 Gy boost (SM+). 10-yr LF: 6.2% + boost vs. 10.2% – boost. Absolute benefit was greatest in women <50 b/c they have a higher risk of LR (24% – boost vs. 13.5% + boost for women <40 yo), but **proportional benefits were seen across all age groups. No difference in 20-yr OS.**

Lyon boost trial (Romestaing P et al., JCO 1997): 1,024 pts, 50 Gy vs. 50 Gy + 10 Gy boost. At 3-yr f/u, LF was reduced in the boost arm (3.6% vs. 4.5%).

Is there a need for a higher tumor boost dose in pts with incomplete tumor excision after BCS?

Show Answer

No. In the EORTC boost trial, 251 pts with microscopically incomplete tumor excision were randomized to low (10 Gy) vs. high (26 Gy) boost. With median f/u of 11.3 yrs, there was no difference in LC or survival. There was significantly more fibrosis in the high-dose arm. (Poortmans PM et al., Radiother Oncol 2009)

What is the next step in the management for a pt who undergoes a lumpectomy with a focal +margin?

Show Answer

This is **controversial.** Most would advocate taking the pt back to Sg for re-excision, which may diminish the 10-yr risk of LR to baseline levels (initial SM–: 7%, SM+: 12%; SM close: 14%; re-excision SM–: 7%, re-excision persistent SM+: 13%, re-excision persistent SM close: 21%). (Freedman G et al., IJROBP 1999)

Is there a subset of women whose LR risk may not be substantially influenced by margin positivity after BCS?

Show Answer

Possibly. There are data to suggest that the effect of margin positivity on LR **may be dependent on age <40 yrs.** In an analysis of 1,752 pts, 193 were SM+. Overall 10-yr LR rate was 6.9% (SM–) vs. 12.2% (SM+). 5-yr LR rate for pts ≤40 yo was 8.4% (SM–) and 37% (SM+) ($p = 0.005$); for pts >40 yo, the LR rate was 2.6% (SM–) and 2.2% (SM+). (Jobsen JJ et al., IJROBP 2003)

Should women with T1–2N0 invasive breast cancer treated with mastectomy to a +margin be treated with adj RT to the CW as well?

Show Answer

In a **British Columbia retrospective study** (Truong PT et al., IJROBP 2004), of 2,570 women with early-stage breast cancer treated with mastectomy, 94 pts had a +margin. About half (41 pts) were treated with

PMRT. B/c of the small numbers, there was a trend to improvement with PMRT in pts **>50 yrs, T2 tumor, grade III, and LVI.** In pts without these features, there was no LR without PMRT.
What is EIC?

Show Answer

EIC is defined as **DCIS both admixed and adjacent to invasive Dz, and comprising >25% of the total tumor mass.** DCIS with focal microinvasive Dz also fits this category.
Does EIC have prognostic significance in the LR risk of pts treated with BCT?

Show Answer

Yes, but it is largely dependent on SM status. From studies mainly out of JCRT, EIC is only prognostic for LF if the margin status is considered. If there is a close or +margin, EIC is associated with a higher risk of recurrence. (Gage I et al., Cancer 1996)
What data suggest that results of BCT can be further improved with the use of tamoxifen?

Show Answer

NSABP B21 (Fisher B et al., JCO 2002): 1,009 pts with ≤1-cm tumors s/p lumpectomy randomized to 3 arms: (a) tamoxifen alone (10 mg bid × 5 yrs), (b) RT alone (50 Gy), and (c) RT + tamoxifen. After 8-yr f/u, the IBTR was 16.5% with tamoxifen alone vs. 9.3% with RT alone vs. 2.8% with RT + tamoxifen. There was no difference in OS. No benefit was seen in ER– tumors. Contralat breast tumor recurrence was 0.9%, 4.2%, and 3.0% in the 3 arms, respectively.
Are there pt subgroups with a low risk of LR who can be treated with BCS and systemic therapy alone without RT?

Show Answer

Yes. Recent trials suggest that pts with **advanced age** (≥65–70 yrs) and **ER+ T1N0** tumors have an acceptably low rate of LR with Sg and endocrine Tx, although LR risk is further reduced by RT. The data suggest that the risk is very low only for **pts >70 yo** and possibly in those with **very small tumors (<1 cm),** so a discussion can be made about withholding RT if the pt is being treated with tamoxifen. The 3 most important trials are the Toronto, CALGB 9343/Intergroup, and PRIME II trials:

Princess Margaret Hospital/Canadian trial (Fyles AW et al., NEJM 2004): 769 women ≥50 yo (median age 68 yrs) with T1 or T2 (≤5 cm) –nodes (in women age ≥65 yrs, either clinical or pathologic evaluation was sufficient and SLN Bx was not routinely done) underwent lumpectomy to –margins and were randomized to (a) tamoxifen alone (20 mg/day × 5 yrs) vs. (b) tamoxifen + RT (40 Gy in 16 fx with a boost of 12.5 Gy in 5 fx). After 8-yr f/u, RT reduced LR from 17.6% to 3.5%. But for tumors ≤1 cm, the risk of relapse was 2.6% vs. 0% for the RT group ($p = 0.02$). In those ≥60 yo with ≤1-cm tumor, the risk was no different b/t the 2 arms (1.2% vs. 0%), but this was unplanned analysis with a short f/u.

CALGB 9343/Intergroup trial (Hughes KS et al., NEJM 2004; updated JCO 2013): 636 women ≥70 yo with T1, clinically N0, ER+ tumors were randomized to tamoxifen vs. tamoxifen + RT after lumpectomy with –margins. Axillary dissection was allowed but not encouraged. RT was 45 Gy to the whole breast with a boost of 14 Gy. At a median of 12.6-yr f/u, the 10-yr LF rate in the tamoxifen alone arm was 10% vs. 2% in tamoxifen + RT. There was no difference in time to mastectomy, DM, breast cancer survival, or OS.

PRIME II (Kunkler, Lancet Oncol 2015): 1,326 women ≥65 yo T1–T2 (up to 3 cm) N0, ER+ tumors receiving adj endocrine Tx randomized to WBI (40–50 Gy) or no RT. 5-yr IBTR 1.3% with RT and 4.1% no RT ($p < .05$). While addition of RT was SS, they question the need for RT given relatively low rates of recurrence.

Can RT be used in the Tx of axillary nodes in place of Sg if axillary nodal dissection is not performed?

Show Answer

In certain cases. Previous era trials in cN0 pts (esp NSABP B04 and Institut Curie) have demonstrated equivalent LC, DM, and OS with nodal RT vs. axillary dissection. In the modern era, **the AMAROS trial** randomized SLN+ pts to completion ALND or nodal RT; 5-yr results showed no significant difference in LRR, DM, or OS and overall better arm function in the RT arm. (Donker M et al., Lancet Oncol 2014) 5-yr axillary recurrence 0.4% ALND vs. 1.2% with axillary RT.

Are there data supporting WBI + RNI for early-stage breast cancer after BCS?

Show Answer

Yes. 2 randomized trials (**MA.20 and EORTC 22922/10925**) have examined this question. **MA.20** (Whelan TJ et al., NEJM 2015) targeted women with +axillary nodes or –nodes but with high-risk features (≥5 cm tumor, or ≥2 cm tumors with inadequate nodal dissection or adverse tumor features. There was a decrease in regional recurrences (2.7% vs. 0.7%) with the addition of nodal irradiation to the upper axillary nodes, SCV region and IM nodes. Distant recurrence was also decreased from 17.3% to 13.4% and DFS increased from 77% to 82% at 10 yrs. **EORTC 22922/10925** (Poortsmans PM et al., NEJM 2015) targeted women with centrally/medially localized primary tumor +/– axillary nodes or externally localized primary with + axillary nodes. At 10-yr f/u, there was a decrease in regional recurrences from 4.2% to 2.7% and a distant metastases rate decrease from 19.6% to 15.9%, as well as breast cancer mortality (14.4%–12.5% [HR 0.82, p = 0.02]). However, neither trials showed OS benefit.

How should chemo be sequenced with radiotherapy after BCS?

Show Answer

JCRT sequencing trial ("Upfront-Outback" trial) (Bellon J et al., JCO 2005): per the initial report (Recht A et al., NEJM 1996), the 5-yr crude rate of distant recurrence was better in the chemo 1st arm (20% vs. 32%). However, in the 11-yr f/u update, there was no difference in DFS, LR, DM, or OS. For those with a –margin, the crude LR rate was 6% in the chemo 1st arm vs. 13% in the RT 1st arm. However, the study was not powered to show any differences. Thus, either sequence is acceptable, depending on pt convenience. Often, the Oncotype DX takes a few wks to return, and radiotherapy can be given in the meantime.

What U.S. trial investigated the role of accelerated partial breast irradiation (APBI)?

Show Answer

NSABP B39/RTOG 0413, which randomized women with stage 0, 1, or 2 breast cancer with tumors ≤3 cm and ≤3 +LN to whole breast RT vs. APBI by any of 3 methods (interstitial, intracavitary, or EBRT). Publication pending.

What is the dose and duration of Tx for APBI on the U.S. randomized trial?

Show Answer

34 Gy in 3.4 Gy bid fx for interstitial and intracavitary Tx and 38.5 Gy in 3.85 Gy bid fx for EBRT. All APBI is given over 5 days. The volume treated is the surgical cavity plus a 1-cm margin for brachytherapy and a 2–2.5 cm for EBRT.

Who can be offered PBI?

Show Answer

ASTRO has published updated guidelines on who may be considered for PBI (Correa C et al., PRO 2017). "Suitable" pts are ≥50 yo, Tis or T1, with DCIS allowed only if screen-detected, low to intermediate grade, size ≤2 cm and

resected with margins negative at ≥3 mm. Age 40–49 are allowed if all other "suitable" criteria are met. Pts ≥50 yo may have one of the adverse pathologic factors without DCIS >3 cm. Pts with <2 mm margins, DCIS ≤3 cm without meeting "suitable" criteria, or age <40 yrs should be considered cautionary.

Is there good evidence to support the use of IMRT for WBI for early-stage breast cancer?

Show Answer

There is potentially data to indicate that homogeneous dose distribution of IMRT benefits pts in terms of acute effects and late-term cosmesis.

Canadian study (Pignol JP et al., JCO 2008) demonstrated in 358 pts that IMRT reduced the occurrence of moist desquamation c/w standard wedge technique (31.2% vs. 47.8%, p = 0.002). MVA shows breast IMRT and smaller breast sizes were associated with decreased risk of moist desquamation.

British study (Mukesh MB et al., JCO 2013) showed in 1,145 pts with 5-yr f/u that overall cosmesis was improved with IMRT c/wstandard techniques (OR 0.68, p = 0.027) as well as skin telangiectasia (OR 0.58, p = 0.021). This benefit was maintained on multivariable analysis. In these settings, IMRT refers to advanced planning techniques that can be achieved with forward planning with dose modulation.

Are there subsets of women who undergo mastectomy for early-stage breast cancers (T1–2N0) who may benefit from PMRT?

Show Answer

Only in limited circumstances. NCCN 2018 guidelines recommend no RT for −axillary nodes, tumor ≤5 cm and margins ≥1 mm. For all other pts, the decision is based on other risk factors, including close or +margins, extensive LVSI, central/medial tumors, young age, etc. If there are +margins, tumor >5 cm, or +axillary nodes, RNI is recommended. PMRT in node-negative pts does not improve survival per EBCTCG 2005 meta-analysis data.

How should a Dx of breast cancer be managed in a pregnant woman?

Show Answer

Management depends on the stage of pregnancy. Timing of Sg depends on need for chemo and RRs to fetus and mother. Chemo can be used to delay Sg until after delivery. Non-taxane chemo (most commonly, FAC) can be used in the 2nd and 3rd trimesters of pregnancy; chemo should be D/C 3 wks before expected delivery to reduce infection and bleeding risks. RT and endocrine therapy must be deferred until postpartum.

FOLLOW-UP/TOXICITY

See Chapter 45 for follow-up and toxicity questions.

45

Locally Advanced Breast Cancer

Updated by Shane R. Stecklein

BACKGROUND

What is locally advanced breast cancer (LABC)?

Show Answer

Typically, the term refers to stage III Dz (T3N1, N2–3, or T4). However, stage IIB pts with T3N0 Dz may be included. IBC is included, but metastatic Dz is not. LABC can be separated into those cancers that are operable and those that are not.

What are the epidemiologic trends and incidence of LABC?

Show Answer

The incidence of **T3–4 Dz decreased by 27% from 1980 to 1987** (coincident with the institution of mammography). Analysis of the SEER database from 1992 to 1999 indicated that **LABC (stage III other than IBC) and IBC made up 4.6% and 1.3% of all female breast carcinomas, respectively.**

What are the diagnostic criteria for inflammatory breast cancer (IBC)?

Show Answer

The consensus min diagnostic criteria for a Dx of IBC are (Dawood et al., Ann Oncol 2011):

. Rapid onset of breast erythema, edema, and/or peau d'orange, and/or warm

breast, with or without an underlying palpable mass
- Duration of Hx of no more than 6 mos
- Erythema occupying at least one-third of the breast
- Pathologic confirmation of invasive carcinoma

What is the pathognomonic feature that is more characteristic of IBC than other forms of LABC?

Show Answer

Presence of tumor emboli (aka dermal lymphatic invasion [DLI]) in the dermis of the skin overlying the breast; however, DLI is not necessary for the Dx of IBC.

What is the prevalence of IBC?

Show Answer

1%–4% of breast cancer (BC) cases are IBC. 70% present with regional Dz and 30% with distant Dz.

What are the histologic subtypes of LABC?

Show Answer

The histologic subtypes are the **same for LABC as for earlier-stage Dz.** Invasive ductal carcinoma is still the most common, but FHs, such as tubular, medullary, and mucinous, are less frequently represented.

Are there genetic/molecular factors associated with LABC?

Show Answer

No. There are no molecular markers that define LABC. However, tumors with avian erythroblastic leukemia viral oncogene homolog 2/human epidermal growth factor receptor 2 (HER2) positivity, BRCA1 mutation, and triple-negative status (ER–, PgR–, HER2–) are associated with aggressive phenotypes. The basal-like and HER2 molecular subtypes are associated with a poor prognosis as well, though outcomes for pts with HER2+ Dz have been

dramatically improved with trastuzumab.

WORKUP/STAGING

What is the workup for locally advanced invasive BC?

Show Answer

Invasive BC workup: H&P, CBC, liver profile, ER/PgR/HER2 status; bilat diagnostic mammogram; imaging with US, CT, PET, bone scan, MRI optional per NCCN (2018)

What are the 5 regional LN stations in BC?

Show Answer

Regional LN stations in BC: infraclavicular (ICV) nodes typically refer to the level III axillary nodes in RT oncology.

Station I: nodes inf/lat to pectoralis minor muscle
Station II: nodes deep to pectoralis minor and the interpectoral Rotter nodes
Station III: nodes sup/med to pectoralis minor
Station IV: SCV nodes
Station V: IM nodes

TREATMENT/PROGNOSIS

What are the most important factors that predict for LRR?

Show Answer

Increasing number of LNs with Dz and breast tumor size are the most important factors that predict for LRR.

What are the basic principles of treating LABC?

Show Answer

Inoperable LABC: neoadj chemo is used to shrink the tumor and potentially convert it to be operable.

Operable LABC: Neoadj or adj chemo are used. Modified radical

mastectomy (MRM) (including levels I–II axillary LNs) is the definitive locoregional Tx. PMRT is indicated in all initial stage III Dz. Hormonal therapy and trastuzumab are incorporated as appropriate per receptor status of Dz.

What is a Halsted radical mastectomy?

Show Answer

Halsted radical mastectomy includes **resection of all breast parenchyma with overlying skin and major and minor pectoral muscles en bloc with axillary LNs.**

What is spared with a MRM?

Show Answer

MRM spares the **pectoralis muscles.**

What is spared with a total or simple mastectomy?

Show Answer

In a total or simple mastectomy, only the breast tissue is removed with overlying skin. **Axillary LNs are not dissected.**

What is considered an “adequate” axillary LND for purposes of staging and clearance?

Show Answer

Oncologic resection of levels I–II is considered standard and adequate. The LNs and axillary fat pad need to be removed en bloc. An axillary LND is considered full if ≥10 LNs are removed without neoadj chemo; often after neoadj chemo the LN yield is reduced. If suspicious nodes are palpable on intraop evaluation of level III, then level III dissection should be performed.

Which major trial demonstrated that not all pts with sentinel lymph node (SLN) Bx+ Dz need completion axillary LND?

Show Answer

The **American College of Surgeons Oncology Group (ACOSOG) Z11** (Guiliano AE et al., Ann Surg 2010) enrolled 856 pts with cN0 T1–2 BC who underwent upfront breast-conserving Sg and SLN Bx. Pts with 1–2+ SLN were randomized to axillary lymph node dissection (ALND) + tangent RT vs. RT alone. There was no difference in breast/axillary recurrence.
Do clinically node+ pts always need axillary LND?

Show Answer

Yes—always! Whether the pt rcv's upfront Sg or neoadj chemo, a full axillary LND is always needed for clinically node positive (cN+) Dz. Omission of ALND should only be considered on protocol.
What is standard systemic chemo?

Show Answer

Standard chemo at present includes an **anthracycline- and taxane-based regimen** (e.g., doxorubicin (adriamycin)/cyclophosphamide [AC] and paclitaxel).
Does adding paclitaxel to standard AC chemo improve the outcomes of pts with BC?

Show Answer

Yes. Adding paclitaxel improves response rates, DFS, and OS.

NSABP 27 randomized operable pts to preop AC, preop AC + taxol, or preop AC + postop taxol. Here, the addition of taxol did not improve survival outcomes but did improve pCR in the preop group (26% vs. 13%). (Rastogi P et al., JCO 2008)

The **CALGB 9344** study randomized 3,121 operable pts with LN+ Dz and found that adding taxol q3wks × 4 to AC × 4 improved DFS and OS (Henderson IC et al., JCO 2003). In a retrospective study of 1,500 pts on **CALGB 9344,** the benefit of taxol appeared to be in HER2+ tumors and not HER2–/ER+ tumors. (Hayes DF et al., NEJM 2007)

ECOG E1199 randomized 4,950 stages II–IIIA BC pts to AC q3wks × 4 → taxol q3wks × 4, AC q3wks × 4 → taxol × 12 weekly, AC q3wks × 4 → Taxotere q3wks × 4, and AC q3wks × 4 → Taxotere × 12 weekly. The weekly taxol arm had improved DFS (HR 1.27) and OS (HR 1.32). The effect was significant in all pts, including those with ER+/HER2– tumors. (Sparano JA et al., NEJM 2008)

Which meta-analysis showed the benefit of anthracyclines?

Show Answer

The EBCTG/Oxford Overview meta-analysis of 18,000 women showed a benefit of anthracyclines over cyclophosphamide/methotrexate/5-fluorouracil (CMF) (improved DFS and OS), although CMF > no chemo.

What is meant by "dose-dense" chemo?

Show Answer

Dose-dense chemo is **administered q2wks** as opposed to q3wks.

Has dose-dense chemo been demonstrated to be sup in a prospective randomized trial?

Show Answer

Yes. Intergroup trial C9741 randomized 2,005 node+ pts to AC × 4 → taxol × 4 given q3wks vs. q2wks. Filgrastim was given for BM support in the q2wks arm. 4-yr DFS improved from 75% to 82% with the q2wk schedule. The risk ratio for OS was 0.69 in favor of the q2wk schedule. Median f/u was 36 mos. Severe neutropenia was also less frequent with the dose-dense schedule.

What is the rationale for the use of neoadj chemo for LABC?

Show Answer

Neoadj chemo may convert pts with unresectable LABC to resectability. It may also be used to shrink large breast tumors requiring mastectomy in resectable pts to be managed with breast conserving surgery (BCS). Neoadj

trials have the advantage of providing pathologic assessment of chemo response at the time of Sg. If the tumor is not responsive to 1 chemo regimen and progresses clinically, a different chemo regimen can be used.
Which pts have inoperable Dz and definitely need neoadj chemo?

Show Answer

Women with fixed axillary LN (stage N2a), major skin involvement (stage T4b–4d), +/- CW involvement.
What major study determined whether neoadj chemo improves survival compared to adj chemo in LABC?

Show Answer

NSABP B18 was designed to assess whether preop AC resulted in improved DFS and OS c/w postop AC. Secondary aims were to assess response to preop AC and correlate with survival and LR outcomes. Rates of BCS were also assessed. All women were deemed operable at enrollment, and the majority had T2 or smaller primary and cN0 Dz. At the most recent f/u (16 yrs) (Rastogi P et al., JCO 2008), there has been no significant difference in OS or DFS b/t the women treated with neoadj vs. adj chemo. There is a trend, however, for women <50 yo for improved DFS and OS when treated preoperatively ($p = 0.09$ and 0.06, respectively). There was a 27% conversion rate from mastectomy to BCS.
What procedures should be done prior to starting neoadj chemo for LABC?

Show Answer

Core Bx and clip localization of the breast tumor (in case the pt has a CR to chemo). If clinically node+, clip should be placed in the involved LN prior to chemo.
In NSABP 18 and 27, did pCR at the time of Sg correlate with good OS and DFS outcomes?

Show Answer

Yes. In both **NSABP 18** and **NSABP 27,** pCR at the time of Sg correlated with improved OS and DFS c/w non-pCR pts.

What other seminal neoadj chemo trials addressed neoadj vs. adj chemo and its role regarding BCS?

Show Answer

EORTC 10902 randomized 698 pts with early BC to preop vs. postop chemo (5-FU/epirubicin/cyclophosphamide × 4). Endpoints were BCS, DFS, OS, and tumor response. At 10-yr f/u, there was no difference in OS or LRR. Neoadj chemo was associated with an improved rate of BCS. (Van der Hage JA et al., JCO 2001)

In EORTC 10902, was there a difference in the # of BCS b/t arms? Was there a difference in outcomes b/t planned breast-conserved pts and breast-converted pts?

Show Answer

BCS increased from 22% to 35% in the preop chemo arm. Although the initial f/u of **EORTC 10902** indicated that converted breast-conserved pts did worse in terms of OS c/wplanned pts—an indication that prechemo staging remains relevant. However, the most recent 10-yr f/u data indicate that there is no difference in survival outcomes b/t these 2 groups. (Van der Hage JA et al., JCO 2001)

PMRT was the standard of care for many decades. Why did it fall out of favor in the 1980s?

Show Answer

Historically, PMRT was typically offered b/c pts presented at later stages and no chemo was given. **Historical series, while uniformly demonstrating improved LC, did not demonstrate survival benefit.**

Meta-analysis by Cuzick et al. (9 trials) demonstrated no OS survival benefit

with PMRT at 10 yrs. (Cancer Treat Rep 1987)

An update by Cuzick demonstrated that PMRT increased cardiac mortality and slightly decreased BC mortality. (JCO 1994)

What are some criticisms of older PMRT data and meta-analysis?

Show Answer

Criticisms of older PMRT data include the **significant heterogeneity of surgical and RT techniques, old RT techniques with associated cardiac and pulmonary toxicity, and lack of systemic therapy,** implying that clinically undetectable systemic Dz was not well controlled.

What 3 randomized prospective trials are considered to represent the "modern" PMRT experience?

Show Answer

The **Premenopausal Danish Trial (DBCG 82b)** (Overgaard M et al., NEJM 1997), the **Postmenopausal Danish Trial (DBCG 82c)** (Overgaard M et al., Lancet 1999), and the **British Columbia PMRT Trial** (Ragaz J et al., JNCI 2005) represent the "modern" PMRT experience.

What were the design and study outcomes of Premenopausal Danish Trial DBCG 82b?

Show Answer

In **Premenopausal Danish Trial DBCG 82b,** 1,708 women were randomized to mastectomy and adj CMF + chemo (8 cycles) or – RT (9 cycles). Inclusion criteria were +axillary LN, tumor >5 cm, or involvement of skin or pectoral fascia. 10-yr OS was 54% (+PMRT) and 45% (–PMRT, p <0.001). Crude cumulative LRR was 32% –PMRT and 9% +PMRT. The survival benefit was seen for all pts (N0–3).

What are some criticisms of DBCG 82b trial?

Show Answer

Criticisms of the **DBCG 82b** trial include the inadequate surgical Tx of axilla

resulting in a median of 7 nodes removed, an excess of LF occurring in the axilla (44% in the CMF arm), and the use of now-outdated CMF chemo.
What were the design and trial outcomes of Postmenopausal Danish Trial 82c?

Show Answer

In **Postmenopausal Danish Trial 82c,** 1,375 postmenopausal women <70 yo were randomized to postmastectomy tamoxifen × 1 yr vs. tamoxifen + PMRT. Inclusion criteria, surgical characteristics, and RT were as for the Premenopausal Danish Trial 82b. PMRT significantly improved LR (–PMRT 35% vs. +PMRT 8%), DFS (–PMRT 24% vs. +PMRT 36%), and OS (–PMRT 34% vs. +PMRT 45%) at 10-yr f/u (all significant).
What are some criticisms of Postmenopausal Danish Trial 82c?

Show Answer

In **Postmenopausal Danish Trial 82c,** as in the Premenopausal Danish Trial 82b, inadequate surgical Tx of the axilla resulted in a median of only 7 axillary LNs removed at Sg. A suboptimal duration of tamoxifen was also employed (1 yr vs. the typical 5 yrs).
What was the Sg performed in the Danish 82b and 82c trials?

Show Answer

Pts were surgically managed with total mastectomy + axillary LN sampling (aimed at removing at least 5 LNs, full dissection was not required). A median of 7 nodes were removed. 15% had only 0–3 LNs removed, and 75% had <9 LNs removed. This is significantly less than most centers in the United States, where ≥10 LNs represent adequate dissection.
How was the RT given in the Danish 82b and 82c trials?

Show Answer

For 82b, PMRT was given after cycle 1 of CMF and 3–5 wks postop. For 82c, PMRT was given 2–4 wks postop. The RT dose was 48–50 Gy given in

22–25 fx to the CW with ant photon fields to cover SCV, ICV, and undissected axillary nodes and an ant electron field to cover the IM nodes and CW. Posterior axillary boost (PAB) was used for pts with a large AP diameter.

What was the design of the British Columbia Trial?

Show Answer

In the British Columbia Trial, 318 premenopausal, high-risk pts with positive axillary LNs were randomized to CMF chemo × 6–12 mos vs. CMF + RT. Sg involved total mastectomy + axillary LND (median removal of 11 LNs). RT used Co-60 to 37.5 Gy in 16 fx. A 5-field technique was employed, including an en face photon field to cover bilat IM nodes.

What are the relevant outcomes of the British Columbia Trial?

Show Answer

In the British Columbia Trial, at 20-yr f/u, adj RT improved LRR before DM (13% vs. 39%), DFS (48% vs. 31%), and OS (47% vs. 37%) (all significant). The benefit was extended to those with 1–3 LN+ Dz as well as those with >4 LN+ Dz.

What are some criticisms of the British Columbia Trial?

Show Answer

In the British Columbia Trial, LRF was high c/wmany current series, CMF chemo was employed, and the RT fields included en face photons for IM nodal coverage (though no excessive cardiac deaths were observed).

What was demonstrated by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) RT meta-analysis?

Show Answer

The EBCTCG meta-analysis (Lancet 2005) included 78 randomized trials of 42,000 women. In node-negative women treated with BCS, the addition of adj RT reduced 5-yr LR from 22.9% to 6.7%, and reduced 15-yr BC

mortality from 31.2% to 26.1%. In node+ women treated with BCS, the addition of adj RT reduced 5-yr LR from 41.1% to 11.0%, and reduced 15-yr BC mortality from 55.0% to 47.9%. In node-negative women treated with mastectomy and axillary clearance, the addition of adj RT reduced 5-yr LR from 6.3% to 2.3%, but **increased** 15-yr BC mortality from 27.7% to 31.3% (absolute loss of 3.6%). In node+ women treated with mastectomy and axillary clearance, the addition of adj RT reduced 5-yr LR from 22.8% to 5.8%, and reduced 15-yr BC mortality from 60.1% to 54.7%. Use of tamoxifen for 5 yrs reduced the risk of LR by appx 50% in ER+ pts. Chemo alone reduced the risk of LR by appx one-third when considering all pts. RT was associated with excess contralat BC, lung cancer, and cardiac mortality, though many other trials were included in this analysis. An updated EBCTCG meta-analysis (Lancet 2014) in mastectomy pts with adequate axillary Sg showed no benefit to PMRT in terms of LR, overall recurrence, or BC mortality in node-negative women, but confirmed a significant reduction in LR and BC mortality in women with 1–3 and ≥4 positive axillary LNs.

Similar conclusions were also supported by 2 other meta-analyses. (Whelan TJ et al., JCO 2000; Gebski V et al., JNCI 2006)

Have there been any prospective randomized trials evaluating PMRT in pts treated with neoadj chemo?

Show Answer

No. There have been no published prospective randomized trials evaluating PMRT in pts treated with neoadj chemo. Trials are currently ongoing.

What was demonstrated in the retrospective series from MDACC regarding PMRT in pts treated with neoadj chemo?

Show Answer

Huang E et al. analyzed the outcomes of 542 pts who had been enrolled in prospective clinical trials and treated with neoadj chemo, mastectomy, and

RT. These pts were c/w134 pts enrolled in the same trials who rcvd no adj RT. Clinical stage, margin status, and hormone receptor status did not favor the adj RT group. CSS was improved with adj RT in pts with clinical stage IIIB or SCV LN+ Dz, clinical T4 tumors, and pathologically ≥4 +nodes. LRR was improved even for those pts with clinical stage III or SCV LN+ Dz who achieved a pCR on neoadj chemo. (JCO 2004)
What is the LR rate without LN RT for pts with clinical LN+ Dz who achieve a pCR to neoadj chemo?

Show Answer

9%–13%. Data from the NSABP B-18 and B-27 trials were pooled to report rates of LRR to the breast/LNs without RT to the regional LN (RT was directed to the breast s/p BCS). (Mamounas et al., JCO 2012)
What is the LR rate without LN RT for pts with clinical LN+ Dz who do not achieve a pCR to neoadj chemo?

Show Answer

15%–21%. Data from the NSABP B-18 and B-27 trials were pooled to report rates of LRR to the breast/LNs without RT to the regional LN (RT was directed to the breast s/p BCS). (Mamounas et al., JCO 2012)
What are the present NCCN guidelines for PMRT?

Show Answer

Per NCCN 2018 guidelines, PMRT is a category 1 recommendation **for pts with ≥4 +LNs. PMRT should be strongly considered for 1–3 +LNs, and "considered" for LN– pts with large tumors (T3, N0).**
What are some arguments for providing PMRT to pts with 1–3 positive axillary LNs?

Show Answer

An argument for treating pts with 1–3 LN Dz with PMRT is that all 3 modern randomized trials (**Danish 82b, Danish 82c, and British Columbia**)

showed significant OS benefit with PMRT. This was true in subgroup analysis of this population and even when analysis was restricted to pts who had at least 8 axillary LNs removed in Danish trials. (Overgaard M et al., Radiother Oncol 2007)

In EBCTCG meta-analysis, pts with 1–3 LN Dz experienced similar reduction in LR and BC mortality with PMRT as pts with ≥4 +LNs (Lancet 2014).

More recent data from the EORTC 22922 trials (Poortmans, NEJM 2015) found a DFS benefit in select pts treated with regional nodal RT. ~1/4 of the pts on this trial were treated with mastectomy (the rest rcvd BCS).

Do the LF rates in pts with N1 Dz (1–3 LN+) in the Danish and British Columbia PMRT trials represent the typical experience in this subset of pts in United States?

Show Answer

No. The cumulative 10-yr LRR +/– DM for pts with 1–3 LN Dz on retrospective review of pts in prospective trials conducted by the NSABP, the ECOG, and MDACC was 4%–13%. (Recht A et al., JCO 1999; Katz A et al., JCO 2000; Taghian AG et al., JCO 2004)

For pts who undergo mastectomy with 1–3 +LNs, what other clinicopathologic factors should be considered when recommending PMRT?

Show Answer

Retrospective studies from the IBCSG, NSABP, and MDACC have suggested that factors such as **+LVI, high grade, younger age, ≤10 LN examined, ≥20% LN+, larger tumor size (T2 or ≥4 cm), and close margins** produce 10-yr LRR >15%.

Under what circumstances should regional LN be treated along with the CW (comprehensive PMRT)?

Show Answer

Comprehensive PMRT (CW + LN) is recommended for most pts who have an LRR risk that warrants PMRT b/c the benefit of RT of regional LN outweighs in most cases the added toxicity. All stage III pts should rcv comprehensive PMRT. Per the 2018 NCCN Guidelines, strongly consider PMRT to CW + LN in the setting of 1–3 + LN and consider PMRT to CW + LN if T3N0 tumor or +margin CW RT alone (without LN RT) can be considered for those with T1–3N0 who are being treated for +margin only. Should the IM nodes be included in all comprehensive PMRT fields?

Show Answer

This is **controversial** and would be an extrapolation from 2 randomized trials which included IM node irradiation as part of comprehensive RT in early-stage BC after BCS, but neither compared comprehensive PMRT with or without IM node irradiation.

EORTC 22922/10925 (Poortmans PM et al., NEJM 2015) trial randomized pts with a central or medial tumor, or a lat tumor with positive axillary LN treated with BCS or mastectomy with ALND (sentinel LN Bx → ALND for sentinel LN+ allowed in the latter yrs) to RT ± RNI (regional nodal irradiation) including the 1st 3–5 intercostal spaces and SCV. RNI reduced 10-yr BC mortality from 14.4% to 12.5% (p = 0.02) and trended toward improving 10-yr OS from 80.7% to 82.3% (p = 0.06).

NCIC MA.20 trial (Whelan TJ et al., NEJM 2015) randomized pts who underwent BCS and sentinel LN Bx or ALND who were either LN+ or LN– but with high-risk features (tumor ≥5 cm or tumor ≥2 cm with <10 axillary nodes removed, and at least 1 of the following: grade 3, ER–, +LVI) to WBI alone or WBI + RNI (including the ipsi IM nodes and SCV). RNI significantly improved 10-yr DFS from 77.0% to 82.0% (p = 0.01), but had no significant effect on BC mortality or OS.

DBCG-IMN is a prospective population-based cohort study which reported survival outcomes for early-stage LN+ BC pts, all of whom rcvd RNI (with IM node RT for right-sided and without IM node RT for left-sided BC)

(Thorsen LBJ et al., JCO 2016). 8-yr OS was improved by 3.7% for right-sided pts, with no difference in deaths from ischemic heart Dz in the 2 groups. Some RT oncologists believe that b/c the IM nodes were included in randomized trials, Tx of the IM nodes should be the gold standard. Others argue that b/c 3 randomized trials examining the role of IM nodal dissection failed to improve OS, that Tx of clinically uninvolved IM nodes is not warranted. (Lacour J et al., Cancer 1976; Meir P et al., Cancer 1989; Veronesi U et al., Eur J Cancer 1999)

NCCN 2018 states that "the NCCN panel recommends irradiation of ICV and supraclavicular areas, IM nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥4 positive nodes; 2A for 1-3 positive nodes)."

Should pts with T3N0 BC who have had a mastectomy without neoadj chemo be treated with PMRT?

Show Answer

This is **controversial.** Traditionally, pts with T3N0 without other risk factors have been treated with CW-only PMRT or comprehensive PMRT. However, 2 recent retrospective studies have demonstrated that the LF rates are low for T3N0 pts after mastectomy alone with adj chemo, questioning the role of PMRT. This is an evolving area of research, so pts with pT3N0 without other risk factors should be considered for PMRT with appropriate discussion of risk and benefits of RT.

Taghian AG et al. (JCO 2006): subset meta-analysis of 5 NSABP postmastectomy chemo trials, with 313 pts with ≥5-cm tumors (N0). The 10-yr isolated LRF was 7.1%, and LRF ± DM was 10%. Almost all LRRs were in the CW. However, the median size of the tumor was 5.5 cm, so the data may not be applicable for very large tumors.

Floyd SR et al. (IJROBP 2006): review of a multi-institutional database for ≥5-cm tumors (N0). Of 70 pts, the 5-yr LRF was 7.6%. LVI was a significant prognostic factor for LF.

Note that the EORTC 22922 trial included regional nodal RT in pts with T3N0 tumors s/p mastectomy and a DFS benefit was seen. (Poortmans et al., NEJM 2015)

How should stage II pts with LN+ BC s/p neoadj chemo and MRM be managed?

Show Answer

For pts who undergo MRM and achieve a pCR in both LN and breast, the LF rate is 0%–10% without RT (NSABP B-18, MDACC data) and omission of PMRT can be considered. For pts who undergo MRM and achieve pCR in LN but have persistent Dz in the breast, the LF rate is 10%–13% without RT (NSABP B-18, MDACC data). These pts can be considered for no RT, CW RT only, or CW + RNI. For pts with persistently +LN s/p neoadj chemo, the LF rate is 15%–20% without RT (NSABP B-18, MDACC data). These pts need comprehensive PMRT.

How should stage II pts with LN+ BC s/p neoadj chemo and BCS be managed?

Show Answer

Pts with pCR in LN and breast will still need WBI. For pts with pCR in LN but persistent Dz in the breast, consider RNI if the pt is young (<50 yo). For pts with persistently +LNs after preop chemo, give WBI + RNI.

What question is the NSABP B-51 trial asking?

Show Answer

NSABP B-51 is randomizing women with cT1–3N1 BC with Bx-proven axillary LN mets who convert to pN0 after neoadj chemo to rcv or omit RNI. BCS pts all rcv WBI and are randomized to ± RNI, and mastectomy pts are randomized to no RT vs. comprehensive RT (CW + RNI).

What question is the Alliance A011202 trial asking?

Show Answer

A011202 is randomizing women with cT1–3N1 BC with Bx-proven axillary LN mets who remain pN1 after neoadj chemo to ALND vs. axillary RT.
How is IBC managed?

Show Answer

IBC is managed using **combined-modality therapy** with neoadj chemo, MRM, and comprehensive PMRT.
What are 2 acceptable PMRT schedules for IBC?

Show Answer

Conventional: 50 Gy comprehensive RT → 10–16 Gy CW boost.
MDACC: hyperfx RT: 1.5 Gy BID to 51 Gy comprehensive RT → 15 Gy boost in 10 fx BID to 66 Gy. Hyperfx is recommended for pts with high-risk features.

In the MDACC retrospective analysis (Bristol IJ et al., IJROBP 2008), which IBC pts benefited from escalation of postmastectomy RT dose from 60 Gy to 66 Gy?

Show Answer

Pts with (a) unknown/close/+margins, (b) less than PgR to neoadj chemo, and (c) age <45 yrs.
What are the options for a pt with poor response and unresectable Dz after induction chemo for IBC?

Show Answer

Alternative chemo; if there is still NR, can consider preop RT (conventional or hyperfractionated) → consideration for Sg.
For pts who want breast reconstruction after mastectomy, when should the breast reconstruction be done relative to the rest of the adj Tx?

Show Answer

Per NCCN guidelines, if implant reconstruction is planned, a tissue

expander can be placed at the time of Sg and it can be exchanged for a permanent implant either before or after RT. However, if autologous reconstruction is planned, this should be performed after RT, b/c cosmesis of the autologous tissue is harmed by RT. In pts with initial T4b–d Dz (i.e., skin involvement), all reconstruction should be delayed to 6–12 mos after RT, b/c skin-sparing mastectomy is contraindicated.

FOLLOW-UP/TOXICITY

What is the typical recommended f/u schedule for pts treated for invasive BC?

Show Answer

Recommended f/u after Tx:

- Interval H&P 1–4 times per yr × 5 yrs, then annually
- Bilat mammogram annually, starting no sooner than 6 mos after completion of RT
- Annual gyn exam for women with intact uterus on tamoxifen
- Bone health assessment (bone mineral density scan) at baseline and periodically during course of use of AIs

For pts who have large breasts with large medial to lat separation (>22–24 cm), what techniques will improve dose homogeneity?

Show Answer

Photon energy >10 MV to keep max inhomogeneity <10% and field segmentation techniques. Avoid medial wedges to reduce scatter to contralat breast in pts <45 yo. Prone Tx can help, but RNI not possible in this position. Breast immobilization with molds (i.e., Aquaplast) can decrease skin toxicity to inframammary fold in the supine position.

What are the acute and late toxicities of whole breast RT?

Show Answer

Acute: RT dermatitis, fatigue, hyperpigmentation, pneumonitis
Late: ST fibrosis, breast size change, telangiectasias, lymphedema, pulmonary fibrosis, precocious cardiovascular Dz, 2nd malignancy

What randomized trials demonstrated the superiority of 3D-IMRT compared to 2D Tx approaches for minimizing cosmetic changes to the breast?

Show Answer

Royal Marsden (Donovan E et al., Radiother Oncol 2007) randomized 306 women to 2D-RT or 3D-IMRT. RT was 50 Gy → boost to 11.1 Gy with electrons. There was a significant cosmetic difference in the breast of 2D-RT (58%) vs. 3D-IMRT (40%) pts. Fewer pts in the IMRT group developed palpable induration. There were no differences in the QOL b/t the groups. A randomized trial (Pignol JP et al., JCO 2008) comparing breast IMRT with standard techniques showed IMRT to be sup with respect to moist desquamation (31% vs. 48%) and improved dose distribution.

What is the risk of 2nd malignancies in pts treated for early BC with RT?

Show Answer

From the WECARE study (Stovall M et al., IJROBP 2008), women <40 yo receiving >1 Gy to the contralat breast had an RR of 3. However, this excessive risk was not seen in pts >40 yo. Sarcomas (mostly angiosarcomas) within the RT field were <1% (~10 cases in 10,000) within 10–30 yrs. (Taghian A et al., IJROBP 1991; Yap J et al., IJROBP 2002; Kirova YM et al., Cancer 2005)

What is the risk of lymphedema in pts treated for BC?

Show Answer

The risk of lymphedema is **~5%** after SLN dissection, and 10%–25% after level I–II axillary dissection. Comprehensive nodal RT after axillary dissection further increases the risk to **15%–35%.** (Refer to a review by

Erickson VS et al., JNCI 2001)

What is the risk of brachial plexopathy for a pt treated for BC?

Show Answer

Median time to developing brachial plexopathy is 10–12 mos (range 1.5–77 mos). It is dependent on RT dose and use of chemo. According to JCRT data (Pierce SM et al., IJROBP 1992), if the dose is kept at <50 Gy, the risk is <1% without chemo and ~4.5% with chemo. If the dose is above 50 Gy, the risk is 5.6%.

What is the risk of cardiac toxicity, such as ischemic heart Dz after BCT for BC?

Show Answer

According to a population-based case-control study (Darby SC et al., NEJM 2013), rates of ischemic heart Dz are proportional to mean heart dose and increase linearly 7.4% per 1 Gy mean heart dose. Risk begins 1–2 yrs after RT and continues >20 yrs. Mean heart dose should be limited, and other cardiac risk factors should be managed.

What is the risk of pulmonary toxicities, such as lung fibrosis and symptomatic pneumonitis, after BCT for BC?

Show Answer

Pulmonary fibrosis occurs in everyone on imaging in the treated pleura, but clinical pneumonitis is rare. Data from the NCIC MA20 trial reported a rate of 0.2% pneumonitis after WBI and 1.2% with WBI + LN RT. (Whelan TJ et al., NEJM 2015)

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Esophageal Cancer

Updated by Samual Francis

BACKGROUND

What are the boundaries of the esophagus that divide it into Cx, upper T, midthoracic, lower T, and abdominal regions?

Show Answer

The esophagus spans from the cricopharyngeus at the cricoid to the **esophageal-gastric junction (EGJ)**. The **Cx esophagus spans from hypopharynx to sternal notch (15 to <20 cm from incisors),** the **upper T from the sternal notch to the azygos vein (20 to <25 cm),** the **middle T from azygos vein to inf pulmonary vein (25 to <30 cm),** the **lower T from the inf pulmonary vein to the EGJ (30 to <40 cm), and the abdominal from EGJ to 2 cm below EGJ (40 to 45 cm).**

Why is esophageal cancer more prone to locoregional spread than other GI cancers?

Show Answer

The esophagus has an adventitial layer but does not have a serosal layer, thus reducing the resistance against local spread of cancer.

What is the incidence and mortality of esophageal cancer in the United States?

Show Answer

There are ~17,000 cases diagnosed and ~16,000 deaths per yr in the United States. Males are more commonly affected than females (3:1).
Is there an association b/t esophageal cancer and HPV infection?

Show Answer

The single largest case-control studies by Cao B et al. showed a risk of HPV 2.7-fold greater in cases of esophageal SCC than in controls. (Carcinogenesis 2005)
What are the risk factors for developing esophageal cancer?

Show Answer

Esophageal SCC risk factors: smoking/alcohol, tylosis, Plummer–Vinson syndrome, Fanconi anemia, Bloom syndrome, caustic injury to the esophagus, Hx of H&N cancer, and achalasia. HPV infection has been associated in ~20% cases in high-incidence areas (China, Africa, and Japan) but none in low-incidence areas (Europe, United States).

Esophageal adenocarcinoma (adeno) risk factors: obesity/GERD, Barrett esophagus, lack of fruits/vegetables, low-socioeconomic status

What are some protective factors for developing esophageal cancers?

Show Answer

Protective factors for developing esophageal cancer include **fruits/vegetables and** Helicobacter pylori **infection** (possible atrophic gastritis).
How do pts with esophageal cancer typically present?

Show Answer

Dysphagia and weight loss (>90%), odynophagia, pain, cough, dyspnea, and hoarseness
What is the pattern of spread of tumors of the esophagus?

Show Answer

Tumors of the esophagus spread **locoregionally through the extensive**

submucosal lymphatic plexus or distantly through hematogenous routes.
What histologies predominate based on the tumor location within the esophagus?

Show Answer

The proximal three-fourths of the esophagus (Cx to midthoracic) are mostly **SCCs** (~30%–40%), whereas **adeno** generally is found in the distal esophagus (~60%–70%).
What more uncommon histologies are seen for tumors of the esophagus?

Show Answer

Adenocystic, mucoepidermoid, small cell, and sarcomatous (leiomyosarcoma) carcinomas (all typically ≤1% of cases). Extremely rare types are lymphoma, Kaposi sarcoma, and melanoma.
What are the common sites of DM seen for esophageal cancers?

Show Answer

Lung, liver, and bone are the most common sites of DM. (Xi M et al., Radiother Oncol 2017)
What is the most important factor that determines nodal mets and DM?

Show Answer

DOI is the most important factor dictating nodal and distant spread. (Mariette C et al., Cancer 2003)
What is the extent of submucosal spread of Dz seen for esophageal cancers, and does it differ by histology?

Show Answer

Gao XS et al. reported the following **for SCC:** mean microscopic proximal and distal spread beyond GTV of 10.5 ± 13.5 mm and 10.6 ± 8.5 mm, respectively, with 94% of pts having all tumor contained within a 30-mm margin. **For adeno**, mean spread of Dz is to 10.3 ± 7.2 mm proximally and

18.3 ± 16.3 mm distally, with a margin of 50 mm required to encompass all tumor in 94% of cases. (IJROBP 2007)

WORKUP/STAGING

What components of the Hx are important in assessing a pt with dysphagia?

Show Answer

Appropriate parts of the Hx in assessing dysphagia Sx include **onset, duration, severity (dysphagia to normal solids, soft solids, liquids, or aphagia), weight loss, other Sx of retrosternal pain, bone pain, cough, hoarseness, Hx of smoking/alcohol, GERD, and Hx of prior H&N cancer.**

What should be included in the workup of suspected esophageal cancer?

Show Answer

Suspected esophageal cancer workup: H&P, labs (LFTs, alk phos, Cr), esophagogastroduodenoscopy with Bx. If cancer, then chest/abdominal ± pelvic CT w/ contrast; if not M1, then PET/CT, EUS + FNA for nodal sampling for tumor and node staging, bronchoscopy (if tumor at or above carina to r/o tracheoesophageal fistula), assign Siewert category, nutritional assessment, smoking cessation, and screen for family Hx. Laparoscopic staging is done in some institutions, with reports of upstaging and sparing the morbidity of more aggressive Tx in 10%–15% of cases. If M1, testing for MSI-H/dMMR including HER2 and PD-L1 if adeno (NCCN 2018).

To what anatomic extent is esophageal cancer being defined?

Show Answer

Esophageal cancer is defined as below hypopharynx (**15 cm from the incisors) to the EGJ and the proximal 2 cm of the stomach.** A tumor epicenter ≥2 cm distal to the EGJ, even if it involves EGJ, is considered stomach cancer.

What is different about the AJCC 8th edition (2017) of the TNM staging

for esophageal cancer?

Show Answer

The AJCC 8th edition redefines tumor location based on location of epicenter rather than proximal border, adds unique tumor, nodes, & metastases clinical staging (cTNM) and tumor, nodes, & metastases pathologic staging post-neoadjuvant therapy (ypTNM) prognostic stage groupings, incorporates pT1a and pT1b into stage grouping, and separates pT2–T3 into pT2 and pT3 for stage grouping.

Tis: high-grade dysplasia and CIS
T1a: invades lamina propria or muscularis mucosae
T1b: invades submucosa
T2: invades muscularis propria
T3: invades adventitia (Note: No serosal layer.)
T4a: invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b: invades other adjacent organs (aorta, vertebral body, airway)
Nx: regional nodes cannot be assessed
N0: no regional node mets
N1: 1–2 regional LN mets, including nodes previously labeled as M1a in AJCC 6th*
N2: 3–6 regional LN mets, including nodes previously labeled as M1a*
N3: ≥7 regional LN mets, including nodes previously labeled as M1a*
*__M1a__ (differ by site): upper T includes Cx LN mets; midthoracic is not applicable; lower T/GE junction includes celiac LN mets. (Note: M1a designation is no longer recognized in the 7th or 8th editions.)
M1: DM (retroperitoneal, P-A LN, lung, liver, bone, etc.)
What are the AJCC 8th edition (2017) stage groupings for esophageal cancer, and what new feature has been added?

Show Answer

Stage IV has been separated to IVA and IVB and there is no longer IIIC;

cTNM and ypTNM groups staging has been added for SCC and adeno:

Staging for SCC

cTNM
Stage 0: TisN0M0
Stage I: T1N0–1M0
Stage II: T2N0–1M0; T3N0M0
Stage III: T3N1M0; T1–3N2M0
Stage IVA: T4 or N3
Stage IVB: M1
Tumor, Nodes, & Metastases pathologic staging (pTNM) (Location is "Any" unless specified)
Stage 0: TisN0M0, N/A
Stage IA: T1aN0M0, G1/GX
Stage IB: T1aN0M0, G2–3; T1bN0M0, any G; T2N0M0, G1
Stage IIA: T2N0M0, G2–3/GX; T3N0M0, any G, Lower; T3N0M0, G1, Upper/Middle
Stage IIB: T3N0M0, G2–3, Upper/Middle; T3N0M0, GX; T1N1M0, any G
Stage IIIA: T1N2M0, any G; T2N1M0, any G
Stage IIIB: T2N2M0, any G; T3N1–2M0, any G; T4aN0–1M0, any G
Stage IVA: T4aN2M0, any G; T4b or N3, any G
Stage IVB: M1
ypTNM
Stage I: T0–2N0M0
Stage II: T3N0M0
Stage IIIA: T0–2N1M0
Stage IIIB: T3N1M0; T0–3N2M0; T4aN0M0
Stage IVA: T4aN1–2/NXM0; T4b or N3
Stage IVB: M1

Staging for Adeno:

cTNM
Stage 0: TisN0M0
Stage I: T1N0M0
Stage IIA: T1N1M0
Stage IIB: T2N0M0
Stage III: T2N1M0; T3N0–1M0; T4aN0–1M0
Stage IVA: T4b or N2–3
Stage IVB: M1
pTNM
Stage 0: TisN0M0, N/A
Stage IA: T1aN0M0, G1/GX
Stage IB: T1aN0M0, G2; T1bN0M0, G1–2/GX
Stage IC: T1N0M0, G3; T2N0M0, G1–2
Stage IIA: T2N0M0, G3/GX;
Stage IIB: T1N1M0, any G; T3N0M0, any G
Stage IIIA: T1N2M0, any G; T2N1M0, any G
Stage IIIB: T2N2M0, any G; T3N1–2M0, any G; T4aN0–1M0, any G
Stage IVA: T4aN2M0, any G; T4b or N3, any G
Stage IVB: M1
ypTNM
Stage I: T0–2N0M0
Stage II: T3N0M0
Stage IIIA: T0–2N1M0
Stage IIIB: T3N1M0; T0–3N2M0; T4aN0M0
Stage IVA: T4aN1–2/NXM0; T4b or N3
Stage IVB: M1
Why does SCC have a separate stage grouping from Adeno?

Show Answer

Tumor location is accounted for in the stage grouping for SCC, with lower regions having better prognosis c/w upper and middle regions.

TREATMENT/PROGNOSIS

What are the most important features that predict for poor outcomes in pts with T1 esophageal cancers treated with surgical resection alone?

Show Answer

T1b Dz, LVI, and tumor length predict poor outcomes in these pts. (Cen P et al., Cancer 2008; Bolton WD et al., J Thorac Cardiovasc Surg 2009)

What are the types of surgical procedures employed for the management of esophageal cancers?

Show Answer

Minimally invasive esophagectomy using laparoscopy, thoracoscopy, or a combination. Traditional surgical approaches include **radical esophagectomy, transhiatal, or transthoracic esophagectomies.**

How do transhiatal and transthoracic esophagectomy procedures compare in terms of dissection extent and location of the Dz?

Show Answer

In general: A transhiatal approach may be less morbid but will have less exposure for tumor clearance and thorough LND c/w a transthoracic approach. Anastomotic leak for the transhiatal approach is easier to manage than the transthoracic approach (Cx vs. intrathoracic leaks).

Transhiatal esophagectomy: Pros: good for distal tumors with possible en bloc resection, laparotomy and a Cx approach (no thoracotomy) with Cx anastomosis, less morbid with less pain, and avoids fatal intrathoracic anastomotic leak. Cons: poor visualization of upper/midthoracic tumors, LND limited to blunt dissection, more anastomotic leaks, and more recurrent laryngeal nerve palsy.

Transthoracic esophagectomy: Pros: Ivor–Lewis (right thoracotomy) is the most common and preferred route and best for exposure for all levels of the esophagus, whereas left thoracotomy provides access to only the distal

esophagus. Ivor–Lewis (right thoracotomy and laparotomy) provides direct visualization and exposure with a better radial margin and a more thorough LND. Cons: intrathoracic leak that can lead to fatal mediastinitis. Generally considered to have higher morbidity and mortality than transhiatal.

Does the # of nodes removed from esophagectomy predict for better outcome?

Show Answer

Yes. Data suggest that the # of nodes removed is an independent predictor of survival. In 1 large study, the optimal # was ≥23. (Peyre CG et al., Ann Surg 2008)

Is there evidence to prove that either transhiatal or transthoracic esophagectomy would be sup for Dz control and outcome?

Show Answer

No. There are no data to date showing that 1 approach is sup to the other. 2 large meta-analyses comparing transhiatal with transthoracic esophagectomy have shown equivalence. (Rindani R et al., Aust N Z J Surg 1999; Hulscher JB et al., Ann Thorac Surg 2001) In general, transthoracic approaches carry greater operative mortality and pulmonary complications, but transhiatal approaches have greater anastomotic leaks and stricture rates as well as recurrent laryngeal nerve injury. 5-yr OS rates are similar b/t the 2 approaches (20%–25%).

What is the 5-yr OS for pts managed with Sg alone for localized esophageal cancers?

Show Answer

5-yr OS is **20%–25%** for pts managed with Sg alone for localized Dz. This is higher for earlier-stage Dz (T1N0 ~77%) but lower for stage III Dz (~10%–15%).

Is there evidence to support the use of preop chemo (no RT) for Tx of resectable esophageal cancers?

Show Answer

This is **controversial.** Several phase II studies have demonstrated benefit, and randomized studies have reported conflicting results on the benefit of preop chemo.

U.S. Intergroup trial (Kelsen DP et al., NEJM 1998; Long-term updated, Kelsen DP et al., JCO 2007): 467 pts (53% adeno, 47% SCC) randomized to 3 × 5-FU/cisplatin preop and 2 × 5-FU/cisplatin postop or immediate surgical resection alone. There were no differences in resectability or survival (4-yr OS 26% vs. 23%, respectively; MS 16 mos vs. 15 mos, respectively). pCR was 2.5%. Pts with complete resection had a 5-yr DFS of 32% vs. 5% with R1–R2 resection.

Is there evidence to support adding radiation to neoadj chemo?

Show Answer

MRC randomized trial of preop chemo (MRC, Lancet 2002): 802 pts (66% adeno, 31% SCC, 3% undifferentiated) randomized to (a) 2 × cisplatin/5-FU preop or (b) immediate Sg. There was a significant benefit of neoadj chemo. MS was 13.3 mos vs. 16.8 mos, respectively, and 2-yr OS was 34% vs. 43%, respectively. The complete resection rate was also improved by chemo (54% vs. 60%, respectively).

German Esophageal Cancer Study Group (POET) trial (Stahl M et al., JCO 2009; Long-term update, Stahl M et al., Eur J Cancer 2017): randomized phase III in pts with T3–4N any M0 adeno of the GE junction or gastric cardia. The study closed early d/t poor accrual (126 of 354 intended). Randomization: (a) induction chemo → Sg or (b) induction chemo → preop CRT → Sg. Chemo was cisplatin/5-FU/leucovorin. RT was 30 Gy in 15 fx. pCR was better in the preop CRT group (15.6% vs. 2%) and in tumor-free LNs (64% vs. 38%). 5-yr OS trended better in the

CRT group (39.5% vs. 24.4%, p = 0.055). Postop mortality higher in the CRT group (10% vs. 3.8%, p = 0.26).

Neoadjuvant Chemotherapy Versus Radiochemotherapy for Cancer of the Esophagus or Cardia (NeoRes) (Klevebro F et al., Ann Oncol 2016): 181 pts with esophageal/EGJ adeno or SCC randomized to (a) preop chemo alone cisplatin/5-FU × 3 or (b) same chemo + concurrent RT (CRT) (40 Gy/20 fx). Primary endpoint met showing CRT improved pCR (28% vs. 9%) and also improved R0 rate (87% vs. 74%), but 3-yr OS (47% vs. 49%) and 3-yr PFS (44% both arms) not improved. CRT increased non-cancer causes of death in 1st year post randomization (46% vs. 15%, p = 0.036).

What is the phase III evidence to support preop CRT over Sg alone?

Show Answer

This had been controversial until the recent publication of the CROSS trial.

Urba SG et al. (JCO 2007): 100 pts (75% adeno, 25% SCC) randomized to cisplatin/vinblastine/5-FU + RT to 45 Gy bid vs. Sg alone. 3-yr OS was 30% vs. 16%, respectively (p = 0.18). DM same in both arms (60%).

Burmeister B et al. (Lancet 2007, TTROG): 256 pts (67% adeno, 33% SCC) randomized to cisplatin + 5-FU with RT to 35 Gy/15 fx. Less intensive chemo (5-FU 800 mg/m^2 vs. 1,000 mg/m^2 in other studies) was used. There was no difference in OS overall, but there was a trend to improved OS in SCC.

CALGB 9781 (Tepper J et al., JCO 2008): 56 pts (75% adeno, 25% SCC) randomized (closed d/t poor accrual) to cisplatin + 5-FU with RT to 50.4 Gy. pCR rate was 40%. 5-yr OS was 39% vs. 16% (p = 0.005). MS was 48 mos vs. 22 mos.

FFCD 9901 (Mariette et al., JCO 2014): pts with stage I/II thoracic esophageal adeno or SCC randomized to (a) Sg alone or (b) neoadj CRT (45 Gy + cisplatin/5-FU × 2 cycles) f/b Sg. CRT improved LRR (15.3% vs. 28.9%), but not 3-yr OS (47.5% vs. 53.0%) or R0 rate (93.8% vs.

92.1%). CRT had higher postop mortality (11.1% vs. 3.4%, p = 0.049).

CROSS (van Hagen P et al., NEJM 2012; Long-term update, Shapiro et al., Lancet Oncol 2015): 368 pts (75% adeno, 23% SCC, 2% undifferentiated) were randomized to Sg alone or CRT f/b Sg. CRT arm was 41.4 Gy in 23 fx with concurrent carboplatin (AUC 2 mg/mL/min) and paclitaxel (Taxol) (50 mg/m^2) for 5 wks f/b Sg. MS was 49 mos with CRT vs. 24 mos. Nonhematologic side effects were comparable in the 2 groups.

In the CROSS trial, what % of pts had R0 resection in the CRT arm vs. Sg alone arm and what % had a pCR to CRT?

Show Answer

In the CROSS trial, 92% had an R0 resection in the CRT arm vs. 69% in the Sg alone arm. 29% (23% of adeno and 49% of SCC) had a pCR to CRT (typical CR avg of randomized trials 25%–30%). (van Hagen P et al., NEJM 2012)

Is there a role for preop RT alone for esophageal cancers?

Show Answer

No. Studies demonstrate no benefit of preop RT alone.

Is there a role for postop RT alone for esophageal cancers?

Show Answer

Postop RT alone has failed to demonstrate a benefit in several randomized trials. Incomplete resection should rcv definitive CRT or palliative chemo or RT alone. Completely resected stages II–III adeno of the EGJ should rcv postop CRT based on the Intergroup gastric trial (20% EGJ tumors). (MacDonald JS et al., NEJM 2001)

What are the data demonstrating efficacy of definitive CRT vs. RT alone?

Show Answer

RTOG 85-01 (Herskovic A et al., NEJM 1992; Cooper JS et al., JAMA 1999): 130 pts (82% SCC, 18% adeno) randomized to 64 Gy RT alone vs. 50

Gy RT + cisplatin/5-FU × 2 during RT and 2 cycles after RT. There was SCC in 88% pts. 5-yr OS was 27% vs. 0% for RT alone. 10-yr OS was 20% for CRT. No outcome difference b/t adeno and SCC. RT technique used in this trial: initial RT field was the whole esophagus to 50 Gy (RT alone) or 30 Gy (CRT) → CD to 14 Gy (RT) or 20 Gy (CRT) to tumor + 5-cm sup/inf margin.

Is there a benefit of escalating the RT dose during CRT for esophageal cancer?

Show Answer

This is **controversial,** b/c **INT 0123** (Minsky BD et al., JCO 2002) is a phase III study that randomized pts to 50.4 Gy vs. 64.8 Gy with cisplatin + 5-FU × 2 → adj cisplatin/5-FU × 2. There was no difference in LC (44% vs. 48%). Excessive deaths in 64.8-Gy arm (11 vs. 2) were seen even before the 50.4-Gy dose (7 of 11 deaths). However, separate analysis excluding the early deaths still did not find a benefit to a higher dose.

RTOG 9207 (Gaspar et al., Cancer 2000) incorporated a brachytherapy boost and resulted in unacceptable toxicity: 10% mortality and 12% esophageal fistula.

Is there evidence to suggest that Sg can be omitted in operable pts with localized esophageal cancer?

Show Answer

There are no strong data suggesting Sg can be omitted in pts with adeno of the esophagus. However, there are 2 randomized trials examining CRT + Sg vs. CRT alone in pts with SCC that demonstrated an LC benefit of adding Sg but not an OS benefit. This is possibly d/t increased postop mortality in pts with SCC.

Bedenne L et al. (JCO 2007): 444 pts enrolled, treated 1st with CRT (45 Gy or split course 15 Gy × 2); the 230 responding pts (88% SCC) were randomized to Sg or no Sg. LC was better with Sg (66% vs. 57%). There

was no difference in survival (34% vs. 40%). The mortality rate was higher in the Sg group (9.3% vs. 0.8%).

Stahl M et al. (JCO 2005): 172 pts with SCC randomized to induction chemo + 40 Gy/chemo + Sg vs. induction chemo + 65 Gy/chemo alone. PFS was better with Sg (64% vs. 41%). Survival was the same b/t arms, with a trend to better survival with Sg. Postop mortality rate was also high in the surgical group (12.6% vs. 3.2%).

The benefit of Sg after CRT may be seen if postop mortality could be minimized, such as operation in high-volume facilities, where postop mortality should be in the range of 2%–4%.

Could salvage therapies (Sg or RT) be performed after definitive CRT or Sg for esophageal cancer management?

Show Answer

Yes. Salvage Sg could be performed for select pts who recur after definitive CRT but with increased operative morbidity/mortality (Tachimori Y et al., J Thorac Cardiovasc Surg 2009). **RTOG 0246** (Swisher S et al., IJROBP 2012) was a phase II trial looking at selective Sg for pt with residual or recurrent Dz after induction chemo + CRT. 51% of pts underwent Sg (19% had recurrent Dz, other had residual). 10% Tx-related mortality. 1-yr OS 71%, which failed to meet hypothesized 1-yr survival of 77.5%.

Salvage RT can be performed for isolated LR after Sg alone, but the dose should be limited to 45 Gy with concurrent chemo b/c of gastric pull-through.

Can RT be performed in pts with tracheoesophageal fistula?

Show Answer

Yes. Although historically it was contraindicated b/c of fear that RT may worsen the fistula, available studies demonstrate that RT does not worsen the fistula and may even cause healing and closure (Muto M et al., Cancer 1999). Also, per NCCN guidelines an esophageal stent may be considered to

decrease tracheoesophageal fistula Sx but complications are common. (Ross W et al., Gastrointestinal endoscopy 2007)

How are cancers of the Cx esophagus managed in general?

Show Answer

B/C of the difficult and morbid Sg (total laryngopharyngoesophagectomy), cancers of the Cx esophagus are Tx **like an H&N primary with a nonsurgical approach and definitive CRT.** Case series using IMRT + 5-FU/cisplatin (Wang SL et al., WJG 2006; Burmeister B et al., AOHNS 2000; McDowell L et al., IJROBP 2017) show that high doses from 60–70 Gy offers good LC and response (LC 88% and 5-yr OS 55% from the Burmeister B et al. series) but an NCDB analysis did not find an association between increased dose and improved OS (De B et al., Dis Esoph 2017). However, late toxicity, such as esophageal stricture, is a problem.

Can definitive RT be used for early-stage (Tis, IA) esophageal cancers?

Show Answer

Yes, for SCC. With doses 60–72 Gy or 55–60 Gy + a brachytherapy boost, the LC and DFS is ~80% in pts with SCC. Tumors >5 cm should rcv CRT b/c of poorer LC (~50%–60%). (Hishikawa Y et al., Radiother Oncol 1991)

What are the radiotherapy doses and techniques for the management of esophageal cancer?

Show Answer

Preop CRT: 41.4–50.4 Gy for adeno and SCC

Definitive CRT: 50–50.4 Gy for adeno and SCC. Higher doses (60–66 Gy per NCCN) may be considered for SCC of the Cx esophagus.

Field size: Respecting anatomic boundaries, CTV = GTV+3–4 cm sup and inf along esophagus and cardia and 1 cm radial expansion & Nodal CTV = nodal GTV + 0.5–1.5 cm. Elective mediastinal or celiac nodes included based GTV location. Consider IMRT for cardiac, lung and/or kidney

sparing as needed, with possible benefit of IMRT vs. 3D in reducing cardiac mortality based on MDACC retrospective and SEER-Medicare data (Lin SH et al., IJROBP 2012; Cancer 2016) and postop complications (Wang J et al., IJROBP 2013). (See IMRT contouring atlas: Wu J et al., IJROBP 2015)

Is there a role for induction chemo prior to neoadj CRT?

Show Answer

Possibly. The **CALBG 80803** phase II crossover trial (Goodman KA et al., ASCO GI 2017) looked at 257 pts randomized to induction chemo, either modified FOLFOX-6 or carboplatin/paclitaxel f/b a repeat PET. Pt who responded (>35% decrease in standardized uptake value [SUV]) went onto CRT (50.4 Gy/28 fx) then Sg. Nonresponders crossed over to alternative chemo with RT, then Sg. The hypothesis was that cross over chemo will improve pCR from the null of <5% to 5–20%. In the FOLFOX group, the responders had a pCR 38% and the nonresponders had pCR 16.2%. In the carboplatin/paclitaxel group, the responders had a pCR 10.7% and the nonresponders had a pCR of 15%. Conclusion was nonresponders had improved pCR from induction and cross-over chemo.

Is there any benefit to adding targeted EGFR inhibition to definitive CRT?

Show Answer

No, 2 randomized trials showed no benefit with the addition of cetuximab.

SCOPE1 phase II/III randomized trial (Crosby T et al., Lancet Oncol 2013) had randomized 258 pts to definitive CRT vs. definitive CRT with cetuximab, before closing trial early before going to phase III d/t futility of experimental arm. The cetuximab arm performed worse than CRT alone for MS (22.1 mos vs. 25.4 mos, HR 1.53, p = 0.035) and with greater grade 3–4 nonhematologic toxicities (79% vs. 63%, p = 0.004).

RTOG 0436 Phase III trial (Suntharalingam M et al., JAMA Oncol 2017) randomized 344 pts to definitive CRT with cisplatin/paclitaxel ±

cetuximab regardless of EGFR expression. Cetuximab did not improve cCR (56% vs. 58% control), LF (3-yr 49% both arms), or OS (3-yr 45% vs. 44%).

What Tx options exist for malignant dysphagia in a metastatic pt?

Show Answer

Consider starting with chemo alone with diet changes as indicated. RT (mainly 20 Gy/5 fx) decreased dysphagia in 75%, lasting for about 5 mos (Murray LJ et al., PRO 2012). Stents work faster but with less durable responses, and complications include pain, migration, and reflux.

FOLLOW-UP/TOXICITY

What is the rate of esophageal stricture following RT alone & CRT?

Show Answer

For esophageal cancer, series of RT alone reveal benign strictures in 12%–30% of pts, and 1 series showed a 12% rate >1 yr after CRT (Adebahr S et al., Best Pract Res Clin Gastroenterol 2016). Balloon dilation is successful for ~80%–90%.

What types of toxicities are experienced during radiotherapy, and what measures should be taken to help minimize these toxicities?

Show Answer

Relief is obtained with **topical anesthesia, narcotics, H2 blockers, feeding tube (J-tube if preop CRT, PEG if definitive CRT), and limiting the dose to critical structures.**

Acute: esophagitis, skin irritation, fatigue, weight loss

Late: dysphagia, stricture, pneumonitis, laryngeal edema, cardiac injury, renal insufficiency, liver injury

Describe an appropriate f/u schedule for pts after completion of Tx for esophageal cancer?

Show Answer

Majority of relapses within 2 yrs. F/u for esophageal cancer after Tx: H&P q3–6 mos for 2 yrs, q6–12 mos for next 3 yrs, then annually; at each visit, basic labs such as CBC/chemistry panel; consider CT chest/abd every 6 mos × 2 yrs, and if bimodality therapy EGD every 3–6 mos × 2 yrs, q6mos for 3rd yr, then as clinically indicated (NCCN 2018); and dilatation for stenosis and nutritional counseling as needed.

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Gastric Cancer

Updated by Bryan Ager

BACKGROUND

What is the estimated incidence of gastric cancer in the United States and worldwide?

Show Answer

United States: 28,000 cases/yr with 10,960 deaths (2017)
Worldwide: ~952,000 new cases/yr; 3rd-leading cause of death
Where are the high-incidence areas in the world?

Show Answer

The highest incidences are found in **East Asia (Japan and China) > Eastern Europe > South America.**
What are some acquired and genetic risk factors for developing gastric cancer?

Show Answer

Acquired factors: Helicobacter pylori infection, high intake of smoked and salted foods, nitrates, diet low in fruits/vegetables, smoking, RT exposure, obesity, Barrett esophagus/gastroesophageal reflux disease (GERD), prior subtotal gastrectomy
Genetic factors: E-cadherin (CDH-1 gene) mutation, type A blood group, pernicious anemia, HNPCC, Li-Fraumeni syndrome

What are the molecular subtypes of gastric adenocarcinoma proposed by The Cancer Genome Atlas (TCGA Nature 2013)?

Show Answer

EBV Positive: Epstein–Barr virus positive, PIK3CA mutation, PD-L1/2 overexpression, extreme deoxyribonucleic acid (DNA) hypermethylation, amplification of JAK2

Microsatellite Instability: hypermutated, MLH1 silencing, mitotic pathways

Genomically Stable: diffuse histology, RHOA mutations or fusions

Chromosomal Instability: intestinal histology, TP53 mutation, amplification of receptor tyrosine kinases

How does tumor location relate to the underlying etiology of gastric adenocarcinoma?

Show Answer

Body and antral lesions are associated with H. pylori infection and chronic atrophic gastritis, whereas proximal gastric lesions (gastroesophageal [GE] junction, gastric cardia) are associated with obesity, GERD, and smoking.

Which has poorer prognosis: proximal or distal gastric cancer?

Show Answer

Stage for stage, **proximal** gastric cancer has a poorer prognosis.

What are the 2 histologic types of gastric adenocarcinoma? How do these 2 types differ in terms of etiology of the gastric cancer?

Show Answer

Intestinal and diffuse are the 2 histologic types of adenocarcinomas described in the **Lauren Classification**.

Intestinal type: differentiated cancers with a tendency to form glands, occur in the distal stomach, and arise from precursor lesions seen mostly in endemic areas and in older people, more commonly men, suggesting an

environmental etiology. Associated with chromosomal instability.

Diffuse type: less differentiated (signet ring cells, mucin producing), have extensive submucosal/distant spread, and tend to be proximal. They do not arise from precancerous lesions, are more common in low-incidence areas, and are more common in women and younger people, suggesting a genetic etiology. Associated with the genomically stable molecular subtype.

What is the Japanese Research Society (JRS) classification of nodal spread?

Show Answer

1st echelon: N1 (stations 1–6)—perigastric nodes (lesser and greater curvature) and periesophageal nodes (proximal gastric)

2nd echelon: N2 (stations 7–11)—celiac axis, common hepatic, splenic

More distant: N3 (stations 12–14)—hepatoduodenal, peripancreatic, mesenteric root; N4 (stations 15, 16)—portocaval, P-A nodes, middle colic

JRS N1–N4 are not the same as AJCC nodal staging, but do correspond to LND (D) classification (see below)

What are the patterns of spread for gastric cancer?

Show Answer

Local extension to adjacent organs, lymphatic mets, peritoneal spread, or hematogenous (liver, lung, and bone). Liver/lung mets are more common for proximal/GE junction tumors.

What is the most important prognostic factor for gastric cancer?

Show Answer

TNM stage is the most important factor. Histologic grade has not been shown to be independently prognostic apart from tumor stage. The prognostic value of molecular subtype remains unclear.

WORKUP/STAGING

How do pts with gastric cancer generally present?

Show Answer

Anorexia, abdominal discomfort, weight loss, fatigue, n/v, melena, weakness from anemia

What aspects of the physical exam are relevant for evaluating a pt for a possible gastric malignancy?

Show Answer

General physical exam with focus on abdominal mass (local extension), liver mets, ovarian mets (Krukenberg tumor), distant LN mets (Virchow: left SCV; Irish: left axillary; Sister Mary Joseph: periumbilical), ascites, Blumer shelf (palpable peritoneal involvement on rectal exam)

What is important in the workup for gastric cancer?

Show Answer

Gastric cancer workup 2018 NCCN Guidelines: H&P (onset, duration, Hx of risk factors), CBC, CMP, esophagogastroduodenoscopy + Bx, CT C/A/P with oral and IV contrast, PET/CT and EUS +/– FNA of regional LN mets if no evidence of M1 Dz, diagnostic laparoscopy to r/o peritoneal seeding, if M1 testing for MSI-H/dMMR including HER2 and PD-L1 if adeno.

How many layers are seen on EUS when imaging the GI tract?

Show Answer

5 layers are seen on EUS: layers 1, 3, and 5 are hyperechoic (bright), and layers 2 and 4 are hypoechoic (dark). Layer 1 is superficial mucosa, layer 2 is deep mucosa, layer 3 is submucosa, layer 4 is muscularis propria, and layer 5 is subserosa fat and serosa.

What is the rate of upstaging to stage IV using diagnostic laparoscopy?

Show Answer

35%–40% of pts are found to have mets using diagnostic laparoscopy.

What is the AJCC 8th edition (2017) T-staging classification for gastric

cancer?

Show Answer

T-staging classification is unchanged from the AJCC 8th edition (2017).

Tis: confined to mucosa without invasion to lamina propria
T1a: invades lamina propria or muscularis mucosae
T1b: invades submucosa
T2: invades muscularis propria
T3*: penetrates subserosa without invasion of visceral peritoneum (serosa) or adjacent organs
T4a*: invades serosa
T4b: invades adjacent structures/organs

*Tumor is classified as T3 if it penetrates through the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or into the greater or lesser omentum without perforation of the visceral peritoneum covering these structures. Tumor is classified as T4 if it penetrates the visceral peritoneum covering the gastric ligaments or the omentum.

What is the AJCC 8th edition (2017) N-staging classification for gastric cancer?

Show Answer

N-staging classification is unchanged from the AJCC 8th edition (2017).

N1: 1–2 LNs
N2: 3–6 LNs
N3: ≥7 LNs
N3a: 7–15 LNs
N3b: >15 LNs

What are the AJCC 8th edition (2017) stage groupings for gastric cancer?

Show Answer

The AJCC 8th edition updated the pathologic (pTNM) stage groupings in addition to creating new clinical (cTNM) and postneoadj therapy (ypTNM) stage groupings.

Clinical (cTNM) Stage Groupings:

Stage I: T1–2N0
Stage IIA: T1–2N1–3
Stage IIB: T3–4aN0
Stage III: T3–4aN1–3
Stage IVA: T4b
Stage IVB: M1

Pathologic (pTNM) Stage Groupings:

Stage IA: T1N0 (adds to 1)
Stage IB: T1N1, T2N0 (adds to 2)
Stage IIA: T1N2, T2N1, T3N0 (adds to 3)
Stage IIB: T1N3a, T2N2, T3N1, T4aN0 (adds to 4)
Stage IIIA: T2N3a, T3N2, T4aN1, T4aN2, T4bN0 (adds to 5 mostly)
Stage IIIB: T1–2N3b, T3–4aN3a, T4bN1–2 (adds to 6 mostly)
Stage IIIC: T3–4bN3b, T4bN3a (adds to 7 mostly)
Stage IV: M1

Post-Neoadj Therapy (ypTNM) Stage Groupings:

Stage I: T1–2N0, T1N1
Stage II: T3–4aN0, T2–3N1, T1–2N2, T1N3
Stage III: T4bN0, T4a–bN1, T3–4bN2, T2–4bN3
Stage IV: M1

TREATMENT/PROGNOSIS

What surgical margin is generally considered adequate in gastric cancer?

Show Answer

En bloc resection with ≥**4-cm margin** from gross tumor

For what tumor location is subtotal vs. total gastrectomy indicated? Is there a benefit with total gastrectomy?

Show Answer

Subtotal gastrectomy for **distal tumors** (antrum/body); **total** gastrectomy for **proximal tumors** (cardia, greater curvature)

No. According to the following 2 trials, there is no benefit of advocating total gastrectomy:

Gouzi JL et al. randomized distal tumors to total gastrectomy vs. subtotal gastrectomy. There were no differences in morbidity/mortality (1.3% vs. 3.2%) or survival outcomes (5-yr OS 48%). (Ann Surg 1989)

Italian data from a 2nd randomized trial (Bozzetti F et al., Ann Surg 1999) showed no difference in 5-yr survival b/t subtotal gastrectomy (65%) and total gastrectomy (62%).

Should splenectomy be performed for proximal gastric tumors to get splenic LN clearance?

Show Answer

No. There was no value of splenectomy in a randomized trial. (Csendes A et al., Surgery 2002) Splenectomy and pancreatectomy had an adverse impact on survival in the Dutch and MRC D1 vs. D2 RCTs (see below).

How are GE junction cancers classified, and how is the classification important therapeutically?

Show Answer

GE junction cancers are classified by the **Siewert classification** as 3 entities:

Type I has lymphatic drainage reminiscent of esophageal primaries (mediastinal and celiac), whereas types II–III drain to celiac, splenic, and P-A nodes. Esophagectomy is typically recommended for type I tumors, & gastrectomy is recommended for types II–III.

Type I: adenocarcinoma of distal esophagus, arising from Barrett metaplasia, epicenter b/t 1 cm and 5 cm proximal to anatomical cardia, treat as esophageal primary

Type II: adenocarcinoma of cardia portion, arising from cardia and short segment of intestinal metaplasia at GE junction, epicenter b/t 1 cm proximal and 2 cm distal to anatomical cardia, treat as esophageal primary

Type III: adenocarcinoma of subcardial stomach, which may infiltrate GE junction or distal esophagus from below, epicenter b/t >2 cm and 5 cm distal to anatomical cardia, treat as gastric primary

What are the types of nodal dissection for gastric cancer?

Show Answer

As per the JRS classification:

D0: no nodal dissection

D1: perigastric nodes removed (stations 1–6)

D2: D1 + celiac axis nodes (left gastric [7], common hepatic [8], celiac trunk [9], splenic hilum [10], splenic artery [11])

D3: D2 + hepatoduodenal (12), peripancreatic (13), mesenteric root (14)

D4: D3 + middle colic (15), portocaval/P-A nodes (16)

Is extended lymphadenectomy necessary for surgical cure of gastric cancer?

Show Answer

No. Although results from numerous randomized trials have not shown an OS advantage of extended lymphadenectomy, CSS and LRR may be improved with extended dissection in the most recent update of the Dutch trial (see below).

What 4 major trials investigated the extent of lymphadenectomy on outcomes?

Show Answer

Dutch trial (Bonenkamp JJ et al., NEJM 1999): 711 pts randomized to D1 vs. D2 dissection. There was greater mortality in the D2 group (10% vs. 4%, SS), and 5-yr OS was 45% vs. 47% (NSS). In the most recent 15-yr update (Songun I et al., Lancet Oncol 2010), the 15-yr OS was 21% in the D1 group and 29% in the D2 group (p = 0.34). However, the gastric cancer–related death rate was significantly higher in the D1 group (48%) vs. the D2 group (37%), while deaths from other Dz were similar in the 2 groups. LR was lower in the D2 group (12% vs. 22%) as well as regional recurrence (13% vs. 19%) (all SS).

MRC trial (Cushieri A et al., Br J Cancer 1999): 400 pts randomized to D1 vs. D2. There was greater mortality in the D2 group (13% vs. 6.5%), and 5-yr OS was the same (35% vs. 33%).

Japanese trial JCOG9501 (D2 vs. D2 + PAND) (Sasako M et al., NEJM 2008) demonstrated that although extended LND does not increase morbidity or mortality, there is also no difference in 5-yr OS (69.2% for D2 vs. 70.3% for D2 + PAND) or for LRR.

An **Italian trial** (D1 vs. D2) (Degiuli M et al., Br J Surg 2014) showed no difference in 5-yr OS and no increased morbidity or mortality with extended lymphadenectomy.

What is the min number of LNs that should be pathologically assessed in a gastrectomy specimen?

Show Answer

In the United States, at least **15 LNs** should be assessed by the pathologist, since survival improves if ≥15 LNs are examined (Hundahl S et al., Cancer 2000).

What are the selection criteria for endoscopic mucosal resection, endoscopic submucosal dissection, or limited surgical resection (without nodal evaluation) of gastric cancer?

Show Answer

Favorable early-stage gastric cancer: **Tis–T1 (but not involving more than superficial submucosa)**, **small** (≤2 cm), **nonulcerated, well differentiated, N0**. In general, these types of tumors have <5% LN mets rate.
When is Sg alone potentially adequate for gastric cancer?

Show Answer

T1N0 or T2N0 (but not beyond the muscularis propria). 5-yr OS for favorable early-stage gastric cancer is 80%–90%. For all others without metastatic Dz, adj Tx is recommended.
What is the relapse pattern after "curative" resection of gastric cancer?

Show Answer

Distant Dz (50%) and LRR. LRR is common in the gastric bed, nearby LNs, anastomotic site, gastric remnant, and duodenal stump. In the classic paper of the University of Minnesota reoperative analysis (Gunderson L et al., IJROBP 1982), local-only recurrence was seen in 29%, LR and/or regional LN mets in 54%, and LF as any component of failure in 88% of pts.
What is the randomized evidence that demonstrated a benefit of adj CRT after surgical resection for gastric cancer?

Show Answer

INT-0116 (Macdonald JS et al., NEJM 2001): 556 pts, stages IB–IV (nonmets) adenocarcinoma of stomach and GE junction (~20%), randomized after en bloc resection with −margin to (a) observation or (b) CRT (1 cycle bolus 5-FU/leucovorin [LV]) before RT, 2 cycles during 45 Gy RT, and 2 cycles after RT. Median f/u was 5 yrs. **CRT was beneficial for all outcomes except for DM**. 3-yr RFS 31% vs. 48%; 3-yr OS 41% vs. 50%; median OS 27 mos vs. 36 mos. Toxic deaths in 1%. Only 2/3 of pts completed full Tx with 41% grade 3 toxicity and 32% grade 4 toxicity. Over 2/3 of pts had T3 or T4 Dz and 85% had nodal involvement.
What is the major criticism for the benefit of CRT seen in INT-0116?

Show Answer

Suboptimal LND (54% D0, 10% D2) is the major criticism of INT-0116.
How was RT delivered in INT-0116?

Show Answer

Most pts were treated **AP:PA to 45 Gy in 25 fx.**
What does the 10-yr f/u data from INT-0116 show?

Show Answer

persistent strong benefit with adj CRT; HRs were 1.32 (p = 0.0046) for OS and 1.51 (p <0.001) for RFS favoring CRT; more 2nd malignancies observed in CRT group (21 vs. 8, NSS). Regarding crudes failure rates for the observation vs. CRT groups, LF was 8% vs. 2%, regional relapse was 39% vs. 22%, and distant relapse was 18% vs. 16%, respectively. (Smalley SR et al., JCO 2012)
Is there a survival benefit to postop CRT vs. chemo alone in pts with more extensive lymphadenectomy?

Show Answer

No. The Korean **ARTIST trial** (Lee J et al., JCO 2011; update Park S et al., JCO 2014) randomized 458 pts after D2, R0 resection to (a) chemo alone with capecitabine and cisplatin chemotherapy (XP) × 6 cycles (capecitabine 2,000 mg/m^2 d1–14 + cisplatin 60 mg/m^2 d1 q3wks) or (b) CRT with XP × 2 cycles → 45 Gy with capecitabine 825 mg/m^2 bid → XP × 2 cycles. At 7 yrs, there was no difference in OS. However, a trend for improved DFS was observed for CRT (p = 0.09). Tx completion rate was much higher than in INT-0116 (82% CRT, 75% chemo alone). Also in contrast to INT-0116, appx 60% of pts had early-stage IB–II Dz, which could contribute to the negative result for CRT.
What was the result from the ARTIST trial subgroup analysis?

Show Answer

CRT significantly improved DFS compared to chemo alone for pts with **node+ Dz** and **intestinal type histology.** (Park S et al., JCO 2014)
Is there a role for preop CRT for gastric cancer?

Show Answer

Possibly, although no phase III studies have been published to date. A phase II study of neoadj CRT (**RTOG 9904:** Ajani JA et al., JCO 2006) using induction chemo × 2 (5-FU/LV/cisplatin) → CRT (continuous infusion [CI] 5-FU/weekly taxol) showed pCR of 26% and R0 resection of 77%.
What is the approach to resectable gastric cancer in Europe and what major RCT is it based on? What is the major weakness of this trial?

Show Answer

Periop chemo (without RT) with ECF regimen (epirubicin/cisplatin/5-FU [ECF]); **MRC Adj Gastric Cancer Infusional Chemo (MAGIC) trial** (Cunningham D et al., NEJM 2006): 503 pts with gastric, GE junction, and distal esophageal adenocarcinoma (26%) randomized to (a) preop ECF × 3 and postop ECF × 3 or (b) Sg alone showed a survival benefit for chemo. 5-yr OS was 36% vs. 23%, respectively (p = 0.009). Only 42% completed all chemo. A **major weakness of the MAGIC trial is that the pCR rate was 0%.**
What major question did the CRITICS trial try to answer, and what were the results?

Show Answer

The **CRITICS trial compared periop chemo with preop chemo and postop CRT in the context of a D1+ (≥15 nodes removed) resection**. The trial randomized 788 pts to (a) preop epirubicin/cisplatin/oxaliplatin, and capecitabine (ECC and EOC) chemo × 3 cycles (epirubicin, cisplatin/oxaliplatin, and capecitabine q3wks) → Sg → postop ECC or EOC × 3 cycles or (b) preop ECC or EOC × 3 cycles → Sg → postop CRT

to 45 Gy/25 fx with concurrent cisplatin and capecitabine. 5-year OS and EFS were equivalent between the 2 arms, and toxicity similar with only clinically irrelevant grade ≥3 non-febrile neutropenia more frequent in the chemo group. Preop chemo compliance was high with >90% dose intensity delivered for all drugs, but only 46% of chemo & 50% of CRT patients completed all treatment as planned. Therefore, in the successor CRITICS-II trial all chemo & RT (docetaxel-based chemo vs. CRT vs. both) will be given preop. (Cats A and Jansen EPM et al., Lancet Oncology 2018)

What is the survival of pts with locally advanced unresectable gastric cancer? How are these pts managed?

Show Answer

5-yr OS is generally **5%–20%.** In most randomized studies of these pts, CRT has benefit over chemo alone (5-yr OS 12%–18% vs. 0%–7%). **GITSG G274** (Schein PS et al., Cancer 1982) used CRT (50 Gy) vs. chemo alone (5-FU/1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea [methyl-CCNU]). There was better survival with CRT (18% vs. 7%).

For metastatic gastric cancer pts, what are some palliative Tx options?

Show Answer

Surgical resection for carefully selected pts with good PS with Sx of obstruction or hemorrhage is better for palliation than stents or bypass. **RT alone or CRT** can be considered for the nonsurgical candidates (30 Gy/10 fx is most common). A large retrospective series showed response rates to palliative RT were 81% for bleeding, 46% for pain, and 53% for obstruction with no dose response for BED10 > 39 Gy (Tey et al., Medicine 2014). **Endoluminal laser ablation** can be used for proximal lesions with esophageal obstruction → **chemo.** Palliative chemo c/w best supportive care had an overall HR of 0.39, and MS increased from 4.3 to 11 mos based on Cochrane meta-analysis. (Wagner A et al., Cochrane Database Sys Rev 2006)

What novel targeted therapy may be considered for select pts with

metastatic or recurrent gastric cancer?

Show Answer

Trastuzumab (Herceptin); based on the trastuzumab for gastric cancer (name of randomized trial) **(ToGA) randomized trial,** which showed improved median OS (13.5 vs. 11.1 mos, p = 0.0048) with addition of trastuzumab to chemo (cisplatin/5-FU) vs. chemo alone (Bang YJ et al., Lancet 2010). The HER2 **positive rate was 22.1%**.

What is the irradiation volume and dose of postop CRT after gastric tumor resection?

Show Answer

Tumor bed and nodal volumes constructed with preop/postop imaging and surgical clip placement. In general, node+ Dz requires wide coverage of the tumor bed, remaining stomach, all resection/anastomotic sites, and nodal drainage areas (which is dependent on tumor location). Use 45 Gy to the initial volume as per RTOG 0116. CD to 50.4 Gy to the surgical bed or at-risk areas if margin+ or gross Dz. Pre-Tx J-tube placement (at time of staging laparoscopy) is helpful for nutritional support (See contouring atlas Wu J. et al., PRO 2013).

When would it be optional to treat the nodal beds in a resected gastric cancer?

Show Answer

Tx would be optional for pts with negative nodes, pts having had adequate Sg and pathologic evaluation for nodes (>10–15 nodes), and wide surgical margins (at least 5 cm).

In general, what are the at-risk regional nodal sites based on anatomic location of the gastric tumor?

Show Answer

. GE junction: mediastinal, periesophageal, celiac, perigastric

- Proximal stomach: perigastric, periesophageal, celiac, pancreaticoduodenal, porta hepatis
- Body: perigastric, splenic, celiac, peripancreatic, porta hepatis
- Distal stomach: perigastric, periduodenal, peripancreatic, porta hepatis, celiac

How does the target volume differ for proximal vs. distal gastric lesions?

Show Answer

For proximal and distal lesions and negative nodes with adequate dissection, the remnant of the stomach does not need to be covered. For body lesions, however, the gastric remnant needs to be covered in all cases.

Proximal lesions: include splenic hilum and left medial diaphragm in the target volume, but inf extent does not need to go to L3 (may just go to L1–2 coverage of the sup mesenteric artery/P-A nodes)

Distal lesions: include 1st portion of the duodenal C-loop but not the splenic hilum

What is the preferred postop RT planning technique?

Show Answer

3D-CRT (e.g., 4 field) or IMRT can spare normal tissues and reduce toxicity better than traditional AP/PA fields, but greater conformality requires a more careful target delineation.

FOLLOW-UP/TOXICITY

What are some long-term complications of gastrectomy?

Show Answer

Dumping syndrome (diarrhea, cramping, palpitations, reactive hypoglycemia) and malabsorption (B12, iron, calcium; supplement if necessary)

What is entailed in the f/u of gastric cancer pts treated with curative intent?

Show Answer

H&P q3–6mos × 1–2 yrs, then 6–12 mos × 3–5 yrs, then annually; CBC/CMP & endoscopy as clinically indicated; CT chest/abd/pelvis q6-12 mos × 2 years, then annually up to 5, and/or PET/CT as indicated; and monitor for B12 and iron deficiency. (NCCN 2018)

48

Pancreatic and Periampullary Adenocarcinoma

Updated by Anna Torgeson

BACKGROUND

Appx how many pancreatic adenocarcinoma (PCA) pts are diagnosed per yr in the United States?

Show Answer

As of 2016, the incidence of PCA is **53,670 cases/yr** in the United States, with 43,090 deaths. Its incidence is higher in developed countries.
Where does PCA rank in cancer incidence in the United States? Cancer mortality?

Show Answer

As of 2016, PCA is the 12th most common cancer Dx but the 4th **most common cause of cancer death in the United States.**
Is there a racial or sex predilection for PCA?

Show Answer

Yes. African Americans are more commonly affected than Caucasians; however, the incidence is similar among males and females.
In what decades of life does PCA incidence peak?

Show Answer

The peak age of PCA is in the **6th–7th decades** of life.
What are 3 environmental exposures associated with PCA?

Show Answer

Most common environmental risk factors for PCA:

- Tobacco smoking
- 2-naphthylamine
- Benzidine

What % of PCA is familial?

Show Answer

~10% of PCA is familial.
What 2 genetic mutations have most frequently been associated with familial PCA?

Show Answer

p16 and BRCA2 are the 2 most common familial associated genetic changes found in PCA.
Is chronic pancreatitis associated with increased risk of PCA?

Show Answer

No. Chronic pancreatitis is not associated with risk of PCA. Historically, there appeared to be an association, but this can be explained by confounding factors.
Appx at what vertebral bodies are the pancreas, celiac axis, and superior mesenteric artery (SMA) located?

Show Answer

Pancreas: L1–2
Celiac axis: T12
SMA: L1

What % of PCA arise in the head, body, and tail of the pancreas?

Show Answer

Common PCA sites are **75% in the head, 15% in the body, and 10% in the tail.**

What is the distribution of local, regional, and metastatic Dz at Dx?

Show Answer

10% of PCA pts have local Dz at Dx.
25% of PCA pts have regional node+ Dz at Dx.
50% of PCA pts have DM at Dx.

For PCA, what are the 3 most common sites of DM?

Show Answer

Common sites of DM for PCA include the **liver, peritoneum, and lungs.**

Is there a role for screening in PCA?

Show Answer

No. There is no current role for PCA screening. There are studies evaluating the role of screening 1st-degree relatives of PCA with EUS, but this is still experimental.

What % of pancreatic tumors are from the exocrine pancreas?

Show Answer

95% of PCA are from the exocrine pancreas.

What are the 4 most common pathologic subtypes of exocrine pancreatic tumors?

Show Answer

Most common subtypes of exocrine pancreatic tumors:

- Ductal adenocarcinoma (80%)
- Mucinous cystadenocarcinoma

- Acinar cell carcinoma
- Adenosquamous carcinoma

What are the most common oncogenes in PCA?

Show Answer

K-ras oncogene is present in >95% of PCA.
p16 mutations are seen in >90% of PCA.
p53 mutations occur in 55%–75% of PCA.
DPC4 mutations occur in ~50% of PCA.
What are the most common presenting signs & Sx of PCA?

Show Answer

Common presenting signs & Sx of PCA are **pancreatic/biliary duct obstruction, jaundice, and abdominal pain.**
What Dz is commonly diagnosed 1–2 yrs prior to a PCA Dx?

Show Answer

60%–80% of PCA pts are diagnosed with diabetes 1–2 yrs prior to Dx. However, only a small proportion of diabetic pts develop PCA.
Periampullary cancers refer to tumors arising from what 4 structures?

Show Answer

Periampullary tumors are those arising from the **ampulla of Vater, common bile duct (CBD), head of the pancreas, and adjacent duodenum.**

WORKUP/STAGING

What is the DDx of a pancreatic mass?

Show Answer

The DDx of a pancreatic mass includes exocrine cancer, islet cell/neuroendocrine cancer, cystic adenomas, papillary cystic neoplasms (e.g., intraductal papillary mucinous tumor), lymphoma, acinar cell

carcinoma, and metastatic cancer.
What is the initial workup for suspected PCA?

Show Answer

Suspected PCA workup includes a focused H&P, labs including CBC, CMP, and CA 19-9, and abdominal CT scan.
In what circumstance will a PCA pt not excrete any CA 19-9?

Show Answer

If a pt is red cell Lewis antigen A–B negative, then the pt cannot excrete CA 19-9. The Lewis antigen– phenotype is present in 5%–10% of the population.
What is the appropriate imaging for suspected PCA?

Show Answer

Dual-phase thin-sliced (preferably submillimeter) CT abdomen, with images obtained in the pancreatic parenchymal and portal venous phases of enhancement.
Name 4 appropriate procedures for obtaining tissue from a suspicious pancreatic mass.

Show Answer

Procedures to obtain tissue from a suspicious pancreatic mass:

. EUS-guided FNA
. CT-guided FNA
. Endoscopic retrograde cholangiopancreatography (ERCP)
. Pancreatic resection (i.e., histologic Dx is not required before Sg)

When is it appropriate to obtain tissue prior to Sg for lesions suspicious on imaging?

Show Answer

Tissue Dx prior to Sg is not routinely necessary, except for: (1) clinical trial enrollment, (2) prior to neoadj therapy, or (3) prior to chemo/CRT in unresectable pts.
What is the major advantage of EUS-guided FNA over CT-guided FNA of a pancreatic mass?

Show Answer

EUS-guided FNA is associated with **lower risk of peritoneal seeding** (2% vs. 16%).
When is ERCP indicated instead of EUS?

Show Answer

ERCP carries a higher risk of iatrogenic pancreatitis, so it is reserved for cases where PCA is causing biliary obstruction and cholangitis requiring stenting.
What is the NCCN 2018 classification scheme for PCA?

Show Answer

PCA are classified into 4 categories

. Resectable (T1–3N0 or N+)
. Borderline resectable (T1–4Nany)
. Locally advanced unresectable (T4Nany)
. Metastatic (TanyNanyM1)

What 3 criteria are necessary for a primary pancreatic tumor to be resectable (per NCCN)?

Show Answer

NCCN resectability for PCA is defined as:

. No distortion of superior mesenteric vein (SMV) or portal vein (PV) & ≤180-degree contact

- Clear fat plane around celiac artery, SMA, and common hepatic artery (CHA)
- No distant mets or mets to nodes beyond field of resection

What characteristics make a primary pancreatic tumor unresectable (per NCCN)?

Show Answer

Unresectable characteristics include:

- >180-degree encasement of SMA, celiac axis, first jejunal branch of SMA for head lesions
- >180-degree encasement of the SMA, celiac axis, or abutment of CA w/ aortic involvement for body/tail lesions
- Unreconstructable SMV/PV occlusion, contact w/ most proximal draining jejunal branch of SMV
- Aortic invasion/encasement

What are the characteristics of borderline resectable pancreatic head/body tumors (per NCCN)?

Show Answer

The definitions vary, but NCCN definition of **borderline resectability** for PCA are:

- SMV/PV involvement (distortion, narrowing or occlusion) that can be resected and reconstructed using nearby vessels.
- Tumor abutment on SMA ≤180 degrees, CHA abutment without extension to celiac axis or hepatic bifurcation.
- Gastroduodenal artery encasement up to the hepatic artery, including up to short segment encasement or direct abutment of the hepatic artery, without celiac axis involvement.

What pancreatic tail lesions are considered “borderline resectable”?

Show Answer

Invasion into the adrenal gland, colon, mesocolon, or kidney are considered borderline resectable for PCA tail lesions.
What location of PCA is associated with higher rates of resectability: head, body, or tail?

Show Answer

PCA **head** tumors are more resectable b/c they cause Sx early (and therefore present with earlier-stage Dz).
At presentation, what % of PCA pts are resectable?

Show Answer

10%–20% of PCA pts are potentially resectable at presentation.
What % of pts with resectable PCA tumors by CT imaging will be resectable at the time of Sg?

Show Answer

~65%–80% of PCA pts deemed resectable by CT are resectable at the time of Sg.
What is the role of staging laparoscopy?

Show Answer

Staging laparoscopy at the time of Sg is not routinely warranted. Select pts with tumors >3 cm, tumors in the body/tail, equivocal CT findings of mets, or CA 19-9 >100 U/mL may benefit.
What imaging is indicated to assess for metastatic Dz?

Show Answer

CT chest with contrast is routinely performed for metastatic workup of PCA. PET-CT may be more sensitive for systemic Dz, but is not yet standard.
What is the significance of a postresection CA 19-9 >90 U/mL?

Show Answer

In **RTOG 9704,** 53 pts (14%) had CA 19-9 >90 U/mL, and only 2 of these pts survived up to 3 yrs.
What is the AJCC 8th edition (2017) T and N staging for PCA?

Show Answer

T1: tumor size ≤2 cm
T1a: ≤0.5 cm
T1b: >0.5 cm and <1
T1c: ≥1cm and ≤2 cm
T2: tumor size >2 cm and ≤4 cm
T3: Tumor size >4 cm
T4: celiac axis, SMA, or CHA involvement
N1: 1–3 regional nodes
N2: ≥4 regional nodes
What are the AJCC 8th edition (2017) stage groupings for PCA?

Show Answer

Stage 0: Tis
Stage IA: T1N0M0
Stage IB: T2N0M0
Stage IIA: T3N0M0
Stage IIB: T1–3N1M0
Stage III: T1–3N2, T4 Any N M0
Stage IV: Any T Any N M1
What is the stage of a PCA pt with positive cytology at time of laparoscopy?

Show Answer

Positive cytology is **stage IV** (M1).
Does the AJCC 8th edition (2017) TNM staging for ampullary, bile duct,

and duodenal cancer differ from PCA?

Show Answer

Yes.

TREATMENT/PROGNOSIS

What is the 5-yr OS for all stages of PCA?

Show Answer

5-yr OS is 7% for all stages of Dz combined.

What surgical procedure is required to resect a pancreatic head lesion?

Show Answer

Sg utilized for pancreatic head resection includes pylorus-preserving pancreaticoduodenectomy (PPPD) or **classic pancreaticoduodenectomy** (Whipple procedure).

What anastomoses are performed in the classic pancreaticoduodenectomy (Whipple)?

Show Answer

There are 3 anastomoses performed for the Whipple procedure:

- Pancreaticojejunostomy
- Choledochojejunostomy (hepaticojejunostomy)
- Gastrojejunostomy

What are the 4 most favorable prognostic factors after resection?

Show Answer

Most favorable prognostic factors after resection of PCA:

- Negative margins (R0)
- Low grade (G1)
- Small tumor size (<2 cm)

. N0 status

What is the modern MS for unresectable, margin– resected, and margin+ resected PCA pts?

Show Answer

The MS for PCA pts with the following surgeries in the era of adj and definitive CRT is:

. Unresectable ~13 mos
. Margin+ resection ~16–18 mos
. Margin− resection ~25 mos

What is the current mortality rate for pancreaticoduodenectomy?

Show Answer

At tertiary care centers with high throughput (min 15–20/yr), the mortality rate for pancreaticoduodenectomy is <4%.

What is the most feared complication for pancreaticoduodenectomy?

Show Answer

Anastamotic leaks are the most important complications after pancreaticoduodenectomy and can lead to peritonitis, abscess, autodigestion, hemorrhage, and delayed gastric emptying.

Is there a benefit to R1 or R2 resection over definitive CRT for PCA?

Show Answer

No. Retrospective evidence suggests that survival is similar b/t PCA pts who had R1 or R2 resection and definitive CRT. Therefore, planned resections should be done in pts where R0 resections are likely. Debulking Sg does not improve outcome over definitive CRT.

Should pts with resectable PCA undergo extended retroperitoneal lymphadenectomy?

Show Answer

No. Resectable PCA pts should not undergo an extended retroperitoneal lymphadenectomy. There is no survival benefit to extended lymphadenectomy by an RCT (5-yr 25% vs. 31%, NSS). (Riall TS et al., J Gastrointest Surg 2005)

Can definitive CRT replace surgical resection for resectable PCA?

Show Answer

No. Sg alone is sup to CRT alone for pts with resectable PCA per the Japanese PCA Study Group in an RCT of Sg alone vs. definitive CRT (50.4 Gy with continuous infusion (CI) 5-FU). The trial was stopped early d/t the benefit of Sg: MS was 12 mos vs. 9 mos, and 5-yr OS was 10% vs. 0%. (Doi R et al., Surg Today 2008)

What are the adj Tx options for a PCA pt s/p resection?

Show Answer

Adj Tx options after a pancreaticoduodenectomy:

- Adj gemcitabine **(CONKO-001)**
- Adj gemcitabine alone → 5-FU/RT→ gemcitabine alone **(RTOG 9704)**
- Adj 5-FU/RT **(GITSG 91–73)**; consider maintenance gemcitabine afterward
- Adj 5-FU → 5-FU/RT → 5-FU **(RTOG 9704)**
- Observation alone

What is the standard postop RT Tx volume, dose, and fractionation for PCA?

Show Answer

Standard adj RT volume includes tumor bed, anastomoses (pancreaticojejunostomy and choledochojejunostomy), and LN basin (peripancreatic, celiac, sup mesenteric artery, porta hepatis, and aortocaval).

The initial volume is treated to 45 Gy in 1.8 Gy/fx with a cone down to 50.4–54 Gy to the surgical bed depending on extent of resection. Keep max small bowel dose <51 Gy.
For pts with resected PCA, LF is the site of 1st failure for what % of pts treated with adj CRT? Distant failure as the 1st site?

Show Answer

Based on **RTOG 9704,** LF was site of 1st failure in 28% of PCA and distant failure was 1st site in 73%.
What U.S. study 1st reported a benefit of adj CRT vs. no additional Tx for resected PCA? Describe the arms of this study and the major results.

Show Answer

The GITSG 91–73 trial 1st reported benefit to adj CRT for PCA in 1985. All pts had R0 resections.

Standard arm: postop observation
Experimental arm: adj CRT using split-course RT to 40 Gy (2-wk break after 20 Gy) with intermittent bolus 5-FU → 2 full yrs of adj 5-FU alone
Improved MS (20 mos vs. 11 mos) and 2-yr OS (42% vs. 15%) in the adj CRT arm. (Kalser MH et al., Arch Surg 1985)

Did the EORTC 40891 study on PCA support or contest the benefit of adj CRT?

Show Answer

Support. The **EORTC 40891** trial used the same randomization as GITSG 91–73, except the Tx arm did not rcv maintenance adj 5-FU for 2 yrs. Median PFS was 17 mos (CRT) vs. 16 mos (observation), NSS; MS was 24 mos (CRT) vs. 19 mos (observation), NSS. For the subset of PCA pts, 5-yr OS was 20% (CRT) vs. 10% (observation) ($p = 0.09$) (Klinkenbijl JH et al., Ann Surg 1999). Of note, in addition to T1–2N0–1 PCA, 45% of pts had periampullary adenocarcinoma, which were excluded in GITSG 91–73, and

generally have better prognosis. Authors concluded that routine adj CRT was not warranted, although statistical reanalysis of this study found a significant survival benefit with adj therapy. (Garofalo MC et al., Ann Surg 2006)
Did the ESPAC-1 study on PCA support or contest the benefit of adj CRT?

Show Answer

Contest. ESPAC-1 included pts with grossly resected adenocarcinoma of the pancreas. The study used a 2 × 2 factorial design; Sg +/− CRT and +/− adj chemo. Adj CRT was similar to GITSG. Adj chemo was 6 mos of 5-FU. MS was 15 mos (CRT) vs. 16 mos (no CRT), NSS; OS was 20 mos (chemo) vs. 14 mos (no chemo) (p = 0.0005).

Criticisms: Physicians could randomize pts into 2 × 2 or directly into 1 of the 2 randomizations. “Background Tx” was allowed (i.e., observed pts may have rcvd chemo +/− RT). There was no central RT QA. (Neoptolemos JP et al., Lancet 2001) Note: Analysis of 2 × 2 subset suggests that CRT had a deleterious effect; 5-yr OS was 10% (CRT) vs. 20% (no CRT) (p = 0.05).

How does the presence of a +margin after resection for PCA influence the decision for adj CRT?

Show Answer

UK Clinical Trials Unit meta-analysis of 5 RCTs, including individual data from 4 RCTs, found that the **benefit of adj CRT was greater in R1 pts compared to R0 pts**, although the **difference was not SS**. Also, the benefit of adj chemo alone decreased in R1 pts compared to R0 pts, suggesting that CRT may have a more important role in R1 pts. (Butturini G et al., Arch Surg 2008) This is being examined in RTOG 0848, which randomizes postop pts, stratified by margin status, to either chemo alone or CRT after 5 cycles of induction chemo.

Which study supports the role for adj gemcitabine for resected PCA over best supportive care? What subset of pts were excluded from this trial?

Show Answer

CONKO-001 included T1–T4, N0–N1 pts in an RCT of observation vs. adj gemcitabine. Outcomes favored adj Tx: median DFS was 13 mos vs. 7 mos (SS). MS was 23 mos vs. 20 mos (SS), and 5-yr OS was 21% vs. 10% (SS), 10-yr OS was 12.2% vs. 7.7%. (Oettle H et al., JAMA 2013) Note: Pts with CA 19-9 >90 (2.5 × upper limit of normal [ULN]) were excluded from this trial.

What study compared adj 5-FU to gemcitabine following surgical resection?

Show Answer

ESPAC-3 showed an MS of 23 mos for pts treated with 5-FU (and folinic acid) vs. 23.6 mos for pts treated with gemcitabine (NSS). (Neoptolemos JP et al., JAMA 2010)

Did the study RTOG 9704 on PCA support or contest a benefit of gemcitabine-based adj CRT?

Show Answer

This is **controversial. RTOG 9704** randomized R0 and R1 PCA pts to CI 5-FU (250 mg/m^2/d) CRT (50.4 Gy) and pre- and post-CRT with either additional 5-FU or gemcitabine. Among all eligible pts, there were no differences. In a preplanned subset analysis of pts with pancreatic head tumors, trends favored gemcitabine: MS was 20.5 mos vs. 16.7 mos, and 3-yr OS was 31% vs. 22%, but results were NSS ($p = 0.09$). The 3-yr LR was significantly better for the gemcitabine arm (23% vs. 28%). Updated 2012 results showed significantly worse survival in pts with CA 19-9 >90 U/mL, positive nodes, & RT quality assurance protocol deviations. (Regine W et al., JAMA 2008; Berger AC et al., IJROBP 2012)

What is the Tx paradigm for borderline resectable PCA?

Show Answer

Borderline resectable PCA Tx paradigm: consider staging laparoscopy, stent placement if jaundice, and neoadj chemo +/− CRT → resection.
What neoadj regimen should be used for borderline resectable PCA?

Show Answer

There is **no standard neoadj Tx for PCA.** Use similar paradigms as for locally advanced cases: multi-agent chemo for at least 4 cycles f/b consideration of fluoropyrimidine-based CRT, e.g., (1) gemcitabine/Abraxane or FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) +/− fluoropyrimidine-based chemo/RT, with RT to 45–50.4 Gy in 1.8–2 Gy/fx or 30 Gy in 3 Gy/fx per the MDACC paradigm. (Breslin TM et al., Ann Surg Oncol 2001)
What is the Tx paradigm for locally advanced PCA?

Show Answer

Locally advanced unresectable PCA Tx paradigm: biliary stent (if jaundice) can be done 1st then based on KPS → (1) induction chemo → restage → CRT, (2) definitive CRT if not candidate for multi-agent chemo, or (3) chemo alone. CRT regimens typically involve 5-FU or gemcitabine. Chemo alone or induction chemo involves gemcitabine (poor KPS or unable to tolerate multiple agents), gemcitabine + Abraxane, FOLFIRINOX, or other combination in clinical study. Multi-agent chemo is preferred, and 4–6 cycles for induction chemo.
What is the role of regional LN RT with neoadj or definitive CRT for borderline resectable or locally advanced PCA?

Show Answer

LN irradiation is controversial in the neoadj or definitive setting. In this setting, some institutions trend toward using smaller fields that treat gross tumor plus a small margin (McGinn CJ et al., JCO 2001), while others have continued to treat LN in the definitive setting (Ben-Josef E et al., IJROBP

2004). Recent Alliance (A021501) & NRG (RTOG 1201) cooperative group clinical trial designs have not involved elective LN RTin the neoadj or definitive setting, respectively.
What is the evidence to support induction chemo prior to CRT in locally advanced PCA?

Show Answer

In a retrospective study of locally advanced PCA pts from MDACC, pts who rcvd induction gemcitabine f/b CRT had longer MS than pts that had initial CRT (12 mos vs. 8 mos). They hypothesize that induction chemo may select for pts that benefit from CRT. (Krishnan S et al., Cancer 2007)
What definitive CRT regimen should be used for locally advanced PCA?

Show Answer

Standard regimen for definitive CRT: 5-FU (CI 250 mg/m^2/d) + RT, with RT to 50–60 Gy in 1.8 Gy/fx or 30 Gy in 3 Gy/fx.
What study established the role of definitive CRT vs. RT alone in locally advanced PCA? What were the study arms and survival outcomes?

Show Answer

The **GITSG 9273** trial (pts enrolled in the 1970s). Arm 1: RT alone, split-course 60 Gy in 2 Gy/fx; arm 2: 5-FU + RT, split-course RT to 40 Gy in 2 Gy/fx; arm 3: 5-FU + RT, split-course RT to 60 Gy in 2 Gy/fx. All arms rcvd maintenance 5-FU × 2 yrs. MS favored the CRT arms: 5.3 mos (arm 1) vs. 9.7 mos (arm 2) vs. 9.3 mos (arm 3). 1-yr OS favored the CRT arms: 10% (arm 1) vs. 35% (arm 2) vs. 46% (arm 3). There were no statistical differences b/t the CRT arms. (Moertel CG et al., Cancer 1981)
What study suggests that gemcitabine alone may be sup to 5-FU–based CRT in locally advanced PCA? What were the study arms and survival outcomes?

Show Answer

FFCD/SFRO study (French). Arm 1: RT (60 Gy) + CI 5-FU + intermittent cisplatin → maintenance gemcitabine; arm 2: induction gemcitabine → maintenance gemcitabine. Upfront CRT was more toxic and had worse survival outcomes. MS was 8.6 mos vs. 13 mos, and 1-yr OS was 32% vs. 53%. Criticism: The upfront CRT was not standard and was very poorly tolerated. (Chauffert B et al., Ann Oncol 2008)
What study suggests that concurrent gemcitabine-based CRT is sup to gemcitabine alone for locally advanced PCA?

Show Answer

ECOG 4201, which closed early d/t slow accrual. 74 pts (71 evaluable). Arm 1: gemcitabine alone; arm 2: gemcitabine + RT, then gemcitabine alone. MS and 2-yr OS were better with CRT (11.1 mos vs. 9.2 mos and 12% vs. 4%, respectively). There were higher G4/5 toxicities with arm 2, but G3/4 toxicities were similar. (Loehrer PJ et al., JCO 2011)
What were the trial design, findings, and criticisms of the recent trial, LAP-07, regarding Tx for locally advanced PCA?

Show Answer

442 pts underwent 4 cycles of **induction chemo w/ gemcitabine +/– erlotinib f/b continued gem or RT+cape 800 mg bid**. RT involved 54 Gy/30 fx w/o prophylactic nodal irradiation. Erlotinib had trend to poorer survival (HR 1.19, p = 0.09). Only ~1/2 of pts underwent 2nd randomization. MS did not differ b/t the CRT (15.2 mos) vs. chemo (16.5 mos) groups (NSS). CRT associated with decreased with LRF (32% vs. 46%, p = 0.03) but increased DM (60% vs. 44%, p = 0.04). Toxicities were similar (except worse nausea with CRT), and there was increased time off therapy for the CRT group (6.1 vs. 3.7 mos, p = 0.02) (Hammel P et al., JAMA 2016). Criticism: use of single-agent chemo in the induction arm. Of note, QA revealed 68% RT plans had minor or major deviations, and 9% of pts randomized to CRT never rcvd RT.

What 2 regimens may have greater activity than gemcitabine alone in metastatic PCA?

Show Answer

FOLFIRINOX and **gemcitabine + Abraxane** both were sup to gemcitabine alone in 2 separate phase III RCTs in metastatic PCA. In a French study of 342 pts, FOLFIRINOX had an MS of 11.1 mos vs. 6.8 mos for gemcitabine and increased QOL despite increased G3/4 toxicities (Conroy T et al., NEJM 2011). The MPACT international study of 861 pts showed gemcitabine + Abraxane had MS of 8.5 mos vs. 6.7 mos for gemcitabine alone. (Von Hoff DD et al., NEJM 2013)

Estimate the MS and 1-yr OS for pts with locally advanced PCA at Dx, based on LAP-07.

Show Answer

Outcomes for locally advanced PCA: **MS was ~13 mos and 1-yr OS was ~50% based on LAP-07.**

In PCA pts, what are 3 Tx options for tumor-associated biliary obstruction?

Show Answer

Tx options for tumor-associated biliary obstruction:

- Endoscopic biliary stent
- Percutaneous biliary drainage with subsequent internalization
- Open biliary-enteric bypass

In PCA pts, what are 3 Tx options for tumor-associated gastric outlet obstruction?

Show Answer

Tx options for tumor-associated outlet obstruction:

- Gastrojejunostomy
- Enteral stent
- PEG tube

In PCA pts, what Tx should be considered for tumor-associated severe abdominal pain refractory to analgesic med?

Show Answer

Celiac plexus neurolysis is an effective option for Tx-refractory pain.

Radiation

Are there any data on stereotactic body radiotherapy (SBRT) for pancreatic cancer?

Show Answer

Several studies have evaluated SBRT for unresectable PCA. Early reports suggest excellent LC; however, a significant proportion of pts experience duodenal toxicity.

Stanford (Chang DT et al., Cancer 2009): 77 pts with unresectable PCA rcvd 25 Gy × 1 with CyberKnife SBRT. The 6- and 12-mo isolated LR rate was 5% and 5%, respectively. The PFS at 6 and 12 mos were 26% and 9%, respectively. The 1-yr OS was 21%. At 12 mos, the ≥G2 late toxicity was 25%, including 1 small bowel perforation (G4), 1 duodenal stricture (G3), and 3 gastric ulcers (G3).

Beth Israel Deaconess (Mahadevan A et al., IJROBP 2010): 36 pts with unresectable PCA rcvd 24–36 Gy CyberKnife SBRT in 3 fx. Gemcitabine was given after SBRT. LC rate was 78%, and MS was 14.3 mos. 39% developed ≥G2 toxicity (25% G2, 14% G3); including 3 pts with vomiting and dehydration (G3) and 2 pts with GI bleed (G3).

John Hopkins, MSKCC, Stanford (Herman J et al., Cancer 2014) 49 pts, rcvd 1 cycle gemcitabine, then 33 Gy in 5 fx, with 1-yr freedom from local progression (FFLP) 78%, MS 13.9 mos, with 11% grade 2 or more

toxicity, 1 G5 GI bleed, 1 G3 bleed, 1 G3 ulcer.

Is there a potential for dose escalation with the use of IMRT in pancreatic cancer?

Show Answer

Yes. A phase I–II trial of IMRT dose-escalation (50–60 Gy) **with concurrent gemcitabine** in 50 pts with unresectable PCA found dose-limiting toxicities in 11 pts, including duodenal bleed (3 pts) and perforation (1 pt). The recommended dose was 55 Gy, with an estimated 24% rate of dose-limiting toxicity (Ben-Josef E et al., IJROBP 2012). Single institution data from MDACC (Krishnan S et al., IJROBP 2016) found improved survival (MS 17.8 vs. 15 mos, p = 0.03) in pts with BED >70 Gy10 compared to biological effective dose (BED) ≤70 Gy10. No increased toxicity was seen in the higher-dose group. An example of BED 70 Gy10 would be 57.27 Gy in 25 fx.

Do Tx paradigms differ b/t pancreatic and periampullary adenocarcinoma?

Show Answer

Yes. Tx paradigms can differ b/t pancreatic vs. periampullary cancers. Consider observation for completely resected T1–T2, N0 ampulla of Vater carcinoma. Retrospective reviews suggest high OS (5-yr OS ~80%) with observation alone (Willett C et al., Surg Gynecol Obstet 1993). Otherwise, periampullary adenocarcinoma generally follows PCA paradigms, especially for T3–T4, poor histologic grade, LVSI/PNI (Krishnan S et al., IJROBP 2008), or node+ pts. (Zhou J et al., Radiother Oncol 2009)

FOLLOW-UP/TOXICITY

What are the expected acute and late RT toxicities associated with Tx of resected and unresectable PCA?

Show Answer

Acute toxicities: nausea, diarrhea, small bowel obstruction, weight loss,

anorexia, abdominal pain

Late toxicities: small bowel obstruction/stenosis/perforation, gastric/small bowel ulceration and/or bleeding, biliary stenosis obstruction, 2nd malignancies

What are duodenal toxicities related to fractionated RT or SBRT for PCA?

Show Answer

RT can induce duodenal injury: ulceration, bleeding, perforation, and fistula formation. These mostly occur in the 1st 12 mos after completing RT.

What is the typical f/u schedule after Tx of pancreatic cancer?

Show Answer

Pancreatic cancer f/u schedule after Tx: surveillance q3–6mos × 2 yrs, then q6–12mos. At each visit, perform full H&P for Sx assessment, and consider CA 19-9 levels, LFTs, and abdominal CT with contrast.

49

Hepatocellular Carcinoma

Updated by Dustin Boothe

BACKGROUND

What liver Dz is associated with hepatocellular carcinoma (HCC)?

Show Answer

Most HCCs develop in pts with cirrhosis from **liver parenchymal Dz.** Exposures and Dz that cause chronic hepatitis and cirrhosis are almost uniformly associated with HCC.

HCC is most common in what 2 regions in the world?

Show Answer

Most common regions for HCC:

- Asia (East > Southeast)
- Africa (middle > East > West)

Name 2 viruses associated with HCC.

Show Answer

Most important viral causes of HCC:

- Hepatitis B virus (HBV) (carrier state without associated cirrhosis is also a cause)
- Hepatitis C virus (HCV)

Name the 2 most important environmental exposures associated with

HCC.

Show Answer

Environmental exposures associated with HCC:

- Heavy ethanol consumption, which leads to cirrhosis
- Aflatoxin B, a mycotoxin that contaminates corn, soybeans, and peanuts, generally in sub-Saharan Africa and East and Southeast Asia

Name 3 hereditary conditions associated with HCC.

Show Answer

Relatively common hereditary conditions associated with HCC:

- Hemochromatosis
- α1-antitrypsin deficiency
- Wilson Dz

Is there a sex predilection for HCC?

Show Answer

Yes. Males are 3 times more likely to develop HCC.
Worldwide, where does HCC rank as a cause of cancer death?

Show Answer

Worldwide, HCC is the **4th leading cause of cancer death** (3rd for men), but rates vary dramatically by region.
HCC incidence peaks in what decade of life?

Show Answer

HCC incidence peaks in the **6th decade** of life.
What is the most common clinical presentation of HCC?

Show Answer

The most common clinical presentation of HCC is **rising AFP in the setting**

of worsening pre-existing liver Dz.

Who should be screened for HCC and how?

Show Answer

Pts with cirrhosis, hepatitis B carrier state, or nonalcoholic steatohepatitis should be screened for HCC. Screen with **AFP and liver US** q6–12 mos.

Do most pts with HCC present with localized or metastatic Dz?

Show Answer

90% of HCC pts present with **localized Dz.**

In HCC, what are the most common sites of mets spread?

Show Answer

HCC most commonly metastasizes to **intra-abdominal LNs and lungs.** Less common sites of mets include bone, brain, and adrenal glands.

WORKUP/STAGING

What is the workup of suspected HCC?

Show Answer

Suspected HCC workup: H&P, AFP, CBC, CMP with LDH, LFTs, PT/INR, hepatitis panel (HBV/HCV studies), triphasic CT abdomen or MRI liver (late hepatic arterial, portal venous, and delayed phases), chest CT, and percutaneous Bx if necessary

For a pt with suspected HCC, when is a Bx unnecessary to establish the Dx?

Show Answer

In HCC, a Bx is not necessary to establish Dx if it has imaging characteristics consistent with HCC (e.g., liver imaging reporting and data system [LI-RADS] [most common], Organ Procurement and Transplantation Network

[OPTN], American Association for the Study of Liver Diseases [AASLD]) based on factors including size, arterial phase hyperenhancement, venous phase washout appearance and capsule appearance, and threshold growth.
In what HCC variant is the AFP level often normal?

Show Answer

AFP levels are normal in the majority of pts with fibrolamellar carcinoma (FLC), a variant of HCC. Note that some authors argue that FLC is not truly a variant of HCC b/c it usually occurs in the absence of cirrhosis, and the better prognosis has been attributed to a lack of liver Dz as pts do not respond any differently to therapies vs. typical HCC. (Liu S et al., Am J Gastroenterol 2009)
What are the characteristic triphasic CT and MRI findings of an HCC liver lesion?

Show Answer

On dynamic CT: early phase, tumor is seen as hyperintense b/c of increased vascularity. In the delayed phase, the tumor is hypodense d/t contrast washout.

On MRI T_1-weighted images: low-signal intensity and intermediate-signal intensity on T2; HCC appears hypervascular, has increased T2 signal, and shows venous invasion

What is the AJCC 8th edition (2017) TNM staging for HCC?

Show Answer

Note: Bold text highlights 8th edition changes.

T1a: solitary tumor ≤2 cm
T1b: solitary tumor >2 cm without vascular invasion
T2: solitary tumor >2 cm with vascular invasion, or multiple tumors ≤5 cm
T3: multiple tumors, at least 1 of which is >5 cm

T4: Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

N1: regional LN mets (hilar, hepatoduodenal ligament, **inf phrenic LN** [no longer classified as M1], and caval LNs)

M1: DMs

What are the AJCC 8th edition (2017) stage groupings for HCC?

Show Answer

Note: Bold text highlights 8th edition changes.

Stage IA: T1aN0
Stage IB: T1bN0
Stage II: T2N0
Stage IIIA: T3N0
Stage IIIB: T4N0
Stage IVA: Any T N1 M0
Stage IVB: Any T Any N M1

Name 3 systems (other than AJCC) used to stage HCC internationally.

Show Answer

Staging systems for HCC commonly used outside the United States: Applicability of each of these staging systems appears to depend on the Tx method.

- BCLC (Barcelona Clinic Liver Cancer)
- CLIP (Cancer of the Liver Italian Program)
- JIS score (Japanese Integrated Staging)

What does a Child–Pugh score predict in pts with chronic liver Dz?

Show Answer

The Child–Pugh score was originally used to estimate operative mortality risk but is currently used to **assess OS prognosis** for pts with liver failure. Based on cumulative scores, pts are divided into class A, B, or C, with C having the poorest prognosis.
What are the 5 components of the Child–Pugh score in chronic liver Dz?

Show Answer

Components of the Child–Pugh score include **total bilirubin, serum albumin, INR, degree of ascites, and degree of hepatic encephalopathy.**
What does the acronym MELD represent, and what does the MELD score predict in chronic liver Dz?

Show Answer

MELD stands for **M**odel for **E**nd-Stage **L**iver **D**isease, initially developed to predict the 3-mo mortality after a transjugular intrahepatic portosystemic shunt procedure. Now, it is **used to assess severity of chronic liver Dz and the 3-mo OS without a liver transplant.** The MELD score is highly correlated with the Child–Pugh score.
What are the 3 components of the MELD score in chronic liver Dz?

Show Answer

Components of the MELD score include **total bilirubin, INR, and Cr.**

TREATMENT/PROGNOSIS

What 3 features of the HCC pt and the pt's tumors define the appropriate Tx paradigm?

Show Answer

The 3 features that define the Tx options for a pt with HCC are whether the pt (a) has metastatic Dz, (b) has resectable localized tumor, and (c) is medically fit for major Sg.
What are the only 2 curative Tx options for HCC?

Show Answer

The only 2 established curative Tx options for HCC are **partial hepatectomy to –margins and liver transplantation,** with 5-yr OS for pts within Milan criteria around 50%–65% and 65% for each Tx, respectively. Potentially curative RT Tx with hypofractionated photons and proton therapy are being explored.

Partial hepatectomy is an option in which HCC pts?

Show Answer

Partial hepatectomy is a potentially curative option in HCC pts who are medically fit for Sg, have a solitary mass without major vascular involvement, are Child–Turcotte–Pugh class A with mild or moderate portal hypertension, and have adequate future liver remnant (if no cirrhosis, require >20% of liver; if Child–Pugh A cirrhosis, require >30% of liver). Attempt at curative resection in HCC pts with multifocal tumors and major vascular invasion is controversial.

What % of HCC pts will have an LR after partial hepatectomy after 5 yrs?

Show Answer

~75% of pts with HCC will have an LR after 5 yrs (new primary or local spread). (Mathurin P et al., Aliment Pharmacal Ther 2003)

What criteria are used to determine if liver transplant is an option for a pt with HCC?

Show Answer

The **United Network for Organ Sharing (UNOS) criteria** are used to determine if liver transplantation is appropriate in a pt with HCC. Per the UNOS criteria, transplantation is an option for medically fit pts with a **single tumor ≤5 cm** or **2–3 tumors ≤3 cm.**

What are the Tx options for an HCC pt with localized Dz who is medically unfit for major Sg?

Show Answer

Tx options for an HCC pt with localized Dz but who is unfit for major Sg include:

- Sorafenib for Child–Pugh A and some B pts
- Tumor ablation procedure (radio frequency, cryoablation, microwave, percutaneous alcohol injection)
- Tumor embolization procedure (chemoembolization [aka transarterial chemoembolization, or TACE], drug-eluting bead trans-arterial chemoembolization (DEB-TACE), bland embolization, radioembolization)
- EBRT, including stereotactic body radiation therapy (SBRT) and proton techniques

In the United States, what radioembolization isotope is most commonly used for HCC?

Show Answer

In the United States, the most commonly used isotope for radioembolization in HCC pts is **yttrium-90,** a pure β emitter.

What are the 2 forms of microspheres used for radioembolization in HCC pts, and what is the difference b/t them?

Show Answer

Microspheres used for radioembolization in HCC pts:

- TheraSphere (glass microspheres)
- Selective internal radiation (SIR)-Spheres (resin microspheres)

Estimate the response rate of HCC to yttrium-90–labeled microspheres.

Show Answer

The response rate of HCC to yttrium-90–labeled microspheres **varies from 50%–80%** depending on the definition of response used.

Is portal vein thrombosis a contraindication to catheter-based therapies?

Show Answer

Portal vein thrombosis is a relative contraindication to TACE, but not radioembolization.

What are the EBRT options with either medically inoperable or technically unresectable HCC?

Show Answer

A number of EBRT options have been used for unresectable or medically inoperable HCC pts:

- Whole liver RT for palliation (21 Gy in 7 fx, Borgelt et al., IJROBP 1981)
- High-dose RT (>50 Gy) with standard fractionation
- Hyperfractionated RT with chemosensitization
- Hypofractionated SBRT
- Hypofractionated proton therapy

What are the Tx options for an HCC pt with metastatic Dz?

Show Answer

The only standard active Tx option for metastatic HCC is **sorafenib, a small molecule TKI that acts against c-raf and platelet-derived growth factor-alpha (PDGF-α)**. HCC typically does not respond to traditional cytotoxic chemo.

What is the MS in metastatic or inoperable HCC pts treated with sorafenib alone?

Show Answer

The MS of metastatic or inoperable HCC pts treated with sorafenib alone is **10.7 mos vs. 7.9 mos** ($p = 0.0058$) **in pts treated with placebo.** No significant difference in time to symptomatic progression (4.1 mos vs. 4.9 mos). (Llovet JM et al., NEJM 2008)

What are the dose and results of SBRT for HCC?

Show Answer

In a sequential phases I–II trial of SBRT for HCC, 102 pts with Child–Pugh class A Dz with **at least 700 cc of non-HCC liver** were treated with **SBRT** (24–54 Gy in 6 fx; median 36 Gy). Median OS was 17 mos with 87% LC at 1 yr. 30% experienced grade ≥3 toxicity. (Bujold A et al., JCO 2013)

Another single institutional experience utilized 12.5 Gy × 3 (<4 cm and no cirrhosis) or 5 Gy × 5 or 10 Gy × 3 (≥4 cm with cirrhosis) with LC rates of 94% and 82% in 1 and 2 yrs, respectively. (Mendez Romero A et al., Acta Oncol 2006)

For HCC, what is the normal volume of liver (liver minus GTV) required to be eligible for stereotactic ablative radiotherapy (SABR)?

Show Answer

For HCC, the normal volume of liver (liver minus GTV) required to be eligible for SABR is **≥700 ccs** (RTOG 1112).

Is there a role for sorafenib with radiotherapy?

Show Answer

Phase I data exist regarding the safety and tolerability of sorafenib with RT and suggests that **sorafenib exacerbates RT toxicity (**Brade AM et al., IJROBP 2016). RTOG 1112 is a phase III study currently randomizing pts with Child–Turcotte–Pugh class A and BCLC b/c HCC to sorafenib alone vs. sequential SBRT f/b sorafenib.

What is the role for proton beam in the management of unresectable HCC?

Show Answer

Potentially delivering high hypofractionated RT dose safely with excellent safety and tumor control outcomes

A Japanese prospective study enrolled 51 pts with tumors >2 cm from the porta hepatis and GI tract and treated them with **66 CGEs in 10 fx. LC was 94.5%** at 3 yrs and 87.8% at 5 yrs. There were minor grade 1 acute adverse events, and only 3 pts were rated higher than grade 2. (Fukumitsu N et al., IJROBP 2009)

A phase II single arm multi-institutional study in 92 pts with HCC or intrahepatic cholangiocarcinoma (ICC), with Child–Pugh A or B, rcvd median dose **58 CGE/15 fx**. Median size 5.0 cm (1.9–12 cm) for HCC and 6.0 cm (2.2–10.9 cm) for ICC. LC at 2 yrs 95% HCC and 94% ICC, and OS 63.2% HCC and 46.5% ICC. (Hong TS et al., JCO 2016)

What studies have compared RT to other modalities for unresectable HCC?

Show Answer

An RCT conducted at Loma Linda **compared 70.2** CGEs of **proton** beam radiotherapy in 15 fx **to TACE** in pts with HCC meeting transplantation criteria. Interim results of 69 pts revealed equivalent survival, with a 2-yr OS of 59%. There was a trend toward improved LC (88% vs. 45%, p = 0.06) and PFS (48% vs. 31%, p = 0.06) with protons. (Bush DA et al., IJROBP 2016)

A meta-analysis of 25 trials **comparing TACE alone to TACE plus radiotherapy** showed significantly improved 1-yr OS in the TACE plus radiotherapy group (OR 1.36, 95% CI, 1.19–1.54). The OS benefit of radiotherapy was persistent at 5 yrs (OR 3.98, 95% CI, 1.86–8.51). (Huo YR et al., JAMA Onc 2015)

Retrospective analysis of 224 pts at the University of Michigan **compared SBRT and radiofrequency ablation (RFA).** Those receiving SBRT had improved LC at 12 mos (97.4% vs. 83.6%) and 2 yrs (83.8% vs. 80.2%). For tumors ≥2 cm, RFA was associated with decreased LC (HR 3.35, p = 0.02). (Wahl DR et al., JCO 2016)

Is there a QOL benefit to palliative radiotherapy for HCC?

Show Answer

A phase II study assessed the benefit of **8 Gy × 1** for pts with HCC or liver mets unsuitable for or refractory to standard therapies. Pts were **premedicated with granisetron 1 mg and dex 2 mg ˜1 hr before RT.** At 1 mo, 48% were noted to have an improvement in Sx (FACT-Hep 29%, EORTC QLQ-C30 functional 11%–21%, Sx 11%–50%). (Soliman H et al., JCO 2013)

FOLLOW-UP/TOXICITY

What are the components of the clinical syndrome of classic radiation-induced liver disease (RILD)?

Show Answer

Signs and Sx of RILD include fatigue, RUQ pain, ascites, anicteric hepatomegaly, and elevated liver enzymes (especially alk phos which occurs 2 wks–3 mos following RT).

What is the histologic hallmark of RILD?

Show Answer

The pathologic hallmark of RILD is **veno-occlusive Dz with venous congestion of the central portion of the liver lobule.** Hepatocyte atrophy and fibrosis eventually develop.

What parameters are predictive of liver function decline following 6 fx SBRT in Child–Pugh A pts?

Show Answer

Elevated baseline Child–Pugh score, low Plt, elevated mean liver dose and liver D800cc. (Velec et al., IJROBP 2017)

50

Biliary Tree and Gallbladder Cancer

Updated by Ned L. Williams

BACKGROUND

What are the 3 anatomic subtypes of biliary cancer (CC)?

Show Answer

CC is grouped into **intrahepatic** (10%), **perihilar/Klatskin** (60%), and **extrahepatic** (30%) subtypes. Klatskin tumors involve the hepatic duct bifurcation.

How is GB cancer distinct from CC?

Show Answer

GB cancer has unique epidemiology, presentation, staging, and surgical Tx.

What are major risk factors for CC?

Show Answer

Primary sclerosing cholangitis, liver flukes (especially in Southeast Asia), and **choledochal cysts** increase the risk for CC by causing bile duct inflammation.

What is the major risk factor for GB cancer?

Show Answer

Cholelithiasis increases the risk for GB cancer (presumably via chronic inflammation).

What is the annual incidence/mortality of CC and GB cancer in the United States?

Show Answer

There are **~11,000/yr new cases** of CC and GB cancer in the United States and **~3,600/yr deaths.**

What is the histology of most CC and GB cancer?

Show Answer

Most CC and GB cancers are **adenocarcinomas.** They are difficult to distinguish from pancreatic adenocarcinoma on histopathology alone.

What less common path subtype of GB cancer and CC has a better prognosis?

Show Answer

Papillary adenocarcinoma is associated with improved prognosis compared to other adenocarcinomas of the biliary tree and GB.

What are the incidence and major sites of DM for CC and GB cancer?

Show Answer

30%–50% of CC and 40%–50% of GB cancer present with DM, most commonly **to liver, peritoneum, and lung.**

What is the MS for unresectable or metastatic Dz?

Show Answer

MS is <6 mos for unresectable or metastatic CC and GB cancer.

What is the incidence of LN mets in resectable CC and GB cancer?

Show Answer

30%–50% of hilar and extrahepatic cholangiocarcinoma (EHCC) have LN mets at resection, but lower for intrahepatic cholangiocarcinoma (IHCC).

40%–50% of GB cancer have LN mets at resection.

What is the LN drainage for hilar or EHCC?

Show Answer

Pericholedochal → portal vein LNs → common hepatic artery LNs → pancreaticoduodenal LNs → celiac axis/SMA LNs → aortocaval LNs. Drainage does not ascend toward hepatic hilum.

How are LN mets different for IHCC?

Show Answer

IHCC has a lower rate of LN mets than hilar or EHCC.

What is the most common route of spread for GB cancer and CC?

Show Answer

GB cancer and CC most commonly spread by **direct extension** (to the liver for GB cancer and along the biliary tree for CC).

What is the most common presenting Sx for CC? GB cancer?

Show Answer

Painless jaundice is the most common presenting Sx of CC. **Biliary colic** and chronic cholecystitis are the most common presenting Sx of GB cancer.

How is GB cancer most commonly diagnosed?

Show Answer

GB cancer is most often incidentally diagnosed at **cholecystectomy** for presumed benign Dz.

What is a common and deadly complication of locally advanced Dz?

Show Answer

Biliary obstruction and **sepsis** is a common complication of poorly controlled locoregional Dz.

WORKUP/STAGING

What initial labs should be sent if suspecting CC or GB cancer?

Show Answer

Bilirubin, alk phos, aspartate aminotransferase (AST), and alanine transaminase (ALT) (can often be normal); γ-glutamyl transpeptidase, CEA, and CA 19-9 are particularly helpful in CC or GB cancer.
In what pts is CA 19-9 less reliable?

Show Answer

Pts without Lewis blood group antigen (10% of population) do not have CA 19-9. **Hyperbilirubinemia** can decrease specificity and accuracy of CA 19-9.
What initial imaging is used for suspected CC and GB cancer?

Show Answer

RUQ US, contrast CT (preferably multiphase), and MRCP are typically performed for suspected CC or GB cancer.
On contrast-enhanced CT, how can hepatocellular carcinoma (HCC) and IHCC be distinguished?

Show Answer

On contrast-enhanced CT of the liver, HCC usually enhances during the arterial phase, while IHCC may show **delayed enhancement.**
What is the imaging study of choice for EHCC?

Show Answer

MRCP is the imaging study of choice for EHCC, as it has improved the ability to define tumor extent and LN involvement.
What invasive imaging strategies are available?

Show Answer

ERCP and percutaneous transhepatic cholangiography (PTC) can help image obstruction, but MRCP/CT is preferred.

How is a pathologic Dx obtained for CC?

Show Answer

For resectable pts without obstruction, pathology can be obtained at Sg. For unresectable pts or pts with obstruction requiring stenting, **duct brushings** can be obtained at ERCP, or **Bx** can be done at time of PTC or EUS.
How is a pathologic Dx obtained for GB cancer?

Show Answer

Definitive resection is the diagnostic approach if GB cancer is suspected. **Bile cytology (low yield) or percutaneous Bx** can be performed in unresectable pts.
When is ERCP- or PTC-based stenting indicated prior to Sg?

Show Answer

If bilirubin is elevated (i.e., >10–15), ERCP- or PTC-guided stents are placed to decompress obstruction and allow liver recovery prior to Sg.
In addition to locoregional imaging, what staging imaging is recommended for GB cancer and CC?

Show Answer

In addition to locoregional imaging, staging for GB cancer and CC should include **CT chest.**
What staging procedure is recommended at the beginning of Sg for GB cancer or CC?

Show Answer

Staging laparoscopy is generally recommended at the beginning of Sg for GB cancer or CC to r/o peritoneal dissemination.
How should tumors arising from mid common bile duct (CBD) be staged?

Show Answer

These EHCCs are exceedingly rare, but they are **staged as distal CCs**.

What is the AJCC 8th edition (2017) T staging for IHCC (changes from 7th edition are in bold for all staging questions)?

Show Answer

Tis: carcinoma in situ

T1a: solitary tumor ≤5 cm without vascular invasion

T1b: solitary tumor >5 cm without vascular invasion

T2: solitary tumor with intrahepatic vascular invasion OR multiple tumors with or without vascular invasion

T3: tumor perforating visceral peritoneum

T4: tumor involving local extrahepatic structures by direct invasion

What is the AJCC 8th edition (2017) T staging for perihilar CC?

Show Answer

Tis: carcinoma in situ/**high-grade dysplasia**

T1: tumor confined to bile duct, with extension up to muscle layer or fibrous tissue

T2a: tumor invades beyond bile duct wall to surrounding fat

T2b: tumor invades hepatic parenchyma

T3: tumor invades unilat branches of portal vein (right or left) or hepatic artery (right or left)

T4: tumor invades any of the following: main portal vein or bilat branches, common hepatic artery, or unilat 2_{nd}-order biliary radicals with contralat portal vein or hepatic artery involvement

What is the AJCC 8th edition (2017) T staging for distal bile duct CC?

Show Answer

Tis: carcinoma in situ/**high-grade dysplasia**

T1: tumor invades the bile duct wall to a depth <5 mm

T2: tumor invades the bile duct wall to a depth 5–12 mm

T3: tumor invades the bile duct wall to a depth >12 mm
T4: tumor invades celiac axis, SMA, **and/or common hepatic artery**
What is the AJCC 8th edition (2017) T staging for GB cancer?

Show Answer

The GB and cystic duct are included in this current classification:

Tis: carcinoma in situ
T1a: tumor invades lamina propria
T1b: tumor invades the muscular layer
T2a: tumor invades perimuscular connective tissue **on the peritoneal side, without involvement of the serosa (visceral peritoneum)**
T2b: tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3: tumor perforates serosa (visceral peritoneum) and/or directly invades liver and/or invades 1 adjacent organ/structure (stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts)
T4: tumor invades main portal vein, hepatic artery, or multiple extrahepatic organs/structures
What is the AJCC 8th edition (2017) N classification for IHCC?

Show Answer

N0: no regional LN
N1: regional LN mets present
What is the AJCC 8th edition (2017) N classification for perihilar CC, distal bile duct CC, and GB cancer?

Show Answer

Regional LNs differ by anatomic site of primary tumor as follows: perihilar: hilar, cystic duct, choledochal (i.e., CBD), portal vein, hepatic artery, post pancreaticoduodenal; distal bile duct: CBD, hepatic artery, post and ant pancreaticoduodenal, and right lat wall of SMA; GB: CBD,

hepatic artery, portal vein, and cystic duct.

N0: no regional LN
N1: 1–3 regional LN mets present
N2: ≥4 regional LN mets present
What are the AJCC 8th edition (2017) groupings for IHCC?

Show Answer

Stage 0: TisN0
Stage IA: T1aN0M0
Stage IB: T1bN0M0
Stage II: T2N0M0
Stage IIIA: T3N0M0
Stage IIIB: T4N0M0 or Any T N1M0
Stage IV: Any T Any N M1
What are the AJCC 8th edition (2017) groupings for perihilar CC?

Show Answer

Stage 0: TisN0
Stage I: T1N0M0
Stage II: T2a–b N0M0
Stage IIIA: T3N0M0
Stage IIIB: T4N0M0
Stage IIIC: Any T N1M0
Stage IVA: Any T N2M0
Stage IVB: Any T Any N M1
What are the AJCC 8th edition (2017) groupings for distal bile duct CC?

Show Answer

Stage 0: TisN0
Stage I: T1N0M0
Stage IIA: T1N1M0 or T2N0M0

Stage IIB: T2N1M0 or T3N0–1M0
Stage IIIA: T1–3N2M0
Stage IIIB: T4 Any N M0
Stage IV: Any T Any N M1
What are the AJCC 8th edition (2017) groupings for GB cancer?

Show Answer

Stage 0: TisN0
Stage I: T1N0M0
Stage IIA: T2aN0M0
Stage IIB: T2bN0M0
Stage IIIA: T3N0M0
Stage IIIB: T1–3N1M0
Stage IVA: T4N0–1M0
Stage IVB: Any T N2M0 or Any T Any N M1

TREATMENT/PROGNOSIS

What % of CC and GB cancers are potentially resectable Dz at presentation?

Show Answer

Intrahepatic: 30%–90%
Hilar: ~50%
Distal extrahepatic: 80%–90%
GB cancer: 10%–30% of preoperatively diagnosed pts (most are incidentally diagnosed)
What is the classification system used to determine resectability of hilar CC?

Show Answer

Bismuth classification; **type IV is unresectable**

Type I/II: involving CBD without involving left/right hepatic ducts
Type III: involving either left or right hepatic duct in addition to CBD
Type IV: involves both left and right hepatic ducts
What is the surgical approach for each subtype of CC and GB cancer?

Show Answer

The surgical approach depends on site:

Intrahepatic: usually requires a lobectomy.
Hilar: at least lobectomy, resection of extrahepatic bile duct, roux-en-Y hepaticojejunostomy, and LN staging.
Distal extrahepatic: pancreaticoduodenectomy (Whipple) with LN staging
GB cancer: extended cholecystectomy with LN staging
When is a routine cholecystectomy sufficient Sg for an incidentally diagnosed GB cancer?

Show Answer

Following cholecystectomy for presumed benign Dz, **pts with T1a** (not beyond the lamina propria) GB cancer do not require a 2nd oncologic resection. 5-yr OS rates approach 100%.
How is an extended cholecystectomy different from a routine cholecystectomy?

Show Answer

Extended cholecystectomy should include en bloc resection of GB, liver segments IVb and V, and regional LN dissection.
What 2nd Sg should be performed after ≥T1b GB cancer is discovered on cholecystectomy?

Show Answer

After cholecystectomy for presumed benign Dz, pts with incidental ≥T1b GB cancer require **radical re-resection of the GB bed (2-cm margins), regional**

nodes, and port sites.
Is liver transplantation more appropriate for IHCC or for EHCC?

Show Answer

Liver transplantation is generally contraindicated for IHCC (d/t poor outcomes); transplantation shows promise in well-selected, early-stage, hilar/**extrahepatic** Dz. (Rea DJ et al., Ann Surg 2005)
What is the 5-yr survival for pts after resection +/- RT or CRT?

Show Answer

IHCC: 17%–40% (MS 26–37 mos)
Hilar CC: 10%–35% (MS 14–37 mos)
Distal EHCC: 23%–50% (MS 18–36 mos)
GB cancer (T3–T4): 0%–45% (MS 23–58 mos)
What prospective data exist supporting adj CRT in CC or GB cancer?

Show Answer

Adj **Gem + cape** × 4 cycles f/b **concurrent cape + EBRT** to 45 Gy to LN and 54–59.4 Gy to tumor bed resulted in MS of 35 mos in the SWOG 0809 phase II trial of pT2–4 or N+ EHCC and GB cancer. (Ben-Josef E et al., JCO 2015)
What is the recommended adj Tx for localized GB cancer?

Show Answer

Acceptable options for R0 resections include observation, 5-FU–based CRT, 5-FU or gemcitabine-based chemo alone, or clinical trial enrollment. Retrospective series and meta-analyses suggest that **adj CRT or chemo alone** may benefit resected GB cancer pts. Pts with **N+, R1, or > stage I pts deriving the most benefit**. (Kresl JJ et al., IJROBP 2002; Ben-David MA et al., IJROBP 2006; Czito BG et al., IJROBP 2005; Yu JB et al., JCO 2008; Gold DJ et al., IJROBP 2009; Horgan AM et al., JCO 2012; Yamanaka K et al., Int JCO 2015; Ma N et al., BMC Cancer 2015; McNamara MG et al., Am

JCO 2015)
What is the Tx approach for localized, unresectable GB cancer?

Show Answer

The approach is similar to unresectable pancreatic cancer: a combination of systemic chemo alone and/or CRT. Gemcitabine and cisplatin is the reference systemic regimen.
What is the recommended adj Tx for localized, resectable CC with good PS?

Show Answer

Single-institution series suggest that **5-FU or gemcitabine-based CRT** is an appropriate adj Tx for localized resectable CC. (Hughes MA et al., IJROBP 2007; Nelson JW et al., IJROBP 2009; Shinohara T et al., IJROBP 2008; Kim TH et al., IJROBP 2011) This is also appropriate for unresectable CC. (Pitt HA et al., Ann Surg 1995)
Does neoadj CRT improve survival in biliary cancer?

Show Answer

Prospectively collected single institution retrospective data suggest NA **gemcitabine** × 3 cycles and **50–60 Gy** (2 Gy/fx) **improves 3-yr RFS** (78% vs. 58%, p = 0.02) **and OS** (p = 0.002, HR 0.35) compared to Sg alone. (Kobayashi S et al., Eur J Surg Oncol 2017)
What is the recommended Tx for localized, unresectable CC?

Show Answer

A **combination of chemo alone and/or CRT** is recommended for definitive Tx of unresectable CC. (Urego M et al., IJROBP 1999; Leong E et al., J GI Cancer 2012; Morganti AG et al., IJROBP 2000; Crane CH et al., IJROBP 2002; Ben-David MA et al., IJROBP 2006; Tao R et al., JCO 2016; Hong TS et al., JCO 2016)

Gem + cisplatin is sup to gemcitabine alone in a phase III RCT (ABC-02) of

locally advanced or metastatic CC or GB cancer (Valle J et al., NEJM 2010), with MS 11.7 mos vs. 8.1 mos.

What evidence supports hypofractionated RT or stereotactic body radiotherapy (SBRT) in unresectable CC?

Show Answer

Phase II data show **2-yr LC of 94.1%** for IHCC treated to **67.5 Gy in 15 fx** (Hong TS et al., JCO 2016). Retrospective data suggest an **MS of 30 mos and 3-yr OS of 73%** vs. 38% when treating with hypofractionated or SBRT to a dose generating a **biologic effective dose of >80.5 Gy_{10}** (3–30 fx, 35–100 Gy). (Tao R et al., JCO 2016)

Define target structures and doses for adj Tx for GB, hilar & EHCC.

Show Answer

For resected GB, hilar and EHCC, SWOG S0809 defined the CTV by the **LN basin** (initial volume, **45 Gy** in 1.8 Gy/fx) and **surgical bed** (boost volume, **9 Gy for R0 & up to 14.4 Gy for R1**). An SIB was allowed with 52.5–55 Gy in 25 fx. Regional basins were defined as retropancreaticoduodenal, celiac, and portal vein nodes for all pts; consider including regional LN basins by site as defined above in the 18th question under workup/staging.

Define target structures and doses for adj Tx for IHCC cancer.

Show Answer

Same as above, except **for adj IHCC regional LN basin is dependent on tumor location.** Left sided: inf phrenic, hilar (pericholedochal, hepatic artery, portal vein, and cystic duct), and gastrohepatic. Right sided: hilar, periduodenal, and peripancreatic LN basin may be limited to pericholedochal LNs if LND was negative at Sg.

What is the target and dose for definitive RT of CC and GB cancer?

Show Answer

For hilar/EHCC, the CTV includes the gross Dz + margin and the LN basin (controversial). **For IHCC and GB cancer**, the CTV includes the gross Dz + margin only. Gross Dz is treated to the highest dose possible, considering OARs, usually ~60 Gy in 1.8–2 Gy/fx.

What are the transarterial Tx approaches for CC and in which Dz subset have they been utilized?

Show Answer

Transarterial embolization, chemoembolization, and radioembolization have been studied in unresectable IHCC. A large retrospective study examined these modalities in 198 pts with unresectable IHCC (Hyder O et al., Ann Surg Oncol 2013). MS was 13.2 mos and did not differ based on therapy.

Which vessel is used to radioembolize liver tumors and why?

Show Answer

The **hepatic artery** is used for embolization because it is the major blood supply to liver tumors, unlike normal liver tissue, which derives its supply primarily from the portal vein.

What is the most used radioisotope for radioembolization in CC? What are its properties?

Show Answer

Yttrium-90-labeled microspheres made of glass or resin are used for radioembolization. Yttrium-90 undergoes **a-decay,** with a half-life of 64 hrs (2.7 days).

FOLLOW-UP/TOXICITY

For issues related to toxicity, please refer to the Hepatocellular Carcinoma chapter.

51

Colorectal and Small Bowel Cancer

Updated by Stacey Scheick and Andrew Orton

BACKGROUND

What is the incidence of rectal cancer in the United States?

Show Answer

34,000 cases/yr of rectal cancer in the United States.

What is the median age for rectal cancer?

Show Answer

The median age for rectal cancer is the **7th decade** of life.

What is the incidence of colon cancer in the United States?

Show Answer

The incidence of colon cancer in the United States is 180,000 cases/yr and is the **#2 cause of cancer deaths in the United States** after lung cancer.

What is the median age for sporadic colon cancer?

Show Answer

The median age for sporadic colon cancer is **63 yrs.**

What is the sup/cranial extent of the rectum, and how long is it?

Show Answer

The rectum begins at **S3** and is ~**15 cm** long.

What are the most common sites of mets in rectal cancer?

Show Answer

Rectal cancer metastasizes mostly to the **liver** (via the sup rectal vein) and next the lung (via the mid and inf rectal veins).

Where in the GI tract does small bowel cancer most frequently arise?

Show Answer

Small bowel cancer arises most frequently in the **duodenum** (duodenum > jejunum > ileum).

What type of adenomas are more likely to progress to invasive rectal cancer?

Show Answer

Villous adenomas are more likely to progress to invasive rectal cancer (than tubular adenomas).

How are avg-risk individuals defined as far as colorectal cancer is concerned?

Show Answer

Avg-risk colorectal individuals are ≥**50 yo asymptomatic pts without a family Hx** of colorectal cancer.

What are the colorectal cancer screening options for avg-risk individuals?

Show Answer

Colonoscopy (q10yrs), fecal occult blood test (q1yr), and sigmoidoscopy (q5yrs) or double-contrast barium enema (q5yrs) are the colorectal screening options for avg-risk individuals.

How frequently should individuals with inflammatory bowel disease (IBD) have a screening colonoscopy?

Show Answer

Individuals with IBD should undergo a screening colonoscopy **q1–2yrs.**

How frequently should individuals with a family Hx of colorectal cancer have a screening colonoscopy? When should screening begin for such individuals?

Show Answer

Individuals with a family Hx of colorectal cancer should have a colonoscopy **q1–5yrs** and should begin at **age 40 yrs or 10 yrs prior to the earliest cancer Dx in the family.**

What are the dietary risk factors for developing colorectal cancer?

Show Answer

Risk factors for colorectal cancer include a diet **rich in fat and low in fiber and antioxidants.**

Is smoking a risk factor for colorectal cancer?

Show Answer

Yes. Smoking is a risk factor for colorectal cancer. (Stürmer T et al., JNCI 2000)

Which supplements and which drug have shown promise as chemopreventative agents in colorectal cancer?

Show Answer

Calcium, vitamin D, and folic acid supplementation have shown some benefit in preventing colorectal cancer, while **aspirin** administration has been associated with a lower risk of developing colorectal polyps.

What are 2 common familial/heritable risk factors for colorectal cancer?

Show Answer

The 2 most common familial conditions associated with colorectal cancer are **FAP** and **HNPCC** (aka Lynch syndrome).

What % of colorectal cancer cases are attributable to HNPCC?

Show Answer

5% of colorectal cancer cases are attributable to HNPCC.
What 2 familial syndromes, other than FAP and HNPCC, have been associated with a higher risk for developing colon cancer?

Show Answer

Cowden syndrome and **Gardner syndrome** predispose pts to developing colon cancer (in addition to other cancers).
Initial mutation of what tumor suppressor gene leads to a greater chance for developing colorectal cancer? With what familial condition is this mutation associated?

Show Answer

Initial mutation in the **APC** tumor suppressor gene leads to a higher chance for developing colorectal cancer; this mutation is also associated with **FAP.**
Mutation of what oncogene leads to a greater chance for developing colorectal cancer?

Show Answer

Initial mutation in the **K-ras** oncogene leads to a higher chance for developing colorectal cancer.
Most familial HNPCC cases have been associated with mutations in what genes? What do these genes regulate?

Show Answer

Most familial cases identified as HNPCC have been associated with mutations in the hMLH1 **or** hMSH2 gene, which **regulate mismatch repair.**
Pts with what chronic inflammatory condition are at a >20-fold increased risk for developing colorectal cancer?

Show Answer

Pts with **ulcerative colitis** are at a >20-fold increased risk for developing colorectal cancer.

WORKUP/STAGING

What must the physical exam include for pts with suspected rectal cancer?

Show Answer

The physical must include DRE and pelvic exam for women.
How is the Dx of rectal cancer typically established?

Show Answer

Endoscopic Bx is a typical way of establishing the Dx. A full colonoscopy should be performed to r/o more proximal lesions.
What studies are performed in the workup of rectal cancer pts, and what is the purpose of each modality?

Show Answer

For staging purposes, EUS or **pelvic MRI** must be performed in rectal cancer pts for T and N staging. **To r/o met Dz, CT C/A/P** with IV and oral contrast is performed.
What labs are collected as part of the staging workup for colorectal cancers?

Show Answer

Labs for the workup of colorectal cancer: **CBC, chem 7, LFTs, CEA**
Is a PET scan routinely indicated for pts with rectal cancer?

Show Answer

No. A PET scan is not routinely indicated in pts with localized rectal cancer.
What is the AJCC 8th edition (2017) T staging for colorectal cancer?

Show Answer

The T staging for rectal cancer is based on the DOI:

Tis: CIS or invasion into lamina propria without extension to the muscularis mucosae
T1: invades submucosa (muscularis mucosae)
T2: invades muscularis propria
T3: invades through muscularis and into pericolorectal tissues
T4a: penetrates surface of visceral peritoneum (including gross bowel perforation)
T4b: invades or adheres to adjacent organs
What is the AJCC 8th edition (2017) N staging for colorectal cancer?

Show Answer

The updated 2017 edition of the AJCC did not alter the N staging for colorectal cancer:

N1a: 1 regional LN
N1b: 2–3 regional LNs
N1c: tumor deposits in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional LN mets
N2a: 4–6 regional LNs
N2b: ≥7 regional LNs
How many regional nodes must be sampled for a dissection to be considered adequate?

Show Answer

At least 12 nodes should be sampled in curative cases. Notably, in pts with N0 Dz, the number of nodes examined is prognostic.
What is the AJCC 8th edition (2017) breakdown of M staging for colorectal cancer?

Show Answer

M1a: Mets to single organ/site (e.g., liver, lung, nonregional LNs) without peritoneal mets

M1b: Mets to ≥2 organs/sites without peritoneal mets
M1c: Mets to peritoneal surface with or without additional organ/site mets
What are the AJCC 8th edition (2017) TNM stage groupings for colorectal cancer?

Show Answer

Stage I: T1–2N0
Stage IIA: T3N0
Stage IIB: T4aN0
Stage IIC: T4bN0
Stage IIIA: T1–2N1 or N1c; T1N2a
Stage IIIB: T3–4aN1 or N1c; T2–3N2a; T1–2N2b
Stage IIIC: T4aN2a; T3–4aN2b; T4bN1–2
Stage IVA: any T or N; M1a
Stage IVB: any T or N; M1b
Stage IVC: any T or N; M1c
What is the AJCC 8th edition (2017) T staging for small intestine cancers?

Show Answer

Tis: high-grade dysplasia/CIS
T1a: invades lamina propria
T1b: invades through mucosa into submucosa
T2: invades into muscularis propria
T3: invades through muscularis propria into subserosa or into nonperitonealized perimuscular tissue (mesentery/retroperitoneum) without serosal penetration
T4: perforates visceral peritoneum or invades adjacent organs (e.g., other loops of small bowel, mesentery of adjacent bowel, and abdominal wall by way of serosa; for duodenum only invasion of pancreas or bile duct)
What are the AJCC 8th edition (2017) N and M staging for small intestine cancers?

Show Answer

N0: no regional LNs
N1: 1–2 LNs
N2: ≥3 LNs
M0: no DM
M1: DMs
What are the AJCC 8th edition (2017) stage groupings for small intestine cancers?

Show Answer

Stage 0: Tis
Stage I: T1–2N0
Stage IIA: T3N0
Stage IIB: T4N0
Stage IIIA: any T; N1
Stage IIIB: any T; N2
Stage IV: any T, any N; M1

Notably, only adenocarcinomas of the small intestine are eligible to rcv a stage group (other histologies rcv TNM staging, but should not be given a stage group).
What special lab test is routinely performed for colorectal cancer pts? Why?

Show Answer

CEA is routinely ordered for pts with colorectal cancer b/c it may help monitor response to therapy and Dz progression.
Describe the CEA trends for colorectal cancer pts after Sg and in the setting of a relapse.

Show Answer

Postresection for colorectal cancer, CEA levels should return to reference range in 4–6 wks. CEA increases 4–6 mos before a recurrence are clinically apparent (a rapid rise suggests hepatic or bony mets, while a slow rise suggests LR).
What is the most powerful predictor of LN involvement in rectal cancer?

Show Answer

The most powerful predictor of LN involvement in rectal cancer is **DOI.**
What % of T1 rectal cancer pts have micrometastatic Dz in the LNs that is undetectable by current imaging techniques?

Show Answer

≤15% of T1 rectal cancer pts have micrometastatic Dz in LNs undetectable by imaging.

TREATMENT/PROGNOSIS

What is the Tx paradigm for nonmet rectal cancer?

Show Answer

Nonmet rectal cancer Tx paradigm: in general, T1–2N0 rectal cancer pts get upfront Sg +/– adj CRT, whereas T3–4 or N+ pts may rcv neoadj CRT → Sg and adj 5-FU/leucovorin or FOLFOX. Total neoadjuvant therapy (TNT), which involves delivering all chemo & CRT before Sg, is gaining in prevalence.
What are the surgical options for rectal cancer pts?

Show Answer

The surgical options for rectal cancer include **transanal excision** (local excision), or transabdominal resection (**APR** for low-lying lesions, or **low anterior resection (LAR)** for mid/upper-lying lesions).
What are the criteria for transanal excision alone in rectal cancer? On what 2 studies is this based?

Show Answer

The criteria for transanal excision alone in rectal cancer include T1 lesion, <3-cm tumor that is superficial (<3 mm submucosal depth), lesion involving ≤1/3 of rectal circumference, N0 by EUS or MRI, low-grade tumor/no LVI, –margins, and reliable pt.

CALGB 89-84 (Steele GD et al., Ann Surg Oncol 1999; update Greenberg J et al., Dis Col Rectum 2008): phases I–II intergroup trial that treated all T1 or T2 Dz with local excision. Eligibility: tumor ≤4 cm, ≤10 cm from dentate line, ≤40% bowel circumference, and ≥2-mm-deep margin. T1 Dz had Sg alone, and T2 Dz all rcvd adj CRT to 54 Gy. 10-yr OS was 78% (T1) and 75% (T2), and 10-yr LF was 8% (T1) and 18% (T2). Therefore, even with adj CRT T2 lesions treated via local excision are associated with high recurrence rates.

RTOG 82-02 (Russell AH et al., IJROBP 2000): similar eligibility criteria as CALGB 89-84, phase II, all transanal excision. T1 lesions ≤3 cm, ≥3-mm margins, well to moderately differentiated tumors, no LVI; normal CEA levels were observed after Sg. Pts with T1 with poor-risk features and all T2–3N0 pts rcvd adj CRT (5-FU). 5-yr OS was 78%, with LF rates of 4% (T1), 16% (T2), and 23% (T3).

For pts who cannot have a definitive transabdominal resection, what are the indications for adj CRT after transanal excision of rectal cancer?

Show Answer

For pts who cannot have a definitive transabdominal resection, adj CRT alone should be administered to pts with a **high-risk T1 lesion** after local excision (poorly differentiated, with bad histologies, margins <3 mm, >3-cm size, and +LVSI); **all T2 cancers** after local excision; and for all T3–4 or N+ cancers after LAR or APR. Low-risk T1 tumors after local excision do not need adj therapy.

What definitive transabdominal surgical approach for rectal cancer permits sphincter preservation?

Show Answer

LAR spares the sphincter and is therefore a preferred surgical option (if feasible) for rectal cancer pts; in contrast, APR requires a colostomy.
What is the approximate LR rate for T3–4 or N1 rectal cancer after Sg alone?

Show Answer

The historic LR rate for T3–4 or N1 rectal cancer is ~**25%.** This is improved with better Sg (i.e., total mesorectal excision [TME], 10-yr LR 11% [van Gijn W et al., Lancet Oncol 2011]).
What is the significance of a positive circumferential margin at the time of Sg for rectal cancer?

Show Answer

A positive circumferential margin predicts for inf LC, DM, and OS rates after Sg for rectal cancer based on meta-analysis. (Nagtegaal ID et al., JCO 2008)
What kind of surgical technique is currently standard in the surgical management of rectal cancer? Why is this important?

Show Answer

TME is a standard surgical technique in the operative management of rectal cancer and is carried out with LAR or APR. It **helps reduce the rate of positive radial margins and improves LC.**
What are the indications for adj CRT after definitive transabdominal resection for rectal cancer?

Show Answer

After a definitive transabdominal resection (LAR or APR—TME or non-TME based) for rectal cancer, adj CRT is indicated **if the pathology is N+ or**

≥**T3.**

What are some options for rectal cancer pts with solitary or oligometastatic Dz to the liver that is resectable?

Show Answer

Surgical resection of the metastatic site is the only modality with proven survival benefit, although SBRT may be considered if surgery is declined. How these cases should be managed needs to be determined on a case-by-case basis in a multidisciplinary setting. Some options for oligometastatic (resectable) rectal cancer include:

- Induction chemo → restaging → resection of the mets → CRT to primary → LAR if possible +/– additional chemo
- If the pt is symptomatic, consider preop CRT or short-course RT (5 Gy × 5) as done in Europe → Sg of both primary and metastatic site → adj chemo (FOLFOX/Avastin)

What are the most commonly used sensitizing chemo regimens given with RT for rectal cancer?

Show Answer

Continuous infusion (CI) 5-FU (225–250 mg/m^2/day) or capecitabine (Xeloda) 825 mg/m^2 bid 5–7 days/wk are commonly used sensitizing chemo regimens.

What did NSABP-04 show regarding the addition of oxaliplatin to preop CRT?

Show Answer

NSABP-04 randomly assigned clinical stage II or III rectal cancer undergoing preop RT (45 Gy in 25 fx over 5 wks + boost of 5.4 Gy–10.8 Gy in 3–6 daily fx) to 1 of 4 chemo regimens in a 2 × 2 design: CI 5-FU (225 mg/m^2 5 days/wk), with or without intravenous oxaliplatin (50 mg/m^2/wk × 5) or oral Cape (825 mg/m^2 bid 5 days/wk), with or without oxaliplatin (50 mg/m^2/wk

× 5). There was no difference in LRF, pCR, DFS, or OS. However, oxaliplatin added significant grade 3–4 GI toxicity, and is therefore not indicated in combination with RT in the preop setting ($p < 0.0001$). Additionally, this trial establishes capecitabine as another standard of care option along with CI 5-FU in the preop setting. (Allegra CJ et al., JNCI 2015)
What are the data addressing adj RT alone in rectal cancer, and what do they show?

Show Answer

There are many RCTs (e.g., **MRC 3, NSABP R-01**) that investigated adj RT alone, showing **improvement in LC only** but **no** improvement in OS, DFS, or MFS); this was confirmed by a meta-analysis. (CCCG, Lancet 2001)
What major studies established a role for adj CRT in rectal cancer?

Show Answer

Gastro-Intestinal Study Group (GITSG) 7175 (GITSG collaborators, NEJM 1985; Thomas PR et al., Radiother Oncol 1988) randomized pts after Sg to observation, chemo alone, RT alone, or CRT and found that adj CRT in rectal cancer significantly improved OS (45% vs. 27% at 10 yrs) and LF rates (10% vs. 25%) when c/w Sg alone.

Intergroup/NCCTG 79-47-51 (Krook JE et al., NEJM 1991) randomized stages II–III rectal cancer pts to RT alone or CRT (5-FU × 2 → 5-FU + RT → 5-FU × 2) after Sg (50% APR). 5-yr LR, DM, and OS were better for CRT (LR: 14% vs. 25%; DM: 29% vs. 46%; OS: 55% vs. 45%). There was worse acute grade 3–4 diarrhea (20% vs. 5%) but no late complications for the CRT arm.

Which study compared Sg alone with preop RT in rectal cancer? What did it find, and what were its limitations?

Show Answer

The **Swedish Rectal Cancer trial** (NEJM 1997) compared neoadj RT (25 Gy

in 5 fx) to Sg alone in rectal cancer and found a significant **improvement in OS** (38% vs. 30%) and LR (9% vs. 26%) at 13 yrs with neoadj RT. The trial is often criticized b/c TME was not used and there was a high-recurrence rate for the Sg alone arm (26%).

Does the use of TME eliminate the benefit from neoadj RT for rectal cancer?

Show Answer

No. TME does not offset the benefit of neoadj RT based on the Dutch TME study (Peeters KC et al., Ann Surg 2007). The study compared TME alone to neoadj RT and TME and found no OS benefit, but there was an improved LR rate (6% vs. 11%) with the addition of neoadj RT. The NCCTG (N1048) PROSPECT study is investigating whether RT may be omitted for T3N0-1M0 or T2N1M0 patients.

What was the RT dose/fx scheme in the Dutch and Swedish rectal cancer studies? How long after the completion of RT do pts go to Sg?

Show Answer

Both the Dutch and Swedish rectal cancer studies used neoadj RT in **25 Gy in 5 fx** (5 Gy × 5). Pts typically underwent surgical resection **within 1 wk** of RT completion.

What were the arms in the MRC CR07/NCIC C016 rectal cancer study, and what were its main findings?

Show Answer

The **MRC CR07/NCIC C016** rectal cancer study (Sebag-Montefiore D et al., Lancet 2009) randomized pts to preop RT (25 Gy in 5 fx) vs. selective postop CRT (45 Gy in 25 fx) and found better outcomes with preop RT for LR (4% vs. 11%, SS) and DFS (77% vs. 71%, SS). OS was similar at 4-yr f/u. A short neoadj RT course is an acceptable option.

Is neoadj short-course RT an acceptable alternative to standard CRT for

locally advanced rectal cancer?

Show Answer

Yes. Trans-Tasman Radiation Oncology Group 01.04 randomized locally advanced rectal cancer pts to neoadj short course RT (5 Gy × 5) and early Sg vs. standard CRT (50.4 Gy + 5-FU 225 mg/m^2/day) and Sg in 4–6 wks. 3-yr LRR were 7.5% vs. 4.4% (p = 0.24) and 5-yr OS was 74% vs. 70%, respectively. Late toxicity rates were not different. In addition, a recent phase III randomized trial from the Polish Colorectal Study Group found a benefit when pts with fixed T3 or T4 tumors were treated with 5 × 5 Gy and 3 cycles of FOLFOX4 (group A) as opposed to 50.4 Gy in 28 fx combined with bolus 5-FU 325 and leucovorin (oxaliplatin was initially included and then removed in 2012). There was no difference in LR or pathologic CR, but the **short course CRT was associated with lower toxicity and improved OS** (73% vs. 65%, p = 0.046). (Bujko K et al., Ann Oncol 2016)

What is the optimal timing for Sg after short course preop RT?

Show Answer

Although Sg is typically done 1 wk after completion of short course radiotherapy, new randomized data suggests fewer postsurgical complications if Sg is delayed 4–8 wks. The Stockholm III was a phase III randomized, nonblinded, noninferiority trial which compared pts planned for an APR who rcvd either 5 × 5 Gy RT dose with Sg within 1 wk (short-course radiotherapy) or after 4–8 wks (short-course radiotherapy with delay) or 25 × 2 Gy RT dose with Sg after 4–8 wks (long-course radiotherapy with delay). Oncologic results were similar in all 3 groups. **Although RT-induced toxicity was seen after short-course radiotherapy with delay, postop complications were significantly reduced c/w short-course radiotherapy** (41% vs. 53%, p = 0.001). (Erlandsson J et al., Lancet Oncol 2017)

Which major European rectal cancer study compared neoadj CRT to adj CRT and what were its findings?

Show Answer

The **German Rectal Cancer trial** (Sauer R et al., NEJM 2004) compared preop to postop CRT in T3–4 or N+ rectal cancer (RT was 50.4 Gy for neoadj arm and 55.8 Gy for postop arm with 5-FU chemo [CI 5-FU days 1–5 at 1,000 mg/day, wks 1 and 5]). All pts rcvd 4 additional cycles of bolus 5-FU (500 mg/m^2/day, days 1–5, q4wks) at 4 wks after completion of initial therapy. The study found a similar 5-yr OS and DFS b/t the 2 arms but better LR rates (6% vs. 13%), fewer acute (27% vs. 40%) and late toxicities (14% vs. 24%), and better sphincter-preservation rates (39% vs. 19%) in the preop CRT arm. Most of the acute and late toxicities were b/c of acute/chronic diarrhea and anastomotic stricture. A recent update confirmed persistent benefit in LRR (7.1% vs. 10.1%, p = 0.05) with no significant differences in DM rates and DFS. (Sauer R et al., JCO 2012)
What is the pathologic CR rate for preop CRT for rectal cancer?

Show Answer

According to the German Rectal Cancer trial, the **pCR rate is 8%.**
What is the pathologic CR rate following TNT for rectal cancer?

Show Answer

The pathologic CR rate with TNT ranges from 14–36%. (Cercek A et al. JAMA Oncology 2018)
Does the extent of pathologic response correlate with outcome?

Show Answer

Yes. For example, the neoadjuvant rectal (NAR) score (George TJ et al. Curr Colorectal Cancer Rep 2015), empirically derived and based on the cT, ypT and ypN stages, has been found to predict OS in rectal cancer clinical trials better than ypCR. It is currently being used as the primary endpoint to more quickly assess the efficacy of novel TNT treatment regimens in the ongoing NRG GI-002 trial.

Is a wait-and-see non-operative approach a viable option for rectal cancer patients?

Show Answer

Although not yet a standard option, a non-operative wait-and-see approach rather than automatic surgery following a TNT regimen has promising initial results (Habr-Gama et al. Ann Surg 2004). A meta-analysis by Dossa et al. (Lancet Gastroenterol Hepatol 2017) involving 867 pts. in 23 studies found clinical CR rates following CRT ranging from 11–78%, with a pooled 2-year regrowth rate of 15.7%. 95.4% of patients with regrowth had salvage therapies, and following a clinical CR no OS or DFS differences were found between whose with non-operative management (including serial DRE, endoscopy & MRI) and those who had surgery. Benefits of non-operative management may include improved quality of life and avoiding colostomy (Hupkens BJP et al. Dis Colon Rectum 2017). This approach is currently being investigated in the multi-institution MSKCC-based organ preservation for rectal cancer (OPRA) study.

What % of pts receiving neoadj CRT will be overtreated b/c of having stage I Dz instead of the presumed more advanced Dz?

Show Answer

~**18%** of pts will be overtreated with neoadj CRT b/c of an apparent stage I Dz. This is based on the results of the postop arm of the German Rectal Cancer trial, where 18% of the pts did not rcv postop CRT b/c of T1–2N0 Dz found at resection. All of these pts were thought to have T3–4 or N+ Dz based on EUS.

What was a major criticism of the German Rectal Cancer trial (Sauer R et al., NEJM 2004)?

Show Answer

A major criticism of the German Rectal Cancer trial (Sauer R et al., NEJM

2004) was that **only 54% of adj pts rcvd a full RT dose** (vs. 92% in the neoadj arm).
Did Sg in the German Rectal Cancer trial involve TME?

Show Answer

Yes. All pts in the German Rectal Cancer trial (Sauer R et al., NEJM 2004) had a TME.
What was the sphincter-preservation rate in the neoadj CRT arm in the German Rectal Cancer trial (Sauer R et al., NEJM 2004)?

Show Answer

The sphincter-preservation rate in the neoadj CRT arm in the German Rectal Cancer trial (Sauer R et al., NEJM 2004) was **39% at 5 yrs** (vs. 19% in the postop CRT arm).
How long after Sg should adj CRT be initiated for rectal cancer?

Show Answer

Adj CRT for rectal cancer should begin **4–6 wks** after Sg.
What did all pts in the German Rectal Cancer trial (Sauer R et al., NEJM 2004) rcv after either Sg (neoadj CRT arm) or CRT (adj arm)?

Show Answer

All pts in the German Rectal Cancer trial (Sauer R et al., NEJM 2004) rcvd 4–5 cycles of **bolus 5-FU** (500 mg/m^2/day, days 1–5, q4wks) 4 wks after either Sg (neoadj CRT arm) or CRT (adj arm).
Which 2 major randomized studies compared neoadj RT to neoadj CRT in rectal cancer, and what did they find? How was CRT delivered in both studies? What was a major limitation of these trials?

Show Answer

The **French FFCD 9203** (Gerard JP et al., JCO 2006) and **EORTC 22921** (Bosset JF et al., NEJM 2006) compared neoadj RT with neoadj CRT in

rectal cancer. The French study found no OS difference but did find improved LR with neoadj CRT at 5 yrs (8% vs. 16%, SS). The EORTC study also found no OS difference and improved LR with neoadj CRT at 5 yrs (9% vs. 17%). Grades 3–4 acute toxicity was higher in the CRT vs. RT arms. Both trials used neoadj CRT with 45 Gy (1.8) and 5-FU (350 mg/m^2/day, wks 1 and 5 of RT). A small % of pts actually rcvd adj CT (EORTC: 43%).
How should rectal cancer pts be simulated in preparation for RT?

Show Answer

Rectal cancer pts should undergo CT simulation **in the prone position, on a belly board, and with a full bladder** (with optional placement of anal/vaginal markers).
What structures should be encompassed within the RT field for rectal cancer?

Show Answer

For rectal cancer, the **tumor bed** (+ 2 cm margin) and **presacral/obturator/internal iliac nodes** should be included in the RT fields. (Anorectal contouring atlases: Myerson RJ et al., IJROBP 2009; Ng M et al., IJROBP 2012; Muirhead R et al., Clin Oncol 2014)
What additional nodal chain should be included in the RT fields with T4 rectal cancer?

Show Answer

The **external iliac nodes** should be encompassed for T4 rectal cancers invading ant structures (e.g., bladder, vagina, prostate) but are not necessary for bony sacrum invasion.
What RT fields are generally employed for rectal cancer?

Show Answer

Whole pelvis fields (3 fields) with a PA field and 2 opposed lat fields are typically employed for rectal cancer; consider adding a lightly weighted AP

field for larger pts.
What are the RT doses for rectal cancer?

Show Answer

RT doses for rectal cancer:

Neoadj/postop: initial whole pelvis (3 field) to 45 Gy in 1.8 Gy/fx; CD to tumor bed + 2–3 cm (opposed lats only, or 3D-CRT) to **50.4 Gy (preop)** (or **55.8 Gy [postop]** if the small bowel is out of the way)
Definitive/unresectable: initial to 45 Gy, CD1 to 50.4 Gy; consider CD2 with conformal RT to **54–59.4 Gy** (if dose to the small bowel is limited)

When is IORT indicated for rectal cancer, and what is the dose?

Show Answer

IORT should be considered in rectal cancer for **close/+margins or as an additional boost,** especially with T4 tumors or with recurrent tumors. The typical dose is **10–15 Gy** to the 90% IDL.
What study showed a benefit with IORT in colorectal cancer?

Show Answer

A retrospective study from Mayo by Gunderson L et al. evaluated IORT in addition to EBRT and found improved OS and LR rates with addition of IORT (10–20 Gy) when c/w historical controls. (IJROBP 1997)
When can RT be considered in colon cancer? When is it given in relation to Sg and to what dose?

Show Answer

RT can be considered **for fixed T4 colon cancer lesions or with a close/+margin.** RT is typically **given after resection/debulking to a dose of 45–50.4 Gy.**
What major study investigated the role of adj RT in colon cancer? What did it find? What was the limitation of this study?

Show Answer

The **Intergroup 0130** study (Martenson JA Jr et al., JCO 2004) compared adj chemo to adj CRT in colon cancer and found no difference in OS or LC with addition of RT. Limitations: study was underpowered to show a difference b/t groups, the operative bed was often not marked by surgeon, and it included T3 pts unlikely to benefit from RT.

Which randomized study investigated the role of elective P-A RT in rectal cancer? What did it conclude?

Show Answer

The **EORTC trial by** Bosset et al. evaluated the role of elective P-A RT in rectal cancer (25 Gy to LNs and liver) and found no benefit in terms of OS, DFS, or LC. (Radiother Oncol 2001)

What is the Tx paradigm for small bowel cancer, and what is the role of adj chemo and/or RT?

Show Answer

Small bowel cancer Tx paradigm: resection → 5-FU–based chemo. CRT is considered in cases of close/+margins, but retrospective studies have found no convincing benefit. (Kelsey CR et al., IJROBP 2007)

Is there a role for IMRT in the Tx for rectal cancer?

Show Answer

RTOG 0822, a single arm phase II study, investigated neoadj XELOX (capecitabine plus oxaliplatin) with IMRT for pts with locally advanced rectal cancer with a primary endpoint of grade ≥2 GI toxicity using RTOG 0247 for historical comparison. Preliminary data reported at ASTRO 2011 showed **no statistically significant benefit** (51% vs. 58%, p = 0.3). Zhu et al. utilized a similar regimen (XELOX plus IMRT) in a single arm prospective study of 42 pts and noted grade 3 hematologic, GI, and skin toxicities of 4.7%, 14.3%, and 26.2%, respectively. Grade 4 toxicity was not observed.

FOLLOW-UP/TOXICITY

How does the toxicity of CI 5-FU differ from that of bolus administration?

Show Answer

Bolus administration of **5-FU confers greater hematologic toxicity,** whereas **CI confers greater GI toxicity (mucositis, diarrhea).** (Smalley SR et al., JCO 2006)

What was a major late complication of neoadj RT in the Swedish Rectal Cancer trial?

Show Answer

SBO was more likely in the neoadj RT arm in the Swedish Rectal Cancer trial (RR 2.5) (Birgisson H et al., Br J Surg 2008), and may be a limitation of a short course regimen (5 Gy × 5).

What 3 toxicities were worse with neoadj RT in the Swedish Rectal Cancer trial?

Show Answer

Median bowel movement frequency (20 movements/wk vs. 10 movements/wk, SS), fecal incontinence (62% vs. 27%, SS), and impaired social life (30% vs. 10%, SS) were worse in the neoadj RT arm when c/w Sg alone in the Swedish Rectal Cancer trial.

What does the post-Tx surveillance include for colorectal cancer?

Show Answer

Post-Tx rectal cancer surveillance: H&P q3–6 mos for 2 yrs (then q6 mos for 5 yrs) and CEA on same schedule for St. II/III pts. CT C/A/P is performed q6–12 mos for 5 yrs and colonoscopy at 1 yr, or within 3–6 mos if not done before treatment due to obstructing lesion.

Which retrospective study found comparable Tx results/toxicity with RT in rectal cancer pts with IBD?

Show Answer

A **Mt. Sinai study by** Green S et al. found comparable Tx results/toxicity with RT in rectal cancer pts with IBD. (IJROBP 1999)
How long after conventional RT can side effects develop, and what are some common side effects of RT?

Show Answer

Signs and Sx can occur as early as **6–18 mos** following RT. Frequent Sx include diarrhea (bloody), colicky abdominal pain, and n/v. Less common are SBO, fistulas, bowel perforation, and severe bleeding. Bowel malabsorption may occur with weight loss. Damage to the ileum can impair resorption of vitamin B12 and bile acid with steatorrhea as a consequence (Guckenberger M et al., Int J Colorectal Dis 2006). Consider pelvic physical therapy including vaginal dilator use to mitigate GI, GU, sexual, and musculoskeletal side effects.

52

Anal Cancer

Updated by Jonathan Frandsen

BACKGROUND

What is the incidence of anal cancer in the United States?

Show Answer

~7,000 cases/yr in the United States.

Is there a sex predilection for anal cancer?

Show Answer

Yes. Anal cancer is more common in **females** than males (2:1).

What are some risk factors for anal cancer?

Show Answer

Hx of STDs/anal warts; multiple sexual partners (>10); anal-receptive intercourse; immunodeficiency (HIV, solid organ transplantation); smoking; Hx of Cx, vulvar, or vaginal cancer (HPV related malignancies).

Is anal cancer an AIDS-defining illness?

Show Answer

No. However, the demographically adjusted rate ratio for HIV-infected men and women relative to uninfected cohorts is 80 and 30, respectively. Cx cancer is an AIDS-defining illness.

What is the predominant histology of anal cancer?

Show Answer

SCC (75%–80%) is the predominant histology.
What virus strains are strongly associated (assoc) with anal cancer?

Show Answer

HPV strains **16, 18, 31, 33, and 35** are strongly assoc with anal cancer. Anal cancers are assoc. with HPV infection in 75%–90% of cases, with HPV16 the most common subtype.
How long is the anal canal, and where does it extend?

Show Answer

The anal canal is **4-cm long,** extending distally from the anal verge (palpable junction b/t the internal sphincter and SQ part of the external sphincter, aka the intersphincteric groove) to the anorectal ring (where the rectum enters the puborectalis sling) proximally.
What is the histopathologic significance of the dentate line (aka pectinate line)?

Show Answer

The dentate line is the anatomic site where mucosa changes from nonkeratinized squamous epithelium distally to colorectal-type columnar mucosa proximally (dividing the upper from the lower anal canal).
Describe the anatomic location of the anal verge.

Show Answer

The anal verge is located at the junction of nonkeratinized squamous epithelium of the anal canal and keratinized squamous epithelium (true epidermis) of perianal skin.
Which site carries a better prognosis: the anal margin or anal canal?

Show Answer

The **anal margin** carries a better prognosis.
Which pathology carries a higher risk for LR and distant recurrence?

Show Answer

Adenocarcinoma carries a higher risk.
What is the significance of the dentate line in terms of LN drainage?

Show Answer

Above dentate line: drains to pudendal/hypogastric/obturator/hemorrhoidal → internal iliac nodes
Below dentate line: drains to inguinal/femoral nodes → external iliacs
What % of anal cancer pts present with +LNs?

Show Answer

25%–35% of these pts present with +LNs.
What are the 2 most common sites of DM?

Show Answer

Liver and lung
What is the occult positivity rate for inguinal nodes (i.e., if clinically–) in anal cancer?

Show Answer

For inguinal nodes, the occult positivity rate is **10%–15%.**
What is the rate of extrapelvic visceral mets at presentation for anal cancer?

Show Answer

Extrapelvic visceral mets are present in **5%–10%** of pts.
In anal cancer, what % of clinically palpable LNs are actually involved by cancer?

Show Answer

50% of clinically palpable LNs involve cancer, while the other 50% are usually reactive hyperplasia.
In anal cancers, what are the most important prognostic factors for LC and survival?

Show Answer

Tumor size and DOI predict for LC. The **extent of inguinal or pelvic LN involvement** predicts for survival.

WORKUP/STAGING

What are 4 common presenting Sx in anal cancer?

Show Answer

Bleeding, pain/sensation of mass, rectal urgency, and pruritus
What does the workup for anal cancer pts include?

Show Answer

Anal cancer workup: H&P (including gyn exam for women with Cx cancer screening), labs (HIV if risk factors), imaging, Bx of lesion, and FNA of suspicious LN
What imaging studies are typically done for anal cancer pts?

Show Answer

Chest/abdominal CT + pelvic CT or MRI with IV contrast. Consider PET/CT in same position as simulation for staging & planning guidance. (NCCN Guidelines 2018)
Is PET/CT more or less sensitive than diagnostic CT alone for detecting locoregional and met Dz?

Show Answer

Mistrangelo M et al. (IJROBP 2012) found PET/CT to be sup to CT in detecting the primary tumor (89% vs. 75%); Bhuva NJ et al. also found

PET/CT diagnosed occult metastatic Dz following CT imaging in 5% of pts and changed staging in 42% of pts, with the majority being upstaged. (Ann Oncol 2012)

What features of anal lesions need to be appreciated on physical exam? Why?

Show Answer

The **degree of circumferential involvement and anal sphincter tone** should be appreciated, b/c these **may dictate Tx.**

What is the approach to suspicious inguinal LNs in anal cancer pts?

Show Answer

FNA Bx should be considered for suspicious inguinal LNs.

On what is the T staging for anal cancer based? Define T1–T4.

Show Answer

T staging as per AJCC 8th edition for anal cancer is based on **tumor size & invasion of adjacent organs.**

TX: Primary tumor not assessed
T0: No evidence of primary tumor
Tis: High-grade squamous intraepithelial lesion
T1: ≤2 cm
T2: >2 but ≤5 cm
T3: >5 cm
T4: Invasion of adjacent organs (vagina, urethra, and bladder)

Does tumor invasion of sphincter muscle by anal cancer constitute a T4 lesion?

Show Answer

No. Direct invasion of the rectal wall, perirectal skin, SQ tissue, or sphincter muscle are not classified as T4.

Most pts with anal cancer present with what T stage?

Show Answer

Most anal cancer pts present at stage **T2 or T3.**
What is the N staging for mets in inguinal, mesorectal, or internal iliac LNs?

Show Answer

Mets to inguinal, mesorectal, or internal iliac LNs is staged as **N1a.**
What is the N staging for mets in external iliac LNs?

Show Answer

Mets to external iliac LNs is staged as **N1b.**
What is the N staging for mets in external iliac LNs with concurrent mets in N1a nodes?

Show Answer

Mets to external iliac LNs with concurrent mets in N1a nodes is N1c.
Is mets to common iliac nodes considered M1 Dz?

Show Answer

Yes. Mets to common iliac LNs is considered M1 Dz**.**
What is the AJCC 8th edition (2017) stage grouping for anal cancer?

Show Answer

Stage I: T1N0
Stage IIA: T2N0
Stage IIB: T3N0
Stage IIIA: T1–2N1
Stage IIIB: T4N0
Stage IIIC: T3N1 or T4N1
Stage IV: Any T Any N M1

What are the 5-yr OS and DFS rates after surgical resection alone for anal cancer?

Show Answer

The 5-yr OS rate after complete surgical resection (APR) is **~70%,** and the DFS rate is **~40%.** (Mayo review of 118 pts: Boman BM et al., Cancer 1984)
What % of pts who relapse develop local recurrent Dz as part of the total failure pattern?

Show Answer

~80% develop local recurrent Dz. (Boman BM et al., Cancer 1984. Note: This was also a surgical series.)
What are the OS and sphincter preservation rates for all-comers with anal cancer at 8 yrs after definitive CRT?

Show Answer

OS is ~70% (**RTOG 9811 & 0529**) and **sphincter preservation rate is ~65%** after CRT alone.

TREATMENT/PROGNOSIS

What are the criteria for local excision alone in anal cancer? What are the LC rates in such carefully selected pts?

Show Answer

Small T1 lesion (<2 cm), well differentiated, –margins, <40% circumferential involvement, no sphincter involvement, compliant pts. For these well-selected pts, there is **>90% LC.** (Boman BM et al., Cancer 1984)
Can radiotherapy alone be employed for early-stage anal cancer?

Show Answer

Yes. However, it can be employed only for **T1N0** lesions. There were excellent LC rates of 100% and CR rates of 96% in 1 series. (Deniaud-

Alexandre E et al., IJROBP 2003)
What was the standard surgical procedure for anal cancer before the advent of CRT? What was the disadvantage of this approach?

Show Answer

APR was the standard surgical procedure, but the disadvantage is that it **requires permanent colostomy.**
Currently, when should Sg alone be considered sufficient for management of anal cancer?

Show Answer

Sg is sufficient **with anal margin cancers in which the sphincter can be spared.**
Historically, what has been the sphincter preservation approach for the Tx of anal cancers?

Show Answer

Radiotherapy alone was employed in Europe since the early 1900s, whereas surgical resection was standard in the United States. Radiotherapy alone produced similar survival and control rates as Sg but allowed sphincter preservation. These results were better for less advanced tumors. Papillon J and Montbarbon JF (Dis Colon Rectum 1987) reported (in the largest series of 159 pts with the use of EBRT and interstitial brachytherapy [30–42 Gy EBRT → implant 15–20 Gy]) a 5-yr OS of 65% and a **sphincter preservation rate of 70%–82% (>4-cm tumor vs. ≤4-cm tumor).**
What 2 seminal studies from the 1970s and 1980s in the United States demonstrated that surgical resection may not be needed after CRT, even after a short course of Tx?

Show Answer

The **Wayne State** experience (Nigro ND et al., Dis Colon Rectum 1974, 1983): preop regimen of **30 Gy/15 fx** with continuous infusion 5-FU (1,000

mg/m^2 × 4 days) and mitomycin-C (MMC) (single 15 mg/m^2 bolus), with APR scheduled 6 wks after the regimen. 31 pts had completion Sg vs. 73 had definitive CRT alone. 71% pts had pCR in the surgical specimen. In the Sg arm, the f/u NED rate was 79%. In the definitive CRT arm, the f/u NED rate was 82%.

Princess Margaret Hospital (Cummings BM et al., IJROBP 1991): prospective nonrandomized studies comparing RT alone, 5-FU + RT, or 5-FU/MMC + RT. OS was 70% in all groups, with LC best in the 5-FU/MMC arm of 93% c/w 60% in the RT-alone arm.

What was the chemo regimen and RT dose delivered in the original anal cancer studies by Nigro ND et al.?

Show Answer

In Nigro ND et al., the regimen was 5-FU (1,000 mg/m^2 × 4 days)/MMC (15 mg/m^2 bolus) with an RT dose of 30 Gy (2 Gy per fx). (Dis Colon Rectum 1974, 1983)

Anal margin tumors are treated like what other cancer?

Show Answer

Anal margin tumors are treated in the same manner as **skin cancer.**

What is the current Tx paradigm for anal canal cancer?

Show Answer

Anal cancer Tx paradigm: definitive CRT

What chemo doses are used in anal cancer, and what is the scheduling?

Show Answer

Anal cancer doses/scheduling: 5-FU 1,000 mg/m^2/day intravenously on days 1–4 and 29–32; MMC 10 mg/m^2 IV bolus on days 1 and 29 or 12 mg/m^2 IV bolus on day 1 only

What is the main radiobiologic advantage of MMC?

Show Answer

MMC is a **hypoxic cell radiosensitizer.**
For which pts is APR currently reserved?

Show Answer

APR is reserved as **salvage for pts who recur post CRT or those who have had prior pelvic RT.**
Are there data directly comparing Sg with CRT in anal cancer?

Show Answer

No. There is no randomized evidence. However, 1 retrospective analysis from Sweden showed better 5-yr OS in pts who rcvd RT ± chemo, supporting CRT as a better initial Tx option. (Goldman S et al., Int J Colorectal Dis 1989)
What 2 major European randomized studies in anal cancer demonstrated the inferiority of definitive RT compared to combined CRT?

Show Answer

UKCCCR (ACT I) (Lancet 1996): 585 pts, any stage, randomized to RT vs. RT + 5-FU/MMC. RT was 45 Gy to the pelvis → 15–25 Gy with ≥50% response. If there was <50% response, then Sg was performed. Response was measured 6 wks after completion of induction therapy. The CR rate trended better in CRT (39% vs. 30%, p = 0.08), with 3-yr LC of 64% vs. 41% (p < 0.0001). The risk of death from anal cancer was also reduced in the CRT arm (HR 0.71, p = 0.02), but there was a nonsignificant benefit of 3-yr OS of 65% vs. 58% (p = 0.25).

13-yr update (Northover J et al., Br J Cancer 2010): The absolute risk of LRR was reduced by 25% and remained stable after 5 yrs. The risk of death was reduced by 12%, and absolute reduction in the colostomy rates remained at 10%, favoring CRT (all SS).

EORTC (Bartelink H et al., JCO 1997): 577 pts, T3–4 or N+, RT vs. RT + 5-FU/MMC. Boost was given based on the response assessed at 6 wks: 20 Gy to CR and 15 Gy to PR. The CR rate was measured after completion of the entire course of therapy. The CR rate was sup in the CRT arm (80% vs. 54%, p = 0.02), as well as 3-yr LC (69% vs. 55%, p = 0.02), but not 3-yr OS (69% vs. 64%).

What is 1 explanation why the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) study had substantially inf rates of CR and LC c/w the EORTC study in anal cancer?

Show Answer

The CR rate was measured 6 wks after induction therapy in the UKCCCR, whereas it was measured 6 wks after completion of all therapy in the EORTC study (which had a longer course of Tx b/c boost was not delivered until after 6 wks of initial therapy).

The definition of LC is different b/t the 2 studies. In the UKCCCR study, the definition was more strict, with failure defined as <50% tumor reduction after just 6 wks of 45 Gy to the pelvis.

Can MMC be removed from the standard regimen of 5-FU/MMC for the Tx of anal cancer? What major study addressed this question?

Show Answer

No. MMC cannot be deleted from the standard regimen.

RTOG 87-04 (Flam M et al., JCO 1996): 291 pts, MMC/5-FU + RT vs. 5-FU + RT. RT was 45–50.4 Gy. The difference in OS was not SS (76% vs. 67%, p = 0.31), but MMC improved the DFS rate (73% vs. 51%, p = 0.0003) and 4-yr colostomy free survival (CFS) rate (71% vs. 59%, p = 0.014). Grade 4 or 5 heme toxicity was worse (26% vs. 7%).

Can cisplatin (CIS) be substituted for MMC in the Tx of anal cancer? What 2 major studies addressed this question?

Show Answer

2 RCTs suggest that substituting CIS for MMC does not improve and possibly worsens outcomes:

RTOG 98-11 (Gunderson LL et al., JCO 2012): 649 pts, all stages except T1 or M1; excluded AIDS or prior cancers; randomized to standard MMC-based therapy vs. 2 cycles of CIS/5-FU → CIS/5-FU × 2 with RT. RT was 45 Gy to the pelvis, with boost for T2 residual to 10–14 Gy. **DFS and OS were significantly sup in MMC-arm.** 5-yr DFS: 67.8% vs. 57.8%, p = 0.006; 5-yr OS: 78.3% vs. 70.7%, p = 0.026. There was a trend toward statistical superiority of MMC arm for CFS, LRF, and colostomy failure. Acute grade 3–4 severe heme toxicity was significantly worse in the MMC arm (61.8% vs. 42.0%, p < 0.001) but not in long-term toxicities (13.1% vs. 10.7%). Major criticism: Neoadj chemo on the experimental arm may have confounded the results.

ACTII (James R et al., Lancet Oncol 2013): 2 × 2 design, 940 pts (T1–2 (50%), T3–4 (43%), 30% N+, 85% anal canal, 15% anal margin) treated with 5-FU (1,000 mg/m^2/day, days 1–4, days 29–32) and RT (50.4 Gy) and randomized to concurrent MMC (12 mg/m^2, day 1) or CIS) (60 mg/m^2, days 1 and 29). 2nd randomization involved adding maintenance therapy (4 wks after CRT) to 2 cycles 5-FU/CIS or no maintenance. Median f/u was 5.1 yrs. Results: No. difference in

CR rate at 26 wks (90.5% MMC vs. 89.6% CIS). Hematologic grade 3–4 side effects occurred in 26% MMC vs. 16% CIS. 3-yr PFS, OS, and CFS did not differ significantly b/t groups. The authors concluded that 5-FU/MMC/RT without maintenance chemo remains the standard of care.

What is the role of brachytherapy in anal cancer?

Show Answer

Brachytherapy is **generally not done** in the United States d/t poor LC (<30% for large lesions) and higher complication rates. An older French experience showed favorable results with combined interstitial (Ir-192) and EBRT.

(Papillon J & Montbarbon JF, Dis Colon Rectum 1987)
Is there a role for dose escalation in anal cancer?

Show Answer

No. A phase III trial from France randomized pts with tumors ≥4 cm, or <4 cm and N1–3M0 to 1 of 4 Tx arms (2 × 2 factorial design). The 1st randomization was plus or minus induction chemo (2 cycles 5-FU and CIS). All pts then rcvd 45 Gy with 5-FU and CIS. 3 wks after completion of CRT, pts were then randomized to 1 of 2 boost doses: the standard-boost dose (15 Gy) or the high-boost dose (20 Gy for complete responders and 25 Gy for partial responders). The endpoint was CFS. There was no difference in CFS at 5 yrs. (Peiffert D et al., JCO 2012)
What is the recurrence rate after definitive CRT for anal cancer, and what are the salvage rates at 5 yrs?

Show Answer

The recurrence rate is stage dependent (Gunderson LL et al., IJROBP 2013) but overall is **~30%**, and the salvage rate at 5 yrs following LR is **~40%–50%.**
Per RTOG 98-11, which anal cancer pts need to rcv a boost beyond 45 Gy?

Show Answer

Pts with **T3, T4, or N+ lesions or T2 lesions with residual Dz after 45 Gy** needed a boost >45 Gy.
What is the dose per fx for anal cancer per RTOG 98-11?

Show Answer

Per **RTOG 98-11,** the dose per fx for anal cancer is **1.8 Gy/fx to 45 Gy initially, then 2 Gy/fx to 55–59 Gy total for the CD portion.**
How far caudally should inguinal nodes be covered in anal cancer?

Show Answer

Inguinal nodes should be covered to the **inf border of the lesser trochanter.**
What is the standard CRT regimen for anal cancer pts who are HIV+?

Show Answer

HIV+ pts can typically be treated with the same RT + 5-FU/MMC regimen as HIV– pts. HIV+ pts with CD4 counts <200/mm^3 or other complications of HIV may require chemo (e.g., CIS instead of MMC or 1 dose of MMC) and/or RT dose adjustments.
What is the role/evidence for IMRT in anal cancer?

Show Answer

RTOG 0529, a phase II single arm study, assessed the utility of 5-FU/MMC and dose-painted IMRT in reducing grade 2+ GI/GU toxicities compared with the conventional arm from RTOG 9811. Of 52 evaluable pts, a **significant reduction was noted in acute grade 2+ hematologic** (73% vs. 85%, p = 0.03), **grade 3+ GI** (21% vs. 36%, p = 0.008) and **grade 3+ dermatologic adverse events** (23% vs. 49%, p < 0.0001). Of note, 81% required dose-painted IMRT replanning on central review (Kachnic LA et al., IJROBP 2013). Cancer control outcomes appear similar vs. RTOG 9811, with **8-yr OS, DFS, and CFS of 68% vs. 69%, 62% vs. 57%, and 66% vs. 63%, respectively** (Kachnic LA et al. ASTRO 2017. Abstract only). In addition, numerous retrospective studies suggest decreased toxicity and comparable efficacy. (Milano MT et al., IJROBP 2000; Menkarios C et al., Radiat Oncol 2007) (Anorectal contouring atlases: Myerson RJ et al., IJROBP 2009; Ng M et al., IJROBP 2012; Muirhead R et al., Clin Oncol 2014)
When treating with IMRT, how might you simulate a pt in order to minimize toxicity?

Show Answer

To **minimize skin toxicity** in the groin, simulate supine in the frog leg position. In larger pts, however, consider treating prone on a belly board **to decrease bowel dose** (smaller pts do not benefit as much) (Olsen J et al., IJROBP 2017), as this appears well tolerated with respect to dermatitis d/t IMRT decreasing skin dose & toxicity vs. 3D-CRT.
What RT dose guidelines exist for small bowel in anal cancer pts?

Show Answer

Findings **from RTOG 0529** showed: small bowel volumes of 186.0 cc, 155.0 cc, 41.0 cc, and 30.4 cc receiving more than 25, 30, 35, and 40 Gy, respectively, correlated with increased risk of acute grade ≥2 GI adverse events. (Olsen J et al., IJROBP 2017)
What is the main toxicity of MMC?

Show Answer

MMC has **acute hematologic toxicities** but does not contribute to late toxicities.
Most anal cancer recurrences are within what timeframe?

Show Answer

Most anal cancers recur within **2 yrs.**
According to the NCCN guidelines (2018), what is the post-Tx f/u for anal cancer?

Show Answer

Post-Tx anal cancer f/u: Evaluate in 8–12 wks after Tx with DRE. **Bx only if there is progressive Dz.** If there is complete remission, perform exam with inguinal nodal evaluation & DRE q3–6 mos for 5 yrs, and anoscopy q6–12 mo × 3 yrs. Consider C/A/P CT with contrast annually × 3 yrs (e.g., if T3–4 or N+).
What is the mean time to tumor regression after CRT?

Show Answer

The mean time to tumor regression after CRT is **3 mos (but can be up to 12 mos);** therefore, there is no benefit to routine post-Tx Bx. (Cummings BJ et al., IJROBP 1991)

If a pt has Bx-proven persistent Dz 3 mos after completing Tx, should the pt be referred immediately for salvage Sg?

Show Answer

No. Pts may be re-evaluated again after 4 wks. If there is still no regression, or if there is progression, consider Bx again and restage if necessary. If there is evidence of regression, continue observation and evaluation in 3 mos.

53

Low-Risk Prostate Cancer

Updated by Kevin T. Nead

BACKGROUND

What proportion of men will develop prostate cancer and what is the annual incidence and mortality in the United States?

Show Answer

1 in 7 men corresponding to **160,000** Dx of and **26,000** deaths from prostate cancer annually.

What are the 4 zones of the prostate?

Show Answer

Zones of the prostate:

. Peripheral zone
. Central zone
. Transitional zone
. Ant fibromuscular stroma

Prostate cancers develop most commonly in which zone?

Show Answer

Two-thirds of prostate cancers arise in the peripheral zone.

Benign prostatic hypertrophy (BPH) develops in which zone?

Show Answer

BPH develops primarily in the **transitional zone.**
What does median lobe hypertrophy refer to?

Show Answer

Median lobe hypertrophy refers to a characteristic transitional zone hypertrophy (BPH) that mushrooms superiorly into bladder lumen.
What tissues likely mediate erectile dysfunction (ED) after prostate RT?

Show Answer

ED likely results from RT injury to the **neurovascular bundles, internal pudendal arteries, corpora cavernosa** and possibly the **penile bulb.** (Spratt DE et al., European Urology 2017)
Name the 3 histologic cell types seen in the normal prostate.

Show Answer

. Secretory cells (produce PSA)
. Basal cells (flattened basement membrane where stem cells that repopulate the secretory layers reside)
. Neuroendocrine cells

Describe the GS and what it represents.

Show Answer

A sum of pathologic grades assigned to prostate cancer that reflect aggressiveness based on the tumor's resemblance to normal glandular tissue. A primary (or predominant) pattern is recorded f/b a secondary or lesser pattern, which are summed to give the overall GS (e.g., 3 + 4).
How do the Gleason Grade Group definitions correspond to the GSs?

Show Answer

. Group 1: GS ≤6
. Group 2: GS 3 + 4 = 7

. Group 3: GS 4 + 3 = 7
. Group 4: GS 4 + 4 = 8; 3 + 5 = 8; 5 + 3 = 8
. Group 5: GS 9–10

How often is higher-grade Dz diagnosed in a radical prostatectomy specimen (upstaging) than that seen in the initial Bx specimens?

Show Answer

One-third
What racial groups are associated with the highest and lowest risks for prostate cancer?

Show Answer

Black men are at highest risk for the development of prostate cancer (and their Dz presents more aggressively [higher GS, more advanced stage]). Asians are at the lowest risk for the development of prostate cancer. A **30- to 50-fold** difference in the incidence of the Dz is observed b/t native Asians and black men. (Ross R et al., Cancer 1995)
Define the incidence of adenocarcinoma of the prostate on autopsy studies as a function of age.

Show Answer

Incidental finding of prostate adenocarcinoma on autopsy studies increases with age, with the average GS b/t 6 and 7. In 1 study, the following incidences of prostate cancer were found:

Age 50–59: 23.4%
Age 60–69: 34.7%
Age 70–81: 45.5%

(Ming Y et al., J Urol 2008)
How does finasteride use impact prostate cancer incidence, aggressiveness, and mortality?

Show Answer

In a phase III trial comparing finasteride vs. placebo, finasteride reduced the incidence of prostate cancer **(30.6% vs. 18.6%),** but increased the risk of more aggressive (Gleason 7–10) tumors **(37% vs. 22%)** (Thompson IM et al., NEJM 2003). Finasteride likely does not impact grade, but rather shrinks the prostate, making high-grade Dz more easily detected (Lucia MS et al., JNCI 2007). There is no impact of finasteride on OS. (Thompson IM et al., NEJM 2013)

Describe 5 factors that can increase the level of PSA.

Show Answer

. Prostate cancer
. Prostate manipulation (prostate Bx or DRE)
. Infection (prostatitis)
. Ejaculation shortly before PSA testing
. BPH

Define the risk of prostate cancer as a function of total PSA level.

Show Answer

Prostate cancer risk increases as the total PSA level increases:

PSA ≤4 ng/mL: 5%–25%
PSA 4–10 ng/mL: 15%–25%
PSA ≥10 ng/mL: 50%–67%

Screening programs for prostate cancer include what 2 clinical assessments?

Show Answer

Screening for prostate cancer includes DRE and a serum PSA.

Describe 4 variants of absolute PSA that can be helpful in assessing a man’s risk of prostate cancer.

Show Answer

Variants of absolute PSA that identify prostate cancer risk:

. PSA as a function of age
. PSA velocity
. PSA density
. Ratio of free to total PSA

Describe the upper limits of normal PSA values as a function of age.

Show Answer

PSA values in men without prostate cancer will increase with age:

40–49 yrs: 1.5–2.5 ng/mL
50–59 yrs: 2.5–4 ng/mL
60–69 yrs: 4–5.5 ng/mL
70–79 yrs: 5.5–7 ng/mL

What is prostate-specific antigen velocity (PSAV), and how is it used in prostate cancer screening?

Show Answer

PSAV is a measure of the rate of change of the total PSA annually. A PSA velocity **≥2 ng/mL/yr** is associated with a higher risk of finding Gleason ≥7 prostate cancer on prostatectomy. (Loeb S et al., Urology 2008)

What is prostate-specific antigen density (PSAD), and how is it used in prostate cancer screening?

Show Answer

PSAD is the total serum PSA value divided by the volume of the prostate gland. A PSAD of **≥0.15 ng/mL/cm^3** identifies men with a higher risk of detecting prostate cancer on a screening Bx.

What is the relationship b/t prostate cancer and the ratio of serum free-to-total PSA?

Show Answer

The end product of normal PSA biosynthesis within the prostate epithelium and ducts is inactive “free PSA,” an fx of which diffuses into the circulation. In prostate cancer, tumors disrupt the prostate basement membrane and allow precursor forms of PSA to leak into the circulation, which decreases the relative proportion of free PSA. The ratio of free-to-total PSA will be lower in men with prostate cancer. A ratio of <7% is highly suspicious for prostate cancer, whereas a ratio of >25% is rarely associated with malignancy.

What are population-based screening recommendations by the American Cancer Society (ACS) for prostate cancer? U.S. Preventive Services Task Force (USPSTF)?

Show Answer

The ACS (2010) recommends that physicians discuss screening with men aged (1) ≥50 yrs at avg risk expected to live ≥10 yrs, (2) ≥45 yrs at high risk (African Americans, 1st-degree relatives diagnosed prior to 65), (3) ≥40 yrs at very high risk (>1 1st-degree relative diagnosed prior to 65 yrs). The USPSTF (2017) acknowledges a small potential mortality benefit with PSA screening that should be discussed with men aged 55–69 yrs of age (C recommendation).

Is there evidence of a mortality benefit with prostate cancer screening?

Show Answer

Yes. The European Randomized study of Screening for Prostate Cancer study with 13 yrs of f/u showed an SS **21% decreased risk** of prostate cancer mortality with PSA screening. The number needed to screen to prevent 1 death in this study was 781. (Schröder FH et al., Lancet 2014)

What has annual DRE and PSA screening in the US population shown in terms of prostate cancer and deaths?

Show Answer

In the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer screening trial, 76,685 men were randomized to (1) annual PSA × 6 yrs + annual DRE × 4 yrs or (2) usual care in which opportunistic screening with PSA or DRE was allowed. After 13 yrs of f/u, the incidence of prostate cancer was higher with PSA testing **(108 vs. 97 cases/10,000 person-yrs).** The incidence of death was similar b/t the groups (**3.7 vs. 3.4 cases/10,000 person-yrs)** (Andriole GL et al., JNCI 2012). However, control group participants reported **higher rates of PSA screening (~90%) than those in the intervention group** (Shoag JE et al., NEJM 2016) making it difficult to draw conclusions from this trial.

What is the most common presentation of prostate cancer?

Show Answer

In the PSA era, most pts present with an abnl PSA and no associated Sx.

In men with symptomatic prostate cancer, what local Sx may arise at Dx?

Show Answer

- Lower urinary tract Sx such as urgency, frequency, nocturia, and dysuria
- Hematuria
- Hematochezia, constipation, intermittent diarrhea, reduced stool caliber
- Renal impairment from bladder outlet obstruction

What is the most common site of metastatic spread of prostate cancer?

Show Answer

Bone is the most common site of metastatic spread. Blastic > lytic lesions.

WORKUP/STAGING

Name 4 important aspects of a focused Hx to include in a pt with newly diagnosed prostate cancer.

Show Answer

GI/GU Sx: may inform the most appropriate type of therapy

Comorbid illnesses: especially Hx of inflammatory bowel Dz or previous bowel Sgs (e.g., candidacy for RT, Sg, hormone suppression)
Meds: especially use of α-blockers or androgen suppression
New-onset bone pain: should result in a thorough evaluation for bone mets
What are the 3 most important clinical and pathologic factors for risk stratifying men with locally confined prostate cancer?

Show Answer

1. Pre-Tx PSA
2. DRE-defined cT
3. Gleason group

Describe the recommended procedure for Bx of the prostate.

Show Answer

Prostate Bx should be performed using a transrectal approach with a US transducer in the rectum. A sextant Bx directed at the peripheral zone should result in 12 cores of prostate tissue.
Describe the appearance of prostate cancer on TRUS.

Show Answer

Prostate cancer on TRUS is usually hypoechoic.
Define the current NCCN (2018) prostate cancer risk groups.

Show Answer

- Very low: T1c, GS ≤6, PSA <10 ng/mL, <3 Bx cores +, ≤50% cancer per core, PSA density <0.15 ng/mL/g
- Low: T1–T2a, GS ≤6, PSA <10 ng/mL
- Favorable Intermediate: T2b–T2c or GS 3 + 4 = 7 or PSA 10–20 ng/mL and <50% postive cores Unfavorable intermediate: T2b–T2c or GS 3 + 4 = 7 or PSA 10–20 ng/mL
- High: T3a or GS 8–10 or PSA >20 ng/mL
- Very high: T3b–T4 or primary Gleason pattern 5 or >4 cores with GS 8–10

What men should undergo a bone scan per NCCN guidelines (2018)?

Show Answer

T2 and PSA >10 ng/mL; high or very high risk groups
What men should undergo pelvic imaging (CT or MRI)?

Show Answer

Per NCCN guidelines (2018) pelvic imaging is indicated for intermediate, high and very high risk groups if nomogram indicated probability of LN involvement >10%. However, developing literature suggests a broader role for MRI. The PROMIS study was a multicenter randomized trial from 2012 to 2015 in 576 Bx-naïve pts who underwent 1.5T MRI plus Bx and found that for clinically significant cancer (GS ≥4 + 3 or a max cancer core length 6 mm or longer), MRI was more sensitive (93% vs. 48%; $p < 0.0001$) but less specific (41% vs. 96%; $p < 0.0001$) than TRUS-Bx. MRI may also be sup in the identification of Gleason ≥3 + 4. (Rais-Bahrami et al., J Urol 2013) T3 MRI has been shown to be advantageous in predicting ECE at Sg with a sensitivity and specificity of 58.2% and 89.1%, respectively. (Somford et al., J Urol 2013)
What is the role of tissue-based molecular assays in decision making for prostate cancer?

Show Answer

A number of tissue-based molecular assays have been developed for treated and untreated men with localized prostate cancer (e.g., Decipher, Oncoptype DX, Prolaris) and shown in retrospective analyses to provide prognostic information beyond NCCN risk groups regarding outcomes such as risk of biochemical failure, metastatic Dz and mortality. Their exact role remains incompletely defined pending prospective evaluation but current Molecular Diagnostic Services Program recommendations support their post-RP with adverse features (Decipher), and post-Bx in low-risk Dz (Oncotype DX;

Prolaris; ProMark).

Describe the AJCC 8th edition (2018) clinical TNM staging of prostate cancer.

Show Answer

Note: Per the AJCC, clinical T staging may use imaging.

cT1: Clinically inapparent tumor not palpable
cTla: Incidental histologic finding in ≤5% of tumor resected
cT1b: Incidental histologic finding in >5% of tissue resected
cT1c: Tumor identified by needle Bx but not palpable
cT2: Palpable organ-confined Dz
cT2a: Tumor involves one-half of 1 side or less
cT2b: Tumor involves more than one-half of 1 side but not both sides
cT2c: Tumor involves both sides
cT3: Extraprostatic tumor that is not fixed or does not invade adjacent structures
cT3a: ECE
cT3b: Seminal vesicle invasion
cT4: Adjacent organ involvement (bladder, external sphincter, rectum, pelvic wall, or levator muscles)
N1: regional LN mets
M1: DMs
M1a: Nonregional LNs
M1b: Bone(s)
M1c: Other sites

Describe the AJCC 8th edition (2018) pathologic TNM staging of prostate cancer.

Show Answer

pT2: Organ-confined Dz
pT3: ECE

pT3a: ECE or microscopic invasion of bladder neck
pT3b: Seminal vesicle involvement
pT4: Adjacent organ involvement (bladder, external sphincter, rectum, pelvic wall, or levator muscles)

Note: Per the AJCC, pathologic assessment is based on evaluation of a prostatectomy specimen, unless a Bx shows involvement of the rectum, seminal vesicles, or extraprostatic tissues.

N1: regional LN mets
M1: DMs
M1a: Nonregional LNs
M1b: Bone(s)
M1c: Other sites

TREATMENT/PROGNOSIS

Define active surveillance, watchful waiting, and observation.

Show Answer

Active surveillance is the postponement of immediate therapy, with active monitoring and definitive Tx given if Dz progresses. Watchful waiting is traditionally defined as forgoing definitive Tx, does not involve active monitoring, and is typically reserved for those with a short life expectancy. However, in order to disambiguate terms often used interchangeably, current guidelines refer to active surveillance vs. observation. Observation indicates monitoring for progression and offering palliative therapy as needed.
In men with early-stage prostate cancer, what is the benefit in terms of upfront surgical management vs. watchful waiting?

Show Answer

A Swedish study, SPCG-4, randomized 695 men with T1–T2 prostate cancer (all grades) to radical prostatectomy vs. observation. Sg improved 18-yr incidence of cause-specific death **(17.7% vs. 28.7%)** and DM **(26.1% vs.**

38.3%). However, this study was conducted in a pre-PSA screening era and included pts with GS 7–10. (Bill-Axelson A et al., NEJM 2014)

Have any randomized studies compared active surveillance, radical prostatectomy, and EBRT in localized prostate cancer?

Show Answer

Yes, the ProtecT trial (Hamdy FC et al., NEJM 2016) randomized 1,643 men with localized prostate cancer (GS 6–10; T1c–T2) diagnosed by PSA testing to active monitoring (n = 545), Sg (n = 553), or radiotherapy + short-course ADT (n = 545). The primary outcome was prostate-cancer mortality. At a median of 10 yrs of f/u there was **no difference in prostate cancer–specific deaths or OS.** Metastatic Dz was more common in the active monitoring group (6.3 events per 1,000 person-yrs) than in the Sg (2.4 per 1,000 person-yrs) or radiotherapy (3.0 per 1,000 person-yrs) groups (p = 0.004). **27 men require Sg and 33 men require radiotherapy to prevent 1 pt from having metastatic Dz.**

What was the active monitoring protocol in the ProtecT trial?

Show Answer

Serum PSA levels were measured q3 mos in the 1st yr and q6–12 mos following. An increase of at least 50% during the previous 12 mos triggered a review. DRE and repeat Bx were not part of the active monitoring protocol. A less comprehensive active monitoring protocol could have contributed to worse outcomes in the active monitoring group (e.g., metastatic Dz).

What are the 2 primary surgical approaches for prostatectomy and have any trials compared them?

Show Answer

The 2 primary surgical approaches are robotic-assisted radical prostatectomy and radical retropubic prostatectomy. A trial (Yaxley J et al., Lancet 2016) randomized 326 men with prostate cancer to robotic-assisted or retropubic

radical prostatectomy and **found no statistically significant differences** at 12 wks regarding urinary function, sexual function, postop complications or margin status.
What is the premise underlying active surveillance in prostate cancer care?

Show Answer

A majority of men with low-risk prostate cancer would not have any adverse clinical consequences if left untreated. Active surveillance delays definitive Tx for the majority while reserving curative for those with Dz progression.
What f/u procedures are involved in active surveillance? When should pts be referred for definitive management?

Show Answer

PSA no more than q6 mos, DRE no more than q12 mos, prostate Bx no more than q12 mos. MRI may be used to aid in the detection of high-grade Dz. Pts are referred for definitive management for increasing GS, increasing volume (as estimated by # of cores and % of cores involved), or pt preference.
Per 2018 NCCN guidelines what prostate cancer risk groups are appropriate for consideration of active surveillance?

Show Answer

Favorable intermediate-, low- and very low-risk groups.
Per 2018 NCCN guidelines what individuals are appropriate for consideration of observation only?

Show Answer

Very low–, low-, and intermediate-risk prostate cancer with <10 yrs life expectancy.
What % of men with low-grade, early-stage Dz will eventually need definitive management with curative intent b/c of progressive Dz? What is their expected prostate-cancer mortality?

Show Answer

In a prospective cohort study at the JHH of low-risk men undergoing active surveillance, the 10- and 15-yr rates of curative intervention were **50% and 57%,** respectively, with a 15-yr **prostate-cancer mortality of 0.4%** (Tosoian JJ et al., JCO 2015). Similar results were demonstrated in a prospective study from Toronto that also included favorable intermediate-risk Dz with 98.5% CSS (Klotz L et al., JCO 2015).

What 3 standard Tx options are available to an otherwise healthy man with no adverse GI/GU Sx and low-risk group Dz?

Show Answer

- Active surveillance
- Radical prostatectomy
- RT (EBRT and/or brachytherapy)

Does dose escalation improve outcomes in men with low-risk prostate cancer?

Show Answer

Dose escalation improves biochemical FFS in men with low-risk prostate cancer. This has been seen in at least 2 randomized trials that included men with low-risk Dz. PROG 9509 (Zietman AL et al., JCO 2010) compared 70.2 Gy vs. 79.2 Gy and found **improved 10-yr biochemical failure (32.2% vs. 16.7%).** The MDACC RCT (Kuban D et al., IJROBP 2008) compared 70 Gy vs. 78 Gy and found that dose escalation **improved 8-yr freedom from failure (78% vs. 59%).** Neither study demonstrated a benefit in cause-specific mortality or OS. RTOG 0126 is a phase III trial comparing 79.2 Gy in 44 fx or 70.2 Gy in 39 fx powered to examine OS. With a median of 7.0 yrs of f/u no differences in OS were reported. (Michalski et al., JAMA Oncology 2018)

Have any trials compared Sg to EBRT for localized prostate cancer?

Show Answer

Yes. The ProtecT trial (Hamdy FC et al., NEJM 2016) showed no differences in death d/t prostate cancer with RP vs. RT + ADT. Pt-reported QOL data (Donovan JL et al., NEJM 2016) showed increased urinary pad use in the RP vs. RT groups at 6 mos **(46% vs. 5%)** and 6 yrs **(17% vs. 4%).** Bowel function was similar b/t groups except an increase in bloody stools in the radiotherapy group. **17% and 27% of men could obtain erections adequate for intercourse at 6 yrs in the RP and RT groups, respectively, compared to 67% at baseline.**

What data support the use of hypofractionation for localized prostate cancer?

Show Answer

The CHHiP trial (Dearnaley D et al., Lancet 2016) randomized 3,216 men from 71 centers with localized prostate cancer (pT1b–T3aN0M0) to 74 Gy in 37 fx vs. 60 Gy in 20 fx vs. 57 in 19 fx. **With a median f/u of 62 mos 60 Gy in 20 fx was noninf to 74 Gy in 37 fx.** There were **no significant differences in side effects at 5 yrs** using 3 clinician- and pt-reported outcome measures. RTOG 0415 (abstract only, ASCO 2016) similarly showed that in men with low-risk prostate cancer, 70 Gy in 28 fx is noninf to 73.8 Gy in 41 fx.

What evidence supports the use of SBRT for localized prostate cancer?

Show Answer

Data supporting SBRT in the Tx of localized prostate cancer are limited to phase I/II studies. A pooled analysis of phase II trials in 1,100 men undergoing CyberKnife to a median dose of 36.25 Gy in 4–5 fx found 5-yr BFFS of 93%. Reported GI and GU QOL returned to baseline within 6 mos following Tx, but toxicity grade was not reported (King CR et al., Radiotherapy and Oncology 2013). A later multi-institutional phase I/II study (Hannan R et al., Eur J Cancer 2016) of 91 low- and intermediate-risk

prostate cancer pts treated with up to 50 Gy in 5 fx found 98.6% BFFS at 5 yrs. 4 grade IV late GU/GI toxicities were observed.
Which pts are candidates for primary brachytherapy?

Show Answer

Brachytherapy monotherapy can be considered in low-risk and low-volume intermediate-risk prostate cancer. Intermediate- and high-risk pts are candidates for combining brachytherapy with EBRT.
What are the American Brachytherapy Society absolute and relative contraindications for brachytherapy?

Show Answer

- Absolute: High operative risk, no rectum, limited life expectancy (<10 yrs), DMs, ataxia telangiectasia
- Relative: High IPSS (cutoff 15–18 in RTOG trials), prior pelvic RT, prior TURP, large median lobe, gland **>60 cc,** inflammatory bowel Dz

Describe the setup of a pt with prostate cancer undergoing CT imaging to plan EBRT.

Show Answer

Techniques vary by institution. One approach is CT simulation in the supine position with knee and foot lock, +/– a pelvic MRI, with a full bladder and rectal balloon. Fiducials may be placed for daily localization. The use of rectal spacer is an emerging modality to decrease ant rectal wall dose.

FOLLOW-UP/TOXICITY

What are the most common side effects after radical prostatectomy?

Show Answer

The most common significant side effects after radical prostatectomy are ED, urinary incontinence, and urethral stricture.
What % of men will be able to maintain erections firm enough for

intercourse following definitive Tx for prostate cancer with RT or Sg?

Show Answer

Traditional teaching states that ~50% of previously potent men will be able to maintain erections for intercourse for both modalities 1–2 yrs post-Tx. In the ProtecT trial (Hamdy FC et al., NEJM 2016) erectile function was **worse at all-time points** following Sg compared to RT, **including during ADT.**

What % of men who undergo a radical prostatectomy have significant postop urinary incontinence? Long-term urinary incontinence?

Show Answer

40% of men who undergo a robotic-assisted radical prostatectomy have significant postop urinary incontinence at 12 wks. (Yaxley J et al., Lancet 2016) In the ProtecT trial 17% continued to require pads at 6 yrs (Hamdy FC et al., NEJM 2016) compared to 4% in the RT group.

What are the most common acute and late side effects of EBRT and brachytherapy?

Show Answer

Acute: fatigue, urinary urgency/frequency, proctitis/diarrhea
Late: ED, cystitis, proctitis (frequency/bleeding)

Estimate the rate of grade 3 or higher late GU or GI RT toxicity with IMRT for prostate cancer.

Show Answer

Numerous retrospective studies suggest that grade 3 or higher late GU or GI RT toxicity with IMRT for prostate cancer is rare (≤1%).

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Intermediate- and High-Risk Prostate Cancer

Updated by Kevin T. Nead

BACKGROUND

What % of newly diagnosed prostate cancer is Gleason ≥7 on Bx?

Show Answer

In the United States, **~1 in 3** of all newly diagnosed prostate cancer in a screened population is Gleason ≥7. (Andriole GL et al., NEJM 2009)

What % of newly diagnosed prostate cancer are Gleason ≥8 on Bx?

Show Answer

In the United States, **~1 in 10** of all newly diagnosed prostate cancer in a screened population is Gleason ≥8. (Andriole GL et al., NEJM 2009)

Estimate the risk of Gleason ≥7 prostate cancer in a man who has pre-Bx PSA of 4–10 ng/mL? ≥10 ng/mL?

Show Answer

~1 in 2 men with a pre-Bx PSA of 4–10 ng/mL will have Gleason ≥7 prostate cancer. ~2 in 3 men with PSA ≥10 ng/mL will have Gleason ≥7 prostate cancer. (Schröder FH et al., J Urol 2000)

In which portion of the prostate is the prostatic capsule not clearly defined?

Show Answer

At the apex of the prostate, the prostatic capsule is not clearly identifiable. Some authors argue that the prostate does not have a true capsule but rather simply has an outer fibromuscular band that continuously transitions to periprostatic tissues and organs. The transition at the apex is particularly difficult to identify. (Ayala AG et al., Am J Surg Pathol 1989)
In which portion of the prostate is ECE most commonly found?

Show Answer

ECE is most commonly found in the posterolat portion of the prostate **at the prostatic neurovascular bundle.**

WORKUP/STAGING

According to the 2018 NCCN guidelines which men are intermediate-risk Dz?

Show Answer

T2b–T2c or GS 3 + 4 = 7 or GS 4 + 3 = 7 or PSA 10–20 ng/mL; no high-risk features
According to the 2018 NCCN guidelines which men are high- or very high–risk Dz?

Show Answer

. High: T3a or GS 8–10 or PSA >20 ng/mL
. Very high: T3b–T4 or primary Gleason pattern 5 or >4 cores with GS 8–10

If a pelvic MRI is ordered as part of the workup for prostate cancer, how long after Bx should it take place?

Show Answer

There is no consensus on the role of pelvic/prostate MRI as part of the workup for prostate cancer nor evidence that it improves outcomes. However,

if an MRI is ordered, it is ideally done **before Bx** or **6–8 wks after Bx to avoid artifact** caused by post-Bx hemorrhage.

TREATMENT/PROGNOSIS

What are the Tx options for a man with localized intermediate-risk prostate cancer?

Show Answer

Tx options for a man with intermediate-risk prostate cancer according to 2018 NCCN guidelines include:

- EBRT +/– short-term androgen suppression (AS) (4–6 mos) +/– brachytherapy boost
- Brachytherapy alone +/– AS
- Prostatectomy (consider likelihood of indications for postop RT)
- Active surveillance if favorable intermediate risk group

If he has a life expectancy <10 yrs, consider observation.

What are the Tx options for a man with localized high-risk prostate cancer?

Show Answer

Tx options for a man with high-risk prostate cancer:

- EBRT + long-term AS (2–3 yrs) +/– pelvic node RT +/– brachytherapy boost
- Prostatectomy (consider likelihood of indications for postop RT)

Estimate the 5-yr biochemical failure-free survival (bFS) for D'Amico intermediate- and high-risk prostate cancer pts treated with prostatectomy alone.

Show Answer

After prostatectomy alone, 5-yr bFS is **~65% for intermediate-risk** and

~35% for high-risk prostate cancer pts. (D'Amico A et al., J Urol 2001)
Estimate the 10-yr bFS for prostate cancer pts with cT2b and ≥cT2c Dz treated with prostatectomy alone.

Show Answer

After prostatectomy alone, 10-yr bFS is **~62% for cT2b, and ~57% for ≥cT2c.** (Han M et al., Urol Clin N Am 2001)
Estimate the 10-yr bFS for prostate cancer pts with Gleason 3 + 4 = 7, 4 + 3 = 7, and Gleason 8–10 Dz treated with prostatectomy alone.

Show Answer

After prostatectomy alone, 10-yr bFS is **~60% with Gleason 3 + 4 = 7, ~33% with 4 + 3 = 7, and ~29% with Gleason 8–10.** (Han M et al., Urol Clin N Am 2001)
Estimate the 10-yr bFS for prostate cancer pts with a pre-Tx prostate-specific antigen (pPSA) from 10–20 and >20 ng/mL treated with prostatectomy alone.

Show Answer

After prostatectomy alone, 10-yr bFS ~57% with pPSA 10–20 ng/mL and 48% with pPSA >20 ng/mL are **57% and 48%,** respectively. (Han M et al., Urol Clin N Am 2001)
What traditionally classied pts as unfavorable vs. favorable intermediate risk?

Show Answer

Factors that may identify an unfavorable intermediate-risk subgroup include primary Gleason 4 Dz, >50% positive cores, or ≥2 intermediate-risk factors. Retrospectively unfavorable pts had higher rates of PSA failure, DM and cause specific mortality. (Zumsteg ZS et al., Eur Urol 2013)
What are the benefits of neoadj AS prior to radical prostatectomy?

Show Answer

The benefits of neoadj AS prior to prostatectomy include **decreased +margin and LN positivity rates.** This has been shown in multiple randomized trials.

Why is neoadj AS prior to radical prostatectomy not commonly used?

Show Answer

Despite improvement in pathologic outcomes with neoadj AS prior to prostatectomy, **long-term bFS rates do not appear to be improved.** This negative result has been found in multiple randomized studies. (Kumar S et al., Cochrane Database Syst Rev 2006)

What is the role of adj AS therapy after prostatectomy?

Show Answer

In prostate cancer pts found to have **node+ Dz after prostatectomy, immediate adj AS** improves OS. (Messing EM et al., Lancet Oncol 2006)

There appears to be no OS or CSS in node– men after prostatectomy (Wirth MP et al., Euro Urol 2004), although the RCT evaluating this question used only an antiandrogen instead of a GnRH agonist or total AS with both.

What study established the role of adj AS for node+ pts after prostatectomy? What is the main criticism of this study?

Show Answer

Messing EM et al. showed an OS benefit of immediate adj AS vs. observation for node+ prostate cancer pts after prostatectomy (MS 13.9 yrs vs. 11.3 yrs, respectively). The main criticism of this study is that **AS was not initiated in the observation arm until clinical Dz progression rather than an elevated absolute PSA or PSA velocity.** (Lancet Oncol 2006)

Is active surveillance a reasonable approach in intermediate-risk Dz?

Show Answer

Per the NCCN guidelines 2018, active surveillance is an option for men with favorable intermediate-risk Dz.
Is LDR brachy alone appropriate for intermediate- or high-risk Dz? Describe 1 study that argues against LDR brachy.

Show Answer

Per the American Brachytherapy Society guidelines, LDR brachy alone is not appropriate for high-risk Dz but may be considered for highly selected pts with intermediate-risk Dz (Davis BJ et al., Brachytherapy 2012). A retrospective study by D'Amico A et al. (JAMA 1998) found that LDR brachy alone was associated with worse 5-yr biochemical progression-free survival (bPFS) compared to prostatectomy and EBRT alone in both intermediate- and high-risk subgroups. However, several single-institution series suggest that well-selected intermediate-risk pts receiving a high-quality implant have excellent outcomes after LDR brachy alone (5-yr bPFS >95%). (Taira AV et al., IJROBP 2009)
What is the role of neoadj AS and LDR brachy for pts with intermediate- or high-risk prostate cancer?

Show Answer

Neoadj AS may be used **to cytoreduce large prostates** (Nag S et al., IJROBP 1999). However, several large retrospective studies have failed to show that AS improves cancer control outcomes in combination with LDR brachy.
What randomized evidence exists for brachytherapy boost following EBRT for intermediate- and high-risk pts?

Show Answer

Hoskin PJ et al. (Radiotherapy and Oncology 2012) randomized mostly intermediate/high-risk men to 55 Gy in 20 fx vs. 35.75 Gy in 13 fx + HDR boost (2 × 8.5 Gy) and found a 31% reduced ($p = 0.01$) risk of recurrence

with HDR boost without excess toxicity. ASCENDE-RT (Morris WJ et al., IJROBP 2017) gave high-risk men 46 Gy to the whole pelvis (WP) and then randomized them to EBRT boost to 78 Gy vs. LDR boost to 115 Gy and found a 50% risk of biochemical failure in the LDR boost arm ($p = 0.004$), but no difference in OS at 6.5 yrs median f/u.

What studies support the use of short-course (4–6 mos) AS with EBRT in localized intermediate-risk prostate cancer?

Show Answer

The 1st study to show a benefit to short-course AS in locally advanced prostate cancer was **RTOG 8610,** although all of these pts were high risk as defined by the D'Amico criteria. None of the published studies of short-course AS specifically studied intermediate-risk pts. **RTOG 9408** enrolled all risk group pts (but mainly intermediate risk) and found a 10-yr OS benefit to the addition of short-course AS (Jones CU et al., NEJM 2011). In addition, intermediate-risk pts were included in D'Amico A et al. (JAMA 2004), Laverdiere J et al. (J Urol 2004), and Denham JW et al. (Lancet Oncol 2005; **TROG 96.01**), all of which showed improved Dz-specific outcomes with the addition of short-course AS to EBRT. It is unclear whether dose escalation mitigates the benefit of short-course AS in intermediate-risk pts.

Describe the study design and results of RTOG 8610, which studied the benefit of short-course AS in locally advanced prostate cancer.

Show Answer

RTOG 8610 enrolled 456 men with cT2–T4 (bulky) prostate cancer. N1 pts were eligible if below the common iliac. All were treated with EBRT (65–70 Gy) and randomized to 4 mos of AS (beginning 2 mos prior to EBRT) or observation with AS at relapse. **10-yr OS and MS favored the short-course AS arm (43% vs. 34% and 8.7 yrs vs. 7.3 yrs, respectively) although the difference was NSS.** Short-course AS improved 10-yr CSM (23% vs. 36%) and distant failure (35% vs. 47%). (Roach M et al., JCO 2008)

Describe the study design and results of RTOG 9408, which studied the benefit of short-course AS in locally confined prostate cancer.

Show Answer

RTOG 9408 enrolled 1,979 pts with T1b–T2b, PSA ≤20, prostate cancer (54% were intermediate risk). Pts were randomized to EBRT alone (66.6 Gy) +/– 4-mo AS (flutamide and LHRH agonist) beginning 2 mos prior to EBRT. **12-yr OS favored the short-course AS arm (54% vs. 61%).** AS also reduced the rates of +prostate Bx at 2 yrs (39% vs. 20%). (Jones CU et al., NEJM 2011)

Describe the study design and results of TROG 96.01, which studied the benefit of short-course AS in locally advanced prostate cancer.

Show Answer

TROG 96.01 enrolled 818 pts with T2b–T4 prostate cancer treated with EBRT (66 Gy in 2 Gy). Pts were randomized to 0, 3, or 6 mos of AS starting 2 mos prior to EBRT. With only a median f/u of 5.9 yrs, the 3- and 6-mo AS arms had improved LF, biochemical failure, and freedom from salvage Tx compared to the no-AS arm. The 6-mo arm also had improved distant failure and prostate cancer–specific survival (PCSS) compared to the no AS arm. As of yet, there are no OS differences among any of the 3 arms and no consistent cancer control differences b/t 3- and 6-mo arms. (Denham JW et al., Lancet Oncol 2005)

Is AS still beneficial with dose-escalated RT?

Show Answer

Two RCTs have evaluated this question. EORTC 22991 (Bolla M et al., JCO 2016) randomized men to intermediate- and high-risk localized prostate cancer pts to 70, 74 or 78 Gy +/– AS and found that AS conferred improved biochemical (HR = 0.53; $p < 0.001$) and clinical (HR = 0.63; $p < 0.001$) failure. DART01/05 GICOR (Zapatero A et al., Lancet Oncology 2015)

treated intermediate- and high-risk pts with 76–82 Gy and randomized them to 4 mos vs. 28 mos ADT and found long-term ADT improved biochemical and overall survival.
When should AS be started in a prostate cancer pt being treated with EBRT and AS?

Show Answer

In prostate cancer pts being treated with EBRT + AS, **AS is usually started 2 mos prior to the start of EBRT.** Preclinical experiments suggest that neoadj AS may improve prostate cancer RT sensitivity compared to concurrent AS, possibly d/t improved tumor oxygenation with neoadj AS. Furthermore, the RCTs that established the role of short-course AS started it neoadjuvantly **(RTOG 8610, D'Amico trial, TROG 96.01).** However, **RTOG 9413,** which compared neoadj/concurrent vs. adj short-course AS, showed no bPFS benefit (or detriment) to neoadj AS.
Describe the study design and results of RTOG 9413, which studied the benefit of the sequence of short-course AS and pelvic node RT in locally advanced prostate cancer.

Show Answer

RTOG 9413 had a 2 × 2 factorial design. It randomized 1,323 intermediate- and high-risk pts to 4 mos of AS beginning 2 mos prior to or immediately following EBRT. The 2nd randomization was regarding RT field size: WP RT vs. prostate and seminal vesicles only. After a median f/u of 7 yrs, there was **no difference in PFS in the neoadj vs. adj AS arms and no difference in PFS in the WP and prostate and seminal vesicles only arms.** Interpretation of this trial is limited by the fact that there was an unexpected interaction b/t the 2 randomizations of this study. (Lawton C et al., IJROBP 2007)
What is the appropriate duration of neoadj AS prior to EBRT in prostate cancer pts?

Show Answer

Prostate cancer pts who are treated with neoadj AS usually rcv 2 mos of AS prior to EBRT. 1 RCT enrolled 378 men with localized prostate cancer of any risk group, and all were treated with EBRT (66–67 Gy) without concurrent AS. Pts were randomized to 3 mos vs. 8 mos of neoadj AS. 5-yr freedom from failure (FFF) did not differ b/t the Tx arms. In an unplanned subgroup analysis, 5-yr DFS was improved for high-risk pts (71% vs. 42%) (Crook J et al., IJROBP 2009). **RTOG 9910** evaluated 8-wks vs. 28 wks of neoadj therapy in men with intermediate-risk Dz and found no difference in cause-specific mortality, OS, locoregional progression or DM. (Pisansky TM et al., JCO 2015)

Which studies support the role of long-term AS in localized high-risk prostate cancer pts treated with EBRT?

Show Answer

An OS benefit of long-term AS in high-risk pts after EBRT was 1st shown in **RTOG 8531.** Multiple subsequent RCTs have also shown improved prostate cancer outcomes: **the Casodex Early Prostate Cancer trial, EORTC 22863, RTOG 9202, and EORTC 22961.**

Describe the study design and results of RTOG 8531, which studied the benefit of the long-term AS in locally advanced prostate cancer.

Show Answer

RTOG 8531 enrolled 945 men with cT3 (nonbulky), pT3 after prostatectomy, or N1 prostate cancer. All were treated with EBRT (definitive dose: 65–70 Gy; postop dose: 60–65 Gy) and randomized to adj AS indefinitely or observation with AS at relapse. **Adj AS improved 10-yr OS (49% vs. 39%), 10-yr CSM (16% vs. 22%), 10-yr LF (23% vs. 38%), and 10-yr distant failure (24% vs. 39%)** (WP). On subset analysis, benefits were limited to the subset with Gleason ≥7 and were especially important in the subset with Gleason ≥8. (Pilepich MV et al., IJROBP 2005)

Describe the study design and results of EORTC 22863, which studied the

benefit of long-term AS in locally advanced prostate cancer.

Show Answer

EORTC 22863 enrolled 412 men with cT3–T4/any grade or cT1–T2/WHO grade 3 prostate cancer. All were treated with EBRT (70 Gy) and randomized to 3 yrs of adj AS (beginning with EBRT) or observation with AS at relapse. Long-term AS improved **5-yr OS (78% vs. 62%), CSS (94% vs. 79%), LF (1.7% vs. 16.4%), and distant failure (9.8% vs. 29.2%).** (Bolla M et al., Lancet 2002)

Describe the study design and results of RTOG 9202, which studied the benefit of the long-term AS in locally advanced prostate cancer.

Show Answer

RTOG 9202 enrolled 1,541 men with cT2c–T4, PSA <150. All were treated with 2 mos of neoadj AS and 2 mos of concurrent AS + EBRT (65–70 Gy). Pts were randomized to an additional 2 yrs of adj AS or observation with AS at relapse. Long-term AS was not associated with OS in the entire cohort, although it did show improved 10-yr CSS (89% vs. 84%), local progression (12% vs. 22%), and DM (15% vs. 23%). In an unplanned subgroup analysis, long-term AS improved 10-yr OS in pts with Gleason ≥8 (45% vs. 32%). (Horwitz EM et al., JCO 2008)

Describe the study design and results of the EORTC 22961 RCT, which compared short-course and long-term AS with EBRT in localized prostate cancer.

Show Answer

EORTC 22961 enrolled 1,113 men with cT2c–T4/N0 or cT1c–T2b/pN1–N2 prostate cancer and randomized to EBRT (70 Gy) with 6 mos vs. 3 yrs of neoadj, concurrent, and adj AS. **Men receiving 3 yrs of AS had sup OS (5-yr OS 85% vs. 81%) and CSM (5-yr CSM 3.2% vs. 4.7%).** Long-term overall QOL did not significantly differ b/t the 2 arms. (Bolla M et al., NEJM

2009)

What is the appropriate duration of long-term AS in localized high-risk prostate cancer pts treated with EBRT?

Show Answer

RTOG 9202 and EORTC 22961 suggested that long-term (2–3 yrs) AS is sup to short-course AS in high-risk pts. However, the optimum duration of long-term AS has not been well studied.

What is the role of pelvic nodal RT in localized intermediate- and high-risk prostate cancer?

Show Answer

The major RCTs that established the role of RT in locally advanced prostate cancer generally irradiated pelvic nodes. However, the role of pelvic nodal RT in localized prostate cancer has been specifically studied in 3 RCTs: **RTOG 7706, RTOG 9413, and GETUG-01,** and none showed a cancer control benefit to irradiating pelvic nodes. Pelvic nodal RT may still be warranted in men at very high risk of harboring nodal Dz, although who these pts are is controversial. RTOG 0924 is currently ongoing to evaluate the role of pelvic nodal irradiation in unfavorable intermediate or favorable high-risk prostate cancer.

What is the appropriate EBRT dose for intermediate- and high-risk prostate cancer?

Show Answer

Men with intermediate- and high-risk prostate cancer who do not rcv AS should be treated to total EBRT doses of **≥74 Gy** (in 2 Gy/fx). There have been at least 4 EBRT dose escalation studies including intermediate- and high-risk pts: the **MDACC dose escalation trial, PROG 9505, the Dutch dose escalation trial, and the MRC RT01 trial.** All 4 RCTs have shown at least improved biochemical control with dose-escalated EBRT. The role of

high-dose EBRT is less clear in the setting of AS. The Dutch dose escalation trial allowed AS, but only a minority of men rcv it (22%) (Peeters ST et al., JCO 2006). The **MRC RT01** trial mandated neoadj and concurrent AS, and 5-yr outcomes favored dose escalation. RTOG 0126 is a phase III trial comparing 79.2Gy in 44 fx or 70.2 Gy in 39 fx powered to examine OS. With a median of 8 yrs of f/u no differences in OS were reported. (Abstract only, ASCO GU 2015)
Describe the study design and results of the MDACC RCT that studied the benefit of dose escalation in localized prostate cancer.

Show Answer

The MDACC dose escalation trial enrolled 301 pts with cT1b–T3 prostate cancer. None were treated with AS. 21% were low risk, 47% were intermediate risk, and 32% were high risk. Pts were randomized to 70 Gy vs. 78 Gy. **Dose escalation improved 8-yr FFF (78% vs. 59%).** This improvement was seen in the low- and high-risk subsets but not in the intermediate-risk subset. **8-yr CSS was not significantly different (99% vs. 95%) nor was 8-yr OS (78% vs. 79%).** (Kuban D et al., IJROBP 2008)
Describe the study design and results of the PROG 9509 RCT, which studied the benefit of dose escalation in localized prostate cancer.

Show Answer

The **PROG 9509** RCT on dose escalation enrolled 393 pts with T1b–T2b, PSA <15 ng/mL prostate cancer. Pts were randomized to 70.2 Gy or 79.2 Gy. CD RT to the prostate only was given by proton RT prior to 50.4 Gy with photon RT to the prostate and seminal vesicle. **Dose escalation improved 5-yr freedom from biochemical failure (80% vs. 61%) and 5-yr LC (48% vs. 55%).** In an unplanned analysis, a significant improvement in freedom from biochemical failure was seen in both low- and intermediate-risk subsets. (Zietman AL et al., JAMA 2005)
Describe the study design and results of the MRC RT01 RCT, which

studied the benefit of dose escalation in the setting of neoadj and concurrent AS for localized prostate cancer.

Show Answer

The **MRC RT01** trial enrolled 843 men with cT1b–T3a, PSA <50 prostate cancer. All men were treated with 3–6 mos of neoadj and concurrent AS and randomized to EBRT 64 Gy or 74 Gy. The **dose escalation arm improved 5-yr bPFS (71% vs. 60%).** LC, freedom from salvage AS, and DMFS favored the dose-escalation arm, although these endpoints were not statistically different. (Dearnaley DP et al., Lancet Oncol 2007)

What is the role of primary AS alone for localized high-risk prostate cancer?

Show Answer

AS alone for localized high-risk prostate cancer may be considered for men who cannot tolerate local management.

Describe the design and results of the Scandinavian RCT (SPCG-7) that studied the long-term AS +/- EBRT in locally advanced prostate cancer.

Show Answer

SPCG-7 enrolled 875 men with cT1b–T2, N0 WHO grade 2–3 or cT3, any grade, N0 prostate cancer. All men were treated with total AS for 3 mos → an antiandrogen alone (flutamide) indefinitely. Pts were randomized to EBRT (70 Gy) starting after 3 mos of AS or no local therapy. With median f/u of 7.6 yrs, the addition of **EBRT improved 10-yr OS (70% vs. 61%) and 10-yr CSS (88% vs. 76%).** The 10-yr prostate cancer–specific mortality was reduced by half with EBRT (12% vs. 24%) (Widmark A et al., Lancet 2009). A 2016 update (Fossa SD et al., Eur Urol 2016) showed that the 15-yr prostate cancer–specific mortality was 34% vs. 17% in the ADT vs. ADT + RT arms, respectively.

Describe the design and results of the Warde RCT that studied the long-

term AS +/- EBRT in locally advanced prostate cancer.

Show Answer

In Intergroup T94-0110 1,205 pts with prostate cancer initially who had cT3–4 Dz (later broadened to include cT2 w/ PSA >40 or PSA >40 and Gleason >8) were randomized to either lifelong AS alone (bilat orchiectomy or LHRH agonist) +/– EBRT (pelvis to 45 Gy → prostate (65–69 Gy) or prostate alone (65–69 Gy). Addition of RT to AS resulted in improved OS (HR 0.70; 95% CI 0.57–0.85) and PCSS (HR 0.46; 95% CI 0.34–0.61) with a median f/u time of 8 yrs. (Mason M et al., JCO 2015)

What is the role of definitive prostate RT in men with node+ prostate cancer?

Show Answer

There has been no RCT to determine whether men with node+ prostate cancer benefit from local RT. A retrospective review by Zagars et al. suggested that **EBRT in addition to long-term AS confers an OS benefit to node+ pts.** (J Urol 2001) Subset analyses from **RTOG 8531** suggest that long-term AS + EBRT confer OS benefit compared to EBRT alone in node+ pts. However, long-term biochemical control (PSA <1.5 ng/mL) was still poor (10% at 9 yrs). (Lawton C et al., JCO 2005)

What evidence exists for the addition of chemo to ADT for initial Tx in high-risk pts undergoing local therapy?

Show Answer

GETUG 12 (Fizazi K et al., Lancet Oncology 2015) randomized men with ≥1 high-risk feature or positive LNs to local Tx with ADT +/– docetaxel and estramustine and found improved 8-yr RFS in the chemo arm (62% vs. 50%; p = 0.017). The STAMPEDE trial randomized 1,917 men (95% newly diagnosed; 5% relapse post local therapy) to ADT +/– abiraterone and prednisone and found that OS was significantly increased with the addition of

abiraterone (3-yr survival 83 vs. 76% with ADT alone, HR 0.63, 95% CI 0.52–0.76).

FOLLOW-UP/TOXICITY

What are the most common acute and late side effects of definitive prostate RT?

Show Answer

Acute side effects: fatigue, urinary urgency/frequency, proctitis/diarrhea
Late side effects: erectile dysfunction (inability to maintain an erection for intercourse), cystitis, proctitis (frequency/bleeding)

Estimate the rate of erectile dysfunction in previously potent men 2+ yrs after Tx with definitive prostate RT.

Show Answer

~50% of men who were previously potent will no longer be able to maintain erections for intercourse 2+ yrs after definitive prostate RT. (Robinson JW et al., IJROBP 2002)

Does the use of short-course or long-term AS affect acute or late GU and GI RT toxicity in prostate cancer pts?

Show Answer

No. Multiple studies have evaluated the effect of AS on GU and GI RT toxicity. There appears to be no strong effect.

What are the common short-term and long-term side effects of AS?

Show Answer

Short-term side effects: hot flashes, decreased libido, fatigue
Long-term side effects: gynecomastia, anemia, decreased muscle mass, decreased bone density, obesity, mood changes, dyslipidemia, insulin resistance, possibly diabetes, coronary artery Dz, cognitive changes.

What are common side effects associated with antiandrogen therapy, and

how long is the Tx course?

Show Answer

Common side effects of bicalutamide, which is most commonly prescribed d/t its favorable toxicity profile, include **breast tenderness and gynecomastia** (50%) as well as **loss of libido, diarrhea, and hepatotoxicity.** It is generally prescribed for the 1st 2–4 wks with a GnRH analog.

55

Adjuvant and Salvage Treatment for Prostate Cancer

Updated by David M. Guttmann

BACKGROUND

In which portion of the prostate is ECE most commonly found?

Show Answer

ECE is most commonly found in the **poseterolateral portion of the prostate, near the prostatic neurovascular bundle.**

What is the ASTRO/American Urological Association (AUA) definition of biochemical recurrence s/p radical prostatectomy?

Show Answer

The AUA definition of biochemical recurrence s/p radical prostatectomy is a serum **PSA ≥0.2 ng/mL,** confirmed by a 2nd determination also ≥0.2 ng/mL.

What is the mean time to PSA nadir after RT for localized prostate cancer?

Show Answer

The mean time to PSA nadir after RT for localized prostate cancer is **18 mos.** Though there are contradictory reports, it seems that the rate of decline in PSA does not appear to correlate with risk of Dz recurrence.

What is the Phoenix criterion (2005 consensus panel) for defining

biochemical recurrence after RT for localized prostate cancer?

Show Answer

Partly to eliminate concerns about the "backdating" associated with the original ASTRO definition, the Phoenix criterion for defining biochemical recurrence after RT for localized prostate cancer is a PSA rise of **≥2 ng/mL above the PSA nadir,** even after the discontinuation of androgen deprivation therapy (ADT). The date of recurrence is the date of the PSA that triggers the definition.

What is the concept of "PSA bounce" in pts who rcvd RT for localized prostate cancer? How should it be managed?

Show Answer

After RT for localized prostate cancer, serum PSA typically falls. However, **it can rise transiently,** called a PSA bounce, usually around **12–18 mos after Tx,** and classically associated with pts having undergone **brachytherapy.** This can occur even without Dz recurrence. Using the Phoenix definition of biochemical failure, a PSA bounce can trigger a false failure in **10%–20% of pts.** There is no definitive method to distinguish a PSA bounce from recurrent Dz. The PSA should be rechecked 3–6 mos later and managed accordingly.

What is the risk of mets or death following biochemical failure after prostatectomy?

Show Answer

In a prominent series of men who developed biochemical failure post prostatectomy and did not undergo subsequent salvage Tx, the median MFS was **10 yrs.** (Pound, JAMA 1999)

WORKUP/STAGING

For men with rising PSA (and no other Sx of Dz) after definitive local Tx for prostate cancer, what is the utility of imaging studies in the workup?

Show Answer

For men with biochemical-only recurrence after definitive local Tx for prostate cancer, the yield of imaging studies is low. The **likelihood of a positive bone scan is <5% if PSA <10 ng/mL, though time to PSA relapse and PSA kinetics can change pretest probability.** (18F)-fluorocholine and fluciclovine-(18F) PET/CT may offer improved sensitivity, though further investigation of these tests is warranted.

What is the utility of prostate Bx for men with a rising PSA (and no other Sx of Dz) after definitive prostate RT?

Show Answer

For post-RT pts with prostate cancer, **TRUS prostate Bx is typically not recommended unless local salvage options are being considered,** such as prostatectomy. Bx should be performed at least 18 mos after RT completion.

What is the utility of prostate bed Bx for men with a rising PSA (and no other Sx of Dz) after radical prostatectomy?

Show Answer

This is controversial, and most recurrences are at the anastomotic site. Palpable prostate bed nodules should probably be biopsied and perhaps given higher doses of RT.

TREATMENT/PROGNOSIS

What is the prognostic significance of PSA-DT after local therapy for prostate cancer?

Show Answer

PSA-DT can help predict MFS and CSS. PSA-DT <3 mos confers a 20-fold higher risk of prostate cancer death than PSA-DT ≥3 mos. **For pts with PSA-DT <3 mos, 5-yr cause-specific mortality after biochemical failure is 35% and 75% for Gleason 7 and ≥8 Dz, respectively.**

Name 5 prognostic factors associated with a favorable outcome after salvage RT.

Show Answer

Prognostic factors associated with a favorable outcome after salvage RT post prostatectomy: **+Margin, low PSA at recurrence, long recurrence-free interval, long PSA-DT, low prostatectomy GS.** (Stephenson AJ et al., JCO 2007)

What are the indications for adj RT after prostatectomy, and what studies support its role?

Show Answer

pT3N0 prostate cancer or positive surgical margins. 3 RCTs using these criteria and showed improved 10-yr biochemical PFS with adj RT compared to observation: **SWOG 8794, EORTC 22911, and ARO 96-02.** The SWOG 8794 study, which has the longest f/u, found an OS benefit with adj RT. Exploratory analyses of the EORTC study suggest that the benefit may be limited to men <70 yo or with +margins after Sg.

Describe the study design and results of the SWOG 8794 RCT that compared adj RT and observation in pts with high-risk features after prostatectomy.

Show Answer

SWOG 8794 enrolled 431 men with pT3N0 prostate cancer or +margin after prostatectomy and randomized to adj RT (60–64 Gy). **Adj RT improved MS (15.2 yrs vs. 13.3 yrs).** Global QOL was initially worse in the adj RT arm but was similar after 2 yrs of f/u and sup thereafter. (Thompson IM et al., J Urol 2009)

Is there any evidence that salvage RT post prostatectomy improves survival c/w observation?

Show Answer

There is no prospective evidence, but there is retrospective evidence (Trock BJ et al., JAMA 2008). 635 pts s/p prostatectomy with biochemical recurrence were treated either with observation, salvage RT alone, or salvage RT + hormone therapy. Adjusted for prognostic factors, **CSS was prolonged in pts who rcvd salvage RT compared to observation, regardless of hormone therapy (5-yr CSS 96% vs. 88%).**

Are there randomized data comparing adj vs. salvage RT in men with locally advanced prostate cancer or biochemical recurrence s/p prostatectomy?

Show Answer

No. The 3 randomized trials on adj therapy **(SWOG 8794, EORTC 22,911, and ARO 96-02)** compared adj RT vs. observation, without strict salvage guidelines at the 1st sign of Dz recurrence. **Nonrandomized series on salvage RT appears to produce results somewhat comparable to adj RT.** The ongoing **RAVES** trial (TROG) randomizes men with PSA <0.1 ng/mL postprostatectomy PSA to adj vs. early-salvage RT.

At what threshold should salvage RT be initiated following biochemical failure post prostatectomy?

Show Answer

Based on Stephenson 2007, superior biochemical control following salvage Tx was obtained when salvage Tx was administered at **PSA <0.5 ng/mL.** This cutoff was later shown to be associated with lower rates of DM, cancer-specific death, and all-cause mortality. (Stish et al., JCO 2016)

What is ultrasensitive PSA and what is its role in the management of biochemical recurrence post prostatectomy?

Show Answer

Ultrasensitive PSA is a newer PSA test with a **lower limit of detection of 0.01 ng/mL or less.** AUA Guidelines do not recommend calculation of PSA-

DT from ultrasensitive measurements. While it has strong NPV, PPV of early PSA-DT may be as low as 40%. The initial validation of PSA-DT as a biomarker was in the context of an assay that only measured PSA >0.2 ng/mL, so the clinical utility of early PSA-DT is still unclear.

What are the appropriate CTV borders for the prostatic fossa?

Show Answer

Below the public symphysis: Ant border is post edge of the pubic bone, post border is ant rectal wall, inf border is 8–12 mm below the vesicourethral anastomosis, and lat borders are levator ani and obturator internus muscles. Above the symphysis: Ant border is post 1–2 cm of the bladder, post border is mesorectal fascia, sup border is cut end of the vas deferens, and lat borders are the sacrorectogenitopubic fascia.

What is the role of pelvic nodal RT in salvage RT post prostatectomy?

Show Answer

The appropriate Tx volume in adj and salvage RT post prostatectomy has not been prospectively determined. Randomized trials in adj RT **(SWOG 8794, EORTC 22,911, and ARO 96-02)** used **small-field RT and did not include regional pelvic nodal irradiation. RTOG-0534** is an ongoing trial looking at extent of pelvic RT, but only in men also receiving hormone therapy.

What should be the RT dose in adj and salvage RT post prostatectomy?

Show Answer

There are no randomized studies addressing the issue of dose in adj and salvage RT post prostatectomy. **The ASTRO consensus panel recommends >64 Gy** and NCCN recommends **64–72 Gy,** with further dose escalation an option for gross LR. SAKK 09/10 is an ongoing trial randomizing men undergoing salvage prostate bed RT to 70 Gy vs. 64 Gy.

Are there randomized data supporting the addition of hormone therapy to salvage RT post prostatectomy?

Show Answer

Yes, 2 phase III RCTs address this question. **RTOG 9601** randomized 761 pts with biochemical recurrence post prostatectomy with PSA 0.2–4.0 ng/mL to 64.8 Gy to the prostatic fossa +/– 2 yrs of bicalutamide. **10-yr OS was significantly improved with bicalutamide (82% vs. 78%).** However, use of antiandrogen monotherapy and liberal PSA entry criteria may question the applicability of this strategy. **GETUG-AFU 16** randomized 743 men with postprostatectomy PSA 0.2–2.0 ng/mL to 66 Gy to the prostatic fossa +/– 6 mos goserelin. **5-yr PFS was significantly improved (80% vs. 62% with ADT).** Longer f/u is awaited to assess the impact on OS. The ongoing trials **RTOG 0534** and **RADICALS** are further attempting to address this question.

Is there a role for salvage prostatectomy for biochemical recurrence after RT for prostate cancer?

Show Answer

Yes. For biochemical recurrence after RT for prostate cancer, salvage prostatectomy can provide long-term Dz control in a significant portion of pts. However, salvage prostatectomy is associated with a higher risk of urinary incontinence and rectal injury, though pts treated with modern IMRT may have better outcomes. Careful pt selection is the key. Outcome is better with pts with lower preop PSA. Based on retrospective series, **5-yr PFS is up to 86% for a PSA <4, 55% for a PSA 4–10, and 28% for a PSA >10.**

Is there a role for cryotherapy or brachytherapy for biochemical recurrence after RT for prostate cancer?

Show Answer

This is **uncertain and there are no prospective studies evaluating these strategies in the setting of biochemical recurrence.** Retrospective studies suggest both strategies may be considered as possible salvage options in this setting.

FOLLOW-UP/TOXICITY

What is the rate of urinary incontinence and anastomotic stricture with salvage prostatectomy for biochemical recurrence after RT for prostate cancer?

Show Answer

These rates are lower in modern series d/t decreased fibrosis with modern RT techniques and improved surgical techniques. In modern series, the rate of many acute and late complications is similar to standard prostatectomy. However, there are still significant rates of **urinary incontinence (30%–50%) and anastomotic stricture (17%–32%).**

Name 5 side effects associated with ADT.

Show Answer

Side effects associated with ADT include **hot flashes, loss of libido, decreased muscle mass, mild anemia, and loss of bone density.**

56

Metastatic Prostate Cancer

Updated by Vivek Narayan

BACKGROUND

What % of newly diagnosed prostate cancer pts present with locally advanced or metastatic Dz?

Show Answer

Appx **10%–20%** of pts will present with at least locally advanced Dz.
Has the incidence of metastatic prostate cancer changed with the introduction of the PSA?

Show Answer

Yes. The introduction of the PSA into general practice in the early 1990s appears to have decreased the incidence of metastatic prostate cancer; a SEER database analysis showed a 52% decrease in the incidence of metastatic prostate cancer Dx from 1990 to 1994. (Stephenson RA et al., World J Urol 1997)
How are most cases of metastatic prostate cancer identified?

Show Answer

The majority of metastatic prostate cancer cases are identified by an **isolated biochemical (PSA-only) recurrence;** a much smaller proportion of cases are detected by signs/Sx of metastatic Dz (pain, pathologic fracture, weight loss, anemia, SC compression, etc.). (Lee WR et al., JCO 1997; D'Amico AV et

al., JNCI 2003)

What is the anticipated natural Hx of prostate cancer after biochemical failure following local therapy?

Show Answer

Following local therapy and subsequent biochemical failure, the median time to development of mets is 8 yrs, and the median time to death is 13 yrs. (Pound CR et al., JAMA 1999; Freedland SJ et al., JAMA 2005)

What are common predictors of a poorer prognosis after biochemical failure following local therapy?

Show Answer

Poor prognostic factors after biochemical failure following local therapy include: (D'Amico AV et al., JNCI 2003; Stephenson RA et al., JAMA 2004; Zhou P et al., JCO 2005; Horwitz EM et al., IJROBP 2008)

1. PSA-DT <3 mos

2. GS ≥8

3. T3b Dz

4. LN involvement

5. Short time to biochemical failure following local therapy (<3 yrs)

What is the most common site of prostate cancer mets?

Show Answer

The most common site is the **axial skeleton, including the pelvis, vertebral column, ribs, and proximal long bones**. Indeed, >80% of pts who die from prostate cancer have bony mets at autopsy. These lesions are usually osteoblastic, but may be lytic as well.

WORKUP/STAGING

What imaging modalities are commonly used for a metastatic workup?

Show Answer

The imaging modalities most commonly used for workup of suspected metastatic prostate cancer include whole body bone scan (technetium-99m bone scintigraphy), CT abdomen/pelvis with contrast, and chest imaging with a CXR or CT. X-ray radiographs or MRI should be used if bone scan findings are equivocal.

How sensitive are bone scans and CT scans for the detection of mets following biochemical failure?

Show Answer

Bone scan and CT scan are rarely positive until PSA values exceed 30 ng/mL in the absence of prior ADT. These scans are also more likely to be positive with faster PSA velocities. (Cher ML et al., J Urol 1998; Kane CJ et al., Urology 2003)

Is there a role for PET scans in the evaluation of metastatic prostate cancer?

Show Answer

PET imaging is an **evolving** diagnostic tool, and multiple PET modalities are currently under investigation. Fluciclovine (^{18}F-FACBC) was recently approved by the FDA for the detection of recurrent prostate cancer in men with rising PSA following Sg or RT. Optimal test characteristics are observed at higher PSA values. Multiple prostate specific membrane antigen (PSMA) targeting PET agents (such as ^{68}Ga-PSMA) are also currently under investigation and may enter routine prostate cancer evaluation in the future.

Is there a role for prostate Bx after biochemical failure in pts initially treated with RT?

Show Answer

Based on an ASTRO consensus statement, prostate re-Bx should be considered if the pt is considering additional local (salvage) therapy and is >2 yrs after the completion of RT. (Cox JD et al., JCO 1999)

TREATMENT/PROGNOSIS

What is the standard initial systemic therapy for metastatic prostate cancer?

Show Answer

ADT via surgical bilat orchiectomy, or more commonly through the use of a GnRH agonist, is the standard 1st-line therapy for metastatic prostate cancer. GnRH agonists act on the ant pituitary to cause a reduction in gonadal testosterone production to castrate levels.

What is the pathophysiology of androgen deprivation in the Tx of prostate cancer?

Show Answer

Since the 1940s, testosterone has been implicated in the growth and survival of prostate cancer. Testosterone is converted to the potent dihydrotestosterone (DHT) in target tissues, and DHT binds with high affinity to the AR in prostate cancer cells. Upon translocation to the cancer cell nucleus, DHT-AR binds to DNA androgen response elements, thereby facilitating multiple prostate cancer growth pathways. Therefore, androgen deprivation can effectively inhibit these growth elements. (Huggins C et al., Cancer Res 1941)

Is GnRH agonist therapy sup to orchiectomy for the Tx of metastatic prostate cancer?

Show Answer

Randomized trials and meta-analyses have confirmed equivalent long-term outcomes. Due to the irreversibility and psychological morbidity associated with surgical orchiectomy, GnRH agonists are generally the preferred approach for androgen deprivation. This therapy has primarily been shown to improve Dz progression and to reduce Dz-related complications. (MRC Prostate Cancer Group, Br J Urol 1997; Wilt T et al., Cochrane Review 2004;

Vogelzang NJ et al., Urology 1995)

What are 3 commonly used GnRH agonists?

Show Answer

The most commonly used GnRH agonists include:

. Goserelin (Zoladex)
. Leuprolide (Lupron)
. Triptorelin (Trelstar)

All 3 are available as depot formulations. These different GnRH agonist formulations are considered to be equally efficacious.

What other modalities of androgen suppression are available?

Show Answer

GnRH antagonists (degarelix) achieve fast declines in testosterone to castrate levels and are not associated with a testosterone flare response.

Antiandrogens (AAs), which are nonsteroidal competitive androgen receptor (AR) antagonists (including bicalutamide, flutamide, or nilutamide) block the peripheral effects of gonadal and extragonadal (adrenal) androgens. (Klotz L et al., BJU Int 2008)

Should ADT be initiated for biochemical recurrence after definitive RT in the absence of clinically evident mets?

Show Answer

The data are mixed, and the answer is therefore **controversial.** Although the effects on distant metastatic risk remain unclear, available data suggest that early initiation of ADT may be particularly beneficial for high-risk cancers (GS >7 and rapid PSA-DT). (Faria SL et al., Urology 2006; Walsh PC et al., J Urol 2001)

Should ADT be initiated for radiographically evident but asymptomatic mets?

Show Answer

In general, yes. Although ADT is not curative and primarily administered with palliative intent in the metastatic setting, studies have shown significantly improved PFS and reduced Dz-related complications with early initiation of ADT when c/w therapy deferred until signs and Sx of clinical progression. (MRC Prostate Cancer Group, Br J Urol 1997; Wilt T et al., Cochrane Review 2004)

Is intermittent ADT as efficacious as continuous ADT for metastatic Dz?

Show Answer

No. Continuous ADT is considered the standard of care for treating metastatic Dz. The premise behind the use of intermittent ADT is to potentially help reduce side effects, cost, and progression to castration-resistant Dz. However; the Intergroup 0162 randomized phase III trial was unable to demonstrate that intermittent therapy was noninf to continuous therapy with respect to survival. However, in men with PSA-only recurrence following definitive RT, intermittent ADT is noninf to continuous ADT. (Hussain M et al., NEJM 2013; Crook JM et al., NEJM 2012)

Can AAs be used as monotherapy for metastatic Dz?

Show Answer

No. The available evidence does not support the routine use of AA monotherapy for metastatic Dz. Randomized studies demonstrated inf outcomes with standard low-dose bicalutamide when compared to castration therapy. In addition, a meta-analysis of several trials showed a trend toward OS benefit with medical/surgical castration compared to nonsteroidal AA therapy. As a result, **common practice involves use of either a GnRH agonist alone or in combination with a nonsteroidal AA (and not AA monotherapy).** (Bales GT et al., Urology 1996; Kaisary AV et al., Eur Urol 1995; Seidenfeld J et al., Ann Int Med 2000)

Should GnRH analogs be used alone or in combination with AAs

(combined androgen blockade [CAB])?

Show Answer

Possibly. Several randomized trials and meta-analyses have shown a small but significant OS benefit with CAB relative to ADT monotherapy. However, the potential benefit of CAB must be balanced with potential increased toxicity in an individual pt. Of note, GnRH monotherapy may cause an initial flare of testosterone and Dz-related Sx, which can be prevented by preceding therapy with a short course of AAs. (PCTCG, Lancet 2000; Samson DJ et al., Cancer 2002; Kuhn JM et al., NEJM 1989)

What is the anticipated median OS for pts with metastatic castration-sensitive prostate cancer initiating Tx with ADT?

Show Answer

The median OS in men with metastatic prostate cancer initiating ADT is appx **4–5 yrs,** depending on the level of Dz burden. (Hussain M et al., NEJM 2013; Sweeney CJ et al., NEJM 2015; James ND et al., Lancet 2016)

Is there a role for chemo in the Tx of castration-sensitive metastatic prostate cancer?

Show Answer

Yes. The randomized phase III CHAARTED and STAMPEDE clinical trials demonstrated a significant improvement in OS with the addition of 6 Tx of docetaxel chemo to standard ADT. In the CHAARTED study, this clinical benefit was most pronounced in pts presenting with a “high-burden” of metastatic Dz, as defined by the presence of visceral mets and/or high-volume osseous mets. (Sweeney CJ et al., NEJM 2015; James ND et al., Lancet 2016)

Typically, how long after initiating ADT does it take before a pt’s prostate cancer becomes castration-resistant?

Show Answer

Castration-resistance usually occurs **within 18–24 mos of starting ADT.** (Eisenberger MA et al., NEJM 1998, Sweeney CJ et al., NEJM 2015)
What are the commonly used initial management strategies for pts with new progression to castration-resistant prostate cancer?

Show Answer

If CAB is being administered, withdrawal of the AA may result in a temporary PSA decline. If a GnRH analog alone is being given, the addition of an AA may help.
What are the 6 systemic therapy options that have demonstrated an OS benefit in metastatic castration-resistant Dz?

Show Answer

The 6 systemic Tx are:
1. Abiraterone (Zytiga)
2. Enzalutamide (Xtandi)
3. Docetaxel (Taxotere)
4. Cabazitaxel (Jevtana)
5. Sipuleucel-T (Provenge)
6. Radium-223 (Xofigo)
What are the next-generation hormonal therapy options for pts with castration-resistant prostate cancer?

Show Answer

Abiraterone is an oral inhibitor of the 17α hydroxylase and the 17,20 lyase enzymes in the adrenal androgen synthetic pathway. **Enzalutamide** is an oral AR antagonist that additionally reduces AR nuclear translocation and DNA binding. Both abiraterone and enzalutamide have demonstrated OS improvements in pts with metastatic castration-resistant Dz, either before or after docetaxel chemo. (de Bono JS et al., NEJM 2011; Ryan CJ et al., NEJM 2013; Scher HI et al., NEJM 2012; Beer TM et al., NEJM 2014)

What chemo options are available to pts with metastatic castration-resistant Dz?

Show Answer

Docetaxel is the standard initial chemo based on efficacy demonstrated in 2 randomized trials: TAX 327 and SWOG 9916 (Tannock IF et al., NEJM 2004; Petrylak DP et al., NEJM 2004). The taxane **cabazitaxel** is considered the preferred 2nd-line chemotherapeutic agent for pts with castration-resistant prostate cancer. Cabazitaxel/prednisone has been shown to improve OS in pts who have progressed following docetaxel in a phase III randomized trial. (de Bono JS et al., Lancet 2010)

What radiopharmaceutical is available for pts with symptomatic bone mets from castration-resistant prostate cancer, and what is its mechanism of action?

Show Answer

Radium-223 is approved for use in pts with symptomatic bone mets and no visceral mets. In the randomized phase III ALSYMPCA trial, radium-223 demonstrated improvement in OS and reduced skeletal-related events (Parker C et al., NEJM 2013). Radium-223 is the first α-particle emitter to be approved for routine clinical practice. The short range and high RBE of the α-particles produced by radium-223 theoretically result in more rapid cell killing and less marrow toxicity when c/w previously tested β-emitters, such as strontium-89 and samarium-153.

What immunotherapy is available to pts with asymptomatic or minimally symptomatic metastatic castration-resistant Dz?

Show Answer

For pts who are asymptomatic or minimally symptomatic, **sipuleucel-T** is considered an appropriate therapy. Sipuleucel-T, an autologous active cellular immunotherapy, demonstrated improvement in OS in a phase III randomized

trial. (Kantoff PW et al., NEJM 2010)
What additional therapy should be offered to pts with castrate-resistant prostate cancer and clinically detectable bone mets?

Show Answer

Denosumab or **zoledronic acid,** which have been shown in randomized trials to improve bone mineral density and decrease the risk of fracture. Palliative focal radiotherapy may also be considered, as appropriate. (Michaelson MD et al., JCO 2007; Smith MR et al., NEJM 2009)

FOLLOW-UP/TOXICITY

What are the common side effects of ADT?

Show Answer

Side effects of ADT include: hot flashes, decreased libido, fatigue, gynecomastia, anemia, decreased muscle mass, decreased bone mineral density, obesity, mood changes, dyslipidemia, insulin resistance, and possible increased risks for diabetes, coronary artery Dz, and cognitive effects. (Higano CS, Urology 2003; Keating NL et al., JCO 2006)
What are the common side effects of AA therapy?

Show Answer

Common side effects of bicalutamide, the most commonly prescribed AA d/t its favorable toxicity profile, include breast tenderness and gynecomastia, decreased libido, diarrhea, and potential hepatotoxicity.

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Prostate Brachytherapy

Updated by Brian C. Baumann

BACKGROUND

What are the 2 most common types of prostate brachytherapy (BT)?

Show Answer

Most common types of prostate BT:

- LDR using permanently implanted iodine-125 **(I-125)** or palladium-103 **(Pd-103)** radioisotopes
- HDR using temporarily implanted iridium-192 **(Ir-192)**

Which prostate cancer pts are good candidates for LDR BT monotherapy?

Show Answer

According to the American Brachytherapy Society (ABS) guidelines, low-risk pts (cT1–2a, GS ≤6, PSA <10) are good candidates for LDR BT monotherapy (Davis et al., Brachytherapy 2012). BT also an option for some intermediate-risk pts with more favorable Dz (PSA 10–20 or small-volume GS 7, preferably with primary GS 3).

Why is the presence of seminal vesicle involvement a relative contraindication to prostate BT monotherapy?

Show Answer

Seminal vesicle involvement is a relative contraindication to BT

monotherapy b/c seminal vesicles are **technically challenging to implant** with acceptable dose coverage and involvement is associated with **higher risk of regional spread** as well as **mets,** rendering LC potentially less effective.

List the relative contraindications to prostate LDR BT.

Show Answer

Relative contraindications to prostate LDR BT: (Davis BJ et al., Brachytherapy 2012)

- Severe pre-existing urinary outlet obstruction Sx (IPSS >20)
- Previous pelvic RT
- Transurethral resection defects
- Large median lobes
- Prostate gland >60 cc
- Inflammatory bowel Dz

Other relative contraindications: very small prostates (<20 cc) or active acute prostatitis.

Why is a prostate size >60 cc a relative contraindication to LDR prostate BT?

Show Answer

Large prostate volumes >60 cc are considered a relative contraindication to BT b/c they have been associated with a **higher rate of post-implant urinary retention and prolonged obstructive urinary Sx.** Implantation is also more technically difficult (Davis BJ et al., Brachytherapy 2012). Size is less of a restriction for HDR BT, and experienced LDR brachytherapists can implant >60 cc prostates.

Is neoadjuvant hormonal therapy (NHT) effective at shrinking prostate size and decreasing the risk of retention?

Show Answer

Prostate volume may be reduced by 25%–40% after 3 mos of ADT. After 6 mos, there is no further volume reduction. It is controversial whether this decreases the risk of urinary retention. A large retrospective series demonstrated that in pts with IPSS scores ≥15, urinary retention occurred in 25% of those not taking NHT vs. 5% in those taking NHT (p = 0.039). (Stone RG et al., J Urol 2010)

Why is the presence of significant pre-existing urinary Sx a contraindication to BT?

Show Answer

Obstructive and irritative urinary Sx are common after BT, and **pre-existing Sx increase the risks and severity** of these side effects.

What are the advantages of prostate BT over EBRT?

Show Answer

Advantages of prostate BT over EBRT:

- Decreased integral dose to the pt, particularly to the rectum and bladder, which allows for dose escalation
- Simplified targeting of RT (i.e., no issues with setup variation, prostate motion, etc.)
- Shorter Tx course
- Potential radiobiologic advantage from hypofractionation with HDR BT given the low alpha/beta of prostate cancer

What is the purpose of ADT prior to BT?

Show Answer

The main purpose of ADT prior to BT is to **downsize large glands prior to implant,** thereby potentially:

- Decreasing urinary Sx post implant
- Decreasing operative time and # of seeds/catheters required

- Decreasing rectal dose d/t smaller gland size
- Decreasing risk of pubic arch interference

Is there an oncologic benefit to adding ADT to BT monotherapy?

Show Answer

Systematic review by Keyes et al. (Brachytherapy 2017) suggested no benefit to adding ADT for low-risk and favorable intermediate-risk pts. Unfavorable intermediate-risk and high-risk pts and those with suboptimal dosimetry may have up to 15% improvement in biochemical recurrence-free survival (bRFS) with 3–12 mos of ADT, although impact on cancer-specific survival is uncertain.

Is there a role for prophylactic alpha-blockers?

Show Answer

Prophylactic use of alpha-blockers does not significantly affect retention rates but does result in significantly faster return of urinary Sx to baseline. (Merrick et al., IJROBP 2002)

WORKUP/STAGING

What is the purpose of the preimplant volume study in prostate cancer pts being treated with LDR BT?

Show Answer

A volume study is done prior to implant to **assess prostate volume and architecture** (presence of median lobe size, assessment for pubic arch interference) and to **develop a preliminary seed distribution plan** for ordering seeds.

What is pubic arch interference, and how can it be avoided?

Show Answer

Pubic arch interference is when the needle paths are obstructed by the pubic arch. It occurs more frequently in pts with large glands and affects the ant and

lat needles. To evaluate for interference, TRUS can be used to compare the largest prostate cross-section with the narrowest portion of the pubic arch. Other than hormonal downsizing, the use of an extended lithotomy position (Trendelenburg) may also alleviate pubic arch interference.
What sources are typically used in LDR prostate BT?

Show Answer

I-125 and Pd-103 are the sources typically used in LDR BT. Cesium-131 (Cs-131) has also been utilized more recently.
What are the half-lives of the 3 most common sources used in LDR BT?

Show Answer

Half-lives of the 3 most common sources:

- I-125 (60 days)
- Pd-103 (17 days)
- Cs-131 (9.7 days)

TREATMENT/PROGNOSIS

What doses are typically prescribed when using monotherapy with I-125, Pd-103, and Cs-131?

Show Answer

Doses typically prescribed for BT monotherapy:

- I-125: **140–160 Gy**
- Pd-103: **110–125 Gy**
- Cs-131: **115 Gy**

What can be done to place sources into the tissues surrounding the prostate to provide extracapsular coverage?

Show Answer

In order to reliably place sources into tissues surrounding the prostate, a

possible technical solution is to place **linked seeds embedded in Vicryl sutures** in the peripheral portions of the prostate.
What is the post-implant evaluation process for LDR BT?

Show Answer

Generally CT-based study performed immediately after BT or ~30 days after. Goals are:

. Verify that the target volume rcvd Rx dose
. Establish that normal tissues did not rcv excessive dose
. Serve as feedback on the quality of the implant process
. Assess dose within the target volume (Davis et al., Brachytherapy 2017)

In prostate LDR BT, what is the D90 and V100 and what are the recommended values for these parameters?

Show Answer

In prostate LDR BT, the **D90 refers to the min dose in the hottest 90% of the post-implant prostate volume** (given as a % of the Rx dose). The goal **D90 is >90%** of the Rx dose. The **V100 refers to the volume of the prostate receiving 100% of the Rx dose.** The goal **V100 is >90%.** Although D90 and V100 are strongly correlated, D90 is used to describe how hot or cold an implant is with respect to the Rx dose and V100 is used to describe how well the implant covers the desired target.
In prostate BT, why is the D90 parameter used and not the D100?

Show Answer

D90 is used instead of D100 to evaluate post-implant dosimetry b/c **retrospective studies have identified D90 as a better predictor of long-term biochemical control.** D90 may be a better predictor of outcomes b/c it is less sensitive to small differences in the way a prostate is contoured b/t users on post-implant CTs. (Potters et al., IJROBP 2001)
In prostate BT, what are the RV100 and the UV150?

Show Answer

RV100 is the volume of the rectum in cc's receiving 100% of the Rx dose.
UV150 is the volume of the urethra receiving 150% of the Rx dose.
What are the goals for RV100 and UV150 in prostate BT planning?

Show Answer

Reasonable goals are to limit RV100 to <1 cc and UV150 to <5%.
What isotope is typically used in HDR BT for prostate cancer?

Show Answer

Ir-192 is typically used for HDR BT to treat prostate cancer.
What is the half-life for Ir-192?

Show Answer

The half-life for Ir-192 is **73.8 days.**
What are common dose/fractionation schedules for HDR BT monotherapy?

Show Answer

No consensus on dose/fractionation. Common fractionation schemes include: 34 Gy in 4 fx; 36–38 Gy in 4 fx; 31.5 Gy in 3 fx; 26 Gy in 2 fx.
What about single-fx HDR monotherapy?

Show Answer

Single-fx HDR monotherapy is investigational but some results are promising. A phase II trial by Hoskin et al. randomized pts to 19–20 Gy × 1, 13 Gy × 2, or 10.5 Gy × 3. There was no difference in bRFS b/t the arms, with 4-yr bRFS of 94% for single fx (Radiother Oncol 2017). Krauss et al. reported 3-yr bRFS of 93% for 19 Gy × 1 (IJROBP 2017). In the trial by Prada et al., 6-yr bRFS was worryingly low (66%) after 19 Gy × 1, tempering some enthusiasm for single-fx HDR (Radiother Oncol 2016). Toxicity results

are encouraging. (Morton et al., Radiother Oncol 2017)
What studies have compared EBRT + BT boost vs. EBRT + EBRT boost in intermediate- and high-risk prostate cancer?

Show Answer

Several. ASCENDE-RT trial (Morris et al., IJROBP 2017): 398 men, 69% with high-risk Dz, were randomized to ADT + 3D conformal EBRT (46 Gy/23 fx whole pelvis WP), prostate boost to 78 Gy/39 fx) vs. ADT + WP EBRT + LDR boost (I-125, min peripheral dose 115 Gy). After median f/u of 6.5 yrs, LDR boost associated with significantly lower rates of biochemical failure (7-yr bRFS 86% vs. 75%) than EBRT boost with no difference in OS. A similar trial by Hoskin et al. also found no difference in OS (Radiother Oncol 2012). In general, the BT boost appears more effective for high-risk pts. A BT boost is allowed on the currently accruing RTOG 0924.
What about BT as salvage after EBRT failure?

Show Answer

LR after EBRT occurs in up to 15% (Zumsteg et al., J Urol 2015). Salvage BT is potentially curative Tx. Key selection criteria from RTOG 0526 trial of salvage LDR BT: Bx-confirmed LR with no extraprostatic Dz on imaging, recurrence >30 mos after EBRT, American Urological Association (AUA) score <15, and pre-salvage PSA <10. Phase II trial of HDR BT at MSKCC reported 5-yr bRFS 68% (Yamada et al., Brachytherapy 2014). The Princeton Radiation Oncology experience using 4–6 mos of neoadj, concurrent, and adj ADT plus salvage BT (LDR or HDR) reported 5-yr bRFS of 79% and 5-yr freedom from late grade 3 GU toxicity of 85% with no late grade ≥2 GI toxicity. (Baumann et al., Brachytherapy 2017)
What is the long-term biochemical control for low-risk pts after LDR monotherapy?

Show Answer

Long-term bRFS rates of 86%–98% have been reported. (Davis et al., Brachytherapy 2017)

What is the data comparing the efficacy of I-125 vs. Pd-103 for prostate BT?

Show Answer

I-125 and Pd-103 appear similarly efficacious. The **Seattle Isotope trial** randomized low-risk prostate cancer pts to I-125 vs. Pd-103 and found no difference in 3-yr bRFS (89% vs. 91%, p = 0.76) and no differences in morbidity. (Wallner K et al., IJROBP 2003)

Describe the PSA bounce and its prognostic significance following BT as monotherapy.

Show Answer

The PSA bounce is the abrupt rise and fall in the PSA value following BT. Bounces may occur in 40%–50% of hormone-naïve pts typically 12–30 mos after BT, more commonly in younger pts. Bounces of >2 ng/mL (i.e., biochemical failure by Phoenix definition) may occur in 15%. PSA bounce does not appear to predict for clinical failure. (Crook et al., IJROBP 2007) Caution is advised when interpreting PSA levels in the first 30 mos after BT. (Davis et al., Brachytherapy 2017)

FOLLOW-UP/TOXICITY

What are the most common acute and late side effects from prostate BT?

Show Answer

Obstructive and irritative urinary Sx and impotence are side effects that are generally experienced d/t prostate seed implantation. Rectal toxicity is relatively rare.

Are phosphodiesterase inhibitors effective for prostate brachy–related erectile dysfunction?

Show Answer

Yes. ~50% of pts who have erectile dysfunction after prostate BT can achieve erections useful for intercourse with the use of phosphodiesterase inhibitors.
How does the intensity and timing of urinary irritation differ b/t men treated with I-125 vs. Pd-103?

Show Answer

Irritative Sx are more intense and occur earlier but resolve more quickly in pts treated with Pd-103 compared to I-125. (Herstein et al., Cancer 2005)
What acute toxicities are associated with prostate BT?

Show Answer

Prostate BT pts experience acute worsening of urinary Sx (frequency, urgency, hesitancy, and weak stream). Acute urinary retention is rare (~3% require catheterization). Acute irritative and/or obstructive Sx tend to be slightly better with HDR.
What late toxicities are associated with prostate BT?

Show Answer

Relatively common: Impotence, mild increased urinary irritative/obstructive Sx, and mild rectal bleeding. **Rare:** Significant late GU toxicity (e.g., urethral strictures), significant rectal bleeding. **Very rare:** rectal fistula, seed embolization, 2nd cancers
How do QOL outcomes compare for BT monotherapy vs. EBRT?

Show Answer

Short- & long-term QOL comparable (Sanda, NEJM 2008; Prado, JCO 2010). In general, erectile function modestly better with BT. Resolution of urinary irritative Sx is less after BT.

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Bladder Cancer

Updated by Sriram Venigalla

BACKGROUND

How prevalent is bladder cancer in the United States?

Show Answer

Bladder cancer is the **4th most commonly diagnosed cancer in men** behind prostate, lung, and colorectal malignancies, but it is only the **11th most common cancer in women.**

How many cases are diagnosed and how many deaths occur annually in the United States?

Show Answer

There are **~77,000 cases** of bladder cancer and **~16,000 deaths** annually.

What are common risk factors for bladder cancer?

Show Answer

Common risk factors include:

- **Smoking**
- Occupational chemical exposures (paint, dye, metal, and petroleum products)
- Chronic bladder irritation (Chronic cystitis, indwelling catheters, etc.)
- Prior pelvic irradiation or chemo (cyclophosphamide)
- Schistosoma haematobium infection (associated only with SCC)

What is the median age at Dx?

Show Answer

The median age is **69 yrs in men** and **71 yrs in women.**
What is the most common histologic subtype in developed and developing countries?

Show Answer

In developed countries, **~90% of bladder cancers are urothelial carcinomas, formerly called transitional cell carcinomas.** In countries where schistosomiasis is endemic, SCC is more common.
What are the different histopathologic types of bladder cancer in order of decreasing frequency?

Show Answer

The most common histology in the United States is urothelial carcinoma (94%) > SCC (3%) > adenocarcinoma (2%) > neuroendocrine tumors (1%).
What % of newly detected bladder tumors are Ta/Tis/T1 lesions?

Show Answer

~70% of bladder cancers are superficial bladder tumors, with 70% of these confined to the mucosa (Ta/Tis) and 30% confined to the submucosa (T1).
What % of pts have DMs at Dx?

Show Answer

~4% have metastatic Dz at presentation, usually involving bones, lungs, or liver.

WORKUP/STAGING

What is the most common presenting Sx of bladder cancer?

Show Answer

The most common presenting Sx is **painless hematuria.**

What are the initial steps in the workup of suspected bladder cancer? What additional workup is needed after a cancer Dx is established?

Show Answer

. Perform **cystoscopy** and **urine cytology.**
. If a lesion is identified that is solid or suspicious for muscle invasion, then obtain a **CT/MRI of the abdomen and pelvis,** ideally prior to Bx so induced inflammatory changes do not result in overstaging.
. Perform an EUA and **TURBT.**
. If a cancer Dx is made, **image the upper urinary tract** (CT or MRI urography, intravenous pyelogram, renal US, retrograde pyelogram, or ureteroscopy).
. For muscle-invasive Dz, obtain **chest imaging** (CXR or CT) and consider a bone scan if the pt is symptomatic or has an elevated alk phos level.
. Recommended blood work includes **CBC/CMP.**

For adequate clinical staging, what should be present in the initial transurethral resection of bladder tumor (TURBT) pathologic specimen?

Show Answer

The Bx specimen should contain **muscle from the bladder wall** to properly stage the tumor.
What are the indications for re-resection after initial TURBT?

Show Answer

Repeat resection should be performed when there is:

. Incomplete resection of gross tumor
. High-grade Dz and no muscle in specimen
. Any T1 lesion

What are the AJCC 8th edition (2017) T-stage criteria for bladder cancer?

Show Answer

Ta: noninvasive papillary carcinoma
Tis: CIS (“flat tumor”)
T1: tumor invades lamina propria (subepithelial connective tissue)
T2a: tumor invades superficial muscularis propria (inner half)
T2b: tumor invades deep muscularis propria (outer half)
T3a: microscopic invasion of perivesical tissue
T3b: macroscopic invasion of perivesical tissue
T4a: tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b: tumor invades pelvic wall, abdominal wall
Can a TURBT be used to define the pT stage?

Show Answer

No. pT stage is defined by an evaluation of a cystectomy specimen. TURBT findings are included in the clinical T-stage (cT) staging.
What is the probability of pathologic pelvic nodal involvement based on the pT stage of a bladder tumor?

Show Answer

Pelvic node involvement by pT stage (Stein JP et al., JCO 2001):

Overall: 24% LN+
pT0–T1: 5%
pT2: 18%
pT3a: 26%
pT3b: 46%
pT4: 42%
Can the cT stage reliably predict occult pathologic pelvic node involvement?

Show Answer

No. cT stage does not reliably predict occult pathologic node involvement b/c

there is significant discordance b/t cT stage and pT stage. (Goldsmith B et al., IJROBP 2014)

What are the AJCC 8th edition (2017) N- and M-stage criteria for bladder cancer?

Show Answer

N0: no regional LN involvement
N1: single +LN in true pelvis (perivesical, obturator, internal and external iliac, or sacral)
N2: multiple regional LNs in true pelvis
N3: mets to common iliac LN
M0: no DMs
M1: DMs
M1a: DMs limited to LNs beyond the common iliacs
M1b: non-LN DMs

Define the AJCC 8th edition (2017) bladder cancer stage grouping based on TNM status.

Show Answer

Stage 0a: Ta, N0, M0
Stage 0is: Tis, N0, M0
Stage I: T1, N0, M0
Stage II: T2a/T2b, N0, M0
Stage IIIA: T3a/T3b/T4a, N0, M0 or T1–T4a, N1, M0
Stage IIIB: T1–T4a, N2/N3, M0
Stage IVA: T4b, Any N, M0 or Any T, Any N, M1a
Stage IVB: Any T, Any N, M1b

Estimate the 5-yr OS by stage.

Show Answer

5-yr OS rates for bladder cancer based on SEER data:

Stage 0: 98%
Stage I: 88%
Stage II: 63%
Stage III: 46%
Stage IV: 15%

TREATMENT/PROGNOSIS

Which pts with non-muscle invasive bladder cancer (NMIBC) can be observed after max TURBT?

Show Answer

Observation is indicated for NMIBC pts after max TURBT with all of the following characteristics:

. Solitary, low-grade Ta tumor
. Completely resected
. <3 cm in diameter

4. No evidence of CIS

What are the indications for adj therapy in NMIBC treated with TURBT?

Show Answer

Pts with NMIBC should be treated with intravesical therapy after TURBT if:

. Grade 2–3 Dz
. T1 lesion
. Presence of CIS
. Multifocal lesions
. Lesions ≥3 cm

What agents are commonly used for intravesical therapy following TURBT for NMIBC?

Show Answer

Intravesical immunotherapy with **Bacillus Calmette-Guerin (BCG)** is the Tx of choice for high-risk pts. Alternatives include intravesical chemo such as mitomycin C, epirubicin, and gemcitabine. BCG decreases the risk of progression and recurrence compared to chemo.

Is there a role for RT in the management of NMIBC?

Show Answer

Possibly. RT is occasionally used for high-grade T1 Dz. A retrospective review of 141 pts with high-risk T1 Dz, intravesical therapy naïve, who rcvd either RT or chemoRT, found a complete cystoscopic response in 88% of pts and tumor progression in 19% and 30% of pts at 5 and 10 yrs, respectively (Weiss C et al., JCO 2006). The ongoing RTOG 0926 is evaluating the efficacy of bladder preservation therapy in high-grade T1 pts who have failed intravesical BCG and are candidates for cystectomy.

Is NMIBC likely to recur?

Show Answer

Yes. Pts with resected non–muscle invasive Dz have a >50% chance of recurrence within 5 yrs.

Which subsets of NMIBC pts are at highest risk of having an muscle-invasive bladder cancer (MIBC) recurrence?

Show Answer

Pts with CIS or high-grade T1 NMIBC are at highest risk of developing an MIBC recurrence.

What are the Tx options for pts with node(-) MIBC (cT2–T4a, N0) who are medically operable?

Show Answer

For **medically operable** pts with node(-) MIBC, standard Tx options include:

. RC + LND +/– neoadj or adj chemo

. Selective bladder preservation following max TURBT with concurrent CRT
. Partial cystectomy + LND +/– neoadj chemo

What is involved in an radical cystectomy (RC)?

Show Answer

RC removes the bladder, distal ureters, pelvic peritoneum, prostate, seminal vesicles, uterus, fallopian tubes, ovaries, and ant vaginal wall. Urine is diverted via a conduit to the abdominal wall or to an orthotopic neobladder.
What LN regions are typically included in a pelvic LND?

Show Answer

A standard pelvic LND includes the distal common iliac, internal and external iliac, and obturator nodes. Evidence suggests that an “extended” LND which includes the proximal common iliacs and presacral nodes may result in sup RFS. The value of extended LND is the subject of 2 ongoing RCTs.
What are the 3 most common types of urinary diversions?

Show Answer

The 3 most common urinary diversions are:

. Continent orthotopic neobladder (e.g., Studer pouch)
. Continent cutaneous diversion (e.g., Indiana pouch)
. Noncontinent diversion with a bowel conduit (e.g., ileal conduit)

Estimate the 5-yr OS after RC for MIBC.

Show Answer

5-yr OS after RC is ~60% for stage T2 and ~40% in stages T3–T4a with most pts dying with DM. (Grossman HB et al., NEJM 2003)
What is the evidence to support neoadj chemo prior to RC in MIBC?

Show Answer

Neoadj chemo is considered the standard of care for pts with MIBC. A 2003 meta-analysis of 11 RCTs demonstrated a **5% OS benefit** with neoadj cisplatin-based chemo + RC compared to RC alone. (Lancet 2003)
What is the role of adj chemo in MIBC?

Show Answer

There is a paucity of high-level evidence regarding the role of adj chemo in MIBC. For pts who did not rcv neoadj chemo prior to RC, adj chemo may be offered for those with **pT3–4 and/or N+ Dz.** Observational series suggest a benefit of adj chemo after RC compare to observation alone.
What % of MIBC pts are found to be pT0 at the time of RC without neoadj chemo?

Show Answer

~15%. Neoadj chemo improves pT0 rate to ~38%. (Grossman HB et al., NEJM 2003)
Name 3 predictors of pelvic failure after RC.

Show Answer

The 3 strongest predictors of pelvic failure (isolated and co-synchronous with DM) are **pT3–4 Dz, +margins,** and **<10 benign or malignant LNs identified** in the LND specimen. (Christodouleas JP et al., Cancer 2014)
Where are pelvic recurrences after RC typically found?

Show Answer

In pT3–4 pts with –margins, failures occur predominantly along the pelvic sidewalls (obturator and iliac regions). In pT3–4 pts with +margins, most pelvic failures are still found along the sidewalls, but recurrences in the cystectomy bed and presacral region increase significantly. (Baumann BC et al., IJROBP 2013)
Is there a role for PORT in MIBC pts with +margins?

Show Answer

Possibly. NCCN guidelines recommend considering adj RT for +margins following RC as the 5-yr pelvic recurrence rate is ~68% and long-term survival after isolated pelvic recurrence is poor (<5%) (Herr HW et al., JCO 2004). There is, however, no randomized evidence supporting the role of adj RT in this subset of pts.

Is there a role for PORT in MIBC pts with –margins?

Show Answer

Possibly. An Egyptian RCT by Zaghloul et al., randomized pts with locally advanced MIBC with –margins to adj RT alone (45 Gy in 1.5 Gy/fx BID), sequential chemo (2 cycles gem/cis before and after RT) plus RT, or chemo alone (4 cycles gem/cis). LRFS was significantly improved in the RT arms compared to chemo alone (87% and 96% vs. 69%). There was no significant difference in DFS or OS, although there was a trend toward improved DFS in the RT-containing arms (63% and 68% vs. 56%). (Zaghloul MS, et al., ASCO GU 2016 Abstract)

What factors are used to select MIBC pts for selective bladder preservation?

Show Answer

Only 6%–19% of medically operable MIBC pts are good candidates for selective bladder preservation (Sweeney P et al., Urol Clin N Am 1992). Ideal candidates for selective bladder preservation have:

- Good baseline bladder function
- Unifocal, cT2–3 tumors
- Limited to no CIS
- No hydronephrosis
- A visibly complete TURBT

What is the difference b/t continuous-course and split-course selective

bladder preservation paradigms?

Show Answer

The **continuous-course paradigm** completes the entire course of planned chemo/RT and assesses response with TURBT ~3 mos later. The **split-course paradigm** involves an induction chemo/RT phase, a planned break with response assessment ~3 wks later, and a consolidation chemo/RT phase if there is a good response to the initial phase; otherwise salvage RC is recommended.

Is there evidence that concurrent chemoRT is sup to RT alone in MIBC?

Show Answer

Yes. The **BC2001** randomized MIBC to concurrent chemo/RT vs. RT alone. 2-yr locoregional DFS favored chemo/RT (67% vs. 54%). (James ND et al., NEJM 2012)

Is there a role for neoadj chemo prior to chemoRT for bladder preservation?

Show Answer

Possibly. RTOG 8903 randomized MIBC pts to neoadj Mtx/cisplatin/vinblastine (MCV) + cisplatin/RT vs. cisplatin/RT alone, but closed prematurely d/t a high rate of severe neutropenia (Shipley WU et al., JCO 1998). A larger RCT by an international collaboration randomized RT and radical cystectomy pts to neoadj MCV and found an ~5% advantage to chemo group which did not vary by type of local therapy. (International Collaboration of Trialists 1999)

Describe the concurrent chemo/RT regimen used in BC2001.

Show Answer

In the concurrent chemo/RT arm of **BC2001,** MIBC pts were treated with **5-FU + mitomycin** and **64 Gy/32 fx qd or 55 Gy/20 fx qd.** The trial included a 2nd randomization to either standard whole bladder RT (PTV: noninvolved

bladder + 1.5-cm margin + 2-cm margin around any extravesicular Dz) or to reduced high-dose volume RT, where dose to uninvolved bladder was 80% of max. Pelvic nodes were not intentionally targeted. (James ND et al., NEJM 2012)

Describe the chemo and RT used in RTOG 8903.

Show Answer

In the concurrent chemo/RT alone arm of **RTOG 8903,** MIBC pts were treated with induction **cisplatin q3 wks + 39.6 Gy/22 fx qd** targeting the small pelvis (whole bladder, perivesicular, obturator, external iliac and internal iliac nodes). Complete responders were treated with consolidation **cisplatin q3 wks + 5.4 Gy/3 fx** to the small pelvis f/b a boost to the tumor bed of **19.8 Gy/11 fx (total 64.8 Gy).** (Shipley WU et al., JCO 1998)

Should clinically uninvolved pelvic LNs be targeted with RT with the bladder preservation approach?

Show Answer

Unclear. Large series have reported that pelvic nodal failure rates with muscle-invasive bladder are relatively high (25%–40%) following cystectomy. In BC2001, however, pelvic nodes were not targeted with RT and the pelvic nodal failure rates were low in both arms—4.9% in the chemoRT arm and 6.7% in the RT alone arm (James ND et al., NEJM 2012). There is practice variation regarding whether pelvic nodes are electively targeted.

How are locally recurrent NMIBC and MIBC treated after bladder preservation?

Show Answer

Recurrent NMIBC may be treated with TURBT + intravesical therapy. Recurrent MIBC is treated with salvage RC.

Estimate the CR rate at initial assessment and 5-yr OS after selective

bladder preservation.

Show Answer

60%–80% of pts have a CR at initial post-Tx TUBRT after selective bladder preservation. **5-yr OS ranges from 40%–60%.** OS after selective bladder preservation appears comparable to OS after RC, but these approaches have not been compared in an RCT.

What are the Tx options for pts with node(-) MIBC (cT2–T4a, N0) who are medically inoperable?

Show Answer

For **medically inoperable** pts with node(-) MIBC, the most well-established option is **definitive chemo/RT.** Pts unfit for definitive chemo/RT should have max safe TURBT and can be offered RT alone, chemo alone, or observation.

How does the chemoRT technique differ for medically operable and inoperable pts?

Show Answer

For medically inoperable pts, the **continuous-course paradigm** is used, since salvage RC is not an option. The RT doses and target volumes are similar, though there is a stronger case for pelvic nodal RT in inoperable pts b/c they often have more advanced Dz, and there is no concern about complicating the urinary diversion of a salvage RC.

What are the Tx options for node(+) or locally advanced bladder cancer (e.g., cN+ or cT4b)?

Show Answer

For cT4b or cN+ bladder cancers, Tx options are:

. Concurrent chemo/RT → cystectomy (if good response) or adj chemo
. Chemo → chemo/RT or cystectomy (if good response) or further systemic

therapy

Estimate the 5-yr OS for medically inoperable or locally advanced MIBC treated with definitive chemoRT.

Show Answer

SWOG 9312 was a single arm trial including 53 pts with cT2–4, any N, who were medically inoperable, unresectable, or refused Sg. Tx included max TURBT → cisplatin/5-FU + 60 Gy → adj cisplatin/5-FU. **5-yr OS ~32%.**
What are the 1st-line chemo regimens for bladder cancer?

Show Answer

Gemcitabine + cisplatin (GC) or **dose-dense MVAC** (methotrexate, vinblastine, doxorubicin, and cisplatin) are considered 1st-line chemo regimens for neoadj, adj, or palliative chemo. (NCCN 2018)
What sensitizing chemo regimens are used for concurrent Tx with RT?

Show Answer

Commonly used regimens are mitocycin and 5-FU, BCON, cisplatin and 5-FU, cisplatin and paclitaxel, cisplatin alone and gemcitabine alone.
How is metastatic bladder cancer treated?

Show Answer

Cisplatin-based combination chemo is the preferred initial Tx. GC, or dose-dense MVAC are frequently used. GC is generally preferred over MVAC as it has similar efficacy with reduced toxicity (von der Maase H et al., JCO 2000). For pts with impaired renal function or ECOG PS ≥2, PD1/L1 inhibitor may be used.
What is the role of immunotherapy in the Tx of metastatic bladder cancer?

Show Answer

Immunotherapy has emerged as the preferred 2nd-line Tx for metastatic Dz

after progression on 1st-line platinum-based chemo. In the phase III Keynote-045 trial, pembrolizumab improved OS and DFS compared to chemo in the 2nd-line metastatic setting (Bellmunt et al., NEJM 2017). Atezolizumab, nivolumab, durvalumab, and avelumab have also been approved for 2nd-line Tx of metastatic urothelial cancer. Based on Phase II data, Atezolizumab has been approved as initial therapy for metastatic Dz in pts who are not candidates for cisplatin-based chemo.

How is mixed histology or pure nonurothelial bladder cancers treated?

Show Answer

Tumors of mixed histology with urothelial elements generally have a poorer prognosis but should be treated like pure urothelial carcinoma. Tumors with a small cell or neuroendocrine component are treated with neoadj chemo f/b RC or RT. Tx of SCC or adenocarcinoma uses chemo specific to the lesion's histology.

FOLLOW-UP/TOXICITY

What are the toxicities associated with RT for organ preservation?

Show Answer

Short-term complications: transient urinary frequency/urgency, dysuria, hematuria, bladder spasms, diarrhea, RT dermatitis, fatigue

Relatively common long-term complications: chronic urinary frequency/urgency, erectile dysfunction, diarrhea

Uncommon long-term complications: chronic hematuria (especially in pts on blood thinners), dysuria, urgency, bowel obstructions or fistulas, pelvic insufficiency fractures, 2nd cancers

What is the impact of bladder preservation approaches on QOL for pts with bladder cancer?

Show Answer

QOL for pts after bladder preservation therapy is good. Urodynamic studies

and pt-reported outcome studies found that 78% of pts retained normal bladder function; bowel Sx were reported by 22% and 50% reported normal erectile function (Zietman ZS et al., J Urol 2003). A recent QOL study compared MIBC pts receiving cystectomy vs. organ preservation trimodality therapy. At 5.6-yr median follow-up, multivariate analysis showed that the organ preservation group a better general QOL as well as better bowel function, fewer bowel Sx, and better sexual function compared to the cystectomy group; urinary Sx scores were similar. (Mak KS et al., IJROBP 2016)

How many pts require cystectomy for palliation of Tx-related toxicities following bladder preservation?

Show Answer

Cystectomies performed for palliation of bladder preservation–related toxicities are very uncommon **(0%–2%).** (Rodel C et al., JCO 2002; Shipley WU et al., J Urol 2002)

What is the recommended f/u for pts with MIBC treated with bladder preservation?

Show Answer

Urine cytology, cystoscopy + Bx, imaging of the upper urinary tracts, abdomen, pelvis q3–6 mos for the 1st 2 yrs, and then at increasing intervals. **LFTs, BMP, and chest imaging performed q6–12 mos.**

59

Seminoma

Updated by Ruben Carmona

BACKGROUND

Clinically, what are the 2 main subgroups of testicular germ cell tumors (GCTs)?

Show Answer

Seminomatous and nonseminomatous germ cell tumors (NSGCTs) are the 2 main subgroups of testicular GCTs. 60% are pure seminoma, 30% are NSGCTs, and 10% are mixed (pts with mixed histology are typically considered to have NSGCTs).

What is the estimated annual incidence and mortality from testicular cancer in the United States? Has the incidence been increasing or decreasing?

Show Answer

In the United States, the annual testicular cancer **incidence is ˜8,700 and mortality is ˜380.** From 1973 to 1998, the **incidence in testicular GCTs rose 44%** in the United States (mostly seminoma).

What is the most common age group for testicular seminoma?

Show Answer

Testicular seminoma is most common in those **15–34 yrs of age.**

In the United States, what is the relative incidence of testicular tumors in

white men vs. black men?

Show Answer

Testicular cancer is **5.4 times more common in white men** than in black men.

What is the best established risk factor for testicular cancer?

Show Answer

A **Hx of cryptorchidism** increases the risk of testicular cancer by ~5 times. The higher the undescended testicle (inguinal canal vs. intra-abdominal), the higher the risk. Orchiopexy prior to puberty lowers this risk. 5%–20% of tumors in pts with a Hx of cryptorchidism develop in the contralat, normally descended testis. The risk is greatest in cases of bilat cryptorchidism.

In a pt with a prior Dx of testicular cancer, what is the cumulative incidence (at 25 yrs) of contralat testicular seminoma?

Show Answer

At 25 yrs following the primary Dx, the cumulative incidence of contralat testicular seminoma is **3.6%.**

What is the most common chromosomal abnormality in testicular GCTs?

Show Answer

A **12p isochromosome** (i.e., a chromosome with 2 copies of the short arm of chromosome 12) is the most common testicular GCT chromosomal abnormality.

Name the layers of tissue surrounding the testes from outer to inner.

Show Answer

Layers of tissue surrounding the testes (outer to inner):

. Skin
. Tunica dartos

. External spermatic fascia
. Cremaster muscle
. Internal spermatic fascia
. Parietal layer of tunica vaginalis
. Visceral layer of tunica vaginalis
. Tunica albuginea

Compare and contrast lymphatic drainage of the left vs. right testis.

Show Answer

Left testicular vein → left renal vein → nodal drainage is primarily to the P-A nodes
Right testicular vein → IVC → paracaval and interaortocaval nodes are most commonly involved (Lymphatic drainage from the right testes commonly crosses over to the left, but the reverse is rare).

What is the chance of pelvic/inguinal nodal involvement from testicular cancer? What increases this risk?

Show Answer

Pelvic/inguinal nodes are rarely (<3%) involved by testicular cancer. Risk of involvement increases with:

. Prior scrotal or inguinal Sg
. Tumor invasion of the tunica vaginalis or lower one-third of epididymis
. Cryptorchidism

What is the DDx of a testicular mass?

Show Answer

The DDx of a testicular mass includes tumor, torsion, hydrocele, varicocele, spermatocele, and epididymitis.

What is the classic presentation of testicular cancer?

Show Answer

A **painless testicular mass** is the classic presentation of testicular cancer. However, up to 45% of pts will present with pain.

WORKUP/STAGING

What imaging modality is preferred for primary evaluation of a testicular mass?

Show Answer

Transscrotal US is preferred for primary evaluation of a testicular mass. Testicular tumors are typically hypoechoic.
What is the preferred primary surgical Tx for a unilat testicular tumor?

Show Answer

Transinguinal orchiectomy is the preferred surgical Tx for unilat testicular tumor.
What are the 3 tumor markers that should be drawn before orchiectomy for testicular tumor?

Show Answer

Before orchiectomy for a testicular tumor, levels of **a-HCG, AFP, and LDH** should be drawn.
What are the half-lives of a-HCG and AFP?

Show Answer

The half-life for **a-HCG is 22 hrs.** The half-life for **AFP is 5 days.**
How commonly are a-HCG and AFP elevated in testicular seminoma vs. NSGCT? What are unrelated etiologies for elevated a-HCG and AFP?

Show Answer

β-HCG is elevated in 15% of seminomas. AFP is NEVER elevated in seminoma. 1 or both markers will be elevated in 85% of NSGCTs. The use of marijuana can elevate β-HCG, and reagent cross-reaction with LH can cause

falsely elevated results. Hepatocellular carcinoma, cirrhosis, and hepatitis can elevate AFP.

What imaging studies, labs, and evaluation should be ordered following transinguinal orchiectomy for seminoma?

Show Answer

Following transinguinal orchiectomy for seminoma, chest imaging (CXR), CT abdomen/pelvis, AFP, β-HCG, and LDH should be ordered. If the CT is positive, bone scan should be added. Pts should also have fertility evaluation and consider sperm banking.

Describe the AJCC 8th edition TNM and S staging for testicular tumors.

Show Answer

pT1: tumor limited to testis (including rete testis invasion) without LVSI
pT1a: tumor smaller than 3 cm
pT1b: tumor 3 cm or larger
pT2: limited to testis (including rete testis) with LVSI OR tumor invading hilar ST or epididymis or penetrating visceral mesothelial layer covering external surface of tunica albuginea with or without LVSI
pT3: involvement of spermatic cord irrespective of LVSI
pT4: scrotal invasion
N1: single or multiple regional nodes, all ≤2 cm in greatest dimension
N2: single or multiple regional nodes, any >2–5 cm in greatest dimension
N3: single or multiple regional nodes, any >5 cm in greatest dimension
M1a: nonretroperitoneal nodal or pulmonary Dz
M1b: nonpulmonary visceral mets
S0: normal LDH, β-HCG, and AFP

S1: LDH <1.5 times normal, β-HCG <5,000 mIU/mL, and AFP <1,000 ng/mL
S2: LDH 1.5–10 times normal, β-HCG 5,000–50,000, or AFP 1,000–10,000
S3: LDH >10 times normal, β-HCG >50,000, or AFP >10,000

Summarize the AJCC 8th edition stage grouping for testicular tumors.

Show Answer

Stage I: no Dz beyond testis/scrotum (i.e., pT1–4N0M0S0–3)
Stage II: regional nodal involvement and S0–S1 tumor markers (IIA = N1, IIB = N2, IIC = N3)
Stage III: S0–S3 tumor markers with N1–3 Dz, or M1 Dz

What is the stage group distribution for testicular seminoma at presentation?

Show Answer

Most testicular seminoma pts present with stage I Dz (70%–80%), 15%–20% have stage II Dz, and 5% have stage III Dz.

In addition to AJCC staging, what is another common staging system for testicular seminoma?

Show Answer

In addition to AJCC staging, **Royal Marsden staging** is also used for testicular seminoma. This staging is largely similar to the AJCC stage grouping:

Stage I: confined to testis
Stage IIA: node <2 cm
Stage IIB: node 2–5 cm
Stage IIC: node 5–10 cm
Stage IID: node >10 cm
Stage III: nodes above/below diaphragm
Stage IV: extralymphatic mets

TREATMENT/PROGNOSIS

Following transinguinal orchiectomy, what is the optimal Tx for stage I seminoma, stages IIA–IIB seminoma, and stage IIC or greater seminoma?

Show Answer

1. **Stage I seminoma → surveillance is preferred** (Can consider adj RT or single-agent carboplatinum.)
2. **Stages IIA–IIB → adj RT preferred.** (Can consider multiagent chemo)
3. **Stage IIC or greater → multiagent chemo**

For pts undergoing surveillance for stage I seminoma, what are the 15-yr relapse, DSS and OS rates?

Show Answer

For pts undergoing surveillance for stage I seminoma, the **15-yr relapse rate was 18.9%** (96% before yr 5). **15-yr DSS and OS rates were 99.3% and 91.6%.** (Mortensen et al., Eur Urol 2014)

For pts undergoing surveillance for stage I seminoma, where do most relapses occur?

Show Answer

85% of relapses are in the infradiaphragmatic **P-A nodes.** Observation should therefore include regular CT assessment of the abdomen and pelvis.

What pathologic factors are associated with increased risk of relapse following transinguinal orchiectomy for stage I seminoma?

Show Answer

Pathologic factors associated with risk of relapse following transinguinal orchiectomy include:

- tumor size >4 cm
- LVSI
- β-HCG >200 IU/L
- Rete testis invasion

(Warde P et al., JCO 2002; Mortensen et al., Eur Urol 2014; Kollmannsberger et al., JCO 2015)

Following P-A relapse in pts observed following transinguinal orchiectomy for stage I seminoma, what are the appropriate Tx options?

Show Answer

Following P-A relapse in pts observed following transinguinal orchiectomy for stage I seminoma, **retroperitoneal RT** (for nodes <5 cm) **or multiagent chemo** are reasonable Tx options.

For pts treated with P-A RT following transinguinal orchiectomy for stage I seminoma, what is the relapse rate? Where do relapses occur?

Show Answer

For pts treated with P-A RT following transinguinal orchiectomy for stage I seminoma, relapse occurs in **0.5%–5%** of pts. Most relapses occur within 2 yrs. In-field relapses are extremely rare; most relapses are mediastinal, lung, left SCV, or (if risk factors are present) inguinal. Surveillance should include regular CXR.

What data support the option of adj chemo for stage I seminoma following transinguinal orchiectomy?

Show Answer

MRC-UK TE19 randomized 1,447 stage I seminoma pts to adj RT (2 Gy/fx to 20 or 30 Gy) vs. 1 cycle of carboplatin. Carboplatin demonstrated noninf 5-yr RFS (94.7% for carboplatin vs. 96% for RT). (Oliver R et al., Lancet 2005, JCO 2011)

In a stage I seminoma pt, what factors would favor active Tx over surveillance?

Show Answer

In a stage I seminoma pt, concern over pt adherence with f/u may favor active Tx.

Why is P-A RT not part of the definitive management of pts with stage IIC seminoma?

Show Answer

P-A RT is not part of the definitive management of pts with stage IIC seminoma d/t **high rates of distant failure** (mediastinal, lung, SCV, or bone). Thus, chemo is needed. In 1 series, 5-yr RFS among stage IIC pts treated with orchiectomy and RT alone was only 44%. (Chung PW et al., Eur Urol 2004)

What is the appropriate Tx for pts with stages I–IIB seminoma following relapse after adj P-A RT?

Show Answer

Pts with stages I–IIB seminoma who relapse following adj P-A RT should be treated with **salvage chemo.**

How should seminoma pts with stage IIC or greater be treated?

Show Answer

4 cycles of cisplatin/etoposide (+/- bleomycin) are appropriate for seminoma pts with stage IIC or greater.

What is the appropriate RT field for stage I seminoma pts?

Show Answer

Stage I seminoma pts (if receiving adj RT) should have the P-A nodes treated. **MRC-UK TE 10** randomized 478 pts to P-A RT +/– pelvic RT and found equivalent 3-yr RFS (96%) (Fossa SD et al., JCO 1999). 4 pelvic failures occurred in the P-A group (vs. none in the P-A + pelvic group).

For adj stage I seminoma, what are the borders for a P-A field and LN regions are being targeted?

Show Answer

. Borders for a P-A field (for adj stage I seminoma):

Superior: T10–11 has been the historical standard, however, cranial

reduction to T11–12 reduces kidney, stomach, and small bowel dose without compromise in RFS. (Bruns F et al., Acta Oncol 2005)

Inferior: L4–L5

Lateral: 2 cm on vertebral bodies. If left-sided primary, give 1-cm border on left renal hilum and sacroiliac joint. CT-based planning using vascular and nodal anatomy may help avoid marginal misses. (Martin JM et al., Radiother Oncol 2005)

. LNs within P-A field (for adj stage I seminoma):

Right sided: at least the paracaval, precaval, and interaortocaval regions

Left sided: at least the lat-aortic and preaortic regions

What is the appropriate field for a stages IIA–IIB seminoma pt and what LN regions are being targeted?

Show Answer

. Modified dog-leg radiotherapy (excluding inguinal LN regions) would be appropriate d/t similar DFS and lower acute grade 3 toxicities compared to standard dog-leg field radiotherapy (NCCN guidelines, Classen et al., JCO 2003)

Superior: T11–12

Inferior: top of acetabulum (note: in pts with prior pelvic or scrotal Sg, place inf border at the top of the ipsi obturator foramen to cover ipsi inguinal nodes)

Ipsilateral: defined by a line from tip of the transverse process of the 5^{th} lumbar vertebra to the superolat border of the ipsi acetabulum

Contralateral: inclusion of transverse process in P-A area down to L5–S1, then diagonally in parallel with ipsi border

. LNs within modified dog-leg fields: paracaval, precaval, interaortocaval, lat-aortic, preaortic, ipsi common iliac, external iliac and proximal internal iliac regions

What is a reasonable dose and fractionation schedule for stage I

seminoma?

Show Answer

For stage I seminoma, common Rx doses include:

Stage IA. **25 Gy** in 1.25 Gy/fx
Stage IB. **25.5 Gy** in 1.5 Gy/fx
Stage IC. **20 Gy** in 2 Gy/fx
The **MRC-UK TE 18** trial compared 2 Gy/fx to 20 Gy vs. 30 Gy and found equivalent relapse rates at 5 yrs. (Jones WG et al., JCO 2005)

What is a reasonable dose and fractionation schedule for stages IIA–IIB seminoma?

Show Answer

For stage IIA–IIB seminoma, the "dogleg" or modified dog-leg field may be treated with a similar dose–fractionation as stage I. Gross LAD may be boosted with an additional 5–10 Gy in 2 Gy/fx (~30 Gy for IIA, ~35 Gy for IIB).

What pathologic subtype of seminoma can be treated with orchiectomy alone?

Show Answer

Spermatocytic seminoma can be treated with orchiectomy alone. This tumor is seen in older pts and, while the precursor cell is unknown, is probably not a true seminoma.

FOLLOW-UP/TOXICITY

What RT dose can induce temporary azoospermia? Doses greater than what may cause permanent aspermia?

Show Answer

RT doses as low as 0.2–0.5 Gy will cause temporary azoospermia. Doses >0.5 Gy can cause extended or permanent aspermia.

What should be done to reduce the testicular RT dose during Tx for testicular seminoma?

Show Answer

During RT for testicular seminoma, a **clamshell should be used** to reduce the dose to the contralat testis.

60

NSGCT

Updated by Ruben Carmona

BACKGROUND

What % of testicular GCTs are NSGCTs?

Show Answer

40% of testicular GCTs are NSGCTs.

Name 5 risk factors for GCTs.

Show Answer

Risk factors for GCTs:

- Prior personal Hx of GCT
- Positive family Hx
- Cryptorchidism
- Testicular dysgenesis
- Klinefelter syndrome

Name 5 histologic types of NSGCTs.

Show Answer

Histologic types of NSGCTs:

- Embryonal cell carcinoma
- Choriocarcinoma
- Yolk sac tumor

- Teratoma
- Mixed

In what 2 ways are teratomas classified?

Show Answer

Teratomas are classified as either **mature or immature** depending on whether they contain adult-type differentiated cell types (mature) or partial somatic differentiation similar to that found in a fetus (immature).
What is a teratoma with malignant transformation?

Show Answer

A teratoma with malignant transformation is a teratoma that **histologically resembles a somatic cancer,** such as an adenocarcinoma or a sarcoma.
How does the presence of a seminoma component influence outcomes in pts with histologically confirmed NSGCTs?

Show Answer

The presence of a seminoma component within a histologically confirmed NSGCT has **no major impact on the clinical outcome.** Such pts are treated based on the NSGCT algorithm.
What is the median age of presentation for pts with NSGCTs, and how does this compare to the median age of presentation for pts with SGCTs?

Show Answer

The median age of presentation for NSGCTs is 27 yrs vs. age 36 yrs for SGCTs and 33 yrs for mixed tumors.
How does the presence of pure choriocarcinoma affect the prognosis?

Show Answer

Pure choriocarcinoma typically presents with widespread mets and a very high β-HCG and has a **poor prognosis.** Note that elements of

choriocarcinoma are found in 10% of NSGCTs and do not affect the prognosis.
Which histology of NSGCTs is most commonly associated with an elevated AFP?

Show Answer

Yolk sac tumors are composed of cells that produce AFP.
What is the most common GCT histology in childhood?

Show Answer

Yolk sac tumors are the most common histology of GCT in childhood.

WORKUP/STAGING

Per NCCN, what 3 blood tests should be performed in the workup of a suspicious testicular mass?

Show Answer

There are 3 blood tests that should be performed in a man with a suspicious testicular mass: **AFP, a-HCG, and a chemistry panel including LDH.**
How should a pt with pure seminoma histology and an elevated AFP be classified?

Show Answer

A pt with pure seminoma histology and an elevated AFP should be **considered and treated as an NSGCT pt. AFP is not considered to be elevated in seminomatous germ cell tumor (SGCT).**
Per NCCN, what imaging study should be performed in the workup of a suspicious testicular mass?

Show Answer

CXR and testicular US should be performed in the workup of a suspicious testicular mass.

How is the AJCC 8th edition staging for NSGCTs different from staging for SGCTs?

Show Answer

The AJCC staging is the **same for both** NSGCTs and seminomas. See seminoma staging for details.

How should an NSGCT be definitively diagnosed?

Show Answer

Definitive Dx of an NSGCT should be via a radical inguinal orchiectomy. Do not Bx a testicular mass (separate inguinal lymphatic drainage of scrotum).

Per NCCN, what should be discussed preoperatively with a pt who has a testicular mass?

Show Answer

The **pros and cons of sperm banking** should be discussed prior to orchiectomy.

Per NCCN, what imaging study should be ordered postoperatively after Dx of NSGCT?

Show Answer

CT abdomen/pelvis (CT A/P) ± chest imaging should be performed postoperatively after the Dx of NSGCTs.

Per the International Germ Cell Cancer Collaborative Group, what 5 factors must be met to be classified as good-risk NSGCT?

Show Answer

Per the International Germ Cell Cancer Collaborative Group (JCO 1997), good-risk NSGCT must meet all of the following:

. Testicular or retroperitoneal primary tumor
. No nonpulmonary visceral mets

- AFP <1,000 ng/mL
- β-HCG <5,000 mIU/mL
- LDH <1.5 times the upper limit of normal

Per the International Germ Cell Cancer Collaborative Group, what 3 factors must be met to be classified as intermediate-risk NSGCT?

Show Answer

Per the International Germ Cell Cancer Collaborative Group (JCO 1997), intermediate-risk NSGCT must meet both of the following:

- Testicular or retroperitoneal primary tumor
- No nonpulmonary visceral mets and any of the following intermediate-risk factors:

3a. AFP 1,000–10,000 ng/mL
3b. β-HCG 5,000–50,000 mIU/mL
3c. LDH 1.5–10 times the upper limit of normal

Per the International Germ Cell Cancer Collaborative Group, the presence of any of which 5 factors leads to classification of poor-risk NSGCT?

Show Answer

Per the International Germ Cell Cancer Collaborative Group (JCO 1997), poor-risk NSGCT has any of the following:

- Mediastinal primary tumor
- Nonpulmonary visceral mets
- AFP >10,000 ng/mL
- β-HCG >50,000 mIU/mL
- LDH >10 times the upper limit of normal

TREATMENT/PROGNOSIS

Per NCCN, what is the Tx of stage I good- or intermediate-risk NSGCT?

Show Answer

The Tx of stage I good- or intermediate-risk NSGCT is **observation** after orchiectomy (preferred for stage IA) if compliant vs. nerve-sparing RPLND vs. bleomycin/etoposide/cisplatin (BEP) chemo × 1 to 2 cycles (stage IB only).

What is the risk of relapse after orchiectomy alone for stage I good- or intermediate-risk NSGCT if tumor markers are normal postoperatively?

Show Answer

The risk of relapse after orchiectomy alone for stage I good- or intermediate-risk NSGCT if tumor markers are normal postoperatively is **~30%.**

Per NCCN, how should pts with stage I NSGCT be monitored in an observation protocol?

Show Answer

Observation in pts with stage I NSGCT should consist of visits, tumor markers and CXR q2 mos for yr 1, q3 mos for yr 2, q4–6 mos for yrs 3–4, then annually in yr 5. CT A/P should be done q4–6 mos for yrs 1–2, then q6 mos to annually for yrs 3–4.

What did the MRC trial TE08 show for pts with stage I NSGCT?

Show Answer

MRC TE08 randomized 414 pts with stage I NSGCT s/p orchiectomy with normal serum markers (10% high risk with LVI) to CT chest/abdomen at 3 and 12 mos vs. CT scans at 3, 6, 9, 12, and 24 mos. At median follow-up of 3.3 yrs, 2-yr RFS was 79% with 2 scans vs. 84% with 5 scans (NSS). The 1st indication of relapse was markers in 39% and CT abdomen in 39%. The conclusion is that CT scans at 3 and 12 mos after orchiectomy might be reasonable in low-risk pts and that chest CT may be unnecessary. (Rustin GJ et al., JCO 2007)

What is the chance of positive nodes on RPLND despite a negative CT

scan in pts with stage I NSGCT?

Show Answer

The risk of positive nodes on RPLND despite negative CT scan in pts with stage I NSGCT is **30%.**
What is the relapse rate in pts with stage I NSGCT after orchiectomy → RPLND?

Show Answer

The relapse rate in pts with stage I NSGCT after orchiectomy → RPLND is **5%–10%,** most commonly to the lungs.
Per NCCN, how should pts with NSGCT and persistently positive tumor markers after orchiectomy be treated?

Show Answer

Pts with NSGCT and persistently positive tumor markers after orchiectomy should be treated with either BEP × 3 cycles or cisplatin/etoposide (EP) × 4 cycles.
What did the German Testicular Study Group AUO trial AH 01/94 show for pts with stage I NSGCT?

Show Answer

The **AUO AH 01/94** trial randomized 382 pts with clinical stage I NSGCT to RPLND vs. BEP × 1 cycle. At median f/u of 4.7 yrs, 2-yr RFS was 92% with Sg and 99% with BEP (HR 7.9, SS). The authors concluded that 1 course of BEP is sup to RPLND in clinical stage I Dz (Albers P et al., JCO 2008). Some question the quality of RPLND in this study.
Per NCCN, how should pts with stage II NSGCT with a +node diagnosed only after RPLND be treated?

Show Answer

pN1 (1–5 nodes <2 cm) may be observed (preferred) or offered 2 cycles of

BEP or EP chemo. pN2 (ENE or any number of nodes <5 cm) chemo is preferred over surveillance. pN3 (any number of nodes >5 cm) should rcv 3 cycles of BEP or 4 cycles of EP. Node should be observed.
Per NCCN, what is the Tx of pts with bulky stage II or III NSGCT?

Show Answer

Pts with bulky stage II or III NSGCT should be treated with either BEP × 3 cycles or EP × 4 cycles (good risk) or BEP × 4 cycles (intermediate risk).
What is the role of RT in the primary Tx of NSGCT?

Show Answer

Although RT may be used for palliation of metastatic Dz, there is no established role for RT in the primary Tx of NSGCT.
Per NCCN, what is the f/u for pts with NSGCT with CR to chemo and/or RPLND?

Show Answer

Surveillance of pts with NSGCT after CR to chemo and/or RPLND should consist of visits and tumor markers q2–3 mos for yrs 1–2, q6 mos for yrs 3–4, then annually in yr 5. CXR should be done q6 mos for yrs 1–2, then annually. CT A/P should be done q6 mos for yr 1, then annually for yr 2, then as clinically indicated.

FOLLOW-UP/TOXICITY

What is the major toxicity associated with RPLND?

Show Answer

The major toxicity associated with RPLND is **retrograde ejaculation resulting in infertility;** however, nerve-sparing techniques can preserve ejaculation in 95% of cases.
What is the pathognomonic complication of bleomycin chemo?

Show Answer

The pathognomonic complication of bleomycin chemo is bleomycin-induced pneumonitis.

61

Penile Cancer

Updated by Brian C. Baumann

BACKGROUND

What is the estimated annual incidence of penile cancer in the United States? What % of male cancers does this represent?

Show Answer

There are **~2,000 new cases/yr** of penile cancer in the United States, representing **<1% of male cancers. In developing countries, it can account for up to 10% of all male cancers.**

What are the major risk factors for developing penile cancer?

Show Answer

Risk factors for penile cancer:

- Lack of circumcision
- Phimosis
- HPV infection (45%–80% of cases are related)
- HIV infection

Others risk factors include: chronic inflammation, poor hygiene, trauma, lichen sclerosus, smoking, and PUVA therapy.

What is penile intraepithelial neoplasia (PeIN)?

Show Answer

PeIN is a premalignant condition at high risk of developing into SCC of the penis and includes bowenoid papulosis, erythroplasia of Queyrat (glans and prepuce), and Bowen Dz (penile shaft).
What are the 2 most common anatomic locations for penile cancer?

Show Answer

The **glans and prepuce** are the 2 most common locations for penile cancer. Less common locations include the coronal sulcus and the shaft. Lesions can appear as a mass, ulceration, or inflammation.
What is the lymphatic drainage for penile cancers?

Show Answer

Superficial inguinal nodes → deep inguinal nodes → external iliac nodes → other pelvic nodes
What % of men with penile cancer and palpable inguinal nodes have pathologically involved inguinal nodes?

Show Answer

Overall, **~58%** of palpable inguinal nodes in pts with penile cancer are pathologically involved.
What is the likelihood of occult nodal Dz in men who are cN0?

Show Answer

The likelihood of occult nodal involvement depends on the tumor stage, grade, and presence of LVI. It is 4%–14% for Tis, Ta, or T1 lesions and 60% for T2 lesions.
What % of men with penile cancer present with DM?

Show Answer

1%–10% present with DM.
What are the most common sites for DM in penile cancer?

Show Answer

Lung, liver, and bone are the most common sites for DM in penile cancer.
What is the most common histology in penile cancer?

Show Answer

SCC accounts for 95% of penile malignancies. Other histologic subtypes include sarcoma, urethral tumors, lymphoma, and basal cell carcinoma.

WORKUP/STAGING

What is the workup for penile cancer?

Show Answer

Penile cancer workup: H&P, basic labs, Bx, MRI or US of penis to assess DOI. CT, MRI, or PET/CT to assess nodes in pts with high BMI, prior inguinal procedures, or palpable inguinal adenopathy.
What is the AJCC 8th edition (2017) T staging for penile cancer?

Show Answer

Tis: CIS only (aka PeIN)
Ta: noninvasive localized SCC
T1: Glans: tumor invades lamina propria

Foreskin: invades dermis, lamina propria, or dartos fascia
Shaft: invades connective tissue b/t epidermis and corpora regardless of location

T1a: grade 1–2, without LVI or PNI
T1b: either LVI, PNI, or grade 3
T2: invades corpora spongiosum (either glans or ventral shaft) with or without urethral invasion
T3: invades corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4: invades into adjacent structures (i.e., scrotum, prostate, pubic bone)

What is the AJCC 8th edition (2017) clinical and pathologic N staging for penile cancer?

Show Answer

cN1: single palpable mobile unilat inguinal LN
cN2: multiple palpable mobile inguinal LNs or bilat inguinal LNs
cN3: palpable fixed inguinal nodal mass or pelvic LNs
pN1: ≤2 unilat inguinal LNs, no ENE
pN2: ≥3 unilat or bilat inguinal LNs
pN3: inguinal LNs with ENE or pelvic LNs
What is the AJCC 8th edition (2017) stage grouping for penile cancer?

Show Answer

Stage I: T1a, N0, M0
Stage IIA: T1b–T2, N0, M0
Stage IIB: T3, N0, M0
Stage IIIA: T1–3, N1, M0
Stage IIIB: T1–3, N2, M0
Stage IV: T4, N3 or M1

TREATMENT/PROGNOSIS

Management of Primary Lesions

How are noninvasive penile cancers treated?

Show Answer

CIS of the penis can be treated with **topical 5-FU or imiquimod** with good LC and excellent cosmetic outcome. Other methods that are acceptable include laser therapy, circumcision and WLE, complete glansectomy, or Mohs Sg. The most common Tx are topic therapy and organ-sparing excision.
What are the Tx options for T1, grade 1–2 Dz?

Show Answer

Limited excision with penile preservation is preferred if feasible. Options include WLE, glansectomy in select cases, Mohs in select cases, laser therapy, or radiotherapy with interstititial brachytherapy (preferred) or EBRT. Circumcision should always precede RT to minimize complications. Higher rates of LF after brachy for lesions >4 cm are reported. (de Crevoisier, IJROBP 2009)

What are the Tx options for T1 (high grade) or ≥T2 Dz?

Show Answer

Partial or total penectomy is generally employed. For tumors encompassing <1/2 of the glans, then WLE or glansectomy can be considered. T1 + grade 3 or T2 tumors <4 cm with negative nodes can be treated with brachy, EBRT alone, or EBRT + chemo. Consider prophylactic inguinal nodal RT if using EBRT (NCCN 2018). 10-yr CSS after brachy in T1–2 and select T3 was 84%. (Crook, World J Urol 2009)

How are large (>4 cm) or locally advanced primary tumors managed?

Show Answer

For tumors >4 cm or surgically unresectable nodal Dz, circumcision f/b EBRT + chemo is often preferred. Total penectomy or neoadj chemo f/b resection is another option. (Dickstein, BJU Int 2016)

What length of corpus cavernosum is required in order for 50% of men to be able to have sexual intercourse?

Show Answer

~45% of men are able to have adequate sexual intercourse with about **4–6 cm** of corpus cavernosum.

What residual penile length is required for men to be able to urinate in the standing position?

Show Answer

~2.5–3 cm of residual penile length is required for men to be able to urinate in the standing position.

Management of the Regional Nodes

What is the most important prognostic factor for OS in penile cancer?

Show Answer

Presence and extent of inguinal node mets.
What 3 factors are most predictive for inguinal nodal Dz?

Show Answer

Primary tumor stage, tumor grade, and presence of **LVI.**
How should the inguinal nodes be staged in pts WITHOUT palpable adenopathy?

Show Answer

Risk stratified approach based on the primary tumor, tumor grade, and presence of LVI:

- **Low risk** (Tis, Ta, and T1a): Imaging of the pelvis not needed to stage the nodes in these pts.
- **Intermediate/high risk** (T1b, ≥T2): Perform CT abd/pelvis or MRI and chest imaging → dynamic sentinel node biopsy (preferred) or superficial or modified inguinal node dissection. (NCCN 2018)

How should suspicious inguinal LNs be evaluated?

Show Answer

Perform FNA. If FNA is positive, perform inguinal dissection. If FNA is negative and pt has low-risk Dz, excisional Bx can be performed. If FNA is negative but pt has higher-risk Dz, can perform a superficial or modified inguinal LND.
When should bilat inguinal LND be performed?

Show Answer

Bilat LND is considered the standard-of-care for high-risk cN0 penile tumors or palpable ipsi nodes.

What is the management for a single pathologically involved inguinal node?

Show Answer

These pts require a complete inguinal LND.

What is the management for ECE or ≥2 pathologically involved inguinal nodes?

Show Answer

Pts with ECE or ≥2 nodes should undergo a complete inguinal and pelvic LND. (Lont, J Urol 2007)

How should a large (>4 cm) ipsi, mobile inguinal node be managed?

Show Answer

If confirmed on FNA or excisional Bx, neoadj chemo should be considered prior to inguinal LND.

How should unilat fixed inguinal nodes or bilat inguinal nodes be managed?

Show Answer

If confirmed, pts should rcv neoadj chemo f/b inguinal and pelvic LND. Postop RT or chemoRT can be considered. (NCCN 2018)

How should positive pelvic LNs be managed?

Show Answer

Nonsurgical candidates should rcv chemoRT. Resectable pts should rcv neoadj chemo f/b bilat inguinal and pelvic LND. Postop RT or chemoRT should be considered but there is limited evidence. (NCCN 2018)

Radiotherapy Details

How are pts with penile cancers simulated for EBRT?

Show Answer

Simulation for EBRT for penile cancer Tx: supine position and frog-legged, Foley catheter, and penis surrounded with bolus material. If treating pelvic and inguinal nodes, the penis is secured cranially into the pelvic field.
In megavoltage EBRT for penile cancer, should bolus be used?

Show Answer

Yes. Bolus should be used in megavoltage EBRT for penile cancer for dose buildup at the surface (usually a wax or plastic cast with the penis suspended above the abdomen or secured against the abdomen if also treating nodes).
In EBRT for penile cancer, what is the CTV and what dose is typically prescribed?

Show Answer

In EBRT for penile cancer, the **CTV can be the entire penile length** depending on size and extent of the primary, and typically goes to **45–50.4 Gy** with standard fractionation, with a 10–20 Gy boost to the tumor + 2-cm margin. Inguinal and pelvic nodal volumes (if included) are treated to 45 Gy. Boost gross nodes to **60–70 Gy.** Consider prophylactic EBRT to the inguinal nodes in pts who cannot get Sg or decline Sg.
What lesions are amenable to brachytherapy?

Show Answer

Penile cancer lesions that can be treated with brachytherapy are typically **<4 cm in diameter** and have **<1 cm of corpora invasion (T1–T2).**
What data support the use of concurrent CRT in treating penile cancer?

Show Answer

There is no prospective data directly supporting the use of concurrent CRT in treating penile cancer, but extrapolation from cervical cancer and anal cancer data have led to the increasing use of concurrent cisplatin-based CRT.
What are the common chemo agents given for penile cancer, for either localized or metastatic Dz?

Show Answer

Cisplatin-based chemo is the standard for penile cancer pts. If given neoadjuvantly, TIP (paclitaxel, ifosfamide, and cisplatin) is a reasonable 1st-line regimen. With RT, cisplatin, 5-FU, or mitomycin-C can be used. For metastatic Dz, TIP or 5-FU/cisplatin are reasonable regimens. Although metastatic penile cancer is chemosensitive, responses are usually brief and incomplete.
What are the expected LC rates for pts managed with EBRT or brachytherapy for penile cancers?

Show Answer

LC estimates vary widely, likely depending on pt selection. In a well-selected pt with T1–T3 penile cancer treated with EBRT or brachytherapy, LC (i.e., penile preservation rate) is **80%–90%** (5–10 yrs f/u). (Crook JM et al., IJROBP 2005)
How does Sg compare to RT as the initial modality in the management of penile cancers?

Show Answer

Retrospective comparisons b/t Sg and RT suggest that Sg is associated with sup initial LC as a primary modality, though these studies suffer from significant selection bias. **Overall LC does not appear to differ when allowing for surgical salvage.** The benefit of RT is penile preservation. Long-term OS appears similar b/t the 2 modalities.
What is the 5-yr cancer-specific survival for penile cancer pts with N0 or

N+ Dz?

Show Answer

pN0: 85%–100%
pN1: 79%–85%
pN2: 17%–60%
pN3: 0%–17% (Ficarra, Urology 2010)

FOLLOW-UP/TOXICITY

How should penile cancer pts who rcv definitive therapy be followed?

Show Answer

Penile cancer pts treated with penectomy with nodal dissection can be followed q6 mos for 2 yrs, then q12 mos for an additional 3 yrs. Pts treated with penile-sparing therapy or those who did not undergo LND should be followed q3 mos for yrs 1–2, then q6 mos for an additional 3 yrs. (NCCN 2018)

What are the main acute side effects of RT for penile cancer?

Show Answer

Urethral mucositis, edema, and RT dermatitis are experienced by nearly all pts during RT for penile cancer. Secondary infection is another common acute side effect.

What are the main late effects from RT for penile cancer?

Show Answer

Telangiectasia, superficial necrosis, urethral stricture, fistula formation, meatal stenosis, dyschromia, and sterility are all common long-term toxicities from RT for penile cancer.

What doses are associated with an increased risk of urethral strictures?

Show Answer

Doses >60 Gy increase the risk of urethral stenosis and fibrosis.
What are the side effects from inguinal node dissection?

Show Answer

Side effects from inguinal LND include LE **edema, wound complications, and DVT.**
How is urothelial carcinoma of the prostatic urethra treated?

Show Answer

TURP + BCG. LRs treated with cystoprostatectomy +/– urethrectomy.
What unique pathologic factors confer additional risk of recurrence in urothelial carcinoma of the prostate?

Show Answer

Acinar invasion and stromal invasion.
How is urothelial carcinoma of the prostate with acinar invasion treated?

Show Answer

Radical cystoprostatectomy +/– urethrectomy OR TURP + BCG with cystoprostatectomy +/– urethrectomy for salvage.
How is urothelial carcinoma of the prostate with stromal invasion treated?

Show Answer

Radical cystoprostatectomy +/– urethrectomy +/– neoadj chemo. Consider adj chemo if no neoadj chemo given. (NCCN 2018)

62

Urethral Cancer

Updated by Brian C. Baumann

BACKGROUND

What is the estimated annual incidence of urethral cancer in the United States?

Show Answer

~500 cases/yr of urethral cancer in the United States. It is a rare but aggressive cancer.

What is the epidemiology of urethral cancer?

Show Answer

Urethral cancer is more common in women (4:1 ratio) and more common in African Americans.

What are the conditions or exposures associated with urethral cancer?

Show Answer

Exposures associated with urethral cancer include chronic inflammation (STDs, stricture, recurrent urinary tract infections) and HPV infection.

Is there an association b/t urethral cancer and other malignancies?

Show Answer

Yes. Urothelial carcinoma of the urethra is often multifocal and is sometimes associated with urothelial cancer in the bladder, ureters or renal pelvis.

What is the avg length of the female urethra and its anatomic divisions?

Show Answer

The avg length of the adult female urethra is **4 cm.** It is anatomically divided into the **distal one-third (ant urethra) and proximal two-thirds (post urethra).**
In a female, what type of epithelium does the proximal and distal urethra have?

Show Answer

The distal two-thirds of the female urethra has stratified squamous epithelium. The proximal one-third has transitional epithelium.
What is the avg length of the male urethra and its anatomic divisions?

Show Answer

The avg length of the adult male urethra is **21 cm.** It is divided into the prostatic, bulbomembranous, and penile urethra.
In a male, what type of epithelium lines the urethra?

Show Answer

- Prostatic and bulbomembranous urethra: transitional epithelium (similar to the bladder)
- Penile urethra: pseudostratified columnar epithelium

What is the histologic prevalence of urethral cancers?

Show Answer

SCCs are the most common f/b urothelial carcinoma and adenocarcinoma. In men, most penile and bulbomembranous tumors are SCC. Most prostatic urethral tumors are urothelial.
What is the most common site of origin of urethral cancer in men?

Show Answer

In men, urethral cancer occurs most frequently in the **bulbomembranous urethra** (60%), penile urethra (30%), and prostatic urethra (10%).
What is the main pattern of spread in urethral cancer?

Show Answer

The main pattern of spread is **direct extension.**
What is the lymphatic drainage for the urethra?

Show Answer

Generally, the distal 1/3 of the urethra in men and women drains to the inguinal nodes. The proximal 2/3 drain to the pelvic nodes.
What portion of urethral cancer pts will be node-positive at Dx?

Show Answer

15%–30% will be node-positive at Dx.
Are most clinically apparent nodes pathologically positive in urethral cancer?

Show Answer

Yes. ~75% of clinically apparent nodes are pathologically positive, unlike in penile cancer where ~50% of enlarged nodes are pathologically positive.
What % of urethral cancer pts have DM at Dx? What are the most common sites of DM?

Show Answer

10% of pts have DM at Dx. The most common sites are the **lung, liver, and bone.**
What are the most common presenting Sx of urethral cancer?

Show Answer

Most women present with irritative voiding Sx or hematuria. In men, Sx are often nonspecific and mimic benign urethral strictures. Men can present with

hematuria or obstructive voiding, urethral discharge, or urinary retention.

WORKUP/STAGING

What is the workup of urethral cancer?

Show Answer

H&P, including palpation of length of urethra in men, inguinal nodal exam, and bimanual exam. Cystourethroscopy with EUA and transurethral or transvaginal Bx, pelvic CT or MRI, and chest imaging (x-ray or CT). If there is palpable inguinal LNs, perform CT C/A/P and LN Bx. (NCCN 2018)

What is the workup for urothelial carcinoma of the prostate?

Show Answer

H&P, PSA, DRE, cystoscopy with bladder Bx, TURP that includes the prostatic stroma. If DRE is abnl, perform needle Bx to exclude primary adenocarcinoma of the prostate. Image upper urinary tract. If stromal or acinar invasion present, perform chest imaging.

What is the AJCC 8th edition (2017) T and N staging for primary tumors of the male penile urethra and female urethra?

Show Answer

Ta: noninvasive papillary carcinoma
Tis: CIS
T1: tumor invades subepithelial connective tissue
T2: tumor invades either corpus spongiosum or periurethral muscle
T3: tumor invades either corpus cavernosum or ant vagina
T4: invasion of other adjacent organs (e.g., bladder wall)
N1: single involved LN in the pelvis or inguinal region
N2: multiple involved LNs in the pelvis or inguinal region

What is the AJCC 8th edition (2017) T staging for urothelial carcinoma of the prostate?

Show Answer

Tis: CIS with involvement of prostatic urethra or periurethral or prostatic ducts without stromal invasion
T1: tumor invades urethral subepithelial connective tissue immediately underlying the urothelium
T2: tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
T3: tumor invades the periprostatic fat
T4: tumor invades other adjacent organs (e.g., extraprostatic invasion of the bladder wall, rectal wall)

TREATMENT/PROGNOSIS

Primary Cancer of the Urethra (Nonprostatic Urethra)

Does location correlate to the stage/prognosis of urethral cancer?

Show Answer

Yes. Proximal lesions more often present at a higher stage and thus carry a worse prognosis.
What are the most important prognostic factors for female pts? For male pts?

Show Answer

The most important prognostic factors for females are tumor size and histology and for males, stage and Dz location (NCCN 2018). Clinical nodal status was the only independent predictor of survival in a multi-institutional series of 154 pts. (Gakis, World J Urol 2016)
What Tx is generally preferred in pts with localized Dz?

Show Answer

Sg is generally preferred (either transurethral resection, excision with partial or total urethrectomy +/– radical cystectomy). RT +/– chemo is another

option.
How is Tis, Ta, or T1 SCC of the urethra treated?

Show Answer

Repeat transurethral or transvaginal resection +/– intraurethral therapy (Bacille Calmette Guerin [BCG], mitomycin, or gemcitabine). Total urethrectomy is an option for pts s/p radical cystectomy.
How is T2 Dz of the penile urethra treated?

Show Answer

Distal urethrectomy or partial penectomy +/– neoadj chemo or chemoRT
How is T2 Dz of the bulbomembranous urethra treated in men?

Show Answer

Urethrectomy +/– cystoprostatectomy. Adj chemo or chemoRT can be considered for ≥pT3 or N+ Dz.
How is T2 Dz in females generally treated?

Show Answer

ChemoRT or urethrectomy with cystectomy. (NCCN 2018)
Is partial urethectomy a good Tx option for female T2 pts?

Show Answer

No. Partial urethrectomy is associated with high urethral failure rates. (Dimarco, Urol Oncol 2004)
How is T3–4 cN0 Dz generally treated?

Show Answer

ChemoRT (preferred) vs. Neoadj chemo plus Sg or RT vs. RT alone (NCCN 2018)
How is cN1/N2 Dz generally treated?

Show Answer

RT +/– chemo (chemoRT preferred for SCC) vs. chemo alone vs. chemoRT f/b consolidative Sg
What is the role of inguinal lymphadenectomy?

Show Answer

The role of inguinal LND is controversial. Routine inguinal LND is not generally indicated except for enlarged nodes on imaging or physical exam. Role of sentinel node Bx is unclear.
What is the typical RT dose for female urethral cancer?

Show Answer

RT is often given as brachytherapy alone or brachytherapy + EBRT. Typical Tx includes (1) brachytherapy alone to 50–60 Gy or (2) EBRT to 40–45 Gy → brachytherapy to 20–25 Gy. Inguinal nodes should be included.
What are the outcomes for urethral cancer in female pts treated with RT alone?

Show Answer

5-yr LC was 64% in a series of 86 pts (Garden, Cancer 1993). A meta-analysis of RT alone in female pts with urethral cancer showed a 5-yr OS of 75% with early-stage Dz and 34% with advanced-stage Dz. (Kreig, Oncology 1999)
What are the OS outcomes based on the SEER database?

Show Answer

5- and 10-yr OS in men were 46% and 29% and 43% and 32% in women. (Rabbani, Cancer 2011 & Champ, Urology 2012)
What is appropriate post-Tx f/u for urethral cancers?

Show Answer

Follow-up q3–4 mos in the 1st 2 yrs and then semiannually for yrs 3–5, and then annually. Follow-up should include physical exam with palpation of the

inguinal nodes, endoscopic evaluation of the urethra +/– cross-sectional imaging.

Urothelial Carcinoma of the Prostate

How is urothelial carcinoma of the prostatic urethra treated?

Show Answer

TURP + BCG. LRs treated with cystoprostatectomy +/– urethrectomy.
What unique pathologic factors confer additional risk of recurrence in urothelial carcinoma of the prostate?

Show Answer

Acinar invasion and stromal invasion.
How is urothelial carcinoma of the prostate with acinar invasion treated?

Show Answer

Radical cystoprostatectomy +/– urethrectomy OR TURP + BCG with cystoprostatectomy +/– urethrectomy for salvage.
How is urothelial carcinoma of the prostate with stromal invasion treated?

Show Answer

Radical cystoprostatectomy +/– urethrectomy +/– neoadj chemo. Consider adj chemo if no neoadj chemo given. (NCCN 2018)

FOLLOW-UP/TOXICITY

What are the expected acute and late RT toxicities associated with Tx of urethral cancer?

Show Answer

Acute toxicities: RT cystitis, urethritis, dermatitis, GI Sx (e.g., diarrhea)
Late toxicities: RT cystitis, urethral stricture/stenosis, fibrosis, chronic penile edema, incontinence, fistula formation (rare)

63

Renal Cell Carcinoma

Updated by David M. Guttmann

BACKGROUND

Order the following 5 tissues from outermost to innermost: renal cortex, Gerota fascia, adrenal gland, perirenal fat, and renal capsule.

Show Answer

From outermost to innermost:

. Gerota fascia
. Perirenal fat
. Adrenal gland (which is embedded in the perirenal fat sup to the kidney)
. Renal capsule
. Renal cortex

Name 3 environmental risk factors for renal cell carcinoma (RCC).

Show Answer

Environmental risk factors for RCC:

. Cigarette smoking
. Phenacetin exposure (found in analgesics)
. Heavy metal exposure

Name the most important nonenvironmental risk factor for RCC.

Show Answer

Obesity. The risk of RCC increases by 7% per unit increase in BMI. (Bergstrom A et al., Br J Cancer 2001)
Familial RCC makes up what % of RCC cases? Name 5 familial syndromes.

Show Answer

Familial RCC makes up **~4%** of RCC cases. Familial syndromes:

- Von Hippel–Lindau
- Birt–Hogg–Dube syndrome
- Tuberous sclerosis
- Hereditary papillary RCC
- Familial clear cell RCC

What is the estimated annual incidence of new RCC cases in the United States?

Show Answer

~58,000 cases/yr of new RCC in the United States
Has the incidence of RCC been increasing or decreasing over the past 30 yrs? Is there a sex predilection?

Show Answer

The incidence of RCC has been **increasing** by 2%/yr over the past 30 yrs according to NCI SEER data. **Men** appear to be more commonly diagnosed with RCC than women.
In which decade of life is RCC typically diagnosed?

Show Answer

RCC is typically diagnosed in the **7th decade of life.**
RCC represents what % of all urinary tract tumors?

Show Answer

RCC represents **~6%** of all urinary tract tumors.
What benign tumors can exist in the kidney?

Show Answer

Benign tumors of the kidney:

- Angiomyolipomas
- Fibromas
- Lipomas
- Lymphangiomas
- Oncocytomas
- Hemangiomas

What % of RCC pts will present with a palpable mass on physical exam?

Show Answer

~10% of RCC pts will have a palpable mass at the time of presentation.
RCC pts are at increased risk of having what other type of synchronous urinary cancer?

Show Answer

RCC pts have an RR of 1.5 of having a synchronous bladder cancer, though the authors do not screen for bladder cancer in RCC pts. This increased risk may be related to smoking.
What is the classic triad of RCC? With what other clinical Sx can pts with RCC present?

Show Answer

Pts with RCC present with classic triad Sx of hematuria, flank pain, and a palpable mass. Sx of fever, night sweats, and weight loss suggest the presence of metastatic Dz.
What are some paraneoplastic syndromes associated with RCC? In what % of pts would these syndromes be found?

Show Answer

Paraneoplastic syndromes associated with RCC:

- Hypercalcemia
- Elevated LFTs
- Hypertension

These paraneoplastic syndromes arise in **20%** of pts.
What % of RCC pts present with bilat kidney involvement?

Show Answer

3% of RCC pts will have bilat involvement at Dx.
What are 4 pathologic subtypes of RCC?

Show Answer

Pathologic subtypes of RCC:

- Clear cell
- Chromophilic (or papillary)
- Chromophobic
- Collecting duct

What is the most common pathologic subtype of RCC?

Show Answer

Clear cell is the most common subtype of RCC (~70%), demonstrating large clear cells with abundant cytoplasm.
What is the most common histologic grading system for RCC?

Show Answer

The most common histologic grading system for RCC is the **Fuhrman grading system** from I to IV based on nuclear roundness, size, nucleoli presence, and the presence of clumped chromatin.
Sporadic RCC is characterized by what genetic mutation?

Show Answer

Sporadic RCC is characterized by a **mutation in the** VHL **tumor suppressor gene on chromosome 3p25,** which is silenced in >50% of sporadic RCC.

WORKUP/STAGING

How is RCC diagnosed?

Show Answer

RCC requires a tissue Dx. Often, nephrectomy is both diagnostic and therapeutic. Percutaneous Bx can also be employed for surgically unfit pts, those considering active surveillance, or at the time of ablative therapy.
What % of biopsied pts have benign Dz?

Show Answer

~33% of small renal masses may be characterized as benign according to the specimen obtained. The risk of benign pathology is inversely proportional to the size of the renal mass.
What imaging is important in the initial workup of RCC?

Show Answer

Imaging workup typically includes contrast-enhanced CT or MRI scan of the abdomen and chest imaging. Consider bone scan and MRI brain if clinically indicated.
Summarize the AJCC 8th edition (2017) T staging for RCC.

Show Answer

TX: primary tumor cannot be assessed
T0: no evidence of primary tumor
T1: limited to kidney and ≤7 cm
T1a: ≤4 cm
T1b: >4 and ≤7 cm
T2: limited to kidney and >7 cm

T2a: >7 cm but ≤10 cm
T2b: >10 cm
T3: invades into major veins or perinephric tissues but not into ipsi adrenal gland and not beyond Gerota fascia
T3a: extends into renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota fascia
T3b: extends into vena cava below diaphragm
T3c: extends into vena cava above diaphragm or invades wall of vena cava
T4: invades beyond Gerota fascia, including contiguous extension into ipsi adrenal gland

Summarize the AJCC 8th edition (2017) stage grouping for RCC.

Show Answer

Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T1–2N1M0 or T3N0–1M0
Stage IV: T4 or M1

What other staging systems are widely used for RCC?

Show Answer

The Flocks and Kadesky system (with or without Robson modification) and Jewett–Strong classification system have been used to stage RCC.

Name 3 prognostic factors for RCC.

Show Answer

Prognostic factors for RCC:

1. TNM stage
2. PS
3. Fuhrman grade

TREATMENT/PROGNOSIS

Describe 5 invasive Tx for locally confined RCC.

Show Answer

Invasive Tx for locally confined RCC:

- Open nephrectomy
- Laparoscopic nephrectomy
- Percutaneous CT-guided cryosurgery
- Percutaneous radiofrequency ablation
- Partial nephrectomy

Are there any studies comparing laparoscopic resection with that of open resection in pts with RCC?

Show Answer

Yes. There are retrospective data that compared laparoscopic resection vs. open resection of RCC. There was no difference in DFS. (Luo JH et al., World J Urol 2009; Marszalek M et al., Eur Urol 2009)

Are there surgical options for pts with bilat RCC or unilat RCC with a diseased contralat kidney?

Show Answer

Yes. Pts with bilat RCC or a diseased contralat kidney can be treated with a partial nephrectomy provided the lesion is amenable to a nephron-sparing approach.

When is recurrence most likely to occur following Sg for RCC?

Show Answer

The median time for recurrence after Sg for RCC is ~2 yrs. Most recurrences occur within 5 yrs.

Name 4 predictors of RCC recurrence after nephrectomy.

Show Answer

Predictors of RCC recurrence after nephrectomy:

. Nuclear grade (Fuhrman grade)
. TNM stage
. DNA ploidy
. Genetic RCC syndromes

What are the most common sites of RCC recurrence after nephrectomy?

Show Answer

Most common sites of RCC recurrence after nephrectomy:

. Lung
. Bone
. Regional LNs

What f/u imaging is recommended for RCC pts after nephrectomy?

Show Answer

RCC pts after nephrectomy should be followed with **CXR/CT chest and CT/MRI abdomen.**

For how long should pts with RCC treated with nephrectomy be followed?

Show Answer

Pts with RCC treated with nephrectomy should be followed **for life** (sporadic RCC recurrences have been documented ≥40 yrs later).

Are there any prospective randomized studies examining the role for adj therapy in pts with RCC treated with initial nephrectomy?

Show Answer

Yes. IFN α-2b within 1 mo after Sg vs. Tx only after postsurgical relapse demonstrated no EFS or OS benefit (Messing EM et al., JCO 2003). 2 phase III trials of antiangiogenic therapy in the adj setting (ASSURE, Lancet 2016;

S-TRAC, NEJM 2016) failed to demonstrate significant differences in OS from the use of a TKI compared to placebo, though in neither case was it the primary endpoint.

What is the 1st-line Tx for pts with metastatic RCC?

Show Answer

1st-line Tx for pts with metastatic RCC:

- Cytoreductive nephrectomy
- Metastasectomy for oligometastases
- Sunitinib
- Temsirolimus
- Bevacizumab and IFN
- High-dose recombinant interleukin-2
- Sorafenib

Cytotoxic chemo for non–clear cell histologies may be considered.

Is there a role for palliative nephrectomy in pts with RCC?

Show Answer

Yes. Palliative nephrectomy is still encouraged to relieve local Sx of pain or intractable hematuria; as well as systemic Sx related to the primary tumor.

What are the data for using cytoreductive Sg in combination with immunotherapy?

Show Answer

Cytoreductive Sg utilized before immunotherapy **may delay time to progression and improve survival of pts with metastatic Dz** (median duration of survival 17 mos vs. 7 mos, SS). (Mickisch GH et al., Lancet 2001)

Is there a role for resection of metastatic lesions in pts with RCC?

Show Answer

Yes. A retrospective study by Kavolius JP et al. suggests that curative resection of metastatic lesions in pts with RCC improves survival compared with the subtotal resection of pts or those with noncurative salvage attempts (44%, 14%, and 11%, respectively). (JCO 1998)
Is there a role for RT in pts with RCC in the definitive setting?

Show Answer

Generally not. 2 classic prospective trials (Finney et al., Br J Urol 1973; Kjaer et al., IJROBP 1987) evaluating the role of postop radiotherapy in localized RCC failed to demonstrate any LRC or OS benefit and RT was associated with Tx-related mortality. Ongoing work is evaluating SBRT in inoperable pts.
What fractionation schemes are under investigation in ongoing trials assessing the role of SBRT for primary RCC?

Show Answer

A range of fractionation schemes are under study, from 40–50 Gy in 5 fx to 48–60 Gy in 3 fx, as well as 23–25 Gy in 1 fx in 1 study. Retrospecitve data suggest better outcomes with higher BED regimens.
Is there a role for RT in pts with RCC in the palliative setting?

Show Answer

Yes. RCC is widely regarded as a radioresistant tumor. However, palliative RT is effective in treating brain mets, bone mets, and other metastatic lesions. Recent evidence suggests that hypofractionation and SBRT/SRS may be more effective than conventional fractionation for the Tx of metastatic lesions.
Is there a role of immunotherapy in pts with metastatic RCC?

Show Answer

Yes. Nivolumab was shown to significantly improve OS in pts with metastatic RCC who progress on antiangiogenic therapy. (Motzer et al.,

NEJM 2015)

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Cervical Cancer

Updated by Jason Edwards

BACKGROUND

What is the annual incidence of cervical cancer in the United States?

Show Answer

~12,000 cases/yr of cervical cancer in the United States.

What is the mean age of presentation for cervical cancer?

Show Answer

The mean age of presentation for cervical cancer is **in the 40s** in the United States.

List the 7 lifestyle factors associated with an increased risk of cervical cancer.

Show Answer

Lifestyle factors associated with increased risk of cervical cancer:

- Early onset of sexual activity
- Larger number of sexual partners
- Exposure to high-risk partners
- Hx of STD
- Smoking
- High parity

. Prolonged use of oral contraceptives

HPV is detectable in what % of cervical cancer?

Show Answer

HPV is detectable in **>99%** of cervical cancer.
Roughly what % reduction in mortality has been achieved with PAP screening for cervical cancer?

Show Answer

There has been an ~7**0% reduction** in cervical cancer mortality with PAP screening.
What does ASCUS stand for (on a PAP result), and how should it be managed?

Show Answer

ASCUS stands for **A**typical **S**quamous **C**ells of **U**nknown **S**ignificance. About two-thirds can resolve spontaneously. Pts can undergo **repeat PAP in 6 mos and then colposcopy if abnl.**
How should LGSIL seen on PAP be managed?

Show Answer

LGSIL resolves spontaneously ~40% of the time; therefore, like with ASCUS, pts can undergo **repeat PAP in 6 mos with colposcopy if abnl.**
How should a HGSIL result from a PAP be managed?

Show Answer

All pts with HGSIL should undergo **colposcopy with Bx.** One-third of these pts can still resolve spontaneously, but waiting without further investigation is not recommended d/t concern for progression.
What % of HGSIL progresses to invasive cancers?

Show Answer

22% of HGSIL progress to invasive cancer. This is in contrast to ASCUS (<1%) and LGSIL (~5%).
What % of cervical cancers are caused by HPV-16 and -18?

Show Answer

>70% of cervical cancers are caused by HPV-16 and -18.
What HPV subtypes cause the most cases of benign warts?

Show Answer

HPV subtypes **6 and 11** cause most cases of benign warts.
What HPV subtypes do Cervarix and Gardasil 9 protect against, respectively?

Show Answer

Cervarix protects against HPV types 16 and 18. Gardasil 9 protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine can be given to males and females of ages 9–26 yo to protect against cervical cancer, vulvar cancer, anal warts, and genital warts.
In the United States, what % of cervical cancers are SCCs vs. adenocarcinomas?

Show Answer

With regard to cervical cancers in the United States, **80% are SCCs,** while **~20% are adenocarcinomas.**
List 5 histologic subtypes of adenocarcinoma of the cervix.

Show Answer

Subtypes of adenocarcinoma of the cervix:

- Mucinous
- Adenosquamous
- Endometrioid

. Clear cell
. Glassy cell

Name the 3 common presenting Sx of cervical cancer.

Show Answer

Most common presenting Sx of cervical cancer:

- Abnl vaginal bleeding
- Postcoital bleeding
- Abnl vaginal discharge
- Dyspareunia
- Pelvic pain

What specific area of the cervix is the most common point of origin for cervical cancer?

Show Answer

The **transformation zone** is the most common point of origin for cervical cancer. It is a dynamic area b/t the original and present squamocolumnar junction.

WORKUP/STAGING

What should be included in the workup for a cervical mass?

Show Answer

Pelvic mass workup: H&P, including HIV status, careful pelvic exam in the office, basic labs, pregnancy test, EUA with Bx, for any visible lesions, and pelvic imaging.

What are the areas at risk for local extension of cervical cancer?

Show Answer

Cervical cancer can spread locally to the **uterine corpus, parametria, and vagina.** These should be carefully assessed during a physical exam. Tumor size and parametrial involvement are better assessed by rectovaginal exam.

Cervical tumors can also spread to the bladder anteriorly or rectum posteriorly.
Name 3 routes of lymphatic drainage from the cervix.

Show Answer

Routes of lymphatic drainage from the cervix:

. Lat to the external iliac nodes via the round ligament
. Post into common iliac and lat sacral nodes via the uterosacral ligament
. Post–lat into internal iliac nodes

What imaging studies are included in FIGO staging of cervical cancer? What common imaging modalities are not allowed?

Show Answer

CXR, barium enema, and intravenous pyelogram data are included in FIGO staging of cervical cancer, as are procedures such as cystoscopy, proctoscopy, and hysteroscopy if there is concern for invasion. **CT, PET, MRI, bone scan, lymphangiography, and laparotomy/laparoscopy data are not allowed** to be used for staging but can be obtained for parametrial invasion, Tx decision making, and planning purposes (but do not influence FIGO staging of the pt).
What is the utility of PET scans in cervical cancer?

Show Answer

PET is generally fairly sensitive (85%–90%) and specific (95%–100%) for detection of para-aortic nodes in pts with locally advanced cervical cancer. Interpretation of the primary tumor at the cervix is not very reliable d/t the high excretion of FDG and the resultant high SUV in the bladder.
In what group of cervical cancer pts is evaluation of the urinary tract required?

Show Answer

Cervical cancer **pts with more than stage IB1 Dz** require imaging of the urinary tract. This can be performed with CT, MRI, or intravenous pyelogram.

What is the FIGO (2010) staging for cervical cancer?

Show Answer

Stage IA: microscopic Dz, with ≤5 mm DOI and ≤7 mm horizontal spread. It is further delineated into IA1 (tumors ≤3 mm depth and ≤7 mm wide) and IA2 (tumors >3 mm but ≤5 mm deep and ≤7 mm wide)

Stage IB: clinically visible tumor or >IA2, with IB1 ≤4 cm, and IB2 being bulky tumors >4 cm

Stage IIA: invades beyond uterus/cervix; involves the upper two-thirds of the vagina without parametrial invasion with IIA1 lesions ≤4 cm and IIA2 lesions >4 cm

Stage IIB: invades beyond uterus/cervix and into parametria but not into pelvic wall or lower 3rd of vagina

Stage IIIA: invades lower 3rd of vagina but no extension into pelvic wall

Stage IIIB: invades pelvic sidewall and/or causes hydronephrosis or nonfunctioning kidney

Stage IVA: invades beyond true pelvis or mucosa of bladder or rectum (must be Bx-proven); bullous edema of bladder or rectum does not count

Stage IVB: DMs

How does the AJCC version 8 (TNM) staging system for cervical cancer compare with the FIGO system?

Show Answer

In AJCC cervical cancer staging, the **T stage corresponds to the FIGO stage, except for FIGO stage IVB.** Positive regional LNs are not included in FIGO, but are N1 in AJCC; however they do not influence AJCC stage grouping. Para-aortic nodes are no longer considered M1 Dz in AJCC version 8.

What factors are predictive of pelvic nodal involvement in cervical cancer?

Show Answer

Factors that predict for nodal involvement in cervical cancer include **DOI, FIGO stage, tumor size, and LVSI** (10% without vs. 25% with). It is controversial whether histologic subtype is an independent predictor for nodal involvement, although some studies show adenocarcinomas having higher rates of DM.

Estimate the risk of pelvic LN involvement based on the following DOIs of a cervical cancer: <3 mm, 3–5 mm, 6–10 mm, and 10–20 mm.

Show Answer

Risk of pelvic nodal involvement by DOI:

≤3 mm: <1%
3–5 mm: 1%–8%
6–10 mm: 15%
10–20 mm: 25%

Estimate the risk of pelvic LN involvement based on the FIGO stage of cervical cancer.

Show Answer

Pelvic LN+ rates for cervical cancer based on the FIGO stage:

Stage IA1: 1%
Stage IA2: 5%
Stage IB: 15%
Stage II: 30%
Stage III: 50%
Stage IVA: 60%

Estimate the risk of P-A nodal involvement based on the FIGO stage of cervical cancer.

Show Answer

P-A LN+ rates for cervical cancer based on the FIGO stage:

Stage IA: 0%
Stage IB: 5%–8%
Stage IIA: ~10%
Stage IIB: ~15%
Stage III: 30%
Stage IVA: 40%

What are the 5-yr OS rates based on the FIGO stage?

Show Answer

5-yr OS based on FIGO stage:

Stage IA: 93%
Stage IB: 75%–80%
Stage IIA: 80%
Stage IIB: 65%–70%
Stage IIIA: 35%
Stage IIIB: 35%–40%
Stage IVA: 10%
Stage IVB: 0%

(AJCC 8th edition 2017)

Which key clinical factors are included in the nomogram by Rose et al.?

Show Answer

The Rose nomogram predicts 2-yr PFS, 5-yr OS, and pelvic recurrence using the prognostic factors of **histology, race/ethnicity, PS, tumor size, FIGO stage, tumor grade, pelvic node status, and Tx with concurrent cisplatin.** (Rose P et al., J Clin Oncol 2015)

TREATMENT/PROGNOSIS

What is the most important prognostic factor in cervical cancer?

Show Answer

Tumor stage is the most important prognostic factor in cervical cancer since FIGO staging is based on prognostic factors. Per stage, extent of nodal involvement is the next most important factor.

What is removed in a radical trachelectomy as Tx for cervical cancer?

Show Answer

In a radical trachelectomy, **all cervical cancer is removed with a margin,** but the internal os is left behind and stitched closed, with a small meatus for menses to escape. This procedure (performed at select centers) allows future pregnancy, delivered via a C-section. This procedure should be reserved for women desiring fertility preservation and with stage IA1 as well as select cases of IA2 and small IB1 and tumors <2.0 cm in size.

How should pts with preinvasive cervical cancer (HGSIL or CIN III) be managed?

Show Answer

Pts with preinvasive cervical cancer should be managed with **colposcopy → conization, LEEP, laser, cryotherapy, or simple hysterectomy.**

In which subset of cervical cancer pts is simple hysterectomy adequate as definitive management?

Show Answer

Pts with IA1 Dz can be treated with simple abdominal hysterectomy. A cone should be done 1st to ensure that there are no foci of invasion beyond 3 mm identified. Sometimes, conization is also adequate for IA1, but there must be DOI <3 mm and no LVSI or dysplasia at the margin. (Van Nagell J et al., Am J Obstet Gynecol 1983) All other pts (≥IA2) should get radical hysterectomy with pelvic LND.

What is the difference b/t a class I–III radical hysterectomy (Piver–

Rutledge–Smith classification)?

Show Answer

In a class I (aka: total abdominal, simple, or extrafascial hysterectomy), the uterus is removed with little or no removal of vaginal tissue, cardinal ligament, or uterosacral ligament. In a class II (modified radical hysterectomy) there is removal of the uterus, ureters are unroofed to remove parametrial and paracervical tissue medial to the ureters and 1–2 cm of vaginal cuff, and the uterine artery is ligated at the ureter. In a class III Sg (radical hysterectomy), there is removal of parametrial and paravaginal tissue to the pelvic sidewall, ligation of the uterine artery at the ureter, and removal of the upper half to two-thirds of the vagina.

What stage of cervical cancer can be treated with brachytherapy alone?

Show Answer

Stage IA cervical cancer can be treated with brachytherapy alone with LDR 65–75 Gy or HDR 7 Gy × 5–6 fx, with LC of 97%. (Grisby P et al., IJROBP 1992)

When treating cervical cancer pts with brachytherapy, is there a Dz control or toxicity difference b/t LDR and HDR?

Show Answer

This is **uncertain.** In Teshima T et al. pts with stages I–III cervical cancer were randomized to HDR Co-60 or LDR cesium-137 therapy. There was no SS difference in 5-yr CSS b/t the 2 groups (stage I, 85%–93%; stage II, 73%–78%; stage III, 47%–53%). Moderate to severe complications were higher in HDR (10% vs. 4%). (Cancer 1993)

Where are points A and B, and what should it correspond to anatomically?

Show Answer

Point A is **2 cm above the external cervical os and 2 cm lat to the central canal/tandem.** This should correspond to the paracervical triangle, where

the uterine vessels cross the ureter.

Point B is **5 cm lat from the midline at the same level as point A** (2 cm above the external cervical os). It is supposed to represent the obturator nodes. The **dose to point B is usually 20% of the dose to point A using a tandem and ovoid system.**

Before CT-based planning, how were the bladder, rectum, and vaginal points defined for cervical cancer brachytherapy?

Show Answer

Before CT-based planning, the bladder point was the post surface of the Foley balloon at midplane of ovoids on a lat x-ray filled with 7 cc radiopaque fluid and pulled down against the urethra. The rectum point was 5 mm behind the post vaginal wall b/t the ovoids at the inf point of the last intrauterine tandem source or mid vaginal source. The vaginal point was the lat edge of the ovoids on AP film and mid ovoid on lat film. In the present age of CT planning, an alternative is to contour the organs and calculate the max dose to the organ using 3D planning.

What are the dose limits to the bladder, rectum, and vaginal points in cervical cancer brachytherapy for 2D and 3D planning?

Show Answer

- In cervical cancer brachytherapy, 2D International Commission on Radiation Units (ICRU) doses are **max point doses.** Typically in 2D planning the max allowed dose to the **rectal point dose is <72 Gy,** the max **bladder point dose is <80 Gy,** and the max **vaginal point dose is <120 Gy.**
- With **3D planning,** limits are **volume based** and quantified as D2cc which is defined as the min dose within the 2-cc volume of greatest dose. **The bladder limit is D2cc <90 Gy equivalent 2 Gy dose (EQD2), rectum and sigmoid limit is D2cc <75 Gy EQD2.** (Viswanathan A et al., Brachy 2012)

What RT dose can cause ovarian failure? What about sterility?

Show Answer

Ovarian failure can occur with **5–10 Gy** of RT. Sterility can occur **after 2–3 Gy.**

What are the typical LDR and HDR in cervical cancer Tx?

Show Answer

In cervical cancer brachytherapy, **LDR range is 40–200 cGy/hr,** while **HDR is much higher >12 Gy/hr.** Typically, 1 HDR Tx of 5.5–6.0 Gy takes appx 5–10 min to deliver.

What is the role for definitive Sg vs. definitive RT for the management of early stage (IB–IIA) cervical cancers? What study tested these 2 modalities?

Show Answer

In Landoni F et al. pts with stages IB and IIA cervical carcinoma were randomized to Sg (class III) vs. RT (without chemo) for definitive therapy. Adj RT was allowed for the Sg group based on preset criteria. 5-yr OS and DFS were equal (83% and 74%, respectively, for both groups). 64% of Sg pts rcvd adj RT. Grades 2–3 morbidity was higher in the Sg arm (28% vs. 12%). Pts with adenocarcinoma of the cervix were found to have a survival benefit with hysterectomy. (Lancet 1997)

What are the benefits of Sg over RT for the Tx of early-stage cervical cancers?

Show Answer

Benefits of Sg over RT include shorter Tx time, preservation of ovarian function, possibly better sexual functioning after Tx, no 2nd malignancy risk, avoidance of long-term RT sequelae, and psychologically easier for many pts to understand. Sg can also better identify the accurate anatomic extent of Dz.

What adverse features after Sg are indications for adj RT alone without chemo?

Show Answer

Pts with cervical cancer s/p hysterectomy with –margins and –nodal status but have ≥**2 risk features (+LVSI, >4-cm tumors, more than one-third stromal invasion)** benefit from adj RT.

The Gynecologic Oncology Group's study **GOG 92** enrolled 277 stage IB cervical cancer pts who underwent Sg and had –nodes but >1 adverse feature: more than one-third stromal invasion, LVI, or tumor >4 cm. Compared to observation, there was a pelvic RT (46–50.4 Gy) RR of recurrence by 46% (21% vs. 14%, p = 0.007) and trend to OS benefit by ~10% (71% vs. 80%, p = 0.074). (Rotman M et al., IJROBP 2006)

What adverse features after Sg are indications for adj chemo–RT?

Show Answer

In **GOG 109,** high-risk pts (with at least 1 of the following features: +margin, +nodes, or microscopic parametrial invasion) with initially staged IA2, IB, and IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy were randomized to standard pelvic field RT (49.3 Gy) vs. RT + cisplatin/5-FU for 4 cycles. CRT was sup in both 4-yr OS (81% vs. 71%) and 4-yr PFS (80% vs. 63%). (Peters W et al., JCO 2000)

What subset of pts from GOG 109 can be managed with adj RT alone?

Show Answer

The subset analysis of **GOG 109** demonstrated that **pts with tumors <2 cm and only 1 +node** did not benefit from CRT compared with RT alone. (Monk B et al., Gyn Oncol 2005)

What trial is currently evaluating adj RT vs. CRT after hysterectomy and LND in pts with intermediate-risk stage I–IIA cervical cancer?

Show Answer

GOG 263 compares adj RT vs. CRT in intermediate-risk pts s/p hysterectomy defined as:

- LVSI and deep 3rd cervical stromal invasion
- LVSI and middle 3rd invasion and tumor ≥2 cm
- LVSI and superficial 3rd invasion and tumor ≥5 cm or
- No LVSI with middle or deep 3rd invasion and tumor ≥4 cm.

For pts with bulky (>4 cm) early-stage cervical cancer, is there an advantage to adding adj hysterectomy to definitive RT?

Show Answer

In **GOG 71,** pts with tumors **>4 cm** were randomized to RT alone vs. RT + adj hysterectomy. RT consisted of EBRT + brachytherapy (80 Gy to point A for the RT-alone group, and 75 Gy to point A for the Sg group). At median 9.6-yr f/u, there was no difference in OS or severe toxicity. There was a trend to improved LR (26% vs. 14%, p = 0.08). (Keys HM et al., Gyn Oncol 2003)

An option is to treat with CRT and assess for response at 2 mos. If residual Dz is evident, then salvage Sg can be considered. A downside to adj hysterectomy is the potential for complications d/t the high-dose radiation delivered to the area, including a relatively high dose to the post bladder wall.

For stage IB2 cervical cancer pts, what is the advantage of preop CRT compared with preop RT alone?

Show Answer

In **GOG 123,** stage IB2 cervical cancer pts were randomized to preop RT vs. CRT → adj simple hysterectomy. RT was whole pelvis (WP) + brachytherapy to a point A dose of 75 Gy. CRT added weekly cisplatin 40 mg/m^2. CRT was sup in 3-yr pCR (52% vs. 41%), OS (83% vs. 74%), and pCR (52% vs. 41%). Note: Adj and immediate hysterectomy was included in this trial prior to the results of GOG 71 being available. (Keys HM, NEJM 1999)

In stage IB cervical cancer, is there a role for neoadj chemo prior to Sg?

Show Answer

Controversial. GOG 141 looked at stage IB2 pts randomized to radical hysterectomy with nodal dissection +/– neoadj vincristine/cisplatin × 3 cycles. The study closed early, but there was comparable LC and OS in both groups, and PORT was needed in 45%–52% of pts. (Eddy GL et al., Gyn Oncol 2007)

A phase III trial from Italy looked at neoadj chemo + Sg vs. RT alone for stages IB2 to III pts and found sup OS and PFS in the chemo + Sg arm. Benefit was significant only for stages IB2 to IIB group. (Benedetti-Panici P et al., JCO 2002)

EORTC 55994 closed prematurely as interim analysis revealed inf OS in the with neoadj chemo arm compared to Sg without chemo. (Katsumata Br J, Cancer 2013)

In locally advanced cervical cancer, what is the OS advantage of definitive CRT over RT alone?

Show Answer

The benefit of CRT over RT alone in locally advanced cervical cancer was evaluated in **RTOG 90-01.** (Eifel P et al., JCO 2004) This study randomized stages IIB–IVA, large stages IB–IIA (>5 cm), or LN+ pts and randomized to RT to the pelvis and P-A nodes vs. pelvis RT + 3 cycles of cisplatin/5-FU. Both arms had brachytherapy with a point A dose of 85 Gy. 8-yr OS was 67% vs. 41%, benefiting the CRT. 5 RCT's show OS benefit with addition of chemo. (NCI press office, 1999)

Which chemo agent is most commonly used during CRT for cervical cancer?

Show Answer

Weekly cisplatin at 40 mg/m^2 is the current standard to be given with definitive RT. **RTOG 90-01** also utilized cisplatin, but at a dose of 75 mg/m^2 q3wks.

To what subset of pts is adding P-A fields to the pelvic field beneficial in the definitive Tx of cervical cancer?

Show Answer

There are 2 indications where the P-A field should be added to the definitive management of cervical cancer pts: (1) pts with +P-A Dz and (2) pts with +pelvic nodal Dz and not receiving CRT. 2 studies have addressed this:

RTOG 79-20 randomized 337 pts with stage IIB Dz without clinical or radiographic evidence of P-A Dz to the WP (45 Gy) alone vs. WP + P-A field (EFRT) (45 Gy). No chemo was given. Adding the P-A field improved 10-yr OS (55% vs. 44%) without improvement in LC or DM. However, there was slightly increased toxicity with the P-A field (8% vs. 4%). (Rotman M et al., JAMA 1995)

RTOG 90-01 randomized 386 pts with locally advanced cervical cancers (stages IIB–IVA or IB–IIA with ≥5 cm) or with a +pelvic LN (no P-A nodal Dz) to WP RT + chemo vs. WP + P-A field alone (EFRT). All pts were treated with post-EBRT brachytherapy of 85 Gy to point A. Chemo was cisplatin 75 mg/m^2 + 5-FU 1,000 mg/day × 4 days per 21-day cycle for 3 cycles. Pelvic CRT was sup to EFRT in 8-yr OS (67% vs. 41%), DFS (61% vs. 46%), LRF (18% vs. 35%), and DM (20% vs. 35%). There was a slight increase in P-A nodal failure in the CRT arm (8% vs. 4%, p = NSS). (Morris M et al., NEJM 1999; Eifel P et al., JCO 2004)

Describe the borders of typical AP and lat fields in cervical cancer Tx.

Show Answer

In cervical cancer therapy, the typical borders of an AP field are sup to L4–5 or L5/S1, inf to 3 cm below the most inf vaginal involvement or inf obturator foramen, and lat 2 cm from the pelvic rim. Lat beams would have the same sup and inf extent, with the ant edge to 1 cm ant of the pubic symphysis with coverage of entire uterus and post edge to include the entire sacrum. For common iliac nodal involvement, extend the field to cover up to L2. For P-A

nodal involvement, extend the field to **the top of T12** with ~70% AP/PA 30% lat field weighting if using 3D. The borders can be tailored for early-stage vs. more advanced Dz. In the CT planning era, the alternative is to contour the organs and nodes of interest to ensure adequate coverage.
Is there benefit in using IMRT to treat intact cervical cancer?

Show Answer

Potentially; a single arm study (Intertecc-2 trial) revealed IMRT reduced acute hematologic and GI toxicity compared to historical 3D outcomes. (Mell L et al., IJROBP 2016)
What is a typical EBRT Rx for cervical cancer?

Show Answer

Typically, cervical cancer pts treated with EBRT rcv RT to the WP to 45 Gy in 1.8 Gy/fx. Sidewall boosts to 50–54 Gy. Persistent or bulky parametrial tumors usually rcv 60 Gy. P-A nodes to 45 Gy if treated electively and sequential boost to 54–65 Gy if positive with 3D-CRT or IMRT.
What should be the total Rx dose to the high-risk (HR) CTV for cervical cancer (sum of EBRT + brachytherapy)? Who needs a sidewall boost?

Show Answer

In cervical cancer radiotherapy, the planning aim for the cumulative EQD2 to the HR-CTV (defined as the GTV + the entire cervix + presumed extracervical tumor extension) **D90 >85 Gy. T_2 MRI after EB** can be used to identify **residual GTV** (EMBRACE study). Pts with residual side wall or parametrial Dz after EB should rcv a boost in the form of EB or interstitial brachytherapy.
Is SBRT boost for cervical cancer equivalent to brachytherapy?

Show Answer

The use of SBRT or other EB modalities has not proven to be sup or

equivalent to brachytherapy. The use of brachytherapy should be utilized to achieve an EQD2 dose of D90 >80 Gy as it has a greater OS vs. SBRT/IMRT boost. (Gill et al., IJROBP 2014) Further, image-guided brachytherapy improves OS and reduces grade 3–4 toxicity vs. standard brachy in prospective STIC trial. (Charra-Brunaud et al., Radiother Oncol 2012)
Does overall Tx time in cervical cancer impact outcome? Ideally, how long should the RT Tx take?

Show Answer

Yes. Prolonged overall RT Tx time in cervical cancer is associated with poorer outcomes. Ideally, **EBRT and brachytherapy should be completed within 7 wks.** The effect is more notable in more advanced-stage pts (stages III–IV).
Per GOG 240, the addition of what agent improves outcomes for pts with recurrent, persistent, or metastatic cervical cancer?

Show Answer

Addition of **bevacizumab** to either topotecan-paclitaxel or cisplatin-paclitaxel resulted in an OS benefit extending MS from 13.3 mos to 17 mos. (Tewari KS et al., Lancet 2017)

FOLLOW-UP/TOXICITY

List 3 procedure-related complications seen in cervical cancer intracavitary brachytherapy.

Show Answer

Procedure-related complications seen in cervical cancer intracavitary brachytherapy:

. Uterine perforation (<3%) although some studies have rates >10%. US is recommended for guidance during insertion. (Small W. et al., Int J Gynecol Cancer 2011)

- Vaginal laceration (<1%)
- DVT (<1%)

Name the most common acute side effects associated with RT for cervical cancer.

Show Answer

Skin irritation, fatigue, hemorrhoids, colitis-diarrhea, cystitis-frequency/dysuria, and nausea are all possible acute side effects from cervical cancer RT.

Name the common long-term side effects associated with cervical cancer RT.

Show Answer

Common long-term side effects of cervical cancer RT include permanent alteration in bowel habit, menopause in the premenopausal age group, chronic cystitis with frequency, and vaginal stenosis with dyspareunia and postcoital bleeding. The major severe long-term toxicities are most commonly bowel related: rectosigmoid stenosis, requiring possible colostomy, and major rectal bleeding. Hematuria, ureteral stricture, fistula, SBO, and hip fracture or sacral insufficiency fracture can also occur.

What should pts do regularly to prevent vaginal stenosis after receiving RT for cervical cancer?

Show Answer

Routine use of a vaginal dilator is essential to preventing vaginal stenosis in pts who have undergone RT for cervical cancer.

What was the rate of fistula formation post RT and bevacizumab in GOG 240?

Show Answer

Fistula (any grade) occurred in 15% of pts treated with bevacizumab (1% in

chemo alone group); all pts previously irradiated. (Tewari KS et al., Lancet 2017)

When after definitive Tx do you order imaging?

Show Answer

A PET/CT is ordered at **3 mos post Tx** to assess response which is predictive of survival. If PR → Bx f/b Sg if + or local brachytherapy for small-volume Dz. If distant progressive Dz treat with chemo.

65

Ovarian

Updated by Adil S. Akthar

BACKGROUND

In the United States, where does ovarian cancer rank as a cause of cancer death in women?

Show Answer

In the United States, ovarian cancer is the **5th leading cause of cancer mortality** in women. It is the 2nd most common gyn malignancy and the leading cause of gyn cancer death.

What is the annual incidence and mortality of ovarian cancer in the United States?

Show Answer

Annually, there are **~22,000 new Dx and ~14,000 deaths** from ovarian cancer in the United States. (Siegel et al., CA Cancer J Clin 2017)

What is the median age at Dx of ovarian cancer?

Show Answer

The median age at Dx of ovarian cancer is **63 yrs.** The incidence increases with age and is most prevalent during the **6th and 7th** decades of life.

Is routine screening for ovarian cancer recommended?

Show Answer

No. Routine **screening is not currently standard of care for ovarian cancer.** This is supported by 3 large randomized screening trials including the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), and Shizuoka Cohort Study of Ovarian Cancer Screening. In the UKCTOCS which was the largest trial, postmenopausal women were randomly assigned to no screening, annual transvaginal ultrasound (TVUS), or multimodality screening (combination of CA125 and TVUS using algorithmic guidelines). After a median f/u of 11 yrs, no reduction in mortality was seen across arms. (Jacobs IJ et al., Lancet 2016)

What are the histopathologic subtypes of ovarian cancer in order of decreasing frequency?

Show Answer

WHO ovarian cancer subtypes are categorized by tissue of origin: **Epithelial ovarian cancer (EOC) (90%)** > ovarian stromal tumors > germ cell neoplasms > carcinosarcomas/malignant mixed müllerian tumors (MMMTs). EOC can be further classified into **4 main cell types** including serous (70%), mucinous, endometrioid, and clear cell.

What risk factors are associated with the development of ovarian cancer?

Show Answer

Risk factors associated with the development of ovarian cancer:

- **Nulliparity**
- **Advanced age at time of 1**st **birth (>35 yrs)**
- HRT
- High fat/lactose diet
- Hx of ≥2 1st-degree relatives with ovarian cancer
- Family Hx of BRCA1/2 or HNPCC (15% of ovarian cancer cases)
- Older age

(Finch A et al., JAMA 2006)

What is the role of prophylactic oophorectomy in BRCA1/2-positive women?

Show Answer

Prophylactic oophorectomy has been shown to reduce the risk of ovarian, fallopian tube, and breast malignancies in BRCA1/2 women; however, the risk of primary peritoneal cancer persists. (Finch A et al., JAMA 2006; Rebbeck TR et al., J Natl Cancer Inst 2009)

What factors are associated with a reduced risk for the development of ovarian cancer?

Show Answer

Factors associated with ↓ lifetime risk of ovarian cancer:

- Younger maternal age at 1st birth (≤25 yrs)
- Use of oral contraception
- Breastfeeding

What are the patterns of spread for ovarian cancer?

Show Answer

The most common route of spread is **transcoelomic,** whereby malignant ovarian cancer cells follow the flow of peritoneal fluid to deposit on peritoneal surfaces. Direct **lymphatic** spread is also possible to pelvic, P-A, and less commonly inguinal LNs. Hematogenous mets are present in only 2%–3% of pts at Dx and common sites include lung, liver, brain, bone, and subcutaneous tissues. (Eifel PJ, Gynecologic Radiation Oncology: A Practical Guide, Philadelphia: Wolters Kluwer, 2017.)

What are the common presenting signs and Sx of ovarian cancer?

Show Answer

Common Sx include: **bloating, abdominal/pelvic pain, difficulty eating,**

early satiety, new urinary Sx (frequency/urgency >12 days/mo), palpable abdominal/pelvic mass, and ascites. (Goff et al., Cancer 2007)
Identification of such Sx should prompt a workup for ovarian cancer.

WORKUP/STAGING

What is CA125, and what is its utility in ovarian cancer?

Show Answer

CA125 is a **mucinous protein encoded by the** MUC16 **gene, which is found in ocular, respiratory, and female genital tract epithelium.** It has been identified to be elevated in many (appx 90%) ovarian cancers, but has also been seen to be elevated in some endometrial, fallopian tube, breast, GI, and lung cancers. It can also be elevated in benign conditions such as endometriosis. **Its primary use is to assess response to Tx and predict prognosis after Tx for ovarian cancer.** Due to its low sensitivity and specificity as a diagnostic test, it has limited potential as a screening test.
What are the initial steps in the workup of pts with an undiagnosed pelvic mass?

Show Answer

Pts with signs/Sx suspicious for ovarian cancer should undergo a full H&P, including a thorough family Hx and bimanual pelvic exam, CBC, CMP. If there is concern that the mass involves the adnexa or female genital tract, obtaining US and a serum CA125 is indicated. Additional studies including a CT abdomen/pelvis, and CXR or CT chest can be used to assess for distant Dz. MRI may be indicated for indeterminate lesions if results will alter management. Use of PET/CT in this setting is not routine and further study is needed. Final staging is determined through surgical/pathologic evaluation of the abdomen and pelvis. (NCCN 2018)
What is the FIGO staging system (2014) for ovarian cancer?

Show Answer

Stage IA: limited to 1 ovary with capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings

Stage IB: limited to both ovaries, otherwise like IA

Stage IC: limited to 1 or both ovaries

Stage IC1: surgical spill

Stage IC2: capsule rupture before Sg, or tumor on ovarian/fallopian surface

Stage IC3: malignant cells in the ascites or peritoneal washings

Stage IIA: extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings

Stage IIB: extension to and/or implants on other pelvic tissues; no malignant cells in ascites or peritoneal washings

Stage IIIA: positive retroperitoneal LNs and/or microscopic mets beyond the pelvis

Stage IIIA1: positive retroperitoneal LNs only

Stage IIIA1(i): Mets ≤10 mm

Stage IIIA(ii): Mets >10 mm

Stage IIIA2: microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal LNs

Stage IIIB: macroscopic, extrapelvic, peritoneal mets ≤2 cm ± positive retroperitoneal LNs. Includes extension to the capsule of liver/spleen.

Stage IIIC: same as stage IIIB, however macroscopic mets >2 cm

Stage IVA: pleural effusion with positive cytology

Stage IVB: hepatic and/or splenic parenchymal mets, mets to extra abdominal organs (including inguinal LNs and LNs outside of the abdominal cavity)

If a pt with ovarian cancer is found to have a liver mets, what stage is she?

Show Answer

In ovarian cancer, the stage implications of a liver mets depend on whether the mets was on the liver capsule or in the parenchyma. **Liver capsule mets are T3/stage III,** and **liver parenchymal mets are M1/stage IV.**

What is the difference b/t the FIGO and AJCC TNM staging for ovarian cancer?

Show Answer

As of 2017, the **FIGO and AJCC 8th edition staging systems do not differ for ovarian cancer.**

What % of pts with newly diagnosed ovarian cancer present with advanced-stage Dz?

Show Answer

~70% of all newly diagnosed ovarian cancer pts present with advanced-stage Dz (stage I, 20%; stage II, 12%; stage III, 45%; stage IV, 23%). Dx at earlier stages is difficult d/t the location of the ovaries.

TREATMENT/PROGNOSIS

What is the general Tx paradigm for ovarian cancer?

Show Answer

Pts with suspected ovarian cancer should undergo a comprehensive diagnostic and therapeutic **laparotomy** for surgical staging and cytoreduction, respectively. This should include: TAH with bilat salpingo-oophorectomy, pelvic and P-A LN sampling, infracolic or infragastric omentectomy, peritoneal cytology, and systematic exploration with Bx of any suspicious areas within the abdomen/pelvis. **Cytoreduction** is often performed when mets are evident, with a goal to cytoreduce to **<1 cm of gross residual Dz**. **Adj chemo** is given for high-risk early-stage (I–II) Dz and advanced-stage (III–IV) Dz.

What is the ~5-yr stage-adjusted survival of pts with ovarian cancer treated with standard of care therapy?

Show Answer

Survival by stage for treated ovarian cancer pts:

Stage I: 80%
Stage II: 60%
Stage III: 30%
Stage IV: 10%
Are there situations where unilat salpingo-oophorectomy may be considered in pts with ovarian cancer?

Show Answer

For a young woman with **early-stage (IA) Dz or a low malignant potential tumor wishing to preserve fertility,** a unilat salpingo-oophorectomy may be considered.
How should early-stage (I–II) ovarian cancer be treated?

Show Answer

The gold standard for Tx of all stages of ovarian cancer is **Sg.** For stages IA–B, grade 1, non–clear cell tumors treated with complete cytoreductive staging laparotomy, 5-yr OS rates approach 95% and no adj therapy is indicated. For these same pts who have had incomplete surgical staging, **consider completion staging** or adj chemo. For high-risk early-stage pts (IC–II, clear cell histology, or grade 3 Dz), **adj chemo** is indicated. (Young RC et al., NEJM 1990; Trimbos JB et al., J Natl Cancer Inst 2003)
What trials support the use of chemo in the postsurgical setting for pts with ovarian cancer?

Show Answer

The ICON1/ACTION trials randomized mostly stages I–II ovarian cancer pts (some advanced-stage pts in ICON1) to postsurgical platinum-based chemo (4–6 cycles) vs. observation. Adj chemo significantly increased 5-yr OS (82% vs. 74%) and RFS (76% vs. 65%). Subset analysis of the ACTION (Adjuvant Chemo Therapy In Ovarian Neoplasm) trial suggested that some early-stage pts who have been optimally staged may not benefit from adj

chemo. (Trimbos JB et al., J Natl Cancer Inst 2003 and 2010)
What is the ideal duration of adj chemo for early-stage ovarian cancer?

Show Answer

3–6 cycles are typically administered. The Gynecologic Oncology Group's study **GOG 157** randomized 427 stages IA–B (grade 2–3), IC, and II ovarian cancer pts to 3 vs. 6 cycles of adj carboplatin and paclitaxel. The estimated 5-yr probability of recurrence (25.4% vs. 20.1%) and OS were not significantly different. Neurotoxicity, anemia, and granulocytopenia were significantly higher in the longer-therapy arm. (Bell J et al., Gynecol Oncol 2006) However, a subsequent ad hoc analysis showed a lower risk of recurrence for 6 cycles compared to 3 cycles in pts with serous tumors, but not other histologic types. (Chan et al., Gynecol Oncol 2010) **GOG 175** was a randomized phase III trial exploring the role of maintenance paclitaxel vs. observation after 3 cycles of adj carboplatin/paclitaxel, which showed no survival benefit and increased grade ≥2 toxicity with the use of maintenance paclitaxel. (Mannel et al., Gyencol Oncol 2012)
How should advanced-stage (III–IV) ovarian cancer be treated?

Show Answer

Advanced-stage pts are treated with **primary surgical cytoreduction f/b systemic therapy, typically carboplatin and paclitaxel. GOG 47** and **GOG 111** established the benefits of platinum- and taxane-based chemo in the postop setting, respectively. (Omura G et al., Cancer 1986; McGuire WP et al., NEJM 1996) **GOG 158** randomized 792 advanced-stage ovarian cancer pts with residual Dz ≤1 cm to adj paclitaxel/cisplatin vs. paclitaxel/carboplatin. There was no significant difference in outcome, yet there were more GI, renal, and hematologic toxicities with cisplatin. (Ozols R et al., JCO 2003) Although most pts with EOC receiving a cCR after standard adj chemo will recur, a meta-analysis reported no significant improvement in OS with the use of additional maintenance chemo. (Mei L et al., Cochrane

Database Syst Rev 2010) **GOG 212** is further investigating the role of maintenance taxanes.

What is the role of neoadj chemo in the Tx of ovarian cancer?

Show Answer

Generally, neoadj chemo may be considered for pts with **inoperable, bulky, advanced-stage, or otherwise those unlikely to tolerate primary cytoreductive Sg.** (Hou JY et al., Gynecol Oncol 2007; Steed H et al., Int J Gynecol Cancer 2006) The EORTC Gynaecological Cancer Group/NCIC Clinical Trials Group randomized primary debulking Sg +/– neoadj chemo in stages IIIC and IV ovarian, fallopian tube, and peritoneal cancer. Neoadj chemo was **not inf** to primary Sg. Median OS was 29 mos vs. 30 mos for initial Sg and neoadj chemo arms, respectively. (Vergote I et al., NEJM 2010)

What is the role of intraperitoneal (IP) chemo and RT in ovarian cancer?

Show Answer

This is **uncertain**. For advanced-stage pts with optimally cytoreduced Dz who have not rcvd neoadj Tx, a meta-analysis has shown sup OS and PFS with IV + IP chemo vs. IV alone. (Jaaback K et al., Cochrane Database Syst Rev 2016) However, preliminary data from **GOG 252** suggests dose-dense IV therapy may result in similar PFS as IV/IP therapy with fewer adverse effects. (Walker JL et al., Annual Meeting on Women's Cancer 2016) The use of IP chemo for early-stage Dz is still considered experimental and is being investigated in clinical trials. Intraperitoneal radioactive chromic phosphate (32P) was once an acceptable therapeutic option, but is no longer given d/t its difficulty to administer and high bowel complication rate. (Young et al., J Clin Oncol 2003)

Is there a role for adj RT in place of chemo following Sg for ovarian cancer?

Show Answer

Historically, whole abdomen irradiation (WAI) was used as a routine Tx for ovarian cancer largely d/t the observation of such high rates of abdominal failure. (Smith JP et al., Natl Cancer Inst Monogr 1975; Chiara S et al., Am J Clin Oncol 1994) Primary limitations of WAI related to the relatively low doses that could be tolerated and the high rates of GI complications. With the advent of platinum-based therapy, **the use of RT in the adj setting has fallen out of favor.**

Is there a role for adj RT combined with chemo following Sg?

Show Answer

There is evidence that **select pts may benefit** from this approach. Swenerton et al. published a population-based experience of 703 stage I–III ovarian cancer pts with no gross residual Dz following Sg who rcvd adj platinum-based chemo with or without WAI. (Ann Oncol 2011) In this review, there was no difference in DFS for pts with serous carcinomas. However, for pts with stage I or II clear cell, endometrioid, or mucinous carcinomas, the authors found improved DFS and OS for combined modality therapy. The fact that RT appears to be particularly effective for subgroups relatively resistant to chemo such as clear cell carcinoma warrants further study.

Is there a role for localized RT therapy for salvage of recurrent Dz?

Show Answer

Although most ovarian cancers disseminate early with intraperitoneal mets, some pts relapse with loco-regionally confined Dz in the absence of DM. The largest retrospective report by Brown et al. included 102 pts who rcvd definitive RT for localized nodal or extranodal recurrence of EOC. Pts rcvd a median of 3 courses of chemo and 50% rcvd more than 1 cancer-related operation prior to receipt of radiotherapy. This study demonstrated **several long-term survivors following the use of localized RT** with a 5-yr OS of 40% and 5-yr PFS of 24%. (Brown et al., Gynecol Oncol 2013)

Can RT be used to effectively palliate recurrent, cisplatin-refractory, focal

ovarian cancer lesions?

Show Answer

Yes. Although there are no prospective, randomized data available, Corn BW et al. retrospectively analyzed the efficacy of RT in palliating focally recurrent, symptomatic ovarian cancer lesions. Complete palliative response was 51%, overall palliative response was 79%, and median duration of palliation was 4 mos. The likelihood of obtaining a complete symptomatic response was related to a KPS ≥70% and a biologic effective dose 10 >44 Gy. (Cancer 1994) For pts with pelvic Sx, a single dose of 8–10 Gy can achieve improvement or cessation of bleeding in more than 75% of pts and significant pain relief in more than 50%. (Adelson et al., Int J Radiat Oncol Biol Phys 1987)

Describe the WAI fields used to treat ovarian cancer pts.

Show Answer

Pts being planned to rcv WAI should undergo CT simulation. An AP/PA open-field technique is historically used with borders as follows:

Superior: top of diaphragm
Inferior: obturator foramen
Lateral: peritoneal reflection

What dose is prescribed when treating ovarian cancer pts with WAI?

Show Answer

Pts being treated with WAI should rcv **30 Gy** in 1.5 Gy/fx with a P-A boost to 45 Gy and pelvic boost to 50 Gy. Kidney and liver blocks should be applied at 15 Gy and 25 Gy, respectively.

Has the utility of IMRT been investigated for WAI?

Show Answer

Yes. The feasibility of applying IMRT to WAI has been reported both in

concept and practice and is shown to allow excellent PTV coverage with better sparing of organs at risk. (Hong L et al., IJROBP 2002; Rochet N et al., Strahlenther Onkol 2008) However, generally even modern radiation techniques cannot overcome the limitations posed by hepatic, renal, and bowel dose constraints, which significantly limit the dose of radiation that can be delivered to the entire peritoneal surface. (Eifel et al., Best Practice & Research Clinical Obstetrics and Gynaecology 2017)

How should pts with a rising CA125 be managed following CR to initial therapy in the absence of clinical or radiographic evidence of Dz recurrence?

Show Answer

Tx should be delayed until Sx/signs of recurrent EOC develop. CA125 can rise a median of 3–6 mos before clinical signs/Sx of relapse are detectable. The MRC 0V05/EORTC 55955 trial registered 1,442 ovarian cancer pts who were in remission after 1st-line platinum-based chemo and followed CA125 q3mos. Pts with a rising CA125 (twice upper limit of normal) were randomized to early vs. delayed (at time of clinical or symptomatic relapse) chemo. This trial found no difference in OS b/t both groups. (Rustin GJ et al., Lancet 2010)

Are most relapses of ovarian cancer local or distant?

Show Answer

~80% of relapsed ovarian cancers are **local.**

How should ovarian cancer relapses be managed?

Show Answer

Pts with **platinum-sensitive** relapsed ovarian cancer (relapse ≥6 mos after initial chemo) should be treated with platinum-based combination chemo. (Fung-Kee-Fung M et al., Curr Oncol 2007) In cases of **platinum-resistant** Dz, cytotoxic single agents such as docetaxel, gemcitabine, etoposide,

pemetrexed, and others can be used. (Mutch DG et al., JCO 2007) Response rates in the latter are 20%–30%. Hormonal therapies (AI, leuprolide, megestrol, tamoxifen), and targeted therapies (bevacizumab, olaparib, rucaparib, and pazopanib) have also been utilized in select settings. Clinical trial participation is encouraged whenever possible.

FOLLOW-UP/TOXICITY

What is the most common severe toxicity experienced by ovarian cancer pts treated with WAI?

Show Answer

Grades 3–4 diarrhea occurs in ~30% of ovarian cancer pts treated with WAI. (Chiara S et al., Am J Clin Oncol 1994)

What is recommended f/u schedule after CR to initial Tx per NCCN (2018)?

Show Answer

Visits q2–4 mos for 2 yrs, then q3–6 mos for 3 yrs, then annually; CA125/tumor markers if initially elevated

66

Endometrial

Updated by Jason Edwards

BACKGROUND

What is the incidence of endometrial cancer in the United States?

Show Answer

Endometrial cancer is the most common gyn malignancy in the United States, with an incidence of **~44,000 cases/yr** annually. It is the 2nd most common cause of gyn cancer deaths.

What are the 2 forms of endometrial cancer?

Show Answer

Forms of endometrial cancer:

- Type I: endometrioid, 70%–80% of cases, estrogen related
- Type II: nonendometrioid, typically papillary serous or clear cell, high grade, not estrogen related, aggressive clinical course

What are the The Cancer Genome Atlas molecular categories of endometrial cancer?

Show Answer

- POLE (ultramutated)
- Micro-satellite instability (MSI) (hypermutated)
- Copy-number low (endometrioid)

. Copy-number high (Serous-like)

(Nature 2013)
What are the risk factors for endometrial cancer?

Show Answer

Risk factors for endometrial cancer:

. Exogenous unopposed estrogen
. Endogenous estrogen (obesity, functional ovarian tumors, late menopause, nulliparity, chronic anovulation/polycystic ovarian syndrome)
. Tamoxifen
. Advancing age (75% postmenopausal)
. Hereditary (HNPCC); 27%–71% lifetime risk of endometrial cancer (Barrow E et al., Clin Genet 2009)
. Family Hx
. HTN

What are protective factors for endometrial cancer?

Show Answer

Protective factors for endometrial cancer include **combination oral contraceptives and physical activity.**
What is the most common clinical presentation of endometrial cancer?

Show Answer

Endometrial cancer presents with **abnl vaginal bleeding** in 90% cases.
What % of postmenopausal women with abnl vaginal bleeding have endometrial cancer?

Show Answer

Only **5%–20%** of postmenopausal women with abnl vaginal bleeding have endometrial cancer.

What are the 3 layers of the uterine wall?

Show Answer

The 3 layers of the uterine wall are the **endometrium, myometrium, and serosa.**

What is the primary lymphatic drainage of the uterus?

Show Answer

The primary lymphatic drainage of the cervix and lower uterine segment is to the **pelvic LNs** (parametrial, internal and external iliacs, obturator, common iliac, presacral). The fundus has direct drainage to the para-aortic nodes. The round ligament can drain directly to the inguinal nodes.

What % of endometrial cancer pts with positive pelvic LNs will also harbor Dz in the P-A LNs? What is the chance of P-A nodal involvement if pelvic nodes are negative?

Show Answer

33%–50% of pts with pelvic LN involvement also have involvement of the P-A nodes. Isolated P-A nodal involvement with negative pelvic LNs is detected in **~1%** of surgically staged cases, though the rate may be higher when dissection is extended above the IMA to the perirenal nodes, especially on the left where direct route of spread might occur.

What determines the grade of endometrial tumors?

Show Answer

The grade of endometrial tumors depends on the **glandular component:**

Grade I: ≤5% nonsquamous solid growth pattern
Grade II: 6%–50% nonsquamous solid growth pattern
Grade III: >50% nonsquamous solid growth pattern

What is the risk of LN involvement by DOI and grade per Gynecologic Oncology Group's GOG 33?

Show Answer

According to **GOG 33,** the risk of LN involvement is <5% for tumors limited to the endometrium (all grades) and 5%–10% for tumors invading the inner and middle 3rd of the myometrium (all grades). For tumors invading the outer 3rd of the myometrium, the risk is 10% for grade 1, 20% for grade 2, and 35% for grade 3. Note: imaging of Pelvis was not obtained in these pts. (Creasman WT et al., Cancer 1987)

What % of pts with +LVSI had Pelvic and P-A node involvement in GOG 33?

Show Answer

In pts with +LVSI, 27% had +pelvic LNs and 19% had +P-A LNs.

What are the most aggressive histologies of epithelial endometrial cancer?

Show Answer

The most aggressive histologies of endometrial cancer are **serous, clear cell, and squamous cell variants (i.e., Adenosquamous).**

What % of endometrial cancers are adenocarcinomas?

Show Answer

75%–80% of endometrial cancers are adenocarcinomas.

According to the American College of Obstetricians and Gynecologists (ACOG), should women be screened for endometrial cancer?

Show Answer

According to the ACOG, there is **no appropriate cost-effective screening test** for endometrial cancer.

WORKUP/STAGING

Per the NCCN (2018), what is the workup for endometrial cancer?

Show Answer

NCCN endometrial cancer workup: H&P, CBC, PAP smear, endometrial Bx, and CXR. If extrauterine Dz is suspected, consider CA125, MRI/CT/PET, cystoscopy, and sigmoidoscopy.
What are the sensitivity and specificity of an endometrial Bx?

Show Answer

Endometrial Bx has **90%–98% sensitivity and 85% specificity.**
When is D&C recommended?

Show Answer

D&C is recommended **if endometrial Bx is nondiagnostic.**
What is involved in the surgical staging of pts with endometrial carcinoma?

Show Answer

Surgical staging for endometrial cancer:

- Vertical incision/or laparoscopy
- Peritoneal washing/cytology (controversial)
- Exploration of all peritoneal surfaces with Bx of any lesions
- Total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO)
- Uterus bivalved in operating room
- Omental Bx (omentectomy for uterine papillary serous carcinoma [UPSC]/clear cell carcinoma [CCC])
- Pelvic/P-A LN sampling vs. dissection

During the surgical staging procedure for endometrial cancer, what features are indications for P-A nodal sampling? Appx what % of pts have these features?

Show Answer

P-A sampling should take place in endometrial cancer pts with the following:

- Gross P-A Dz
- Positive Pelvic
- Gross adnexal mass or peritoneal Dz
- More than 1/3 myometrial invasion
- High-grade histology

~25% of pts have these features, but they account for 98% of all positive P-A LNs.

What is the AJCC 8th edition (2017)/FIGO (2009) pathologic staging for endometrial cancer?

Show Answer

Stage T1a/IA: limited to endometrium or less than one-half of myometrium including endocervical glandular involvement.

Stage T1b/IB: invades half or more of myometrium

Note: Endocervical glandular involvement only is considered AJCC T1 and FIGO stage I.

Stage T2/II: invades connective tissue of cervix but does not extend beyond uterus

Stage T3a/IIIA: tumor involves serosa and/or adnexa by direct extension of mets

Stage T3b/IIIB: vaginal involvement or parametrial involvement

Stage T4/IVA: tumor invades bladder mucosa (bullous edema is not sufficient) and/or bowel mucosa

Stage N0: no regional LN mets

Stage N1/IIIC1: regional LN mets to pelvic nodes

Stage N2/IIIC2: regional LN mets to P-A nodes

Stage M1/IVB: DMs

Note: Per the AJCC 8th edition (2017) and FIGO (2009), positive cytology no longer alters stage. Endometrial intraepithelial carcinoma is considered T1.

LN micro mets >0.2 mm and <2 mm are considered N1mi and N2mi respectively.

TREATMENT/PROGNOSIS

What is the primary Tx modality for endometrial cancer?

Show Answer

Sg is the primary Tx modality for endometrial cancer.
What is resected in a TAH?

Show Answer

TAH removes **the uterus and a small rim of vaginal cuff.**
What is resected in a modified radical hysterectomy?

Show Answer

Modified radical hysterectomy:

. Removal of uterus and 1–2 cm of vaginal cuff
. Wide excision of parametrial and paravaginal tissues (including median one-half of cardinal and uterosacral ligaments)
. Ligation of uterine artery at ureter

What is resected in a radical hysterectomy?

Show Answer

Radical hysterectomy:

. Resection of uterus and upper vagina
. Dissection of paravaginal and parametrial tissues to pelvic sidewalls
. Ligation of uterine artery at its origin at internal iliac artery

Pelvic and P-A lymphadenectomy is recommended in which pts with endometrial cancer?

Show Answer

Although controversial, LNs are commonly assessed at the time of initial Sg for endometrial cancer. Pelvic lymphadenectomy may not be indicated in women with Dz clinically confined to the uterus. The ASTEC (A Study in the Treatment of Endometrial Carcinoma) trial randomized 1,408 pts with endometrial cancer that was clinically confined to the uterus to standard Sg (TAH + BSO, peritoneal washing, palpation of P-A nodes) vs. standard Sg + pelvic lymphadenectomy. Those at intermediate or high risk for recurrence (independent of nodal status) were further randomized to rcv pelvic RT or not. There was no benefit to pelvic lymphadenectomy in terms of OS or RFS; however pts had increased morbidity. (ASTEC Study Group et al., Lancet 2009)

What is the risk of lymphedema following Sg for uterine malignancies?

Show Answer

According to an MSKCC retrospective review of 1,289 pts, the rate of lymphedema at a median f/u of 3 yrs was 1.2%. When ≥10 LNs were removed, the rate of symptomatic lymphedema was 3.4%. (Abu-Rustum NR et al., Gyn Oncol 2006)

What are considered negative prognostic factors for endometrial cancer?

Show Answer

Negative prognostic indicators for endometrial cancer:

- LVSI
- Age >60 yrs
- Grade 3/nonendometrioid histology
- Deep myometrial invasion (>50% based on GOG 249)
- Tumor size
- Lower uterine segment involvement
- Anemia
- Poor KPS

What adj therapy is indicated for completely surgically staged endometrial cancers limited to the endometrium?

Show Answer

No adj therapy is indicated for endometrial cancers limited to the endometrium, except for grade 3, where vaginal cuff brachytherapy is considered. In grade 3 tumors with adverse risk factors and incomplete surgical staging, adj therapy should be considered.

Which endometrioid endometrial cancers can be treated with vaginal brachytherapy (VBT) alone?

Show Answer

Surgically staged pts with true high-intermediate–risk Dz, namely stage IA tumors, grades 2–3 without LVSI; Stage IB tumors, grade 1–2 without LVSI; and 1B tumors, grade 1–2 with LVSI. Stage 1B grade 3 tumors are controversial as they were not included in the PORTEC randomization, however, in well-staged pts, this may be an acceptable Tx option.

Which endometrioid endometrial cancers should be managed with pelvic RT é VBT?

Show Answer

- Stage IB, grade 3 or other higher-grade histology with multiple adverse prognostic factors.
- Incompletely surgical staging—low LN count, only 1-side sampled, etc. For incompletely staged grade 3 tumors, chemo may be considered as well.
- If LVSI is present without LND, strongly consider with whole pelvis (WP) RT.

Which clinical situations should VBT be added to pelvic RT?

Show Answer

The overall benefit of adding VBT to pelvic RT is currently under question.

Several retrospective series have suggested there to be small/negligible benefit. Currently accepted situations include:

- **Adj pelvic RT and VBT** is indicated for endometrial cancers that invade the cervical stroma. If grade 3, consider chemo.
- **Tumors with the combination of deep myometrial invasion (>50%)** and **LVSI.**

When is chemo indicated for endometrial cancer?

Show Answer

Adj chemo should be considered for grade 3, nonendometrioid histology (serous and clear cell), and in pts with stage III–IV Dz.

Describe the whole pelvic RT field for endometrial cancer. What total doses are typically prescribed?

Show Answer

Borders of the WP RT field for endometrial cancer:

Superior: L4–5 or L5/S1
Inferior: bottom of obturator foramen
Lateral: 1.5–2.0 cm lat to pelvic brim
Anterior: front of pubic symphysis
Posterior: split sacrum to S3
Treat to 45–50.4 Gy.

What is the border of an extended RT field for endometrial cancer, and when should extended fields be used?

Show Answer

The sup border of an extended RT field for endometrial cancer depends on the upper extend of the para-aortic nodes to be treated. If only pelvic LNs are involved, the upper border can be placed at the level of the renal vessels, or L2–3. In situations where the entire para-aortic LN chain is being treated (for

positive P-A LNs), then the upper border should be **T10–11 or T11–12.**
According to the American Brachytherapy Society (ABS), what are the Tx site and depth for vaginal cuff brachytherapy for endometrial cancer?

Show Answer

According to the ABS, for endometrioid carcinoma of the endometrium, the proximal 3–5 cm of the vagina (appx one-half) should be treated. For CCC, UPSC, or stage IIIB, the target is the entire vaginal canal up to the urethra. Rx is typically vaginal surface or 0.5 cm beyond the vaginal mucosa. (Small W, Brachytherapy 2012)
What LDR and HDR dose/fractionation schemes are typically used for adj intracavitary RT alone for stage 1 endometrial cancer?

Show Answer

For adj intracavitary RT therapy alone, the LDR is 50–60 Gy over 72 hrs (0.7–0.8 Gy/hr). The HDR Rx in PORTEC-2 was 21 Gy (7 Gy × 3) at 0.5 cm depth; alternatively 6 Gy × 5 prescribed to the surface can also be used. The proximal 1/2 or 4 cm at 2 fx per wk is commonly used for endometrioid histology. (Harkenrider M et al., Brachytherapy 2016)
What LDR and HDR dose/fractionation schemes are commonly used for adj intracavitary RT given with WP RT for endometrial cancer?

Show Answer

When given in combination with WP RT, LDR doses of 30–40 Gy and HDR doses of 15 Gy (5 Gy × 3) prescribed to the vaginal surface is commonly used.
How are nonbulky vaginal cuff recurrences managed in endometrial cancer pts?

Show Answer

. For nonbulky vaginal cuff recurrences in pts with no prior RT, a **combination of pelvic RT and brachytherapy** is typically used. Treat to

45 Gy pelvic RT and assess the response. If the residual is ≤0.5 cm, add HDR VBT at 7 Gy × 3 to 0.5-cm depth beyond the vaginal mucosa. (Nag S et al., IJROBP 2000)

- For endometrial cancer pts with vaginal cuff recurrences that are bulky (>0.5 cm thickness) or in a previously irradiated field, **interstitial brachytherapy may be employed (salvage LC ranges from 50%–75%).**

When do inguinal nodes need to be included in the RT fields for endometrial cancer?

Show Answer

In cases with **distal vaginal involvement,** the entire vagina and inguinal nodes need to be included in EBRT fields.

How should inoperable endometrial cancer be treated with RT?

Show Answer

Consider pelvic RT to 45 Gy → intracavitary RT boost using 1–3 tandem intrauterine applicators to 6.3 Gy × 3 prescribed to 2-cm depth (serosal surface). If pelvic RT is contraindicated, consider definitive intracavitary RT alone (7.3 Gy × 5 prescribed to 2-cm depth). (Nag S et al., IJROBP 2000)

Describe the design and results of PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma).

Show Answer

In **PORTEC-1,** 714 pts grade 1 with ≥50% myometrial invasion, grade 2 with any invasion, or grade 3 <50% myometrial invasion underwent TAH/BSO with washings with no lymphadenectomy and were randomized to adj EBRT (46 Gy) vs. observation. EBRT reduced LRR from 14% to 5% at 10 yrs. 74% of LRs were in the vaginal vault. There was no difference in 10-yr OS. Note that with central pathology review, there was a significant shift from grade 2 to grade 1. (Creutzberg CL et al., Lancet 2000; Scholten AN et al., IJROBP 2005)

Describe the design and results of GOG 99.

Show Answer

In **GOG 99,** 392 endometrial cancer pts with myometrial and/or occult cervical invasion underwent TAH/BSO, pelvic and P-A LN sampling, and peritoneal cytology and then were randomized to observation vs. WP RT (50.4 Gy). Inclusion criteria were revised during the trial to include only high-intermediate–risk pts defined as: (1) age >70 yrs with 1 risk factor (grade 2 or 3, LVI, outer one-third myometrial invasion), (2) age >50 yrs with 2 risk factors, and (3) any age with 3 risk factors. RT improved LR from 12% to 3%. The greatest benefit in LR was in high-intermediate–risk pts from 26% to 6% vs. low-intermediate–risk pts from 6% to 2%. There was no change in OS, but the study was not powered to detect this. Conclusion: Limit pelvic RT to high-intermediate–risk pts. The major flaw of this study is that grade 2 was grouped with grade 3 even though grade 2 Dz tends to behave more similarly to grade 1. (Keys HM et al., Gyn Oncol 2004)
Describe the design and results of PORTEC-2.

Show Answer

PORTEC-2 randomized 427 pts with intermediate-high–risk endometrial cancer defined as:

- Age >60 yrs and inner 1/3 (IA) myometrial invasion and grade 3
- Age >60 yrs and outer 2/3 (IB and IC) myometrial invasion and grades 1–2
- Invasion of cervical glandular epithelium and grades 1–2 except grade 3 with > 1/2 myometrial invasion.

All pts were s/p TAH/BSO without pelvic LND and were randomized to EBRT (46 Gy) vs. VBT alone (21 Gy in 3 fx or 30 Gy). At median f/u at 3.8 yrs, VBT was similar to EBRT with respect to 5-yr outcomes: vaginal relapse (1.8% vs. 1.6%), isolated pelvic relapse (1.5% vs. 0.5%), LRR (5.1% vs. 2.1%), or OS (85% vs. 80%). However, there were significantly higher rates

of acute grades 1–2 GI toxicity in the EBRT group. The authors concluded that VBT should be standard in intermediate-high–risk endometrial cancer. (Nout RA et al., Lancet 2010)

What is the strongest predictor for LR, DM, and OS based off the PORTEC studies?

Show Answer

Substantial LVSI is the strongest independent prognostic factor for LR, DM, and OS based off pooled analysis of PORTEC 1 and 2. Only EBRT reduced the risk of pelvic recurrence. (Bosse T et al., Eur J Cancer 2015)

Describe the design and results of GOG 122.

Show Answer

In **GOG 122,** 388 pts with endometrial tumors invading beyond the uterus (all histologies) underwent TAH/BSO and surgical staging with <2-cm residual tumor. P-A LNs were allowed, but mets to the chest or SCV nodes were not allowed. Pts were randomized to whole abdomen irradiation (30 Gy AP/PA +15 Gy boost to pelvic +/– P-A LNs) vs. chemo (doxorubicin/cisplatin q3wks × 8 cycles). At 5 yrs, chemo had improved stage-adjusted OS (55% vs. 42%) and PFS (38% vs. 50%). Chemo had increased grades 3–4 heme toxicity (88% vs. 14%) and increased GI, cardiac, and neurologic toxicity. (Randall ME et al., JCO 2006)

Describe the design of GOG 249.

Show Answer

GOG 249 comparing EBRT alone vs. VBT + carbo/taxol in early stage high-intermediate–risk pts. Initial reports show similar rates of RFS, PFS, and OS with higher toxicity and poorer QOL in the VB + chemo arm. (59^{th} Annual ASTRO Meeting presentation, 2017)

Describe the design and results of the TIME-C trial.

Show Answer

Time-C trial compared 3D vs. IMRT for **postop** endometrial and cervical pts evaluating GU and GI outcomes. Initial reports show improved GI and GU toxicity with IMRT. (58th Annual ASTRO Meeting presentation, 2016)
Describe the design and results of the Nordic Society of Gynaecological Oncology (NSGO)–EORTC trial that evaluated adj RT é chemo in high-risk endometrial cancer.

Show Answer

The NSGO–EORTC trial enrolled 367 endometrial cancer pts with surgical stages I–II, positive peritoneal fluid cytology or positive pelvic LNs. Most had ≥2 risk factors: grade 3, deep myometrial invasion, or DNA nondiploidy. Pts with serous, clear cell, or anaplastic carcinomas were eligible regardless of risk factors. Pts were randomized to RT vs. RT + chemo (various regimens allowed). RT was pelvic EBRT (44 Gy) +/– VBT. 5-yr PFS favored the RT + chemo arm (82% vs. 75%). (Hogberg T et al., ASCO 2007 abstract)
Which major prospective trials for endometrial cancer are currently forthcoming?

Show Answer

- PORTEC-3 trial comparing pelvic RT vs. Pelvic RT + chemo in high-risk pts.
- PORTEC-4 trial comparing VBT and Observation after Sg in pts with endometrial cancer and high-intermediate–risk features.
- GOG 258 trial in stage 3 and 4 pts comparing RT + cisplatin (concurrent) f/b carbo/taxol vs. carbo/taxol alone.

FOLLOW-UP/TOXICITY

What is the RT tolerance of proximal and distal vagina?

Show Answer

The RT tolerance of the mucosa of the proximal vagina is 120 Gy and distal

vagina is 98 Gy. (Hintz BL et al., IJROBP 1980)
At what RT dose does ovarian failure occur?

Show Answer

Ovarian failure occurs after **5–10 Gy.**
At what RT dose does sterilization occur in women?

Show Answer

Sterilization in women occurs after **2–3 Gy.**
What are the expected acute and late RT toxicities associated with RT Tx for endometrial cancer?

Show Answer

Acute toxicities: diarrhea, proctitis, abdominal cramps, fatigue, bladder irritation, drop in blood counts, n/v
Late toxicities: vaginal dryness and atrophy, pubic hair loss, vaginal stenosis and fibrosis (recommend vaginal dilators), urethral stricture, fistula formation, SBO, chronic urinary and bowel frequency, and secondary malignancy.
What is the recommended f/u schedule post Tx per NCCN (2018)?

Show Answer

Exam q3–6 mos for 2–3 yrs, then q6–12 mos; CA125 only if initially elevated and imaging if clinically indicated.

67

Sarcoma of Uterus

Updated by Mark Edmund Bernard

BACKGROUND

What % of uterine malignancies are sarcomas?

Show Answer

Sarcomas account for <10% of uterine malignancies.

What are the 3 most common histologic subtypes of uterine sarcoma?

Show Answer

Most common uterine sarcomas (From most common to least common):

- Leiomyosarcoma (LMS)
- Endometrial stromal sarcoma (ESS)
- Adenosarcoma

By strict definition, **Carcinosarcoma**, aka malignant mixed müllerian tumor **(MMMT),** is **not** considered to be a sarcoma, but rather an **epithelial malignancy** (carcinoma). The **epithelial component** predicts for lymphatic spread and the sarcomatous component predicts for local spread. (Tropé CG et al., Acta Oncol 2012)

How does a uterine sarcoma typically present?

Show Answer

Typical presentation by histologic subtype:

LMS and ESS: similar Sx and signs as uterine fibroids—fullness, early satiety, etc.
MMMT: vaginal bleeding
What is the incidence of nodal mets?

Show Answer

MMMT: 30% (20%–38%)
LMS: 8% (6.6%–9.1%), usually associated with extrauterine Dz
ESS: traditionally thought to be low. (A recent study of 831 pts with ESS showed a 10% incidence.) (Chan JK et al., Br J Cancer 2008)
How does the risk of DM compare b/t endometrial cancer and uterine sarcoma?

Show Answer

In general, **uterine sarcomas have a higher rate of DM** than endometrial cancer.
What is the most common site of mets in uterine sarcoma?

Show Answer

In uterine sarcoma, the most common site of mets is the **lung.**
For which histologic subtype of uterine sarcoma is grade most important?

Show Answer

Grade is most important for **ESS.** Low-grade ESS is a hormone-sensitive low-grade malignancy with an indolent course, whereas high-grade ESS is characterized by an aggressive clinical course and is now considered a different Dz entity.
What 4 categories comprise ESS?

Show Answer

. Endometrial stromal nodule
. ESS-low grade

. ESS-high grade
. Undifferentiated Uterine Sarcoma

WORKUP/STAGING

What is the FIGO staging for uterine sarcoma?

Show Answer

MMMT is still staged according to the FIGO system for endometrial adenocarcinoma.

LMS and ESS staging:

FIGO I: limited to uterus
FIGO IA: ≤5 cm
FIGO IB: >5 cm
FIGO II: extends beyond uterus within pelvis
FIGO IIA: adnexal involvement
FIGO IIB: involves other pelvic structures
FIGO III: invades abdominal tissues (not just protruding into abdomen)
FIGO IIIA: 1 abdominal site
FIGO IIIB: >1 abdominal site
FIGO IIIC: mets to pelvic LNs, para-aortic (P-A) LNs, or both
FIGO IVA: invades bladder or rectum
FIGO IVB: DM (excludes abdominal, pelvic, or adnexa tissue)
What is the AJCC 8th edition staging for LMS and EMS?

Show Answer

T1a = FIGO IA
T1b = FIGO IB
T2a = FIGO IIA
T2b = FIGO IIB
T3a = FIGO IIIA

T3b = FIGO IIIB
T4 = FIGO IVA
N0(i+) = isolated tumor cells ≤0.2 mm (note, no FIGO staging for N0(i+))
N1 = IIIC
M1 = FIGO IVB
What is the FIGO and AJCC 8th edition staging for adenosarcoma?

Show Answer

FIGO I (T1): limited within uterus
FIGO IA (T1a): only in endometrium and/or endocervix
FIGO IB (T1b): <50% myometrium
FIGO IC (T1c): >50% myometrium
FIGO II (T2): beyond uterus within pelvis
FIGO IIA (T2a): adnexa
FIGO IIB (T2b): other pelvic structures
FIGO III (T3): invades tissues of abdomen
FIGO IIIA (T3a): 1 site
FIGO IIIB (T3b): >1 site
FIGO IIIC (N1): mets to pelvic LNs, P-A LNs, or both
FIGO IVA: invades bladder or rectum
FIGO IVB: DMs
How should the initial workup for uterine sarcoma differ from the workup for endometrial cancer?

Show Answer

The initial workup for uterine sarcoma is identical to the workup for endometrial cancer, but it should include a chest CT b/c of the increased risk of pulmonary mets. Pelvic MRI should also be considered to determine extent of local spread. There is also anecdotal evidence that PET/CT may be useful.

TREATMENT/PROGNOSIS

What is the primary Tx modality for uterine sarcoma?

Show Answer

Uterine sarcoma primary Tx modality: Type I hysterectomy and BSO is the mainstay. Ovarian preservation may be considered in young pts with early-stage LMS and low-grade ESS. The role of RT, chemo, and HRT is still controversial.

What is the role of LND in the Tx of uterine sarcoma?

Show Answer

Pelvic LND, P-A LND, or both for uterine sarcoma is considered controversial. They usually are recommended in MMMT and undifferentiated sarcoma. They usually are not recommended in LMS and ESS without extrauterine Dz.

Is there a benefit to postop pelvic RT for the management of uterine sarcomas?

Show Answer

The role of adj RT remains **controversial.** The issue has been addressed in at least 1 randomized trial and multiple retrospective studies. In general, the data suggest adj RT offers LC benefit with a limited, if any, OS benefit for MMMT. The role of adj RT in LMS, which has a high DM rate, is unclear but likely limited, if any.

Princess Margaret reported on 69 pts with primary **uterine LMS** who rcvd hysterectomy +/– pelvic RT. 7% were low grade and 93% were high grade. Median dose of RT was 45Gy. RT was associated with a decrease in 3-yr LR (39→19%) and increase in OS (35→69%). (Wong P et al., Radiat Oncol 2013)

EORTC 55874 randomized 224 pts with stages I–II high-grade uterine sarcoma (46% LMS, 41% carcinosarcoma, 13% endometrial stromal tumor) s/p TSH/BSO, washings (75%), and optional nodal sampling (25%)

to either (1) observation or (2) pelvic RT to 50.4 Gy. The results suggest that **pelvic RT improves LC but not OS or PFS for MMMT**; however, there is no benefit for LMS. (Reed NS, Eur J Cancer 2008)

A **SEER-based study** found that adj RT offered survival benefits in pts with early MMMT but not in LMS. (Wright JD et al., Am J Obstet Gynecol 2008)

A **Mayo Clinic** retrospective study included 208 pts with uterine LMS. Pelvic RT had no impact on DSS (p = 0.06), but it was associated with a significant improvement in LR. (Giuntoli R et al., Gyn Oncol 2003)

What is the role of whole abdomen irradiation (WAI) in MMMT?

Show Answer

GOG 150 was a randomized trial of WAI vs. 3 cycles of cisplatin/ifosfamide/mesna (CIM) as postsurgical therapy in stages I–IV carcinosarcoma of the uterus. Neither Tx was particularly effective. Vaginal recurrence increased and abdominal recurrence fell in the chemo group. WAI was associated with a significant increase in serious late adverse events. (Wolfson AH et al., Gynecol Oncol 2007)

For which pts with MMMT is pelvic irradiation typically indicated?

Show Answer

Similar to epithelial cancers, pelvic irradiation is typically recommended for MMMT with **deep myometrial involvement, cervical involvement, nodal involvement, or R1/2 resections.** VBT alone may be given for FIGO IA pathology.

For which pts with LMS is adj irradiation typically indicated?

Show Answer

Although controversial, adj irradiation may be considered in **pts with uterine LMS with an R1 or R2 resection,** particularly in the context of a clinical trial.

How do the RT volumes for uterine sarcoma differ from those used for endometrial carcinoma?

Show Answer

The **RT volumes are essentially the same** for uterine sarcoma and endometrial carcinoma. Although, for **LMS, nodal volumes can be excluded.**

Does the prognostic index developed for STS apply to uterine sarcomas?

Show Answer

No. The prognostic index for STS does not apply to uterine sarcomas.

FOLLOW-UP/TOXICITY

What are the expected acute and late toxicities associated with RT Tx for uterine sarcoma?

Show Answer

Acute toxicities: n/v, diarrhea, mucositis, fatigue, bladder irritation

Late toxicities: vaginal dryness, telangiectasias, and atrophy, pubic hair loss, vaginal stenosis and fibrosis (recommend vaginal dilators), urethral stricture, fistula formation, SBO.

68

Vulvar

Updated by Mark Edmund Bernard

BACKGROUND

Appx how many pts are affected by vulvar cancer per yr in the United States? What is the incidence of vulvar cancer in the United States?

Show Answer

~**6,020** pts are estimated to be affected in 2017 by vulvar cancer in the United States. The incidence is **2.5/100,000 people.**

Vulvar cancer accounts for what % of gyn malignancies? What % of all malignancies in women are vulvar malignancies?

Show Answer

Vulvar cancer represents **3%–5% of all gyn malignancies.** This comprises **1%–2% of all cancers in women.**

What are the risk factors for vulvar cancer?

Show Answer

Risk factors for vulvar cancer:

- Increasing age
- HPV
- Vulvar intraepithelial neoplasia (VIN)
- Bowen Dz (squamous cell CIS)
- Paget Dz (lesions arising from Bartholin gland, urethra, or rectum)

. Smoking
. Immune deficiency
. Lichen sclerosis

What HPV subtypes are associated with vulvar cancer?

Show Answer

HPV subtypes associated with vulvar cancer include **6, 16, 18, and 33.**
What is the function of HPV-associated oncoproteins?

Show Answer

It is thought that HPV-associated oncoproteins **bind and inactivate tumor suppressor proteins** such as Rb, p53, and p21.
What are the subsites of the vulva?

Show Answer

Subsites of the vulva:

. Ant and post fourchette
. Clitoris (clitoral hood and gland)
. Labia minora and majora
. Mons pubis
. Perineal body
. Urethral meatus
. Vaginal orifice

If a malignancy with the epicenter in the vagina involves the vulva, what is the primary?

Show Answer

Vulvar primary. Considering primary vaginal cancers are rare, any tumor within the vagina touching the vulva should be considered a vulvar primary.
What histology constitutes the vast majority of vulvar cancers? Name

other histologies of tumors found on the vulva.

Show Answer

- The most common vulvar histology is **squamous cell carcinoma** (80%–90%). Verrucous is a less aggressive subtype of vulvar SCC with rare LN spread.
- Other histologies include **melanoma, basal cell, Merkel cell, sarcoma, and adenocarcinomas of the Bartholin glands.**

What are the most common presenting Sx of pts with vulvar cancer?

Show Answer

Common presenting Sx of vulvar cancer: pruritus, vulvar discomfort or pain, dysuria, oozing, or bleeding.
In which subsites does vulvar cancer most commonly arise?

Show Answer

70% of vulvar cancers arise from the **labia majora/minora.**
How is “locally advanced” vulvar cancer defined?

Show Answer

Locally advanced vulvar cancer is defined as **T2 tumors >4 cm or extension into anus and/or vagina, or T3.** Also defined as **any burden that cannot be resected without exenterative Sg.**
What are the 1st-, 2nd-, and 3rd-echelon LN regions in vulvar cancer, and which subsite is associated with skip nodal mets?

Show Answer

LN regions in vulvar cancer:

1st echelon: superficial inguinofemoral
2nd echelon: deep inguinofemoral and femoral
3rd echelon: external iliac nodes

The **clitoris** can drain directly to the deep inguinofemoral or pelvic nodes.
What is the strongest predictor of LN involvement in vulvar cancer?

Show Answer

The strongest predictor of LN involvement in vulvar cancer is **DOI.**
Estimate the risk of inguinal LN involvement based on the DOI of a vulvar tumor: <1 mm, 1–3 mm, 3–5 mm, and >5 mm.

Show Answer

LN involvement by cervical tumor DOI:

≤1 mm: <5%
1–3 mm: 8%
3–5 mm: 27%
5 mm: 34%

(Hacker NF et al., Cancer 1993)
What is the rate of pathologic inguinal positivity for cN0 pts?

Show Answer

25%–30%
(Van Der Z**e**e et al., GROINSS-V 2008)
If someone is found to have a positive inguinal LN, what is the rate of positive pelvic LNs and contralat inguinal LNs?

Show Answer

Pelvic LN+: 30%
Contralat inguinal LN+: 25%–30%
(Homesley HD et al., Obstet Gynecol 1986)

WORKUP/STAGING

What is the Bx approach for small (<1 cm) vulvar lesions?

Show Answer

For small (<1 cm) vulvar lesions, **excisional Bx with a 1-cm margin, including the skin, dermis, and connective tissue.**
What is the Bx approach for large (>1 cm) vulvar lesions?

Show Answer

For large (>1 cm) vulvar lesions, **wedge Bx including surrounding skin.** These should be taken from the edge of the lesion to include the interface b/t normal skin and the tumor to determine whether there is invasion of adjacent epithelium. (Baldwin P et al., Curr Obst Gyn 2005)
What is the basic workup of vulvar cancer?

Show Answer

Vulvar cancer workup:

- H&P (includes inguinal LN assessment, DRE)
- EUA if adequate assessment cannot be done due to pain while awake, routine PAP smear of cervix, and colposcopy of the vagina and rest of vulva. Other investigations such as cysto or proctoscopy only if clinically indicated (e.g., involvement of urethra or anus)
- Labs: CBC (to check for anemia); UA (to r/o infection), HIV testing (to r/o immunodeficiency when clinically indicated), BMP, LFTs
- Imaging: PET/CT C/A/P with IV contrast. Pelvic MRI to assist in delineating primary and Tx planning.

Summarize the FIGO staging for vulvar cancer.

Show Answer

FIGO IA: lesion **≤2 cm,** confined to vulva and/or perineum with stromal invasion **≤1 mm**, N0

FIGO IB: lesion >2 cm, confined to vulva and/or perineum with stromal invasion >1 mm, N0

FIGO II: lesion of any size with extension to **adjacent** structures (lower-third of urethra, lower-third of vagina, or anus), N0

FIGO III: positive inguinofemoral LN
FIGO IIIA: 1–2 LNs each <5 mm
FIGO IIIB: ≥3 LNs each <5 mm or ≥2 LNs = 5 mm
FIGO IIIC: node(s) with extracapsular spread
FIGO IVA: extension into **bladder or rectal mucosa** (not muscle/wall), pelvic bone fixation, extension into upper 2/3 of urethra or vagina, or fixed or ulcerated regional LN mets
FIGO IVB: DMs, including pelvic LN

Summarize the AJCC 2017 staging for vulvar cancer.

Show Answer

T1a = FIGO IA
T1b = FIGO IB
T2 = FIGO II
T3 = FIGO IVA
N0 = No inguinofemoral LN(s)
N0(i+) = ITC† in the inguinofemoral regions, ≤0.2 mm
N1a* = 1–2 LNs <5 mm
N1b = 1 LN ≥5 mm
N2a* = ≥3 LNs each <5 mm
N2b = ≥2 LNs ≥5 mm
N2c = regional LN(s) with extracapsular spread
N3 = fixed or ulcerated regional LN

†Isolated tumor cells
*Includes micromets
*When recording LN results, include size, location, and laterality

Which pts with vulvar cancer require inguinal LND?

Show Answer

In vulvar cancer, **all pts with clinically suspicious nodes** require bilat inguinal LND unless there are bulky unresectable nodes. For pts with no

clinically suspicious nodes, the need for nodal evaluation depends primarily on DOI. **If the DOI is <1 mm, a nodal evaluation may not be needed unless there is LVSI or high grade.**
Which pts can have sentinal lymph node biopsy (SLNB) for nodal evaluation?

Show Answer

Pt with low-risk Dz: cN0, unifocal T1–2 (<4 cm) with DOI >1 mm. The **GROINSS-V** (Groningen International Study on Sentinel Nodes in Vulvar Cancer) study evaluated safety of SLNB in early stage vulvar cancer. 403 pts with T1/T2 (<4 cm) SCC with DOI >1 mm and cN0 underwent SLNB. If SLNB was negative → observation. If SLNB positive → inguinofemoral LND. RT was recommended if ECE or ≥2 LN+ (10% of the SLN+ received). **Initial results** showed SLN– pts (69%) had an isolated groin recurrence of 2.5%. Morbidity was low in the SLNB-only arm. (Van der Zee et al., JCO 2008)

Updated Results showed the following:

- SLNB–: 5-yr LR = 25%; 10-yr LR = 36%; isolated groin recurrence = 2.5%
- SLNB+: 5-yr LR = 33%; 10-yr LR = 46%; isolated groin recurrence = 8%
- 10-yr DSS: SLNB– 91% vs. SLNB+ 65%; if LR: 70% (all comers), SLNB– 81%, SLNB+ 45%
- 10-yr OS: SLNB– 69% vs. SLNB+ 44%

Size of SLNB from the GROINNS-V was important

- DFS decreased with SLNB mets >2 mm (95% → 70%)
- Rate of Non-SLNB LN positivity: ITC* = 4%, ≤2 mm = 11%, 2–5 mm = 13%, >5 mm = 48%

*ITC = individual tumor cells

(Te Grootenhuis NC et al., Gynecol Oncol 2016)

The Gynecologic Oncology Group's **GOG 173** study assessed sensitivity of SLNB. 452 women with SCC limited to vulvar 2–6 cm and DOI ≥1 mm underwent lymphatic mapping, SLNB, and then LND. Only 11 pts with a +LN on dissection were negative on SLNB. Sensitivity of SLNB was 92%. In tumors <4 cm, the FN rate was 2%. (Levenback CF et al., JCO 2012)
In which pts with vulvar cancer is a unilat (instead of bilat) LND sufficient for workup?

Show Answer

Pts with a **well-lateralized primary (>2 cm from midline)** may undergo a unilat LND only.
Is the staging system for vulvar cancer surgical or clinical?

Show Answer

FIGO **surgical** staging is used for vulvar cancer.
Do imaging results affect the FIGO stage in vulvar cancer?

Show Answer

No. Imaging results are not included in FIGO staging.

TREATMENT/PROGNOSIS

What is the Tx for vulvar CIS or VIN?

Show Answer

Pts with vulvar CIS or VIN can be treated with **superficial local excision.** If the labia minora or clitoris is involved, consider laser ablation.
How should the primary of a pt with FIGO stage I or II vulvar cancer be treated?

Show Answer

In a pt with stage I or II vulvar cancer, the primary can be resected via a **WLE,** which includes resection of the tumor + a gross 1.0-cm margin of

normal tissue around it. WLE has the same LR as radical vulvectomy for stage I and II vulvar carcinomas. (Hacker NF et al., Cancer 1993)
Which large retrospective study failed to confirm significance of wide (>8 mm) margins for resected T1–2 lesions?

Show Answer

AGO-CaRE-1 (Arbeitsgemeinschaft Gyn↑kologische Onkologie Chemo and Radiotherapy in Epithelial Vulvar Cancer): At median f/u of 35 mos, vulvar recurrence rates were 12.6% in pts with a margin <8 mm and 10.2% in pts with a margin >8 mm (NSS). (Woelber L et al., Eur J Cancer 2016)
What is the next step if margins are positive following surgical resection of vulvar cancer?

Show Answer

Re-excise if possible; otherwise, give adj RT. Adj RT is associated with an increase in LC and survival. (Chapman BV et al., Int J Radiat Oncol Biol Phys 2017; Faul CM et al., IJROBP 1997)
What are the guidelines for LN assessment for stage I–II vulvar carcinoma?

Show Answer

. Nodal assessment may be excluded if <1 mm depth invasion and cN0
. All other cN0: SLNB or inguinal LND
  - SLND established for unifocal stage I–II carcinoma, <4 cm, cN0
    - If ITC or micromets (>0.2 mm–2.0 mm) → RT or LND
    - If macromets (>2.0 mm) → full LND → RT
      - Strongly consider adding concurrent chemo for LN positive (Gill et al., Gynecol Oncol 2015)
    - Contralat assessment if <2 cm from midline (<3% risk)
. If clinically LN positive → Inguinofemoral LND
  - Adequate Inguinal LND

    - >10 nodes each side
    - Superficial and deep assessment needed
    - LN+ to total LN removed ratio on each size needs to be ≤20% (GOG 37)
- LND increases risk of lymphedema to ~25% (GROINSS-V)
    - Attempts to lower morbidity by superficial dissection alone lead to higher rates of recurrence (GOG 74)

In which vulvar cancer pts is adj RT to the bilat groin and pelvis indicated? What RCTs explored this question?

Show Answer

. Adj RT to the bilat groin and pelvis is recommended **in pts with ≥2 +LN, >20% nodal positivity, a single node >5 mm, presence of ECE**, **or pts with SLN positive yet no nodal dissection was performed.**

. In **GOG 37,** 114 pts s/p radical vulvectomy + bilat inguinal LND. If LN+ were randomized to pelvic node dissection or pelvic and groin RT. The dose was 45–50 Gy.

Updated Analysis showed pelvic and groin RT group had a higher 6-yr RFS (48→59%) and CSS (49→71%). Subset analysis showed RT benefitted pts with clinical suspected or fixed ulcerated groin nodes or ≥2 groin LN. A ratio of >20% ipsi positive groin node/groin node dissected was associated with a decrease in cancer-related mortality, relapse, and contralat LN mets, but had a better OS in the RT group. The initial 2-yr OS benefit to RT (54→68%) was not significant at 6 yr (41 vs. 51%, p = NS). The benefit of RT was likely d/t the decrease in groin recurrence (24→5%), as recurrence in the pelvis (2% vs. 5%), vulvar (7% vs. 8%), or DM (15% vs. 16%) were the same.

(Kunos C et al., Obstet Gynecol 2009)

(Homesley HD et al., Obstet Gynecol 1986)

- Also **AGO-CaRE-1** (Arbeitsgemeinschaft Gyn↑kologische Onkologie Chemo and Radiotherapy in Epithelial Vulvar Cancer) was a retrospective study evaluating 1,249 vulvar pts of which 447 (36%) were found to have positive pathologic groin nodes. 55% (244/447) of node positive pts rcvd adj Tx of which 84% was adj RT and 14% was adj CRT. Part of the analysis evaluated pts treated with or without adj RT or CRT. Adj Tx was associated with an increase in 3-yr PFS (26→40%). However, on subset analysis, the benefit was only for those with ≥2 positive LNs. (Mahner S et al., J Natl Cancer Inst 2015)

Is there data specifically supporting concurrent chemo being added to adj RT for LN positive pts?

Show Answer

Yes. A National Cancer Data Base (NCDB) analysis on pathologic inguinal LN pts treated with adj RT was conducted to determine the impact of the addition of adj chemo. The addition of adj chemo was associated with an increase in unadjusted MS (30→44 mos) and on adjusted propensity score matching, a 38% reduction in risk of death. (Gill BS et al., Gynecol Oncol 2015)

In pts with N0 vulvar cancer, does groin RT eliminate the need for inguinal LND? What RCT explored this question?

Show Answer

- The need for inguinal node dissection in N0 vulvar cancer prior to groin RT is **controversial.** In **GOG 88,** 58 pts with cN0 vulvar cancer s/p radical vulvectomy were randomized to bilat inguinofemoral and pelvic LND (+nodes rcvd RT) vs. bilat groin-only EBRT (50 Gy). LR, PFS, and OS favored the LND arm. (Stehman FB et al., Cancer 1992)
- But there are **major criticisms of GOG 88**
  a. CT was not used for staging.
  b. 50 Gy is not adequate for pts with gross nodes evident by CT.

c. Pts were treated with electron fields prescribed to a depth of 3 cm, which may not adequately cover the inguinal/femoral nodal regions. Koh et al. reported the avg femoral vessel depth ranges from 2 to 18 cm. He also reported on 5 pts who recurred after prophylactic RT in GOG 88 and showed all rcvd potential doses of <47 Gy and 3 pts rcvd more than 30% under dosing. (Koh WJ et al., Int J Radiat Oncol Biol Phys 1993)

What are the indications for adj RT to the primary site after surgical management?

Show Answer

The relative indications for adj RT to the primary site are based upon Heaps factors.

- +Margins
- Close margins (<8 mm fixed specimen or <1 cm by frozen)
- LVSI
- 2+ Heaps factors (thickness >2.5 mm, >1 cm deep, LVSI, infiltrative/mixed growth pattern)

(Heaps JM et al., Gynecol Oncol 1990)

The most important risk for local recurrence is +margin. Salvage surgery leads to a lot of morbidity.

What is the Tx approach for pts with stages III–IV vulvar cancer?

Show Answer

Tx options for stages III–IV vulvar cancer:

- Surgery (if –margins can be achieved) + RT(+/– chemo)
- Neoadj CRT (phase II) → surgery; for those initially unresectable
- Definitive CRT

What studies support neoadj CRT in initially unresectable vulvar cancer?

Show Answer

. **GOG 205** was a phase II trial of 58 pts with T3–4 vulvar SCC unable to obtain radical vulvectomy s/p CRT with 40 mg/m^2 of weekly cisplatin. RT was 57.6 Gy @ 1.8 Gy/daily with a CD after 45 Gy to gross Dz + margin with **no Tx break.** cCR was 64% and pCR rate was 50% (22% with cCR still had residual Dz). When compared to prior GOG 101, the cCR (48→64%) and pCR (31→50%) was higher. (Moore DH et al., Gynecol Oncol 2012)
. **GOG 101** was a phase II study of 73 pts with unresectable vulvar cancer given concurrent cisplatin/5-FU + RT. RT was bid to 47.6 Gy with **planned Tx break.** 97% of pts were converted to resectable Dz. (Moore DH et al., IJROBP 1998)

Estimate the 5-yr OS by FIGO stage.

Show Answer

5-yr estimated OS by FIGO stage:

Stage I: 90%
Stage II: 81%
Stage III: 68%
Stage IV: 20%

(Gonzalez-Bosquet J et al., Gyn Oncol 2005)
What are the commonly used neoadj, adj and definitive RT doses for vulvar cancer?

Show Answer

. Neoadj RT doses
  a. Nodal regions and vulva: **45.0–50.4 Gy**
  b. High-risk sites (gross Dz): **55.8–59.4 Gy**
. Adj RT doses

a. –Margin, +LVSI: **50.4–54.0 Gy**
b. Close or margin positive: **56.0–59.4 Gy**
c. Inguinal LN positive regions: **50.4–54.0 Gy**
d. ECE regions: **56.0–59.4 Gy**

. Definitive RT doses
a. Unresectable Dz: **66–70 Gy to primary site** with concurrent weekly cisplatin +/– 5-FU
b. Gross nodal Dz: **56–59.4 Gy**

(Chapman BV et al., Int J Radiat Oncol Biol Phys 2017)

(Viswanathan AN et al., Gynecol Oncol 2013)
What are the anatomic boundaries of the inguinal LNs?

Show Answer

The key point to remember is that the groin nodes are usually very **medial** to the inguinal–femoral vessels. Therefore, the classic 7 mm–1 cm margin around the vessels, commonly done for pelvic LN contouring is inaccurate.

. Radial boundaries: Sartorius muscle, Rectus Femoris, Iliopsoas, lat edge of pectinus or medial edge of abductor longus
. Cranially: Follow the external iliac transitioning to the inguinal vessels
. Caudal: Either the inf trochanter or 2 cm below the junction of the great saphenous and the common femoral vein

(Beriwal et al., Pract Radiat Oncol 2012)

(Gaffney DK et al., Int J Radiat Oncol Biol Phys 2016)
What are the ongoing trials for vulvar carcinoma pts?

Show Answer

. **GOG 279 is a phase II** trial evaluating the addition of concurrent gemcitabine and cisplatin to IMRT. Pts with primary locally advanced (T2/3, N0–3, M0) unresectable by standard radical vulvectomy rcv

concurrent weekly gemcitabine and cisplatin with IMRT. Pts rcv a core Bx to vulvar or if gross Dz present, surgical removal of gross Dz at primary and/or groin LNs, within 6–8 wks after completion of therapy. Primary outcome is pCR. Secondary outcomes are cCR, vulvar-PFS, groin-PFS, and toxicity.

. **GOG 270/GROINSS-V II**
   a. T<4 cm w/ DOI>1 mm; cN0
   b. Originally: SLNB– → observation, SLNB+ → RT
   c. Pts with macromets: 20% risk of additional +LNs vs. 2% with micromets
      i. Crossed prespecified safety border in macromets cohort
      ii. Amended: SLNB+ (<2 mm) → RT; if >2 mm, LND → RT +/– chemo

FOLLOW-UP/TOXICITY

What are the acute RT toxicities of the vulva, pelvis, and inguinal nodes?

Show Answer

Acute RT toxicities of the vulva, pelvis, and inguinal nodes include **severe RT dermatitis of the vulva and groins (which results in need for Tx interruption), n/v, diarrhea, urethritis, cystitis, and myelosuppression.**
Strongly consider performing skin checks in the groin and vulvar sites weekly while the pt is on the Tx table before Tx begins.
What are the late RT toxicities associated with the vulva and inguinal nodes?

Show Answer

Late RT toxicities of the vulva, pelvis, and inguinal nodes include **vaginal atrophy, itching and discharge, SBO, lymphedema, and femoral neck fracture.**
Estimate the risk of femoral neck fracture after 50 Gy.

Show Answer

50 Gy to the femoral neck is associated with an **11% risk of fracture at 5 yrs.** (Grisby JS et al., Med Dos 2004)
What is the NCCN (2018)-recommended f/u frequency post Tx?

Show Answer

q3–6 mos for 2 yrs, q6–12 mos for 3 yrs, then annually.

69

Vaginal Cancer

Updated by Sunpreet Rakhra

BACKGROUND

Vaginal cancer typically presents in what age group?

Show Answer

70% of primary vaginal malignancies are detected in women **≥60 yo.**
What 3 lifestyle risk factors are associated with increased incidence of vaginal cancer? How common is HPV detected?

Show Answer

- Increased risk of vaginal cancer is associated with the **# of lifetime sexual partners, early onset of intercourse, and current smoking.**
- **HPV DNA is detected in 64%–91% of invasive vaginal cancers.**

What % of cancers involving the vagina are not primary vaginal cancers?

Show Answer

~75% of malignancies involving the vagina originate at other sites.
What is the most common histology for vaginal cancer? What are 5 other rare vaginal cancer histologies?

Show Answer

Squamous cell carcinoma is the most common primary vaginal histology.
Melanoma, sarcoma, lymphoma, adenocarcinoma, and clear cell

adenocarcinoma are much more rare.
Increased risk for clear cell adenocarcinoma is linked with what exposure?

Show Answer

In utero exposure to the synthetic estrogen **diethylstilbestrol (DES)** is linked with an increased risk for clear cell adenocarcinoma.
What type of vaginal sarcoma is most common in adults? In children?

Show Answer

Adults: leiomyosarcoma
Children (≤6 yo): embryonal RMS (i.e., sarcoma botryoides)
If an elderly woman has had a hysterectomy d/t early-stage cervical cancer, is it reasonable to continue PAP smear screening of the vaginal vault?

Show Answer

Yes. Though the value of continued screening is not proven, PAP smears of the vaginal vault in elderly women who have had hysterectomy for invasive/preinvasive cervical cancer seems reasonable given the increased risk for vaginal cancer.
What is the nodal drainage of the upper two-thirds of the vagina? Of the lower one-third of the vagina?

Show Answer

The upper two-thirds of the vagina drain to the obturator, internal, external, and common iliac nodes. The lower one-third of the vagina may drain to the inguinofemoral nodes.
What are 4 common presenting Sx of vaginal cancer? What 2 additional Sx may suggest locally advanced Dz?

Show Answer

Vaginal cancer may present with **bleeding, discharge, pruritus, and**

dyspareunia. Pain or change in bowel/bladder habits may suggest locally advanced Dz.

Where in the vagina is vaginal cancer most often located?

Show Answer

Vaginal cancer is most often found in the **post wall, sup one-third** of the vagina (the speculum must be rotated to ensure exam of this region).

WORKUP/STAGING

What staging exams/studies contribute to the FIGO stage?

Show Answer

Exams/studies that contribute to the FIGO stage include clinical exam of the pelvis and vagina (possibly under anesthesia), cystoscopy, and proctosigmoidoscopy in women with locally advanced Dz, CXR, LFTs, and alk phos.

What imaging studies can be obtained but are not required in order to assign an FIGO stage?

Show Answer

Advanced imaging such as **CT, MRI, and PET** do not contribute to the FIGO stage (but still should be used to assess the Dz extent and plan therapy).

What is the AJCC 8th edition/FIGO staging for vaginal cancer?

Show Answer

T1a/I: Tumor confined to the vagina, measuring ≤2 cm
T1b/I: Tumor confined to the vagina, measuring >2 cm
T2a/II: Tumor invading paravaginal tissues but not to pelvic sidewall, measuring ≤2 cm
T2b/II: Tumor invading paravaginal tissues but not to pelvic sidewall, measuring >2 cm

T3/III: Tumor extending to the pelvic sidewall and/or involving the lower-third of the vagina and/or causing hydronephrosis or nonfunctioning kidney

T4/IVA: Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

N1/III: Pelvic or inguinal LN mets

MI/IVB: DM

A vaginal cancer is never considered a vaginal primary if it involves either of what 2 structures?

Show Answer

Cancer involving the **vulva or cervix** is never considered to be a vaginal primary (even if the bulk of Dz lies in the vagina).

When working up a presumed vaginal cancer primary, what other 3 sites should be evaluated for synchronous in situ or invasive Dz?

Show Answer

When working up a presumed vaginal cancer primary, always evaluate for synchronous **cervical, vulvar, and/or anal Dz.**

TREATMENT/PROGNOSIS

What are 3 appropriate Tx options for vaginal intraepithelial neoplasia (VAIN)?

Show Answer

Surgical excision, laser vaporization, and topical 5-FU are all appropriate Tx for VAIN.

VAIN is multifocal in what % of pts?

Show Answer

Up to 60% of pts with VAIN have multifocal Dz. Close f/u is essential.

In general, what is the preferred definitive Tx modality for vaginal cancer?

Show Answer

Although Sg may be appropriate for early, stage I lesions, **definitive RT** is generally the preferred Tx modality (as morbidity is less compared with radical Sg).

What are the estimates of 5-yr pelvic Dz control and DSS for stages I, II, and III–IVA vaginal cancer managed with definitive RT?

Show Answer

For vaginal cancer managed with definitive RT, 5-yr pelvic Dz control is 86%, 84%, and 71% for FIGO stages I, II, and III–IVA, respectively. 5-yr DSS is 85%, 78%, and 58%, respectively. (Frank SJ et al., IJROBP 2005)

Is concurrent CRT a reasonable consideration in advanced-stage vaginal cancer?

Show Answer

Yes. Extrapolating from the cervical, vulvar, and anal cancer literature, concurrent CRT (typically, cisplatin-based) is reasonable to consider for advanced-stage vaginal cancer (i.e., stages III–IVA).

Is vaginal cylinder brachytherapy alone (without EBRT) appropriate in any vaginal cancer pts?

Show Answer

Possibly. Although whole pelvis EBRT combined with brachytherapy is generally preferred, vaginal cylinder brachytherapy alone may be acceptable for pts with VAIN or very early stage I vaginal cancer <5-mm thick.

What brachytherapy technique is commonly required for stages II–III vaginal cancer (in addition to EBRT Tx)? How important is it to include brachytherapy?

Show Answer

- **Interstitial brachytherapy needle implants** are commonly required to achieve adequate brachytherapy dose coverage for stages II–III vaginal cancers (the depth–dose characteristics of intracavitary applicators are not favorable enough to treat deep lesions).
- **Recently published SEER analysis (**Orton A et al., Gynecol Oncol 2016**) compared pts with primary vaginal cancer treated with EBRT alone vs. EBRT with brachtherapy. All FIGO stages benefited with a reduced rate of death by more than 20%.**

Describe the regions that are targeted in whole pelvis RT for vaginal cancer.

Show Answer

A whole pelvis field for vaginal cancer typically targets the common, internal, and external iliac nodes, obturator nodes, and the entire vagina (or 3 cm below the Dz extent). If the lower-third of the vagina is involved, then the inguinal nodes may be targeted as well (as per vulvar or anal cancer).
What are the appropriate EB and cumulative (EB + brachytherapy) RT doses for vaginal cancer?

Show Answer

Whole pelvis (+/– inguinal nodes) EB doses are typically **45–50 Gy** → brachytherapy boost to a total dose of 65–75 Gy. **70–80 Gy has been recommended when RT alone (without chemo) is used.**
Among pts who fail following definitive RT, what % have LR as a component of their relapse?

Show Answer

~75% of pts with relapse following definitive RT for vaginal cancer will experience LF. (Frank SJ et al., IJROBP 2005)

FOLLOW-UP/TOXICITY

What are the 5- and 10-yr grades 3–4 toxicity rates following definitive RT for vaginal cancer?

Show Answer

Grades 3–4 toxicity rates are **10% and 17% at 5 and 10 yrs, respectively,** following RT for vaginal cancer. (Frank SJ et al., IJROBP 2005)

What are the 4 most common grades 3–4 late effects following definitive RT for vaginal cancer?

Show Answer

Following definitive RT for vaginal cancer, **proctitis (requiring transfusion), rectal fistula, SBO, and hemorrhagic cystitis** are the most common grades 3–4 toxicities.

What common late effect may limit sexual function as well as f/u for vaginal cancer?

Show Answer

Vaginal stenosis is very common following RT for vaginal cancer. All pts should use a vaginal dilator.

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Hodgkin Lymphoma

Updated by Joanna C. Yang

BACKGROUND

What age does Hodgkin Lymphoma (HL) most commonly occur?

Show Answer

HL has a bimodal peak with peaks at **age 15–35 yrs and over age 50.**
What are 2 broad histologic categories of HL? Which is more common?

Show Answer

Broad histologic categories of HL:

- Classical (more common: 95%)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL: 5%)

What are the subtypes of classical HL, and which is most common in the United States?

Show Answer

Subtypes of classical HL:

- Nodular sclerosis (most common in the United States)
- Mixed cellularity
- Lymphocyte depleted
- Lymphocyte rich

What are the 2 most commonly involved LN regions at the initial Dx of classical HL?

Show Answer

Most commonly involved LN regions at initial Dx of HL:

- Cervical chains
- Mediastinum

90% of pts have contiguous nodes.
Pts who present with mediastinal LAD are most likely to have which subtype of HL?

Show Answer

Pts who present with mediastinal LAD are most likely to have **nodular sclerosis** HL.
In classical HL, what is the most common pathologic feature and CD15, -30, -45, and -20 staining pattern?

Show Answer

Classical HL is characterized by Reed–Sternberg cells in an inflammatory background. In classical HL, tumors are typically **CD15+ and 30+ but CD45- and 20-.**
In NLPHL, what is the common pathologic feature and CD15, -30, -45, and -20 staining pattern?

Show Answer

NLPHL is characterized by lymphocyte-predominant cells, previously called “popcorn” cells. In NLPHL, tumors are typically **CD15- and 30- but CD45+ and 20+** (i.e., the reverse of classic HL).
Which classical HL subtype has the best prognosis?

Show Answer

Lymphocyte-rich HL has the best prognosis.
Which HL subtype has the worst prognosis?

Show Answer

Lymphocyte-depleted HL has the worst prognosis.
Which HL subtype is associated with older age or HIV+ pts?

Show Answer

Lymphocyte-depleted HL is associated with older age and HIV+ pts.
Pts with which subtype of HL are at greatest risk of developing a subsequent NHL?

Show Answer

Pts with **NLPHL** are at greatest risk of developing a subsequent NHL.
What are the “B Sx” of lymphoma?

Show Answer

B Sx include:

- Unexplained fevers >38°C (100.4°F)
- 10% body weight loss in 6 mos
- Drenching night sweats

How is bulky mediastinal Dz commonly defined?

Show Answer

Bulky mediastinal Dz is commonly defined as a **mass greater than one-third of the intrathoracic diameter on an upright PA film. In the CT era, the definition of >10 cm has been used.**
How is bulky Dz defined outside of the mediastinum?

Show Answer

Outside of the mediastinum, bulky Dz is variably defined in clinical trials,

but **most often is any mass >10 cm.**

WORKUP/STAGING

What kind of Bx is preferred for Dx of HL and why?

Show Answer

Excisional Bx is preferred for the Dx of lymphomas b/c **it shows LN architecture.**

What imaging studies are typically ordered as part of the workup of HL?

Show Answer

An **integrated PET/CT** is commonly used in the workup imaging for HL.

What lab work is required as part of the workup of HL?

Show Answer

The following labs have prognostic implications: ESR, CBC, albumin, and LDH. Labs necessary for Tx planning are BUN, Cr, and a pregnancy test in women of childbearing age.

How is HL staged?

Show Answer

HL is staged using the **Ann Arbor system:**

Stage I: involvement of 1 LN region or localized involvement of a single extralymphatic organ or site (IE)

Stage II: involvement of ≥2 LN regions on same side of diaphragm or localized involvement of a single associated extralymphatic organ or site and its regional LN with or without involvement of other LN regions on same side of diaphragm (IIE)

Stage III: involvement of LN regions on both sides of diaphragm

Stage IV: multifocal involvement of ≥1 extralymphatic organ, with or without associated LN involvement, or isolated extralymphatic organ involvement with distant nodal involvement.

Note: Pts with B Sx are designated with a B, otherwise with an A. Pts with splenic involvement are designated with an S. Pts with bulky Dz are designated with an X. Pts with extranodal Dz are designated with an E.
Involvement of which sites is considered stage IV Dz?

Show Answer

Pts with involvement of extralymphatic structures, such as the BM, liver, and lung, have stage IV Dz.
Name the 14 distinct LN regions as per the Rye classification.

Show Answer

LN regions per the Rye classification:

1. Waldeyer ring
2. Occipital, cervical, preauricular, and SCV
3. Infraclavicular
4. Axillary
5. Epitrochlear
6. Mediastinum
7. Right hilum
8. Left hilum
9. P-A
10. Spleen
11. Mesenteric
12. Iliac
13. Inguinofemoral
14. Popliteal

Is involvement of the Waldeyer ring, thymus, or spleen considered extranodal?

Show Answer

No. Waldeyer ring, thymus, and spleen are typically considered nodal sites.

What does the Waldeyer ring include?

Show Answer

The Waldeyer ring includes:

- Pharyngeal tonsil (adenoids)
- Palatine tonsil
- Lingual tonsil (base of tongue)

What are unfavorable factors for early HL?

Show Answer

Risk factors used to stratify early-stage HL in clinical trials vary. Unfavorable factors for early HL:

- Age ≥50 yrs
- Bulky Dz (at least one-third max T diameter by the German Hodgkin Study Group [GHSG] or >10 cm by Stanford or NCCN guidelines)
- ≥4 sites (≥3 sites by GHSG)
- ESR >50 if no B Sx or >30 if B Sx
- Presence of extranodal sites
- Mixed-cellularity or lymphocyte-depleted histology

What are unfavorable factors for advanced HL used in the International Prognostic Score (IPS)?

Show Answer

Unfavorable factors for advanced HL used in the IPS:

WBC ≥15 × 10^9 cells/L
Albumin <4 g/dL
Lymphocytes (ANC) <600 or <8%
Stage IV
Hgb <10.5 g/dL

Age ≥45 yrs
Male
(Mnemonic: **WALSH AM**)
In the pre-PET era, what % of pts with favorable early-stage HL had occult splenic involvement?

Show Answer

In the pre-PET era, **30%** of pts with favorable early-stage HL had occult splenic involvement. (Carde P et al., JCO 1993)
How many times are HL pts assessed by PET/CT?

Show Answer

HL pts should have a PET-CT performed at the time of Dx for upfront staging. Then, PET-CT scans are performed to assess Tx response. Often, a PET-CT will be performed after 2 cycles of chemo and at the completion of upfront chemo.

TREATMENT/PROGNOSIS

What are the 3 most common multiagent chemo regimens used for HL?

Show Answer

Most common chemo regimens used for HL:

- **ABVD**
- **Stanford V**
- **Dose-escalated BEACOPP**

What agents are included in ABVD chemo for HL?

Show Answer

ABVD includes:

- Adriamycin
- Bleomycin

. Vinblastine
. Dacarbazine

What agents are included in the Stanford V regimen for HL?

Show Answer

There are 7 drugs in the Stanford V regimen (MOPE-ABV), listed below. Although ABVD is sometimes used without consolidation RT, the Stanford V regimen requires consolidation RT to sites originally ≥5 cm and/or to macroscopic splenic Dz. The Stanford V protocol dictates that RT should be administered 2–4 wks after chemo.

. Mechlorethamine
. Vincristine
. Prednisone
. Etoposide
. Adriamycin
. Bleomycin
. Vinblastine

What agents are included in BEACOPP?

Show Answer

There are 7 agents included in the BEACOPP regimen, as listed below. Escalated-dose BEACOPP is typically used for advanced-stage HL with poor prognostic factors. It is more commonly used in Europe than in the United States.

. Bleomycin
. Etoposide
. Adriamycin
. Cyclophosphamide
. Vincristine
. Procarbazine

. Prednisone

What is the common Tx strategy for stages I–II classic HL?

Show Answer

Chemo f/b consolidation RT. Pts with favorable risk Dz according to the GHSG criteria are generally treated with ABVD × 2 cycles f/b 20 Gy ISRT according to the HL10 study. Long-term f/u from this study has shown 10-yr PFS of 87% and OS of 94%. (Sasse S et al., JCO 2017) Pts with unfavorable risk Dz according to the GHSG criteria are generally treated with ABVD × 4 cycles f/b 30 Gy ISRT according to the HL11 study.
In early-stage HL, which factors are considered "unfavorable" according to the GHSG criteria?

Show Answer

Early-stage HL is considered "unfavorable" in the presence of 1 or more of the following:

- **3** or more sites of involvement based on the GHSG definition of sites (i.e., 5 "sites" above the diaphragm: R neck, L neck, mediastinum, R axilla, L axilla)
- **B**ulk, defined as a mediastinal-mass ratio >1/3, the ratio of the max width of the mass and the max intrathoracic diameter.
- **E**SR >50, or ESR >30 in the presence of B Sx
- **E**xtranodal Dz

(Mnemonic: **3-BEE**)
What are common Tx strategies for stages III–IV classic HL?

Show Answer

Common Tx strategies for stages III–IV classic HL:

. ABVD × 6 cycles +/– ISRT to initial bulky Dz and/or residual PET+ sites at restaging

- Stanford V + ISRT to initial bulky Dz and residual PET+ sites
- Escalated-dose BEACOPP +/– ISRT to initial bulky Dz and residual PET+ sites

What is the Tx paradigm for stages I–II NLPHL?

Show Answer

Stages I–II NLPHL Tx paradigm: Tx is similar to Tx for a low-grade NHL. Stage I and contiguous stage II NLPHL can be treated with **RT alone ("generous" ISRT)** or chemo + ISRT (if bulk or B Sx are present).
What is the Tx paradigm for stages III–IV NLPHL?

Show Answer

Stages III–IV NLPHL is treated with chemo + rituximab +/– ISRT, or rituximab alone, or local RT for palliation.
What are the commonly used RT doses in HL after initial chemo?

Show Answer

Sites without bulky Dz are typically treated to 20–30 Gy after chemo. Sites of initial bulky Dz are typically treated to 30–36 Gy after chemo.
Describe the evidence that suggests improved outcomes with CRT c/w RT alone in early-stage favorable HL.

Show Answer

In the 1990s, CRT vs. RT alone was evaluated in at least 4 major randomized trials, listed below. Although the chemo and RT techniques varied in these studies, long-term relapse rates consistently favored the CRT arms. The conclusion of these studies was that CRT is associated with improved Dz control, when compared to RT alone. In **EORTC H8 F,** 10-yr OS was significantly improved with CRT (97% vs. 92%), but long-term OS was not significantly different in the other studies.

- **EORTC H7 F** (Noordijk EM et al., JCO 2006)

- **EORTC H8 F** (Ferme C et al., NEJM 2007)
- **German HL7** (Engert A et al., JCO 2007)
- **SWOG S9133** (Press OW et al., JCO 2001)

Summarize the evidence for and against the elimination of consolidative RT in pts who achieve a CR after chemo in early-stage HL.

Show Answer

- **EORTC GELA H9 F** randomized favorable stages I–II HL pts with a CR after epirubicin/bleomycin/vinblastine/prednisone (EBVP) × 6 cycles to 36 Gy IFRT vs. 20 Gy IFRT vs. no RT. 5-yr EFS was similar b/t the 36 Gy and 20 Gy arms (89% vs. 84%, respectively) but was significantly lower in the no-IFRT arm (70%). (Thomas TM et al., IJROBP 2018)
- **EORTC H10** compared outcomes of early-stage HL pts treated with (i) ABVD + INRT vs. (ii) ABVD alone (more cycles) without RT for pts with a negative PET after ABVD × 2. Risk of early relapse in nonirradiated pts was significantly higher than in standard combined modality treated pts, even in this selected group of pts with an early negative PET. (Raemakers JM, JCO 2014)
- **UK RAPID** randomized pts with negative PET after 3 cycles of ABVD to IFRT vs. no further Tx. 3-yr PFS was 94.6% in the RT group and 90.8% in the no-RT group. This was designed as a noninferiority study and failed to meet this endpoint. (Radford J et al., NEJM 2015)
- A recent Cochrane library meta-analysis included RCTs comparing chemo alone with chemo + RT in pts with early-stage HL. For the comparison with the same numbers of chemo cycles in both arms, there was moderate-quality evidence that PFS is sup in pts receiving chemo + RT than in those receiving chemo alone. The addition of RT to chemo resulted in little or no difference in OS. However, a sensitivity analysis without the trials with potential high risk of bias showed that chemo + RT is associated with improved OS compared to chemo alone. (Blank O et al., Cochrane

Database of Systematic Reviews 2017)

Summarize the evidence to support the use of IFRT instead of more extensive RT fields in HL pts receiving CRT.

Show Answer

At least 4 RCTs have compared IFRT to more extensive RT fields in HL pts receiving CRT, as listed below:

. **Groupe Pierre-et-Marie-Curie (GPMC)** (Zittoun R et al., JCO 1985)
. **German HL8** (Klimm B et al., Ann Oncol 2007)
. **Milan study** (Bonadonna G et al., JCO 2004)
. **EORTC H8-U** (Ferme C et al., NEJM 2007)

The 5–12-yr OS outcomes were similar in all of these studies, suggesting that more extensive fields are not necessary.
Summarize the evidence to support the use of IFRT at 20 Gy after induction chemo in favorable stages I–II HL pts.

Show Answer

The use of <30 Gy in favorable stage I–II HL pts after initial chemo has been studied in at least 2 RCTs:

. **HL10** from the GHSG randomized pts to 2 vs. 4 cycles of ABVD f/b 20 Gy vs. 30 Gy IFRT (2 × 2 factorial design). 10-yr PFS, FFTF, and OS were similar b/t the chemo comparison and the RT dose comparison. This study supports the use of ABVD × 2 + 20 Gy in pts with early-stage, favorable HL according to the GHSG criteria. (Engert A et al., NEJM 2010; Sasse S et al., JCO 2017)
. **EORTC GELA H9 F** (see above)

Summarize the evidence to support the use of consolidative RT in advanced-stage HL to treat sites that responded only partially to chemo.

Show Answer

- Aleman et al. randomized pts with stages III–IV HL who achieved a CR after 4 or 6 cycles of MOPP-ABV to IFRT or observation. Pts with PR after 6 cycles rcvd IFRT to 30 Gy with a 4–10 Gy boost. Rates of EFS and OS in a pt with PR who rcvd IFRT were similar to those of pts in CR. In pts with CR, there was no difference in 8-yr EFS (observation, 77% vs. IFRT, 73%) or 8-yr OS (observation, 85% vs. IFRT, 78%). (IJROBP 2007)
- HL12 randomized pts to 2 BEACOPP regimens and pts with initial bulky Dz or a PR to chemo to consolidative RT to 30 Gy vs. no consolidative RT. RT improved FFTF in pts with residual Dz after chemo but not in pts with initially bulky Dz with a CR. (Borchmann P, JCO 2011)

What are the historic fields used to treat HL?

Show Answer

The **mantle field** is a classic comprehensive field including major nodal regions above the diaphragm. **TLI** treats a mantle field and “inverted Y” to include the P-A LNs, pelvic LNs, and spleen. **Sub-Total Lymphoid Irradiation** excludes the pelvic LNs.

What is the difference b/t IFRT vs. RFRT vs. INRT vs. ISRT?

Show Answer

IFRT covers the involved lymphoid region defined by the Rye classification, and field borders are based upon bony anatomy as defined by Yahalom et al. (Ann Oncol 2002). RFRT covers the involved regions + the immediately adjacent LN regions. ISRT covers only the prechemo tumor volume, accounting for uncertainties in imaging and changes in anatomy that occur with chemo (e.g., in the mediastinum, normal lung tissue is omitted from the Tx volume, b/c the tumor that once pushed into the lung has regressed with chemo). ISRT is the current standard of care and is an adaptation of INRT in situations where adequate prechemo imaging is not available. INRT relies on ideal prechemo imaging with PET/CT in the Tx planning position, while ISRT is used when this ideal prechemo imaging is not available. For this

reason, the CTV cannot be reduced to the same extent with ISRT as with INRT; therefore, clinical judgment is used along with imaging to create a larger CTV in order to accommodate for these uncertainties. (Specht L et al., IJROBP 2014)
Describe INRT.

Show Answer

INRT relies on ideal prechemo imaging. The prechemo PET/CT is fused with the postchemo RT planning CT. The prechemo GTV (based on prechemo CT and PET imaging) is drawn. The CTV is then created by modifying the prechemo GTV based on the postchemo CT scan to exclude normal structures that were never involved by lymphoma. For details regarding INRT as well as ISRT, see S Specht L et al. (IJROBP 2014)
According to Children's Oncology Group AHOD0031, where do pts tend to relapse after chemo and RT?

Show Answer

The mediastinum was the most common site of relapse. Relapses typically involved sites that had been involved at the time of initial Dx +/– new sites, but they rarely involved new sites only. Relapses occurred at both initially bulky and nonbulky Dz sites. (Dharmarajan KV et al., IJROBP 2015)

FOLLOW-UP/TOXICITY

In pts treated for HL, what is the RR for a 2nd solid malignancy after 30 yrs?

Show Answer

In pts who survived >5 yrs, the 30-yr cumulative risk of a second cancer for men and women diagnosed with HL at 30 yrs of age were 18% and 26%, respectively, c/w 7% and 9%, respectively, in the general population (Hodgson DC et al., JCO 2007). In another population study, the 30-yr cumulative incidence of breast cancer in women diagnosed with HL at

younger than 35 yrs of age was 13.8%. (Sud A et al., JCO 2017)
Which type of secondary cancer occurs sooner after HL Tx: leukemias or solid malignancies?

Show Answer

Leukemias tend to occur <5 yrs after Tx, whereas solid malignancies typically occur >7 yrs after Tx.
What is the impact of family Hx of cancer on secondary malignancies in HL survivors?

Show Answer

The risk of all second cancers is 1.3-fold higher for HL survivors with a 1st-degree relative with cancer ($p < .001$), with a 3.3-fold difference for lung cancer, a 2.1-fold difference for colorectal cancer, and a 1.8-fold difference for breast cancer. (Sud A et al., JCO 2017)
What are the long-term neurocognitive effects in adult survivors of childhood HL?

Show Answer

HL survivors demonstrate lower performance on sustained attention, short-term memory, long-term memory, working memory, naming speed, and cognitive fluency. MRI revealed leukoencephalopathy in 53% of survivors and 37% had evidence of cerebrovascular injury. (Krull KR et al., JCO 2012)

TARGETED AGENTS

What phase II data exists for the use of pembrolizumab in relapsed/refractory HL?

Show Answer

The KEYNOTE-087 trial was a single-arm phase II study of pembrolizumab in pts with relapsed/refractory HL. It showed an ORR of 69% and a CRR of 22.4%. (Chen R et al., JCO 2017)

What data exists for the use of brentuximab vedotin in relapsed/refractory HL?

Show Answer

In a single-center, phase II study, brentuximab vedotin f/b augmented ICE resulted in 76% of pts with relapsed/refractory HL achieving PET negativity prior to ASCT. (Moskowitz AJ et al., Lancet Oncol 2015)

The AETHERA study was a phase III trial randomizing pts with unfavorable risk, relapsed/refractory HL to early consolidation with maintenance BV or no maintenance BV. PFS was 42.9 mos for pts with maintenance BV and 24.1 mos in the placebo group, p = 0.0013. (Moskowitz CH et al., Lancet 2016)

Why is bleomycin omitted when combined with brentuximab vedotin?

Show Answer

During a phase I, dose-escalation study comparing BV combined with ABVD or AVD, there was unacceptable grade 3 or worse pulmonary toxicity in the BV and ABVD group observed in 24% of pts. (Younes A et al., Lancet Oncol 2013)

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Non-Hodgkin Lymphoma

Updated by Natalie Ausborn Lockney

BACKGROUND

What is the pathologic definition of NHL?

Show Answer

NHL is a **monoclonal expansion of malignant B or T cells that lacks the pathologic characteristics of** Hodgkin lymphoma (HL) (no Reed–Sternberg cells) and is typically characterized by nodal/focal involvement vs. the more disseminated presentation of leukemias.

How does the clinical presentation of NHL differ from that of HL?

Show Answer

NHL is more likely to be extranodal, is more likely to spread in a noncontiguous fashion, and has a prognosis that is more strongly affected by histologic subtype than HL.

What are the most common presenting signs or Sx of NHL?

Show Answer

Painless adenopathy (axillary, inguinal, and femoral) is the most common presenting sign of NHL. ~30% of pts have B Sx. Waxing and waning adenopathy suggests an indolent form of NHL. Tumor bulk may cause airway compression, intestinal obstruction, urinary tract obstruction, or nerve impingement.

What are the B Sx?

Show Answer

The B Sx include unexplained fever >38°C (100.4°F), >10% body weight loss in 6 mos, or drenching night sweats.

What is the NCI working formulation for NHL?

Show Answer

The NCI's working formulation groups NHL by clinical aggressiveness or grade with subgroups based on cell type or presentation.

Low-grade NHL: follicular (grades 1–2), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mucosa-associated lymphoid tissue (MALT) lymphoma, mycosis fungoides

Intermediate-grade NHL: follicular (grade 3), mantle cell, diffuse large B-cell lymphoma (DLBCL), natural killer (NK)/T cell, peripheral T cell, anaplastic large cell

High-grade NHL: Burkitt, lymphoblastic

What is the WHO classification of NHL?

Show Answer

The WHO classification is based on morphology and cell lineage, dividing NHL into B- and T-cell/NK cell neoplasms. The **indolent, aggressive,** and **highly aggressive** subgroups roughly correlate to the aforementioned working formulation groups.

Is there a relationship b/t clinical aggressiveness and curability of NHL?

Show Answer

Advanced-stage indolent NHL is rarely curable. Intermediate-grade NHL may be curable even in advanced stages.

Without Tx, what is the life expectancy for pts with NHL of varying aggressiveness?

Show Answer

Pts with indolent NHL have survival measured in yrs. Pts with aggressive NHL have survival measured in mos, and those pts with highly aggressive Dz have an expected survival of wks.

What % of NHL is indolent, and what are the most prevalent subtypes?

Show Answer

~35% of NHL is indolent by the WHO classification. The most common indolent NHL subtypes are **follicular lymphoma** (FL) (grades 1–2; 65%), **CLL/SLL** (18%), and **marginal zone B-cell lymphoma** (12%, most commonly MALT lymphoma).

What are the common cytogenetic abnormalities associated with indolent NHL?

Show Answer

t(14;18) is seen in 90% of FLs. This results in overexpression of antiapoptotic Bcl-2. **Chromosomal deletions of 11q, 13q, and 17p,** and **trisomy 12** are associated with CLL/SLL. **Trisomy 3** (60%) and **t(11:18)** (25%–40%) are associated with MALT lymphoma. **c-myc overexpression t(8:14)** is associated with Burkitt lymphoma.

How is FL graded?

Show Answer

FL demonstrates a mix of centrocytes (small, cleaved cells) and centroblasts (large, noncleaved cells). **Grade correlates to the density of centroblasts** (e.g., 0–5 centroblasts/high power field (hpf), grade 1; >15 centroblasts/hpf, grade 3).

What is SLL?

Show Answer

SLL is the same Dz entity as CLL but with a **predominant manifestation in**

the spleen, liver, or nodes as opposed to peripheral blood or BM.
What is Richter syndrome? What is its rate of occurrence?

Show Answer

Richter syndrome is the **transformation of SLL or CLL into an aggressive lymphoma, most commonly DLBCL.** It occurs in **~5% of cases.**
How is bulky Dz commonly defined in DLBCL?

Show Answer

Recent trials of DLBCL have defined bulk as Dz measuring at least 7.5 cm.

WORKUP/STAGING

What are the pertinent focused aspects of the physical exam in a person with suspected NHL?

Show Answer

The physical exam should include complete nodal assessment including epitrochlear and popliteal groups. Cervical adenopathy palpable above the hyoid bone should prompt an ENT exam. (The Waldeyer ring is more frequently involved in NHL than in HL.) Exam of other at-risk sites including the liver, spleen, testicles, bones, abdomen, and flanks is appropriate.
What lab studies should be performed?

Show Answer

Lab studies should include CBC with differential, CMP, LDH, β2-microglobulin, serum protein electrophoresis, HIV, hepatitis B virus (essential as it may reactivate with rituximab [Rituxan] Tx), and hepatitis C virus. BM Bx should be performed for all lymphomas. LP should be performed for CNS Sx, testicular or PNS involvement, or immunodeficiency.
What imaging studies should be performed?

Show Answer

The imaging workup should include CT neck, chest, abdomen, pelvis (N/C/A/P). PET is appropriate in most cases but may be less useful in indolent lymphomas with variable FDG-avidity. MRI brain should be performed for CNS Sx, testicular or PNS involvement, or immunodeficiency.
How is NHL staged?

Show Answer

NHL is staged similar to HL using the **Ann Arbor (AA) system:**

Stage 1: involvement of 1 LN region or localized involvement of 1 extralymphatic organ or site (IE)
Stage 2: involvement of ≥2 LN regions on the same side of diaphragm or localized involvement of 1 associated extralymphatic organ or site and its regional LN, with or without involvement of other LN regions on same side of diaphragm (IIE)
Stage 3: involvement of LN regions on both sides of diaphragm, which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE)
Stage 4: multifocal involvement of ≥1 extralymphatic organ, with or without associated LN involvement, or isolated extralymphatic organ involvement with distant nodal involvement

Note: Pts with B Sx are designated with a B, otherwise with an A. Pts with splenic involvement are designated with an S. Pts with bulky Dz are designated with an X. Pts with extranodal Dz are designated with an E.

TREATMENT/PROGNOSIS

What are prognostic factors for NHL?

Show Answer

Although grade remains the most important factor, several attempts have been made to combine multiple prognostic factors into a single numerical prognostic index to determine prognosis within a grade stratification of NHL.

The most well-known is the **International Prognostic Index (IPI)** based on aggressive NHL. Derivatives of the IPI include the **age adjusted, stage adjusted,** and revised-IPI. Other derivatives include the FLIPI (for FL) and the MIPI (for mantle cell lymphoma).
What factors are included in the IPI?

Show Answer

IPI factors: **A**ge >60 yrs, ECOG **P**S ≥2, **L**DH > normal, >1 **E**xtranodal group, AA **S**tages III–IV (Mnemonic: **APLES**)
Estimate the 5-yr OS for aggressive NHL based on the number of IPI factors, in the pre-rituximab era.

Show Answer

Number of IPI factors as associated with 5-yr OS in the pre-rituximab era:

Low: 0–1 factors → 73%
Low-intermediate: 2 factors → 51%
High-intermediate: 3 factors → 43%
High: 4–5 factors → 26%
What were the Dz characteristics and the Tx strategies employed for the pts whose outcome data were used to generate the IPI formulation?

Show Answer

The data used to generate the IPI come from 2031 adult patients treated for aggressive NHL of any stage with a combination-chemotherapy regimen containing doxorubicin as part of a phase 2 or 3 study between 1982 and 1987. (Shipp et al., NEJM 1993)
What is the R-IPI for intermediate-risk NHL incorporating the use of rituximab?

Show Answer

The R-IPI incorporates the same 5 factors as the standard IPI but with

substantial changes in the prognosis of these pts.
Estimate the 5-yr OS for aggressive NHL based on the number of R-IPI factors.

Show Answer

Number of **R-IPI factors** as associated with 5-yr OS:

0 factors: 94%
1–2 factors: 79%
3–5 factors: 55%

(Sehn LH et al., Blood 2007)
What factors are included in the FLIPI?

Show Answer

FLIPI factors: **H**gb <12 g/dL, **A**ge >60 yrs, **S**tages III–IV, **≥5** extranodal **S**ites, **L**DH > normal (Mnemonic: FLIPI is a **HASSL**). Note: These are FLIPI-specific nodal sites, not AA nodal groups.
Estimate the 5-yr OS based on the number of FLIPI factors.

Show Answer

Number of **FLIPI factors** as associated with 5-yr OS:

0–1 factors: 90%
2 factors: 80%
3–5 factors: 55%

(Solal-Celigny P et al., Blood 2004)
What was demonstrated by the Stanford retrospective series supporting RT alone in the management of stages I–II, low-grade FL?

Show Answer

The Stanford series of 177 pts treated from 1961–1994 (MacManus MP et al., JCO 1996) demonstrated an MS of 13.8 yrs, 5-, 10-, and 15-yr RFS of 55%,

44%, and 40%, respectively, and 5-, 10-, and 15-yr OS of 82%, 64%, and 44%, respectively. RT-included IFRT, EFRT, and total lymphoid irradiation. Doses ranged from 35–50 Gy. Age <60 yrs was associated with better OS and FFR. Only 5 of 47 pts who reached 10 years without relapse developed recurrence subsequently.

What was demonstrated in the retrospective Stanford series of stages I–IIA, low-grade FL not treated immediately?

Show Answer

In this series, 43 highly-selected pts (11 pts stage I) with a median age of 58 yrs rcvd no initial Tx for various reasons. At a median f/u of 86 mos, 63% had not been treated. Estimated OS at 5, 10, and 20 yrs were 97%, 85%, and 22%, respectively. (Advani R et al., JCO 2004)

Has adj chemo demonstrated a benefit in randomized trials of early-stage, low-grade FL?

Show Answer

Several randomized trials have compared RT to RT + chemotherapy (ex. cyclophosphamide/vincristine/prednisone). These trials have failed to demonstrate an overall survival difference. However, several of these trials have demonstrated improved PFS with the addition of chemotherapy.

- Nissen NI et al., Cancer 1983
- Monfardini S et al., IJROBP 1980
- Carde P et al., Radiother Oncol 1984
- Yahalom J et al., Cancer 1993
- Kelsey SM et al., Med Oncol 1994
- MacManus et al., Hematological Oncology 2017

What is the evidence for reduced doses of RT to control FL?

Show Answer

A U.K. phase III trial randomized pts with indolent lymphomas (both follicular and marginal zone) to 40–45 Gy in 20–23 fx vs. 24 Gy in 12 fx. With a median f/u of 5.6 yrs, there was no difference in in-field failure, OS, or PFS. (Lowry et al., R&O 2011)

The Follicular Radiotherapy Trial (FoRT) phase III trial (Hoskin PJ et al., Lancet Oncol 2014) randomized pts (follicular or marginal zone) to either 24 Gy or 4 Gy and found better CR with 24 Gy (68% vs. 49%) and better local PFS, which was the primary endpoint. HR for time to local progression of 3.42 ($p < 0.0001$). Nonetheless, the ORR to just 4 Gy was 81%. Given the relatively high response rates, ease of administration and min toxicity associated with 4 Gy, the authors concluded that this lower dose is a useful alternative for palliative Tx, when durable response might be less important.

What remains the Tx standard for localized, low-grade FL?

Show Answer

Locoregional RT to 24–30 Gy remains standard for stage I and contiguous stage II, grade 1–2 FL. However, observation, lower dose RT (4 Gy), and combined modality Tx are considered viable options depending on the pt and Dz characteristics.

What are the basic Tx principles for stages III–IV, low-grade FL?

Show Answer

No Tx is considered curative. Several randomized trials have indicated that therapy can be deferred without reducing survival. Tx is reserved for the following:

- Symptomatic Dz
- Threatened end organ dysfunction
- Cytopenias
- Bulky Dz

. Steady Dz progression
. Clinical trial
. Pt preference

What is the evidence for radioimmunotherapy in advanced-stage FL?

Show Answer

SWOG S0016 randomized pts with advanced-stage FL to R-CHOP × 6 vs. CHOP-RIT with Bexxar (I-131-tositumomab, a CD-20 radiotherapeutic antibody). There was no difference in 2-yr PFS (80% vs. 76%) or 2-yr OS (93% vs. 97%). (Press OW et al., JCO 2013)
What is the role of RT for stages III–IV, low-grade FL?

Show Answer

In advanced-stage indolent lymphomas, RT is reserved for **palliation of Sx.**
What is a typical RT Tx for symptomatic stages III–IV FL?

Show Answer

24 Gy in 12 fx should be used when durable LC is needed. Otherwise, 4 Gy in 2 fx is an effective, convenient, and well-tolerated alternative, based on the FORT trial.
What is the role of RT in the Tx of CLL/SLL?

Show Answer

RT is used for **palliation of symptomatic lesions.** CLL/SLL does not respond as well to 4 Gy in 2 fx as FL or MZL. From various reports, the response rates of CLL/SLL to 4 Gy are ~10%–25% CR, and ~40%–50% PR. 4 Gy may be tried as a palliative dose; however, a higher total dose (e.g., 24–30 Gy) may be needed, particularly if durable LC is a priority.
What is the role of RT in treating nodal MZLs?

Show Answer

Nodal MZL is rare and is managed like low-grade FL. RT may be used for definitive therapy in localized Dz and for palliation in advanced-stage Dz.
What is the most common initial multiagent chemo used in the management of intermediate- or high-grade NHL?

Show Answer

The most common initial multiagent chemo used in NHL is **R-CHOP,** which uses the following drugs:

. Rituximab
. Cyclophosphamide
. Hydroxydaunomycin (Adriamycin)
. Vincristine (Oncovin)
. Prednisone

What are the current indications for RT in early-stage, intermediate- or high-grade NHL?

Show Answer

The inclusion of RT in early-stage, intermediate- or high-grade NHL is **institution dependent.** It may be included as consolidation after 3–4 cycles (i.e., an abbreviated course) of R-CHOP in favorable Dz, or in appropriately selected pts with a PR to chemo. Recent research has focused on identifying the subgroups of pts that benefit from consolidative RT, after experiencing a CR to rituximab and chemo. For example, the RICOVER noRTh study demonstrated improved outcomes in pts who rcvd consolidative RT to initially bulky sites of Dz. (Held et al., J Clin Oncol 2014;32(11):1112–8) Other work has demonstrated improved outcomes associated with RT to skeletal sites of involvement. (Held G et al., J Clin Oncol 2013;31(32):4115–22) The results of ongoing randomized trials from the modern era are eagerly anticipated to further guide selection of candidates for RT.
What is the present Tx paradigm for advanced stage, intermediate- or

high-grade NHL?

Show Answer

Advanced-stage, intermediate- or high-grade NHL Tx paradigm: R-CHOP × 6 cycles. IFRT may be considered for initially bulky sites, based on the RICOVER noRTh study, and for skeletal sites. (Held et al., 2013).
Estimate the prognosis of limited-stage aggressive B-cell lymphoma treated with R-CHOP and IFRT.

Show Answer

SWOG 0014 (phase II) enrolled 60 pts with limited-stage aggressive NHL and at least 1 adverse risk factor. Pts were treated with R-CHOP × 3 + IFRT: 4-yr PFS was 88%, and OS was 92%. (Persky DO et al., JCO 2008)
What is the long-term DFS for pts with localized DLBCL treated with RT alone? What were the typical Tx doses used in clinical trials?

Show Answer

Using **45–50 Gy** to maximize LC, **only 40% of pts with localized DLBCL had long-term DFS** based on historical RT-alone data. (Chen MG et al., Cancer 1979; Sweet DL et al., Blood 1981; Kaminski MS et al., Ann Intern Med 1986)
What was demonstrated in the initial publication of the SWOG 8736 study comparing chemo alone to abbreviated CRT in localized intermediate-grade NHL?

Show Answer

In **SWOG 8736,** 401 pts with stage I or IE (including bulky Dz) and stage II or IIE (nonbulky) intermediate-grade NHL were randomized to CHOP × 8 cycles vs. CHOP × 3 + IFRT. RT doses of 40–55 Gy were employed. At 5-yr f/u, PFS and OS favored the combined therapy group (OS: 82% vs. 72%). (Miller TP et al., NEJM 1998) However, extended data with median 17.7 yrs f/u showed no difference in OS or PFS b/t the 2 groups and increased late

relapses in the combined modality therapy arm. (Stephens DM et al., JCO 2016) These findings suggest that the use of RT cannot compensate for inadequate chemo.

What was demonstrated in the ECOG E1484 study randomizing postchemo complete responders to observation vs. IFRT?

Show Answer

In **ECOG E1484,** 352 pts with intermediate-grade, bulky stages I–IE or nonbulky stages II–IIE Dz were administered CHOP × 8 cycles. Complete responders (215 pts) were randomized to IFRT vs. observation. At 6 yrs, DFS favored IFRT (73% vs. 56%), but OS was equivalent. FFS was equivalent in partial responders administered IFRT (40 Gy) and in CR pts (30 Gy). Failure at initial sites was greater in pts not given IFRT. (Horning SJ et al., JCO 2004)

What was demonstrated in the GELA LNH-93-1 study comparing aggressive chemo vs. standard chemo and RT in pts less than or equal to 60 yo?

Show Answer

In **GELA LNH-93-1,** 647 pts ≤60 yo with low-risk (IPI 0), stages I or II, intermediate-risk NHL (extranodal or bulky Dz allowed) were randomized to doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone (ACVBP) × 3, then Mtx/etoposide/ifosfamide/cytarabine vs. CHOP × 3, then IFRT to 30–40 Gy. ACVBP without RT improved 5-yr EFS (82% vs. 74%) and OS (90% vs. 81%) regardless of the presence of bulky Dz. (Reyes F et al., NEJM 2005) However, ACVBP is considered to be a toxic regimen (dose intensity 150% of CHOP; requires hospitalization to administer; associated with high rates of secondary acute myeloid leukemia and lung cancer); therefore, it is not used standardly.

What was demonstrated in the GELA LNH-93-4 study evaluating pts age >60 yrs with low-risk, localized, intermediate-grade NHL?

Show Answer

In **GELA LNH-93-4,** 576 pts age >60 yrs with low-risk (age-adjusted IPI 0), stage I or II NHL (bulky [8%] or extranodal [56%] Dz allowed) were randomized to CHOP × 4 vs. CHOP × 4 + IFRT to 40 Gy. The 5-yr EFS (~62%) and OS (~70%) were equivalent in both Tx arms. (Bonnet C et al., JCO 2007)

What is the present Tx paradigm for relapsed intermediate- or high-grade NHL?

Show Answer

Relapsed intermediate- or high-grade NHL Tx paradigm: high-dose chemo + autologous stem cell transplant

FOLLOW-UP/TOXICITY

What are the expected RT toxicities associated with Tx of NHL?

Show Answer

The RT toxicities depend on the site of Tx. B/c of high rates of long-term survival and frequent Tx with doxorubicin; the cardiac effects of mediastinal RT are an important concern. The later age at presentation, when compared to HL, should be considered with respect to the risk of 2nd malignancies.

72

MALT Lymphoma (Gastric and Ocular Adnexa and Other Sites)

Updated by Suchit H. Patel

BACKGROUND

What does MALT stand for? Where is MALT generally located?

Show Answer

MALT stands for **mucosa-associated lymphoid tissue.** It consists of small concentrations of lymphoid tissue found in the mucosa of various sites of the body, such as the GI tract.

What is the etiology of MALT lymphomas?

Show Answer

Chronic inflammation from infection or autoimmune disorder predisposes to the development of MALT lymphomas.

What are the most common locations of MALT lymphoma in the body?

Show Answer

The most common locations of MALT lymphoma are the GI tract (stomach > small intestine > colon), lung, thyroid, salivary gland, tonsil, breast, and orbit.

What types of infectious or autoimmune conditions are associated with MALT lymphoma in the stomach? Ocular adnexa? Salivary gland? Skin? Thyroid?

Show Answer

Infections or autoimmune conditions associated with MALT:

Stomach: Helicobacter pylori
Ocular adnexa: Chlamydia psittaci
Salivary gland: Sjögren syndrome, hepatitis C
Skin: Borrelia burgdorferi
Thyroid: Hashimoto thyroiditis
What is the natural Hx of MALT lymphoma?

Show Answer

The natural Hx follows an **indolent clinical course,** as a low-grade lymphoma. MALT lymphomas typically remain localized to the tissue of origin.
From where do MALT lymphomas typically arise in the lymphoid follicle?

Show Answer

MALT lymphomas typically arise from the **marginal zone** of the lymphoid follicle (and therefore are also termed as extranodal marginal zone lymphoma).
What are some important cytogenetic abnormalities in MALT lymphomas?

Show Answer

Important cytogenetic abnormalities include **t(11;18)(q21:q21) and trisomy 3.**
What is the immunophenotype of MALT lymphoma?

Show Answer

MALT lymphoma is a **low-grade B-cell lymphoma that is CD20+, CD35+, CD5–, and CD10–.**

WORKUP/STAGING

What is the typical stage of MALT lymphomas?

Show Answer

Because MALT lymphomas remained localized to a particular tissue, most are usually Ann Arbor stage **IAE** (80%).

What is the typical presentation of a pt with gastric MALT?

Show Answer

The typical presentation of gastric MALT is **dyspepsia (#1), epigastric pain or discomfort, n/v, GI bleed, and B Sx (rare).**

What workup should be included in a pt with suspected MALT lymphoma of the stomach?

Show Answer

Suspected MALT lymphoma of the stomach workup: Complete H&P (with emphasis on B Sx and evaluation of all LNs, including the Waldeyer ring [15% association; check hepatosplenomegaly]), CBC/CMP, LDH, CXR, CT abdomen/pelvis, esophagogastroduodenoscopy (EGD) with Bx, and EUS if available (to assess DOI). Test for H. pylori infection with a rapid urease test (RUT) on the Bx specimen and test for t(11;18) with FISH or PCR. Consider BM Bx in pts with suspected systemic Dz. Routine PET/CT is not considered necessary but may be useful in some cases.

What is the sensitivity and specificity of the RUT for H. pylori? What are other alternatives if the RUT is negative?

Show Answer

The sensitivity and specificity of RUT are >90%. However, if the test on the tissue sample is negative and the clinical suspicion is high, preferred noninvasive tests are (1) H. pylori serum serology (antibody), (2) urea breath test, or (3) stool antigen test.

How is the Ann Arbor system used for staging MALT lymphoma of the GI tract?

Show Answer

Ann Arbor staging for MALT lymphoma of the GI tract if no B Sx:

Stage IAE: confined to GI tract
Stage IIAE: GI + nodal involvement below diaphragm
Stage IIIAE: GI + nodes above diaphragm +/– nodes below diaphragm
Stage IVAE: GI + other extranodal involvement (BM, liver, etc.) +/– nodes above or below diaphragm

TREATMENT/PROGNOSIS

What is the 1st-line therapy used for the Tx of gastric MALT lymphoma?

Show Answer

If there is documented H. pylori infection, the initial therapy is H. pylori **eradication** (triple therapy of clarithromycin/metronidazole/proton pump inhibitor (PPI) or clarithromycin/amoxicillin/PPI). If there is lymphoma but the pt is H. pylori–, consider RT as a primary therapeutic approach, especially if there are chromosomal abnormalities.
How is the eradication of H. pylori determined?

Show Answer

A **urea breath test should be done 1 mo after antibiotic use.** If there is persistence of tumor and H. pylori infection, switch to a different antibiotic regimen.
What response rate is expected from 1st-line Tx of gastric MALT lymphoma?

Show Answer

75%–80% of pts have a CR (Wündisch T et al., JCO 2005), with an extremely low rate of relapse.

What is the typical response period to antibiotics in MALT lymphoma?

Show Answer

In MALT lymphoma, regression can be slow. In 1 study of 120 pts, the 1st CR after antibiotic therapy was diagnosed between 1 mo and 28 mos after the start of the H. pylori eradication Tx. The majority of pts (61%) achieved a CR within the 1st 3 mos after Tx. However, in some pts, it took up to 28 mos for all histologic evidence of lymphoma to resolve. (Wundisch T et al., JCO 2005)

How should response be assessed when using antibiotics for gastric MALT lymphoma?

Show Answer

Response to antibiotics in MALT lymphoma is assessed by **EGD with visual inspection and Bx q3mos.** Dz should be stable or regressing. If Dz if progressing, consider RT. If it is stable or regressing and the pt is asymptomatic, repeat the EGD in 3 mos as pts may enter a delayed CR. If CR is attained, monitor for relapse with EGD every 6 mos for 2 yrs and then as clinically indicated.

What should be done with minimal histologic residual Dz in the setting of otherwise normalized endoscopy and H. pylori eradication?

Show Answer

The vast majority of these pts will either remain with localized Dz or eventually enter into a CR with observation alone without further oncologic therapy. Hence, such pts should be observed with regular endoscopy and Bx. (Fischbach W et al., Gut 2007)

What are 3 tumor characteristics that portend a poor response to the use of antibiotics for the Tx of gastric MALT lymphoma?

Show Answer

Tumor characteristics that portend a poor response with antibiotics for MALT

lymphoma include **t(11;18), trisomy 3, and DOI beyond the submucosa** (muscularis/serosa/adjacent organs). In 1 study of 22 pts, there was an 86% CR rate with DOI < submucosa and 0% if invasion was beyond the submucosa. (Sackmann M et al., Gastroenterology 1997)
What are the options for antibiotic-resistant MALT lymphomas?

Show Answer

Given the indolent nature of the Dz, there are many options. ISRT should be considered. In an early study of 17 pts treated with RT for gastric MALT, all 17 obtained a Bx-confirmed CR. At a median f/u of 27 mos after RT, EFS was 100%. Tx was well tolerated, with no significant acute side effects. (Schechter et al., JCO 1998) Systemic therapy, such as rituximab (Rituxan), can be considered after RT failure or in advanced Dz.
When should RT be considered for the Tx of gastric MALT lymphoma?

Show Answer

RT for MALT lymphoma should be considered in the following situations:

- H. pylori– with stage IAE lymphoma, with or without initial use of antibiotics
- t(11;18)
- Invasion beyond submucosa (muscularis/serosa/adjacent organs)
- Documented progression after initial use of antibiotics
- Documented failure of 2nd course of antibiotics
- Rapid symptomatic progression of Dz

What are some important prognostic factors for MALT lymphomas?

Show Answer

Important prognostic factors for MALT lymphomas:

- Cytogenetics
- Histology/grade

. DOI
. Stage/LN involvement
. Tumor size

What are the factors in the MALT International Prognostic Index (MALT-IPI) that predict prognosis in MALT?

Show Answer

. Age greater than or equal to 70
. Stage III–IV Dz
. LDH abnl

(Thieblemont et al., Blood 2017)
Is there a benefit of adding chemo in low-risk MALT?

Show Answer

No. Outcomes are excellent with ISRT alone, which remains the standard 1st-line modality. (Schechter et al., JCO 1998) Consideration may be given to the addition of rituximab in high-risk cases.
What is the 3rd-line therapy for Tx of gastric MALT lymphoma?

Show Answer

The 3rd-line therapy for MALT lymphoma is **chemo (e.g., rituximab +/– bendamustine, R-CHOP, R-CVP, single-agent cyclosphosphamide).**
What is the Tx paradigm for DLBCL of the stomach?

Show Answer

DLBCL of the stomach Tx paradigm:
rituximab/cyclophosphamide/hydroxydaunomycin (Adriamycin)/vincristine (Oncovin)/prednisone (R-CHOP) + ISRT
What are the simulation procedures for RT planning for Tx of MALT lymphoma of the stomach?

Show Answer

Pt in a fasting state, supine, arms up and consider a small volume of oral contrast. Use methods to determine respiratory excursion or consider breath hold. IV contrast can be considered if nodal Dz is suspected. Field should encompass the entire stomach. Include regional LNs if they were suspicious for Dz. 4-field 3D-CRT may reduce kidney dose. IMRT may improve kidney and liver dose. (Della Biancia C et al., IJROBP 2005; Goda JS, Cancer 2010) Consider daily CT-guidance to allow for the use of small margins. (Wang et al., PRO 2017)

What are common RT Rx for MALT lymphoma of the stomach?

Show Answer

Rx dose: 30 Gy in 1.5 Gy/fx for 20 fx. Consider boosting the area of Dz to 36 Gy. Another option is 24 Gy in 2 Gy/fx for 12 fx, since this is an accepted dose for definitive RT to treat indolent NHL. (Lowry et al., Radiother and Oncol 2011)

What are the long-term outcomes with the use of ISRT for Tx of gastric MALT lymphoma?

Show Answer

Appx a 90% recurrence-free rate at 10 yrs.
(Goda JS, Cancer 2010; Wirth A, Ann Oncol 2013)

What is the most common site for non-gastric MALT?

Show Answer

Orbital MALT is the most common nongastric MALT.

Which organism is often associated with orbital MALT?

Show Answer

C. psittaci is often associated with orbital MALT, and eradication of the organism with antibiotics (doxycycline) can result in a CR.

What volume is treated and what are common RT Rx for orbital MALT?

Show Answer

Typically, the whole bony orbit is treated with care taken to include extraorbital extension. Partial orbital RT may be considered if the site of disease can be visualized and delineated. Dose: 24–30 Gy in 10–20 fx has been used, with >95% LC but with high incidence of late toxicity, arguing for using the lower doses. (Goda JS, IJROBP 2011) ILROG recommendations currently are for 24–25 Gy in 1.5–2.0 Gy daily fx. (Yahalom J, IJROBP 2015) However, excellent results have been observed after Tx with just 4 Gy in 2 fx. (Fasola et al., IJROBP 2013; Pinnix et al., Head & Neck 2017) This ultra-low dose is effective and well tolerated, with the option of re-irradiation in the case of locoregional refractoriness/relapse.

What is the typical natural Hx of orbital MALT?

Show Answer

Pts experience excellent overall and CSS. The 10-yr recurrence-free rate is 67% after RT for orbital MALT. Recurrences typically involve the contralat, untreated orbit or distant sites. (Goda JS, Cancer 2010)

What is typically associated with MALT of the salivary gland?

Show Answer

MALT of the salivary gland is associated with **Sjögren syndrome.**

What are the fields, volumes, and doses used for MALT of salivary gland?

Show Answer

The ILROG guidelines suggest treatment of the whole gland involved (e.g., superficial and deep lobe of the parotid) with IMRT or 3D-CRT. However, treatment of a portion of the gland may be considered if the site of disease can be delineated. For pts with stage IIE Dz (cervical nodal involvement), encompass the ipsi cervical LN stations. Treat the bilat parotid if there is bilat involvement. The standard definitive dose has been 24–30 Gy. To minimize

risk of xerostomia, consideration may be given to initial Tx with 4 Gy in 2 fx, f/b dose escalation if inadequate response.
What are the long-term outcomes for MALT of the salivary gland treated with RT?

Show Answer

A 10-yr recurrence-free rate of 68% has been reported with the contralat parotid gland as the predominant site of failure. (Goda JS et al., Cancer 2010) Overall and CSS rates are excellent.
What is typically offered for MALT of the lung?

Show Answer

ISRT should be offered, given the high response rate. Observation is a reasonable strategy in the setting of completely excised Dz.
How is MALT of the skin managed?

Show Answer

MALT of the skin may be managed by **surgical excision for small lesions. ISRT using electrons with bolus is another effective strategy.** High rates of Dz response are seen after localized RT, even with low doses such as 4 Gy. (Akhtari M et al., Leuk Lymphoma 2016)
What is the regimen used for management of advanced low-grade lymphoma?

Show Answer

For advanced low-grade lymphoma, use **systemic agents such as rituximab +/– bendamustine;** however, cure is rare. **Palliative RT** is very effective. A high overall response rate (80%–90%) is seen with the use of 4 Gy (2 Gy × 2).
Which systemic options are available for relapsed/refractory indolent lymphomas?

Show Answer

Multiple systemic options exist to treat indolent NHL, including bendamustine + rituximab, R-CVP, R-CHOP, single-agent rituximab, lenalidomide + rituximab, and single-agent cyclophosphamide.

FOLLOW-UP/TOXICITY

To what RT doses should the kidneys and liver be limited in MALT of the stomach?

Show Answer

Pts experience excellent long-term survival, so minimizing the toxicity of therapy is of critical importance. Keep the mean dose to both kidneys to <10–15 Gy (or 20% of left kidney to <20 Gy). The dose to the liver should be V25 <50%. Patient shifts may be necessary during treatment with daily volumetric image guidance, so consider using a kidney PRV (planning risk volume) avoidance structure.

What are expected toxicities for using ISRT for Tx of MALT lymphoma of the stomach?

Show Answer

Anorexia and n/v are toxicities associated with ISRT for MALT lymphoma of the stomach and can be lessened with prophylactic daily antiemetics prior to Tx. More significant side effects, such as ulceration, are rare.

73

Plasmacytoma/Multiple Myeloma

Updated by Joanna C. Yang

BACKGROUND

What is the cell of origin in multiple myeloma (MM), and what does this cell usually secrete?

Show Answer

Mature B cells are the cell of origin in MM, and they usually secrete **immunoglobulins.** An M-protein is an abnl immunoglobulin fragment, such as an immunoglobulin light chain, that is produced in excess by a monoclonal proliferation of plasma cells in MM.

Appx how many cases of MM are diagnosed annually in the United States?

Show Answer

The American Cancer Society's estimates for MM in the United States for 2017 are:

- ~30,280 new cases will be diagnosed (17,490 in men and 12,790 in women)
- ~12,590 deaths will occur (6,660 in men and 5,930 in women)

What % of plasma cell tumors are MM? Solitary plasmacytoma (SP)?

Show Answer

MM constitute 90% of plasma cell tumors, while **SP constitute 10%** of

plasma cell tumors.
Is there a racial or sex predilection for MM?

Show Answer

Yes. The incidence of MM is **greater in blacks** than whites (2:1). The incidence is slightly higher among men than women.
What is the avg decade of life in which pts present with MM?

Show Answer

On avg, pts present with MM in the **5th–6th decades of life.**
What are the 2 forms of SP?

Show Answer

The 2 forms of SP are **solitary bone plasmacytoma** (SBP) and **solitary extramedullary plasmacytoma** (SEP).
What environmental or genetic alterations are consistently associated with MM?

Show Answer

There are **no strong genetic or environmental patterns associated with MM.** However, a family Hx of MM is associated with increased risk. There may be a modest but increased risk of MM with exposure to ionizing RT (latency 20+ yrs) or the chemical alachlor, a commonly used pesticide.
What % of pts with SBP will progress to MM at 10 yrs?

Show Answer

SBP will progress to MM in **50%–80%** of pts at 10 yrs. (Hu K et al., Oncology 2000; de Waal EG et al., Br J Haematol 2016)
What % of pts with SEP will progress to MM at 10 yrs?

Show Answer

SEP will progress to MM in **10%–40%** of pts at 10 yrs. (Hu K et al.,

Oncology 2000)
What is the most common site of SEP?

Show Answer

The most common site of SEP is the **H&N** region (80% of SEP); the nasal cavity and PNS are the most common subsites for SEP.
What is the relationship b/t secretory patterns in SBP vs. SEP?

Show Answer

Most pts with SBP have a secretory tumor, whereas SEP is more commonly nonsecretory.
What is the relationship b/t LN involvement in SBP vs. SEP?

Show Answer

SBP rarely involves LNs, but SEP will have LN involvement ~30% of the time.
What 3 lab abnormalities may prompt a clinician to evaluate for a plasma cell neoplasm?

Show Answer

Lab abnormalities that may prompt evaluation for a plasma cell neoplasm:

. Unexplained normochromic/normocytic anemia
. Unexplained renal insufficiency
. Hypercalcemia

What lab tests are used for screening of a plasma cell abnormality?

Show Answer

Serum protein electrophoresis (SPEP) and **urine protein electrophoresis** (UPEP) are lab tests used to screen for a plasma cell abnormality. A positive screen on these tests results when a monoclonal population (or spike) is detected.

What is the common pattern of bone Dz in MM?

Show Answer

Lytic bone lesions are the most common bone abnormality seen on imaging of pts with MM.
What is monoclonal gammopathy of undetermined significance (MGUS), and how often will it transform to MM?

Show Answer

MGUS is a **condition with clonal proliferation of an immunoglobulin in the absence of clinical, radiographic, or lab evidence of MM.** The risk of transformation from MGUS to MM is 1% per yr.
What is 1 factor that predicts the risk of transformation from MGUS to MM?

Show Answer

The risk of transformation from MGUS to MM is predicted by the **initial size of the M-protein peak.**
What is the most common clinical Sx seen at Dx of MM or SP?

Show Answer

Bone pain is the most common clinical Sx seen at Dx of MM or SP. A subset of these pts will present with a pathologic fracture.
What is POEMS syndrome?

Show Answer

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) is a **variant of MM with solitary or limited sclerotic bone lesions** that often responds to radiotherapy with a spontaneous improvement in neuropathy. (Humeniuk MS et al., Blood 2013)
What diagnostic criteria are required for MM?

Show Answer

According to the International Myeloma Working Group, the criteria for the Dx of MM are:

Clonal BM plasma cells >10% or a Bx-proven plasmacytoma AND any 1 or more of the following CRAB features:

- Hypercalcemia
- Renal insufficiency
- Anemia
- or more osteolytic bone lesions

Any 1 or more of the following is sufficient to make the Dx:

- 60% or greater clonal plasma cells in the BM
- Serum involved/uninvolved free light chain ratio of 100 or greater
- More than 1 plasmacytoma

Name 7 factors that can be used as evidence of end organ damage in MM.

Show Answer

Factors that can be used as evidence of end organ damage in MM:

. Hypercalcemia
. Renal insufficiency
. Anemia
. Bone lesions
. Frequent severe infections
. Amyloidosis
. Hyperviscosity syndrome

(No author, Br J Haematol 2003)

What is the difference b/t symptomatic MM and asymptomatic (smoldering) MM?

Show Answer

Smoldering (or asymptomatic) MM requires the presence of serum

monoclonal protein ≥3 g/dL and/or BM plasma cells ≥10% but no evidence of end organ damage attributable to plasma cell dyscrasia. (No author, Br J Haematol 2003)
What 3 criteria are necessary for the Dx of MGUS?

Show Answer

Criteria necessary for the Dx of MGUS:

- Serum monoclonal protein <3 g/dL
- BM plasma cell <10%
- No end organ damage attributable to plasma cell dyscrasia

What 4 criteria are necessary for the Dx of SBP?

Show Answer

Criteria necessary for the Dx of SP:

- Solitary bone lesion on skeletal survey &/or PET &/or MRI
- Histologic evidence of plasmacytoma by Bx
- Normal BM with no evidence of clonal plasma cells
- No other end organ damage attributable to plasma cell dyscrasia

WORKUP/STAGING

What is β_2-microglobulin (β_2M)?

Show Answer

β2M is a component of major histocompatibility complex class 1 molecules. Increasing levels of β2M are associated with a worse prognosis in MM.
What are the 2 most commonly used staging systems for MM?

Show Answer

The 2 most commonly used staging systems for MM are the **Durie–Salmon Staging and the International Staging System** (ISS).
What 2 factors are used to stage pts in the ISS system, and how are they

grouped?

Show Answer

The 2 factors used in the ISS system are **β_2M and albumin.** They are used to stage pts as follows:

Stage I: β2M <3.5 mg/L, albumin ≥3.5 g/dL
Stage II: β2M <3.5 mg/L, albumin <3.5 g/dL, or β2M ≥3.5 and <5.5
Stage III: β2M ≥5.5
What is the MS of MM by ISS stage?

Show Answer

In the publication that introduced the ISS, MS of MM based on stage was:

Stage I: 62 mos
Stage II: 44 mos
Stage III: 29 mos

(Greipp PR et al., JCO 2005)
What is the Durie–Salmon staging scheme for MM?

Show Answer

The Durie–Salmon staging scheme for MM:

Stage I: all of the following are required:
a. Hgb >10 g/dL
b. normal calcium
c. skeletal survey with no lytic bone lesions
d. serum paraprotein level <5 if IgG (<3 if IgA)
e. urinary light chain excretion <4 g/24 hrs
Stage II: not fitting stage I or III
Stage III: 1 or more of the following:
a. Hgb <8.5 g/dL
b. calcium >12

c. skeletal survey with ≥3 lytic lesions
d. serum paraprotein level >7 if IgG (>5 if IgA)
e. urinary light chain excretion >12 g/24 hrs

The Durie–Salmon staging system gives a subclassification of A or B based on what factor?

Show Answer

The Durie–Salmon staging subclassification distinguishes pts based on **serum Cr:** A, Cr <2 mg/dL; B, Cr ≥2 mg/dL.

Besides a careful H&P, what lab and radiographic studies are necessary to evaluate a pt with newly diagnosed or suspected MM?

Show Answer

The lab and radiographic workup of MM includes CBC with differential, LDH, calcium albumin, Cr, β2M, serum immunoglobulins and light chains, 24-hr total urine protein, SPEP/UPEP, SIFE/UIFE, PET or MRI of the whole body (or skeletal survey and spine MRI) and unilat BM aspirate and Bx (with BM flow cytometry or immunohistochemistry). Other studies that may be helpful in select cases include Bx of a suspected plasmacytoma & CT or MRI of the affected area.

What is the role of a bone scan in the workup and staging for plasma cell neoplasms?

Show Answer

There is **no role for routine staging** with a bone scan in pts with plasma cell neoplasms b/c the lesions are primarily lytic with little evidence of bone repair and consequent low isotope uptake.

TREATMENT/PROGNOSIS

What is the recommended management of smoldering (asymptomatic) MM?

Show Answer

The recommended management of smoldering MM is **close observation (watch-and-wait strategy) or a clinical trial.** However, a phase III trial of pts with high-risk smoldering MM found that induction lenalidomide plus dexamethasone f/b maintenance lenalidomide was sup to observation in delaying progression to active Dz. It was also found to increase OS (94% vs. 80%). (Mateos MV et al., NEJM 2013) Research is underway to characterize those pts who benefit from early Tx vs. those who can be observed as an initial strategy.

What is the recommended management of SBP?

Show Answer

The recommended management of SBP is **involved-site RT, typically to 40–50 Gy.** (Mendenhall C et al., IJROBP 1980) However, more recent data suggest that lower doses may be sufficient. (Ozsahin M et al., IJROBP 2006)

What is the recommended management of SEP?

Show Answer

As in SBP, the recommended management of SEP is **involved-site RT to 40–50 Gy.** (Mendenhall C et al., IJROBP 1980) However, more recent data suggest that lower doses may be sufficient. (Ozsahin M et al., IJROBP 2006)

In what subgroup of pts with SBP or SEP may combined modality therapy (Sg → RT) be preferred?

Show Answer

Sg may be considered if the plasmacytoma is causing structural instability or neurologic compression.

What is the role of RT in the Tx of MM, and what dose should be given?

Show Answer

The role of RT in the management of MM is for the **palliation of**

symptomatic bone lesions, prevention of pathologic fractures, and relief of cord compression. The dose of RT given in MM is generally **20–36 Gy in 1.5–2 Gy/fx.**

Why is the dose of RT for the management of SP higher than the dose used in MM?

Show Answer

RT used in MM is for palliation of Sx, and doses of 20–30 Gy are generally sufficient to palliate this radio-responsive tumor. By definition, SP is a localized neoplasm, and a curative paradigm is employed. Dose escalation is used under the assumption that **complete eradication of tumor can occur at higher doses.** Doses of >40 Gy have been associated with improved Dz control in some reports of plasmacytoma pts. (Menendhall C et al., IJROBP 1980)

What is the role of bisphosphonates in the management of MM?

Show Answer

Bisphosphonates are given with 1st-line antimyeloma therapy b/c they have been shown to **decrease the risk of skeletal events** (41% vs. 24%) and **decrease bone pain.** (Berenson JR et al., NEJM 1996)

What is the initial management of pts with MM?

Show Answer

The recommended initial management of pts with MM is **induction with a bisphosphonate, bortezomib, dexamethasone, and either cyclophosphamide, doxorubicin, or lenalidomide. (**NCCN Guidelines 2018**)**

What type of SCT is preferred in the management of MM?

Show Answer

Autologous SCT is the standard of care for eligible pts whose Dz responds to primary therapy. It is associated with improved PFS. Even in pts treated with

RVD (lenalidomide/bortezomib/dexamethasone), a promising new primary therapy, consolidation with autologous SCT improves PFS. (Attal M et al., NEJM 2017)
What is the preferred conditioning regimen for pts receiving a myeloablative SCT in MM?

Show Answer

High-dose melphalan is the preferred conditioning regimen in pts with MM undergoing BMT. A randomized study of high-dose melphalan vs. TBI (8 Gy in 4 fx) + low-dose melphalan showed worse hematologic toxicity and worse OS in pts treated with RT. (Moreau P et al., Blood 2002)
What area should be targeted with RT in the management of SBP?

Show Answer

The area to be irradiated should include the radiographic abnormality appreciated by CT, PET, and MRI. In the era of PET and MRI, it is not necessary to include bone that is not radiographically involved. For example, it is not necessary to treat 1–2 vertebral bodies above and below a vertebral body involved by SBP, as was done historically.
What area should be targeted with RT in the management of SEP?

Show Answer

The area to be irradiated should include the radiographic abnormality appreciated by CT, PET, and MRI. Any suspicious, adjacent LNs should be included. In the era of PET and MRI, elective nodal irradiation is not necessary, although it was used historically.
What is the recommended f/u for pts with SP?

Show Answer

Recommended SP f/u: clinical evaluation + CBC, Cr, albumin, calcium, quantitative immunoglobulins, SPEP, UPEP, and serum-free light chains q3–6 mos. As clinically indicated, may obtain an LDH, β2M, BM Bx, skeletal

survey, CT, MRI, PET.
What is daratumumab?

Show Answer

It is a human IgG1k monoclonal antibody that binds with high affinity to the CD38 molecule, which is highly expressed on the surface of MM cells. It is believed to induce rapid tumor cell death through antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

74

sMycosis Fungoides

Updated by Robert Samstein

BACKGROUND

What subtypes of disorders are encompassed in the general term cutaneous T-cell lymphoma (CTCL)?

Show Answer

There are multiple subtypes of CTCL. The most common are mycosis fungoides (MF) and Sezary syndrome.
What is MF?

Show Answer

A low-grade NHL caused by skin-homing CD4+ T cells that form cutaneous lesions.
MF comprises what % of all lymphomas? What % of all CTCL?

Show Answer

MF comprises ~**2%** of all lymphomas but is the most common type of primary cutaneous lymphoma. MF comprises 50% of all CTCLs.
What is the median age at presentation in MF?

Show Answer

The median age at presentation of MF is **55–60 yrs.**
Is there a race and sex predilection for MF?

Show Answer

Yes. Black race (2:1) and male gender (2.2:1) are known risk factors for having MF.

What do MF pts have an increased susceptibility to?

Show Answer

MF pts have an increased susceptibility to **infections and other malignancies,** possibly d/t an impaired immune system.

What is the histopathologic hallmark of MF?

Show Answer

The histopathologic hallmark of MF is the **Pautrier abscess** (sometimes called microabscess), which refers to the clustering of atypical lymphocytes, usually around a Langerhans cell, in the epidermis.

What is the most common presentation of early MF?

Show Answer

The most common presentation of early MF is the **presence of erythematous, scaly, and pruritic macules** on an area of skin not commonly exposed to the sun.

What are the clinical presentations/phases of MF?

Show Answer

Clinical presentations/phases of MF:

. Premycotic (erythematous macule) phase
. Patch phase
. Plaque phase
. Tumor phase
. Erythroderma (>80% surface area involvement)

What % of MF pts present with Dz localized to the skin only?

Show Answer

70%–80% of pts are diagnosed in early stages with skin involvement only. They do not have involvement of LNs or internal organs.

What is Sézary syndrome?

Show Answer

Compared to MF, Sézary syndrome is a more aggressive, leukemic form of CTCL, with widespread skin involvement (erythroderma) and the presence of significant numbers of malignant lymphocytes in the peripheral blood ("Sézary cells").

WORKUP/STAGING

What is the workup of MF?

Show Answer

Hx: focus on B Sx and skin lesions with attention to duration, distribution, changes, and associated pain or pruritus.

Physical exam: focus on entire skin (including soles, perineum, nails, and auditory canals) and LNs. Delineate skin involvement with photographs. Perform a min of 2 Bx of involved skin, with pathologic evaluation including T-cell receptor gene analysis.

Blood work: obtain a Sézary cell count, flow cytometry (if available), and a T-cell receptor gene analysis, CBC, CMP, LDH, and LFTs.

Imaging: CXR for early stage, CT C/A/P or PET/CT for suspected stages IIA–IV to assess for extracutaneous manifestations. If concerning LN, excisional Bx (reactive LN are common). Consider BM Bx in pts with blood or visceral involvement.

Describe the difference b/t a patch and a plaque.

Show Answer

A patch does not have elevation or induration. A plaque has elevation or

induration.

Describe the T classification system for MF.

Show Answer

T1: limited patch/plaque (<10% total skin surface):
(a) patch only
(b) plaque +/– patch
T2: generalized patch/plaque (≥10% total skin surface):
(a) patch only
(b) plaque +/– patch
T3: tumor(s) ≥1 cm in diameter
T4: generalized erythroderma covering ≥80% of body surface area

Describe the N and M classification system for MF.

Show Answer

N0: uninvolved
N1: clinically abnl peripheral LN, histopathologically Dutch grade 1 or NCI LN 0–2:
(a) T-cell clone negative
(b) T-cell clone positive
N2: clinically abnl peripheral LNs, histopathologically Dutch grade 2 or NCI LN 3:
(a) T-cell clone negative
(b) T-cell clone positive
N3: clinically abnl peripheral LN, histopathologically Dutch grades 3–4 or NCI LN 4, clone positive or negative
M0: no visceral involvement
M1: visceral involvement

Describe the B classification of MF.

Show Answer

B0: absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are Sézary cells:
(a) clone negative
(b) clone positive

B1: low blood tumor burden: >5% of peripheral blood lymphocytes are Sézary cells, but pt not B2:
(a) clone negative
(b) clone positive

B2: high blood tumor burden: ≥1,000/μL Sézary cells with a positive T-cell clone

Describing the stage grouping of MF.

Show Answer

Stage IA: T1, N0, M0, B0–1
Stage IB: T2, N0, M0, B0–1
Stage IIA: T1–2, N1–2, M0, B0–1
Stage IIB: T3, N0–2. M0, B0–1
Stage IIIA: T4, N0–2, M0, B0
Stage IIIB: T4, N0–2, M0, B1
Stage IVA1: any T, N0–2, M0, B2
Stage IVA2: any T, N3, M0, any B
Stage IVB: any T, any N, M1, any B

If MF involves <10% of the body surface area, what T stage is this?

Show Answer

A **T1** MF lesion involves <10% of the body surface area.

How would erythroderma be staged for MF?

Show Answer

Erythroderma constitutes a **T4 lesion** for MF.

What constitutes stage I Dz in MF?

Show Answer

A pt with **T1 or T2, N0, M0, B0–1** would be stage I in MF.
What constitutes stage III Dz in MF?

Show Answer

A pt with **T4, N0–2, M0, B0–1** would be stage III in MF.

TREATMENT/PROGNOSIS

What are the Tx options for MF that are limited to the skin?

Show Answer

Tx options for MF limited to skin:

- Topical nitrogen mustard
- Topical carmustine (BCNU)
- Topical steroids
- Topical imiquimod (immunomodulator that acts on Toll-like receptor 7)
- PUVA (psoralen + UVA)
- UVB therapy
- Local or total skin electron beam therapy (TSEBT)

How is PUVA different from UVB therapy?

Show Answer

PUVA stands for psoralen + long-wave ultraviolet radiation (UVA). UVB is less penetrating and its use is limited to thin patches, whereas UVA is more penetrating and can effectively treat some plaques. UVA activates 8-methoxypsoralen, which results in DNA cross-linking and apoptosis.
How are PUVA and UVB administered?

Show Answer

PUVA and UVB are initially administered **q2–3days and then this time interval is gradually increased to q1mo once a CR is achieved.** Pts can be

continued on this therapy for several yrs.
What are the response rates of patch or plaque phase MF treated with PUVA or UVB?

Show Answer

Response rates are high (70%–90% CR rate), but long-term DFS remains poor.
What are systemic Tx options for MF?

Show Answer

Systemic Tx options for MF:

- IFN-alfa-2a
- Retinoids including bexarotene
- Extracorporeal photochemo (photophoresis)
- HDAC inhibitors (vorinostat, romidepsin)
- Cytotoxic chemo (Mtx, etoposide, chlorambucil)
- Targeted therapy (e.g., brentuximab in CD30+ Dz)

Describe photophoresis used in MF pts.

Show Answer

Photophoresis is **often used to treat pts with erythrodermic MF.** It involves the use of leukapheresis to collect a pt's WBCs, which are then treated with PUVA and transfused back to the pt.
What are prognostic factors for MF?

Show Answer

The Cutaneous Lymphoma International Prognostic Index includes male gender, age >60, plaques, folliculotropic Dz, and N1 stage for IA–IIA Dz and male gender, age >60, stages B1/B2, N2/3 and visceral involvement for IIB–IVB pts. (Benton et al., Eur J Cancer 2013)
What RT total dose and fractionation should be used in pts with MF?

Show Answer

Several studies have shown high CR rates (95%–100%) with doses **>30 Gy in 1.5–2 Gy/fx.** (Hoppe RT et al., IJROBP 1978; Cotter GW et al., IJROBP 1983) The initially used Rx for TSEBT was 36 Gy in 1.5–2 Gy/fx; however more recent data have shown that TSEBT of 12 Gy results in a 27% CR and 88% ORR. Re-Tx is easier when this lower dose is used (Hoppe RT et al., J Am Acad Derm 2015). For small localized fields or palliation, doses of 8–12 Gy with response assessment are recommended and may be escalated to 20–24 Gy if needed for LC. (Specht L et al., IJROBP 2015) In some pts with patch/plaque Dz, even lower doses, such as 4 Gy in 2 fx, induce excellent clinical responses.

Describe the Stanford TSEBT setup for MF.

Show Answer

For TSEBT, pts are treated in the standing position, 3.5 m **from the electron source** with a three-eighths-inch Lucite plate degrader in the beam path. Beams are angled upward and downward 18 degrees to improve homogeneity and decrease photon contamination. Pts are treated using 6 different pt positions (all standing) that result in AP, PA, RAO, LAO, RPO, and LPO fields. (Hoppe RT et al., Derm Thera 2003)

In the Stanford TSEBT technique, are all 6 fields treated daily?

Show Answer

No. In the Stanford TSEBT Tx, only 3 fields are treated per day. For each field, both upward and downward (18-degree) angles are treated. (Hoppe RT et al., Derm Thera 2003)

In the Stanford TSEBT technique for MF, what areas of skin may be underdosed and would require boosting? How are these areas boosted?

Show Answer

Areas that may be underdosed using the Stanford TSEBT technique:

- Top of scalp
- Perineum/inner thighs/groins
- Soles of feet
- Inframammary folds in women
- Under panniculus in obese pts
- Axillae
- Shoulders

Boost fields are with conventional electrons or low-voltage x-rays at conventional SSDs.
In TSEBT for MF, what areas may require shielding?

Show Answer

In TSEBT, shield the **eyes** with internal or external eye shields. Consider shielding the **scalp** (to avoid permanent alopecia) and **hands/feet** (to avoid intense acute reaction) for a portion of the Tx.
How effective is TSEBT for pts with T2 or T3 MF?

Show Answer

After TSEBT to a dose of at least 30 Gy, the ORR is 100%, with an ~60% CR rate (T2 Dz: 75%; T3 Dz: 47%). The duration of response with CR is 29 mos and 9 mos for T2 and T3 Dz, respectively. (Navi D et al., Arch Dermatol 2011)
Describe the EORTC criteria for TSEBT.

Show Answer

80% isodose should be ≥4-mm deep to the skin surface. The 20% IDL should be <20 mm from the skin surface. Total dose to BM should be <0.7 Gy.
Is there evidence to support early aggressive Tx with TSEBT and systemic chemo over less aggressive Tx with sequential topical Tx?

Show Answer

No. Kay et al. randomized 103 MF pts (all stages) to TSEBT + systemic chemo vs. sequential topical Tx. Although the aggressive arm had a sup CR rate, there was no difference in long-term DFS or OS. The authors concluded that early aggressive Tx is not warranted. (NEJM 1989)
What are the Tx options for MF pts that fail 1st-line topical therapies?

Show Answer

Pts that recur after 1st-line therapy for MF can be re-treated with topical therapies before switching to alternative therapies (RT, UV therapy, steroids, or systemic Tx), as many will have a continued response to the same Tx.
Estimate the 5-yr OS of MF pts with stage IA and stage IV Dz.

Show Answer

MF pts with stage IA Dz have a 5-yr OS that is no different from matched normal controls (97%). 5-yr OS for stage IV MF is 27%. (Kim YH et al., Arch Dermatol 2003)

FOLLOW-UP/TOXICITY

Describe the acute (during and within 6 mos of Tx) toxicities of TSEBT.

Show Answer

During TSEBT, MF pts commonly experience erythema/desquamation (76%), blisters (52%), hyperpigmentation (50%), skin pain (48%), and skin infections (32%). (Lloyd S et al., J Am Acad Dermatol 2013) They may also experience swelling/tenderness of the hands and feet, or irritation of the eyes/periocular skin. In the mos after TSEBT, pts may experience alopecia, loss of fingernails and/or toenails, and hypohidrosis (inability to sweat properly).
Describe the late toxicities of TSEBT.

Show Answer

Late toxicities of TSEBT include chronic dry skin, atrophy, telangiectasias,

and premature aging. Additionally, secondary squamous and basal cell carcinomas as well as melanomas have been described.

75

Transplant/Total Body Irradiation (TBI)

Updated by Jonathan E. Leeman

BACKGROUND

Define hematopoietic stem cell transplantation (HSCT).

Show Answer

HSCT is a **procedure to infuse hematopoietic cells** in order to restore normal hematopoiesis and/or to treat cancer.

What is the difference b/t allogeneic and autologous?

Show Answer

Allogeneic: stem cells from another person

Autologous: stem cells from the affected pt

What is a syngeneic transplant?

Show Answer

A syngeneic transplant uses an **identical twin as the donor.**

Name 3 sources of stem cells.

Show Answer

Umbilical cord blood, BM, and peripheral blood are 3 sources of stem cells.

What source of stem cells is most often used for transplant?

Show Answer

Most stem cells for transplant are obtained from **peripheral blood.**
What is a minitransplant?

Show Answer

A minitransplant, also known as nonmyeloablative or reduced-intensity transplant, **employs less toxic preparatory regimens and is used preferentially for elderly patients or patients with comorbidities.**
Name 4 malignancies routinely treated with autologous transplant.

Show Answer

Malignancies routinely treated with autologous transplant:

- Relapsed/refractory Hodgkin Dz
- Multiple myeloma
- Chemosensitive aggressive NHL
- Refractory testicular cancer

Which type of transplant is associated with a graft vs. tumor effect?

Show Answer

Allogeneic transplants have graft vs. tumor effect.
Why is there decreased mortality with an autologous transplant in comparison to an allogeneic transplant?

Show Answer

Graft-versus-host disease (GVHD) is a major cause of morbidity and mortality that is unique to allogeneic transplantation.
What limits the use of allogeneic transplant?

Show Answer

The use of allogeneic transplant is limited by **availability of donors.**
Allogeneic transplant is used most commonly in what type of malignancy?

Show Answer

Allogeneic transplant is most commonly used to treat **acute leukemias.**
What are the 2 main goals of myeloablative TBI as part of an allogeneic ablative HSCT?

Show Answer

A TBI dose of ~10–16 Gy is used with 2 goals:

1. **Cytotoxicity:** to eradicate residual cancer
2. **Immunosuppression:** to decrease the likelihood of host rejection of donor stem cells

What is the main goal of nonmyeloablative TBI as part of an allogeneic HSCT?

Show Answer

A TBI dose of ~2 Gy is used for immunosuppression to promote donor engraftment.

WORKUP/STAGING

What evaluations should be done prior to TBI?

Show Answer

TBI evaluation: complete H&P, PFTs, LFTs, serum Cr, and fertility counseling to include potential cryopreservation.

TREATMENT/PROGNOSIS

What randomized data support the use of fractionated rather than single-Tx TBI?

Show Answer

The majority of TBI schedules in use today are either fractionated or hyperfractionated. This practice is supported by a **French (Institut Gustave Roussy) study** of single vs. hyperfractionated TBI randomized 160 pts with

various hematologic malignancies to 10 Gy single dose or 14.85 Gy/11 fx. OS at 8 yrs was nonsignificantly higher in the hyperfractionated arm (45% vs. 38%) as well as CSS (77% vs. 63.5%). The rate of interstitial pneumonitis was similar b/t the 2 arms (14% and 19%); however, the rate of liver veno-occlusive Dz was significantly higher with a single fx (4% vs. 14%). (Girinsky T et al., JCO 2000)

What is the main site of recurrence after transplant for lymphoma?

Show Answer

Following transplant for lymphoma, **local tumor** recurrence is the main cause of failure.

Which chemotherapeutics are commonly used in conjunction with TBI as part of HSCT?

Show Answer

1. **Cyclophosphamide** (most commonly used)
2. **Etoposide**
3. **Ara-C**
4. **Fludarabine** (nonmyeloablative)
5. **Melphalan**
6. **Busulfan**

What pt positions are used for TBI?

Show Answer

TBI pt Tx positions include **supine, lat recumbent, or standing.**

Why are beam spoilers used for TBI?

Show Answer

Beam spoilers are used to **ensure adequate superficial dose in the skin;** a screen of tissue-equivalent material (often acryclic 1–2 cm thick) is positioned b/t the pt and the beam.

What variation in homogeneity is considered acceptable for TBI?

Show Answer

Homogeneity +/– **10%** is considered acceptable for TBI.
Why is the dose rate lowered in TBI?

Show Answer

An LDR is used in TBI to **decrease the incidence of interstitial pneumonitis,** normally <20 cGy/min.
What compensators are often used in TBI?

Show Answer

H&N compensators are often used in TBI to improve homogeneity, since the H&N are a narrow part of the body.
What organs are most frequently blocked in TBI?

Show Answer

The **lungs** and **kidneys** are most frequently blocked in TBI. An electron boost is may be used to compensate dose to the CW behind the blocks.
What areas may be boosted in TBI?

Show Answer

When using TBI for lymphomas, the **site of residual Dz** may be boosted to decrease the chance of LR. CNS and testes boosts may be employed in select leukemia cases.
Where is dose prescribed to in TBI?

Show Answer

Dose is usually prescribed to midplane at the area of widest separation (often the umbilicus).

FOLLOW-UP/TOXICITY

What is a major complication that is unique to allogeneic transplants?

Show Answer

A major complication of allogeneic transplants is **GVHD.**
What is acute GVHD?

Show Answer

Acute GVHD is an immune-mediated reaction of donor cells against host tissues. The tissues that are affected most commonly include the skin, liver, and GI tract.
What is chronic GVHD?

Show Answer

The chronic form of GVHD **occurs >3 mos after transplant** and can affect many organs such as the GI tract, skin, liver, lungs, and eyes.
Name the acute toxicities from TBI.

Show Answer

Most common acute toxicities from TBI:

. N/v
. Diarrhea
. Xerostomia
. Parotitis
. Mucositis
. Fatigue
. Alopecia

What is the most common acute side effect?

Show Answer

The most common acute side effect of TBI is **n/v.**
Name 9 chronic toxicities from TBI.

Show Answer

Chronic toxicities from TBI:

. Cataracts
. Change in cognitive function
. Endocrinopathies
. Interstitial pneumonitis/pulmonary fibrosis
. Hepatic dysfunction
. Renal dysfunction
. Growth retardation
. Infertility
. 2nd malignancies

What is a major dose-limiting toxicity of TBI?

Show Answer

A major dose-limiting toxicity of TBI is **pneumonitis.**

76

Osteosarcoma

Updated by Christopher Morrison

BACKGROUND

Describe the histologic defining feature of osteosarcoma.

Show Answer

Production of immature osteoid bone is the defining feature of osteosarcoma. Most are high-grade intramedullary tumors.

What is the difference b/t conventional osteosarcoma and juxtacortical osteosarcoma?

Show Answer

Conventional or "classic" osteosarcoma refers to the most common (75%) variant of osteosarcoma, typically presents within areas of rapidly proliferating intramedullary bone. **Juxtacortical osteosarcoma** is a less frequently seen osteosarcoma variant that arises adjacent to the outer surface of the cortical bone. (Calvert GT et al., Sarcoma 2012)

Describe juxtacortical osteosarcoma in terms of pathologic grade and prognosis.

Show Answer

Juxtacortical osteosarcoma is usually **low-grade (parosteal)** or **intermediate-grade (periosteal)** although high-grade surface osteosarcoma exists in lesser frequency. Parosteal osteosarcoma is **curable** with Sg alone.

Periosteal osteosarcoma has appx a 20% risk of mets and the role of chemo is controversial. (Grimer RJ et al., Eur J Cancer 2005)
What is the incidence of osteosarcoma in the United States population?

Show Answer

In people younger than 25, the age-adjusted incidence is 4.4 per million. In the elderly (age >60) the age-adjusted incidence is 4.2 per million. For adults b/t these 2 age groups (25–60) the age-adjusted incidence is only 1.7 per million.
Name the 2 most common types of malignant bone tumors in the pediatric population.

Show Answer

The 2 most common types of malignant bone tumors in the pediatric population are **osteosarcoma (55% of total) and EWS (36% of total).** Both cancers are relatively rare accounting for less than 1% of all cancers diagnosed in the United States. (SEER 2009)
Describe the distribution of osteosarcoma cases as a function of population age.

Show Answer

Osteosarcoma has a **bimodal distribution** as a function of age, with the majority of cases occurring during the teenage yrs with a 2nd period of increased incidence in the elderly (age >60 yrs). The osteosarcomas that develop later in life are often associated with other conditions (Paget Dz, fibrous dysplasia).
Osteosarcoma is associated with what other pediatric tumor?

Show Answer

Pts with **retinoblastoma** have an increased risk of osteosarcoma, both within and outside the irradiated tissue (i.e., the osteosarcoma can occur as a secondary malignancy within bone that rcvd RT or in distant long bone sites,

putatively d/t the germline mutation, which increases risk of both retinoblastoma and osteosarcoma).

What genetic syndromes are associated with osteosarcoma?

Show Answer

Osteosarcoma is associated with **Li-Fraumeni syndrome**, **retinoblastoma and RecQ helicase gene syndromes.** Inactivation of tumor suppression pathways is common in osteosarcoma.

Describe the sex and racial factors associated with osteosarcoma.

Show Answer

Osteosarcoma is more common in **boys**. Incidence is higher for ages 0–24 yrs in the Asian/Pacific Islander population and in the Black population for ages ≥25. (SEER 2009)

What are the most common risk factors associated with the development of osteosarcoma?

Show Answer

A high rate of bone production and turnover (as in puberty or Paget Dz) is associated with the development of osteosarcoma. **Osteosarcoma is also the most common secondary cancer in adults who rcvd RT or chemo for a childhood solid tumor.**

Osteosarcoma is most likely to develop in which bones and in what part of those bones?

Show Answer

Osteosarcoma arises most frequently in the **appendicular skeleton** (80% of cases), most commonly at the **metaphyseal** portions of the distal femur, proximal tibia, and humerus.

What are the 2 most common presenting Sx of osteosarcoma?

Show Answer

Pts with osteosarcoma typically present with **localized bone pain** (often associated with an injury) of several mos duration and a **ST mass.**
What % of osteosarcoma pts have localized Dz at Dx?

Show Answer

90% of pts with osteosarcoma have localized Dz at Dx.
What % of osteosarcoma pts with localized Dz will develop DMs without chemo?

Show Answer

90% of pts with localized Dz will develop mets without chemo. (Link M et al., Clin Pediatr Oncol 1991) Chemo is now a standard part of Tx for localized osteosarcoma.

WORKUP/STAGING

Define the lab and radiographic studies used in the workup and staging of osteosarcoma.

Show Answer

Osteosarcoma workup: basic labs (CBC, CMP) as well as alk phos, LDH, and ESR. After plain films of the affected bone are obtained; **MRI +/– CT of the primary site with contrast and chest CT are needed.** PET/CT or bone scan may be used for systemic staging.
Define 3 principles used in the Bx of a suspected bone tumor.

Show Answer

Principles used in the Bx of a suspected bone tumor:

. Bx should be performed at the same institution where the definitive resection will take place, preferably by the same surgeon who will undertake the definitive resection.
. Bx should be placed carefully to avoid contamination of other areas, as can happen with a hematoma formation.

. The Bx should not increase the extent of subsequent Sg.

What radiographic features distinguish osteosarcoma from EWS?

Show Answer

Osteosarcoma is usually sclerotic, involves the metaphysis, and has periosteal new bone formation **(sunburst pattern),** whereas **EWS** is usually lytic, located in the diaphysis, and displays an **onion skin** effect. (Lee B et al., Handbook of Radiation Oncology 2007)

What is the most common site of mets from osteosarcoma?

Show Answer

The **lung** is the most common site of osteosarcoma mets. Hence, cross-sectional chest imaging is an important part of osteosarcoma staging.

What are the AJCC 8th edition (2017) TNM stage categories for bone tumors? (Note: Lymphoma and multiple myeloma have separate staging systems.)

Show Answer

Appendicular Skeleton, Trunk, Skull, and Facial Bones

T1: ≤8 cm
T2: >8 cm
T3: Discontinuous tumors in primary bone site

Spine

T1: 1 or 2 adjacent vertebra
T2: 3 adjacent vertebra
T3: ≥4 vertebra, or nonadjacent vertebra
T4a: Extension into spinal canal
T4b: Gross vascular invasion or tumor thrombus in great vessels

Pelvis

T1a: ≤8 cm confined to 1 pelvic segment
T1b: >8 cm confined to 1 pelvic segment
T2a: ≤8 cm confined to 1 pelvic segment with extraosseous extension or 2 segments without extraosseous extension
T2b: >8 cm confined to 1 pelvic segment with extraosseous extension or 2 segments without extraosseous extension
T3a: ≤8 cm in 2 pelvic segments with extraosseous extension
T3b: >8 cm in 2 pelvic segments with extraosseous extension

T4a: SI joint/sacral neuroforamen
T4b: Encasement of external iliac vessels or tumor thrombus in major pelvic vessels
N1: Regional LN mets
M1a: Lung
M1b: Bone or other
What is the AJCC stage grouping for bone tumors?

Show Answer

Appendicular Skeleton, Trunk, Skull, and Facial Bones.

Stage IA: T1, N0, Grade 1–X
Stage IB: T2–3, N0, Grade 1–X
Stage IIA: T1, N0, Grade 2–3
Stage IIB: T2, N0, Grade 2–3
Stage III: T3, N0, Grade 2–3
Stage IVA: M1a
Stage IVB: N1 or M1b
No AJCC group staging for spine and pelvis.

TREATMENT/PROGNOSIS

What is the standard Tx paradigm for conventional or high-grade osteosarcoma?

Show Answer

Standard Tx paradigm for osteosarcoma is: **neoadj chemo → surgical resection → adj chemo.**
What data support the use of multiagent chemo in the management of osteosarcoma?

Show Answer

Multiple randomized studies have **established the role of adj and neoadj chemo** in osteosarcoma management. Link et al. was one of the 1st studies that compared multiagent chemo to no adj management in 36 pts who underwent definitive Sg. At 2 yrs, the RFS was 17% in the control group and 66% in the Tx group. (NEJM 1986) Further studies show that doublet chemo using doxorubicin and cisplatin are better tolerated with no difference in survival for localized, operable osteosarcoma. (Souhami RL et al., Lancet 1997)
What determines a "good" response to neoadj chemo and how does that response relate to overall prognosis?

Show Answer

>90% necrosis of the postop pathology specimen is considered a **"good" response. These pts have significantly higher event-free and OS rates.**
Is there data to support changing or intensifying the adj chemo regimen if the pt's tumor was not a "good" responder to neoadj chemo?

Show Answer

Despite the link b/t pathologic response to neoadj chemo and prognosis, numerous trials among cooperative groups, including the international multigroup EURAMOS-1 trial, did not provide convincing evidence that changing or intensifying postop chemo regimens improves outcomes.
Under what conditions might RT be used in the management of osteosarcoma?

Show Answer

(1) Pts with a close or positive surgical margin (SM) that cannot be improved surgically, (2) surgically inoperable lesions, (3) palliation of painful primary tumors in pts with metastatic Dz, (4) possible SBRT to nonoperable oligometastatic Dz in the lung.

What is the preferred dose of RT for management of an unresectable osteosarcoma or following an R2 resection (definitive paradigm)?

Show Answer

For unresectable Dz, a dose of at least 60–70 Gy is recommended. The preferred dose following an R2 resection is >**55 Gy with boost to 64–68 Gy to the area of highest risk.** In 1 retrospective review, pts receiving doses of >55 Gy had improved LC.

(DeLaney TF et al., IJROBP 2005)

What radioisotopes are currently being investigated for use in the management of osteosarcoma?

Show Answer

Samarium-153-EDTMP is a bone-seeking radioisotope taken up during osteoid formation that has been investigated and found to be safe in pts with poor prognosis that have been heavily treated already with chemo. Early trials of this approach have shown marginal benefit. Trials investigating the use of Radium-223 to treat metastatic osteosarcomas are also underway.

What is the 5-yr survival rate for nonmetastatic and metastatic osteosarcoma treated with chemo and Sg?

Show Answer

The 5-yr survival for localized osteosarcoma treated with chemo and Sg is **50%–70%** but for **metastatic osteosarcoma the survival is closer to 20%.**

77

Chondrosarcoma

Updated by Uma Goyal

BACKGROUND

What is the most common subtype of chondrosarcoma?

Show Answer

Conventional chondrosarcoma constitutes 85% of chondrosarcomas, 90% of which are low-intermediate grade. The WHO 2013 classification system has reclassified grade 1 conventional chondrosarcoma as an **atypical cartilaginous tumor/chondrosarcoma grade I (ACT /CS1).** Grades 2 and 3 conventional chondrosarcomas are classified as malignant due to metastatic potential.

What are some other subtypes of chondrosarcoma?

Show Answer

Dedifferentiated (10%), mesenchymal (<2%), and clear cell (<2%) are other chondrosarcoma subtypes, classified under the category of malignant by WHO. Dedifferentiated and mesenchymal are high grade. Clear cell is low grade.

How are conventional chondrosarcomas further subdivided?

Show Answer

Conventional chondrosarcomas are further classified by their location in bone. ~75% of all chondrosarcomas are **central chondrosarcomas,** based on

their location in the medullary cavity. The majority are thought to arise primarily (i.e., without a benign precursor lesion). **Peripheral chondrosarcomas,** by definition, arise by the malignant transformation of a pre-existing benign osteochondroma in the cartilage cap.
What is the typical grade of a conventional secondary chondrosarcoma?

Show Answer

Typically **high grade.** Conventional primary central chondrosarcoma can vary in grade from low to high.
Chondrosarcoma accounts for what % of primary bone tumors?

Show Answer

Chondrosarcoma accounts for **~30%** of primary bone tumors (behind osteosarcoma and multiple myeloma).
Which subtypes occur in older adults? Which subtypes present in younger pts?

Show Answer

Dedifferentiated, conventional primary central, and conventional secondary peripheral chondrosarcoma typically present in older pts. Clear cell and mesenchymal chondrosarcoma can present in any age, but peak incidence occurs in younger adults. Periosteal chondrosarcoma in adults in their 20s and 30s.
What 2 benign precursor lesions may give rise to conventional chondrosarcoma?

Show Answer

Osteochondroma, majority in the long bones, is a precursor lesion for conventional secondary peripheral chondrosarcoma. **Enchondromas develop in the medulla of the bone,** and are hypothesized to be a precursor lesion in up to 40% of conventional central chondrosarcoma, with the highest risk in pelvis.

What are the most common locations for conventional primary chondrosarcomas?

Show Answer

Most chondrosarcomas (~75%) arise in the **proximal femur, pelvis, or proximal humerus.**

Chondrosarcomas of the skull base typically arise from what structures?

Show Answer

Although chondrosarcomas of the skull base may arise from the clivus, most originate **laterally from the spheno-occipital junction** or less commonly from the sphenoethmoid complex.

What is the typical pattern of spread for chondrosarcoma of the skull base?

Show Answer

Chondrosarcomas of the skull base are **locally aggressive and may expand,** destroying bone and compressing adjacent tissues.

What other tumor may often be mistaken for chondrosarcoma at the skull base? How can they be distinguished histologically?

Show Answer

Chordoma (particularly the chondroid variant) may appear similar to chondrosarcoma. Chordoma typically show positivity for epithelial membrane antigen (EMA) and pan-cytokeratin (panCK); whereas chondrosarcoma is positive for **D2–40.**

What are the common presenting Sx associated with chondrosarcoma?

Show Answer

Conventional chondrosarcoma often presents with pain of insidious onset and progressive chronology and localized swelling.

WORKUP/STAGING

What are the 3 imaging tests commonly ordered for the workup of a possible chondrosarcoma?

Show Answer

Plain radiographs, MRI, and CT are commonly ordered for the workup of a possible chondrosarcoma. CT is best for examining tumor matrix mineralization, while MRI is best for assessing marrow and soft tissue involvement. In addition, CT C/A/P may be indicated to evaluate for metastatic Dz, particularly for high-grade histologies. If ≥40 y/o then rule out potential bone mets.

What is the characteristic plain film appearance of chondrosarcoma?

Show Answer

Although chondrosarcoma has a variable plain radiograph appearance, mineralization of chondroid matrix may produce a **punctate or ring-and-arc pattern of calcification.**

What 2 subspecialty referrals/workups should be performed prior to Tx of skull base chondrosarcoma?

Show Answer

Baseline neuro-ophthalmology and endocrinology workup is indicated for skull base chondrosarcoma.

What are the AJCC 8th edition (2017) TNM stage categories for bone tumors? (Note: Lymphoma and multiple myeloma have separate staging systems.)

Show Answer

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Stage IB: T2–3, N0, Grade 1–X
Stage IIA: T1, N0, Grade 2–3

Stage IIB: T2, N0, Grade 2–3
Stage III: T3, N0, Grade 2–3
Stage IVA: M1a
Stage IVB: N1 or M1b
No AJCC group staging for spine and pelvis.
What are the preferred techniques to confirm primary bone cancer?

Show Answer

Core needle or **open Bx** is recommended to confirm Dx. FNA is not suitable due to lower diagnostic accuracy.

TREATMENT/PROGNOSIS

What type of surgical resection is typically recommended for chondrosarcoma?

Show Answer

WLE is typically recommended for definitive surgical Tx of chondrosarcoma. For ACT/CS1 intracompartmental chondrosarcomas, **intralesional curettage** f/b **adj cryosurgery** can be used as an alternative to WLE with acceptable outcome for extremity tumors.
When is RT recommended for chondrosarcoma? What are the typical doses?

Show Answer

RT is typically recommended for unresectable base of skull tumors or postop therapy to >70 Gy. For extracranial sites, preop RT up to 50.4 Gy if + SMs likely f/b final total RT doses of 70 Gy (R1) or 72–78 Gy (R2). For postop high grade/dedifferentiated/mesenchymal subtypes with close or + SMs use 60–70 Gy.
What is the recommended definitive Tx for skull base chondrosarcoma?

Show Answer

Max surgical resection is recommended for skull base chondrosarcoma. Because complete resection is generally not feasible due to anatomic constraints, adj RT is frequently recommended due to residual Dz.
What adj RT doses are necessary for control of skull base chondrosarcoma?

Show Answer

Adj RT doses **>70 Gy** are needed for control of skull base chondrosarcoma. (NCCN 2018) **IMRT, stereotactic RT, or charged particle therapy** are modalities to consider in the effort to minimize dose to normal critical structures.
When treated with surgical resection and adj RT, what control rates can be expected for skull base chondrosarcoma?

Show Answer

When treated with surgical resection and adj RT (to doses >65 Gy), control rates **>95%** can be expected for skull base chondrosarcoma; these rates are sup to those of chordoma. (Rosenberg AE et al., Am J Surg Pathol 1999)
What role does systemic therapy play for chondrosarcoma?

Show Answer

Chemo is not recommended for ACT/CS1 nor for clear cell chondrosarcoma. Its role is undefined for higher-grade chondrosarcomas, although there have been some reports that have advocated a role for chemo for the **mesenchymal subtype.**
What is a reasonable f/u schedule for low- and high-grade chondrosarcoma?

Show Answer

For f/u for low grade, consider clinical exam, imaging of primary site and chest as clinically indicated q6–12 mos for 2 yrs, then yearly. For high grade f/u, H&P, imaging of primary site as clinically indicated, and chest q3–6 mos

for 5 yrs the yearly for min 10 yrs. Relapses beyond 5 yrs are more common for chondrosarcomas than for other sarcomas.

78

Chordoma

Updated by Srinivas Raman

BACKGROUND

What are chordomas?

Show Answer

Chordomas are **rare, slow-growing, locally aggressive neoplasms of bone** arising from embryonic remnants of the notochord.

What are the most common histologic subtypes seen for chordomas?

Show Answer

Most common histologic subtypes of chordoma:

- **Conventional:** most common, no cartilaginous or mesenchymal components
- **Chondroid:** 5%–15%, contains cartilaginous components but is distinct from chondrosarcoma
- **Dedifferentiated or sarcomatous transformation:** 2%–8%, aneuploid tumors interspersed in areas of conventional chordomas, worse survival

What features characterize conventional chordomas?

Show Answer

Macroscopically tumors are expansile, lobulated structures with a blue/slate-gray, gelatinous matrix that may exhibit solid areas.

Microscopically, characteristic highly vacuolated “physaliphorous cells” are present.

What histologic types of chordomas are most commonly found in the skull base?

Show Answer

Conventional is still the most common, although the **chondroid** type has a predilection for the cranial region (1/3rd of cranial chordomas are chondroid).

What are the immunohistochemical findings that can help distinguish chordomas from other histologically similar lesions?

Show Answer

S-100 immunoreactivity distinguishes chordoma from metastatic adenocarcinoma and meningioma, and **epithelial membrane antigen (EMA)** immunoreactivity distinguishes it from chondroma, chondrosarcoma, and melanoma.

Brachyurystaining can distinguish chordomas from other chondroid lesions with similar morphologic or immunophenotypic features. Brachyury is a transcription factor associated with notochord differentiation.

Where do chordomas most commonly arise?

Show Answer

Chordomas most commonly arise in 3 locations in the axial skeleton: **sacrum, skull base** and **mobile spine.** Historically sacrum thought to be most common site; however, more recent evidence from SEER database suggests **equal distribution b/t the 3 sites.**

What is the DDx of a tumor involving sacral bone?

Show Answer

Metastatic lesions and **multiple myeloma** make up the overwhelming majority of sacral and spinal neoplasms. **Chordomas** are the most frequently occurring primary malignant bone tumor in both the sacrum and the mobile

spine. Other primary sacral tumors include chondrosarcoma, EWS, osteosarcoma, PNET, Paget sarcoma, and benign tumors including giant cell tumor and hemangioma.
What is the rate of DM for chordoma, and what distant sites can be involved?

Show Answer

DM have been found in up to 5% of pts at the time of Dz and up to 30%–40% of pts can develop mets later. Sites of mets most commonly include lungs. Other sites: Soft tissues, bone, skin and brain.

WORKUP/STAGING

How do pts with chordomas present clinically?

Show Answer

Depends on the site of origin, but pain of a gradual and insidious onset is reported to be the most common presenting Sx regardless of location. Chordomas encroaching on the spinal canal may cause compression of the SC or nerve roots, resulting in neurologic Sx. Chordomas involving the cervical region may cause dysphagia, dysphonia, or Horner syndrome. Chordomas in the sacral region can create nerve root dysfunction as well as obstipation, constipation, and tenesmus. Pts with base of skull chordomas can present with intermittent diplopia, HA, neck pain, or other lower CN findings.
Is transrectal Bx a recommended method to obtain tissue Dx for chordoma?

Show Answer

No. Due to a propensity to seed along Bx tracts, transrectal Bx should be avoided so as to prevent spread of chordoma into the rectum. All Bx tracts should be marked and removed in the subsequent Sg.
What comprises oncologic staging for chordoma?

Show Answer

H&P, MRI/CT of primary site and MRI spinal axis, CT C/A/P, lab studies, and Bx. PET/CT or bone scan (if PET negative primary) may also be considered.

What are the T1-T2 MRI features of chordomas?

Show Answer

T1-T2 MRI features of chordomas:

T1: intermediate to low signal intensity, with heterogeneous enhancement with gadolinium

T2: high, heterogenous signal intensity

What are the AJCC 8th edition (2017) TNM stage categories for bone tumors? (Note: Lymphoma and multiple myeloma have separate staging systems.)

Show Answer

Appendicular Skeleton, Trunk, Skull, and Facial Bones

T1: ≤8 cm
T2: >8 cm
T3: Discontinuous tumors in primary bone site

Spine

T1: 1 or 2 adjacent vertebra
T2: 3 adjacent vertebra
T3: ≥4 vertebra, or nonadjacent vertebra
T4a: Extension into spinal canal
T4b: Gross vascular invasion or tumor thrombus in great vessels

Pelvis

T1a: ≤8 cm confined to 1 pelvic segment

T1b: >8 cm confined to 1 pelvic segment
T2a: ≤8 cm confined to 1 pelvic segment with extraosseous extension or 2 segments without extraosseous extension
T2b: >8 cm confined to 1 pelvic segment with extraosseous extension or 2 segments without extraosseous extension
T3a: ≤8 cm in 2 pelvic segments with extraosseous extension
T3b: >8 cm in 2 pelvic segments with extraosseous extension
T4a: SI joint/sacral neuroforamen
T4b: Encasement of external iliac vessels or tumor thrombus in major pelvic vessels
N1: Regional LN mets
M1a: Lung
M1b: Bone or other
What is the AJCC stage grouping for bone tumors?

Show Answer

Appendicular Skeleton, Trunk, Skull, and Facial Bones

Stage IA: T1, N0, Grade 1–X
Stage IB: T2–3, N0, Grade 1–X
Stage IIA: T1, N0, Grade 2–3
Stage IIB: T2, N0, Grade 2–3
Stage III: T3, N0, Grade 2–3
Stage IVA: M1a
Stage IVB: N1 or M1b
No AJCC group staging for spine and pelvis.

TREATMENT/PROGNOSIS

What is the mainstay of Tx for chordomas?

Show Answer

Sg is the mainstay of Tx of chordomas, with studies demonstrating a direct

correlation b/t the extent of surgical resection and the length of RFS. Definitive RT is an alternative and usually reserved for unresectable cases.
Why is intralesional excision for a vertebral body chordoma a suboptimal surgical Tx?

Show Answer

Intralesional excision has been shown to have a high rate of LR and to negatively affect OS. **En bloc spondylectomy** is preferred.
How are sacral amputations classified?

Show Answer

Based on the location of the highest level of nerve root sacrificed: low (sacrifice of at least 1 S4 nerve root or below), middle (sacrifice of at least 1 S3 nerve root), or high (at least 1 S2 nerve root). Total sacrectomy is performed when both S1 nerve roots are sacrificed.
What Tx is most commonly employed after surgical resection?

Show Answer

Most chordomas are not fully resectable and **postop RT** is often employed, even with a GTR.
Is aggressive management of chordomas at initial presentation (Sg + adj RT) important to improve outcomes compared to the same Tx at the time of recurrence (salvage RT)?

Show Answer

Yes. Adj RT may improve outcomes compared to a strategy of observation, reserving RT for salvage. A retrospective series from France (Carpentier A et al., J Neurosurg 2002) found that pts managed aggressively at initial presentation (Sg + RT) compared to those treated aggressively at the time of recurrence (after initial Sg) had improved outcomes (5- and 10-yr survival: 80% and 65% for aggressive vs. 50% and 0% for salvage).
Is there a role for neoadj RT?

Show Answer

A prospective phase II trial incorporating high-dose RT advocated for preop RT in addition to postop as it allowed for smaller volumes and reduced the risk of iatrogenic tumor seeding into the tumor bed. 1/23 primary chordomas recurred locally at a median f/u of 7.3 yrs. The findings favored a dose of ~77.4 Gy RBE for primary tumors, and ~70 Gy in the adj setting. (Delaney TF et al., J Surg Oncol 2014)

Is conventional fractionated photon RT an effective Tx for chordomas?

Show Answer

Yes. Conventional fractionated photon RT is effective for treating chordomas. Using image guidance, IMRT and median RT dose of 76 Gy in skull base chordomas, retrospective series from Toronto showed 5-yr LC rate of 65% and OS rate of 86% with acceptable toxicity rates. (Sahgal et al., Neuro Oncol 2015)

What is the role of SRS in the management of chordomas?

Show Answer

There is growing evidence supporting the role of SRS for chordoma. An MSKCC series that included unresectable pts reported a 95% LC rate at a median f/u of 24 mos with single fx SRS with a median dose of 24 Gy. (Yamada Y et al., Neurosurg 2013)

What other RT modalities can be utilized for skull base chordomas?

Show Answer

Proton beam, charged ion therapy and SRS have all been reported to control the tumor and improve cranial neuropathy.

What factor(s) determines the risk for recurrence after Tx with proton beam therapy?

Show Answer

In a series from Loma Linda, for residual tumors **with brainstem involvement** or **volume** >25 mL, the control rate was about 50% in the f/u period (mean, 33 mos); those not abutting the brainstem or <25 mL residual Dz did not have recurrence. (Hug EB et al., J Neurosurg 1999)
What is the pattern of recurrence of chordomas after Tx?

Show Answer

LR is most common (95%), with up to 40% of pts having both LR and DM. The most common sites of distant Dz are lung and bone. (Fagundes MA et al., IJROBP 1995; McPherson CM et al., J Neurosurg Spine 2006)
What is the typical LC and OS for chordomas compared to chondrosarcomas after 70 CGE of proton beam therapy?

Show Answer

In the Loma Linda series of 58 pts (33 chordomas and 25 chondrosarcomas), with a mean f/u of 33 mos, LC was 76% for chordoma and 92% for chondrosarcoma. The 5-yr OS rates were 79% for chordoma and 100% for chondrosarcoma. (Hug EB et al., J Neurosurg 1999)
What is the role of chemo or molecularly targeted agents in the management of chordomas?

Show Answer

Chordomas are generally not sensitive to chemo. However, PDGFR, EGFR, and mammalian target of rapamycin (mTOR) pathways have been implicated in the pathogenesis of chordomas. Small clinical series of targeted therapies have reported PRs and stable Dz in advanced pts (74% of pts experienced stable Dz with imatinib).
What is the survival of pts with recurrent Dz who rcvd salvage Tx compared to supportive care?

Show Answer

The outcomes after recurrence are **generally poor,** but salvage Tx (Sg + RT)

can be used after recurrence, with 2-yr survival of 63% vs. 21% with supportive care. However, most pts die even with therapy, with 5-yr survival only 6% after recurrence. (Fagundes MA et al., IJROBP 1995)

Salvage therapy with proton or carbon ions may offer more effective LC over standard photon therapy. (Delaney TF et al., J Surg Oncol 2014; Uhl et al., Strahlenther Onkol 2014)

FOLLOW-UP/TOXICITY

What are some common late toxicities that manifest after the Tx of skull base chordomas?

Show Answer

~26% of skull base chordoma pts develop endocrine abnormalities, while 5%–10% of pts develop vision loss, brainstem injury, or temporal lobe injury in 2–5 yrs. (Berson AM et al., IJROBP 1988; Santoni R et al., IJROBP 1998)

The risk for sacral neuropathy increases with doses ≥76.6 Gy. (Delaney TF et al., J Surg Oncol 2014)

79

General and Extremity Soft Tissue Sarcoma

Updated by Yanqun Dong and Thomas Churilla

BACKGROUND

What is the most common type of sarcoma?

Show Answer

The most common type of sarcoma is **soft tissue sarcoma** (STS), accounting for ~80% of sarcomas. The remainders arise from bone.

Where does STS originate?

Show Answer

STS originates from the **primitive mesenchyme of the mesoderm,** which gives rise to muscle, fat, fibrous tissues, blood vessels, and supporting cells of the peripheral nervous system.

How many different histologic subtypes of STS have been identified?

Show Answer

>50 histologic subtypes of STS have been identified.

What are the 6 most common types of STS?

Show Answer

The most common types (~75%) of diagnosed STS are:

- Undifferentiated pleomorphic sarcoma (previously called malignant fibrous histiocytoma)
- Liposarcoma
- Leiomyosarcoma
- Myxofibrosarcoma
- Synovial sarcoma
- Malignant peripheral nerve sheath tumor (MPNST)

Appx how many cases of STS are diagnosed annually in the United States? How many deaths occur?

Show Answer

~12,400 cases/yr of STS are diagnosed in the United States, with **~5,000 deaths/yr.**

What are the 3 most common sites of STS?

Show Answer

The 3 most common sites of STS are the **extremity** (60%), **retroperitoneal** (15%), and **trunk/H&N** (10% each).

What % of extremity STS involves the LE?

Show Answer

67% of extremity STS involve the LE.

What % of LE STS is at or above the knee?

Show Answer

75% of LE STS is at or above the knee.

What are the chromosomal translocations seen for (1) synovial sarcoma, (2) clear cell sarcoma, (3) EWS/PNET, and (4) alveolar RMS?

Show Answer

Chromosomal translocations:

- Synovial sarcoma: t(X, 18) SY18-SSX (SY18-SSX1, SY18-SSX2 or SY18-SSX4)
- Clear cell sarcoma: t(12, 22) EWSR1-ATF1
- EWS/PNET: t(11, 22) EWSR1-FLI1—most common chromosomal translocation
- Alveolar RMS: t(2, 13); t(1, 13) PAX-FOXO1 (PAX3-FOX01 or PAX7-FOX01)

Name 4 genetic syndromes associated with sarcoma and the type of sarcoma associated with each of these syndromes.

Show Answer

Genetic syndromes associated with sarcoma and their type:

- Gardner (a subtype of FAP) (desmoid tumors)
- Retinoblastoma (osteosarcoma and STS)
- NF-1 (neurofibromas, MPNSTs, GISTs, giant cell lesions, RMSs, and glomus tumors)
- Li-Fraumeni (osteosarcoma, RMS, and STS)

Are there any environmental risk factors associated with STS?

Show Answer

Environmental risk factors may include RT exposure (e.g., RT, radiocontrast agent Thorotrast), and chemicals (e.g., chlorophenols in pesticides/herbicides, vinyl chloride to produce PVC, dioxin). However, most STS are not known to be associated with specific environmental hazards.
What is the RR of secondary sarcoma in children who rcvd RT?

Show Answer

According to the Childhood Cancer Survivorship Study, RT is associated with an RR of 3.1 for developing a secondary sarcoma. (Henderson TO et al., JNCI 2007)

What is Stewart–Treves syndrome?

Show Answer

Stewart–Treves syndrome is an **angiosarcoma that arises from chronic lymphedema,** most often as a complication of Tx for breast cancer.
What role do viral infection and immunodeficiency play in sarcoma development?

Show Answer

Human herpes virus 8 plays a key role in the development of Kaposi sarcoma. And **EBV** has been associated with smooth muscle tumors in immunocompromised pts. (Deyrup AT et al., Am J Surg Pathol 2006)
What is the median age at Dx of STS?

Show Answer

The median age at Dx of STS is **45–55 yrs.**
What is the most common presentation of STS?

Show Answer

The most common presentation of STS is a **painless mass.**
What is the DDx of a painless mass of the extremity?

Show Answer

Painless mass of the extremity DDx: STS, primary or metastatic carcinoma, lymphoma, melanoma, desmoid tumor, and benign lesions (lipoma, lymphangioma, leiomyoma, neuroma, schwannoma, etc.)
What % of M0 STS have +LNs at Dx?

Show Answer

~2.6%–10.8% of STS have +LNs at Dx. (Brennan et al., Management of Soft Tissue Sarcoma 2013)
Which types of STS have an increased risk of LN mets?

Show Answer

STS types that have an increased risk of LN mets:

. **C**lear cell sarcoma
. **A**ngiosarcoma
. **R**MS
. **E**pithelioid sarcoma

(Mnemonic: **CARE**)
What is the most common site of DM from STS?

Show Answer

The most common site of DM from STS is to the **lung** (70%–80%). Retroperitoneal and intra-abdominal visceral sarcomas also tend to metastasize to the liver.
What factors are associated with an increased risk of LR in pts with STS?

Show Answer

Pt/tumor factors associated with an increased risk of LR in pts with STS:

. Grade
. Size
. Age
. Margin status
. Histology
. Site

Name 6 prognostic factors for survival in pts with STS.

Show Answer

Factors associated with an increased risk of decreased survival in pts with STS:

. Grade

- Size
- Deep location (superficial/deep to fascia)
- Site (extremity vs. trunk/RP) or (distal vs. proximal)
- LN involvement
- Age (young better than old)

(Baldini EH ASTRO Review 2015)
What dose of RT can be used for KS?

Show Answer

Doses of **15 Gy** for oral lesions, **20 Gy** for lesions involving eyelids, conjunctiva, and genitals, and **30 Gy** for cutaneous lesions have been shown to be sufficient to produce an objective response of 92%. (Kirova YM et al., Radiother Oncol 1998)

WORKUP/STAGING

What is an appropriate workup for a painless mass?

Show Answer

H&P including exam of the primary site and draining LN regions, CBC/BMP/LFTs, chest imaging, MRI +/– CT primary site, and core Bx or incisional Bx placed along planned resection axis.
What are the changes in TMN stage in AJCC 8th edition (2017) compared to 7th edition (2011)?

Show Answer

A greater emphasis is placed on the anatomic primary site of the STS, which has implications for LR and metastatic Dz. Superficial vs. deep location has been removed as part of T stage criteria.

Head and Neck

T1: ≤2 cm
T2: >2 and ≤4 cm

T3: >4 cm

T4a: Invasion into: orbit, skull base/dura, central compartment viscera, facial skeleton or pterygoid muscles

T4b: Invasion into: brain, prevertebral muscle, carotid artery encasement, or CNS spread

N1: Regional LN mets

M1: Mets

Trunk and Extremities

T1: ≤5 cm

T2: >5 and ≤10 cm

T3: >10 and ≤15 cm

T4: >15 cm

N1: Regional LN mets

M1: Mets

Abdomen and Thoracic Visceral Organs

T1: Organ confined

T2a: Invades serosa/visceral peritoneum

T2b: Beyond serosa

T3: Invades another organ

T4a: Multifocal (2 sites)

T4b: 3–5 sites

T4c: >5 sites

N1: LNs

M1: Mets

What are the AJCC 8th edition (2017) stage groupings with TNM and grade for STS?

Show Answer

Head and Neck

No AJCC group staging at this time

Trunk and Extremities

Stage IA: T1, N0, Grade 1, Grade X
Stage IB: T2–T4, N0, Grade 1, Grade X
Stage II: T1, N0, Grade 2–3
Stage IIIA: T2, N0, Grade 2–3
Stage IIIB: T3–T4, N0, Grade 2–3
Stage IV: N1 or M1

Abdomen and Thoracic Visceral Organs

No AJCC group staging at this time
The French Federation of Cancer Centers Sarcoma Group system, recognized by the AJCC Staging Manual, is determined by what 3 parameters?

Show Answer

Differentiation, mitotic activity, and extent of necrosis

Under what circumstances are PET, CT, or MRI potentially useful in the workup of STS?

Show Answer

FDG-PET: may be useful for staging, prognostication and grading as well as to determine response to chemo
CT abdomen/pelvis: myxoid/round cell liposarcoma, epithelial sarcoma, angiosarcoma, and leiomyosarcoma
MRI of total spine: myxoid/round cell liposarcoma
MRI brain: **alveolar soft part sarcoma** or **angiosarcoma**

TREATMENT/PROGNOSIS

What is the primary Tx modality for STS?

Show Answer

Sg is the primary Tx modality for STS.

What is the LR rate after Sg alone for STS?

Show Answer

LR after Sg alone **depends on the extent of resection.** Based on limited, historical data for all STS LR is 93% after simple excision, 73% after local excision → wide excision, 60% after wide excision, and 8% after amputation, where LR defined as failure to control the primary. (Gerner RE et al., Ann Surg 1975)

What prospective trial examined Sg alone in selected pts?

Show Answer

MDACC treated T1 (<5 cm), any grade STS with limb-sparing surgery (LSS) alone if R0 resection (74 pts). They found that LR at 10 yrs was 10.6% and that the **vast majority of recurrences occurred in high-grade tumors.** (Pisters PW et al., Ann Surg 2007)

What is the LR rate and DFS after primary RT alone for STS?

Show Answer

2-yr LR is 66% and **2-yr DFS is 17%** after primary RT alone for STS. (Lindberg RD et al., Proc Natl Cancer Conf 1972)

Sg alone is adequate for which pts with STS of the extremity?

Show Answer

According to the NCCN, pts with low-grade extremity STS **(stage I)** s/p surgical resection with **appropriate margins** do not require adj therapy. Consider RT for margin <1 cm or LR.

What are the management options for a pt with stage II or III resectable STS?

Show Answer

Stage II or III resectable STS management options:

- Sg → RT +/– chemo
- Preop RT +/– chemo → Sg → +/– adj chemo
- Preop chemo → Sg → adj RT +/– chemo

What is the evidence that a LSS approach of local excision with PORT yields equivalent outcomes compared to amputation alone in the management of high-grade extremity STS?

Show Answer

The **NCI trial** randomized 43 pts with high-grade extremity STS to amputation vs. LSS + RT. Randomization favored limb sparing (2:1). 4 of 27 pts in the RT group had +SMs. There was no difference in 5-yr DFS (78% amputation vs. 71% RT) or OS (88% vs. 83%). There were 4 LRs in the LSS group vs. none in the amputation group. (Rosenberg SA et al., Ann Surg 1982)

What studies support the use of adj RT following LSS in high- and low-grade STS?

Show Answer

There have been 2 RCTs that have evaluated the impact of adj RT after LSS in STS:

Yang et al. from the NCI, randomized pts with STS of the extremity treated with LSS to adj EBRT (63 Gy) vs. no RT. (JCO 1998) Pts with high-grade STS rcvd adj Adr/cyclophosphamide. For high-grade pts, 10-yr LC significantly favored RT (100% vs. 78%), but there was no difference in 10-yr DMFS or OS. For low-grade pts, LC favored the RT arm (96% vs. 67%), but there was also no difference in DMFS or OS.

Pisters et al. randomized (in the operating room) pts with high- and low-grade STS who had a complete resection to iridium-192 brachytherapy implant (42–45 Gy) over 4–6 days vs. no RT. (JCO 1996) For high-grade pts, 5-yr LC favored the RT arm (89% vs. 66%), but there was no LC benefit to RT

for low-grade pts. DSS was not significantly impacted by RT.

What RCT compared preop RT vs. PORT for extremity STS, and what did it show?

Show Answer

The **NCIC trial** randomized pts with extremity STS to preop RT (50 Gy/25 fx + 16–20 Gy boost for +SMs) vs. PORT (50 Gy/25 fx + 16–20 Gy boost). The initial field was a 5-cm proximal and distal margin, and boost was a 2-cm proximal and distal margin. The primary endpoint was major wound complications. The trial closed after accruing 190 pts b/c of **significantly greater acute wound complications with preop RT (35%)** vs. **PORT (17%),** with the highest rates of **complications in the ant thigh (45%)**. 6-wk function was better with PORT. (O'Sullivan B et al., Lancet 2002)

At median f/u of 6.9 yrs, there was no difference in LC (93% preop RT vs. 92% PORT), RFS (58% vs. 59%), or OS (73% vs. 67%). Predictors for outcome included surgical margin status for LC and size and grade for RFS and OS. (O'Sullivan B et al., Proc ASCO 2004) The decision regarding preop vs. postop therapy was driven by toxicity profiles.

At a longer f/u endpoint of 2 yrs, **PORT was associated with worse fibrosis and joint stiffness (grade 2 fibrosis was 32% vs. 48%,** p **= 0.07)**. (Davis AM et al., Radiother Oncol 2005)

What are the advantages and disadvantages of preop RT compared to PORT for the management of extremity STS?

Show Answer

Advantages of preop RT for Tx of extremity STS:

- Lower RT dose
- Smaller Tx volume
- Improved resectability
- Margin-negative resections

- Better oxygenation of tumor cells
- Fewer long-term toxicities

Disadvantages of preop RT for Tx of extremity STS:

- Increased acute wound complications

What is the benefit of adding adj chemo for high-grade extremity STS after Sg?

Show Answer

The updated sarcoma meta-analysis collaboration (SMAC) included 1,953 pts with STS s/p WLE +/– adj doxorubicin-based chemo. **Chemo improved LC (OR 0.73), DMFS (OR 0.67), and OS (HR 0.77).** Doxorubicin + ifosfamide better than doxorubicin alone (11% vs. 5% absolute OS improvement). (Pervaiz N et al., Cancer 2008)

Should adj chemo be used in all high-grade STS pts?

Show Answer

This is **controversial.** Adj chemo is toxic and its survival benefits are marginal in most STS, therefore, it should not be adopted as standard practice, regardless of histology or tumor size. It may be considered for pts with large, high-grade tumors; +SMs or gross residual Dz, synovial sarcoma, or myxoid liposarcoma (chemosensitive histologies in metastatic setting). However, a pooled analysis of the 2 EORTC-STBSG adj chemo trials in high-grade STS (both negative trials; only 1 trial included in SMAC meta-analysis) failed to identify tumor size or histologic subgroups that benefit from adj chemo. Poor quality of initial Sg was the most important prognostic factor for utility of chemo. (Le Cesne et al., Ann Oncol 2014)

Which pts with extremity STS should be treated with neoadj therapy?

Show Answer

Neoadj RT, chemo, or CRT are reasonable options for all pts with **stage II or**

III extremity STS, though Sg → adj therapy is also an option for these pts. Neoadj therapy is the preferred option in pts with stage II or III extremity STS when Dz is only potentially resectable or the risk of adverse functional outcomes is high (e.g., in pts who require extensive resection such as disarticulation, amputation, or hemipelvectomy).
Cite 2 studies that demonstrate the efficacy of aggressive neoadj sequential CRT for large extremity STS.

Show Answer

The **Harvard retrospective study (**DeLaney TF et al., IJROBP 2003) **and RTOG 9514 (**Kraybill WG et al., Cancer 2010) are 2 studies that demonstrate the efficacy of neoadj sequential chemo-RT-chemo-RT-chemo for large extremity STS.
What were the results of RTOG 9514 study of neoadj sequential chemoRT for STS?

Show Answer

RTOG 9514 was a phase II trial enrolling 64 pts with ≥8 cm grade 2–3 STS of the extremity or torso with expected R0 resection. 44% had malignant fibrous histiocytoma, 13% leiomyosarcoma, and 88% STS of the extremity. Pts were treated with mesna, doxorubicin (Adriamycin), ifosfamide, and dacarbazine chemotherapy (MAID) → RT (22 Gy in 11 fx) → MAID → RT (22 Gy in 11 fx) → MAID → Sg → MAID × 3 → a 16 Gy postop boost for +SMs. 91% were R0 resections, and 59% rcvd the full chemo course. 3-yr LRF was 18% (if amputation was considered a failure and 10% if not). **5-yr LRF was 22%, distant mets 28%, DFS was 56%, distant DFS was 64%, OS was 71%,** and there was a 91% amputation-free rate. There were **5% Tx-related deaths** (mostly secondary acute myelogenous leukemia [AML]), and 83% of pts had grade 4 toxicity (mostly hematologic). The authors concluded that the regimen is effective, but substantial toxicity makes this approach controversial. (Kraybill WG et al., Cancer 2010) RTOG 9514 used a more

intense version of MAID than was used in the Harvard study, which probably worsened toxicity.

What is the optimal regimen for neoadj CRT?

Show Answer

There is no consensus as to the optimal approach to CRT. Some centers use concomitant CRT with single-agent doxorubicin, while others prefer sequential RT and an anthracycline plus ifosfamide-based chemo regimen, or RT combined with alternative chemo agents (such as gemcitabine). There are no randomized trials to define the most effective option, and Tx strategies vary widely b/t different countries and centers.

What were the results of the MSKCC retrospective review comparing IMRT vs. conventional EBRT for extremity STS?

Show Answer

MSKCC reported a retrospective series of 319 consecutive pts with extremity STS treated with LSS and adj RT (IMRT = 51.7%, conventional EBRT = 48.3%). Tumor location, size, depth, and histology were similar. IMRT pts had higher proportions of close/+SMs, high grade histology, age >50, preop RT use, nerve manipulation, and recent Tx yrs. The 5-yr rate of LR was improved among IMRT (7.6%) vs. conventional EBRT (15.1%), ($p = 0.05$), which persisted in multivariable analysis (HR = 0.46). **IMRT was associated with less acute grade 2+ dermatitis (31.5% vs. 48.7%) and late grade 2+ edema (7.9% vs. 14.9%)**. (Folkert MR et al., JCO 2014)

How long after Sg should adj RT for STS begin?

Show Answer

PORT for STS preferably begins **after healing is completed, by 3–8 wks post Sg.**

What dose is recommended for adj RT for STS?

Show Answer

A commonly used Rx for adj RT for STS is 50 Gy in 2 Gy/fx → a 10–16 Gy boost for –SMs, a 16–20 Gy boost for microscopically +SMs, and a 20–26 Gy boost for grossly +SMs.
Sg should take place appx how long after completion of neoadj RT for STS?

Show Answer

Sg preferably takes place **3–6 wks after completion of neoadj RT** in order to decrease the risk of wound complications.
What dose is recommended for neoadj RT for extremity STS?

Show Answer

A commonly used Rx for neoadj RT for extremity STS is **50 Gy in 2 Gy/fx.** If postop SMs are close/+, consider a boost using IORT (single 10–15 Gy), brachytherapy (12–20 Gy), or EBRT (10–14 Gy for close SMs, 16–18 Gy for microscopically +SMs, and 20–26 Gy for grossly +SMs). However, the value of adding a post-operative boost is questionable (Yami A et al., IJROBP 2010).
What are the RT Tx volumes for STS in the preop setting?

Show Answer

Historically, initial CTV = GTV + 5 cm longitudinally and 2 cm radially. PTV = CTV + 1 cm. However, reduced volumes with image guidance were explored in RTOG 0630:

GTV = MRI T1 + contrast images.
CTV = G2–3, tumor ≥8 cm: GTV + 3-cm margin longitudinally and 1.5-cm margin radially + suspicious edema on MRI T2. G1 tumor or G2–G3 tumor <8 cm: GTV + 2-cm margin and 1-cm margin radially + suspicious edema. CTV is limited at bone and by the compartment in which tumor arises.
PTV = CTV + 0.5 cm.

What were the results of RTOG 0630 regarding reduced preop Tx volumes in STS?

Show Answer

RTOG 0630 (Wang D et al., JCO 2015) was a single arm phase II study (n = 79) evaluating reduced volumes for preop RT with IGRT. Compared to the NCIC SR2 trial, the **late grade 2+ toxicity rate at 2 yr was significantly improved (10.5% vs. 37%)**. LC was 94% with all recurrences in field. **Toxicities included fibrosis (5.3%), edema (5.3%) and joint stiffness (3.5%).**

What are the initial and boost RT Tx volumes for STS in the postop setting?

Show Answer

Postop RT is delivered in two phases: initial volume includes surgical bed + margin f/b a boost volume to include the tumor bed + margin. (Haas et al., IJROBP 2012)

Initial CTV = Postop bed + 4 cm longitudinally and 1.5 cm radially.

Boost CTV = Resection GTV (tumor bed) + 2 cm longitudinally and 1.5 cm radially.

Resection GTV = reconstruction of primary tumor GTV using preop MRI and/or CT registered to postop CT simulation.

PTV = CTV + 0.5–1 cm

What are important dose constraints in the extremity?

Show Answer

For 3D-CRT spare 1–2 cm strip of skin. Per RTOG 0630, no more than 50% of a longitudinal strip of skin/tissue should rcv >20 Gy and <50% of a weight-bearing bone should rcv 50 Gy. Lower risk of RT-induced bone fx with V40 < 64%, mean bone dose < 37 Gy, and max bone dose < 59 Gy. (Dickie CI et al., IJROBP 2009)

Pathologic fx were associated with 50 Gy to the entire bone circumference, bone exposure, periosteal stripping, and periop chemo. 10-yr fx rate = 2% when the 50 Gy IDL encompassed the entire bone circumference without other risk factors, but was 37% when all 4 Tx-related factors were present. (Bishop AJ et al., PRO 2016)

How is postop brachytherapy performed for the Tx of high-grade STS of the extremity?

Show Answer

Catheters are placed in the operating room after tumor resection, 1 cm apart, with a 2 cm longitudinal and 1–1.5 cm circumferential margin on the tumor bed. Tx begins on or after the 6th postop day to allow for wound healing.

How should pts with unresectable STS be managed?

Show Answer

Consider preop RT, chemo, or CRT. If still deemed unresectable, consider definitive RT, chemo, palliative Sg, observation, or the best supportive care.

What dose of RT is recommended for unresectable STS?

Show Answer

If possible, the dose should be ≥**70–80 Gy** using sophisticated Tx planning (IMRT or proton beam).

FOLLOW-UP/TOXICITY

What are the short- and long-term toxicities associated with RT for STS of the extremity?

Show Answer

Short-term toxicities increased (usually reversible) with preop RT whereas late-term toxicities (usually irreversible) increased with postop RT.

Toxicities associated with RT for extremity STS:

Short-term: wound complications, dermatitis, recall reactions with

doxorubicin and dactinomycin, epilation

Long-term: abnl bone and ST growth and development, leg length discrepancy, risk of fx, fibrosis, lymphedema, skin discoloration, telangiectasias, 2nd malignancy

What is the recommended f/u after Tx of STS?

Show Answer

Consider evaluation by occupational/PT for functional restoration, H&P and chest imaging (CXR or CT chest) q3–6 mos × 2–3 yrs, then q6mos for the next 2 yrs, then annually. Consider baseline and periodic imaging of the primary site (MRI, CT, or US) to assess LR.

80

Hemangiopericytoma and Solitary Fibrous Tumors

Updated by Nicholas G. Zaorsky

BACKGROUND

How are hemangiopericytomas (HPCs) classified vs. solitary fibrous tumors (SFTs)?

Show Answer

The revised 2013 (4th edition) WHO classification schemata now groups these tumors together as SFTs. Current neuropathologic practice, however, still distinguishes b/t HPC and SFT.

Are SFTs benign or malignant lesions?

Show Answer

Although most cases are benign, SFTs may display metastatic potential in 20% of cases. In general, meningeal HPCs behave more aggressively than SFTs of other sites.

What is the cell of origin of SFTs?

Show Answer

HPCs were originally thought to be a vascular neoplasm originating from **pericytes** of the smooth muscle cells of vessels. Currently SFTs are recognized as a form of fibroblastic/myofibroblastic tumors.

What fusion protein is noted in HPCs/SFTs?

Show Answer

NAB2–STAT6 fusion protein, arising from recurrent intrachromosomal rearrangements on chromosome 12q. (Schweizer, Acta Neuropathol 2013)
What is the rate of LR for resected CNS HPC?

Show Answer

Very high, the recurrence rate is as high as 92% at 15 yrs in modern series. (Schiariti et al., Journal of Neurosurgery 2011)
What does the prognosis of SFTs primarily depend on?

Show Answer

The prognosis depends primarily on **tumor location and ability to achieve GTR;** for example, for CNS tumors, supratentorial tumors have a better prognosis than PF and base of skull tumors.

WORKUP/STAGING

What are the typical presenting Sx of a pt with SFT or HPC?

Show Answer

In the CNS, HA or neurologic Sx are typical in pts with HPC. At other sites pts with SFTs present with a firm, painless, localized mass.
How do intracranial/HPCs appear on imaging (CT, MRI)? What do they have in common with meningiomas?

Show Answer

On CT HPCs are typically solid, discrete, extra-axial masses. They hyperattenuate with marked heterogeneous enhancement after contrast. On T1 MRI the lesions are isointense and heterogeneous with areas of both low- and high-signal intensity and prominent vascular flow voids. The hypervascularity shows marked heterogeneous enhancement after

gadolinium. **Tumors show thickening of the adjacent meninges (dural tail) or tentorium. Erosion of the adjacent skull may also occur.** (Keraliya et al., Radiol Clin N Am 2016)

TREATMENT/PROGNOSIS

What is the Tx paradigm for managing SFT/HPCs?

Show Answer

Complete surgical resection is the mainstay of therapy + **adj or neoadj RT, chemo, or CRT.** Unresectable cases can be treated with either RT alone or CRT.

Is there a role for systemic therapy in the management of SFT/HPCs?

Show Answer

Yes. Sunitinib is the effective therapy in pts with advanced SFT/HPC. (George S et al., JCO 2009; Stacchiotti S, Ann Oncol 2012) **Sorafenib** therapy is another multitargeted TKI that has some activity in SFT. (Valentin et al., Invest New Drugs 2013) Bevacizumab and TMZ were shown to have evidence of activity. (Park et al., Cancer 2011)

What is the typical PORT dose used for treating SFT/HPCs after GTR?

Show Answer

The typical PORT dose is **50–60 Gy** to the surgical bed with the margin varying by site; some studies (Ghia AJ et al., Neurosurgery 2013) suggest better LC with doses >60 Gy (HR 0.12, p = 0.045). SRS (12–20 Gy) may also be used.

What is the 5-yr OS for HPC of the meninges?

Show Answer

5-yr OS is 83%. (Sonabend AM et al., J Neurosurg 2014)

What should be strongly considered adj for completely resected HPC?

Show Answer

RT. In a recent SEER analysis of 227 pts (Sonabend AM et al., J Neurosurg 2013), **GTR plus adj RT was associated with improved OS.**

FOLLOW-UP/TOXICITY

What is the metastatic propensity of HPCs?

Show Answer

High metastatic propensity despite aggressive initial Tx; as high as 68% at 15 yrs in some studies. (Vuorinen VSP et al., Acta Neurochir 1996)
Therefore, these pts require long-term f/u care.

81

Desmoid Tumors

Updated by Ramiz Abu-Hijlih

BACKGROUND

What are desmoid tumors (DT)?

Show Answer

DTs are rare, **benign, slow-growing fibroblastic neoplasms** that arise from musculoaponeurotic stromal elements, and tend to recur locally.

What is another commonly used name for DT?

Show Answer

DT is also known as **aggressive fibromatosis; musculoaponeurotic fibromatosis; or desmoid-like fibromatosis** (previously called fibrosarcoma grade I of desmoids type).

DT appears histologically similar to what tumors?

Show Answer

DT appears histologically similar to **well-differentiated fibrosarcoma.**

Any histopathologic features to differentiate DT from these tumors?

Show Answer

Most neoplasms resembling DT have specific histologic diagnostic features and lack nuclear β-catenin immunoreactivity. 70%–75% of **DTs express nuclear a-catenin**. (WHO 4th edition, 2013)

What is the approximate incidence of DT?

Show Answer

2.4–4.3 cases/million population; this risk increases **1,000-fold** in pts with **FAP.**

What genetic abnormality is associated with DT?

Show Answer

5%–15% of DTs are associated with **mutations to the** APC **gene,** resulting in FAP.

What is the clinical syndrome associated with DT?

Show Answer

Gardner syndrome is associated with DT, and 10%–20% of pts with this syndrome will develop DT.

Sebaceous cysts,
Osteomas, and
Desmoid tumors.

(Mnemonic: Gardner **SOD**)

What genetic mutation presents in DT sporadic cases?

Show Answer

Activating **Wnt/a-catenin (**CTNNB1**) pathway,** identified in appx 85% of cases of sporadic DT.

Is there a sex or age predilection for DT?

Show Answer

Yes, DTs typically present in **women** during **childbearing yrs**. There is no racial or ethnic predilection.

What 2 environmental conditions are associated with DT?

Show Answer

DTs have been associated with high estrogen states (such as pregnancy) and trauma per retrospective and anecdotal reports.
What is the typical presentation of an extremity DT?

Show Answer

Most DTs of the extremity present as a **deep-seated, painless mass** with a Hx of slow growth.
What % of DTs are intra-abdominal, and with what clinical syndrome are intra-abdominal DTs associated?

Show Answer

10%–30% of DTs are intra-abdominal, and they are associated with Gardner syndrome. Intra-abdominal DTs are often a source of significant morbidity and mortality.
What is the typical presentation of an intra-abdominal DT?

Show Answer

An intra-abdominal DT can present with bowel ischemia, obstruction, or complications with ileoanal anastomosis after colectomy for FAP.
What is the natural Hx of untreated DTs?

Show Answer

DTs can regress spontaneously or remain stable, however, **~50%** will continue to grow slowly and invade into surrounding structures.
Do DTs have metastatic potential?

Show Answer

No. DTs do not have metastatic potential but are locally aggressive with a predilection for LR.

WORKUP/STAGING

After a careful H&P, what imaging should be done to evaluate for a DT?

Show Answer

An **MRI of the extremity** is recommended to evaluate the extent of an extremity DT. A **CT** or **MRI of the abdomen** may be helpful to evaluate an intra-abdominal or abdominal wall mass.

How do DTs display on MRI imaging?

Show Answer

On T1, DTs are near homogeneous and isointense to muscle; on T2 they are more heterogeneous. After initial growth, spontaneous evolution of desmoids is characterized by shrinking and an increase in low-signal areas on T2.

What is the metastatic workup for DTs?

Show Answer

DTs are benign and do not have metastatic potential. Consequently, **no systemic imaging** is needed outside of the primary tumor.

Can DT be distinguished from malignant ST tumors on the basis of imaging?

Show Answer

No. DT cannot be distinguished from malignant ST tumors on the basis of imaging.

Define the staging system for DT.

Show Answer

DTs are NOT included in AJCC 8th edition. There is no defined staging system for DT. **Important features to guide the management include location, size, and the ability to resect with a wide margin.**

What type of Bx should be done to evaluate a mass suspected of being a DT?

Show Answer

A **core needle or open incisional Bx** is the preferred method for any tumor that may be a malignant STS.

TREATMENT/PROGNOSIS

What is considered the primary modality for Tx of DT?

Show Answer

Surgical resection used to be the gold standard. However, based on recent data describing a **high rate of PFS (50%)** and **spontaneous regression (28%)** a "**watch and wait**" policy is a reasonable option.

What are the indications for Sg in pts with DT?

Show Answer

Features to identify pts at low risk of progression, whom would most benefit from a "watch and wait" policy, have not yet been established. Sg is still a valuable option when the expected morbidity is low (**function-preserving Sg)** with **wide (2 cm) –SMs.**

For what type of pts is nonoperative initial management of DT always entertained?

Show Answer

For pts with DTs that are large, slow-growing, involve the mesentery; encase vessels or joints or when anesthesia or Sg carries morbidity.

What is the recurrence rate after margin– Sg vs. margin+ Sg for primary DT?

Show Answer

In primary DT Tx with Sg, **LR is 15% for –margin resection,** and **LR is 33% for +margin resection.** (Janssen et al., BJS 2017)

What is the recurrence rate after Sg (with +ve/indeterminate margin) for primary DT with or without adj RT?

Show Answer

In DT Tx with Sg (+ve/indeterminate margin), **LR is 23% after RT,** and **LR is 40% without RT.** (Janssen et al., BJS 2017)
What factors should be considered when determining whether or not to offer adj RT for DT?

Show Answer

Factors to be considered when considering adj RT for DT:

- **Margin status.** Margin– pts are unlikely to benefit.
- **Location.** Adj RT for resected **retroperitoneal/intra-abdominal DTs** is associated with significant Tx risks.
- **Salvage options.** Lesions that may undergo repeat resections may be appropriately observed.
- **Pt age.** There should be a high threshold for using adj RT in children.

What is the response rate (complete or partial) for inoperable DT treated with RT alone?

Show Answer

For inoperable DT treated with RT alone **50%** showed complete or partial response. (EORTC 62991-22998, Ann Oncol 2013)
What dose of RT is needed to control DT with RT alone?

Show Answer

A dose **>50 Gy** is needed to treat DT with RT alone. The recommended dose for gross Dz is **56 Gy.**
What dose of RT is recommended after an R1 resection of DT in a pt who cannot be salvaged with repeat resection?

Show Answer

A pt treated with adj RT after an R1 resection should be treated to a dose of **50 Gy in 1.8–2 Gy/fx.**
Define the CTV for RT in the management of DT.

Show Answer

The CTV to include when treating DT with RT includes the tumor bed (and/or gross tumor), a portion of the muscle compartment to cover fascial planes, or neurovascular structures along which tumor may track with a 3–5 cm CTV margin longitudinally and 2 cm in all other directions **respecting bony, facial and compartmental boundaries.**

What are potential medical approaches to treat DT?

Show Answer

ER modulators (tamoxifen), NSAIDs, low-dose cytotoxic chemo (Mtx, vinblastine or doxorubicin based), interferon, TKI.

What are recent projections for the trajectory of systemic medical Tx in DT?

Show Answer

Lev et al. from MDACC, showed a significant increase in systemic medical Tx in recent yrs with decreased reliance on Sg alone and suggested neoadj Tx may be associated with improved outcomes.

De Camargo et al. (Cancer 2010) observed greatest radiological response with antiestrogens and anthracycline regimens than other agents.

FOLLOW-UP/TOXICITY

What are the potential late complications associated with RT Tx to the extremity?

Show Answer

Late complications associated with RT to the extremities:

- Fibrosis
- Edema
- Fracture
- 2nd malignancy

- Joint stiffness
- Neuropathy

How did IMRT affect RT complications?

Show Answer

IMRT and IGRT resulted in decrease of RT side effects. Reports on extremity sarcoma treated with IMRT from **MSKCC** and **PMH** showed **edema** 7.9%, 11.1% and **stiffness** 14.5%, 5.6% respectively.

82

Retroperitoneal

Updated by Talha Shaikh

BACKGROUND

What % of STS are retroperitoneal?

Show Answer

10%–15% of STS are retroperitoneal.

What are the most common histologies of retroperitoneal sarcoma (RPS) in adults and children?

Show Answer

The 2 most common histologies for RPS in adults include **liposarcoma** and **leiomyosarcoma.**

The most common histology of RPS in children is **rhabdomyosarcoma.**

What % are malignant?

Show Answer

80% of retroperitoneal tumors are malignant.

Describe the demographics of RPS.

Show Answer

There are a wide range of ages at presentation, but **most pts are in their 50s with about equal numbers of men and women.**

What are the boundaries of the retroperitoneal space?

Show Answer

Boundaries of the retroperitoneal space:
Superior: diaphragm
Inferior: pelvic diaphragm
Lateral: lat edge of quadratus lumborum, but lat edge of 12th rib is also considered b/c it corresponds to origin of transversus abdominis aponeurosis
Anterior: parietal peritoneum where it anchors to colon and small bowel
Posterior: muscular wall composed of psoas and quadratus lumborum in abdomen; iliacus, obturator internus, and pyriformis in pelvis
Which organs are retroperitoneal?

Show Answer

Suprarenal (adrenal) glands, **A**orta/IVC, **D**uodenum (2nd and 3rd parts), **P**ancreas, **U**reters, **C**olon (ascending and descending), **K**idneys, **E**sophagus, **R**ectum (Mnemonic: **SADPUCKER**)
What is the typical presentation of pts with an RPS?

Show Answer

Pts typically present with vague abdominal complaints or are incidental findings.
What is the DDx of a retroperitoneal ST mass?

Show Answer

The DDx of a retroperitoneal mass includes **either malignant or benign tumors.**

Malignant etiology includes:

- Sarcoma
- Gastrointestinal stromal tumor
- Lymphoma

- Germ cell tumor
- Metastatic testicular cancer
- Malignant peripheral nerve sheath tumor
- Paraganglioma

Benign etiology includes:

- Desmoid tumor
- Lipoma
- Peripheral nerve sheath tumor
- Teratoma
- Paraganglioma
- Castleman Dz
- Retroperitoneal fibrosis

What is the median diameter of RPS at presentation?

Show Answer

The median diameter of retroperitoneal STS is **15 cm.**

WORKUP/STAGING

How is RPS staged according to AJCC (8th edition, 2017) staging?

Show Answer

T1: ≤5 cm
T2: >5 cm and ≤10 cm
T3: >10 cm and ≤15 cm
T4: >15 cm
N1: Regional LN mets
M1: DMs
Stage IA: T1, N0, Grade 1-X
Stage IB: T2–4, N0, Grade 1-X
Stage II: T1, N0, Grade 2–3

Stage IIIA: T2, N0, Grade 2–3
Stage IIIB: T3–4, N0, Grade 2–3 or any T, N1
Stage IV: M1
Do all pts with suspected RPS require a preop Bx?

Show Answer

No. Preop Bx is not required if the suspicion for RPS is high. However, CT-guided core Bx should first be performed in pts undergoing neoadj therapy.
What imaging studies should be performed to stage RPS?

Show Answer

Recommended staging studies for RPS include **CT C/A/P with contrast and optional MRI.**

TREATMENT/PROGNOSIS

What is the primary Tx modality for sarcoma RPS?

Show Answer

Sg (en bloc resection of the tumor and involved organs with the goal of attaining –SMs)
What is the most important Tx factor which predicts survival for RPS?

Show Answer

Postop SM status is the most important factor in predicting survival. MSKCC analysis of >500 pts showed MS = 103 mos if GTR vs. only 18 mos for less than GTR. (Lewis JJ et al., Ann Surg 1998)
What are the Tx paradigms for RPS?

Show Answer

Note: Postop EBRT is discouraged relative to preop. Consideration of IORT boost for + SMs may be given.

. Sg (+/– IORT)

. Neoadj RT and/or chemo → Sg (+/– IORT)
. Sg (+/– IORT) → adj RT and/or chemo

What is the role of CRT in pts with RPS?

Show Answer

There is **controversy.** A phase I study (Pisters et al., JCO 2003) evaluated concurrent preop doxorubicin and escalating RT. Preop 50.4 Gy w/doxorubicin was found feasible. 4 pts required hospitalization and 18% had grade 3–4 nausea. A recent phase I–II study (Gronchi et al., Eur J Cancer 2014) evaluated the addition of high-dose, long-infusion ifosfamide and RT as preop Tx for resectable RPS. The combination was feasible in 2/3^{rds} of pts.
What % of RPS are amenable to a GTR?

Show Answer

(50%–67%) of RPS are amenable to a GTR.
Is recurrence after Sg for RPS more likely to be local or distant?

Show Answer

Most recurrences after Sg for RPS are **local.**
What is the LR rate after GTR (R0 or R1) for RPS?

Show Answer

LR ranges from **50%–95%** in pts who have undergone GTR for RPS.
Summarize the argument in favor of preop RT over PORT.

Show Answer

Preop RT may be sup to PORT for RPS b/c it allows for better tumor volume definition, displacement of normal viscera by tumor, smaller Tx fields, intraop tumor seeding theoretically reduced, and the potential radiobiologic advantage of having normal vasculature/oxygenation in place that, extrapolating from extremity sarcoma data, make 50 Gy preop comparative to

60–66 Gy postop. No RCT exists comparing preop RT vs. PORT, however, Ballo et al. found significantly worse 5-yr RT related complication rate with PORT (23% vs. 0%). (IJROBP 2007)

Is there a benefit of adding IORT after the surgical management of RPS?

Show Answer

Possibly. There are at least 2 studies that suggest IORT improves LC when added to EBRT, but it is unclear if this improves OS. An **NCI trial** (Sindelar WF et al., Arch Surg 1993) compared PORT to PORT + IORT for RPS. 35 pts were randomized to postop EBRT (35–40 Gy) vs. PORT (50–55 Gy) + IORT (20 Gy) coadministered with misonidazole. Chemo (doxorubicin/cyclophosphamide/Mtx) was used for a portion of the trial. There was a significant improvement in "in-field" LR with IORT (40% IORT vs. 80% PORT). RT enteritis occurred in 13% of pts with IORT and 50% of pts with PORT. Peripheral neuropathy was found in 60% of pts with IORT vs. 5% of pts with PORT.

22 (39%) MDACC pts rcvd 15 Gy IORT after 18 Gy–50.4 Gy in a prospective trial of neoadj RT and low-dose doxorubicin with favorable results. However, there was no association of DFS or OS with IORT. (Pawlik et al.)

Summarize the outcomes of the Toronto Sarcoma Group and the MDACC prospective trials of preop EBRT for localized intermediate- or high-grade RPS.

Show Answer

The Toronto Sarcoma Group and the MDACC prospective trials enrolled 72 pts with intermediate- or high-grade RPS. 75% were primary, and 25% were recurrent. Pts were treated preop to a median dose of 45 Gy (18–50.4 Gy). The MDACC pt population also rcvd concurrent low-dose doxorubicin. 89% underwent laparotomy with curative intent 4–8 wks after RT. 60% had an intraop/postop boost. (Due to high morbidity, modification to selective

brachytherapy to the lower abdomen/pelvis only was adopted.) At median f/u of 3.4 yrs, 52% of pts with GTR developed recurrent Dz. 5-yr LRFS was 60%, DFS was 46%, and OS was 50%. (Pawlik TM et al., Ann Surg Oncol 2006) Results compared favorably to historical controls of Sg alone.

Are there any prospective randomized trials examining the role of RT in the management of RPS?

Show Answer

ACOSOG Z9031 randomized pts to **Sg alone vs. preop RT + Sg** for primary RPS. The target accrual was 370 pts in 4.5 yrs. The primary endpoint was PFS. This study closed d/t poor accrual.

The STRASS trial (conducted by the EORTC) is randomizing pts to Sg alone vs. preop RT + Sg. Accrual is complete and results anticipated shortly.

What EBRT dose is typically used for preop RT for RPS?

Show Answer

RPS is typically treated **45–50.4 Gy** preop. On protocol or at experienced centers, a SIB to 57.5–63 Gy may also be utilized.

Is a preop EBRT boost to a region of presumed high risk for + SMs effective?

Show Answer

This is **uncertain.** The efficacy of limited RT or an SIB is under investigation. There is an ongoing multicenter phase I–II trial of preop image-guided photon IMRT and proton RT with SIB to the high-risk margin sponsored by Mass General Hospital.

Is there a benefit of IMRT over 3D-CRT for the preop management of RPSs?

Show Answer

Yes, in general pts should be treated using IMRT to limit dose to surrounding

tissue**.** The Emory retrospective review compared 3D-CRT with IMRT for 10 pts with RPS and showed improved tumor coverage with better sparing of organs at risk with IMRT. (Koshy M et al., Sarcoma 2003)
What are the recommended expansions for RPS?

Show Answer

As recommended by a recent consensus panel

CTV = GTV + 1.5 cm
Edit CTV as follows:
Bone: 0 mm
Renal and hepatic interfaces: 0 mm
Bowel and air cavity: 5 mm
Skin surface: 3 mm
If tumor extends through inguinal canal, add 3 cm distally (as per extremity STS)
The preliminary consensus further details coverage of surrounding organs and Tx volume expansions per motion management technique at the time of CT-simulation. (Baldini et al., IJROBP 2015)

FOLLOW-UP/TOXICITY

What are acute and late toxicities associated with RT for RPS?

Show Answer

Acute and subacute toxicities: n/v, diarrhea, fatigue, erythema, wound complications, duodenitis/gastritis
Late toxicities: SBO (as well as stenosis and perforation), fistula, kidney failure, RILD, myelopathy, peripheral neuropathy, 2nd malignancy

83

Melanoma

Updated by Courtney Pollard, III

BACKGROUND

What is the incidence of melanoma in the United States?

Show Answer

~87,000 cases/yr of melanoma in the United States (and **rising**).

What are some risk factors for developing melanoma?

Show Answer

UV RT, fair complexion, light hair/eyes, numerous benign nevi or larger atypical nevi (>5 mm, variable pigmentation, asymmetric, indistinct borders), personal Hx of melanoma (900 times), family Hx of melanoma, and polyvinyl chloride exposure

In terms of UV exposure, what is the most important risk factor associated with development of melanoma?

Show Answer

Intermittent intense exposure to UVA and UVB, such as Hx of blistering burns in childhood, is the most important risk factor for developing melanoma.

What are the sex differences in terms of body distribution of melanoma lesions?

Show Answer

Males: lesions predominantly on trunk (e.g., upper back)
Females: lesions predominantly on extremities
What % of melanomas derive from melanocytic nevi?

Show Answer

~15% of melanomas derive from melanocytic nevi.
What are the 2 common types of noncutaneous melanoma?

Show Answer

Uveal melanoma and mucosal melanoma
What is the most common site of mucosal melanoma?

Show Answer

H&N, then anorectal and vulvovaginal regions
What % of melanoma pts have LN involvement at Dx, and how does this differ by T stage?

Show Answer

15% of pts have LN involvement at Dx, **5% of T1 pts and 25% of ≥T2 pts.**
What % of melanoma pts present with DM at Dx?

Show Answer

5% of pts present with DM at Dx.
What proportion of DM pts present with DM from an unknown melanoma primary?

Show Answer

One-third of DM pts or 1%–2% of all pts present with mets from an unknown primary.
What are the 5 subtypes of melanoma?

Show Answer

Superficial spreading, nodular, lentigo maligna, acral lentiginous, and desmoplastic variant

Which of the 5 melanoma subtypes is the most common?

Show Answer

Superficial spreading (70%) is the most common subtype → nodular (25%).

What are typical features of desmoplastic melanoma?

Show Answer

Features of the desmoplastic subtype include older pts (60–70 yo), more infiltrative, higher rate of PNI, amelanotic, **higher LF rates,** and **lower nodal mets/DM rates.**

Which melanoma subtype has the best prognosis?

Show Answer

Lentigo maligna melanoma has the best prognosis.

What subtype commonly presents in dark-skinned populations, and what body locations do it commonly affect?

Show Answer

Acral lentiginous, which **commonly affects the palms/soles and subungual areas,** is the most common melanoma subtype in dark-skinned populations.

Which subtype of melanoma is most common and has the worst prognosis?

Show Answer

Superficial spreading is the most common subtype. This subtype also has the worst prognosis.

What are 3 commonly used immunohistochemical stains for melanoma?

Show Answer

S100, HNB-45, and Melan-A stains are commonly used for melanoma.

WORKUP/STAGING

A pt presents with a pigmented lesion. What in the Hx can help to determine if this is a suspicious lesion?

Show Answer

Changes in **A**symmetry, **B**orders, **C**olor, **D**iameter (>6 mm), and **E**nlargement (Mnemonic: **ABCDE**)

Per the latest NCCN guidelines, for what melanoma pts should imaging be performed?

Show Answer

Per the NCCN, imaging should be performed for **specific signs/Sx or stage ≥III** (not recommended for Stages IA–II).

What are some common DM sites for melanoma?

Show Answer

The **skin, SQ tissues, distant LNs, lung, liver, viscera, and brain** are common melanoma DM sites.

What is the preferred method of tissue Dx for a suspected melanoma?

Show Answer

For suspected melanoma, **full-thickness or excisional Bx** (elliptical/punch) with a 1–3-mm margin is preferred for tissue Dx.

Why should wider margins on excisional Dx be avoided?

Show Answer

Avoid wide margins **to permit accurate subsequent lymphatic mapping.**

For what locations is full-thickness incisional or punch Bx adequate?

Show Answer

Full-thickness incisional and punch Bx are adequate for the **palms/soles,**

digits, face, and ears or for very large lesions.

When is a shave Bx sufficient?

Show Answer

Shave Bx is sufficient **when the index of suspicion for melanoma is low.**

What is the latest AJCC (8th edition) T staging for melanoma?

Show Answer

The latest AJCC T staging of malignant melanoma:

T1: ≤1 mm thickness
- **T1a:** ≤0.8 mm without ulceration
- **T1b:** ≤0.8 mm with ulceration or 0.8–1 mm with or without ulceration

T2: >1–2 mm thickness
- **T2a:** no ulceration
- **T2b:** ulceration

T3: >2–4 mm thickness
- **T3a:** no ulceration
- **T3b:** ulceration

T4: >4 mm thickness
- **T4a:** no ulceration
- **T4b:** ulceration

What is considered N1, N2, and N3 in melanoma staging?

Show Answer

All regional LN mets:

N1: 1 + node

N2: 2–3 + nodes

N3: ≥4, or matted, or in-transit mets with mets to regional node(s)

For melanoma nodal groups, into what further categories are N1–N3 stages broken into and on what basis (for AJCC 8th edition)?

Show Answer

N1a: 1 occult (SLN Bx) node and no in-transit/satellite, and/or microsatellite mets

N1b: 1 clinical node and no in-transit/satellite, and/or microsatellite mets

N1c: no +LNs with in-transit/satellite, and/or microsatellite mets

N2a: 2–3 occult (SLN Bx) nodes and no in-transit/satellite, and/or microsatellite mets

N2b: 2–3 + nodes, ≥1 clinically detected, and no in-transit/satellite, and/or microsatellite mets

N2c: 1 occult or clinical node with in-transit/satellite, and/or microsatellite mets

N3a: ≥4 occult (SLN Bx) nodes and no in-transit/satellite, and/or microsatellite mets

N3b: ≥4, one of which clinical node or any number of matted nodes and no in-transit/satellite, and/or microsatellite mets

N3c: 2 or more occult/clinical nodes and/or any matted nodes with in-transit/satellite, and/or microsatellite mets

For AJCC 8th edition, what replaces the micromets vs. macromets distinction for nodal staging?

Show Answer

Clinically occult (typically found on SLNB) = “a,” vs. clinically detected (by exam or imaging) = “b”

How do M1a, M1b, M1c, and M1d differ in a pt with metastatic melanoma?

Show Answer

M1a: skin, ST, distant LNs

M1b: lung only with or without M1a sites

M1c: non-CNS viscera or other sites with/without M1a or M1b sites

M1d: CNS mets with or without M1a, M1b, M1c sites

What does the parenthetical 0 or 1 denote in the most current M-staging (e.g., M1a(0) vs. M1a(1))?

Show Answer

(0): normal LDH
(1): elevated LDH
Describe the overall clinical stage groupings per the latest AJCC classification.

Show Answer

Stage 0: TisN0
Stage IA: T1aN0
Stage IB: T2aN0 or T1bN0
Stage IIA: T3aN0 or T2bN0
Stage IIB: T4aN0 or T3bN0
Stage IIC: T4bN0
Stage III: any N+
Stage IV: any M1
Describe the overall pathologic stage groupings per the latest AJCC classification.

Show Answer

Stage 0: TisN0
Stage IA: T1a or T1bN0
Stage IB: T2aN0
Stage IIA: T3aN0 or T2bN0
Stage IIB: T4aN0 or T3bN0
Stage IIC: T4bN0
Stage III: any N+ (see AJCC manual for specific breakdown of IIIA–D)
Stage IV: any M1
What are the Clark levels? Under what circumstance does the Clark level

need to be known on the pathology report for a pt with melanoma?

Show Answer

Level I: epidermis only
Level II: invasion of papillary dermis
Level III: filling papillary dermis, compressing reticular dermis
Level IV: invading reticular dermis
Level V: SQ tissue
The Clark level should be provided on the pathology report for lesions ≤1 mm; not used in latest AJCC staging system.
What are the similarities and differences b/t clinical and pathologic staging for melanomatous lesions?

Show Answer

Both require microstaging of the primary after resection:

Clinical staging: clinical exam + radiology allowed (after complete resection)
Pathologic staging: pathology assessment of LN after dissection
What should the pathology report reveal about the primary tumor in a pt with a newly diagnosed melanoma after surgical resection?

Show Answer

The pathology report should list the tumor **thickness, ulceration status, mitotic rate, deep/peripheral margins, LN/ECE status, evidence of satellitosis, and Clark level** (for lesions ≤1 mm).
What are some adverse features on pathology after surgical resection for a melanoma?

Show Answer

Adverse pathology features after surgical resection include **+margins (+ deep margin), LVSI, and a mitotic rate >1/mm^2.**
For clinical staging purposes, what stage designates regional nodal

involvement?

Show Answer

Stage III designates nodal involvement in melanoma staging.
What is the most powerful prognostic factor for recurrence and survival for pts with melanoma?

Show Answer

Tumor thickness
What are 3 favorable clinical factors at presentation for pts with a newly diagnosed melanoma?

Show Answer

Female sex, young age, and extremity location are all favorable prognostic factors.
What are 5 poor prognostic factors on pathology in melanoma?

Show Answer

Increasing thickness, # of nodes involved, ulceration, Clark level (if <1 mm), and satellitosis are 5 poor prognostic factors in melanoma.
What are microsatellites as seen with melanoma?

Show Answer

With melanoma, microsatellites are **discrete nest of cells >0.05 mm that are separated from the body of the primary lesion by collagen or fat.**
What are satellite mets as seen with melanoma?

Show Answer

Gross cutaneous or SQ intralymphatic mets, observed **≤2 cm from primary** Dz.
What are the in-transit mets seen with melanoma?

Show Answer

Gross cutaneous or SQ intralymphatic mets, observed **>2 cm from primary** Dz, but **before reaching the 1st echelon nodes.**
In order of frequency, which melanoma sites have the highest LR rates after Sg?

Show Answer

Melanoma sites with the highest LR rates after Sg (in descending order of frequency): **H&N (9.4%)** > distal extremities (5%) > trunk (3%) > proximal extremities (1%) (Balch CM et al., Ann Surg Oncol 2001)
What is the approximate 5-yr OS for melanoma by stage (NCI/SEER)?

Show Answer

Stage I–II: 97%
Stage III: 60%
Stage IV: 16%

TREATMENT/PROGNOSIS

When is WLE alone adequate as Tx of melanoma?

Show Answer

WLE alone is adequate for **in situ or Stage IA lesions** without adverse features on Bx.
When is SLN Bx clearly indicated?

Show Answer

Tumor thickness ≥1 mm.
What is the risk of regional node mets in pts with thin (<1 mm) melanomas undergoing SLNB?

Show Answer

5%
In which pts with thin melanomas (<1 mm) might you consider SLNB?

Show Answer

Breslow thickness ≥0.75 mm, Clark level ≥IV, and/or ulceration.
In pts with a positive SLNB, is immediate completion LND required?

Show Answer

No. A trial randomizing these pts to completion LND vs. observation with serial US showed no difference in melanoma-specific survival. (MSLT-II, Faries MB et al., NEJM 2017)
What volume of Dz did most pts on MSLT II have upon SLNB?

Show Answer

Most pts had low-volume (<1 mm) metastatic deposits.
In the MSLT-II trial, were there any endpoints that were improved with immediate LND, compared to observation with LND upon regional LN recurrence?

Show Answer

DFS and lower rate of regional LN recurrence.
What is the LN recurrence rate for pN+ melanoma pts after LND?

Show Answer

After LND, the LN recurrence rate for pN+ pts is **30% at 10 yrs.** (Lee RJ et al., IJROBP 2000: no adj RT; 45% rcvd chemo)
What min surgical margins are required by T stage for the optimal surgical management of melanoma?

Show Answer

Min surgical margins for optical surgical management:

Tis: 5 mm
T1: 1 cm
T2: 1–2 cm

T3–T4: 2 cm

Which randomized trials support the surgical margins currently used in the management of melanoma?

Show Answer

Balch et al. (Ann Surg Oncol 2001): 2 cm vs. 4 cm for >T2; no difference in outcome

Thomas et al. (NEJM 2004): 1 cm vs. 3 cm; 3 cm resulted in better LC for >T2 lesions, but no OS benefit

When is elective iliac or obturator LND necessary after resection of an LE melanoma?

Show Answer

Elective iliac or obturator LND is necessary if there are **clinically positive superficial nodes, ≥3 superficial +LNs, or if pelvic CT shows LAD.**

When is primary RT ever indicated for Tx of melanoma?

Show Answer

Primary RT is indicated for **medically inoperable pts or lentigo maligna of the face** (cosmetic outcome better); this is given as 50 Gy/20 fx or 7–9 Gy × 6 biweekly (Farshad A et al., Br J Dermatol 2002), 1.5-cm margin, 100–250 kV photons.

When is adj RT indicated for primary resected melanoma?

Show Answer

Per NCCN: deep desmoplastic melanoma with narrow margins, extensive neurotropism, or locally recurrent Dz

When should you consider adj RT for Stage III pts?

Show Answer

In select pts with clinically appreciable nodes s/p LND, with ECE and/or:

- Parotid ≥1 node involved

- Neck ≥2 nodes involved and/or ≥3 cm in single node
- Axilla ≥2 nodes involved and/or ≥4 cm in single node
- Inguinal ≥3 nodes involved and/or ≥4 cm in single node

What RCT showed that adj RT improves LN field control, based on the above inclusion criteria?

Show Answer

ANZMTG 01.02/TROG 02.01. (Burmeister et al., Lancet Oncol 2013, updated Henderson et al., Lancet Oncol 2015) 217 pts at high risk for further LN relapse randomized to adj RT (**48 Gy/20 fx**) or observation. LN field relapse was significantly lower in adj RT arm (HR = 0.56; p = 0.041), but no difference in RFS and OS.

In the TROG 02.01 study, what was the most common side effect of RT?

Show Answer

Tissue fibrosis, usually minor in severity

In the TROG 02.01 study, which pts experienced significant increase in limb edema after adj RT?

Show Answer

There was a significant increase in lower limb volumes/edema in the pts receiving inguinal nodal RT. There was no significant difference in upper limb sites.

Which studies suggest that RT can make up for a lack of formal neck dissection in H&N pts?

Show Answer

MDACC data by Ballo et al. (Head Neck 2005): cN+ in neck s/p local excision only with adj RT; 5-yr LC 93%

Ang et al. (IJROBP 1994): high-risk pts ± LND; 5-yr LC 88%

What RT hypofractionation scheme has been used in the adj setting for melanoma of the H&N?

Show Answer

Biweekly 6 Gy/fx × 5 (30 Gy) based on the Ang et al. study (MDACC data): 5-yr LRC was 88%, OS was 47%, and there was min acute/late toxicity. (IJROBP 1994)
What was the 1st adj systemic therapy that was demonstrated to improve survival for pts with high-risk Stage III Dz?

Show Answer

High-dose Interferon alfa (**IFNa**), based on ECOG 1684 and Intergroup E1694 studies.
Has adj immunotherapy been shown to improve survival for high-risk Stage III pts?

Show Answer

Yes, ipilimumab (Ab against CTLA-4) at 10 mg/kg (higher dose than 3 mg/kg used in metastatic setting) improved OS compared to placebo, in the EORTC 18071 trial (Eggermont et al., NEJM 2016)
What main toxicities were observed with ipilimumab in the adj setting?

Show Answer

Considerable toxicity was observed with ipilimumab at 10 mg/kg. Grade 3 or 4 immune-mediated toxicity occurred in 42%, with some deaths. The most common were dermatologic, GI, endocrine, and hepatic toxicities.
Is there a benefit to hypofractionating RT for melanoma in the adj setting?

Show Answer

No. RTOG 8305 showed no difference b/t 8 Gy × 4 fx and 2.5 Gy × 20 fx. (Sause WT et al., IJROBP 1991)
What did the University of Florida experience/study (Chang DT et al., IJROBP 2006) demonstrate regarding adj nodal RT in pts with melanoma lesions of the H&N?

Show Answer

The University of Florida study showed excellent 5-yr LC (87%) and no difference b/t hypofractionation (6 Gy × 5 fx) and standard (60 Gy in 30 fx) dosing. The major cause of mortality was DM.

What is generally recommended for a pt with nodal recurrence after primary management for melanoma?

Show Answer

Restaging, FNA or LN Bx → LND if no previous dissection → consider adj RT, immunotherapy, or clinical trial.

How is salvage RT delivered in melanoma pts with isolated axillary nodal recurrences?

Show Answer

After axillary LND, RT to the axilla alone is sufficient (the SCV region may be omitted), using 6 Gy × 5 fx (30 Gy) per MDACC data. (Beadle BM et al., IJROBP 2009) The 5-yr LC rate was 88%.

What systemic agents are currently being used for metastatic melanoma?

Show Answer

Pembrolizumab (category 1), anti–PD-1 monoclonal antibody demonstrates PFS of ~35%–50% in advanced melanoma. (Robert C et al., Lancet 2014; Robert C et al., NEJM 2015; Ribas A et al., Lancet Oncol 2015; Ribas A et al., JAMA 2016)

Nivolumab (category 1), anti–PD-1 monoclonal antibody out performs chemo regarding OS and objective response rate in advanced melanoma. (Robert C et al., NEJM 2015; Weber et al., Lancet Oncol 2015)

Ipilimumab, a monoclonal antibody to the immune checkpoint receptor CTLA-4. (Hodi FS et al., NEJM 2010; Robert C et al., NEJM 2011; Margolin K et al., Lancet Oncol 2012)

The combination of ipilimumab and anti–PD-1 ab nivolumab is more

active than either monotherapy, but is associated with increased toxicity, and was explored in the CheckMate 067 phase III trial (Wolchok JD et al., NEJM 2017); 3-yr OS with both drugs was 58% vs. 52% with nivolumab, and 34% with ipilimumab (Grade 3–4 toxicity was 59% vs. 21% and 28% respectively).

Vemurafenib, a specific inhibitor of V600E mutated BRAF (~50% of all melanomas). (Chapman PB et al., NEJM 2011; Sosman JA et al., NEJM 2012) In the phase III randomized trial (Chapman et al.) that compared vemurafenib to dacarbazine, vemurafenib had a response rate of 48% (vs. 5%) and an improved OS.

What intralesional injection agent has shown efficacy in the phase III setting for pts with unresectable, Stage IIIB–IV melanoma?

Show Answer

Talimogene Laherparepvec (**T-VEC**): modified HSV that induces tumor cell lysis. (Andtbacka, J Clin Oncol 2015) BCG, IL-2, and Rose Bengal have demonstrated efficacy in phase I/II clinical trials.

FOLLOW-UP/TOXICITY

What is the rate of lymphedema when treating different LN regions with hypofractionated RT?

Show Answer

The rates for lymphedema are **39% for the groin, 30% for the axilla, and 11% for H&N sites.** (MDACC data: Ballo MT et al., Head Neck 2005)

What is the α/β ratio of melanoma?

Show Answer

For melanoma, the estimated α/β ratio is **2.5.** (Overgaard J et al., Lancet 1995)

When using a hypofractionated regimen (e.g., 6 Gy × 5 [30 Gy]), at what dose should one come off the cord and small bowel?

Show Answer

24 Gy is the dose tolerance of the cord/small bowel when hypofractionating with 6 Gy/fx.

Is there potential for increased toxicity when combining RT with BRAF inhibitors?

Show Answer

YES. There have been reports of radio-sensitization and RT recall (in some cases severe) in pts receiving RT in close proximity to vemurafenib and dabrafenib. Therefore holding Tx with a BRAF inhibitor for some period of time before and after receipt of RT is prudent.

Has unexpected toxicity been observed when combining RT with immune checkpoint inhibitors?

Show Answer

There are emerging data for the combination of RT and immunotherapy, and no unexpected toxicity has been reported. (Hiniker et al., Int J Radiat Oncol Biol Phys 2016; Luke et al., JCO 2018)

What are the NCCN (2018) f/u recommendations for melanoma by stage?

Show Answer

NCCN melanoma f/u recommendations:

- Annual skin exam for life (all stages)
- For Stages IA–IIA: H&P q6–12mos for 5 yrs, then annually; routine labs/imaging not recommended
- For Stages IIB–IV: H&P q3–6mos for 2 yrs, then q3–12mos for 3 yrs, then annually; routine labs for 1st 5 yrs; consider imaging (CXR, PET/CT, annual MRI brain)

What are some toxicities expected after RT for skin cancer?

Show Answer

Telangiectasia, skin atrophy, changes in pigmentation, skin necrosis, fibrosis, osteonecrosis, chondritis, xerostomia, and hearing loss (if treating near the inner ear).
If cartilage is in the RT field, what should the dose/fx be kept below?

Show Answer

The dose should be kept at **<3 Gy/fx** to reduce the risk of cartilage necrosis.
What is the incidence of skin necrosis after RT?

Show Answer

Skin necrosis occurs in **3%** of pts (in 13% if fx size is >4–6 Gy).
To what dose should middle ear/canal lesions be limited? Why?

Show Answer

Limit middle ear/canal lesions to **65–70 Gy** b/c of higher rates (>10%) of **osteoradionecrosis** with doses >70 Gy.
What can be done to reduce the toxicities to surrounding normal tissues from skin irradiation in the H&N region when using electrons?

Show Answer

To reduce toxicities to normal tissues, use **lead shielding** to block the lens, cornea, nasal septum, teeth, and gums. Use **dental wax** on the side from which the beam enters to absorb backscatter.
Per the latest NCCN guidelines, what should be the f/u intervals for pts with non-melanoma skin cancers?

Show Answer

NCCN non-melanoma skin cancer f/u intervals:

- Complete skin exam for life at least once/yr
- For local Dz: H&P q3–12 mos for yrs 1–2, q6–12 mos for yrs 3–5, then annually

. For regional Dz: H&P q1–3 mos for yr 1, q2–4 mos for yr 2, q4–6 mos for yrs 3–5, then q6–12 mos for life

84

Squamous Cell and Basal Cell Carcinoma of the Skin

Updated by Steven W. Davis

BACKGROUND

What is the incidence of non-melanoma skin cancer (NMSC) in the United States?

Show Answer

>2 million cases/yr in the United States (exceeds incidence of all other cancers combined)

Which is more common: basal cell carcinoma (BCC) or SCC?

Show Answer

BCC (80%) is more common than SCC (20%).

What is the sex predilection for skin cancers?

Show Answer

Males are more commonly affected than females **(4:1).**

What % of skin cancer deaths are attributable to cutaneous SCC?

Show Answer

20%

What is the primary etiology of NMSC?

Show Answer

Mutagenesis from UV light
What signaling pathway is involved in BCC pathogenesis?

Show Answer

Sonic hedgehog signaling pathway. Vismodegib, FDA approved for BCC, targets this pathway.
According to NCCN, how are anatomic skin areas divided? (see also Connolly et al., Dermatol Surg 2012)

Show Answer

H: "mask areas" (central face, eyelids, eyebrows, periorbital nose, lips, chin, mandible, preauricular, postauricular, temple, ear), genitalia, hands, feet
M: cheek, forehead, scalp, neck, pretibial
L: trunk and extremities (except pretibial, hands, feet, nails, ankles)
What is the "mask area" and why is it considered higher-risk?

Show Answer

It corresponds to the midface, where the embryologic fusion lines lie, and may represent a higher risk for deep invasion or LR.
According to NCCN, what are the risk factors for recurrence for BCC?

Show Answer

Area L ≥20 mm, area M ≥10 mm, area H (any size), poorly-defined borders, recurrent, immunosuppression, prior RT, PNI, and aggressive histology pattern (morpheaform, basosquamous, sclerosing, mixed infiltrative, and micronodular)
What are the high-risk factors for SCC?

Show Answer

Those listed above for BCC **and** rapidly growing, neurologic Sx, poorly

differentiated, unfavorable histology (adenoid, adenosquamous, desmoplastic or metaplastic), ≥2-mm thick or Clark level IV or V.

What genetic/inherited disorders are associated with skin cancer?

Show Answer

Phenylketonuria, Gorlin syndrome, xeroderma pigmentosa, and albinism have a genetic/inherited association with skin cancer.

What is the incidence of PNI and mets with BCC?

Show Answer

PNI: 1%

Mets: <0.1% (nodes or distant sites)

What is the incidence of PNI and mets with cutaneous SCC?

Show Answer

PNI: 2%–15%

Mets: nodes: 1%–30% (1% for grade 1, 10% for grade 3, 30% from burn-associated SCC); distant: 2% (lung > liver > bones)

What are the major determinants of LN spread for cutaneous SCC?

Show Answer

Poor differentiation, size/depth (>3 cm/>4 mm), PNI/LVI, location (lips, scars/burns, ear), and recurrent lesions

What LN regions are most commonly involved in cutaneous SCC?

Show Answer

The (1) parotid and (2) **upper cervical nodes** are most commonly involved, mostly from H&N SCC.

Sun exposure at what stage of life correlates with BCC vs. SCC?

Show Answer

BCC: early in life/childhood

SCC: decade preceding Dx
What is Bowen Dz?

Show Answer

Bowen Dz is **SCC in situ.**
How often does actinic keratosis (AK) progress to invasive SCC?

Show Answer

AK (proliferation of atypical keratinocyte) lesions are on the continuum with SCC, and progress to invasive SCC at a rate of ~0.6% per yr.
What is a Marjolin ulcer?

Show Answer

Marjolin ulcer is **SCC arising in a burn scar.**
What is the most common site for sebaceous carcinomas?

Show Answer

Ocular adnexa
What is the most common primary site in a pt with SCC of an intraparotid LN?

Show Answer

Cutaneous SCC of the H&N
What are the most common histologies of NMSC of the outer vs. the inner ear?

Show Answer

Pinna: BCC
Rest (canal, middle ear, mastoid): SCC (85%)

WORKUP/STAGING

What are the high-risk features defining the primary tumor as T3 in the 8th edition AJCC for cutaneous SCC?

Show Answer

Large caliber PNI (≥0.1 mm or nerve beneath the dermis), deep invasion (>6 mm or beyond SQ fat), and minor bone erosion. Other high-risk features (poor differentiation, LVI, and anatomic location) no longer affect T stage.
What is the latest T staging according to the 8th edition of AJCC cancer staging manual (2017) for SCC/BCC?

Show Answer

There is no AJCC staging for SCC/BCC outside of the H&N. For cutaneous SCC of the H&N (including BCC) the following T staging applies:

Tis: CIS
T1: <2 cm
T2: 2 cm or larger but smaller than 4 cm
T3: 4 cm or larger or minor bone erosion, deep invasion, or PNI
T4a: gross cortical bone or marrow invasion
T4b: skull base invasion and/or skull base foramen involvement
How is bone invasion staged per the 8th edition AJCC?

Show Answer

Minor bone erosion is stage T3, gross cortical bone or marrow invasion is stage T4a and skull base invasion is T4b.
How is PNI staged per the 8th edition AJCC?

Show Answer

Large caliber PNI (≥0.1 mm diameter or nerve beneath the dermis) or clinical or radiographic named–nerve involvement is T3, while skull base foramen involvement is T4b.
How is deep invasion staged per the 8th edition AJCC?

Show Answer

Deep invasion, defined as invasion beyond the SC fat or >6 mm from the

granular layer, is T3.

What are 2 major changes in nodal staging for cutaneous cancers of the H&N in the 8th edition of AJCC?

Show Answer

Clinical (all pts) and pathologic (neck dissection pts) staging criteria and the addition of extranodal extension (ENE) as a major criteria of nodal staging.

What are the different clinical N-stages (cN) in the 8th AJCC for cutaneous carcinomas?

Show Answer

N1: single, ipsi, ≤3 cm, ENE (–)
N2a: single, ipsi, 3–6 cm, ENE (–)
N2b: multiple, ipsi, ≤ 6 cm, ENE (–)
N2c: bilat or contralat LNs, ≤6 cm, ENE (–)
N3a: any LNs >6 cm, ENE (–)
N3b: any LN with ENE (+)

What are the different pathologic N-stages (pN) in the 8th AJCC for cutaneous carcinomas?

Show Answer

N1: single, ipsi, ≤3 cm, ENE (–)
N2a: single, ipsi, ≤3 cm, ENE (+), or single, ipsi, 3–6 cm, ENE (–)
N2b: multiple, ipsi, ≤6 cm, ENE (–)
N2c: bilat or contralat LNs, ≤6 cm, ENE (–)
N3a: any LNs >6 cm, ENE (–)
N3b: single, ipsi >3 cm, ENE (+), or multiple, contralat or bilat LN, ENE (+)

What defines stage groupings I, II, III, and IV?

Show Answer

Stage I: T1N0
Stage II: T2N0

Stage III: T3N0 or T1–3N1
Stage IV: N2–3, T4, or M1
What anatomic sites are considered high-risk per the 8th edition of AJCC?

Show Answer

Lip (vermillion and hair-bearing), ear, temple, and cheek
What cutaneous malignancy is often described as a “pearly papule”?

Show Answer

BCC
How is cutaneous SCC often described clinically?

Show Answer

Flesh-toned and variably keratotic
On H&P, what aspects should be the focus of the exam?

Show Answer

Hx: presence and distribution of paresthesias. Exam: Extent of tumor, CN exam, regional LN evaluation, audiometry/otoscopy for cancers of the ear, clinical ENE (+).
When is it appropriate to obtain imaging, per NCCN?

Show Answer

Primary MRI with contrast if large nerve involvement suspected. If bone involvement is suspected, CT is recommended.

TREATMENT/PROGNOSIS

Name 4 potential Tx options for NMSC.

Show Answer

. Surgery (WLE, Mohs surgery, surgical excision with complete circumferential peripheral and deep margin assessment)
. Curettage and electrodesiccation (C&E)

. Superficial therapies
. Primary RT

Describe Mohs Sg.

Show Answer

In Mohs Sg, a superficial slice of skin is taken and then sectioned into quadrants. Tissue is examined microscopically in real time. Additional layers are taken in the quadrants that show persistent Dz.
When are C&E and superficial therapies appropriate for skin cancer?

Show Answer

Only low-risk NMSC. (Cannot evaluate histologic margins with these techniques.)
List Tx considered superficial therapies.

Show Answer

Topical 5-FU, imiquimod, photodynamic therapy, and cryotherapy
What % of BCC recurs if a margin is (+) at the time of resection?

Show Answer

BCC recurs in **30% for a (+) lat margin** and **>50% for a (+) deep margin.**
What % of SCC recurs if a margin is (+) at the time of resection?

Show Answer

Nearly 100% of SCCs recur if margin is (+).
When is RT preferred as the primary Tx modality for skin cancer?

Show Answer

RT is preferred for pts >60 yo and who are not candidates for primary Sg. RT should be offered for lesions of the central face, lip, eyelid, and ears if Sg will lead to inf cosmetic or functional outcomes.
What is the best predictor of LC after definitive RT?

Show Answer

T stage is the best predictor for LC.
What is the LC after definitive RT for BCC vs. SCC?

Show Answer

LC is similar for BCC and SCC with T1 lesions (95%) and lower for SCC than BCC if T2 (75%–85%) or T3 (50%).
What should be done with a (+) margin resection?

Show Answer

Re-excise if possible, otherwise adj RT.
What are 3 indications for adj RT to the primary site with skin cancer?

Show Answer

– (+) Margin
– Large nerve or extensive PNI
– Invasion of bone, cartilage, or skeletal muscle
What are relative contraindications to RT in the Tx of skin cancers?

Show Answer

Relative contraindications to RT for skin cancer include areas prone to trauma (hands and feet, or beltline) or with poor blood supply (below knees/elbows), age <50 yrs, post-RT recurrence, Gorlin syndrome, CD4 count <200, high occupational sun exposure, and exposed area of bone/cartilage.
When should adj nodal RT be considered after surgical resection?

Show Answer

Consider adj nodal RT after surgical resection for T3/T4 tumors, **multiple +LNs, large (>3 cm) LNs, or close neck dissection margins.**
When should adj CRT be considered?

Show Answer

Consider for ENE (+), or **neck dissection margins (+).** Note**: this is extrapolated from mucosal H&N cancers. There are no data demonstrating improved survival for cutaneous SCC of the skin.**
According to NCCN guidelines, what dose schemes are typically employed with the Tx of skin cancers <2 cm?

Show Answer

64 Gy in 32 fx over 6–6.4 wks
55 Gy in 20 fx over 4 wks
50 Gy in 15 fx over 3 wks
35 Gy in 5 fx over 5 days
According to NCCN guidelines, what dose schemes are typically employed with the Tx of skin cancers >2 cm?

Show Answer

66 Gy in 33 fx over 6–6.6 wks
55 Gy in 20 fx over 4 wks
According to NCCN guidelines, what dose schemes are typically employed for adj RT for skin cancers?

Show Answer

60 Gy in 30 fx over 6 wks
50 Gy in 20 fx over 4 wks
What is the margin/dose modification if electrons are used? Why?

Show Answer

If electrons are used, add an additional 0.5-cm margin on the skin surface and use 10%–15% higher daily/total dose b/c of bowing in of isodose curves and a lower RBE (0.85–0.9) of electrons.
What is the Rx point if orthovoltage (100–200 kV) RT is employed?

Show Answer

Dmax (90% of the IDL has to encompass the tumor). Do not use this if the lesion is >1 cm deep.
When treating with electrons, how deep should the 90% IDL extend in relation to the lesion?

Show Answer

The IDL should extend at least **5–10 mm deeper than the deepest aspect of the lesion.**
When treating skin lesions with electrons, what rule is typically employed to choose the correct beam energy?

Show Answer

Electron energy (in MeV) should be **>3 times the lesion depth** (i.e., a 9-MeV beam is needed for a 2-cm lesion depth). Also, can use generality: Electron energy (in MeV)/4 is depth of 90% IDL. You must account for bolus in your depth calculation.
What is the RT volume if a named nerve is involved by SCC?

Show Answer

The RT volume should include the nerve retrograde to the skull base. Consider IMRT/elective nodal RT.
Where do basosquamous skin cancers occur? What is the Tx paradigm?

Show Answer

Basosquamous skin cancers occur on the **face.** These are treated like SCC, as they have similar rates of nodal mets.
What kind of shields are used, and where should they be placed? Why?

Show Answer

Wax-covered lead shields are used b/c of backscattered electrons with low

MeV beams. They are typically placed behind/downstream of tumor.
How should fx size be tailored for skin cancer depending on the RT field size? On location of the tumor (face vs. extremity)?

Show Answer

In general, the larger the field, the smaller the fx size should be. For cosmetically sensitive areas like the face, smaller fx are typically used.
If simple excision is performed for BCC, what are the min margins required?

Show Answer

Low risk: 4 mm
High risk: 10 mm
What is the preferred RT modality for bone-invasive skin cancer? For cartilage invasion?

Show Answer

Megavoltage photons are the preferred Tx modality for bone invasion b/c of a more homogenous distribution compared to orthovoltage d/t the f-factor; however, this is not so with cartilage invasion, as orthovoltage beams have little difference in distribution in cartilage regardless of energy.
If treating recurrent BCC or morpheaform BCC, what type of margins should be used?

Show Answer

Because these tumors infiltrate more extensively, an **extra 0.5–1-cm margin** should be added on the surface.
How should SCC of the mastoid be treated?

Show Answer

Mastoidectomy or temporal bone resection → PORT
How long should a skin graft heal before starting RT?

Show Answer

6–8 wks of healing time is required after skin grafting before RT should be initiated.

FOLLOW-UP/TOXICITY

What are some toxicities expected after RT for skin cancer?

Show Answer

Telangiectasia, skin atrophy, changes in pigmentation, skin necrosis, fibrosis, osteonecrosis, chondritis, xerostomia, and hearing loss (if treating near the inner ear).

If cartilage is in the RT field, what should the dose/fx be kept below?

Show Answer

The dose should be kept at **<3 Gy/fx** to reduce the risk of cartilage necrosis.

What is the incidence of skin necrosis after RT?

Show Answer

Skin necrosis occurs in **3%** of pts (in 13% if fx size is >4–6 Gy).

To what dose should middle ear/canal lesions be limited? Why?

Show Answer

Limit middle ear/canal lesions to **65–70 Gy** b/c of higher rates (>10%) of **osteoradionecrosis** with doses >70 Gy.

What can be done to reduce the toxicities to surrounding normal tissues from skin irradiation in the H&N region when using electrons?

Show Answer

To reduce toxicities to normal tissues, use **lead shielding** to block the lens, cornea, nasal septum, teeth, and gums. Use **dental wax** on the side from which the beam enters to absorb backscatter.

Per the latest NCCN guidelines, what should be the f/u intervals for pts

with non-melanoma skin cancers?

Show Answer

NCCN non-melanoma skin cancer f/u intervals:

. Complete skin exam for life at least once/yr
. For local Dz: H&P q3–12 mos for yrs 1–2, q6–12 mos for yrs 3–5, then annually
. For regional Dz: H&P q1–3 mos for yr 1, q2–4 mos for yr 2, q4–6 mos for yrs 3–5, then q6–12 mos for life

85

Merkel Cell Carcinoma

Updated by Courtney Pollard, III

BACKGROUND

What is the annual incidence of Merkel cell carcinoma (MCC) in the United States?

Show Answer

~500 cases/yr of MCC in the United States. Higher in Australia and NZ.
What is the median age of Dx for MCC?

Show Answer

The median age of Dx is **75 yrs** (90% >50 yrs). Presents earlier in immunosuppressed pts.
What is the cell type of origin for MCC?

Show Answer

Neuroendocrine (dermal sensory cells)—aka primary **small cell cancer** of the skin.
What virus is associated with MCC?

Show Answer

Merkel cell polyomavirus (detected in 43%–100%).
What is the prognosis of MCC as compared to other skin cancers?

Show Answer

Of skin cancers, MCC has the **worst prognosis** (even worse than melanoma).
What % of pts have LN involvement at Dx?

Show Answer

~25% have LN involvement at Dx.
DMs develop in what % of pts with MCC?

Show Answer

50%–60% of MCC pts develop DMs. ~10% DM rate at presentation.
Is MCC a radiosensitive or radioresistant tumor?

Show Answer

MCC is considered **radiosensitive.**
What demographic group does MCC affect predominantly?

Show Answer

Elderly white males are primarily affected by MCC (M:F, 2:1).
Immunocompromised pts, 24-fold increase risk in transplant pts.
Where do most MCCs arise anatomically?

Show Answer

H&N region (~45%) > UEs (~25%) > LEs (~15%) > trunk (~10%) > other (~5%–10%)
MCC tumors at which sites have a particularly poor prognosis?

Show Answer

Vulva and/or perineum MCC is associated with a particularly poor prognosis.
To what tumor type is the histologic appearance of MCC similar?

Show Answer

The histologic appearance of MCC is similar to **small cell carcinoma of the**

lung.

What is the most important prognostic factor in MCC?

Show Answer

LN status at presentation.

WORKUP/STAGING

What clinical features are common in MCC?

Show Answer

. **A**symptomatic
. **E**xpand (grow) rapidly
. **I**mmune suppression
. **O**lder than 50 yo
. **U**V exposed area in fair skin individual

What is the workup for MCC?

Show Answer

MCC workup: H&P (focused on skin and regional nodes), CBC, CMP, CT N/C/A/P, PET/CT, ± MRI Brain

What markers should be included in the immuno panel?

Show Answer

CK-20 (specific for MCC) and TTF-1 (specific for lung and thyroid).

Why obtain chest imaging at staging?

Show Answer

To **r/o the possibility of small cell lung cancer with mets to the skin** as an etiology, especially when CK-20–.

Outline the informal staging system commonly utilized by various institutions for MCC, and approximate 5-yr OS.

Show Answer

Stage I: localized (5-yr OS 51%)
Stage II: LN+ (5-yr OS 35%)
Stage III: DMs (5-yr OS 14%)
Outline the 8th edition AJCC TNM staging.

Show Answer

T1: ≤2 cm
T2: >2 cm and ≤5 cm
T3: >5 cm
T4: invades bone, muscle, fascia, or cartilage
N1: regional LN mets
N1a: clinically occult mets on LND; N1a(sn) if detected on SLN Bx
N1b: clinically/radiographically evident mets
N2: in-transit mets (b/t primary and nodal basin or distal to primary) without LN mets
N3: in-transit mets (b/t primary and nodal basin or distal to primary) with LN mets
M1a: mets to skin, SQ tissue, or distant LN
M1b: mets to lung
M1c: mets to all other visceral sites
What is the definition of in-transit mets or N2/N3 Dz per the 8th edition AJCC classification?

Show Answer

"In-transit" is defined as tumor distinct from the primary tumor and either b/t the primary and the nodal basin or distal to the primary.
Outline the latest AJCC stage groupings for MCC.

Show Answer

Clinical	Pathologic
Stage I: T1N0	**Stage I:** T1N0

Stage IIA: T2–3N0 **Stage IIB:** T4N0 **Stage III:** any TN1–3 **Stage IV:** M1	**Stage IB:** T1cN0 **Stage IIA:** T2–3N0 **Stage IIB:** T4N0 **Stage IIIA:** T0N1b **Stage IIIA:** any TN1a(sn) or N1a **Stage IIIB:** any TN1b–3 **Stage IV:** M1

TREATMENT/PROGNOSIS

What is the Tx paradigm for MCC?

Show Answer

MCC Tx paradigm: Sg (WLE or Mohs) with sentinel LN Bx +/– LND +/– adj RT.

In which group of pts is an SLNB more likely to be unreliable?

Show Answer

SLNB in the H&N region is more likely to be unsuccessful; in these cases RT to the regional draining nodes should be considered.

What surgical margins are recommended for WLE?

Show Answer

1–2 cm (NCCN 2018)

When is adj RT indicated for MCC?

Show Answer

Historically, adj RT has been included in the Tx course for the majority of MCC pts. A study by Allen et al. (JCO 2005) suggested that adj RT was of no benefit in margin– pts with surgically staged low-risk nodal Dz. A SEER analysis of 1,665 cases showed adj RT to be associated with better OS. (Mojica et al., JCO 2007) Strong indications for RT include:

- **Tumor >2 cm**
- **+/Close margins**
- **Angiolymphatic invasion**
- **LN+ or no LN evaluation**
- **Immunocompromised pts**

Per the NCCN, what RT doses are commonly used for MCC?

Show Answer

Commonly used total doses for MCC:

Negative margins: **50–56 Gy**
Microscopically+ margins: **56–60 Gy**
Gross residual or unresectable: **60–66 Gy**
No LN Bx or LND, clinically node–: **46–50 Gy**
No LN Bx or LND, clinically node+: **60–66 Gy**
SLN–, no LND: **Observe**
SLN+, no LND: **50–56 Gy**
LND+: **50–60 Gy**
What RT margins and techniques are typically used for MCC?

Show Answer

For MCC, the typical RT margin is **5 cm around the primary tumor** (i.e., not the scar) with bolus.
When are regional LNs covered in the RT volume for MCC?

Show Answer

Regional LNs are typically covered for all MCC pts. Retrospective data suggest that the inclusion of regional LNs in the RT field is associated with sup outcomes. (Eich HT et al., Am J Clin Oncol 2002; Jabbour J et al., Ann Surg Oncol 2007) However, the role of LN coverage in sentinel LN Bx– or LND– pts is controversial.
What is the evidence for concurrent CRT after Sg for MCC?

Show Answer

Data on concurrent CRT for MCC are **limited.** Phase II trials have shown that CRT is tolerable (Poulsen MG et al., IJROBP 2006), but no trials have established sup efficacy over RT alone.
What is the historical LF rate after Sg alone, and with adj RT?

Show Answer

Historical rates are **45%–75%** with Sg alone, and **15%–25%** with adj RT.
After recurrence, can Merkel cell be retreated?

Show Answer

Yes. Multimodality Sg +/– RT +/– chemo is recommended, with improved survival over single modality for recurrent Dz. (Eng TY et al., IJROBP 2004)
Are there any effective systemic therapies for metastatic MCC?

Show Answer

Yes, PD-L1 inhibitor Avelumab has been approved by the FDA.
Carboplatin/etoposide is 1st-line chemo.

FOLLOW-UP/TOXICITY

What specific f/u studies do MCC pts require?

Show Answer

Frequent CXR imaging, complete LN exam, and total skin exam for life (high rates of 2nd skin cancers).
What follow-up intervals are recommended by the NCCN for MCC?

Show Answer

NCCN recommended f/u schedule: H&P and clinically indicated imaging q3–6mos for 3 yrs, and q6–12mos thereafter.
What are the major toxicities in pts receiving CRT for MCC?

Show Answer

Skin (grade 3–4) toxicity is ~60% and **neutropenia** is ~40%. (Poulsen M et al., IJROBP 2001)

86

Brain Mets

Updated by W. Tristram Arscott

BACKGROUND

What is the most common intracranial tumor?

Show Answer

Brain met is the most common intracranial tumor (outnumber primary brain tumors 8:1).

What is the annual incidence of brain mets in the United States?

Show Answer

170,000–200,000 cases/yr of brain mets in the United States, with development in up to 30% of pts with systemic cancer.

Why is the incidence of brain mets increasing?

Show Answer

The incidence is increasing due to advancements in systemic therapy (improved extracranial control) with limited penetration of the blood–brain barrier in conjunction with increased utilization of MRI/surveillance imaging.

What cancers are associated with hemorrhagic brain mets?

Show Answer

Hemorrhagic brain mets are most commonly associated with **melanoma, RCC, and choriocarcinoma.**

What do the terms solitary and single brain met connote?

Show Answer

A solitary brain met is **only 1 brain lesion and no other sites of Dz progression.**
A single brain met is **only 1 brain lesion in addition to other sites of met Dz.**

What cancers are most likely to metastasize to the brain?

Show Answer

Cancers associated with brain mets: lung (40%–50%), breast (15%), melanoma (10%)

In what % of pts are brain mets the 1st manifestation of Dz?

Show Answer

5%–20% of pts present with brain mets from an unknown primary. Pts presenting with brain mets without a prior Dx of cancer most often have a **lung primary.**

Should Bx or resection be recommended if a new Dx of brain mets is suspected?

Show Answer

Yes. Bx should be considered in pts with a new Dx of brain mets as 11% of pts (6/54) enrolled in the 1st Patchell trial were found to have a primary brain tumor (3 pts) or inflammatory/infectious process (3 pts) despite MRI or CT findings consistent with metastatic Dz. (Patchell R et al., NEJM 1990)

What is the more common type of brain mets: single or multiple?

Show Answer

Most pts have **multiple** brain mets rather than a single lesion, with increased detection of small, multifocal lesions on MRI typically not appreciated on CT.

How do pts with brain mets present?

Show Answer

Presentation of pts with brain mets: Sx of ↑ ICP (HA, n/v), weakness, change in sensation, mental status changes, and seizure

What is carcinomatous meningitis?

Show Answer

Carcinomatous meningitis is a clinical syndrome caused by leptomeningeal met with widespread involvement of the cerebral cortex. The Dx is associated with a poor prognosis.

Where do most brain mets occur?

Show Answer

Most brain mets arise in the **gray/white matter junction** due to hematogenous dissemination with narrowing of blood vessels. (Delattre J et al., Arch Neurol 1988)

Are most brain mets infra- or supratentorial?

Show Answer

The majority of brain mets are **supratentorial.**

What is the distribution of brain mets within the brain?

Show Answer

The distribution of brain mets correlates with relative weight and blood flow:

Cerebral hemispheres: 80%
Cerebellum: 15%
Brainstem: 5%

(Delattre J et al., Arch Neurol 1988)

What is the overall median time from initial cancer Dx to development of brain mets?

Show Answer

The median overall time from initial cancer Dx to development of brain mets is **1 yr.**

Do most pts with brain mets die from their CNS Dz?

Show Answer

No. ~30%–50% of pts with brain mets die from their CNS Dz.

WORKUP/STAGING

Describe the workup of a brain met.

Show Answer

Brain met workup: H&P focus on characterization of any neurologic Sx, evaluation for infectious causes (fever, CBC), careful neurologic exam, MRI brain +/– gadolinium, assessment for status of extracranial Dz, determination of KPS, and neurosurgery consult

What is the DDx for a new lesion in the brain?

Show Answer

Brain lesion DDx: mets, infection/abscess, hemorrhage, primary brain tumor, infarct, tumefactive demyelinating lesion, and RT necrosis

What imaging features are suggestive of brain mets?

Show Answer

Imaging features suggestive of brain mets include lesions at gray/white matter junction, multiple lesions, ring-enhancing lesions, and significant vasogenic edema

What is triple-dose gadolinium, and why is it used?

Show Answer

Triple-dose gadolinium: **0.3 mmol/kg.** It is used **to increase the sensitivity of MRI.**

TREATMENT/PROGNOSIS

Describe the RTOG recursive partitioning analysis (RPA) classes for brain mets. (Gaspar L et al., IJROBP 1997)

Show Answer

Class	KPS	Age	Disease
1	≥70	<65	Primary controlled, and no extracranial mets
2	≥70	**Either** age >65	**Or** primary uncontrolled
3	<70		

KPS, Karnofsky performance score.

What is the MS time for RTOG RPA classes I, II, and III?

Show Answer

MS according to the RTOG brain met RPA:

Class I: 7.2 mos
Class II: 4.2 mos
Class III: 2.3 mos

What is the Sperduto Index?

Show Answer

The Sperduto Index is a graded prognostic assessment based on age, KPS, # of brain mets, and the presence or absence of extracranial mets developed from an analysis of 1,960 pts in the RTOG database. Criteria is based on a point system:

0 points: age >60 yrs, KPS <70, >3 brain mets, presence of extracranial mets
0.5 points: age 50–59 yrs, KPS 70–80, 2 CNS mets

1 point: age <50 yrs, KPS 90–100, 1 CNS met, no extracranial mets

The sum of points predicts MS in mos:

0–1 point: 2.6 mos
1.5–2.5 points: 3.8 mos
3 points: 6.9 mos
3.5–4 points: 11 mos

(Sperduto P et al., IJROBP 2007)
What is the Diagnosis Specific Graded Prognostic Assessment (DS-GPA)?

Show Answer

The DS-GPA is a graded prognostic assessment developed from a retrospective database of 4,259 eligible pts from 11 institutions with determination of significant prognostic factors based on the primary histology. (Sperduto P et al., IJROBP 2010)
What are the significant prognostic factors?

Show Answer

The significant prognostic factors vary by Dx:

Non-small cell lung cancer (NSCLC)/small cell lung cancer: age, KPS, presence of extracranial mets and number of brain mets
Renal cell/melanoma: KPS and the number of brain mets
Breast/GI: KPS
In pts with untreated brain mets, what is the MS?

Show Answer

MS of untreated brain mets is **1 mo.**
What Tx may be used for brain mets?

Show Answer

Brain met Tx: steroids, Sg, fractionated RT (WBRT), and SRS

In pts with brain mets treated with steroids alone, what is the MS?

Show Answer

MS in pts with brain mets treated with steroids alone is **2 mos.**
What randomized data investigated pt survival or QOL with the addition of WBRT to best supportive care?

Show Answer

The completed MRC Quartz trial was a randomized, noninferiority phase III trial investigating the role of optimal supportive care (OSC) + WBRT (4 Gy × 5 fx) vs. OSC alone in pts with inoperable brain mets from NSCLC. The primary outcome measure was quality-adjusted life yrs (QALY). The trial did not show a difference in QALY with the addition of WBRT to OSC—though conclusions related to the specific population examined in the trial.
(Mulvenna P et al., Lancet 2016)
What are some criticisms of the QUARTZ trial?

Show Answer

Potential bias toward enrollment of pts with poor PS (40% with KPS <70), and perceived shorter life expectancy, as MS was ~2 mos compared to historical WBRT trials of ~4 months. Additionally, the WBRT dose/fractionation scheme is not routinely used in pts with perceived longer life expectancy, also suggesting there may have been a bias toward pts with shorter life expectancy/poor PS.
Why are steroids used for brain mets and how are they typically prescribed?

Show Answer

In pts with symptomatic brain mets, **steroids reduce leakage from tumor vessels,** therefore decreasing edema and mass effect. Steroid dose for newly diagnosed brain mets: **4 mg dexamethasone q6hrs;** may give initial loading dose of 10 mg. Other dosing regimens, such as dexamethasone 8 mg BID, are

occasionally used to simplify dose scheduling. Moving the last dose to early afternoon or evening can sometimes help mitigate the insomnia side effect.
What pharmacologic Tx should always accompany steroid Tx?

Show Answer

When prescribing steroids, also provide **GI prophylaxis with a proton-pump inhibitor or H2 blocker.**
Should anticonvulsants be used prophylactically?

Show Answer

No. In accordance with guidelines from the American Academy of Neurology, pts with newly diagnosed brain tumors should not be started on prophylactic anticonvulsants. (Glantz M et al., Neurology 2000) The 2010 guidelines from the American Association of Neurological Surgeons/Congress of Neurological Surgeons do not recommend routine prophylactic use of anticonvulsants. (Mikkelsen T et al., J Neurooncol 2010)
Are there any randomized data on the dose for WBRT?

Show Answer

Yes. The RTOG conducted several RCTs from 1970–1995 of WBRT alone, assessing different fractionation schemes. The 1st 2 trials **(RTOG 6901 and 7361)** included >1,800 pts randomized to 40 Gy/20, 40 Gy/15, 30 Gy/15, 30 Gy/10, or 20 Gy/5. No significant difference was found in response rates, length of response, or OS. The MS in the 1st study was 4.1 mos and 3.4 mos in the 2nd. (Borgelt B et al., IJROBP 1980)

2 ultrarapid fractionation schemes were also tested on these studies and reported separately; 10 Gy/1 **(RTOG 6901)** and 12 Gy/2 **(RTOG 7361)** in 26 and 33 pts, respectively. These schedules were associated with worse toxicity and time to neurologic progression than the standard fractionation. (Borgelt B et al., IJROBP 1981)

2 studies showed no MS advantage to giving a higher total dose. **RTOG**

7606 randomized 255 pts to 30 Gy/10 vs. 50 Gy/20. MS was 4.1 and 3.9 mos, respectively. (Kurtz J et al., IJROBP 1981) **RTOG 9104** randomized 429 pts to 30 Gy/10 vs. 54.4/1.6 Gy bid. MS was 4.5 mos in both arms. (Murray K et al., IJROBP 1997)

What dose and fractionation schemes are considered standard for WBRT?

Show Answer

The most commonly utilized WBRT dose is **30 Gy/10.** Pts with a good KPS and longer life expectancy may be treated to 37.5 Gy/15, 40 Gy/20, or 50 Gy/20. An alternative is 20 Gy/5 fx, particularly for pts with short prognosis.

What % of brain met pts have Sx improvement with WBRT?

Show Answer

WBRT improves Sx from brain mets in **~60%** of cases.

What is the rate of CR to WBRT for brain mets?

Show Answer

~25% of pts have a CR to WBRT for brain mets.

What data support Sg + RT rather than Bx + RT for brain mets?

Show Answer

The **1st Patchell study** for brain mets randomized 48 pts with 1 brain met and KPS ≥70 to Sg + WBRT vs. Bx + WBRT. WBRT in both arms was 36 Gy in 3 Gy/fx. Pts treated with Sg had a longer MS (40 wks vs. 15 wks, $p < 0.01$), longer functional independence (38 wks vs. 8 wks), and ↓LR (20% vs. 52%, $p < 0.02$). (Patchell R et al., NEJM 1990)

Did the Netherlands trial of WBRT +/- Sg support or refute the Patchell study?

Show Answer

The Noordijk study **supported** the findings of the 1st Patchell study. It randomized 63 pts to WBRT alone or Sg + WBRT. WBRT was 40 Gy in 2

Gy bid fx. Pts treated with Sg had improved MS (10 mos vs. 6 mos, p = 0.04) and longer functional independence (7.5 mos vs. 3.5 mos, p = 0.06). (Noordijk E et al., IJROBP 1994)
Does adj WBRT after surgical resection of a brain met improve OS?

Show Answer

No. Postop WBRT following resection of a brain met does not improve survival. In the **2nd Patchell study** for brain mets, 95 pts following surgical resection of a single met were randomized to no further Tx or WBRT (50.4 Gy in 1.8 Gy/fx). WBRT decreased LR (10% vs. 46%), decreased the rate of any brain failure (18% vs. 70%), and decreased the rate of neurologic death (14% vs. 44%) but did not significantly change MS (48 wks vs. 43 wks). (Patchell R et al., JAMA 1998)
Why did the investigators choose a nonstandard WBRT dose?

Show Answer

The dose and fractionation schedule were chosen to achieve 90% microscopic Dz control probability.
What are the indications for surgical resection?

Show Answer

Single lesion amenable to resection, controlled or absent extracranial Dz, **KPS >70, age <60 yo, life expectancy >2 mos, need for immediate relief of neurologic Sx secondary to mass effect, need to establish a tissue Dx.**
Are there any current randomized studies that support the role of adj WBRT?

Show Answer

Yes. EORTC 22952 enrolled 359 pts with 1–3 brain mets s/p Sg or SRS randomized to no further Tx vs. WBRT (30 Gy in 3 Gy/fx). Adj WBRT reduced the 2-yr relapse rate both at initial sites (Sg: 59% to 27%; SRS: 31% to 19%) and new sites (Sg: 42% to 23%; SRS: 48% to 33%) with decreased

rates of death secondary to intracranial progression (44% vs. 28%) **without** improvement in the duration of functional independence or OS. Pts randomized to observation were more likely to require salvage therapy (51% vs. 16%). (Kocher M et al., JCO 2010)

What is the rationale for SRS in the Tx of brain mets?

Show Answer

Spherical/pseudospherical target, generally noninfiltrative lesions (<3–4 cm) located along the gray–white junction (noneloquent regions), ability to deliver a higher dose than can be achieved with WBRT alone (improved LC), Tx of unresectable lesions; also, reduced risk of neurocognitive decline depending on location of lesion(s).

What was the 1st RCT study of WBRT +/- an SRS boost?

Show Answer

The 1st RCT of WBRT +/– an SRS boost was conducted at the **University of Pittsburgh.** 27 pts with KPS ≥70 and 2–4 mets ≤2.5 cm that were at least 5 mm from the chiasm were randomized to WBRT (30 Gy/12 fx) +/– a 16-Gy boost. The trial closed early b/c of significant difference in brain control. The SRS arm had a longer time to LF (36 mos vs. 6 mos, p = 0.0005) and longer time to any brain failure (34 mos vs. 5 mos, p = 0.002) but no difference in OS (11 mos vs. 7.5 mos, p = 0.11). (Kondziolka D et al., IJROBP 1999)

According to RTOG 9508, which pts had a survival advantage with the addition of an SRS boost to WBRT?

Show Answer

RTOG 9508 randomized 331 pts with 1–3 brain mets to WBRT + SRS boost vs. WBRT alone. WBRT on both arms was 37.5 Gy in 2.5 Gy/fx. The SRS boost dose was dependent on size in accordance with RTOG 9005. On univariate analysis, the addition of SRS improved the MS for pts with a single brain met (6.5 mos vs. 4.9 mos, p = 0.39). On subgroup MVA, RPA

class I pts had improved survival with the SRS boost, as did pts with a lung cancer primary. (Andrews D et al., Lancet 2004)
What is the main determinant in selecting the Rx dose for SRS Tx of a brain mets?

Show Answer

The SRS Rx dose for a brain met is determined by **size** in accordance with the results of **RTOG 9005,** a dose escalation study: 24 Gy if <2-cm diameter, 18 Gy if 2–3 cm, and 15 Gy if 3–4 cm. (Shaw H et al., IJROBP 1996)
In the RTOG SRS dose escalation study, did pts rcv WBRT?

Show Answer

Yes. In **RTOG 9005,** an SRS dose escalation study, 64% of pts had recurrent brain mets (median prior dose of fractionated RT 30 Gy) while 36% of pts had recurrent primary brain tumors (median initial dose of 60 Gy).
What retrospective data support the omission of upfront WBRT in pts treated with SRS for brain mets?

Show Answer

Sneed et al. compiled a database from 10 U.S. institutions to assess the effect of omitting upfront WBRT in pts treated with SRS for brain mets. 983 pts were analyzed and excluded pts treated with Sg (159 pts) and pts with a >1-mo interval b/t WBRT and SRS (179 pts). Of 569 evaluable pts, 268 had SRS alone and 301 had upfront WBRT + SRS. When adjusted for RPA class, there was no difference in survival. 37% of pts Tx with SRS alone rcvd salvage therapy (median 5.7 mos) vs. 7% of pts Tx with SRS + WBRT (median 8.0 mos). No LC data were provided. (IJROBP 2002)
What data argue against omission of WBRT following SRS alone?

Show Answer

Regine et al. retrospectively analyzed 36 pts Tx with planned observation following SRS alone (median dose 20 Gy). With an MS of 9 mos, brain

tumor recurrence occurred in 47% (17/16 pts) with 71% symptomatic at the time of recurrence and 59% with a neurologic deficit. (IJROBP 2002)
According to randomized data, what is the effect of delaying WBRT after SRS for pts with 1–4 brain mets?

Show Answer

JROSG99–1 showed that the omission of WBRT after SRS for 1–4 brain mets does not affect survival but increases the risk of intracranial relapse (46% with SRS + WBRT vs. 76.4% with SRS alone) and thus increases the need for salvage Tx. (Aoyama H et al., JAMA 2006)
What was the 1st randomized trial to assess the effect of delaying WBRT after SRS?

Show Answer

The 1st trial to assess the effect of delaying WBRT after SRS was **JROSG99–1.** 132 pts with 1–4 mets were randomized to SRS or WBRT + SRS. The SRS dose was based on size (lesions ≤2 cm to 22–25 Gy; lesions >2 cm to 18–20 Gy) and randomization (30% SRS dose reduction for pts on the WBRT arm). The WBRT dose was 30 Gy in 10 fx. (Aoyama H et al., JAMA 2006)
What prospective data support the omission of WBRT in pts treated with SRS alone?

Show Answer

Chang EL et al. randomized 58 pts with 1–3 brain mets (57% single) with KPS ≥70 to SRS alone vs. SRS + WBRT (30 Gy in 2.5 Gy/fx). SRS + WBRT resulted in a significant decline in 4-mo recall (24% vs. 52%) and median OS (15 mos vs. 6 mos) as compared to SRS alone. Pts treated with SRS + WBRT experience improved 1-yr LC (100% vs. 67%) and 1-yr distant brain control (73% vs. 44%) with SRS alone pts requiring more frequent salvage therapy. (Lancet 2009)

What are some criticisms of the Chang EL et al. trial?

Show Answer

Utilization of a single neurocognitive metric to assess learning and memory (HTLV-R) at a single time point (4 mos post-Tx); decreased survival in the SRS + WBRT group despite 100% 1-yr LC and improved neurologic DFS (73% vs. 27%); incomplete accrual (stopped early due to worse cognitive outcomes in the WBRT + SRS arm).

What were the results of the NCCTG (Alliance) N0574 study investigating SRS +/- WBRT?

Show Answer

N0574 reported on 213 pts randomized to SRS alone vs. SRS + WBRT (30 Gy in 2.5 Gy/fx), and also found improved LC at 3 mos with the addition of WBRT to SRS (97% vs. 75.3%). However, they also found no significant difference in OS b/t the 2 groups (10.4 mos with SRS alone vs. 7.4 mos), and additionally demonstrated improved QOL and less cognitive decline in the SRS alone group. This supports the recommendation for initial Tx of 1–3 newly diagnosed brain mets with SRS alone f/b close observation in order to preserve cognitive function. (Brown PD et al., JAMA 2016)

Are there any data on SRS dosing with planned WBRT?

Show Answer

Yes. Retrospective data from the **University of Kentucky** showed that optimal control of brain mets ≤2 cm was achieved with SRS of 20 Gy + WBRT. Pts treated with >20 Gy SRS + WBRT had higher rates of grade 3–4 neurotoxicity. (Shehata M et al., IJROBP 2004)

Are there any data comparing Sg + WBRT with SRS alone?

Show Answer

Yes. Retrospective data from **Germany** comparing RPA class I–II pts with 1–2 brain mets treated either with Sg + WBRT or SRS alone suggests that

SRS is as effective. Of 206 pts treated from 1994–2006, 94 pts had SRS alone (18–25 Gy), and 112 pts had resection + WBRT (30 Gy/10 or 40 Gy/20). At 12 mos, there was no difference in OS (~50% in both groups), LC, or brain control. There was no difference according to the RPA group. (Rades D et al., Cancer 2007)

What is the role for stereotactic body radiotherapy (SBRT)?

Show Answer

Large mets (>3 cm) and irregular shaped lesions correlate with inf outcomes and increased toxicity with SRS. Martens B et al. retrospectively analyzed therapeutic results in 75 pts with 108 intracranial mets (48% rcvd primary SBRT while 52% were treated following prior WBRT) with a variety of dose concepts (primary SBRT: 5 Gy × 6–7 fx and 6 Gy × 5 fx; recurrent SBRT 4 Gy × 7–10 fx and 5 Gy × 5–6 fx). A cumulative EQD2 (equivalent dose 2 Gy) of ≥35 Gy resulted in improved LC with acceptable toxicity. (Cancer 2012)

Can pts treated with WBRT for brain mets be reirradiated?

Show Answer

Yes. Wong WW et al. reported on a series of 86 pts Tx with reirradiation (median dose 20 Gy) due to progressive brain mets (median initial dose 30 Gy). 70% experienced neurologic improvement (24% complete resolution; 47% partial resolution). (IJROBP 1996)

What dose should be used for reirradiation after WBRT for brain mets?

Show Answer

The optimal dose for reirradiation after WBRT is **unknown.** 20 Gy in 10 fx is often used.

How are the fields arranged for WBRT?

Show Answer

WBRT is delivered using opposed lat fields; a post gantry tilt of 3–5 degrees

is used to avoid divergence into the eyes; and multileaf collimation or custom blocks are used to ensure adequate coverage of the cribriform plate, temporal lobe, and brainstem while protecting the eyes, nasal cavity, and oral cavity. The inf border is generally set at C1–2.

Should Sg be used for recurrent tumors?

Show Answer

Yes. Retrospective data from MDACC have suggested that reoperation for recurrent brain mets can prolong survival and improve QOL. MVA revealed several negative prognostic factors: presence of systemic Dz, KPS <70, short time to recurrence (<4 mos), age ≥40 yrs, and breast and melanoma primaries. (Bindal R et al., J Neurosurg 1995)

What is the advantage of tumor bed radiosurgery after brain met resection?

Show Answer

Retrospective data from the University of Sherbrooke in Canada have suggested that SRS to the tumor bed following resection for brain mets achieves LC rates that are comparable to WBRT but does not impact the development of remote brain mets. 40 pts underwent resection → SRS at a median of 4 wks post resection. 73% achieved LC, and 54% developed new brain mets. (Mathieu D et al., Neurosurgery 2008)

Are any prospective trials investigating the role of SRS vs. WBRT for resected metastatic brain Dz?

Show Answer

Yes, RTOG 1270 is an RCT open to accrual investigating the role of postop SRS boost to the surgical cavity vs. adj WBRT following surgical resection of intracranial mets. Interim analysis reported at the ASTRO 2016 annual meeting suggest equivalent survival with improved preservation of cognitive function with SRS, however greater long-term control of CNS mets with

WBRT. The study is ongoing, and formal publication is awaited.

Are professional guidelines available to provide Tx recommendations for pts with newly diagnosed brain mets?

Show Answer

Yes, ASTRO published an evidence-based guideline of Tx recommendations dependent on the goal of Tx (survival, LC, distant brain control, and neurocognitive function) and estimated prognosis. (PRO 2012)

What is the recommended interval for surveillance imaging after Tx of brain mets?

Show Answer

MRI is generally recommended every 2–4 mos in pts with good PS and potential for salvage therapy if additional mets are identified.

FOLLOW-UP/TOXICITY

What are potential acute toxicities of WBRT?

Show Answer

Potential WBRT acute toxicities: alopecia, fatigue, HA, n/v, ototoxicity

What are potential long-term toxicities of WBRT?

Show Answer

Potential WBRT chronic toxicities: thinned hair, decline in short-term memory, altered executive function, leukoencephalopathy, brain atrophy, normal pressure hydrocephalus, RT necrosis

What is the relationship between WBRT-induced brain mets shrinkage and neurocognitive function?

Show Answer

WBRT-induced brain met shrinkage correlates with improved neurocognitive function. This was demonstrated in an analysis of 208 pts with brain mets

randomized to WBRT alone on a phase III trial of WBRT +/– motexafin gadolinium. Pts with a good response to WBRT (>45% tumor volume reduction at 2 mos) had a longer time to decline in neurocognitive function. (Li J et al., JCO 2007)
What is the reported risk of severe dementia with WBRT?

Show Answer

DeAngelis L et al. reported an 11% (5 pts) risk of radiation-induced dementia in long-term brain mets survivors (>12 mos) based on a retrospective review of 47 pts Tx with WBRT. 3 pts were treated with nonstandard fractionation, 1 pt rcvd concurrent Adr, and 1 pt rcvd 30 Gy in 3 Gy/fx with a radiosensitizer. Of 15 pts Tx with **<3 Gy/fx without systemic therapy, 0 developed severe dementia or neurocognitive Sx.** (Neurosurgery 1989)
What is the most important determinant of neurocognitive function?

Show Answer

The most important determinant is brain tumor control/delay of intracranial progression.
What other factors contribute to neurocognitive decline?

Show Answer

Anticonvulsants, benzodiazepines, opioids, chemo, surgical intervention (craniotomy), and systemic progression of Dz
What daily fx size in WBRT is associated with RT necrosis?

Show Answer

WBRT administered in fx sizes **>3 Gy/day** are associated with RT necrosis. (DeAngelis L et al., Neurology 1989)
Name the potential acute toxicities of SRS for brain mets.

Show Answer

Potential acute toxicities of SRS for brain mets: HA, nausea,

dizziness/vertigo, seizure

What is the risk of symptomatic RT necrosis after SRS for brain mets?

Show Answer

There is an **~5%** risk of symptomatic RT necrosis secondary to SRS for brain mets. This is usually treated with steroids but may require Sg or bevacizumab for refractory cases.

What are the dose limits to critical structures with SRS?

Show Answer

Brainstem 12.5 Gy, optic chiasm or optic nerves 10 Gy, other cranial nerves 12 Gy

87

Bone Mets

Updated by W. Tristram Arscott

BACKGROUND

What are the top 3 sites of metastatic Dz?

Show Answer

Top 3 sites of metastatic Dz:

. Lung
. Liver
. Bone

What is the route of spread of cancer cells to the bone?

Show Answer

Most bone mets arise from **hematogenous** spread of cancer cells.
What part of the skeleton is more commonly affected by bone mets: axial or appendicular?

Show Answer

Bone mets more commonly affect the **axial** rather than the appendicular skeleton.
What part of the spine is most commonly affected by bone mets?

Show Answer

The T spine is the most common site of bone mets. (Bartels RH et al., CA

Cancer J 2008)

What 5 tumors are known to stimulate osteoclast activity?

Show Answer

Tumors known to stimulate osteoclast activity:

. Breast
. Prostate
. Lung
. Renal
. Thyroid

In decreasing order, what 5 tumors carry the highest risk of bone mets?

Show Answer

Top 5 tumors with regard to the risk of bone mets (in decreasing order):

. Prostate
. Breast
. Kidney
. Thyroid
. Lung

What is the most common presenting Sx of bone mets?

Show Answer

Most pts with bone mets present with **pain.**

WORKUP/STAGING

What is the workup for bone mets?

Show Answer

Bone met workup: H&P, characterization of pain, assessment of fracture risk, assessment for weight-bearing bone, orthopedic consult as necessary, plain films, and bone scan

What imaging test is 1st line in evaluating bone mets?

Show Answer

Initial imaging of asymptomatic bone mets usually involves a **bone scan** (skeletal scintigraphy). If symptomatic, directed plain films and bone scan as well as subsequent clinically directed CT and/or MRI may be beneficial.
When may plain films be useful when evaluating bone mets?

Show Answer

In the setting of **bone pain with a positive bone scan,** plain films may show an impending fracture or a pathologic fracture.
What cancer is associated with mixed lytic and sclerotic lesions?

Show Answer

Breast cancer is associated with mixed sclerotic and lytic lesions.
What cancers are associated with primarily blastic lesions?

Show Answer

Tumors with predominantly blastic lesions:

- Prostate
- Small cell lung cancer
- Hodgkin lymphoma

What cancers are associated with primarily lytic lesions?

Show Answer

Tumors with predominantly lytic lesions:

- Renal cell
- Melanoma
- Multiple myeloma
- Thyroid
- Non–small cell lung cancer

. NHL

What imaging test can help to differentiate degenerative Dz from mets?

Show Answer

CT and/or MRI can help to distinguish b/t degenerative Dz and bone mets.
When cord compression is suspected, what imaging is indicated?

Show Answer

MRI of the entire spine is indicated if cord compression is suspected.
What scoring system predicts for pathologic fracture?

Show Answer

The **Mirels scoring system** is a weighted system based on a retrospective review that predicts the risk of pathologic fracture through metastatic lesions in long bones. Score ranges from 4–12. A score <7 can be treated with RT alone, while a score ≥8 requires internal fixation prior to RT. (Mirels H et al., Clin Ortho Res 1989)
What are the components of the Mirels scoring system?

Show Answer

Score	Pain	Location	Cortical Destruction	Appearance
1	Mild	Upper limb	<1/3	Blastic
2	Moderate	Lower limb	1/3–2/3	Mixed
3	Severe	Peritrochanteric	>2/3	Lytic

(Mirels H et al., Clin Ortho Res 1989)
What 2 risk factors predict for pathologic fracture of the femur?

Show Answer

Factors predicting for pathologic fracture of the femur:

(Van der Linden Y et al., J Bone Joint Surg Br 2004)

. Axial cortical involvement >30 mm
. Circumferential cortical involvement >50%

What scoring system can predict for stability of a spine met, and what are its components?

Show Answer

The Spine Instability Neoplastic Score (SINS) was found to be a useful tool to evaluate spine stability. It takes into account location (junctional are higher risk), pain, bone lesion type (lytic are higher risk), spinal alignment on films, degree of vertebral height collapse (>50% is higher risk), and involvement of post spinal elements (bilat is higher risk). Higher scores predicted higher risk. Refer to Fourney et al., JCO 2011.

TREATMENT/PROGNOSIS

Name 6 Tx for bone mets.

Show Answer

Bone met Tx:

. Chemo
. Radionuclides
. Local EBRT
. Endocrine therapy
. NSAIDs
. Narcotics

What supportive measures can be used for pts with painful bone mets?

Show Answer

Supportive care for bone mets may include orthopedic braces such as

thoracolumbosacral orthosis, canes, walkers, and wheelchairs.
What interventional procedures can decrease pain from cancer-associated vertebral body collapse (i.e., compression fracture)?

Show Answer

Kyphoplasty and vertebroplasty are procedures performed by interventional radiologists that can address pain from vertebral body collapse. They are often performed in conjunction with EBRT.
What is the difference b/t kyphoplasty and vertebroplasty?

Show Answer

Vertebroplasty utilizes fluoroscopic guidance to inject bone cement (methyl methacrylate) into the collapsed vertebral body. In **kyphoplasty,** an inflatable bone tamp is inserted to restore the height of the vertebral body, creating a cavity that can be filled with bone cement.
According to the ASTRO Guidelines for Palliative RT for bone mets, what factors favor the inclusion of surgical decompression in addition to EBRT for SC compression?

Show Answer

. Solitary site of tumor progression
. Absence of visceral or brain mets
. Spinal instability
. Age <65 yrs
. KPS ≥70
. Projected survival >3 mos
. Slow progression of neurologic Sx
. Maintained ambulation
. Nonambulatory for <48 hrs
. Relatively radioresistant tumor (i.e., melanoma)
. Site of origin suggesting relatively indolent course (i.e., prostate, breast,

kidney)

. Previous EBRT failed

(Lutz S et al., PRO 2017)

In what cancers may chemo eradicate bone mets?

Show Answer

Chemo can cure bone mets from **lymphomas and germ cell tumors.**

What is the chief action of bisphosphonates? Name 2 common ones.

Show Answer

Bisphosphonates **inhibit osteoclast activity. Pamidronate and zoledronic acid** are 2 common bisphosphonates.

What is denosumab (XGEVA)?

Show Answer

Denosumab is a fully human monoclonal antibody that targets receptor activator of nuclear factor-kappa beta ligand (**RANKL**), thereby inhibiting maturation of osteoclasts.

What are the American Society for Clinical Oncology (ASCO) 2017 guidelines for bone-modifying agents (BMAs) in the Tx of bone mets from breast cancer?

Show Answer

ASCO 2017 guidelines state that either zoledronic acid (IV, q6mos) or clodronate (PO, daily) should be given to postmenopausal women deemed candidates for adj therapy. Data for denosumab are promising, however not included in the current guidelines due to insufficient evidence. BMAs are adjunctive therapy, not recommended for 1st-line therapy and should be used concurrently for pain relief with analgesics, chemo, RT, and/or hormonal therapy. (Dhesy-Thind S et al., JCO 2017)

Name 4 radionuclides used to treat bone mets.

Show Answer

Radionuclides available in the United States for Tx of bone mets:

. Strontium-89
. Samarium-153
. Phosphorus-32
. Radium-223 (currently for prostate cancer only)

For each of these radionuclides, name the method of decay, half-life, avg particle energy per decay, and particle range.

Show Answer

	Sr-89	**Sm-153**	**P-32**	**Ra-223**
Decay method	β emission to Y-89	β and γ emission	β emission to S-32	α emission
Half-life	50.6 days	1.9 days	14.3 days	11.4 days
Avg decay energy	0.58 MeV	0.22 MeV	0.69 MeV	27.4 MeV
Range	7 mm	4 mm	8.5 mm	<0.1 mm

Describe the clinical implications of the differences in physical properties between strontium-89, samarium-153, phosphorus-32, and radium-223.

Show Answer

. Both strontium-89 and phosphorus-32 emit β particles with higher energy than those of samarium-153, causing deeper tissue penetration. Though these higher-energy β particles may have a therapeutic benefit, they can also cause greater marrow toxicity.
. The half-life of samarium-153 is much shorter than that of strontium-89. Thus, the planned RT dose from samarium-153 is delivered more quickly,

leading to faster time to pain relief in many published trials.

- Radium-223 emits high-energy α particles, which have high linear energy transfer inducing double-stranded DNA breaks, but a short range resulting in very limited toxic effects on adjacent healthy tissues.

Why is phosphorus-32 seldom used for bone mets?

Show Answer

Phosphorus-32 was the 1st radionuclide to be used for bone mets, but it has **greater hematologic toxicity** compared with the other radionuclides available in the United States.

When should radionuclides be considered?

Show Answer

Radionuclides should be considered in pts with **adequate blood counts and multifocal painful bone mets** imaged on bone scan.

What are some contraindications to radionuclides for bone pain?

Show Answer

Contraindications for using radionuclides for bone pain:

- Myelosuppression
- Impaired renal function
- Pregnancy
- Cord compression
- Nerve root compression
- Impending pathologic fracture
- Extensive ST component

What randomized data support the use of samarium-153?

Show Answer

A **double-blind placebo controlled study** of samarium-153 supports its use.

118 pts with symptomatic bone mets were randomized to low-dose samarium-153 (0.5 mCi/kg), high-dose samarium-153 (1 mCi/kg), or placebo. Pts receiving high-dose samarium-153 had significant improvement in pain during the 1st 4 wks per pt and medical evaluation. Relief persisted until at least wk 16 in 43% of pts. There was a significant reduction in the pain score and analgesic use only in pts receiving the high dose. (Serafini A et al., JCO 1998)
What randomized data supports the use of radium-223?

Show Answer

ALSYMPCA is a multi-institution **double-blind placebo controlled study** of radium-223 that showed an **OS benefit** for pts with castrate-resistant metastatic prostate cancer (14.9 mos vs. 11.3 mos, $p < 0.001$). 901 pts completing Tx were randomized 2:1 to 6 IV injections of radium-223 (dose 50 kBq/kg) q4wks vs. placebo injections on the same schedule. The trial was stopped early due to OS benefit on planned interim analysis. (Parker C et al., NEJM 2013)
What RTOG study originally reported no difference in bone pain relief b/t different fractionation schemes?

Show Answer

RTOG 7402 randomized 759 pts. Those with solitary bone mets were randomized to 40.5 Gy (2.7 Gy × 15) vs. 20 Gy (4 Gy × 5). Pts with multiple mets were randomized to 30 Gy (3 Gy × 10), 15 Gy (3 Gy × 5), 20 Gy (4 Gy × 5), or 25 Gy (5 Gy × 5). The initial report revealed that 90% of pts had some pain relief, and 54% had eventual CR of pain. There was no difference b/t regimens. (Tong D et al., Cancer 1982) Reanalysis showed that a higher # of fx correlated with CR of pain, suggesting that a more protracted course was more effective. The analysis was based only on physician assessment of pain. (Blitzer P et al., Cancer 1985)
Which pts are generally excluded from RCTs of different fractionations

for bone-met RT?

Show Answer

RCTs assessing different fractionation schemes for the Tx of bone mets have generally excluded **pts with cord compression and pathologic fracture.**
Did the study by the Bone Pain Trial Working Party support single- or multi-fx Tx of bone mets?

Show Answer

The Bone Pain Trial Working Party supported **single-fx** Tx. The study (UK/NZ) randomized 765 pts with painful bone mets to 8 Gy × 1 vs. a protracted regimen (2 Gy × 5 or 3 Gy × 10). Pain relief was evaluated for up to 1 yr post-Tx by the use of a validated pt questionnaire. There was no difference in pain control b/t the arms. Re-Tx was twice as common with single-fx Tx (23% vs. 10%), though this may have been due to a greater willingness to re-treat pts who rcvd only 8 Gy × 1. (No author, Radiother Oncol 1999)
Did the Dutch Bone Metastasis Study support single- or multi-fx Tx of bone mets?

Show Answer

The Dutch Bone Metastasis Study supported **single-fx** Tx. 1,171 pts were randomized to 8 Gy × 1 fx vs. 4 Gy × 6 fx. Pain relief was evaluated for up to 2 yrs post-Tx by the use of a validated pt questionnaire. No difference was seen with respect to pain relief. However, re-Tx was more common in the single-fx arm (25% vs. 7%). (Steenland E et al., Radiother Oncol 1999)
Reanalysis suggested that the higher rate of re-Tx in the single-fx arm may be related to a greater willingness to re-Tx pts who rcvd only 8 Gy × 1 fx. (Van der Linden YM et al., IJROBP 2004)
Did RTOG 9714 support single- or multi-fx Tx of bone mets?

Show Answer

RTOG 9714 supported **single-fx Tx.** The study randomized 898 pts with breast or prostate cancer to 8 Gy × 1 fx vs. 3 Gy × 10 fx. There was no difference in complete pain relief (15% vs. 18%) or partial pain relief (50% vs. 48%), but there was increased acute toxicity in the 3 Gy × 10 arm (10% vs. 17%). The re-Tx rate was significantly greater in the 8 Gy × 1 arm. (Hartsell W et al., JNCI 2005)

What were the results of the Chow et al. meta-analysis of trials comparing single- vs. multi-fx Tx of bone mets?

Show Answer

In this meta-analysis of trials comparing single- vs. multi-fx Tx of bone mets, no significant differences b/t fractionation schemes with respect to pain control were shown. However, re-Tx was more common with single-fx Tx. (Chow et al., JCO 2007)

What study supported use of hemibody irradiation (HBI) after focal RT for bone mets?

Show Answer

RTOG 8206 randomized pts treated with focal RT to HBI (8 Gy) vs. no further Tx. HBI increased the time to progression as well as the time to re-Tx. (Poulter C et al., IJROBP 1992) This continues to be studied.

What are the published response rates of RT for palliation of symptomatic bone mets irrespective of the fractionation scheme?

Show Answer

The published response rates of RT for palliation of symptomatic bone mets are **60%–80%.**

What is the benefit of PORT after orthopedic stabilization?

Show Answer

PORT following orthopedic stabilization of impending or pathologic fracture decreases the need for 2nd Sg (2% vs. 15%) and increases the rate of

regaining normal function (53% vs. 11.5%) as c/w Sg alone. (Townsend P et al., JCO 1994)

What data support the use of SBRT/SRS for spinal mets?

Show Answer

Prospective nonrandomized data from the **University of Pittsburgh** support the use of SRS for spinal mets. 500 cases were treated with CyberKnife to a median dose of 20 Gy. SRS improved pain in 86% of cases (defined as a 3-point improvement on a 10-point pain scale). The majority of pts had prior Tx; however, in the 65 cases treated with SRS as the primary modality, the LC was 90%. (Gerstzen P et al., Spine 2007)

The current ASTRO 2017 Bone Mets Guidelines recommend that pts be part of ongoing clinical trials or registries if being treated with SBRT to mets, in order to collect toxicity and effectiveness data, of which solid and comparative data are lacking.

What factors contribute to median survival in pts with bone mets, and what is the MS of pts who present for palliative RT?

Show Answer

Risk factors: (1) non-breast primary, (2) sites of mets other than bone, (3) KPS ≤60.

# of risk factors	**MS**
0–1	**~60 wks**
2	**~25 wks**
3	**~10 wks**

(Chow E et al., JCO 2008)

When should re-Tx of previously treated painful bone mets be considered?

Show Answer

ASTRO 2017 consensus statement on bone mets recommends re-Tx of met sites if they are still painful after or pain recurs >1 mo post-Tx, including both spine and peripheral sites of pain recurrence.

FOLLOW-UP/TOXICITY

What are the expected acute and late RT toxicities associated with Tx of bone mets?

Show Answer

Potential toxicities from focal RT for bone mets:

Acute: skin irritation, pain flare (30%–40% of pts)
Late: fibrosis, nerve damage, fracture, lymphedema

What can be done to reduce pain flare caused by radiating bone mets?

Show Answer

Dexamethasone 8 mg given at least 1 hr prior to the start of RT Tx and then for 4 days following Tx has been shown to reduce pain flare by nearly 10% in a phase III randomized trial. Hyperglycemic events only occurred in 3 pts in the dexamethasone group (2%), and none with adverse consequences. (Chow E et al., Lancet 2015)

What is the main toxicity of radionuclide Tx?

Show Answer

Radionuclide Tx can cause **significant myelosuppression.**

Have there been increased toxicities reported from single fx (8 Gy × 1) vs. multi-fx palliative regimens?

Show Answer

No, the ASTRO 2017 guidelines statement summarizes the numerous clinical trials of single-fx vs. multi-fx regimens for palliation of pain, including no increased risk of RT myelopathy for the Tx of spine mets from single-fx regimens.

88

Cord Compression

Updated by Michael J. LaRiviere

BACKGROUND

What % of cancer pts develop cord compression?

Show Answer

5%–10% of cancer pts develop cord compression.

What is the MS in pts with cord compression?

Show Answer

MS in pts with cord compression is ~3 mos (dependent on Hx of primary, extent of visceral/osseous met, degree of motor dysfunction, and PS).

What is the most important prognostic factor?

Show Answer

Pre-Tx ambulatory status directly influences functional outcome and survival.

What are 3 routes of metastatic spread to the spine?

Show Answer

Routes of metastatic spread to the spine: hematogenous, direct extension, and CSF. (Abeloff's Clin Oncology, 5th ed., 2014)

What malignancies commonly cause cord compression?

Show Answer

Lung, breast, and prostate each account for 15%–20% of cases, whereas renal

cell, lymphoma, and multiple myeloma each account for 5%–10% of cases of cord compression.
What is the most common site of origin?

Show Answer

Cord compression origin: epidural (extradural) in 95% > leptomeningeal (intradural extramedullary) in 4%–5% > intramedullary in 0.5%–1%
How do pts with cord compression present?

Show Answer

Presenting Sx of cord compression: back pain, radicular pain, weakness, sensory deficits, bowel/bladder dysfunction, and paralysis
What is the most common presenting Sx of cord compression?

Show Answer

The most common Sx of cord compression is **back pain** present in 90%–95% of pts (often precedes neurologic Sx > 2 mos).
Describe the presentation of cauda equina syndrome.

Show Answer

Presenting Sx of cauda equina syndrome: pain, LE weakness, sensory disturbance (“saddle anesthesia”), and autonomic dysfunction including urinary retention and fecal incontinence
What is the pathophysiology of cord compression?

Show Answer

Gradual progression results in epidural venous congestion, vasogenic edema, and demyelination (potentially reversible) while rapid progression results in disruption of arterial blood resulting in ischemia and cord infarction (irreversible).
What part of the vertebra is most commonly involved by metastatic Dz?

Show Answer

Metastatic Dz typically involves the **vertebral body** rather than the post elements. Compression originates directly from the vertebrae (85%–90%) or via neural foramina extension (5%–10%).
What part of the spine is most often involved in cord compression?

Show Answer

The **T** spine (70%) is most commonly affected by cord compression > lumbosacral (20%) > cervical (10%).

WORKUP/STAGING

Describe the workup of cord compression.

Show Answer

Cord compression workup: H&P with careful attention to complete neurologic exam to include DRE, evaluation of sensation to determine level of the lesion, assessment of pain, prior cancer management to include prior RT, assessment of bowel/bladder function, and screening MRI of the full cervical/thoracic/lumbar (C/T/L) spine
Why is a screening MRI of the spine ordered to evaluate cord compression?

Show Answer

Pts with suspected cord compression should be evaluated with a screening MRI of the full C/T/L spine b/c **multilevel involvement is not uncommon.**
Is a gadolinium-enhanced MRI necessary to evaluate cord compression?

Show Answer

No, it is not required to diagnose epidural compression. Contrast improves identification of leptomeningeal and intramedullary mets.
Why is CT useful in evaluating cord compression?

Show Answer

CT evaluation of SC compression **helps to delineate osseous structures,** including retropulsed fragments, and **aids in surgical planning.**

TREATMENT/PROGNOSIS

What modalities are used to treat SC compression?

Show Answer

Modalities used to treat SC compression: steroids, Sg, and RT (in select cases chemo is used for chemosensitive tumors)

What is the initial management of cord compression?

Show Answer

For initial management of cord compression, start dexamethasone (include GI prophylaxis with proton-pump inhibitor or H2 blocker) and consult neurosurgery or orthopedics, depending on the institution, to assess spine stability. If there is any concern for a hematologic malignancy without Bx proof, stat multidisciplinary discussion is needed before starting steroids to consider whether to Bx first.

What initial bolus dose of dexamethasone should be used in cord compression?

Show Answer

For newly diagnosed cord compression, a loading dose of 10 mg IV is generally given → 4 mg orally q6hrs. Vecht CJ et al. randomized 37 pts to 10 mg IV vs. 100 mg IV, both → 16 mg daily in divided oral doses. There was no difference in pain control, rate of ambulation, or bladder function. (Neurology 1989) In practice, a higher loading dose of 20 mg IV dexamethasone can be considered in cases of severe neurologic dysfunction.

Historically, what type of Sg was used to treat SC compression?

Show Answer

Historically, **laminectomy** was used to treat SC compression. However, this was abandoned b/c it can lead to instability, and improved surgical stabilization techniques have allowed for ant decompressive approaches.
What pts with cord compression are appropriate for decompressive Sg?

Show Answer

Pts with MRI evidence of cord compression in a single area and a life expectancy >3 mos who do not have radiosensitive tumors (lymphomas, leukemias, germ cell tumors, and multiple myeloma) may be good candidates for decompressive Sg → RT. (Patchell R et al., Lancet 2005)
What are further indications for Sg?

Show Answer

Spinal instability and/or bony retropulsion, previous RT, Dz progression despite RT, unknown primary tumor (therapeutic and diagnostic), paraplegia <48 hrs
What was the trial design and outcome of the Patchell study of decompressive Sg for cord compression?

Show Answer

The Patchell cord compression trial was a multi-institutional RCT of 101 pts with MRI-confirmed SC compression restricted to a single area with >3-mo life expectancy. Exclusion criteria included being paraplegic >48 hrs, radiosensitive tumors, Hx of prior cord compression, and other pre-existing neurologic conditions. Pts were randomized to decompressive Sg + RT vs. RT alone. RT was 30 Gy/10 delivered to the lesion + 1 vertebral body above and below. Sg was tailored to the individual lesion to provide circumferential decompression and stabilization as needed (ant corpectomy for 60% of cases involving only the vertebral body). The study was stopped at interim analysis. Sg significantly improved the ambulatory rate (84% vs. 57%), duration of ambulatory status (122 days vs. 13 days), and survival (126 days vs. 100

days). Pts nonambulatory prior to Tx were more likely to walk after Sg (62% vs. 19%). (Patchell R et al., Lancet 2005)
What are some criticisms of the Patchell data?

Show Answer

RT alone results were worse than historical prospective controls, small sample size, 18 pts in the RT alone group had an “unstable” spine, Sg provides immediate decompression in pts with rapid onset of Sx (delayed response with RT).
Can Sg be delayed following RT?

Show Answer

Due to a decline in neurologic function (nonambulatory), 10 pts in the RT group (20%) underwent Sg; 3 regained the ability to walk (30%) with results inf to Sg upfront.
Is SBRT utilized for primary Tx of cord compression?

Show Answer

No. Although ASTRO guidelines suggest that SBRT can be considered as part of a clinical trial or prospective registry, direct tumor contact with the SC (epidural compression within 3 mm) and/or spinal instability are considered contraindications to SBRT.
What pts with cord compression should be treated with RT alone?

Show Answer

Cord compression pts treated with RT alone: life expectancy <3 mos, no spinal instability or bony compression, multilevel involvement and radiosensitive tumor
Estimate the survival for a pt with metastatic SC compression.

Show Answer

Rades et al. reviewed 1,852 pts with cord compression and found that

survival depends on 6 factors. Validated in a series of 439 pts, they developed a scoring system that includes:

– **tumor histology** (myeloma/lymphoma = 9, breast = 8, prostate = 7, other = 4, lung = 3)
– **Dx to metastatic cord compression** (>15 mos = 7, ≤15 mos = 4)
– **additional visceral mets** (no = 8, yes = 2)
– **additional bone mets** (no = 7, yes = 5)
– **ability to ambulate** (yes = 7, no = 3)
– **days since the development of motor deficits** (>14 = 8, 8–14 = 6, ≤7 = 3)

6-mo OS by score was:

– 36–45 points: 80%
– 31–35 points: 56%
– 20–30 points: 14%

(Cancer 2010)
Does the interval b/t development of motor deficits and RT predict response?

Show Answer

Yes, a longer time interval results in **improved** functional outcome. A retrospective review of 96 pts demonstrated improved function in 86% of pts when motor Sx were present >14 days. In contrast, only 10% improved when Sx were present <7 days. (Rades D et al., IJROBP 1999)
How are conventional RT fields arranged to treat the cervical, thoracic, and lumbar spine?

Show Answer

Field arrangement for cord compression:

Encompass the lesion + 1–2 vertebral levels above and below.

Cervical: opposed lats
Thoracic: AP/PA or PA alone, respecting cord tolerance
Lumbar: AP/PA
Are there data to support the use of hypofractionation for cord compression?

Show Answer

Marranzano et al. enrolled 300 pts with metastatic SC compression and short life expectancy (≤6 mos) randomized to short-course (8 Gy × 2 fx, 1 wk apart) or split-course (5 Gy × 3 fx, 4-day rest, and then 3 Gy × 5 fx). No significant difference was observed b/t the 2 schedules with median f/u of 33 mos (response, duration of response, survival or toxicity). (JCO 2005)
A f/u trial randomized 327 pts to 8 Gy × 2 fx (1 wk apart) vs. 8 Gy × 1 fx without a difference in outcome. No myelopathy was registered with a median f/u of 31 mos. (Radiother Oncol 2009)

More recently, in the SCORE-2 trial, Rades et al. randomized 203 pts with poor to intermediate expected survival to 4 Gy × 5 fx vs. 3 Gy × 10 fx; 155 pts were evaluable at 1 mo. Motor function was stable or improved in 87.2% vs. 89.6% (NSS), and ambulation was 71.8% vs. 74.0% (NSS). Similarly, no significant difference in ambulation was seen at 3 or 6 mos. (JCO 2016)

In addition, Hoskin et al. recently presented SCORAD III at ASCO 2017 which randomized 688 pts with SC compression to 8 Gy × 1 vs. 4 Gy × 5; ambulatory status at 8 wks was 69.5% with single fx and 73% with 5 fx (NSS) and OS was similar at 12.4 wks vs. 13.7 wks. Final manuscript pending.

Is reirradiation possible with recurrent cord compression?

Show Answer

Rades et al. reviewed the outcome of 124 pts with in-field recurrence (69% ambulatory) with improvement in 36% and stable motor function in 50%

with reirradiation. No RT myelopathy was observed at a median f/u of 11 mos with cumulative BED ≤120 Gy2 in 92%. (Cancer 2008)

Maranzano et al. analyzed Italian data from 2 randomized trials and found 12 pts who rcvd SC reirradiation. Re-Tx preserved ambulation in 6/7 pts, but not reverse nonambulatory status in the remaining 5/5 pts. All pts died prior to analysis, but with 5 mos MS (1–24 mos), no RT myelopathy was seen. (Radiother Oncol 2011)

In 2014, Rades et al. reported that among pts aged 65 or older, reirradiation was safe, with motor improvement in 42% of 60 pts at 1 mo and 69% of 32 pts alive at 6 mos. No difference was seen b/t 8 Gy × 1, 4 Gy × 5, 3 Gy × 5–7, and 2 Gy × 10–12. No in-field recurrences were reported after reirradiation. At death or median 7 mos (2–45 mos) f/u, no RT myelopathy was seen. The pts' cumulative BED was 80–137 Gy2 (median 100 Gy2, α/β = 2). (Anticancer Research 2014)

FOLLOW-UP/TOXICITY

What are potential acute toxicities of RT for cord compression?

Show Answer

Potential toxicities of RT for cord compression: odynophagia, globus, esophagitis, nausea, diarrhea, myelosuppression, rare SC injury

89

SVC Syndrome

Updated by W. Tristram Arscott

BACKGROUND

What vessels form the SVC?

Show Answer

The **right and left brachiocephalic veins** join to form the SVC.

What is SVC syndrome?

Show Answer

SVC syndrome is extrinsic or intrinsic obstruction of blood flow through the SVC, leading to venous congestion proximal to the obstruction.

Describe the course of the SVC.

Show Answer

The SVC begins at the **sternal angle,** extends inferiorly along the right lat side of the ascending aorta, and inserts into the right atrium.

What predisposes the SVC to compression?

Show Answer

The SVC is a thin-walled vessel with relatively low intravascular pressure and is therefore susceptible to compression by **surrounding rigid structures** including enlarged LNs and the trachea, sternum, pulmonary artery, and right main stem bronchus.

What vessels form the collateral system of the SVC?

Show Answer

The collateral system of SVC is formed by the azygos, mammary, vertebral, lat thoracic, paraspinous, and esophageal vessels.
What vessels join to form the azygos vein?

Show Answer

The **right subcostal and right ascending lumbar veins** coalesce to form the azygos vein.
What is the most common cause of SVC syndrome?

Show Answer

Malignancy is the most common cause of SVC syndrome accounting for ~60% of cases. Malignancy previously accounted for 90% of cases, but with increased use of implantable intravenous devices (i.e., central venous catheters, pacemaker leads), this has decreased. (McCurdy M et al., Crit Care Med 2012)
Name 5 benign causes of SVC syndrome.

Show Answer

Benign causes of SVC syndrome:

. Catheter-induced thrombosis
. Chronic mediastinitis
. Retrosternal goiter
. CHF
. Aortic aneurysm

Name 6 cancers most commonly associated with SVC syndrome, in decreasing order of incidence.

Show Answer

Cancers associated with SVC syndrome:

. NSCLC: 50%
. SCLC: 22%
. Lymphoma: 12%
. Mets: 9%
. Germ cell tumors: 3%
. Thymoma: 2%

(Wilson L et al., NEJM 2007)
Are NSCLC or SCLC pts more likely to develop SVC syndrome?

Show Answer

SCLC pts are more likely to develop SVC syndrome than NSCLC pts b/c of their propensity toward rapid growth in central airways.
What is the most common cause of SVC syndrome in pts <50 yo?

Show Answer

In pts <50 yo, the most common cause of SVC syndrome is **lymphoma.**
Which types of NHL are associated with SVC syndrome?

Show Answer

NHL types associated with SVC syndrome:

. Diffuse large B-cell lymphoma
. Lymphoblastic lymphoma
. Primary mediastinal B-cell lymphoma

What is the typical duration of Sx prior to presentation with SVC syndrome?

Show Answer

Pts with SVC syndrome may have Sx over days to wks but usually present **within 1 mo of onset.**

Do most pts presenting with SVC syndrome have a prior cancer Dx?

Show Answer

No. Most pts presenting with SVC syndrome do not have a prior cancer Dx.
Why is SVC syndrome considered an emergency?

Show Answer

SVC syndrome **may cause airway obstruction and cerebral edema;** however, severe Sx are uncommon, and life-threatening Sx are rare.
What are the common presenting Sx of SVC syndrome?

Show Answer

Presenting Sx of SVC syndrome:

- Face and neck swelling
- UE swelling
- Cough/stridor
- Dyspnea
- Dilated chest veins (collateral blood flow)

(Rice T et al., Medicine 2006)
What is the most common Sx of SVC syndrome?

Show Answer

The most common Sx of SVC syndrome is **facial swelling.**
What physical exam findings are associated with SVC syndrome?

Show Answer

Signs of SVC syndrome: facial plethora, facial edema, jugular venous distension, and visible collateral venous drainage on the ant chest

WORKUP/STAGING

Describe the workup of SVC syndrome.

Show Answer

SVC syndrome workup: H&P, assessment of respiratory status, CXR and/or CT chest with contrast (best to visualize the extent of blockage), determination of the best Bx route if Dx is unknown, labs (AFP, LDH, β-HCG), and BM aspirate and Bx

Name 5 ways to obtain tissue Dx for SVC syndrome.

Show Answer

Methods to obtain tissue Dx in SVC syndrome:

- Sputum cytology
- Bx of palpable LNs
- Bronchoscopy
- Mediastinoscopy
- Video-assisted thoracoscopic Sg

What is usually seen on CXR in SVC syndrome?

Show Answer

CXR findings in SVC syndrome include a widened mediastinum and the presence of a mass near the SVC.

What CT finding is closely associated with SVC syndrome?

Show Answer

The **presence of collateral vessels** is a CT finding that closely relates to SVC syndrome.

Why should RT not be given prior to a histologic Dx in SVC syndrome?

Show Answer

RT **may obscure the histologic Dx** and should be deferred until diagnostic Bx is obtained in SVC syndrome. However, empiric Tx may be considered in the setting of airway obstruction or cerebral edema.

TREATMENT/PROGNOSIS

What is the 1st step in Tx of SVC syndrome?

Show Answer

The 1st step in treating SVC syndrome is to **establish a pathologic Dx,** which will determine further interventions.

What Tx may be used for SVC syndrome?

Show Answer

SVC syndrome Tx: RT, chemo, Sg, and stents

What supportive measures can be taken to manage SVC syndrome?

Show Answer

Elevation of head of bed and supplemental oxygen. Diuretics can be used for cerebral edema. Remove indwelling catheter if SVC syndrome due to thrombosis. (McCurdy M et al., Crit Care Med 2012)

What is the role of steroids in SVC syndrome?

Show Answer

Steroids are **frequently used** in SVC syndrome, but there are limited data to support their use except in lymphoma and thymoma.

In which malignant causes of SVC syndrome is chemo 1st-line Tx?

Show Answer

Chemo is the Tx of choice in SVC syndrome caused by **lymphoma, germ cell tumors, and SCLC.**

What is the most rapid way to manage SVC thrombosis?

Show Answer

The most rapid method to manage SVC thrombosis is by **intraluminal stenting.**

What Tx should be considered if a pt with SVC syndrome presents with

thrombosis?

Show Answer

Use **anticoagulation therapy** for pts with SVC syndrome presenting with thrombosis unless contraindications are present.
Which pts with SVC syndrome require emergent Tx?

Show Answer

SVC syndrome pts with central airway compromise, severe laryngeal edema, or altered mental status/coma secondary to cerebral edema require emergent Tx.
What fractionation is used to emergently treat SVC syndrome?

Show Answer

Fractionation for emergent SVC Tx is **3–4 Gy × 3 fx.** There are conflicting retrospective data on the benefit of hypofractionation.
When treating SVC syndrome, what should the RT fields encompass?

Show Answer

RT fields for SVC syndrome include encompassing gross Dz and adjacent nodal tissue while respecting normal tissue toxicity, esp the lungs and heart.
What should guide the total RT dose used for SVC syndrome?

Show Answer

The total RT dose for SVC syndrome depends on the **underlying histology** (i.e., lung cancers are treated to ≥60 Gy, while lymphomas are treated to 35–45 Gy). Palliative regimens such as 3 Gy × 10 may also be appropriate depending on the overall clinical status.
Does SVC syndrome portend a bad prognosis?

Show Answer

Not necessarily. The prognosis in SVC syndrome depends on the underlying

cause rather than the presence of the syndrome itself. MS is about 6 mos for cancer-induced SVC syndrome. However, based on etiology, many will survive longer or even be cured.
What is the overall symptomatic response to RT in SVC syndrome?

Show Answer

The ORR to RT for SVC syndrome is **~60%.**
Over what approximate timeline can pts expect Sx relief from RT?

Show Answer

Normally, response time to RT is **7–15 days,** but in some cases, relief may be experienced as soon as 72 hrs. (Wan J et al., Emerg Med Clin N Am 2009)
Does RT for SVC syndrome restore normal flow in the SVC?

Show Answer

No. RT for SVC syndrome does not generally restore normal vascular flow despite improving Sx.
What non-Tx event likely contributes to symptomatic improvement in SVC syndrome?

Show Answer

The **development of collateral vessels** largely contributes to Sx improvement in SVC syndrome.
What is the Tx if RT or chemo is not effective?

Show Answer

Vascular stents are recommended, with angioplasty 1st if the lumen needs to be expanded.

FOLLOW-UP/TOXICITY

What are potential acute toxicities of emergent RT for SVC syndrome?

Show Answer

Potential acute toxicities of emergent RT for SVC syndrome: fatigue, skin irritation, cough, esophagitis

What are potential subacute and chronic toxicities of RT for SVC syndrome?

Show Answer

Potential subacute and chronic toxicities of RT for SVC syndrome: RT pneumonitis, pericarditis, pulmonary fibrosis, esophageal stenosis.

90

Heterotopic Ossification Prophylaxis

Updated by Kristina Demas Woodhouse

BACKGROUND

What is heterotopic ossification (HO)?

Show Answer

HO refers to **abnl lamellar bone formation in nonosseous tissues such as muscles, nerves and connective tissue.** It often appears after trauma or Sg in periarticular ST and is commonly associated with injury to the hip.

What are common Sx of HO?

Show Answer

In HO, **functional impairment** such as joint stiffness and decreased ROM are the most common Sx. **Pain** can also occur, beginning as early as a few days after Sg.

What is the etiology of HO?

Show Answer

The etiology of HO is not completely understood. It is assumed that pluri potent mesenchymal cells present in periarticular ST and develop into osteoblastic stem cells, which then produce bone.

What are the highest risk factors for developing HO?

Show Answer

Pts who already have ipsi or contralat HO carry the greatest risk of developing further HO. Their risk is 80%–100%. Pts with osteophytes at the femoral head and socket, acetabular fractures, ankylosing spondylitis, and other hyperostosis conditions of the skeleton also carry a high risk for HO. This condition is more common in males than in females.

WORKUP/STAGING

How soon after Sg can radiologic evidence of HO be detected?

Show Answer

Radiologic evidence of HO can be detected **2–6 wks** after Sg as calcified structures with blurred contours on x-ray. Bone scans typically show increased uptake in the STs adjacent to the hip and can detect HO several days before it becomes apparent on plain film.

What is the most common staging system used for HO?

Show Answer

The most common staging system used for HO was developed by Brooker et al.

Grade 1: bone islands in ST around hip
Grade 2: exophytes in pelvis or proximal end of femur with at least 1 cm b/t opposing bone surfaces
Grade 3: exophytes in pelvis or proximal end of femur with <1 cm b/t opposing bone surfaces
Grade 4: bony ankylosis b/t proximal femur and pelvis

Grades 3–4 are considered clinically relevant even if there is no pain or impaired mobility.

TREATMENT/PROGNOSIS

What is the role of Sg in the Tx of HO?

Show Answer

Clinically relevant HO should be surgically removed. The risk of subsequent recurrence may be lower if the ectopic bone is removed after it has reached maturity. At the time of Sg, prophylaxis against future HO should be taken. Other than RT, are there any other effective methods for prophylaxis against HO?

Show Answer

For prophylaxis against HO, **indomethacin and ibuprofen** (prostaglandin synthesis inhibitors) have been shown to decrease the incidence of HO compared to placebo. (Fransen M et al., Cochrane Database Syst Rev 2004) What should be the RT dose and fractionation for prophylaxis against HO?

Show Answer

There have been multiple randomized trials and retrospective series on the RT dose and fractionation for prophylaxis against HO:

Sylvester J et al. (IJROBP 1988) compared 20 Gy in 10 fx vs. 10 Gy in 5 fx, and Pellegrini V et al. (J Bone Joint Surg Am 1992) looked at 8 Gy × 1 fx vs. 10 Gy in 5 fx. There were no differences b/t those doses and fractionation schemes. More recent studies looked at using lower doses.

Healy W et al. (J Bone Joint Surg Am 1995) compared 7 Gy × 1 fx against 5.5 Gy and concluded that 5.5 Gy is not a sufficient dose.

Padgett D et al. (J Arthroplasty 2003) looked at 5 Gy × 2 fx or 10 Gy in 5 fx. There was a trend toward increased HO of any grade in the 5-Gy group.

Milakovic et al. (Radiotherapy and Oncology 2015) performed a meta-analysis and found that there seems to be no relationship b/t BED greater or less than 2,500 cGy and the efficacy of HO prophylaxis. They also report that multiple fx seem to be more effective than single-fx radiotherapy in preventing HO progression.

What is the efficacy of preop RT for HO prophylaxis c/w PORT? What are the advantages and disadvantages of preop RT vs. PORT?

Show Answer

In 1 study, preop RT at 7–8 Gy × 1 fx gave the same rates of prophylaxis as the same dose given PORT. (Gregoritch S et al., IJROBP 1994) Preop RT decreases pt discomfort associated with transport and positioning for RT but is often not feasible d/t scheduling issues. A meta-analysis by Milakovic E et al. (Radiotherapy and Oncology 2015) looked at 12 randomized trials comparing preop RT vs. PORT. They concluded that there was no difference b/t postop or preop radiotherapy in preventing HO progression.

How soon should PORT be given after Sg for prophylaxis against HO?

Show Answer

PORT prophylaxis against HO should be given **no later than 4 days and ideally within 3 days** of Sg. (Seegenschmiedt M et al., IJROBP 2001)

What is the timeframe for giving preop RT for HO prophylaxis?

Show Answer

The randomized trial comparing preop RT vs. PORT for HO prophylaxis using 7–8 Gy × 1 fx (Gregoritch S et al., IJROBP 1994) gave preop RT within 4 hrs of Sg. Other nonrandomized series have suggested that preop RT can be given as early as 8 hrs preop without a significant decrease in efficacy. (Seegenschmiedt M et al., IJROBP 2001)

Are there randomized trials comparing RT against indomethacin in HO prophylaxis?

Show Answer

Yes. Burd T et al. (J Bone Joint Surg Am 2001) randomized 166 pts to rcv either indomethacin or RT postoperatively for HO prophylaxis. Grades 3–4 HO occurred in 14% of the indomethacin group as c/w 7% of the RT group, but the results were not SS ($p = 0.22$).

A meta-analysis by Pakos E et al. (IJROBP 2004) looked at 7 randomized trials comparing RT vs. NSAIDs. They concluded that RT postop >6 Gy

tended to be more effective than NSAIDs in preventing Brooker grade 3 or 4 HO, but the absolute difference was only 1.2%.

What is the typical RT field for HO prophylaxis?

Show Answer

The RT fields for HO prophylaxis typically includes the usual area at risk for HO. When treating the hip for HO prophylaxis, the cranial border is usually 3 cm above the acetabulum and inferiorly includes two-thirds of the shaft of the implant. Field size is usually around 14 × 14 cm. The prosthesis may be blocked from RT if a cementless fixation is used, but observational data suggest that this blocking strategy is associated with higher rates of subsequent HO.

FOLLOW-UP/TOXICITY

What are the rates of increased wound-healing complications after RT for HO prophylaxis?

Show Answer

RT for HO prophylaxis has not been associated with an increased incidence of wound-healing complications.

Is there an increased risk of nonfixation of cementless implants after RT for HO prophylaxis?

Show Answer

No. There is not an increased risk of nonfixation of cementless implants after RT for HO prophylaxis based on multiple studies. (Seegenschmiedt M et al., IJROBP 2001) Animal studies have shown a transient decrease in force required to remove an implant after RT, but this difference resolved by wk 3. (Konski A et al., IJROBP 1990)

What is the rate of RT-induced tumor after RT for HO prophylaxis?

Show Answer

Rates of RT-induced tumor after RT for HO prophylaxis appear to be low. There are at least 2 case reports of RT-induced tumors after RT for HO prophylaxis. (Farris M et al., Radiat Oncol 2012; Mourad et al., PRO 2012) The rarity is thought to be d/t the use of low doses of RT as well as typically older age of the pt population. As RT is employed for younger pts, this risk is worth considering.

91

Keloids

Updated by Kristina Demas Woodhouse

BACKGROUND

What is a keloid?

Show Answer

A keloid is a **benign fibroproliferative growth** resulting from a connective tissue response to a variety of proposed factors such as Sg, burns, trauma, inflammation, foreign body reactions, endocrine dysfunction, and occasional spontaneous occurrence. Classically, they appear as a firm, bosselated, and often shiny mass.

Is there a racial predilection for keloid formation?

Show Answer

Yes. People of African descent are more likely to be predisposed to keloid formation than other ethnic groups. Any skin insult (piercings, lacerations, infected skin lesions, burns, Sg) can cause keloid formation in predisposed individuals. Less commonly, lesions can occur de novo.

Name 3 common locations for keloids.

Show Answer

Keloids most commonly affect areas of increased skin tension such as the ears, neck, jaw, presternal chest, shoulders, and upper back.

Name 3 Sx commonly associated with keloids.

Show Answer

Keloids can be asymptomatic but often are pruritic, tender to palpation, or occasionally cause pain.

WORKUP/STAGING

What is the difference b/t a keloid and a hypertrophic scar?

Show Answer

Hypertrophic scars may initially appear similar to keloids, but do not extend beyond the margins of the scar. Keloids are more infiltrative and can cause a local reaction such as pain and inflammation. Hypertrophic scars are much less likely to recur after resection.

TREATMENT/PROGNOSIS

What are the indications for RT in keloid Tx?

Show Answer

The indications for RT in keloid Tx include demonstrated recurrence after resection, marginal or incomplete resection, an unfavorable location, a larger lesion or after keloid management is refractory to nonsurgical options such as corticosteroid injection, laser, or cryotherapy.

Within what time frame should RT be given postop after keloid resection?

Show Answer

PORT for keloids should be initiated **within 24 hrs** after resection.

What is the typical target RT volume for keloid Tx?

Show Answer

The typical target RT volume for keloid Tx is **scar + a 1- to 1.5-cm margin.**

What is the typical RT dose and fractionation for keloids?

Show Answer

The typical RT dose and fractionation for keloids is **15–18 Gy in 3–4 fx.**

Single doses of 7.5–10 Gy are also effective. (Ragoowansi R et al., Plast Reconstr Surg 2003) Some series suggest that a dose of at least 9 Gy is required to maximize the benefit from RT. (Lo T et al., Radiother Oncol 1990; Doornbos J et al., IJROBP 1990) Another series from Pittsburgh suggests that doses of at least 5–6 Gy/fx for 3 fx may be needed for 90%–95% control for earlobe keloids and 7–8 Gy/fx for 3 fx may be needed for similar control at other sites. (Flickinger J, IJROBP 2011)

What RT modalities can be used in the Tx of keloids?

Show Answer

For RT Tx of keloids, the most common modalities are **lower megavoltage electrons, kilovoltage photons, or brachytherapy.**

Name 7 Tx options for keloids other than Sg and RT.

Show Answer

Tx options for keloids other than Sg and RT include steroid injections, pressure earrings, silicone gel sheeting, cryosurgery, laser therapy, imiquimod, and injections of fluorouracil or verapamil.

What is the recurrence rate for keloids after PORT?

Show Answer

The recurrence rate for keloids after PORT is typically **10%–35%.** This can vary depending on the size, location, extent of excision, etiology, and other factors.

Is there any randomized data comparing Sg + RT against Sg + steroid injection?

Show Answer

Yes. A prospective randomized trial conducted by Sclafani A et al. looked at a series of 31 pts, comparing PORT vs. intralesional steroid injection. The recurrence rate after Sg + RT was 12.5%; the recurrence rate after Sg + steroid injection was 33%. (Dermatol Surg 1996)

For unresectable keloids, what is the efficacy of using RT alone?

Show Answer

Malaker K et al. looked at 86 keloids in 64 pts treated with RT alone. 97% had significant regression 18 mos after completing radiotherapy. 63% of the pts surveyed were very happy with the outcome of their Tx. (Clin Oncol 2004)

FOLLOW-UP/TOXICITY

What are the most common side effects after RT for keloids?

Show Answer

The most common side effects of RT for keloids are **hyperpigmentation, pruritus, and erythema.**

Is there a risk of RT-induced malignancy after Tx for keloid?

Show Answer

There are a few anecdotal reports in the medical literature of malignant tumors developing in association with radiotherapy for keloid formation, but this outcome is extremely rare. Caution is warranted and risks should be discussed when considering radiotherapy for keloids in the very young and in particular for lesions involving the chest or breast tissue in young females. (Botwood N et al., Br J Radiol 1999)

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Immunotherapy Primer

Authored by Steven Eric Finkelstein and John P. Christodouleas

What are the key functions of the innate immune system?

Show Answer

The innate immune response is nonspecific and provides an initial and rapid (hrs) response to infections by other organisms, but does not provide long-lasting immunity. Its 5 key functions include:

(1) Recruiting immune cells to sites of infection, through the production of factors, including cytokines
(2) Activating the complement cascade
(3) Removing foreign substances present in organs, tissues, blood and lymph, by WBCs
(4) Activating the adaptive immune system through antigen presentation
(5) Providing a physical and chemical barrier to infectious agents

What are the key functions of the adaptive immune system?

Show Answer

The adaptive (acquired) immune response develops more slowly (days) than the innate immune response to an initial exposure but prepares for future immunologic challenges by creating memory to a specific pathogen. It leads to an enhanced response to subsequent encounters with that pathogen. There are 2 types of adaptive immune responses:

(1) Antibody (humoral)—the core function of B lymphocytes which produce antibodies (immunoglobulins)
(2) Cell-mediated—the core function of T lymphocytes

How does the adaptive immune response provide long-lasting protection?

Show Answer

This response is highly adaptable b/c of somatic hypermutation (defined as a process of accelerated somatic mutations), and V(D)J recombination (defined as an irreversible genetic recombination of antigen receptor gene segments). A small number of genes can generate a vast number of different antigen receptors, uniquely expressed on each individual lymphocyte. Since the gene rearrangement leads to an irreversible change in the genetic code, cellular prodigy (memory T cells and memory B cells) inherit the same receptor specificity that confer long-lived specific immunity.

How does cancer evade the immune system?

Show Answer

Cancer cells evade immune surveillance through numerous mechanisms, including:

(1) reduced expression of tumor antigens
(2) downregulation of MHC class I and II molecules thus reducing tumor-antigen presentation
(3) immunosuppressive cytokines such as tumor growth factor-β
(4) induction of immunosuppressive cells (regulatory T cells or myeloid-derived suppressor cells [MDSC])
(5) overexpression of immune checkpoint ligands

Name 4 major types of immunotherapy.

Show Answer

1. Checkpoint inhibitors
2. Adoptive cell transfer

3. Antibody-based therapeutics

4. Vaccines

How do checkpoint inhibitors work?

Show Answer

The immune system has checkpoint ligands that protect an organism against an excessive inflammatory response to viral or bacterial infection. Tumors co-opt this mechanism to evade immune cells. For example, tumor cells expressing programmed death ligand-1 **(PD-L1) promote T-cell exhaustion,** where T cells proliferate slowly and do not function effectively. Cytotoxic T-lymphocyte–associated protein 4 **(CTLA-4) expression on tumors can upregulate regulatory T cells** which inhibit effector T cells. There are many distinct checkpoint pathways and thus many inhibitors that can be rationally combined.

What type of cancers are most successfully treated with checkpoint inhibitor immunotherapy?

Show Answer

Cancers with a high mutational burden (concept of “altered self”) appear more likely to respond to checkpoint inhibitors. In particular, tumors are more likely to respond if they have neoantigens with **high recognition potential,** which describes the likelihood that a neoantigen will be presented by MHC molecules and subsequently recognized by T cells.

What are the side effects of checkpoint inhibitors and how are they managed?

Show Answer

Checkpoint inhibitors can cause side effects that appear similar to autoimmune Dz such as skin rash, pneumonitis, colitis, rheumatoid arthritis–like Sx (joint pain, muscle pain), hypophysitis (inflammation of the pituitary) and thyroiditis. These Sx can often be controlled with steroids.

Is dual agent checkpoint inhibition more effective than single agent?

Show Answer

Different classes of checkpoint inhibitors are potentially complementary. Preliminary studies in melanoma and non–small cell lung cancer pts show **improved response rates** but also increased toxicity **with combination** PD-1 and CTLA-4 **inhibition. CheckMate 067** was a 3-arm trial that randomized Tx-naïve melanoma pts to nivolumab (nivo, PD-1 inhibitor) plus ipilimumab (ipi, CTLA-4 inhibitor) f/b nivo vs. nivo alone vs. ipi alone. 3-yr OS was 58%, 52%, and 34% in combo, nivo alone and ipi alone groups. The overall HR was significantly better in the combo compared to both single agents. But, Tx-related G3–4 AEs occurred in 59% with combo, compared to 21% and 28% with nivo alone and ipi alone. (Wolchok JD et al., NEJM 2017)

How does adoptive cell transfer work?

Show Answer

Adoptive cell transfer involves removing immune cells from the pt, potentially altering them to target a given cancer, growing them ex vivo and then re-infusing them. There are 3 main sources of tumor-specific immune cells: tumor-infiltrating lymphocytes found in surgical tumor specimens which can be cultured, antigen-specific immune cells that are created through repeated exposure to the antigen of interest or antigen-specific T cells that can be created artificially using genetic engineering.

What is CAR T-cell therapy?

Show Answer

Chimeric antigen receptor (CAR) T-cell therapy is a type of adoptive cell transfer therapy where T cells are engineered to target tumor antigens expressed on the membrane of cancer cells. CARs are hybrid (i.e., chimeric) receptors formed by the fusion of 3 parts: an extracellular tumor-

specific antibody, a transmembrane portion and an intracellular portion that stimulates T-cell activity when the antigen binds the extracellular antibody. CAR T-cell therapy is not dependent on MHC neoantigen presentation and thus can be effective when MHC molecules have been downregulated by a tumor.

Describe the ELIANA trial which resulted in the 1st FDA approval of a CAR T-cell therapy.

Show Answer

ELIANA included pediatric and young adults with relapsed/refractory B cell acute lymphoblastic leukemia (ALL). CAR T cells were engineered to react to **CD19,** a protein that is common on B cells. 83% of pts achieved a CR or CR with incomplete blood count recovery within 3 mos of infusion. In the study, 49% of pts experienced grade 3–4 **cytokine release syndrome.** Within 8 wks of Tx, 18% of pts experienced grade 3–4 neurologic events. (Kymriah [tisagenlecleucel] Prescribing information, Novartis, August 2017)

How does sipuleucel-T works?

Show Answer

Sipuleucel-T refers to an adoptive cell transfer therapy for prostate cancer where a pt's dendritic cells are extracted and incubated with a protein that contains antigen prostatic acid phosphatase (PAP) which helps the dendritic cells mature. The activated cells are then re-infused into the pt. A complete Tx includes 3 infusions at 2-wk intervals.

What evidence supports the benefit of sipuleucel-T?

Show Answer

The **IMPACT trial** compared sipuleucel-T to standard of care in men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Sipuleucel-T improved median OS (25.8 vs. 21.7 mo) and 3-yr OS (31.7% vs. 23.0%). (Kantoff PW et al., NEJM 2010)

What is the abscopal effect?

Show Answer

The abscopal effect refers to the ability of a local therapy (e.g., RT, radiofrequency ablation) delivered to 1 or more sites to generate an immune response at distant sites of Dz. Preclinical and clinical studies suggest local RT damages DNA within tumor cells leading to tumor-cell apoptosis/necrosis and tumor-antigen release. These tumor antigens induce antitumor-specific immune responses systemically using similar pathways by which viral/bacterial antigens cause systemic immunity. Abscopal responses d/t RT alone are very rare but appear more common in the setting of checkpoint inhibitors.

Is there evidence to support the use of RT to improve the rate and durability of the systemic response of checkpoint inhibitors in metastatic Dz?

Show Answer

In addition to anectodal observations of the abscopal effect, there are retrospective studies in metastatic non–small cell lung cancer that a Hx of prior RT may improve outcomes of checkpoint inhibitors. A retrospective study by Shaverdian N et al. (Lancet Oncol 2017) found that metastatic non–small cell lung cancer pts who were treated with pembrolizumab (PD-1 inhibitor) who had a Hx of prior RT lived longer than those without prior RT (median OS 10.7 vs. 5.3 mos). Similarly, Hwang WL et al. (JAMA Oncol 2017) found a reduction (NSS) in all-cause mortality in metastatic lung cancer pts treated with PD-1/PD-L1 inhibitors who had a prior Hx of thoracic radiotherapy.

How may RT promote immune-mediated killing of an irradiated tumor?

Show Answer

In addition to direct cell death via DNA damage, RT may promote tumor-

specific immune responses through:

. Release of tumor antigens and other molecules collectively known as damage-associated molecular patterns (DAMPs). In particular, DNA particles in a cell's cytosol can trigger the cGAS–STING pathway which triggers the transcription of inflammatory genes and ultimately activates an innate immune response. (STING = STimulator of Interferon Genes)
. Increased tumor-specific antigen expression
. Upregulation of MHC antigen presentation
. Decreased expression of immunosuppressive ligands, like PD-L1
. Upregulation of proteins that support T-cell adhesion, tethering and chemotaxis in tumor-micro-environment

APPENDIX

Normal Tissue Constraint Guidelines

INTRODUCTION

The radiation dose constraints below are meant to serve as a guide only and may not be applicable to all clinical scenarios. Most doses are derived from randomized studies or consensus guidelines and we have attempted to provide the sources for these recommendations. Please refer to the individual pediatric chapters for dose constraints in the pediatric population as these can vary greatly from protocol to protocol and tend to be particularly site and age dependent.

What Are the Recommended Dose Constraints for the Following Organs and Clinical Scenarios?	
Organ	**Constraints**
CNS (1.8–2.0 Gy/fx)	
Spinal cord	**max 50 Gy** (full cord cross-section); tolerance increases by 25% 6 mos after 1st course (for reirradiation) (QUANTEC); consider max 45Gy with chemo (NRG/RTOG, NCCN), for hyperfx (1.5 Gy bid up to 42 Gy for small cell lung

	cancer per CONVERT trial), dose **≤**41 Gy (RTOG 0538)
Brain	**max 60 Gy** (whole organ)(QUANTEC)
Chiasm/optic nerves	**$D_{0.03\ cc}$ £ 55 Gy** (RTOG 0825); chiasm **max 56 Gy** (RTOG 0825), optic nerves **max 55 Gy** (RTOG 0825)
Brainstem	**entire brainstem max <54 Gy (**QUANTEC), **max 60 Gy** (RTOG 0825)
Eyes (globe)	**mean <35 Gy** (RTOG 0225), **max 50 Gy** (RTOG 0615)
Lens	**max <27 Gy** (RTOG 0825)
Retina	**max 50 Gy** (RTOG 0539), **mean dose <38 Gy**
Lacrimal gland	**max dose point 36 Gy, V20 <1 cc**
Inner ear/cochlea	**mean ≤40 Gy** (consider constraining to **≤**35 Gy with concurrent cisplatin) (QUANTEC), **V55 ≤5%** (RTOG 0615)
Pituitary gland	**max 45 Gy** (for panhypopituitarism, lower for GH deficiency) (LENT)
Cauda equina	**max 60 Gy** (LENT)
CNS (single fraction)	
Spinal cord	**max 13 Gy** (QUANTEC), **V10 <0.35 cc, V7 <1.2 cc** (TG-101)
CNS (single fraction)	
Brain	**V12 Gy <5–10 cc** (QUANTEC)
Chiasm/optic nerves	**max <8 Gy, V8 <0.2 cc** (TG-101)
Brainstem	**max 12.5 Gy** (QUANTEC), **V10 <0.55 cc** (TG-101)
Sacral plexus	**V16 <0.035 cc, V14 <5 cc** (RTOG 0631)
H&N (1.8–2.0 Gy/fx)	
Parotid gland(s)	**mean <25 Gy** (both glands) or **mean <20 Gy** (1 gland) (QUANTEC), **D50% <30 Gy (one), V20**

	<20 cc (both) (RTOG 0912), **Dmax = 32 Gy (one side), V20 <7 cc (one side)**
Submandibular gland(s)	**mean <35 Gy** (QUANTEC)
Larynx	**mean <44 Gy, V50 <27%, max 66 Gy** (20% vocal dysfunction rate) (QUANTEC), **Dmax <46 Gy, V40 <3 cc**
TMJ/mandible	**max 70 Gy** (if not possible, then V75 **<**1 cc) (RTOG 0225), **Dmax = 65 Gy, V60 <1 cc**
Oral cavity	nonoral cavity cancer: **mean <30 Gy, avoid hot spots >60 Gy** (RTOG 0920) oral cavity cancer: **mean <50 Gy, V55 <1 cc, max 65 Gy** (RTOG 0920)
Esophagus	**V45 <33%** (RTOG 0920), **Mean dose <34 Gy** (45 Gy if necessary), **V54 <15%** (RTOG 0920)
Pharyngeal constrictors	**mean <50 Gy** (QUANTEC), **V50 <51%, V52 <60%** (Caglar)
Thyroid	**mean <30 Gy** for hypothyroidism (Monnier)
Thoracic (1.8–2.0 Gy/fx)	
Brachial plexus	**max <66 Gy, V60 <5%** (RTOG 0619)
Lung (combined lung for lung cancer Tx)	**mean <20** (RTOG 0623), **V5 <65%, V20 <35%** (lung minus GTV) (QUANTEC and NCCN), **V14 <1,500 cc** (minus GTV), **V15 <1,000 cc** (minus GTV)
Lung (ipsi lung for breast cancer Tx)	**V20 <15%, V10 <35%, V5 <50%** (RTOG 1005)
Single lung (after pneumonectomy)	**V5 <60%, V20 <4%–10%, MLD <8 Gy** (QUANTEC)
Trachea, large bronchi	**Dmax = 66 Gy, V60 <5 cc**
Heart (lung cancer Tx)	**V40 <80%; V45 <60%; V60 <30%; mean <26 Gy** (NCCN), **V30 <46%** (QUANTEC), **Dmax = 60 Gy, V60 <15 cc**
Heart (breast cancer Tx)	**V25 <10%** (QUANTEC)

	V20 <5%, V10 <30%, mean <4 Gy (RTOG 1005)
Esophagus	**V50 <32%** (Maguire), **V60 <33%** (LENT), **mean <34 Gy** (NCCN 2018) (QUANTEC), V60<17% (Palma et al., IJROBP 2013)
SBRT Dose Constraints	Total recommended cumulative dose by the number of fx per NCCN 2018 unless cited otherwise (based on constraints used in RTOG 0618, 0813, 0915). 15 fx constraints based on NRG LU-004 protocol.
Spinal cord	1 fx: **14 Gy, V10 <0.35 cc, V7 <1.2 cc** (TG-101) 3 fx: **18 Gy** (6 Gy/fx), **Dmax = 21.9 Gy, V18 <0.35 cc, V12.3 <1.2 cc** (TG-101) 4 fx: **26 Gy** (6.5 Gy/fx), **V18 <0.35 cc, V13.6 <1.2 cc** 5 fx: **30 Gy** (6 Gy/fx), **V23 <0.35 cc, V14.5 <1.2 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤36.5–40.2 Gy;** PRV/cord+3mm **$D_{0.03\ cc}$ ≤40.2–43.9 Gy**
Esophagus	1 fx: **15.4 Gy**, **V11.9 <5 cc** (TG-101) 3 fx: **27 Gy** (9 Gy/fx), **Dmax = 25.2 Gy, V17.7 <5 cc** (TG-101) 4 fx: **30 Gy** (7.5 Gy/fx), **V18.8 <5 cc** 5 fx: **105% of Rx for central tumor**, **Dmax = 35 Gy, V19.5 <5 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤58.9–61.3 Gy, Mean ≤31–32 Gy**
Brachial plexus	1 fx: **17.5 Gy**, **V14 <3 cc** (TG-101) 3 fx: **24 Gy** (8 Gy/fx), **V20.4 <3 cc** (TG-101) 4 fx: **27.2 Gy** (6.8 Gy/fx), **Dmax = 29.6 Gy, V24.8 <3 cc**

	5 fx: **32 Gy** (6.4 Gy/fx), **Dmax = 30.5 Gy, V27 <3 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤49.8–52 Gy**
Heart/pericardium	1 fx: **22 Gy**, **V16 <15 cc** (TG-101) 3 fx: **30 Gy** (10 Gy/fx), **V24 <15 cc** (TG-101) 4 fx: 34 Gy (8.5 Gy/fx), **V28 < 15 cc** 5 fx: **105% of Rx for central tumor, Dmax = 38 Gy, V32 <15 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤49.8–52 Gy, Mean ≤16.5–18.5 Gy**
Great vessels	1 fx: **37 Gy**, **V31 <10 cc** (TG-101) 3 fx: **Dmax = 45 Gy, V39 <10 cc** (TG-101) 4 fx: **49 Gy** (12.25 Gy/fx), **V43 <10 cc** 5 fx: **105% of Rx for central tumor**, **Dmax = 53 Gy, V47 <10 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤53.5–55 Gy**
Trachea/large bronchus	1 fx: **20.2 Gy, V10.5 <4 cc** (TG-101) 3 fx: **30 Gy** (10 Gy/fx), **V15 <4 cc** (TG-101) 4 fx: **34.8 Gy** (8.7 Gy/fx), **V28.8 <5 cc** 5 fx: **105% of Rx for central tumor**, **Dmax = 40 Gy, V16.5 <4 cc** (TG-101) 15 fx: **$D_{0.03\ cc}$ ≤53.5–55 Gy** (NRG LU-004)
Rib	1 fx: **30 Gy, V22 <1 cc** (TG-101), **V28 <5 cc** 3 fx: **30 Gy** (10 Gy/fx), **Dmax** = **36.9 Gy, V28.8 <1 cc, V30 <30 cc** (TG-101) 4 fx: **40 Gy** (10 Gy/fx), **Dmax = 54 Gy, V43 <5 cc** 5 fx: **Dmax = 43 Gy, V35 <1 cc** (TG-101)
Skin	1 fx: **26 Gy, V23 <10 cc** (TG-101) 3 fx: **24 Gy** (8 Gy/fx), **Dmax <33 Gy, V30 <10 cc** (TG-101) 4 fx: **36 Gy** (9 Gy/fx), **V33.6 <10 cc**

Stomach	5 fx: **32 Gy** (6.4 Gy/fx), **Dmax = 39.5 Gy, V36.5 <10 cc** (TG-101) 1 fx: **12.4 Gy, V11.2 <10 cc** (TG-101) 3 fx: **Dmax** = **22.2 Gy, V16.5 <10 cc** (TG-101) 4 fx: **27.2 Gy** (6.8 Gy/fx), **Dmax** = **33.2 Gy, V25 <5 cc** 5 fx: **Dmax** = **32 Gy, V18 <10 cc** (TG-101)
GI (1.8–2.0 Gy/fx)	
Stomach	**TD 5/5 whole stomach: 45 Gy** (QUANTEC), **Dmax = 54 Gy, V50 <2%, V45 <25%** (Spalding), **V45 <50 cc**
Duodenum	**V55<1cm3, max 60 Gy** (Kelly)
Small intestine (small bowel)	**V45 <195 cc** (QUANTEC, volume based on entire potential space within the peritoneal cavity) **$D_{186\ cc}$ ≤25 Gy, $D_{155\ cc}$ ≤30 Gy, $D_{41\ cc}$ ≤35 Gy, $D_{30.4\ cc}$ ≤40 Gy** (Olsen, volume based on individual loops with chemo) **Dmax = 50 Gy, V40 <100 cc, V35 <180 cc, V45 <65 cc** (RTOG 0822)
Liver (metastatic Dz)	**mean liver <32 Gy** (liver = normal liver minus gross Dz) (QUANTEC), **V35 <50%, V30 <100%** (RTOG 0436), **V30 <700 cc** (liver minus GTV)
Liver (primary liver cancer)	**mean liver <28 Gy** (liver = liver minus GTV) (QUANTEC), **V35 <50%, V30 <100%** (RTOG 0436), **V30 <700 cc** (liver minus GTV)
Large intestine (colon)	**45 Gy, max dose 55 Gy** (LENT), **V54 <20 cc**
Kidney (bilat)	**mean <15–18 Gy, V28 <20%, V23 <30%, V20 <32%, V12 <55%.** (If mean kidney dose to 1 kidney >18 Gy, then constrain remaining

	kidney to V6 <30%.) (QUANTEC, Bilateral Whole Kidney), **V50 <33%, V30 <67%, V23 <100%** (RTOG 0436), **V22 <200 cc** (renal cortex, right and left as 1 structure), **V42 <15 cc** (renal hilum/vascular trunk, each side separately)
GI (single fraction)	Dose constraints per RTOG 0631 unless cited otherwise
Duodenum	**V16 <0.035 cc, V11.2 <5 cc, Dmax = 12.4 Gy, V9 <10 cc** (TG-101)
Kidney (cortex)	**V8.4 <200 cc, Volume to spare: >200 cc, 8.4 Gy** (renal cortex right and left) (TG-101)
Kidney (hilum)	**V10.6 <66%**
Colon	**V14.3 <20 cc, Dmax = 18.4 Gy and V18.4 <0.035 cc**
Jejunum/ileum	**Dmax = 15.4 Gy, V15.4 <0.035 cc, V11.9 <5 cc**
Stomach	**V16 <0.035 cc, V11.2 <10 cc, Dmax = 12.4 Gy** (TG-101)
Rectum	**Dmax = 18.4 Gy, V14.3 <20 cc** (TG-101)
GI (3 and 5 fractions)	Dose constraints per NRG-BR001 unless cited otherwise
Duodenum	3 fx: **V24 <0.03 cc** 5 fx: **V30 <0.5 cc, V18.3 <5 cc**
Kidney (total)	3 fx: **V15 <200 cc** 5 fx: **V18 <200 cc**
Kidney (hilum)	3 fx: **V19.5 <15 cc** 5 fx: **V23 <15 cc**
Bowel	3 fx: **V34.5 <0.03 cc** 5 fx: **V40 <0.03 cc**
Stomach	3 fx: **V30 <0.03 cc, V22.5 <10 cc** 5 fx: **V35 <0.5 cc, V26.5 <5 cc**

Rectum	3 fx: **V49.5 <0.03 cc, V45 <3.5 cc, V27.5 <20 cc** 5 fx: **V55 <0.03 cc, V50 <3.5 cc, V32.5 <20 cc**
GU (1.8–2.0 Gy/fx)	
Femoral heads	**V50 <5%** (RTOG GU Consensus), **Dmax = 50 Gy, V45 <25%, V40 <40%** (RTOG 0822), **V48 <10 cc**
Rectum	**V75 <15%, V70 <20%, V65 <25%, V60 <35%, V50 <50%** (QUANTEC), **V75 <10 cc, V70 <20 cc, V65 <30 cc, V60 <40 cc** (Rectum, 10 cm above PTV and inf to anal sphincter)
Bladder	**V80 <15%, V75 <25%, V70 <35%, V65 <50%** (QUANTEC and RTOG 0126), **V70 <90 cc, V65 <150 cc** (bladder with urine)
Testis	**V3 <50%** (RTOG 0630)
Penile bulb	**mean dose to 95% of the volume <50 Gy, D70 <70 Gy, D90 <50 Gy** (QUANTEC), **mean dose <52.5 Gy** (RTOG 0126), **Dmax = 56 Gy, V48 <3 cc**
GU (LDR prostate brachytherapy)	
Urethra	urethral volume receiving a % of Rx dose **(UV5) <150%, (UV30) <125%,** difficult to achieve in small (<20 cc) prostates (ABS 2012)
Rectum	volume of rectum receiving 100% of Rx dose **(RV100) <1 cc** on day 1; **<1.3 cc** on day 30 (ABS 2012)
GYN	
Bladder (cervical brachytherapy)	**D2cc ≤90 Gy** (ABS 2012 LDR) **D2cc ≤90 Gy EQD2** (ABS 2012 HDR)
Rectum (cervical brachytherapy)	**Rectum: D2cc ≤75 Gy** (ABS 2012 HDR) **Sigmoid: D2cc ≤75 Gy** (ABS 2012 HDR)

	Rectum: D2cc ≤75 Gy EQD2 (ABS 2012 HDR) **Sigmoid: D2cc ≤75 Gy EQD2** (ABS 2012 HDR)
Proximal vagina (mucosa) (cervical brachytherapy)	**max 120 Gy** (LDR equivalent dose) (Hintz)
Distal vagina (mucosa) (cervical brachytherapy)	**max 98 Gy** (LDR equivalent dose) (Hintz)

Source: **ABS 2012:** American Brachytherapy Society consensus guidelines: (Brachytherapy 11, 1–76, 2012); **Caglar et al.** (IJROBP 72, 1110–1118, 2008); **CONVERT** Trial: **Kelly:** Duodenal toxicity after fractionated chemoradiation for unresectable pancreatic cancer (Kelly P et al., IJROBP 2013); **LENT:** Late Effects of Normal Tissues (LENT) Consensus Conference (IJROBP 31:5, 1995); **Hintz:** Radiation tolerance of the vaginal mucosa (Hintz BL et al., IJROBP 6(6): 711–716, 1980); **Maguire:** Clinical and dosimetric predictors of radiation-induced esophageal toxicity (Maguire PD et al., IJROBP 45:97–103, 1999); **Monnier:** Late effects of ionizing radiations on the thyroid gland (Monnier A, Cancer Radiother 1(6):717–731, 1997); **NCCN:** NCCN 2018 guidelines (www.nccn.org); **NRG:** NRG Oncology (https://www.nrgoncology.org); **Olsen:** Predictors of Radiation Therapy–Related Gastrointestinal Toxicity From Anal Cancer Dose-Painted Intensity Modulated Radiation Therapy: Secondary Analysis of NRG Oncology RTOG 0529 (Olsen J et al., IJROBP 2017); **Parsons:** Response of the normal eye to highdose radiotherapy (Parsons JT et al., Oncology 10(6):837–847, 2006); **QUANTEC:** QUANTEC Consensus Guidelines (panel of experts, IJROBP 76(3), Suppl, 2010); **RTOG** protocols: www.rtog.org; **RTOG GU** consensus: RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer (Lawton CA et al., IJROBP 74(2):383–387, 2009); **Spalding:** (Spalding et al., Med Phys 34, 521–525, 2007); **TG-101:** Stereotactic body radiation therapy: The report of AAPM Task Group 101 (Benedict SH et al.,

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