Clinical Radiation Oncology Review

Daniel M. Trifiletti
University of Virginia

Disclaimer: The following is meant to serve as a brief review of information in preparation for board examinations in Radiation Oncology and allow for an open-access, printable, updatable resource for trainees. Recommendations are briefly summarized, vary by institution, and there may be errors. NCCN guidelines are taken from 2014 and may be out-dated. This should be taken into consideration when reading.
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<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IVA</td>
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<tr>
<td>IB</td>
<td>IIB</td>
<td>IIIB</td>
<td>IVB</td>
</tr>
<tr>
<td>IC</td>
<td>IIC</td>
<td>IIIC</td>
<td>IVC</td>
</tr>
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</table>

Acknowledgements: To Neil Shah, BS for aiding in the preparation of this review.
Pediatrics
• T1 – confined to site of origin
  • T1a - ≤5cm
  • T1b - >5cm
• T2 – extension beyond site of origin
  • T2a - ≤5cm
  • T2b - >5cm
• N1 – nodes

Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Sites</th>
<th>TNM</th>
<th>5 yr OS</th>
</tr>
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<tbody>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fav: Orbit, H&amp;N, GU, biliary</td>
<td>Any T, Any N</td>
<td>90%</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfav: Parameningeal, Bladder/Prostate, Extremity, Other</td>
<td>≤5cm and N0</td>
<td>85%</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same as II</td>
<td></td>
<td>&gt;5cm or N1</td>
</tr>
<tr>
<td>Stage 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>M1</td>
<td>30%</td>
</tr>
</tbody>
</table>

Parameningeal Sites (25%): Infratemporal fossa, Middle ear, Mastoid region, Nasal cavity, Nasopharynx, Paranasal sinus, Pterygopalatine fossa, Parapharyngeal region (IMMNNPPP) [not orbital]

Overview
- ~3% of childhood cancers
- Hyperdiploid does better
- Embryonal assoc with LOH 11p15.5
- Alveolar assoc with t(2:13) and t(1:13). This is FKHR, PAX3, PAX7
- VAC: vincristine/actinomycinD/cyclophosphamide
- Workup: H&P, labs, CT/MRI, CT chest/abd, BMBx
- If parameningeal: LP with cytology +/- neuraxis MRI

Trials
- Heyn 1974: VA after surgery improved OS
- IRS I: Group I patients didn’t benefit from RT unless alveolar/undiff. Huge RT fields don’t help. 5 yr OS 55%
- IRS II: LC improved for >40Gy (93% LC). RT was tumor +5cm. 5 yr OS 63%
- IRS III: RT was tumor+2cm. bladder/vagina/uterus doesn’t need RT after CR to chemo. 5 yr OS 73%
- IRS IV: no benefit to VAC-IE or BID RT.
- COG D9803: int risk→ VAC vs VAC alt with VTC. No difference in DFS or LF
- Mandell 1990: retrospective of group II pts. No LC difference between <40 and >40Gy.

Technique
- Orbit: biopsy only→45Gy to tumor+2cm
- Otherwise CTV = GTV+1cm
- Include entire LN chain if N+
- If >1 lung met→ whole lung RT (15 Gy in 10 fx)
- Dose limits
  • Kidney <14.4 Gy
  • Liver < 23.4 Gy mean
  • Lungs <15 Gy at 1.5/fx
  • Whole abd < 24 Gy at 1.5/fx

<table>
<thead>
<tr>
<th>RT doses</th>
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<tbody>
<tr>
<td>R0, N0</td>
<td>36Gy</td>
</tr>
<tr>
<td>R1 or N1</td>
<td>41.4Gy</td>
</tr>
<tr>
<td>R2</td>
<td>50.4Gy</td>
</tr>
<tr>
<td>Orbits</td>
<td>45Gy</td>
</tr>
</tbody>
</table>

Histology | Freq | Locations | OS
---|------|----------|----
Embryonal | 60%  | H&N or GU | 66%
Alveolar   | 25%  | Trunk or abd | 54%
Botryoid   | 10%  | GU, nasophar, biliary | 95%
Undiff     | 5%   |          | 40%
Spindle cell | <5% | paratesticular | 88%

General Guidelines
- Provides site-specific recs
  • can move and replant gonads
  • LND required for paratesticular, pelvic, extremities (>20% LN+ rate)
  • cCR after chemo in bladder/vagina/uterus doesn’t need RT
- Low Risk
  • Stage 1-3, Group I: surgery→chemo (VA or VAC). No RT
  • Stage 1, Group II: surgery→chemo(VA) +RT at week 3 (36Gy for N0, 41.4Gy for N1)
  • Stage 1, Group III: surgery→chemo(VA) + RT (50.4Gy except orbit=45Gy)
  • Stage 2 Group II: surgery→VAC→RT at wk 3 (36Gy)
  • Stage 3, Group II: surgery→VAC→RT at wk 3 (36Gy for N0, 41.4 for N1)
- Int Risk
  • Surgery→chemo→(repeat surgery if possible)→RT(50.4Gy)
- High Risk
  • Chemo (VCPT→VAC). RT to primary and metastatic sites (45-50.4Gy)
**Ewing’s Sarcoma**

- (same as bone sarcoma, not commonly used)
- **T1** - ≤8cm
- **T2** - >8cm
- **T3** – discontinuous tumors

- **N1** – nodes

- **M1a** - lung
- **M1b** - other

**Overview**
- 200 cases/yr
- Ewing’s family: Ewing’s sarcoma (87%), Extraosseous Ewing’s (8%), PNET (5%), Askin’s tumor
- t(11:22): involves the EWS gene on ch22
- "c-myc activity ("n-myc in neuroblastoma)
- CD99+, vimentin+, NSE- (PNETs are CD99+, vimentin+, NSE+)
- Workup: H&P, labs, plain film (onion skinning)
- CT/MRI, bone scan, CT chest
- Bx, BMBx?

**Trials**
- IESS-1: nonmetastatic dz → VAC+D vs VAC vs VAC+prophylactic whole lung RT. VAC+D won. 5 yr RFS (60→24→44%)
- IESS-2: VAC+D high dose vs continuous. High dose improved RFS but not OS
- IESS-3: VACD +/- IE. More chemo won. 5yr OS 61→72%. Did not improve OS for M1 disease
- CESS 86: chemo→ surgery vs surgery+PORT vs RT alone. No difference in 5 yr OS (69%). LC worse without surgery (100→95→86%)
- POG 8346: chemo→surgery or RT. RT was randomized whole bone+boost vs 4cm margin +boost. No difference in LC or RFS
- EICESS analysis: any patients with lung mets benefited from WLI with improved EFS
- Schuck 2002: Askin tumors. 7 yr EFS improved with hemithorax RT and boost to primary

**Technique**
- 45 Gy to CTV (initial GTV+1-1.5cm) with PTV margin
- Boost postchemo volume with same margin to 55.8Gy
- "consider boosting to 59.4 for chemo response <50%"
- Paraspinal tumors stop at 45Gy
- Lung primary (Askin’s): hemithorax RT (15-20 Gy at 1.5/fx) followed by boost of primary
- Lung mets: whole lung RT
  - <14 yo: 15 Gy at 1.5/fx (current COG study says 12 Gy for <6 yo)
  - >14 yo: 18 Gy at 1.5/fx

**NCCN**
- Induction VAC-IE x12wks→local treatment (surgery or RT) with VAC→ adj chemo
- Consider preop RT if marginally resectable (36-45Gy)
- Postop RT (adequate margin is >1cm)
  - R0 with poor chemo response: 45 Gy
  - R1: 45 Gy
  - R2/bx: 45 Gy + boost to 55.8Gy
Wilms Tumor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>R0, Limited to kidney, capsule intact, LN neg</td>
</tr>
<tr>
<td>II</td>
<td>R0, capsule broken, into vessels</td>
</tr>
<tr>
<td>III</td>
<td>R1, R2, LN+, into peritoneum, spillage, piecemeal</td>
</tr>
<tr>
<td>IV</td>
<td>Distant mets or LN outside abd/pelv</td>
</tr>
<tr>
<td>V</td>
<td>Bilateral tumors</td>
</tr>
</tbody>
</table>

Overview

- 450 cases/yr usually 3-4 year olds
- Unfavorable histology: anaplastic, sarcomatous, clear cell, rhabdoid
- Del ch22q, LOH 1p and LOH 16q have poorer RFS and OS
- Clear cell and Rhabdoid are not actually Wilm’s tumors
- 10% of Wilms is assoc with congenital abn:
  - WAGR syndrome (del 11p13, WT1)
  - Denys-drash syndrome (WT1 mutation)
  - Beckwith-Wiedemann syn (WT2 mut, 11p15.5)
- Workup: H&P, u/s, labs, CT/MRI, CT chest, NO Bx
- Clear cell: add bone scan, MRI brain, BMBx
- Rhabdoid: MRI (15% have brain tumor)

Trials

- NWTS 1: showed no RT needed for group 1, <2 yo if given chemo. RT should start <9 days after surgery
- NWTS 2: showed RT not needed for all group 1. adding Adriamycin improved OS
- NWTS 3: showed RT not needed for stage II if chemo given. 10 Gy for stage III if Adriamycin used
- NWTS 4: showed pulse-intensive chemo less toxic than standard
- NWTS 5: stage I, FH and <550g tumor can be observed after surgery (2 yr DFS 87%, OS 100%). LOH 1p or 16q assoc with relapse and death. For UH, etoposide improved OS

Technique

- Start by day 9 postop
- Flank RT: usually AP/PA, 1.8Gy/fx. Preop GTV+1cm
  - Treat entire vertebral body
  - Stage I-II, FH: no RT
  - Stage III or UF: 10.8Gy
  - Diffuse anaplasia or rhabdoid: 19.8Gy
  - 10.8Gy for infants
  - Boost R2 another 10 Gy
  - Opposite kidney ≤14.4 Gy
- WLI: 12 Gy in 8 fx (add PO Bactrim)
- Brain mets
  - <16 yo: 21.6 Gy with 10.8Gy boost
  - >16 yo: 30.6 Gy in 17fx
- Liver mets: 19.8 Gy in 11fx
- Bone mets
  - 25.2 Gy in 14 fx (3cm margin)
  - 30.6 Gy is >16 yo

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Meaning</th>
<th>Tx after nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk FH</td>
<td>≤2 yo, tumor &lt;550g</td>
<td>• Obs</td>
</tr>
<tr>
<td>Low risk FH</td>
<td>≥2 yo, tumor ≥550g, no LOH (1p, 16q)</td>
<td>• VA (no RT)</td>
</tr>
<tr>
<td>Std risk FH</td>
<td>I-II with LOH</td>
<td>• VAD (no RT)</td>
</tr>
<tr>
<td></td>
<td>III with no LOH</td>
<td>• RT→VAD</td>
</tr>
<tr>
<td></td>
<td>IV, no LOH, with rapid response to chemo</td>
<td>• RT→VAD (no lung RT)</td>
</tr>
<tr>
<td>High risk FH</td>
<td>III with LOH</td>
<td>• RT→VAD/C/E</td>
</tr>
<tr>
<td></td>
<td>IV with LOH or slow responder to chemo</td>
<td>• RT→VAD/C/E (include whole lung)</td>
</tr>
<tr>
<td>High risk UF</td>
<td>Any focal anaplasia</td>
<td>• RT→VAD</td>
</tr>
<tr>
<td></td>
<td>Stage I diffuse anaplasia</td>
<td>• RT→VDC/CE</td>
</tr>
<tr>
<td></td>
<td>I-III clear cell</td>
<td>• RT→chemo→RT to mets</td>
</tr>
<tr>
<td>Highest risk</td>
<td>II-IV diffuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV clear cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I-IV rhabdoid</td>
<td></td>
</tr>
</tbody>
</table>
**Neuroblastoma**

### INRGSS Staging (preop)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized tumor</td>
</tr>
<tr>
<td>L2</td>
<td>Locally invasive by defined criteria</td>
</tr>
<tr>
<td>M</td>
<td>Metastatic disease except MS</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic to only skin/liver/marrow and &lt;18m</td>
</tr>
</tbody>
</table>

### INSS Staging (postop)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R0, R1, Localized tumor, LN -</td>
</tr>
<tr>
<td>2A</td>
<td>Stage 1 but R2</td>
</tr>
<tr>
<td>2B</td>
<td>Stage 2B but ipsi LN+</td>
</tr>
<tr>
<td>3</td>
<td>Midline/contralateral primary or LNs</td>
</tr>
<tr>
<td>4</td>
<td>Mets except 4S</td>
</tr>
<tr>
<td>4S</td>
<td>Stage 1-2B w/ mets only to skin/liver/marrow &amp; &lt;1yr</td>
</tr>
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</table>

### COG RISK GROUPINGS

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stage 1</td>
<td>&lt;1 yo, stage 3, no MYCN</td>
<td>Any MYCN</td>
</tr>
<tr>
<td>&lt;1 yo, stage 2</td>
<td>&gt;1 yo, stage 3, no MYCN, fav hist</td>
<td>&gt;18 months, stage 3, unfav hist</td>
</tr>
<tr>
<td>Stage 2, no MYCN</td>
<td>&lt;1 yo, 4S, no MYCN</td>
<td>&gt;18 months, stage 4</td>
</tr>
<tr>
<td>&lt;1 yo, 4S, fav hist, hyperdip and no MYCN</td>
<td>&lt;1 yo, 4S, no MYCN, non-hyperdip and/or unfav hist</td>
<td></td>
</tr>
</tbody>
</table>

### Overview
- 650 cases/yr
- Median dx is 17m (wilms is 3-4 yo)
- Primitive neural crest cells (usually calcified, wilms isn’t)
- Homer-Wright pseudorosettes
- Stains NSE+, synaptophysin+, neurofilament+
- Shimada classification: based on stroma, age, diff, mitoses, nodular/diffuse (SAD MiNd)
- Poorer prognosis: ↑stage, ↑age, n-myc amp, diploid, Shimada (SANDS)
- Also poorer prognosis: LOH 1p or 11q,↑telomerase
- Tumors can spontaneously regress, so screening not helpful
- Blueberry muffin sign, raccoon eyes, opsoclonus-myooclonus-trucal ataxia
- Chemos: carboplatin, etoposide, cyclophosphamide, doxorubicin, ifosfamide
- Workup: H&P, labs, urine catecholamines (VMA, HVA), BMBx
- CT/MRI, MIBG scan, CT chest

### Low Risk
- POG 8104: 101 pts with INSS 1 → GTR → obs. 2 year DFS 89%
- CCG 3881: 374 pts with INSS 1-2B→surgery alone → stage 1 EFS 93%, stage 2 81%. Patients with n-myc amp, UF, LN+ at higher risk

### Intermediate Risk
- Castleberry 1991: phase III, 62 pts >1 yo, INSS 2B-3 → surgery→ postop chemo +/- RT → surgery→ chemo. RT was 24-30 Gy based on age. CRT improved DFS (31→58%).
- POG 8742: phase II, INSS 2B-3→surgery → chemo x5→ surgery → RT for residual→chemoRT. 24-30Gy based on age. 2 year EFS was 85%.

### High Risk
- CCG 3891: phase III, 539 pts→chemo x5m→surgery (+10Gy if STR) → bone marrow transplant +/- TBI. Then randomized to +/- cis-retinoic acid. TBI improved and cis-retinoic acid improved 5 yr OS.
- Matthay 2007: phase II of refractory NB. Showed a 36% reponse rate with I-131 MIBG

### Technique
- Usually cover tumor +2cm
- 24Gy for int risk (controversial +/- RT)
- 21.6 Gy for high risk (1.8/fx)
  - Target postchemo, preop tumor bed and boost gross residual to 36Gy
  - No ENI
- 4S liver involvement 4.5Gy @ 1.5/fx to whole liver
- For cord compression
  - <3 yo: 9 Gy @1.8
  - ≥3 yo: 21.6 Gy @1.8
- Dose contraints
  - Contralateral kidney <15 Gy
  - Lung V15 <66%
  - Liver V15 <66%

### Guidelines
- Low risk
  - surgery
  - obs if GTR
  - STR or recur→chemo
- RT (24Gy) if cord compression, etc
- Can obs if clinically stable 4S low risk
- Int risk
  - surgery→chemo (RT for residual disease)
- High risk
  - High dose chemo→surgery→high dose chemo
  - All patients get RT (21.6Gy at 1.8/fx).
  - Then cis-retinoic acid
Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≤3mm height, ≥3mm from fovea, ≥1.5mm from ON</td>
</tr>
<tr>
<td>B</td>
<td>&gt;3mm height, clear subretinal fluid</td>
</tr>
</tbody>
</table>
| C     | C1: localized subretinal seeding  
         C2: ≤3mm from tumor margin  
         C3: both |
| D     | Same as Group C but diffuse seeding |
| E     | No visual potential: tumor in anterior segment, ON, ciliary body, neovascular glaucoma, hemorrhage, phthisical eye, orbital cellulitis, extraocular disease |

Overview
- 250 cases/yr
- RB1 tumor suppressor on ch13→defect in G1/S checkpoint
- Flexner-Wintersteiner rosettes
- Trilateral RB: bilateraleral RB + midline CNS PNET: uniformly fatal
- Pts are prone to osteosarcomas
- Workup: H&P, optho exam, labs, genetic counseling?
- Bilateral ultrasound, MRI
- If extraocular: bone scan, LP
- Biopsy not required

Trials
- Shields 1997: retrospective of chemo +/- local therapy. Local treatment reduced LC from ~70→0%

Technique
- Anesthesia?
- Supine, mask, IMRT, +/- bolus
- Cover entire retina and 5-8mm of optic nerve
- Dose is 36-40Gy in 1.8-2/fx (26Gy if postchemo)
- Protons spare orbital bone and lens
- RT increases risk of secondary malig from 25→50% at 50 years

Guidelines
- Unilateral: eye/sight preservation ~75% with EBRT
  - **Chemo**: vincristine/carbo/etoposide x6c
  - Laser: small, far from fovea
  - EBRT (36-40Gy): small tumors or failed non-RT therapy
  - I-125 plaque: dose is 40Gy to apex
  - Cryotherapy, photocoagulation
  - enucleation
- Bilateral: treat as separate primaries
- Extraocular: orbital EBRT and chemo (high dose chemo + SCT?)
- Trilateral: treat eyes, chemo, CSI? (MS is 11m)
Medulloblastoma

- T1 - <3cm
- T2 - ≥3cm
- T3
  - T3a - >3cm into aqueduct or foramen Luschka
  - T3b - >3cm invading brainstem
- T4 - >3cm past foramen magnum
- M1 – CSF+
- M2 – nodules in cranium
- M3 – nodules in spine
- M4 - outside CSF

<table>
<thead>
<tr>
<th>Age</th>
<th>Residual</th>
<th>M</th>
<th>5 yr EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std Risk</td>
<td>&gt;3 yr</td>
<td>&lt;1.5 cm²</td>
<td>0</td>
</tr>
<tr>
<td>High Risk</td>
<td>&lt;3 yr</td>
<td>≥1.5 cm²</td>
<td>+, or PNET</td>
</tr>
</tbody>
</table>

**General**
1. 500 cases/yr US
2. Bimodal (7 y/o and 25 y/o)
3. Assoc with Gorlin syndrome (PTCH1) and Turcot syndrome (APC)
4. Cell of origin is neuroectodermal cells from the germinal matrix of the cerebellum
5. Medullo has an intact INI1 (loss of INI1 is an ATRT)
6. Homer-wright rossettes (same as all blastomas but retinoblastoma)
7. Variants
   a. Classic
   b. Nodular/desmoplastic: good prog (LOH 9q)
   c. Large cell/anaplastic: poor prog
   d. Four genetic subgroups
      i. WNT group: CTNNB1 mut, assoc with Turcot (10%, good prog)
      ii. SHH group: PTCH1, GLI3, MYCN mut, usually desmoplastic (30%, int prog)
      iii. Group 3: MYC amp, usually large cell (poor prog)
      iv. Group 4: MYCN, CDK6 amp (int prog)

**Workup**
1. H&P, labs, fundoscopic exam, audiometry, IQ
2. Preop MRI brain/spine
3. MRI brain 24-48 hours postop
4. MRI spine 10-14 days postop
5. CSF cytology 10-14 days postop

**Trials**
1. POG 8631: std risk → 36 vs 23.4 Gy (no chemo. No diff
2. CCG 9892: std risk → 23.4 with vincristine→55.8 Gy PF boost→adj chemo. Favorable EFS (phase II)
3. Baby POG: <3 yo treated with chemo alone until 3 yo. 5 yr OS was 40%
4. German BTSG: similar to baby POG (58% 5 yr OS)
5. Retrospective series show low failures outside tumor bed (ANCS0331 is studying this)

**Simulation/Planning**
1. Prone, neck extended, mask, protons?
2. CSI technique
   a. Cranial iso behind the lenses
   b. Place spine fields first
   c. Inferior spine border is S2-3
   d. Lateral spine border is 1cm past pedicles, wider lower
   e. Rotate head colimator to arctan (½ length of thorax field/SSD)
   f. Kick couch for head fields arctan (½ length of cranial field/SAD) toward beam
   g. Skin gap = ((0.5 x length1 x d)/SSD1) + ((0.5 x length2 x d)/SSD2)
   h. Feather: move the junction superiorly 0.5cm on 7th and 13th fraction
3. Dose constraints
   a. Cochlea: V30<50%, max 35 Gy

**COG approach**
1. Standard risk over 3 y/o
   a. Resection
   b. RT with vincristine
      i. CSI to 36 Gy
      ii. Post fossa to 54 Gy (36 Gy?)
      iii. Cavity/residual to 54-55.8 Gy
   c. Adj cisplatin/CCNU/vincristine
      i. 8 cycles, Q6wks
2. High risk over 3 y/o
   a. Resection
   b. RT with vincristine
      i. CSI to 36 Gy
      ii. Cavity/residual 54-55.8 Gy
      iii. Brain/thecal mets 54-55.8 Gy
      iv. Spinal mets 45 Gy
      v. Diffuse spinal disease 39.6 Gy
   c. Adj cisplatin/CCNU/vincristine
      i. 8 cycles, Q6wks
3. Under 3 y/o
   a. Resection
   b. Adj chemo until 3 yo
   c. Then consider CSI/chemo
**Ependymoma**

1. **Bimodal (5 yo and 35 yo)**
2. **Cell of origin is the ependymal cell**
3. **Assoc with NF2 (ch 22)**
4. **WHO classification**
   - Grade I: myxopapillary and subependymoma
   - Grade II: classic
   - Grade III: anaplastic
   - Grade IV: ependymoblastoma
5. **Perivascular pseudorosettes**
6. **Poor prognosis**
   - erbB-2/erbB-4 overexpression
   - age <4 yo
   - supratentorial location

**Workup**
1. H&P, labs, fundoscopic exam, audiometry, IQ
2. Preop MRI brain/spine
3. MRI spine 10-14 days postop
4. **CSF cytology 10-14 days postop**

**Trials**
1. Rogers 2005: posterior fossa ependymomas, retrospective. 10 yr LC improved with RT (50%→100%)
2. Merhant 2009 and Koshy 2011 suggest RT → ↑OS in children under 3 yo
3. Retrospective series show no benefit to CSI

**Simulation/Planning**
1. **Preop GTV + 1-2cm to 54-59.4 Gy**

**COG approach**
1. If supratentorial, grade I-II and GTR: can observe
2. If infratentorial
   - Over 3 yo: Resection and adj RT (~54 Gy)
   - Under 3 yo: Resection and adj chemo (cisplatin/cyclophos/etoposide)
     - Can give 2 cycles then re-resection vs RT
3. If Spinal: RT for incomplete resection or anaplastic histology
   - 2 vertebral bodies above/below to 45 Gy
   - Boost to 50.4-59.4 Gy if no cord in field
4. **Ependymoblastoma**
   - Treat like high risk medulloblastoma (CSI to 36 Gy)
5. **Follow up**
   - for >10 yrs, late recurrences happen
   - craniospinal MRI Q3-6m then Q1yr

---

**Germ cell and Non-Germ cell tumors, Pineal Tumors**

1. **Histology**
   - Germinomas (more common)
     - AFP ≤10nl/mL (always)
     - Usually bHcG<50
     - Stains with placental alkaline phosphatase
   - NGGCT
     - Endodermal sinus tumor (yolk sac)
       - ↑AFP
     - Teratoma
     - Embryonal
       - ↑bHcG and ↑AFP
     - Mixed
   - Usually arise from proximal 3rd ventricle (pineal or suprasellar)
   - Parinaud syndrome: poor upward gaze, accomodates but abnl light response (caused by pressure on the superior colliculus)

**Workup**
1. H&P, labs, bHcG, AFP
2. MRI brain/spine
3. **CSF cytology with AFP and bHcG**

**Trials**
1. SIOP CNS GCT96: M0 → CSI 24 Gy + 16 Gy boost vs chemo+IFRT 40 Gy. All CRT failures were in the ventricles
2. Rogers 2008: lit review with similar results

**COG approach**
1. Localized germinoma: RT only
   - WVRT to 21-24 Gy
   - Boost primary to 40-45 Gy
   - Protocols evaluating neoadj chemo
2. +CSF germinoma (like low risk medullo)
   - CSI to 24 Gy
   - Boost to 45 Gy
3. **NGGCT:** all get chemo
   - chemoRT
     - Induction platinum-based chemo
     - Then CSI 30-36 Gy
     - Then boost 50.4-54 Gy
   - Surgery + chemo
     - Resection
     - Adj platinum-based chemo
     - Restage
     - CSI (36→50.4) vs IFRT
4. **Pineoblastoma:** Treat like a high risk medullo (CSI to 36, boost to 54 Gy)
5. **Pineocytoma:** treat like low grade glioma (delayed RT)
### Craniopharyngioma\textsuperscript{1-5,40}

**General**
1. Rathke’s pouch origin
2. Bimodal (10 yo and 50 yo)

**Workup**
1. H&P, labs, endocrine labs
2. MRI brain
3. CSF cytology with AFP and bHcG

**Trials**
1. Stripp 2004: 10 yr LC with surgery worse than surgery+RT (42%→84%), but if RT used as salvage 10 yr LC was unchanged

**COG approach**
1. Max safe resection (usually STR) then RT (or can observe)
2. 50.4-54 Gy to GTV + 5-10mm (no CTV)
   a. Watch for welling
3. Can use intracystic bleomycin
4. Can use β-emitters (Y90, P32, Rh186). Rx is 200-250 Gy to cyst wall
   a. P32 is 0.7MeV, t1/2 14 days, effective depth is 4mm

### Brainstem Glioma\textsuperscript{1-5,40-46}

**General**
1. 2 classes
   a. Focal: upper midbrain/lower medulla
   b. Diffuse: pons and upper medulla

**Workup**
1. H&P, labs
2. MRI brain/spine
3. No biopsy

**Trials**
1. Cohen 2011: no benefit to concurrent/adj TMZ
2. POG/CCG trials showed no benefit to hyperfrac or dose escalation
3. Janssens 2013: hypofractioned treatment has same OS and PFS

**COG approach**
1. Steroids and 54Gy
Central Nervous System
Low Grade Glioma

General
1. 20% of gliomas
2. 70% present with seizures (better prognosis)
3. Juvenile Pilocytic Astrocytoma (JPA)
   a. Rosenthal fibers histologically
   b. WHO I: treat with surgery, consider PORT if STR
   c. Pilomyxoid astrocytoma is an atypical JPA, more aggressive
4. Subependymal giant cell tumor
   a. Associated with tuberous sclerosis (ch9)
   b. WHO I
5. LGGs commonly do not enhance, but usually show T2 signal and mass effect
6. 75% will progress to high grade glioma
7. Postop MRI indicated within 72 hrs of surgery
8. 4 features of glioma grading (AMEN): atypia, mitosis, endothelial proliferation, and necrosis
9. Gemistocytic subtype is more aggressive (could consider it a grade III)

Workup
1. H&P, neuro exam
2. MRI w/o gadolinium
3. Hearing/ortho eval?
4. Surgery eval for maximum safe resection. No biopsy unless unresectable

Trials
1. Smith 2008: retrospective, 216 pts, resection >90% correlated with 5yr OS (97% vs 76%)
2. EORTC 22845 (nonbelievers): 311 pts, WHO I-II. Surgery (42% GTR) → obs vs 54 Gy. OS was the same (~66%), but RT had better median PFS (5.3 vs 3.4 yr). 65% of obs arm got RT at progression
3. EORTC 22844 (believers): 343 pts, WHO I-II. Surgery (30% GTR) → 45 Gy vs 59.4 Gy. Same OS (59%), PFS (49%). Determined that <40yo, oligo histology, GTR and good KPS were prognostic
4. INT/NCCTG (Shaw): 203 pts, WHO I-II. Surgery (14% GTR) → 50.4Gy vs 64.8Gy. Same 5 yr OS (~70%), 92% of failures in in field
5. RTOG 9802: pending (high risk pts get RT +/- PCV). Early results show that PCV improves PFS but not OS
6. RTOG 0424: pending (high risk pts get RT +/- TMZ)

Simulation/Planning
1. Supine, aquaplast, fuse MRI
2. GTV = T1 enhancing + FLAIR
3. CTV = GTV + 1-2cm

NCCN
1. Surgical resection then postop MRI within 72 hours, Testing for 1p/19q, IDH1/2
   a. If low risk and GTR: observe with RT if progression
   b. If low risk and STR: RT (cat 2a) or chemo (cat 2b, TMZ or PCV)
   c. If high risk regardless of resection: PORT (cat 2a) or chemo (cat 2b, TMZ or PCV)
2. Follow up MRI Q6m for 5 yrs then annually
### General
1. Most common primary malignant brain tumor
2. MGMT repairs DNA damage
   a. Removes alkyl group from O6 guanine
   b. Hypermethylated promoter silences MGMT
3. Pseudoprogression: up to 50% of patients, more common if MGMT hypermethylated
4. Primary GBM: EGFR/MDM2 amp, LOH 10/p16 loss
5. Secondary GBM: p53 mut, LOH 19q, LOH10/p16 loss
6. RTOG RPA: age +/-50, histology, KPS +/-70, MS changes, Sx+/-3m
7. Additional prognostic factors: MGMT, extent of resection

### Workup
1. H&P, neuro exam
2. +/- dex, +/- keppra
3. MRI w/wo gadolinium
4. Hearing/ophtho eval?
5. Surgery eval for maximum safe resection. No biopsy unless unresectable
6. MR spectroscopy?
   a. NAA: neuronal marker
   b. Choline: cellular integrity
   c. Creatine: cellular energy
   d. Lactate: anaerobic metabolism

### Surgery +/- RT
1. Keime-Guibert 2007: 81 pts, elderly GBM, >70 yo, KPS >70. Surgery +/- 50.4Gy. Stopped early, RT won. MS 4.3 →7.3m, independent of extent of resection
2. Bauman 1994: 29 pts, elderly GBM, >65 yo. 30/10 WBRT improved MS over observation (10m vs 1m)

### RT dose/fractionation
1. Roa 2004: 100 pts, 60/30 vs 40/15. No difference in MS
2. RTOG 7401: No benefit to 70 Gy over 60 Gy
3. Chan 2002: no benefit to 90 Gy
4. MRC 1991: 474 pts. 45/20 vs 60/30. 60 Gy improved MS (9m vs 12m)
5. RTOG 9305: 203 pts, surgery + 60 Gy + BCNU +/- SRS. No differences
6. RTOG 0023: phase 2 trial of fractionated SRS. No differences

### ChemoRT
1. Stupp 2009: 573 pts, GBM, RT +/- TMZ. TMZ was concurent (75mg/m2/day) and adjuvant (150-200mg/m2/day x5days Q4wks x6months). TMZ won. MS 12.1→14.6m. 5 yr OS 1.9→9.8%. MGMT hypermethylated pts did the best
2. Walker 1980: 476 pts. RT alone vs RT+MeCCNU vs RT+BCNU. No differences
3. RTOG 0525: tested dose dense TMZ, no benefit, long term results pending
4. RTOG 9402: 289 pts grade III tumors. Surgery +/- adj PCV 4c, then RT. All pts got RT. RT went to 59.4Gy (50.4+9). MS same, but PFS improved with PCV (1.7→2.6yrs). 1p19q codel pts had better prognosis and had the only benefit from PCV
5. EORTC 26951: 368 pts, grade III tumors. Surgery → RT → +/-PCV6c. RT went to 59.4 Gy (45+14.4). MS same, PFS improved with PCV (13→23m). 1p19q codel pts did better, but PCV benefited everyone
6. NOA-04: grade III tumors, RT vs PCV (or TMZ). PFS and OS same between groups,

### Simulation/Planning
1. Supine, aquaplast, fuse MRI
2. CTV1 = (T1+g + T2) + 2cm
3. CTV2 = (T1+g) + 1-2cm

### NCCN
1. Surgical resection +/- carmustine wafer
   a. then postop MRI within 72 hours, Testing for MGMT, IDH1/2
   b. oligo 1p19q codel
      i. RT + adj or neoadj PCV (cat 1, adj preferred)
      ii. RT +TMZ
      iii. TMA or PCV alone (cat 2b)
   c. AA or 1p19q non-codel
      i. RT alone (cat 1)
      ii. RT +TMZ
      iii. TMA or PCV alone
   d. GBM
      i. 60 Gy with TMZ and adjuvant TMZ
      ii. RT alone?
      iii. TMZ alone?
      iv. Supportive care?
2. Recurrent disease: 25/5 vs chemo vs pall care
3. Follow up MRI at 6wk then Q2m for 3 yrs
Primary CNS Lymphoma

General
1. 1000 cases/yr, 4% of primary brain tumors
2. Associated with immunodeficiency (AIDS), EBV, DLBCL
3. Gain of chr12 → ↑MDM2 → ↓p53
4. NHL assoc with CNS spread: Burkitt, lymphoblastic, immunocompromised, BM+, parameningeal, testicular relapse
5. All are stage IE (extranodal NHL)

Workup
1. H&P, labs, HIV, LDH, bHcG, EBV, toxoplasmosis titer
2. CSF cytology
3. Slit lamp exam
4. Testicular ultrasound? PETCT?
5. MRI +/-spine
6. CT CAP
7. SPECT if immunocompromised
8. Delay steroids and bx

RT dose/omission
1. RTOG 8315: WBRT (40Gy) → boost to 60Gy. 80% failed in boost field
2. RTOG 9310: 45 Gy (1.8/fx) vs 36 Gy (1.2/fx BID). Same OS and DFS, but worse neurotoxicity with BID (4%→23%)
3. Abrey 2000 (MSKCC): 52 pts, chemo+WBRT+chemo. Not all got RT, but it improved DFS. OS was not better with RT
4. NABTT 9607: HD MTX Q2wks until CR (or 8 cycles). Then more MTX. Not RT. MS was 22.8 (comparatively favorable)

Ocular Lymphoma
1. Usually DLBCL
2. 75% will go on to develop CNS lymphoma
3. Dx by vitrectomy
4. Tx is 36 Gy to orbit or intraocular chemo
5. Mean OS is 6-18m (uniformly fatal)

Simulation/Planning
1. helmet field (to C2, include orbits): 36 Gy
2. cone down to WBRT: 45 Gy
3. if leptomeningeal: CSI to 36 Gy +/- boost to 45
4. If CR: 24-36Gy WBRT, or obs
5. If PR: 36-45 Gy

NCCN
1. KPS > 40: high dose MTX
   a. If CR: observe or 24-36 Gy WBRT
   b. If not: 36 Gy WBRT + boost to 45 Gy
2. KPS < 40: steroids
   a. If ↑KPS: RT
### Meningioma

**General**

1. Risk factors: prior RT, NF2 (ch22, Merlin gene), HRT
2. Psammoma bodies and calcifications
3. Grading
   a. Grade I: benign
   b. Grade II: atypical (clear cell, choroid)
   c. Grade III: anaplastic (rhabdoid, papillary)
4. Dural tails are not thought to have tumor cells
5. Simpson grading
   a. I: GTR including dura/bone
   b. II: GTR and coagulate dura
   c. III: GTR without coagulation
   d. IV: STR
   e. V: decompression alone

**Workup**

1. H&P, labs, MRI

**Trials**

1. Goldsmith 1994: improved PFS with dose ↑52 Gy

**NCCN**

1. Observation
2. Surgery with RT if STR, grade II-III, or recurrent
   a. 54 Gy is benign
   b. 60 Gy if malignant
   c. 12-16 Gy SRS (50% isodose)

### Pituitary Tumors

**General**

1. 75% functional, 25% nonfunctional
2. Assoc with MEN-1 (auto dominant, 3 P’s)
3. Derives from Rathke’s pouch or 3rd ventricle
4. Presents as ↑hormone or bitemp hemianopsia
5. Subtypes
   a. Prolactinoma (30%): nl prolactin 2-25
      i. Bromocriptine or
   b. GH (25%): nl GH <10
      i. Somatostatin, octreotide
   c. ACTH (15%)
      i. Ketoconazole, cyproheptadine, RU-486
   d. TSH (<1%)
6. Macroadenoma (≥1cm) vs microadenoma (<1cm)
7. Can take years (5-10) to correct horomones
8. 95% LC afer transsphenoidal resection overall
   a. Risk for ↓LC: ↑age, >2cm, TSH-secreting
   b. RT along LC is ~90%

**Workup**

1. H&P, labs, hormone levels MRI

**Trials**

1. McCollough 1991: 10 yr LC was 95%, better if >45 Gy

**Simulation/Planning**

1. 45-50.4Gy for no GTV
2. 50-54 Gy if gross disease
3. SRS for microadenomas
   a. 20 Gy if functioning
   b. 14-18 Gy if nonfunctioning
   c. Optic nerve max 8 Gy
Head and Neck
### Ocular Melanoma

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<th>Apical Height</th>
<th>Basal Diameter</th>
<th>10yr OS</th>
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<tr>
<td>Diffuse</td>
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<tr>
<td>Metastatic</td>
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</table>

#### Overview
- 2,000 cases/yr (1/3 asymptomatic)
- 98% caucasians
- Usually arises from choroid
- Usually mets to liver (90%)
- BAP1 inactivation found in most ocular melanoma
- Workup: H&P, eye exam, slit lamp, B-scan u/s, LFTs, liver u/s, no bx

#### Trials
- COMS 1997: obs small tumors. 5 yr OS 94%, 33% progressed
- COMS 28: (COMS medium)→enucleation vs eye plaque. Same 12 yr OS (~60%), 13% of plaque pts ended up getting enucleations 2/2 tumor or pain
- Quivey 1993: retrospective I-125. 13% local failure

#### Plaque Technique
- I-125 seeds
- 85 Gy to apex (if less then 5mm apex→Rx to 5mm)
- 2mm around tumor

#### Treatment
- COMS small: observation or local therapy. 33% progress with obx
- COMS medium: enucleation, plaque, SRS(25-40Gy to 50% isodose), or protons (56cGyE)
- COMS large: enucleation or protons
Nasopharyngeal Cancer

- T1 – NP, OP, or nasal cavity
- T2 – parapharyngeal space extension
- T3 – bony structures or paranasal sinuses
- T4 – intracranial, CNs, infratemporal fossa, hypopharynx, orbit, masticator space

- N1 – unilateral ≤6cm (RP LNs can be bilateral)
- N2 – bilateral, ≤6cm
- N3a – >6cm
- N3b – supraclav (defined by Ho)

Pathology
- WHO grade
  - I: keratinizing SCC (smokers, USA)
  - II: nonker SCC (EBV assoc)
  - III: undiff (lymnoepithelioma, EBV assoc)
- EBV: titers >1500 copies/ml → ↓OS. Persistent EBV after tx → ↓OS (Lin et al)
  - 70% cN+, 90% pN+, 50% BL N+

Anatomy
- Borders
  - Ant: choanae
  - Post: clivus, C1, C2
  - Sup: sphenoid sinus
  - Inf: soft palate
  - Lat: Eustachian tube, torus tubarius, fossa of Rosenmueller (deep is parapharyngeal space)
- Villaret/Jugular foramen syndrome: parapharyngeal space invasion (CN IX-XII, sympathetic nerve palsy)
- Rotundum: V2
- Ovale: V3
- Lacerum: carotid→cavernous sinus→cranial fossa (Jacod syndrome)
- Cavernous sinus: carotid, III, IV, V2, V3, VI
- Triangle of Ho: superior clavicle, point where neck meets shoulder

Workup
- H&P, FNL, otoscopy, CN exam, labs (EBV IgA/DNA)
- MRI + CT, CT chest, +/- PET

RT +/- chemo
- Al Sarraf, Int 0099 (mostly WHO I) stage III/IV:70/35 +- HD cis and adj cis/5FU: CRT won; 3 yr OS 47→78%, PFS 24→65%
- Wee, 2005: confirmed Int 0999 for WHO III: 2 yr OS 78→85%
- Chen, 2005: RT +/- LD cis: 59→70%, lower toxicity
- Baujet: metaanalysis, chemo improved OS when given concurrent
- Chen 2012: CRT +/-adj cis/5FU: no benefit to added chemo, long term data pending

Neoadj chemo
- Debated, mostly no benefit in phase III trials

IMRT
- Lee et al: IMRT to 70 Gy: 4 yr OS 88%, LRC 87%
- RTOG 0225: phase II: 70 Gy @2.12 w/ cis + adj cis/5FU: 2 yr LRC 91%, OS 79%

Sim/planning (based on Nancy Lee’s reecs)
- Dental eval, aquaplast, supine, 33 fx IMRT, MRI fusion
- CTV70: @2.12 = GTV
- CTV9.4 @ 1.8 = nasopharynx, sphenoid sinus, cavernous sinus, skull base, clivus, RPN, post 1/3 maxillary, post 1/3 nasal, pteryopalatine fossa (V2), pterygopalatine and nasopharyngeal space (V3)
- CTV 54 @ 1.64: RS space, BL Ib-V, supraclav for N+
- Dose limits:
  - Brainstem: 54 Gy (60 Gy max)
  - Optics: 54 Gy
  - Retina 45 Gy, lens 10 Gy
  - Parotid mean < 26Gy
  - Inner ear < 50 Gy
  - Larynx: V50 <30%

NCCN
- I: RT alone (70/35 or 66/30)
- II-IVB: CRT with cis (70 Gy) + adj cis/5FU
- Surgery for residual disease
Maxillary Sinus Cancer\textsuperscript{1-5,82-84}

- **T1** – limited to maxillary sinus without bone erosion
- **T2** – invading hard palate, middle nasal meatus
- **T3** – posterior wall of maxillary sinus, subQ, orbital wall, pterygoid fossa, ethmoid
- **T4** -
  - T4a – anterior orbit, skin, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid/frontal sinuses
  - T4b – orbital apex, dura, brain, middle cranial fossa, CNs other than V2, nasopharynx, clivus

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

Nasal Cavity and Ethmoid Sinus Cancer\textsuperscript{1-5,82-84}

- **T1** – one subsite, no bony invasion
- **T2** – two subsites, +/- bony invasion
- **T3** – maxillary sinus, orbital wall, palate, cribiform plate
- **T4** -
  - T4a – anterior orbit, skin, pterygoid plates, cranial fossa, sphenoid/frontal sinuses
  - T4b – orbital apex, dur, brain, middle cranial fossa, CNs other than V2, nasopharynx, clivus

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**Histology**
- SCC most common, also Adenoid cystic, plasmacytoma, lymphoma, SNUC, etc

**Anatomy**
- Subsites: septum, floor, lateral wall, vestibule
- Lamina papyracea: medial wall of orbit (thin bone)
- Ohngren’s Line: medial canthus to angle of mandible (superior-posterior to this is worse)
- Lymph drains to IB, parotid, RPN, II

**Workup**
- H&P, FNL, CN exam, biopsy
- CT/MRI, CT chest, +/- PET

**Nasal Cavity**
- Dulguerov et al, 2001: mixed group, 5 yr OS 40%, LRC 59%. Worse prognosis: petrygomaxillary fossa, frontal/sphenoid sinuses, cribiform/dural erosion. If periorbital fat or ocular muscle invasion →enucleation (no enucleation if just bone).

**Maxillary Sinus**
- Le et al, 2000: retrospective, +/- surgery, +/-RT: 20% neck failure without ENI but 0% neck failure with ENI
- Bristol et al, 2007: retrospective, surgery + adj RT: clinical outcomes similar, but justifies base of skull and ENI coverage in at-risk patients

**Chemo?**
- Sinus cancers not included in postop CRT trials, but usually extrapolated for SCC histology

Sim/planning (based on Nancy Lee’s rees)
- Dentistry, supine, mask, eyes straight, bite block
- Brachytherapy for nasal cavity?
- Esthesios: here we do chemo x2 cycles, then 50 Gy (with ENI), then resection.
- Dose limits:
  - Brainstem: 54 Gy (60 Gy max)
  - Optics: 54 Gy
  - Retina 45 Gy, lens 10 Gy
  - Parotid mean < 26Gy
  - Pituitary/thyroid (62% develop hormone deficiencies)

**NCCN**
- Resectable: surgery + RT for T3, T4,+margin, PNI, ACC, ethmoid (all ethmoid tumors need adj RT)
  - Add chemo for +margin, ECE, SNUC
  - 60-66 Gy to primary, 50-54 to necks
- Unresectable: chemorT to 70 Gy, cisplatin
  - Consider alt fractionation for tissue sparing
    - Accelerated: BID once per week (6 fx/wk)
    - Concomitant boost: BID last 2 wks
    - Hyperfractionation: BID throughout
- IMRT preferred for normal tissue sparing
- Preop RT or CRT to 50 Gy accepted
Oral Cavity Cancer1-5,85-98

- T1 – ≤2cm
- T2 – 2-4cm
- T3 – >4cm
- T4 -
  - T4a – cortical bone, deep muscles of tongue (genio, hyo, stylo, palatoglossus)
  - T4b – masticator space, pterygoid plates, skull base, encases carotid

- N1 – single, ≤3cm
- N2
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- N3 – >6cm

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<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4a</th>
<th>T4b</th>
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<tr>
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<tr>
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<td>IVA</td>
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<td>N3</td>
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<tr>
<td>M1</td>
<td></td>
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<td></td>
<td>IVC</td>
</tr>
</tbody>
</table>

Pathology
- Tobacco, ETOH, poor hygiene, betel/acreca nuts
- Oral leukoplakia (10% risk)
- Erythroplakia (30% risk)

Anatomy
- Subsites: lips, gingivobuccal sulcus, buccal mucosa, gingival, retromolar trigone, hard palate, FOM, ant 2/3 tongue
- CN XII: motor, CN V: sensory, CN VII: taste (BOT CN IX taste)
- Ear pain? Auriculotemporal nerve (CN V3)
- Oral Tongue requiring LND: ≥3mm DOI, grade 3, +LVSI, recurrence
- Adequate margin in OC SCC: 1cm (1.5cm for tongue)
- Extrinsic tongue muscles: Genioglossus, Styloglossus, Palatoglossus, Hyoglossus

Workup
- H&P, palpation, FNL, CN exam, bx, labs
- MRI + CT, CT chest, +/- PET
- Dentistry

Lip
- Commisure involvement→↑nodal risk
- Surgery preferred unless concern for postop function
- T1/2: electrons (+bolus), orthovoltage, brachy (50/25 + boost of 10-16 Gy), no neck tx

- T3: 50/25 + boost of 20 Gy, treat neck levels I/II
- T4 or N+: same as T3 but treat neck I-IV

Brachytherapy
- can use LDR (Granenbauer 2001), PDR (Melzner 2007) or HDR (Martinex-Monge 2009)
- can be alone or as EBRT boost (~50 Gy EBRT)

Altered fractionation (no chemo)
- RTOG 9003: advanced H&N SCC→ 70/35 (std) vs 81.6 @1.2 BID (hyperfrac) vs 67.2 @1.6 BID split (split) vs 72 w/ last 12x BID (conboost). Hyperfrac and Conboost won (LRC 54%, DFS 39%, OS 53%). ↑toxicity
- MARCH metaanalysis: 6,515 pts. 3.4% OS benefit at 5 years for altered fractionation, mostly for young pts

ChemoRT
- MACH-NC metaanalysis: 17,346 pts: 4.5% OS benefit with any CRT, greater with concurrent (6.5%). Platinum-monotherapy is gold standard, no benefit if age >71

Postop RT, CRT
- Ang 2001: OC SCC: +margin, PNI, ECE had ↑failure without postop RT
- EORTC 22931: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharnx: postop 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 5yr DFS 36→47%, OS 40→53%, LRC 69→82% (DM unchanged ~25%). ↑toxicity (21→41%)
- RTOG 9501: operable H&N (≥2 LN, ECE, +margin): 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 2 yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity
- Metaanalysis: CRT improved OS, DFS and LRC for ECE or +margins. Trend for stage III/IV, PNI, LVSI, low neck nodes

Sim/planning
- Dental eval, PEG?, aquaplast, supine, bite block
- Dose limits:
  - Cord < 45 Gy max
  - Parotid mean < 26Gy
  - Larynx mean <43.5 Gy
  - Mandible <70 Gy max

NCCN
- I-II: RT alone (70/35 or 66/30) or surgery alone
  - Postop RT for T3+, N2+, PNI, LVSI (6wks postop)
  - Postop CRT for +margin, +ECE
- III-IVB: CRT with cis (70 Gy), 100mg/m2 Q3wks
  - Alt frac if no chemo given
  - Induction chemo (category 3)
- Surgery for residual disease
Oropharyngeal Cancer

- T1 – ≤2 cm
- T2 – 2-4 cm
- T3 – >4 cm or lingual surface of epiglottis
- T4 -  
  - T4a – larynx, deep tongue muscles, medial pterygoid, hard palate, mandible
  - T4b – lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base, carotid

- N1 – single, ≤3 cm
- N2 -  
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6 cm
  - N2c – contralateral, ≤6 cm
- N3 – >6 cm

HPV-Associated SCC  
- Younger, nonsmokers (~60% of new cancers)
- subtypes 16(80%), 18: ↑nodes, ↑mets
- E6→↓p53; E7→↓Rb→↑p16
- RTOG 0129: better 3 yr OS for HPV+ (57→82%)

Anatomy  
- Subsites: soft palate, palatine tonsils, tonsillar pillars, base of tongue, pharyngeal wall
- Borders: superior soft palate, to superior hyoid bone (floor of vallecula)
- Ear pain?
  - Oral tongue: auriculotoemporal nerve (CN V)
  - BOT: Jacobson’s nerve (CN IX)
  - Larynx/HPX: Arnold’s nerve (CN X)

Workup  
- H&P, palpation, FNL, CN exam, biopsy (p16)
- MRI + CT, CT chest, +/- PET, dentistry

Preop vs Postop RT  
- RTOG 7303: advanced H&N SCC→50 Gy preop vs 60 Gy postop→postop improved LRC 48→65% overall and OS for oropharynx (26→38%)

Altered fractionation (no chemo)  
- RTOG 0022: T1-2N0-1 OP SCC: 66 Gy in 30 fx (@2.2): 91% 2 yr LRC (N staging clinical only)
- RTOG 9003: advanced H&N SCC→70/35 (std) vs 81.6 @1.2 BID (hyperfrac) vs 67.2 @1.6 BID (split) vs 72 w/ last 12fx BID (conboost). Hyperfrac and Conboost won (LRC 54%, DFS 39%). No difference in OS 53%. ↑toxicity
- EORTC 22791: T2/3 oropharynx 70/35 vs 80.5 @1.15 BID. Hyperfrac ↑LRC 40→59%, OS 31→47%. No BOT in this trial
- MARCH metaanalysis: 6,515 pts. 3.4% OS benefit at 5 yrs for altered fractionation, mostly in young pts

ChemoRT  
- GORTEC 9401: stage III/IV oropharynx: 70/35 +/- carbo/5FU. CRT improved LC 25→48%, DFS 15→27%, OS 16→23%

- Adelstein 2003: stage III/IV H&N SCC: RT +/- cisplatin (100mg/m2 Q3wks): CRT won. 3 yr OS 23→37%, DFS 33→51%
- Bonner 2006: advanced OP, larynx, hypopharynx: RT vs CRT (cetuximab). CRT won. 3 yr LRC 34→47%, OS 45→55%. Rash with cetuximab
- GORTEC 9902: advanced H&N SCC: carbo/5FU+RT. RT was 70/35 vs 70/30 vs 64.8/18 (no chemo). Similar outcomes except ↑toxicity in 64.8/18 arm
- MACH-NC metaanalysis: 17,346 pts: 4.5% OS benefit with any CRT, greater with concurrent (6.5%). Platinum-monotherapy is gold standard, no benefit if age >71

Postop RT +/- chemo  
- EORTC 22931: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharynx (ECE, +margin, PNI, LVSI, level IV/V nodes): postop 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 5yr DFS 36→47%, OS 40→53%, LRC 69→82% (DM unchanged ~25%). ↑toxicity (21→41%)
- RTOG 9501: operable H&N (≥2 LN, ECE, +margin): 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 2 yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity
- Metaanalysis: CRT improved OS, DFS and LRC for ECE or +margins. Trend for stage III/IV, PNI, LVSI, low neck nodes

Induction chemo  
- TAX323: unresectable H&N SCC: TPF vs PF induction→RT alone. TPF increased MS 16→19months
- TAX 324: Posner: unresectable H&N SCC: TPF vs PF induction→CRT with carboplatin. Induction CRT won. 3 yr OS 48→62%. 25% of patients never made it to RT (progressed, died, withdrew)
- DeCIDE trial: locally advanced H&N SCC: CRT with docetaxol, 5FU, hydroxyurea, BID fx vs TPF induction then same CRT: no OS advantage, underpowered
- PARADIGM trial: TPF induction + CRT with docetaxol or carboplatin vs CRT with cisplatin: no difference (3 yr OS 73% induction; 78% CRT)

Sim/planning  
- Dental eval, PEG?, aquaplast, supine, 35 fx IMRT
- Bilateral neck unless T1-2N0 tonsil with <1cm BOT of soft palate invasion (OSullivan 2001: 3.5% contralateral neck failure, all N+)

NCCN  
- I-II: RT alone (70/35 or 66/30) or surgery alone
  - Postop RT for T3+, N2+, PNI, LVSI,
  - Postop CRT for +margin, +ECE
- III-IVB: CRT with cis (70 Gy), 100mg/m2 Q3wks
  - Alt frac if no chemo given
  - Induction chemo (category 3)
- Surgery for residual disease
Salivary Gland Cancer\textsuperscript{1-5,99-105}

- **T1** - ≤2cm w/o extraparenchymal extension
- **T2** – 2-4cm w/o extraparenchymal extension
- **T3** - >4cm or extraparenchymal extension
- **T4**
  - T4a – skin, mandible, ear, CN VII
  - T4b – skull base, pterygoid plates, carotid
- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

**Histology**
- Benign most common: usually pleomorphic adenoma (consider postop RT for multifocal, PNI, residual, recurrent)
- Most common malignant: mucoepidermoid carcinoma
- Also ACC, Acinic cell,
- ACC, ductal, undifferentiated → ↑DM (lung, bone, liver)

**Anatomy**
- Parotid: facial nerve, Stensen’s duct, most common, malignant less common (20%)
- Submandibular: lingual nerve (V3) and XII, Wharton’s duct, more likely malignant (50%)
- Sublingual: superior to mylohyoid, Rivinus/Bartholin’s ducts, incidence debated (90%?)
- Minor glands: most likely malignant (90%)
- Frey’s syndrome, auriculotemporal nerve syndrome, gustatory sweating (CN VII damage)

**Workup**
- H&P, bimanual palpation, FNL, CN exam, biopsy (FNA)
- MRI + CT, CT chest, +/- PET, dentistry

**Postop RT and Elective nodal Irradiation**
- Terhaard 2005: retrospective; surgery +/-RT: 10 yr LC improved (T3-4 18→84%) (close 55→95%) (+margin 18→84%) (+bone 54→86%) (PNI 60→88%
- Chen 2007: cN0 salivary gland→surgery+RT: ENI reduced nodal failure from 26→0% (more with ↑T, SCC, undiff, adeno). Usually ipsilateral only

**Adenoid cystic carcinoma**
- Garden 1995: ACC→surgery+RT: 10 yr LRC 86%, worse for +margins and clinical PNI. Provides justification for definitive tx if M1 (long natural hx)
- Mendenhall 2004: ACC: surgery+RT better than RT alone (91% vs 43%) worse for T3-4 and clinical PNI
- For ACC irradiate nerve to skull base, ultimately 40% will develop lung mets

**Neutrons**
- RTOG-MRC trial: 32 inoperable salivary gland: neutron vs photon/electron: closed early, neutrons won: 10 yr LRC 17→56%, OS unchanged (15→25%)
- 19.2nGy to GTV (1.2nGy x4/wk), 13.2nGy to PTV2

**Sim/planning**
- Dental eval, PEG?, aquaplast, supine, 35 fx IMRT
- Bilateral neck unless T1-2N0 tonsil with <1cm BOT of soft palate invasion (OSullivan 2001: 3.5% contralateral neck failure, all N+)

**NCCN**
- Operable: surgery with END for G3, T4
  - Postop RT for T3+, N+, +margin, close margin, PNI, LVSI, G2-3, ACC, recurrent
  - No defined role for chemo if M0 (RTOG 1002 pending)
- Inoperable: RT +/- chemo, consider neutrons
### Laryngeal and Hypopharyngeal Cancer

<table>
<thead>
<tr>
<th>Subglottis</th>
<th>Glottis</th>
<th>Subglottis</th>
<th>Hypopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 subsite*, normal VCs</td>
<td>Normal VC movement (T1a one cord, T1b both)</td>
<td>Subglottis only</td>
</tr>
<tr>
<td>T2</td>
<td>2+ subsites or glottis</td>
<td>Supra/subglottis or impaired VC</td>
<td>To VCs</td>
</tr>
<tr>
<td>T3</td>
<td>Fixed cord, paraglottic space, inner cartilage, pre-epiglottic space</td>
<td>Fixed cord, paraglottic space, inner cartilage, post-cricoid area</td>
<td>Fixed cord</td>
</tr>
<tr>
<td>T4a</td>
<td>Through cartilage, beyond larynx</td>
<td>Through cartilage, beyond larynx</td>
<td>Cricoid invasion, ANY cartilage invasion, outside larynx</td>
</tr>
</tbody>
</table>

**Prevertebral space, carotid, mediastinum**

*Supraglottic subsites: false cords, arytenoids, suprahypopharyngeal epiglottis, infrapharyngeal epiglottis, aryepiglottic folds

** Hypopharynx subsites: pyriform sinus, Hypopharyngeal wall, postcricoid region

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

### Anatomy

- Larynx Subsites
  - Supraglottis: epiglottis, AE folds, arytenoids, false cords, ventricle
  - Glottis: TVCs, ant/post commissures
  - Subglottis: 5mm below glottis to inferior cricoid
  - Hypopharynx: Superior Hyoid to inferior cricoids
  - Subsites: Pyriform sinus, hypopharyngeal walls, postcricoid area
- Ear pain?
  - Oral tongue: auriculotemporal nerve (CN V)
  - BOT: Jacobson’s nerve (CN IX)
  - Larynx/HPX: Arnold’s nerve (CN X)

### Workup

- H&P, FNL, biopsy
- CT +/- MRI, CT chest, +/- PET, dentistry

### RT alone fractionation

- Yamazaki 2006: phase III, T1 glottis: 2Gy/fx to 60-66 Gy vs 2.25 Gy/fx to 56-63 Gy. Hypofrac won. 5 yr LC 77→92%, CSS & toxicity unchanged
- RTOG 95-12: T2 glottis: 70/35 vs 79.2 BID (1.2 Gy). No change, trend for ↑LC (70→79%, p>0.11)
- RTOG 90-03 included larynx/hypopharynx primaries

### Larynx Preservation

- VA Larynx Trial: III/IV larynx: surgery+PORT vs cis/5FU x3c then RT. PR or CR required before RT. 64% larynx preservation at 2 yrs, OS unchanged (68%), LC lower for CRT (98→88%). Non-chemo responders got surgery.
- RTOG 91-11: III/IV larynx: RT alone vs chemo→RT vs CRT. Induction chemo was cis/5FU. All cN2 patients got planned neck dissection after RT. Concurrent CRT won. 5 yr larynx preservation 84→71→66%, LRC 69→55→51%. Chemo reduced DMs (13 vs 22%). OS unchanged.

### ChemoRT

- TAX 324 (Posner): unresectable head & neck (33% larynx/hypopharynx): induction TPF vs PF x3 cycles, then 70 Gy. TPF won. 3 yr OS 48→62%, LRC 62→70%, DM unchanged. TPF was toxic
- EORTC 24891: same as VA trial but with pyriform sinus and required CR. Same OS (~40%). 5 yr functional larynx 35%

### Sim/planning

- Mask, shoulders down
- T1 glottis: 5x5cm opposed laterals (top of thyroid cartilage through cricoid, flash to anterior vert body
- T2 glottis: same by 6x6cm down to 1st tracheal ring
- Hypopharynx: always treat nodes II-V and RPNs
- Boost stoma for emergent trach, subglottic extension, or anterior soft tissue extension

### NCCN Larynx

- Tis: cord stripping (laser/CO2) or RT
- T1a: RT or cordectomy
- 63Gy @2.25 to 66Gy @2.0
- T1b: RT or hemilaryngectomy
- 65.25Gy @2.25 to 70Gy @2.0
- T3 or N+: chemoRT (surgery salvage) or induction chemo or laryngectomy
- After induction: surgery for residual, RT for CR, consider chemoRT for PR
- T4: laryngectomy or chemoRT

### NCCN Hypopharynx

- T1-2: RT or organ sparing surgery if able
- T2-3: induction chemo or surgery or chemoRT
- After induction: surgery for residual, RT for CR or PR (consider chemoRT)
- T4a: surgery or induction or CRT
- T4: laryngectomy or chemoRT
Thyroid Cancer

<table>
<thead>
<tr>
<th>Papillary/Follicular</th>
<th>Papillary/Follicular</th>
<th>MTC</th>
<th>Anaplastic</th>
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</thead>
<tbody>
<tr>
<td>&lt;45 years old</td>
<td>&gt;45 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0M0 I</td>
<td>T1 I</td>
<td>T1 I</td>
<td>I</td>
</tr>
<tr>
<td>M1 II</td>
<td>T2 II</td>
<td>T2-3II</td>
<td>II</td>
</tr>
<tr>
<td>T3 or N1a III</td>
<td>T4a or N1b IVA</td>
<td>T4a or N1b IVA</td>
<td>T4a IVA</td>
</tr>
<tr>
<td>T4a or N1b IVB</td>
<td>T4b IVB</td>
<td>T4b IVB</td>
<td></td>
</tr>
<tr>
<td>T4b IVB</td>
<td>M1 IVC</td>
<td>M1 IVC</td>
<td></td>
</tr>
</tbody>
</table>

Pathology

- Papillary carcinoma (Follicular cells)
  - Has a ‘follicular variant’
  - Good prognosis except diffuse sclerosing, tall cell, columnar cell
  - Takes up RAI
- Follicular carcinoma (Follicular cells)
  - Looks like follicular adenoma but invasive
  - Takes up RAI
- Hurthle Cell (oncocytic carcinoma)
  - Can be benign or malignant
  - Takes up RAI
- Medullary carcinoma (parafollicular/C cells)
  - Excrete calcitonin (↓ serum calcium)
  - 25% associated w/ MEN syndrome (RET, Ch 10)
  - MEN2A: pheochromocytoma, parathyroid, MTC
  - MEN2B: marfanoid, ganglioneuromas, pheochromocytoma, MTC
  - Don’t take up RAI, but can use by bystander affect
  - Anaplastic carcinoma
- ↑age, mets, does not take up RAI

Workup

- H&P, ultrasound, FNA, TSH, T3, T4
- CT (no iodine), +/- CT chest, +/- RAI scan
- For MTC: calcitonin, CEA, catecholamines, RET

Differentiated Thyroid Cancer

- PMH and Hong Kong retrospective reviews show ~90% LC, improved with RAI if stage II+, >45 y/o.
- EBRT ↑LRC, but not OS or CSS

Anaplastic Carcinoma

- SEER (Chen): EBRT improved OS for patients with >1m survival and ETE, by no mets
- De Crevoiser 2004: suggests treating with surgery then chemo then 40 Gy BID then chemo again (cisplatin and doxorubicin)

Radioactive Iodine

- Use in PTC, FTC, HTC, and some MTC
- Avoid iodine contrast 4-6 months prior to treatment
- $^{131}$I: 8d half life, 364keV, beta minus
- Rx is 100-200 mCi with 5 days of scan
- Rescan 7-10 days following to ensure uptake, then 4-6 months later to eval for new sites
- Low iodine diet, stop levothyroxine for 6 wks (can give T3 for the first 3 weeks)
- Recombinant TSH (thyrogen) avoids withdrawal symptoms prior to RAI scan
- Side effects: sialadenitis, xerostomia, cystitis, gastritis, diarrhea, oligospermia
- Maximum lifetime RAI dose is 1,000 mCi

NCCN

- Contains criteria for biopsy (anything >2cm)
- Surgery if feasible
- Neck dissection if <15 y/o, >45 y/o, RT history, T3+, N+
- RAI indications: ETE, >4cm, postop Thyroglobulin >5ng/mL (consider for N+, >1cm, LVSI, anti Tg antibodies, poorly differentiated)
- EBRT: no defined role, consider for:
  - Unresectable disease that doesn’t take RAI
  - Postop locally invasive MTC (50/25)
  - Consider in anaplastic carcinoma
  - Bulky mets after RAI
  - Doses similar to SCC (50→70Gy)
• N1 – single, ≤3cm
• N2
  • N2a – single ipsi, 3-6
  • N2b – multiple ipsi, ≤6cm
  • N2c – contralateral, ≤6cm
• N3 – >6cm

**General**
- 45% tonsil, 40% BOT, 10% pyriform sinus
- 25% of N1 will fail at primary site if neck alone is treated
- “neck violation”: incisional/excisional biopsy of node
- PET scan PPV 90%, NPV 75%
- Waldeyer’s ring: palatine, tubal, pharyngeal, and lingual tonsils

**Workup**
- H&P, skin exam, FNL, FNA, labs, CT neck/chest, +/-MRI, +/-PET (before biopsy)
- Test for EBV, HPV
- Direct laryngoscopy detects 50% of cases. Biopsy:
  • Nasopharynx
  • Tonsils (or tonsillectomies)
  • Base of tongue
  • Pyriform sinuses
  • Triple endoscopy if levels IV-V

**Retrospective Reports**
- McQuone 1998: improved diagnostic yield with tonsillectomy over biopsy
- UF 2001: LC 78%, OS 47%
- Baker 2005: larynx-sparing RT is just as effective, less toxic
- Loyola 1997: unilateral neck RT led to 44% contralateral neck failure and 44% primary emergence rate
- Soushtari 2011 (UVA): all IMRT. 5 yr OS 71%, DFS 85%. All nodal failures had bulky disease.

**Technique**
- Standard head & neck, IMRT
- Target nasopharynx, oropharynx, RPNs, bilateral IB-IV
- Conventional: opposed laterals matched to AP yoke w/ larynx block
  • Match-line based on nodal disease (don’t bisect a positive node)

**NCCN**
- Surgery +/- PORT preferred for N1
  • RT alone for N1 category 2B
- ChemoRT for ≥N2 with surgery if residual disease after treatment
  • 70 Gy to GTV
  • 50-66 Gy to “mucosa”
  • 44-50 (@2Gy) or 54-63 (@1.8Gy) to low risk

**UVA IMRT Technique (Soushtari 2011)**
- N1/N2a without ECE: RT alone then neck dissection
  • 56 Gy to GTV then planned neck dissection
  • 50-56 Gy to pharyngeal axis
  • 504 Gy to bilateral necks
- N2b-N3 or any +ECE: chemoRT then neck dissection
  • Chemo
  • 56-70 Gy to GTV then neck dissection
  • 50-56 Gy to pharyngeal axis
  • 50.4 Gy to bilateral neck
Melanoma

- **T1** - ≤1 mm thick
  - T1a – nonulcerated, mitotic rate <1/mm²
  - T1b – ulcerated or mitotic rate ≥1/mm²
- **T2** – 1.01-2 mm thick
  - T2a - nonulcerated
  - T2b - ulcerated
- **T3** – 2.01-4 mm thick
  - T3a - nonulcerated
  - T3b – ulcerated
- **T4** - >4 mm thick
  - T4a - nonulcerated
  - T4b – ulcerated

- **N0** – 0 nodes
- **N1** – 1 node
  - N1a – micro
  - N1b – macro
- **N2** – 2-3 nodes or in-transit met
  - N2a – micro
  - N2b – macro
- **N3** – ≥4 nodes or matted or in-transit+node

General

- Subtypes: superficial spreading (65%), nodular (25%) lentigo maligna, acral lentiginous
- Clark Levels
  - I: epidermis only
  - II: into papillary dermis
  - III: filling papillary dermis, compressing reticular dermis
  - IV: invading reticular dermis
  - V: into subQ
- S-100+, melan-A+

Workup

- WLE with SLN
- <1 mm: nothing special
- >1 mm, labs, CXR, consider CT for nodes
- LN+: PET-CT, MRI

Adjuvant Therapy

- Interferon alpha (ECOG 1684/1690/1694): IFN-alpha for T4 or N+ pts provided ↑ 10% RFS
- Ang 1994: phase II, 79 pts WLE + 30/5 twice weekly (some patients got LND). 5 yr LRC 88%, OS 47%
- Chang 2006: 56 pts retrospective, 30/5 vs 60/30: no difference, more complications with 30/5
- TROG 96.06: 234 pts, 48/20 (if +margin got 50/21). 5 yr in field failure 6.8%, OS 36%
- Ballo et al: multiple reports from MDACC on 30/5 adjuvant
- TROG 0201: phase III, 250 pts. Observation vs 48/20. Had to have palpable LN disease and high risk. RT ↑LRC (60→80%) but did not affect OS

Definitive RT

- RTOG 8305: Showed 32/4 same as 50/20, CR ~25%
- Overgaard 1995: 24 or 27 Gy in 3 fx over 8 days followed by hyperthermia. Hyperthermia and 27 Gy improved LC (each ~25→50%)

Metastatic disease

- Ipilimumab (CTLA4 antibody) improves OS
- Vemurafenib, Dabrafenib (BRAF inhibitors, V600 mutation)
- IL-2
- Imatinib (C-kit)

Technique

- Primary RT: (Overgaard) 50 Gy in 20 fx with 100-250 kv, 1.5 cm margin and hyperthermia. Consider in lentigo maligna of the face
- Cord max: 24 Gy in 4 fractions

NCCN

- Surgery for everyone
- Stage I/II: observation
- Stage III: obs or IFN-alpha and/or RT (RT is cat 2B)
- Stage IV:
  - Adjuvant RT if
    - LDH < 1.5 ULN AND
    - ECE and/or
    - Any parotid node, 2+ cervical LNs, 2+ axillary LNs, 3+ inguinal LNs
Squamous Cell and Basal Cell Carcinoma of the Skin1-5,141-145

- **T1** - ≤2cm, ≤1 high risk feature
- **T2** - >2cm; or ≥2 high risk features
- **T3** – into maxilla, orbit, temporal bone
- **T4** – skeleton or PNI to skull base

*high risk features:
- DOI>2mm, Clark level≥IV, +PNI
- Ear, hair-bearing lip
- G3 or G4

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

**General**
- Associated conditions: albino, xeroderma pigmentosum, Turcot syndrome, Fanconi Anemia, Gorlin syndrome
- Marjolin’s ulcer: SCC from chronic inflammation

**Workup**
- H&P, exam, biopsy

**Retrospective Reports**
- Rogers & Coldiron 2009: showed that RT was most expensive treatment of available options
- Roussy 1988: survey vs RT (interstitial or orthovoltage). Surgery won. LC 7.5→0.7%.
  - Orthovoltage was best of RT options (5%)
- Balamucki et al: pts with BCC or SCC with PNI benefit from ENI (18% to 0% neck failure)

**Common Fractionation**
- 0-42 Gy/ 5-7 fractions 2-3 times per week
- 45-57 Gy/ 10-19 fractions 2-5 times per week
- 66-72 Gy/ 33-35 fractions for large T4 unresectable cancers or when pathologic nodes are being treated
- 12-20 Gy/ 1 fraction for symptomatic management of large bleeding tumors of very ill/ nursing home type patient

**NCCN**
- Surgery with PORT for high risk features (T3/4, parotid gland, +margin)
- Topical 5FU/imiquimod for low risk superficial BCC
- RT for nonsurgical candidates
- Neck treatment same as other H&N cancer

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
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<tr>
<td>N0</td>
<td>I</td>
<td>H1</td>
<td>H1</td>
<td>IV</td>
</tr>
<tr>
<td>N1</td>
<td>I</td>
<td>H1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Merkel Cell Carcinoma

- **T1** - ≤2cm
- **T2** - 2-5cm
- **T3** - >5cm
- **T4** – into bone, muscle, fascia, cartilage

- **N1** –
  - **N1a** – micro
  - **N1b** – macro
  - **N2** – in-transit mets

- **M1a** – skin, subQ, distant nodes
- **M1b** – lung
- **M1c** – other

**General**
- Arises from Merkel cells (tactile receptors, maybe neural crest derived)
- 80% caused by Merkel cell Polymyxoma virus
- S-100 neg, leukocyte antigen neg, Enolase +,

**Workup**
- Same as melanoma
- Use of SLNBx debated as drainage can be erratic

**Retrospective Reports**
- Mojica 2007: SEER analysis, 1665 pts, surgery +/- PORT. RT improved mean survival for all size tumors
- TROG 96.07: phase II, high risk disease: 50/25 with concurrent carbo/etop. 3 yr OS 76%, increased toxicity

**Technique**
- NCCN doses in table
- 5cm margins on primary

**NCCN**
- Surgery for everyone
- Primary RT for everyone
- Nodal RT if N+ or high risk

**Dose recommendations for radiation therapy:**
- **Primary Site:**
  - Negative resection margins
  - Microscopic (+) resection margins
  - Gross (+) resection margins or unresectable
- **Nodal Bed:**
  - No SLNB or LN dissection
    - Clinically (-) but at risk for subclinical disease
    - Clinically evident lymphadenopathy
  - After SLNB without LN Dissection
    - Negative SLN biopsy: axilla or groin
    - Negative SLN biopsy: head and neck, if at risk for false-negative biopsy
    - Microscopic N+ on SLNB: axilla or groin
    - Microscopic N+ on SLNB: head and neck
  - After LN Dissection
    - Lymph node dissection: axilla or groin
    - Lymph node dissection: head and neck

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
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<th>T3</th>
<th>T4</th>
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<tr>
<td>pN0</td>
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<td>IA</td>
<td>IA</td>
<td>IA</td>
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<td>cN0</td>
<td>IB</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIC</td>
</tr>
<tr>
<td>N1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td>IV</td>
</tr>
</tbody>
</table>
Thorax
Early Stage Non-Small Cell Lung Cancer\textsuperscript{1,5,149-158}

- **T1** – ≤3cm
  - **T1a** – ≤2cm
  - **T1b** – 2-3cm
- **T2** – 3-7cm
  - **T2a** – 3-5cm; or mainstem bronchus (>2cm from carina), visceral pleura, atelectasis
  - **T2b** – 5-7cm
- **T3** – >7cm; or parietal pleura, chest wall, diaphragm, phrenic nerve, pericardium, bronchus <2cm from carina, whole lung atelectasis, tumor in same lobe
- **T4** – mediastinum, heart, great vessels, trachea, recurrent laryngeal, esophagus, vertebrae, carina, tumor in same lung

**N1** – ipsi intrapulmonary, hilar (N10-14)
- **N2** – ipsi mediastinal (N1-9)
- **N3** – contra mediastinal, hilar; BL scalene, supraclav
- **M1a** – tumor in contra lung, pleural nodules, malignant effusion
- **M1b** – disant mets

**Overview**
- Lung ca: 228,200 cases/yr, 160,000 deaths
- Risk factors: smoking, asbestos, radon
- 5 lobes, 5 segments/lobe (except RUL-3 and RML-2)
- 50% adeno, 35% SCC, 15% large cell
- Adeno in situ (BAC): not assc with smoking. Spreads along alveoli, responds to TKIs
- Stains TTF-1+ (except SCC).
- +/- EGFR (90% SCC, 30% adeno) exon 19
  - TKIs work until T790M mutation\textsuperscript{149,159-176}
  - Kras and \(\uparrow\)ERCC1 don’t respond well to platinums
  - Workup: H&P, labs, CT chest, PETCT, MRI for stage II-IV, bx
  - Medically inop: FEV1<40% or (<1.2L for lobe, <2L for pneumonectomy), DLCO <60%, FVC <70%
  - Smoking cessation
- USPSTF screening: current or recent smokers, 55-79 yo, more than 30 pack/ys→ low dose CT annually

**Surgery**
- Cervical mediastinoscopy: evals 1-4R
- Ant Mediastinoscopy (chamberlain): adds 4L-7
- LCSG 821: T1N0→ lobe vs wedge. Wedge \(\uparrow\)LF (6→18%)

**Conventional RT alone**
- Dosoretz 1996: T1-3N0 med inop review. Dose >64 Gy improved PFS
- Sibley 1998: T1-2N0 review. 60-66Gy. 5 yr OS was 15%. 50% LF
- RTOG 9311: dose escalation safe up to 90.3 Gy. 84 Gy recommended LRC ~60%. No ENI given and nodal failure <10%

**SBRT**
- Timmerman 2006: T1-3N0→60-66 Gy in 3 fx. LC 88%, OS 43%, 9% regional failure
- Onishi 2004: 245 pts, BED ≥100Gy improved LF (26→8%) and 3 yr OS (69→88%)
- RTOG 0236: T1-3N0 peripheral→20Gy x 3 fx. 2 yr LC 94%, OS 72%
- RTOG 0618: operable SBRT. 33 pts, 18x3 SBRT. 2 yr LF 19.2%, OS 84.4%

**Postop therapy**
- LACE meta-analysis: 5% improvement at 5 yrs for stage I-II after resection.
  - Most benefit in N1 pts
  - Pre vs postop chemo: no difference (EORTC 08012, CHEST trial, NATCH spanish trial)
  - Italian study: 104 pts, pN0→ PORT vs obs. 50.4 Gy. PORT improved LF (23→2%) and 5 yrs OS (58→67%)

**Technique**
- Supine, arms up +/-contrast, 4D?
- SBRT: ITV +/-5mm radial 8mm sup/inf
- PORT
  - CTV: bronchial stump + nodal stations
  - 50-54 Gy

**NCCN**
- T1-3N0-1
  - mediastinal sampling/dissection and resection
  - R0 and N0: observe
  - pN1: chemo
  - pN2: CRT (50-54 Gy)
  - R1: reresect or sequential CRT
  - R2: concurrent CRT
  - Med inop: SABR (if N1→conventional CRT)

---

**Table 3. Maximum Dose Constraints for SABR**

<table>
<thead>
<tr>
<th>GAV/Regimen</th>
<th>1 Fraction</th>
<th>3 Fractions</th>
<th>4 Fractions</th>
<th>5 Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>14 Gy</td>
<td>18 Gy (6 Gy/Fx)</td>
<td>26 Gy (6.5 Gy/Fx)</td>
<td>36 Gy (6 Gy/Fx)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>15.4 Gy</td>
<td>17.5 Gy (9 Gy/Fx)</td>
<td>27 Gy (9 Gy/Fx)</td>
<td>30 Gy (10 Gy/Fx)</td>
</tr>
<tr>
<td>Bronchial Pleura</td>
<td>22 Gy (9 Gy/Fx)</td>
<td>27 Gy (9 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
</tr>
<tr>
<td>Heart/Pericardium</td>
<td>22 Gy (9 Gy/Fx)</td>
<td>27 Gy (9 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
</tr>
<tr>
<td>Great Vessels</td>
<td>22 Gy (16 Gy/Fx)</td>
<td>27 Gy (16 Gy/Fx)</td>
<td>34 Gy (16 Gy/Fx)</td>
<td>34 Gy (16 Gy/Fx)</td>
</tr>
<tr>
<td>Trachea &amp; Bronchial Lumen</td>
<td>30 Gy (10 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
<td>34 Gy (10 Gy/Fx)</td>
</tr>
<tr>
<td>Rib</td>
<td>30 Gy (16 Gy/Fx)</td>
<td>40 Gy (16 Gy/Fx)</td>
<td>40 Gy (16 Gy/Fx)</td>
<td>40 Gy (16 Gy/Fx)</td>
</tr>
<tr>
<td>Skin</td>
<td>26 Gy (8 Gy/Fx)</td>
<td>36 Gy (9 Gy/Fx)</td>
<td>36 Gy (9 Gy/Fx)</td>
<td>36 Gy (9 Gy/Fx)</td>
</tr>
<tr>
<td>Stomach</td>
<td>12.4 Gy</td>
<td>27.2 Gy (8 Gy/Fx)</td>
<td>27.2 Gy (8 Gy/Fx)</td>
<td>27.2 Gy (8 Gy/Fx)</td>
</tr>
</tbody>
</table>

*Based on constraints used in recent RTOG SABR trials (RTOG 0116, 0615, & 6915).
*For central tumor location. NS = not specified.

**Table 2. Commonly Used Doses for SABR**

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Frx</th>
<th>Example Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34 Gy</td>
<td>1</td>
<td>Periphera, small (&lt;2 cm) tumors, esp. &gt;1 cm from chest wall</td>
</tr>
<tr>
<td>45-60 Gy</td>
<td>3</td>
<td>Peripheral tumors and &lt;1 cm from chest wall</td>
</tr>
<tr>
<td>48-50 Gy</td>
<td>4</td>
<td>Central or peripheral tumors &lt;4-5 cm, especially &lt;1 cm from chest wall</td>
</tr>
</tbody>
</table>

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34
Induction Chemo
- MDACC (1998): surgery +/- neoadj cis/etop/cyclophos. Chemo ↑MS (14→21m)
- Madrid (1999): same as MDACC but cis/ifos/mitoC. MS 10→22m.
- Spanish Trial 9901: phase II. N2 or T4→cis/gem/docetaxel x3c→surgery. pCR 13%. MS 16m
- EORTC 08941: IIIA→chemo→surgery vs RT. PORT permitted. Same OS. Pts did worse after pneumonectomy
- See Dillman regemin

Neoadj CRT
- German LCCGT: stage IIIA-B→induction cis/etop x3c→surgery. Randomized to preop CRT or postop RT. pCR improved with preop CRT (20→60%), but same OS. Worse OS if pneumonectomy.
- INT-0139: IIIA→CRT (45Gy) + surgery vs CRT alone (61Gy). Both got post cis/etop. Surgery improved LF (22→10%), but same OS. OS worse if pneumonectomy.
- SWOG 9416: superior sulcus phase II of induction CRT to 45 Gy with cis/etop. Then surgery and postop chemo. 94% R0 resection, 56% pCR, 5 yr OS 44%.

Adjuvant PORT
- LCSG 774: T3 or N2→obs vs PORT (50Gy). PORT improved LR (41→3%) but same OS.
- PORT metaanalysis trial: 10 trials. PORT→↓OS, mostly in stage I-II
- No benefit to CRT over PORT alone (INT 0115, RTOG 9105)
- PCI: RTOG 0214: PCI reduced brain failure, but same OS

Definitive CRT
↑Dose
- RTOG 7301: dose escalation. 40→60Gy. 60Gy won
- RTOG 8311: dose escalation BID. 1.2/fx→69.6Gy won
- RTOG 9311: dose escalation with chemo. 70→90Gy. 83.8 Gy won
- RTOG 0617: 60 vs 74 Gy and +/- Cetuximab. Closed early. 74Gy more toxic, worse OS. +/- cetux had same OS
- CHART: 54 Gy at 1.5Gy TID (x12 conec days) vs 60/30. TID improved 3 yr OS by 10% but ↑tox. Mostly SCC +/-Chemo
- CALGB 8433 (Dillman): IIIA→60/30 vs cis/vinblast+60/30 (sequential). CRT improved ↑MS (10→14m). 5 yr OS (7→19%)
- RTOG 8808: II-IIIB→60/30 vs 69.6BID vs cis/vinblast+60/30(dillman). CRT improved MS (11.4→12→13.2m)
- RTOG 9410: 3 arms→Dillman to 63Gy vs concurrent CRT to 63Gy vs 69.6Gy CRT BID. Chemo was cis/vinblast, but BID arm got cis/etop. Conventional CRT improved MS (14.6→17→15.6m). more tox with chemo
- cis/etop and cis/vinblast can be given full dose with RT
- Carbo/taxol, gem, vinorelbine require dose reduction

Induction chemo
- LAMP trial: 3 arms: Dillman (chemo→RT) vs (chemo→CRT) vs (CRT→chemo). Chemo was carbo/taxol. CRT→chemo improved MS (13→16.3→12.7m)
- CALGB 39801: CRT +/- induction chemo (carbo/taxol). Same OS

Technique
- PTV = GTV + 1-1.5cm

NCCN
- Superior Sulcus Tumor (T3-4N0-1): preop CRT (45-50 Gy)
- T4NX: definitive CRT
- N2-3M0: definitive CRT (cat 1) or neoadj chemo +/- RT (45Gy)
- Contralateral nodules: treat as 2 primary tumors if curable
- Dose: 60-70 Gy (2/fx)

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Total Dose</th>
<th>Fraction Size</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive RT with or without chemotherapy</td>
<td>60–70 Gy</td>
<td>2 Gy</td>
<td>6–7 weeks</td>
</tr>
<tr>
<td>Preoperative CRT</td>
<td>45–50 Gy</td>
<td>1.8–2 Gy</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Postoperative CRT</td>
<td>50–54 Gy</td>
<td>1.8–2 Gy</td>
<td>6–6 weeks</td>
</tr>
<tr>
<td></td>
<td>54–60 Gy</td>
<td>1.8–2 Gy</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>60–70 Gy</td>
<td>2 Gy</td>
<td>6–7 weeks</td>
</tr>
<tr>
<td>Palliative CRT</td>
<td>30–45 Gy</td>
<td>3 Gy</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td></td>
<td>20–30 Gy</td>
<td>4–3 Gy</td>
<td>1–2 weeks</td>
</tr>
<tr>
<td></td>
<td>8–30 Gy</td>
<td>8–3 Gy</td>
<td>1 day–2 weeks</td>
</tr>
<tr>
<td></td>
<td>CNS GLa*</td>
<td>CNS GLa*</td>
<td>CNS GLa*</td>
</tr>
<tr>
<td></td>
<td>17 Gy</td>
<td>8.5 Gy</td>
<td>1–2 weeks</td>
</tr>
<tr>
<td></td>
<td>8–20 Gy</td>
<td>8–4 Gy</td>
<td>1 day–1 week</td>
</tr>
</tbody>
</table>

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Constraints in 30–35 Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAR</td>
<td>Constraints in 30–35 Fractions</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Max ≤50 Gy</td>
</tr>
<tr>
<td>Lung</td>
<td>V20 ≤35%; V5 ≤65%; MLD ≤20 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Mean ≤34 Gy; Max ≤105% of prescription dose</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>Max ≤66 Gy</td>
</tr>
</tbody>
</table>

Vxx = % of the whole OAR receiving xx Gy.
Small Cell Lung Cancer\textsuperscript{1-5,178-186}

Overview
- 15\% of lung cancer
- 1/3 pts present with limited stage dz
- Paraneoplastic syndromes: SIADH, ACTH production, Lambert-Eaton syndrome
- Markers: S100, synaptophysin, chromogranin, neurotensin, EGFR-
- Del3p, amplification of bcl2 and c-myc family
- Workup: H&P, labs, biopsy, PET-CT, MRI brain, BM bx if ↑LDH

Limited stage: \textasciitilde24 month OS
- Pignon 1992: metaanalysis (2140 pts) of chemo +/- thoracic RT. RT improved 3 yr OS (8.9→14.3\%)
- Fried 2004: metaanalysis of early vs delayed RT. Early improved 2yr OS by 5.2\%
- Takada 2002: concurrent vs sequential CRT. Concurrent improved 5 yr OS (20→30\%).
- INT 0096 (Turrisi): 417 pts→cis/etop with RT (45/25 vs 45 Gy at 1.5/fx BID). BID ↓LF (52→36\%) and ↑5yr OS (15→26\%).
- RTOG 0239: phase II→ RT to 61.2 Gy, partially BID. Improved OS compared to Turrisi
- CALGB 8837: phase I trial, dose escalated to over 70 Gy with good results
- RTOG 0538: pending. Turrisi vs RTOG 0329 vs 70/35 (CALGB 8837). This trial includes ENI

PCI
- Auperin 1999: metaanalysis of PCI. PCI reduced 3 yr brain mets (59→33\%) and increased 3 yr OS (15.3→20.7\%). Better if given early
- Le Pechoux 2003: randomized LS cCR patients to 25/10 vs 36/18 PCI. Same brain met rate, worse OS in high dose
- Slotman 2007: ES with response to chemo→ +/- PCI. PCI improved 1 yr OS (13→27\%). No routine MRIs done.

Extensive stage: \textasciitilde9 month OS
- Jeremic 1999: PR or CR after chemo→ chest RT vs more chemo. RT improved 5 yr OS (3.7→9.1\%)
- Slotman 2014:ES with PR or CR→ +/- thoracic RT (30/10). RT improved 2 yr OS (+/− thoracic RT (30/10). RT improved 2 yr OS (3→13\%).

Technique
- High dose = GTV+1cm
- Lung V20\<30\%
- Esophagus V60\<50\%
- Heart V40\<50\%

NCCN
- T1-2N0: mediastinal sampling. If neg→lobectomy and node dissection
  - Postop chemo, postop CRT for N+
- Above T1-2N0: chemoRT, usually cis/etop
  - 45 Gy BID or 60-70Gy
  - +/- ENI
  - then PCI for PR or CR
- M1: chemo +/-RT

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
OAR & Constraints in 30-35 Fractions \\
\hline
Spinal cord & Max ≤50 Gy \\
\hline
Lung & V20 ≤35\%; V5 ≤65\%; MLD ≤20 Gy \\
\hline
Heart & V40 ≤80\%; V45 ≤60\%; V60 ≤30\%; Mean ≤35 Gy \\
\hline
Esophagus & Mean ≤34 Gy; Max ≤105% of prescription dose \\
\hline
Brachial plexus & Max ≤66 Gy \\
\hline
\end{tabular}
\caption{Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT}
\end{table}

\textit{Vxx = % of the whole OAR receiving \textasciitilde xx Gy.}
Thymoma and Thymic Carcinoma1-5,187-191

Masaoka Staging
- **T1** - encapsulated
- **T2** - through capsule
  - T2a – microscopic invasion
  - T2b – adhesion to fat/pleura
- **T3** – into organs
  - T3a – into adj organs
  - T3b – into great vessels
- **T4** – pleural/pericardial invasion

**Overview**
- Anterior mediastinal mass
- Assoc with MG, red cell aplasia, hypogammaglobulinemia
- 50% of thymomas have MG, 15% of MGs have thymoma
- WHO grading (A, AB, B1-3, C)
- Thymic carcinoid/carcinoma (30% N+)
- Workup: same as NSCLC, rule out germ cell tumor

**PORT**
- Forquer 2009: SEER database. PORT improved 5 yr OS for stage II-III (5 yr OS 66→76%), but not stage I.
- Curren 1988: 103 pts. No recurrence for stage I without RT. Stage II-III patients had ↓LF with PORT (53→0%). 21% if subtotal resection and PORT.
- Mangi 2002 and Haniuda 1996 challenged PORT for stage II thymoma

adj Chemo
- Mornex 1995: +/- cisplatin, not prognositic
- Wright 2008: phase II. cis/etop x2c neoadj had good results.

**Pleural Mesothelioma**1-5,192-194

- **T1** -
  - T1a – ipsi parietal pleura, no visceral
  - T1b – ipsi parietal pleura, +visceral
- **T2** – into diaphragm or pulmonary parenchyma
- **T3** –endothoracic fascia, mediastinal fat, chestwall, outer pericardium
- **T4** - multifocal, into peritoneum, contralateral pleura, mediastinal organ, spine, internal pericardium

**Overview**
- 2500 cases/yr
- 80% involve asbestos
- Stains for calretinin, vimentin WT1, cytokeratin
- Workup: same as NSCLC

**Surgery**
- Extrapleural pneumonectomy (EPP) removes parietal/visceral pleura, lung, mediastinal nodes, pericardium, ipsi diaphragm (~20% mortality)
- Pleurectomy/decortication: more like debulking

**Adj RT**
- Rusch 2001: phase II→ EPP and hemithoracic 54 Gy. MS 34m for Stage I-II, 10m for stage III-IV
- Flores 2006: induction gem/cis→EPP→54Gy. MS 33m

**Chemotherapy**
- Vogelzang 2003: metastatic→cis +/-pemetrexed. Pem improved MS 9→12m

**Technique**
- Hemithoracic RT 4-8 wks postop to 54 Gy
- Contralateral lung V20<7%, V5<50%, mean <8.5Gy
- Heart V40Gy<50%

**Hanson and Roach guidelines**
- Stage I-II: extrapleural pneumonectomy (EPP)
  - With PORT (54 Gy)
  - Inoperable: neoadj chemo to shrink
- Stage III-IV: same
Breast
Ductal and Lobular Carcinoma In-situ

General
- DCIS
  - 15-20% of all breast cancer
  - 1/3 progress to IDC at 10yrs
  - ~10% risk of IBTR for lump only
  - E-cadherin +
- LCIS
  - 25% risk of invasive cancer in either breast
  - Mammographically occult
  - E-cadherin – (indian file)
- Molecular subtypes (invasive disease)
  - Luminal A: +/+/--
  - Luminal B: +/+/+
  - Basal: --/--/--
  - Her2u: --/--/+/

Workup
- H&P (GYN/cardiac history), breast exam, LN exam
- Bilateral diagnostic mammo, u/s, biopsy (hormone/Her2 staining), labs, CXR
- Breast MRI controversial (consider for young or BRCA+)
- T4, N2+ or symptoms: Bone scan & CT chest/abd/pelv, +/- PET, +/- MRI

Lumpectomy +/- RT
- NSABP B-17: lump +/- 50 Gy. At 12 yrs RT reduced LF 32→16%, same DM and OS
- EORTC 10853: lump +/- 50 Gy. At 10 yr RT reduced LRF 26→15%, same DM and OS
- Swedish: lump +/- 50 Gy. At 5 yr RT reduced LF 22→7%, same DM and OS
- UKCCR: lump then (50Gy, tamox, neither, both). All breast events 8, 18, 22, 6% respectively
- Metaanalysis of above: BCS +/-RT: HR 0.49, all subgroups benefit from RT without significant long-term toxicity

Tamoxifen
- NSABP B-24: lump +50Gy +/- Tamox(5yrs). At 10 yr tamox improved IBRT (15→11%) and contralateral cancer (5.4→4.5%). Same DM and OS. If ER+, 50% risk reduction
- UKCCCR trial above

Technique
- Absolute contraindications to BCT (NCCN): pregnant, diffuse microcalc, poor cosmesis expected, +margin
- Relative contraindications to BCT (NCCN): prior RT, connective tissue disease (scleroderma/lupus), tumors >5cm, focally +margin, BRCA+
- Supine, arms up, head turned slightly, vac lok
- Wire scar/drain and 2cm beyond breast tissue (medial midline)
- Iso at midpoint between med & lat wires
- Half-beam block at deep edge
- High tangents: top border 2cm below humerus
- Dose constraints for APBI
  - Contralateral Dmax ≤3 Gy
  - Ipsilateral Lung V20<15%, V5<50%
  - Contra lung V5%<15%
  - Heart V20<5%, mean < 4 Gy
- NCCN dose guidelines
  - WBRT: 45-50 at 1.8-2/fx or 42.5 at 2.66/fx
  - WBRT boost recommended if <50 yo and G3 (10-16 Gy at 2Gy/fx)
  - 3field: 50-50.4 at 1.8-2/fx ( +/- 10Gy boost)
  - APBI (experimental): 34/10 with brachy or 38.5/10 BID with photons

NCCN
- LCIS: surgical resection, then cancer risk reduction, no RT indicated
- DCIS
  - Lumpectomy (no ALND) + WBRT (cat 1)
    - Consider boost for margins <1mm
  - TM +/- SLNBx +/- reconstruction (altered lymph flow after TM)
  - Lumpectomy (no ALND) without WBRT (cat 2B)
  - (Tamoxifen x5 yrs if ER+)
- Exam and mammo annually x5 years
Early Stage Breast Cancer

- **T1** - ≤ 2cm
  - **T1mi** - ≤ 0.1cm
  - **T1a** - > 0.1 and ≤ 0.5cm
  - **T1b** - > 0.5 and ≤ 1cm
  - **T1c** - > 1.0 and ≤ 2cm
- **T2** - > 2.0 and ≤ 5cm
- **T3** - > 5cm
- **T4** -
  - **T4a** – chest wall (not pec)
  - **T4b** – skin edema, ulceration
  - **T4c** – T4a + T4b
- **T4d** - inflammatory

**General**
- Extensive intraductal component: ≥25% DCIS
- Tubular & Mucinous histologies are favorable

**Surgery**
- Lumpectomy > WLE > quadrantectomy (quad) > total (simple) mastectomy (TM) > MRM > Radical Mastectomy (RM)
- NSABP B-04: If cN0: RM vs TM+RT vs MRM if pN+. If cN+: RM vs TM+RT. At 25 yr f/u, no difference in DFS or OS. Nodal treatment (by RT or LND) reduced LRF from 19% to 4%
- SLNBx
  - NSABP B-32: ALND vs SLNBx (ALND if pos). SLNBx accuracy 97%, 9.8% false neg, NPV 96%
  - Kim 2006: metaanalysis of SLNBx. False neg rate 7.3%
- Unaffected by neoadjuv chemo? (Buchholz 2008)

**Mastectomy vs BCS**
- NSABP B-06: stage I/II, <4cm, neg margins: TM vs lump vs lump+50Gy. At 20 yrs, same DFS, OS, and DMFS. RT decreased LF from 39→14%.
- EORTC 10801: stage I/II: MRM vs lump+50Gy+boost. At 10 yrs MRM reduced LF (20→12%) but same OS (65%). 48% in lumpectomy group had pos margins
- Milan I: T1N0, RM vs quad+60Gy, at 20 yrs RM reduced LF 8.8→2.3%, same OS

**Lumpectomy +/- RT**
- NSABP B-06 above
- Milan III: <70 yo, ≤2.5cm. quad+ALND +/- 60Gy. At 10 yrs RT reduced LF (23.5→8%), same OS. All patients received systemic therapy
- Swedish Trial: ≤3cm. lump +/- 50Gy. At 5 yrs LR 14→4%, same OS
- PMH: stage I/II. Tamox +/- RT. At 8 yrs RT reduced LR (12.2→4.1%), same OS
- CALGB 9343 (Hughes): >70 yo, pT1N0, ER+. Tamox +/- RT. RT improved 8yr LF (7→1%), but OS same
- NSABP B-21: pN0, ≤1cm. three arms (tamox vs RT vs both). At 8 yr LF 16.5%, 9.3% and 2.8% respectively, same OS

**Timing**
- JCRT Sequencing: stage I/II. chemoRT vs RTchemo. At 11 yrs, same OS, DM etc. For close margins (<1mm) LR improved with RT first (32→4%), for +margins, no difference

**Boost**
- EORTC Boost Trial: stage I/II s/p lump +50Gy +/- 16 Gy boost. At 10 yrs boost improved LF 10.2→6.2%. All patients benefited, but more for <40 yo. Boost had more severe fibrosis (1.6→4.4%)
- Lyon Boost Trial: <3cm. lump+ALND+50Gy +/- 10Gy boost. At 3 yrs boost improved LF 4.5→3.6%. cosmesis unchanged

**Hypofractionation**
- Whelan (Canadian): 50/25 vs 42.5/16. No boost, no >25cm separation.10 yr LR unchanged (~6.4%), cosmesis good
- START A: 50/25 vs 41.6/15. Same findings as START A. Less adverse effects with hypofrac.
- RMH/GO3: similar doses to START A. showed that 42.9/13 had lowest IBTR

**NCCN**
- ≤T3, ≤N1
  - Lumpectomy with aSLNBx
    - chemo 1st if (>1cm, pN+)
    - (pN0) WBRT +/- boost
    - (pN+) 3field +/- boost
    - (pT1N0, ER+, >70yo): HT +/- RT
    - HT/Herceptin based on, N, ER, HER2
  - TAM + SLNBx (RT if N+)
  - Neoadj chemo (aiming for BCT)
    - Core bx with clips placed, LN eval
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Locally Advanced Breast Cancer

General
- Inflammatory: rapid erythema, warmth, edema
- Risk of IMN+
  - 5% of tumors have IMN as sentinel node
  - 10% if Ax node neg
  - 20-50% if Ax node pos

Workup
- Staging above
- See above, include bone scan, CT chest/abd/pelv, +/-PET-CT, MRI brain

Chemotherapy
- Agents
  - CMF: cyclophosphamide, methotrexate, 5FU
  - FAC: 5FU, Adriamycin, cyclophosphamide
  - AC: Adriamycin, cyclophosphamide
  - ACT: AC then paclitaxel
  - TAC: docetaxel (taxotere), Adriamycin, cyclophosphamide
  - FEC: 5FU, epirubicin, cyclophosphamide
  - TC: docetaxel (taxotere), cyclophosphamide
  - Trastuzumab: monoclonal antibody for HER2/neu
  - Tamoxifen: SERM, hot flashes, ↑thromboembolic dz, ↑uterine cancer
  - Anastrozole, letrozole: Aromatase inhibitors, postmenopausal pts only
- EBCTCG chemo-HT: metaanalysis, 6m anthracycline-based chemo reduced breast ca death by 38% if <50 yo and 20% if 50-69 yo. Tamoxifen x5 yrs reduced breast ca death by 31%
- NSABP B-20: surgery and pN0, ER+. Randomized to Tamox vs Tamox +MF chemo vs Tamox + CMF. Chemo improved 12 yr DFS, but not OS (p=0.068)
- NSABP B-28: LN+ pts randomized to AC vs ACT. Taxane improved 5 yr DFS 72→76%
- CALGB 9741: showed that dose dense ACT improved 4 yr DFS 75→82%
- NSABP B-18: preop vs postop AC x4c. at 9 yrs, no difference in DFS or OS. More BCT in preop group (~25% converted), but more LR in those patients (10.7 vs 7.6%). More LR if mastectomy converted to BCT (9.6 vs 15.7%)  
- NSABP B-31: HER2+ pts: ACT vs ACT+H. Herceptin improved 3 yr DFS (75→87%) and OS (92→94%)
- NSABP B-14: ER+ pts: Tamox x5 yrs vs placebo. Tamox improved 15 yr DFS and OS
- ATAC Trial: ER+/+ postmen pts: anastrozole, tamox, or both. AI improved DFS over tamox (89 vs 87%), both was 87%, but only for ER+ pts

Post-Mastectomy RT
- Danish 82b: premenopausal. MRM+CMF +/- RT. At 10 yrs PMRT improved LRF (32→9%), DFS (34→48%), and OS (45→54%). Improvements regardless of tumor size or #LNs. (mean 7 LNs excised). +IMN RT
- Danish 82c: postmenopausal. MRM+tamox +/- RT. At 10 yrs PMRT improved LRF (35→8%), DFS (24→36%), and OS (36→45%). No benefit for N0 patients. +IMN RT
- British Columbia trail: premenopausal. MRM+CMF +/-RT. At 20 yrs PMRT improved LRF (26→10%) and OS (37→47%). (mean 11 LNs excised). +IMN RT
- EBCTCG metaanalysis: PMRT improves LR (~18% at 5 yrs) and breast cancer mortality (5.4% at 15 yrs). 4:1 ratio. RT ↑ contralateral breast cancer, lung cancer, and heart disease

Axillary dissection
- ACOSOG Z0011:T1-2, cN0, SLNBx+ (1 or 2 SLN by H&E). lumpectomy with neg margins +/- ALND. All got PORT (tangents). 97% got systemic therapy (HT or chemo). 5 yr regional control same (99%), OS same (92%). Radiation field design varied widely (some included nodal RT).

Technique
- Iso at midaxillary line, 4cm deep
- Half beam block deep and superior borders
- If long breasted, kick couch away on tangents
- 15° oblique off cord on supraclav field
- Bolus?

NCCN
- T4+, N2+
  - Neoadj chemo → MRM → 3f RT
  - Consider for Herceptin/HT
- Inflammatory breast cancer
  - same
Gastrointestinal
Esophageal Cancer\textsuperscript{1-5,231-241}

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa
- **T2** – muscularis propria
- **T3** - adventitia
- **T4** – adj structures
  - T4a – pleura, pericardium, diaphragm
  - T4b – aorta, vertebrae, trachea

- **N1** – 1-2 nodes
- **N2** – 3-6 nodes
- **N3** – 7+ nodes

Overview

- 16,500 cases/yr, 14,200 deaths/yr
- Risk factors: tobacco, ETOH, nitrosamines, Plummer Vinson syndrome, achalasia, GERD

Anatomy

- Cervical: cricoid to thoracic inlet (15-18cm)
- Upper thoracic: to carina (18-24cm)
- Mid thoracic: to GE junction (24-32cm)
- Low thoracic: GE junction (32-40cm)
- Workup: H&P, supraclav, labs, EGD, EUS, bronch, PFTs, PET-CT

Surgical Techniques

- Endoscopic mucosal resection
  - No ulceration, T1N0, no LVSI, <2cm, G1-2
  - 98% OS (Ell 2007)
- Transhiatal esophagectomy: no thoracotomy, pull up. Difficult LN dissection but better tolerated
- Ivor-Lewis (right thoracotomy): good exposure, risk mediastinitis
- Left thoracotomy: good for lower 3rd resections
- Optimum # nodes = 23 (Peyre 2008)
- Surgery alone ~20% three year OS

Preop Chemo

- RTOG 8911: T1-2Nx → surgery +/- preop cis5FU. Same OS, 2.5% pCR
- MAGIC trial: T1-3N0-1 gastric/GE/loweresophagus → surgery +/- periop epirubicin, cisplatin, 5FU. Chemo improved 5 yr OS (23→36%)

Preop CRT

- Gebski 2007: metanalysis with 1209 pts. Preop CRT improves OS compared to surgery alone

- EORTC (Bossset): T1-3N0 or T1-2N1, SCC only → surgery +/- preopCRT (cis x2c with 37/10 split course). pCR 26%, same OS (18m)
- CALGB 9781 (Tepper): T1-3N1→surgery +/- preop CRT (cis5FU with 50.4Gy). CRT ↓5yr OS (16→39%). 40% pCR
- Burmeister 2006: T1-2N0-1→surgery +/- preop CRT (cis5FU with 35/15). Same DFS and OS (35%). 13% pCR
- Stahl 2009: T3-4NX adeno → neoadj chemo +/- RT (30/15). All got surgery. Closed early but CRT had better pCR (2→15.6%), and trended better OS (28→47%)
- CROSS: 368 pts (75% adeno)→surgery +/- preop CRT. 41.4 Gy in 23 fx with carbo/taxol. CRT ↓OS (24m→49.4m).
  - ↑R0 resection with CRT (69→92%)
  - pCRT 23% adeno and 49% SCC

Definitive CRT

- RTOG 8501: T1-3N0-1→RT (64 Gy) vs CRT (cis5FU with 50 Gy). CRT improved 5 yr OS (0→27%)
- INT0123 (RTOG 9405): T1-4N0-1→CRT to 50 Gy vs 65 Gy. Stopped early because of ↑death (2→10%)
- Stahl 2008: T3-4N0-1 SCC→ chemo x 3c → RT alone (64/32) vs RT+surgery (40/20). Surgery improved LC but CRT had less treatment related mortality (13→4%)

Technique

- Generally Sim supine, arms up, PO contrast
  - Cervical eso: supraclav, neck nodes
  - Upper thoracic: include SCV and mediastinal nodes
  - Mid thoracic: paraesophageal nodes
  - Low thoracic: consider gastric nodes, celiac axis
- CTV: tumor +3-4cm up/down and 1cm radially
- Boost same but 2cm up/down
- Dose limitations
  - cord, liver, kidneys,
  - Lung V5<50%, V10<40%, V20<20%
  - Heart V40<30%

NCCN

- Tis-T1a: EMR vs esophagectomy
- T1bN0: esophagectomy (postop CRT if R1, R2, or N+)
- T2-T4a or N+
  - Preop CRT (41.4-50.4)
  - Defin CRT if cervical or decline surg (50-50.4)
    - then PET/EGD. Can observe if cCR and SCC
  - Esophagectomy (if low risk tumor)
- T4b: defin CRT (50-50.4)
Gastric Cancer\textsuperscript{1-5,234,242-250}

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa

- **T2** – muscularis propria

- **T3** – subserosa

- **T4**
  - T4a – serosa
  - T4b – adj structures

- **N1** – 1-2 nodes
- **N2** – 3-6 nodes
- **N3** – 7+ nodes
  - N3a – 7-15 nodes
  - N3b – 16+ nodes

**Overview**
- 22,700 cases/yr, 12,000 deaths/yr
- Risk factors: salt, nitrates, H pylori, pernicious anemia
- 22.1% HER2 positive

**Anatomy**
- GEJ, fundus: 35%, diffuse
- Body: 25%
- Antrum: 40%, intestinal
- LN groups: perigastric, gastroduodenal, Pas, celiac, portahepatic, suprapancreatic, splenic, +/- paraesophageal
- Workup: H&P, nodal eval, labs, CEA, Hpylori
- EGD, EUS, bx, PET
- PEG tube?

**Surgery**
- Aim for >3cm margins, ≥15 LNs
- D0: no nodes
- D1: perigastric nodes
- D2: D1+ left gastric, hepatic, celiac and splenic nodes
- D3: D2 + hepatoduodenal, peripancreatic, portocaval, PA nodes, middle colic
- Gouzi 1989: subtotal vs total gastrectomy: no difference
- Dutch trial: D1 vs D2. D2 had more complications/deaths. Same 11 yr OS, but the 15 yr data showed D2 ↑CSS (37→48%)
- MRC trial: D1 vs D2. Same 5 yr OS, more tox with D2
- JCOG trial: D2 vs D2+Pas. Same as Dutch
- Taiwanese trial: D1 vs D3. D3 improved 5 yr OS (54→60%). No adj chemo or RT

**Preop Chemo and RT**
- MAGIC Trial: mostly stomach, but some GEJ/eso→surgery +/- pre/postop chemo (ECF). pCR rate 0%. Chemo improved downstaging, R0, OS (23→36%)
- RTOG 9904: phase II: preop CRT (45 Gy with 5FU+taxol). pCR 26%,

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**Postop CRT**
- Macdonald 2009 (INT 0116): 556 pts, surgery +/- CRT. 54% D0 resection. Chemo was 5FU, leucovorin. RT was 45/25. CRT improved DFS and OS (HR 1.32).
- Kim 2005: retrospective. 990 pts with D2 +/-CRT. 5 yr OS improved with CRT (51→57%)
- CALGB 80101: surgery→(5FU + 45 Gy) vs (ECF +45 Gy). Given as chemo→CRT→chemo sandwhich. 3 yr data show similar outcomes.

**Metastatic**
- ToGA trial: metastatic gastric, cis/5FU +/- trastuzumab. Improved median OS (11→13.5m)

**Technique**
- Fast for 3 hrs before sim
- Supine, arms up, IV contrast, oral contrast, 4D?
- CTVp: residual dz + remaining stomach + anastomosis, 3-5cm margin
- CTVn
  - Always: perigastrics
  - T4 or N+: celiac, suprapancreatic, portahepatic, splenic
  - Consider paraesophageal splenic for high tumors
- Heart V40<30%
- Liver V30<60% mean <25Gy
- At least 2/3 one kidney <20 Gy

**NCCN**
- Tis-1aN0: endoscopic resection or gastrectomy alone
- T1b: surgery alone
- T2+ or N+
  - preop chemo +/-RT
  - surgery then CRT (sandwhich C→CRT→C)
    - could obs pt2N0 with R0 resection
    - could chemo only after D2
    - Dose is 45-50.4 Gy (1.8/fx)
- Unresectable: 5FU based CRT
Pancreatic Cancer

T1 - ≤2cm
T2 - >2cm
T3 - beyond pancreas
T4 - involves SMA or celiac

N1 - nodes
N0 - IA IB IIA IIB
M1 - I IV

Overview
- 45,000 cases/yr, 35,000 deaths/yr in US
- Risk factors: tobacco, dietary fat, RT, chemo
- 1st echelon LNs: pancreaticoduodenal, suprapancreatic, pyloric, pancreaticosplenic
- 50% are M1 at diagnosis
- Workup: H&P, jaundice, DRE, LFTs, CA19-9
- EGD, EUS, ERCP, bx, stent?, CT C/A/P, +/-MRI

Surgery
- For head lesions: pancreaticoduodenectomy (classic or pylorus-sparing): ~4% mortality (Pancreateicjejunostomy, Choledochojejunostomy, Gastrojejunoscopy)
- No benefit to extended LND (Riall 2005)

Pro-Postop RT
- GITSG 9173: 43 pts. Surgery → CRT (5FU + 40 Gy split). CRT improved OS (5→14%).
- Mayo Clinic (2008): retrospective, 472 pts. T1-3N0-1 with R0 resection. Patients who got 5FU+50.4 Gy did better than observation (MS 19→25m)
- Johns Hopkins (2008): same as mayo clinic
- Hazard 2007: SEER analysis. RT→↑OS (12→17m MS). No benefit for T1-2N0
- RTOG 9704: 451 pts→GTR→CRT sandwich. Gem/5FU/Gem vs 5FU/5FU/5FU. RT was 50.4 Gy. Gem was Qwk. Gem arm trended toward 3 yr ↑OS (22→31%). ~75% of pts failed distantly first
- EORTC 40891: surgery +/- CRT (5FU + 40Gy split). Same 10 yr OS (18%). Included periampullary. For pancreatic tumors OS was improved (10→20%)

Anti-Postop RT
- ESPAC-1: surgery→2x2 (+/-5FU, +/-40Gy split). Chemo ↑OS (14→19m), but CRT worsened 5 yr OS (20→10%). Included periampullary cancers
- Stocken 2005: metaanalysis, 875 pts, chemo improved MS (14→19m), but not CRT (~15m). RT improved outcomes for positive margins

Chemo trials
- CONKO-001: 368pts→R0 or R1 +/- gemcitabine x6c. Gem → ↑DFS (6.9→13.4m) but not OS (~21m). No RT
- ESPAC-3: 5FU vs gem. No RT. Same MS (~23m)
- Krishnan 2007: retrospective. Induction chemo → CRT had longer MS then upfront CRT (8→12m)
- Conroy 2011: FOLFIRINOX > gem
- VonHoff 2013: gem+abraxane > gem

Unresectable
- GITSG: 40Gy+5FU vs 60Gy+5FU vs 60Gy. First two were split course but CRT improved MS (22→42m)
- RTOG 9812: phase II: 50.4Gy + paclitaxel. MS was 11m
- Tempero 2003: big bolus vs small bolus gemcitabine. Slow infusion ↑OS (5→8m)
- French FFCD: phase III. gem +/ RT with 5FU. CRT had worse survival (13→8.6m)
- ECOG 4201: close early. 71 pts→ gem +/- RT. CRT improved 2yr OS (4→12%), but more toxicity
- LAP-07: gem +/- erlotinib. If response then chemo vs CRT (54Gy with xeloda). CRT provided no OS benefit (OS ~15m)

Technique
- Sim supine, arms up, +IV and PO contrast
- Intact
  - GTV + 2-3cm
  - GCV: pancreaticoduodenal, suprapancreatic, celiac, porta hepatitis, duodenal loop (splenic for tail tumors)
- Postop
  - Peripancreatic nodes, anastomoses, tumor bed
  - Postop nodal beds +1cm
- Tolerances
  - Kidney V18 <50%
  - Bowel/stomach max 55 Gy, V50<10%
  - Liver mean <30 Gy

NCCN
- Resectable
  - Resection→ gem or 5FU or sandwich with RT
  - 45-46 Gy (1.8-2/fx) + 5-9 Gy boost
- Borderline
  - Neoadj chemo(FOLFIRINOX or gem/abraxane) +/-RT
  - Resection (cat 2b) follow above
- Unresectable
  - FOLFIRINOX or gem+/abraxane or 5FU
    - RT after “adequate course of chemo”
    - 45-54 Gy (1.8-2.5/fx) or 36 Gy (2.4/fx)
Hepatocellular Carcinoma

- **T1** – single tumor, no vascular invasion
- **T2** – single + vascular invasion or multiple tumors
- **T3**
  - T3a – >5cm
  - T3b – into portal/hepatic vein
- **T4** – adj organs or visceral peritoneum
- **N1** – nodes

**Overview**
- 22,000 cases/yr, 17,000 deaths/yr
- Assoc with cirrhosis, hepB, hepC, aflatoxin B
- Cirrhosis or HepB+ → annual screening u/s and AFP
- Workup: labs, LFTs, AFP, hep panels, ultrasound
- Triphasic liver CT or MRI, chest CT
- No need to biopsy if >1cm and classic on 2 modalities

**Surgery**
- Partial hepatectomy: 5 yr OS ~40%
- Transplant: 5 yr OS ~70%
- Lau 2008: surgery + 131I-lipiodol→↑OS

**IR procedures**
- RFA: better for deep tumors <3cm
- Cryoablation: can treat up to 6cm (not in US)
- ETOH injection (not in US)
- TACE: 50% response but no ↑OS

**Sorafenib**
- TKI against c-rad and PDGF-α
- Llovet 2008: advanced HCC→ sorafenib vs placebo. Sorafenib ↑OS (7.9→10.7m)

<table>
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<th></th>
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<tr>
<td>M1</td>
<td>IVB</td>
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**SBRT**
- Traditionally was 50+ Gy (2 Gy/fx) 3D or IMRT
- Tse 2008: 41 pts median 36 Gy in 6 fx. Median OS 11.7m
- Rusthoven 2009: 60Gy in 3 fx. 2 yr LC 92%, OS 30%
  - Maintained 700cc liver <15 Gy
- Bujold 2013: 102 pts, median 36/6, OS 17m, LC 87%, 30% grade 3+ tox
- Dawson 2012: phase I suggests sorafenib ↑RT tox
- Technique:
  - Gated sim with contrast
  - CTV: GTV+1cm

**Whole Liver RT**
- Russell 1993: 1.5 Gy BID dose escalation. Recommended dose of 30Gy
- Hanson recommends 21 Gy in 7 fx
- Soliman 2013: phase II of 8 Gy x1 to whole liver, improved QOL, 48% had ↓symptoms at 1month
- Technique:
  - Gated sim with contrast
  - CTV: GTV+1cm

**Radioembolization**
- Y90: 50-80% response

**NCCN**
- Resect if feasible
- If not: ablation or TACE (SBRT is cat 2B)
- UNOS criteria for transplant: one tumor <5cm or 2-3 tumors <3cm each, no vascular involvement, N0M0
- Avoid Y90 if bili < 2mg/dL or CP class C
Colorectal Cancer

- T1 - submucosa
- T2 – muscularis propria
- T3 – pericolorectal tissues
- T4 -
  - T4a – visceral peritoneum
  - T4b – adj organs

<table>
<thead>
<tr>
<th>N0</th>
<th>N1</th>
<th>N1a</th>
<th>N1b</th>
<th>N1c</th>
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<tr>
<td>IIIA</td>
<td>IIIB</td>
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</table>

Overview
- 110,000 colon cancer/yr, 41,000 rectal cancer/yr
- Screening: ≥50 yr colonoscopy Q10yrs
- FAP: APC gene, HNPCC: DNA mismatch
- Rectum: rectosigmoid (S3) to 2cm prox to dentate line
- Workup: H&P, DRE, pelvic, labs (CEA), colonoscopy, bx
- CT C/A/P, Ultrasound +/- MRI

Transanal Excision
- Criteria: T1, within 8cm from anal verge, mobile, <30% circumference, <3cm tumor, >3mm margin, grade 1-2, N0, no LVSI, no PNI, reliable pt
- Data supporting this approach: CALGB 89-84: 10yr LF 8%......RTOG 89-02: 5yr LF 4%
- Adj CRT or completion APR/LAR if doesn’t meet criteria

Adj Chemo
- NSABP R-01: Dukes B&C pts→ obs vs MOF chemo vs 46 Gy. Chemo improved DFS and OS, RT → ↑LRC
- GITSG 7175: surgery→ obs vs chemo vs RT vs CRT (2x2), CRT improved OS 10 yrs (45 vs 27%) and LRR
- Intergroup/NCCTG 794751: stage II-III postop→ RT alone vs CRT. CRT improved OS (55 vs 45%), DM, and LR, but had worse toxicity

Preop RT
- Swedish: surgery +/- preop 25/5. RT ↑OS (38 vs 30%), CSS, and LRR (9 vs 26%). TME was not used
- Dutch TME trial: TME +/- preop 25/5. No OS benefit, but RT ↓LRR (5.6 vs 10.9%). No chemo

Preop CRT
- Swedish Uppsala: 25/5 preop vs 60 Gy postop (split course). No OS difference, but preop ↓LR (13 vs 22%)
- German: T3+ or N+→ preop 50.4+5FU (1000mg x2c) vs postop 55.8+5FU (1000mg x2c). All pts got postop 5FU (500mg/m2/day x 4c). Preop CRT won, but only 54% of adj pts got full dose
  - Same 5 yr OS (~75%)
  - LR: 13→6%, pCR: 8%
  - Sphincter-preservation: 19→39%
  - Acute tox: 40→27%, Late tox: 24→14%
  - 18% overtreated

NSABP R-03: T3+ or N+. same design as GRCT, but poor accrual. Trend toward ↑OS with neoadj. pCR in 15%
- French 9203: preop RT vs preop CRT (5FU). CRT had worse tox, but ↓5yr LR (16.5→8.1%) and →pCR (3.6→11.4%). Same OS
- EORTC 22921:+/-chemo, +/-RT. Showed that CRT improves LC but not OS compared to RT alone
- NSABP R-04: 5FU vs capetiabine: no difference. Adding oxaliplatin only worsened tox

Colon Cancer
- Intergroup 0130: T4 or T3N1-2 of colon→ adj chemo or adj CRT. No difference in 5 yr OS or DFS and tox worse. Only accrued 222/700 pts

Technique
- Prone, bellow board, PO contrast, full bladder, (wire scar and include if postop)
- 3-4 fields
  - Sup: L5/S1
  - Inf: 3cm below tumor of below obturator foramen
  - Lateral: 2cm outside pelvic brim
  - Post: entire sacrum and presacral space
  - Ant: T3 (post to pub symph), T4 (ant to pub symph, but ensure 3cm margin on tumor)
- Boost GTV +2-3cm
- 45 Gy WPRT + 5.4 Gy boost if preop
- Up to 54 if postop

NCCN
- Colon
  - consider pre or postop RT for T4 or pos margins
  - 45-50 Gy with 5FU
- Rectal
  - T1N0: transanal vs APR/LAR
    - If high risk, then TME and postop CRT if T3+ or N+
    - High risk: T2, +margin, LVSI, G3
  - T3+ or N+: neoadj CRT, then TME, then adj chemo
    - 50.4 Gy with xeloda
Overview
- 7000 cases/year
- HPV associated (16, 18), AIDS associ
- 33% are N+, but only 50% of cN+ are pN+
- Anatomy: anal canal is 3-4cm long, from anal verge to anorectal ring. Dentate line divides histology
- Anal margin: 5cm ring around anus, treat like skin cancer
- Above dentate drains to rectal nodes. Below drains to inguinals
- Workup: H&P, GYN exam, DRE, labs, HIV, PET-CT, +/- MRI, anoscopy
- Mitomycin C: hypoxic cell radiosensitizer
- 5FU: 1000mg/m2/day continuous infusion
- mitoC: 10mg/m2 bolus on days 1 and 29
- capecitabine: 825mg/m2 BID mon-fri

Local excision alone or RT alone
- Boman 1984: T1, G1, neg margins, <40% circumference, no sphincter involvement (LC >90%)
- Deniaud-Alexandre 2003: RT alone for T1N0, 100% LC

RT vs CRT
- Nigro 1974: 30/15 + 5FU+mitoC then surgery for some. 71% pCR. Same control with or without APR (~80%)
- ACT I: 45Gy=boost +/- 5FU+mitoC. Split course RT. CRT improved LC (36→59%), but no OS.
- ACT II: 50.4Gy with 5FU + mitoC vs cisplatin. No difference
- EORTC trial: same as ACT I
- RTOG 8704: 45Gy with 5FU +/- mitoC. MitoC improved CR rate (85→92%), and ↓colostomy rate, but same OS
- CALGB 9281: neoadj chemo trial, no clear benefit. Showed 70% OS and 70% sphincter preservation
- RTOG 9811: 5FU + cis with induction vs 5FU + mitoC without induction. 5 yr OS with mitoC better (71→78%). Same toxicity
- Gylme-Jones 2008: phase II data of capecitabine instead of 5FU. Good results

NCCN
- RT + 5FU/MitoC for any M0 disease. Or can use xeloda
  - 30.6 Gy/17fx then 14.4 Gy boost to the field below the SI joints (can treat cN0 nodes to 36 Gy)
  - Min dose of 45 Gy to primary, at least 2.5cm margin
  - T3/4 or N+ needs 54-59 Gy total dose
  - Include inguinals, anus, perineum from L5/S1
- Anal margin: can excise, skin cancer reccomendations
Genitourinary
Low Risk Prostate Cancer

- T1 - clinically unapparent
  - T1a - incidental <5% of tissue resected
  - T1b - incidental >5% of tissue resected
  - T1c - needle biopsy (PSA)
- T2 - confined within prostate
  - T2a - ≤ ½ of one lobe
  - T2b - > ½ of one lobe
  - T2c - both lobes
- T3 - through capsule
  - T3a - EPE or microscopic invasion of bladder neck
  - T3b - seminal vesicles
- T4 - invades adjacent structures: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

• N1 – pelvic, hypogastric, obturator, iliac (internal, external), sacral
• M1a - non-regional lymph nodes
• M1b - bone
• M1c - other sites

<table>
<thead>
<tr>
<th>Group</th>
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<th>II B</th>
<th>III</th>
<th>IV</th>
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<tr>
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<td>10yr bPFS</td>
<td>90%</td>
<td>85%</td>
<td>60%</td>
<td>30-50%</td>
<td>&lt;20%</td>
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</table>

Overview
- 230,000 cases, 27,000 deaths annually
- Zones: Peripheral (2/3 cancers), Transitional (BPH), Central, Anterior fibromuscular stroma
- PSA velocity: ≥2ng/ml/yr →↑GS7
- PSA density (PSA/gland volume): >7% → ↑risk
- Free PSA <25% → ↑cancer
- Screening: 50 y/o, DRE & PSA, debated
- 1,400 screened→ 48 cancers → 1 death prevented
- Work up: DRE, PSA, Alk Phos, CBC, BMP, LFTs,
- Active Surveillance: biannual DRE/PSA, annual Bx (25% will end up getting treated)

EBRT
- Swedish Trial (Bill-Axelson): mixed group, RP vs WW: RP improves CSS, not OS. Before PSA-era.
- RP vs EBRT vs brachy (Kupelian 2004) = 80% 5yr FFS (51% if <72Gy)

Dose escalation trials: (↑ bPFS ~20%, no change in OS)
- PROG 9509: low risk; 50.4 then proton boost to 70.2 vs 79.2 GyE; 10yr bFail: 32→17%
- MDACC: mixed risk; 70 vs 78 Gy; 8yr FFF 59→78%; CSS (97%) and OS (78%) unchanged
- Netherlands: 68 vs 78 Gy; 7yr bPFS 45→56%
- MRC: 64 vs 74 Gy, 5yr bPFS 60→71%
- GETUG: 70 vs 80 Gy; 5yr PSA failure 31→24%

EBRT Dose constraints

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<tr>
<th>Rectum</th>
<th>Bladder</th>
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<tr>
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<td>Femur</td>
</tr>
<tr>
<td>V45&lt;195cc</td>
<td>V50&lt;5%</td>
</tr>
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Brachytherapy
- 125Pd: 17d, 21keV, EC, 125 Gy mono, 100 Gy w/ EBRT
- 125I: 60d, 28keV, EC, 145 Gy mono, 110 w/ EBRT
- 192Ir: 74d, 3.8MeV (~13.5 Gy x2 or 10.5 Gy x3 mono, 15 Gy x1 or 9.5 Gy x2 w/ EBRT)
- Relative contraindications: Prev RT or TURP, int/high risk, SVI, pub arch interference, median lobe, >60cc gland, AUA>15, DM (add EBRT for T2c, GS7 or PSA>10)
- GS 7 can get LDR monotherapy if all this: 3+4, PSA<10, ≤4/12 cores, ≤T2a, ≤50% each core, between 20-65cc gland
- 5mm TRUS slices, 5mm PTV expansion (3mm ant, 0mm post)

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<tr>
<th>LDR PTV</th>
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<tr>
<td>D90 &gt;105%</td>
<td>V100 &gt;95%</td>
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<tr>
<td>V150 &lt;70%</td>
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<td>V200 &lt;40%</td>
<td>V200 0%</td>
</tr>
<tr>
<td>Rectum V100%&lt;1cc</td>
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- Post implant dosimetry
- Post-brachy obstruction risk ≈ AUA score (%)

Toxicity
- RP: ED, incontinence, stricture (50% potent, 75% continent)
- RT: urinary freq, proctitis (50% potent, ≤1% late GI/GU)

NCCN Guidelines
- 75.6-79.2 Gy @ 2/fx (up to 81 Gy for int/high risk)
- No nodes/ADT for low risk
Intermediate/High Risk Prostate Cancer

- Consider CT abd/pelv, bone scan, +/- pelvic MRI

- **Roach formulas**
  - ECE = 3/2(PSA) + 10(GS-3)
  - SVI = PSA + 10(GS-6)
  - LN = 2/3(PSA) + 10(GS-6)
    - treat nodes for >15%

- **ADT +/- RT**
  - Scandanavian (SPCG-7): int/high risk; 3m ADT +/- 70 Gy; 10yr OS 61→70%, CSS 76→88%

- **Int risk RT +/- ADT: most improve OS 5-10%**
  - RTOG 8610: high risk; 70 Gy +/- 4m ADT; 10 yr CSS 64→77%, DM, OS trend
  - RTOG 9408: int risk; 68 Gy +/- 4m ADT; 12 yr OS 51→56%
  - D-Amico: mostly int risk; 70 Gy +/- 6m ADT; 8 yr OS 61→74%
  - TTROG 96.01: mostly high risk; 66 Gy +/- ADT (0m, 3m, 6m); DFS 32→49→52%, OS with ADT
  - Crook: mixed risk: 66 Gy + ADT (3m vs 6m); no differences (longer better for high risk)
  - RTOG 9413: int/high risk, 2x2 (+/- WP, neoadj/adj ADT): mixed data, no clear result

- **High risk RT +/- ADT: improves OS**
  - RTOG 8531: WP RT; 70 Gy +/- indefinite goserelin; 10yr OS 39→49%
  - EORTC 22863: WP RT; 70 Gy +/- 3yr goserelin; 10yr OS 32→42%

- **Duration of ADT**
  - RTOG 9202: WP RT; ~70Gy + 2m vs 2yr ADT; OS 32→45%
  - EORTC 22961: WP RT; 70 Gy + 6m vs 3yr ADT; 5 yr OS 81→85%

- **Types of ADT**
  - Castration
  - GnRH agonists
    - Goserelin (Zoladex)
    - Leuprolide (Lupron)
    - Triptorelin (Trelstar)
  - Antiandrogens: bicalutamide (Casodex)
  - Non-steroidal antiandrogen: Flutamide
  - Estrogens
  - Ketoconazole: blocks P450
  - Degarelix: GnRH antagonist, no initial flare

- **Whole Pelvis RT?**
  - All failed to show a clear subgroup with benefit
    - RTOG 7706
    - RTOG 9413
    - GETUG-01

- **NCCN**
  - Up to 81 Gy permitted
  - +/- nodes
  - +/- 4-6 m ADT int risk
  - +/- 2-3 yrs ADT high risk
  - If brachy then +/- EBRT/ADT

Adjuvant/Salvage and Metastatic Prostate Cancer

- **Adjuvant vs Salvage RT**
  - SWOG 8794: pT3N0 or +M; obs with salv RT vs adj RT; 15yr OS 37→47%, LF 22→8%
  - EORTC 22911: pT3N0 or +M; obs with salv RT vs adj RT; 5yr bPFS 53→74%, OS same
  - German ARO 9602: pT3N0 or +M; obs with salv RT vs adj RT; bPFS 54→72%, OS same

- **NCCN**
  - Postop dosing: 64-70 Gy @ 2Gy/fx

- **PSA Failure**
  - After RP: ≥0.2 ng/mL
  - 1996 ASTRO definition: 3 consecutive rises, then back-dated
  - 2005 Phoenix definition: rise of 2 ng/mL over nadir
  - PSA bounce: ↑2ng/mL ~12m out (~20% risk)

- **Salvage ADT?**
  - King (2004): Salvage RT +/- ADT; 5 yr OS 87→100%, bPFS 31→57%

- **Node Positive**
  - Messing Trial: pN++; RP +/- ADT; 12yr MS 11.3→13.0yrs
  - RTOG 8531: cN++; RT +/- ADT; 9yr OS 38→62%
  - Zangers trial: N++; ADT +/- 70 Gy; 10yr OS 46→67%

- **Metastatic**
  - 1st line: ADT
  - 2nd line: Docetaxel/Prednisone
    - SWOG 9916
    - TAX 327
  - $^{22}$Ra (Alpharadin): bone only mets
    - 11.4d, alpha emitter, 5.8 MeV avg
    - 1000kBq/ml, Rx is 50kBq/kg Q4wks x 6 treatments
    - Requires
      - ANC ≥ 1.5 x10^9/L
      - PLT ≥ 100x10^9/L
      - Hgb ≥ 10 g/dL
Bladder Cancer 1-5,324-330

- Tis, Ta – CIS, non-invasive, papillary
- T1 - subepithelial
- T2 - muscularis propria
  - T2a - inner half
  - T2b - outer half
- T3 - perivesical tissue
  - T3a - microscopic
  - T3b - macroscopic
- T4 - adjacent organs
  - T4a - prostatic stroma, uterus, vagina
  - T4b - pelvic wall, abd wall

- N1 - single LN below common iliac
- N2 - multiple LNs below common iliac
- N3 - common iliac LN

Overview
- Risk factors: smoking, dyes, irritation (foley)
- 93% TCC (5% SCC, 2% adenocarcinoma)
- 75% Ta, Tis, T1 at presentation
- Cystectomy: en block removal of bladder, perivesicular tissue, urethra, prostate (or uterus)

Workup
- H&P, labs, UA, alk phos, urine cytology
- Cystoscopy, biopsy, bladder mapping, EUA, TURBT
- Superficial: CT pelv + IVP
- Muscle invasive: CT chest/abd/pelv +/- MRI

Neoadjuvant chemo and RT
- Chemo metaanalysis 2003: 5% OS advantage at 5 yrs with multiagent cisplatin
- Cole 1995: MDACC: preop 50/25 vs no preop therapy 5 yr LC improved 72→91%, but nothing else

Bladder Preservation Data
- NCIC Coppin 1996: T2-4: preop RT +/- cisplatin. Chemo ↓LRF, but same OS
- RTOG 8512: T2-4N0-2: phase II: RT 40/20 +cisplatin then restage and 24/12 for CR. 67% CR, 5 yr OS 52%, LC 42%
- RTOG 8903: 123 pts cT2-4aNx: RT 39.6/22 with cisplatin +/- neoadj MCV 2c. 25.2 Gy boost for CR (64.8 Gy). Stopped early (14% of MCV arm died). No change in CR, OS

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<th>Nodal Risk</th>
<th>LR with cystectomy</th>
<th>5 yr OS</th>
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<tr>
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<td>5%</td>
<td>&lt;5%</td>
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<td>18%</td>
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<td>pT3b</td>
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<td></td>
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</tr>
<tr>
<td>pT4</td>
<td>42%</td>
<td>50%</td>
<td>15%</td>
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</table>

- RTOG 9506: 34 pts T2-4aNx: similar to prior. 3 yr OS 83%, 66% intact bladder, 45% Tis failure
- MGH Shipley 2002: same as RTOG 8903, 190 pts. 5 yr OS 54%, intact bladder 46%, hydronephrosis didn’t matter
- RTOG 9906: same as others but BID RT and added paclitaxel concurrent and adjuvant gemcitabine. Same results.

Bladder Preservation Technique
- Maximal TURBT (to negative margin)
- Sim bladder empty
- 45 Gy to whole bladder + nodes with concurrent cisplatin or 5FU/mitomycinC
- Cystoscopy w/ biopsies and cytology (75% CR)
- Boost to 60-65 Gy if no tumor remaining (T0 and neg cytology)

NCCN
- Tis: BCG
- Ta: observation or TURBT +/-BCG
- T1: TURBT + BCG (upfront cystectomy for high grade)
- Stage II-III
  - Neoadjuvant chemo + radical cystectomy +/- adj chemo for pT3-4 or N+ (postop RT for +margin or pT3-4)
  - Bladder preservation as above (cat 2B)
    - Consider cystectomy if multifocal, cT3b-4, component of Tis, hydronephrosis, subtotal TURBT
- T4b or N+: chemo or CRT then surgery vs more RT
Renal Cell Cancer

- T1 - ≤ 7cm, kidney only
  - T1a - ≤ 4 cm
  - T1b - 4-7 cm
- T2 - > 7 cm, kidney only
  - T2a – 7-10 cm
  - T2b - >10 cm
- T3 - into major veins or perinephric tissues
  - T3a - into renal vein or perirenal fat
  - T3b - into vena cava below diaphragm

- T3c - into vena cava above the diaphragm or wall of vena cava
- T4 - invades Gerota's fascia
- N1 – renal hilum, caval (para/pre/retrocaval), interaortocaval, aortic (para/pre/retroaortic)

Overview
- Genetic conditions: VHL, Dirt-Hogg-Dube syndrome, Tuberous sclerosis, met proto-oncogene
- Sporadic RCC: mutation in the VHL tumor suppressor gene on 3p25
- Classic triad: hematuria, flank pain, mass
- Paraneoplastic syndromes (20%): ↑Ca, HTN, ↑LFTs
- Pathologic subtypes: clear cell (70%), chromophlic, chromophobic, collecting duct

Workup
- H&P, labs CT chest/abd/pelv +/- MRI

Select trials
- 4 randomized trials show no benefit to PORT (Rotterdam, Sweden, Fugitt, Kjaer)

Stein 1992: 147 pts, PORT vs obs: in T3N0 pts, PORT won. LR 37%→10%.
- Escudier/AVOREN: stage IV RCC given IFα +/- Avastin. Avastin doubled PFS (5→10months)
- Escudier/TARGET: treatment resistant RCC +/- sorafenib. Sorafenib doubled PFS (2.8→5.5mo)
- Motzer, 2007: metastatic RCC: sunitinib vs IFα, sunitinib won

NCCN
- Local disease: surgery (no radiation)
- Metastatic disease: surgery (palliative nephrectomy), sunitinib (multi-TKI), temsirolimus, bevacizumab & IFN, interleukin-2, sorafenib (Multi-TKI)

Urethral Cancer

- Ta, Tis - non-invasive papillary, polypoid, or verrucous carcinoma
- T1 – super epithelial
- T2 – spongiosum, prostate, periurethral muscle
- T3 - cavernosum, EPE, ant vagina, bladder neck
- T4 - adj organs (including bladder)

- N1 – single, ≤2cm
- N2 – >2cm or multiple

Anatomy
- Epithelium transitions from squamous (outside) to pseudostratified to transitional cell
- Most common site in men: bulbomembranous (~60%)

Workup
- H&P, labs, UA, alk phos, urine cytology
- Cystoscopy, biopsy
- MRI pelvis, chest imaging

Male Early stage
- Surgery: MSKCC (Dalbagni 1999): Tis-T1, 10 pts, surgery only 5 yr DFS 83%
- RT: (Heysek 1985): 5 pts, LC in 4/5

Male Locally Advanced
- Surgery: MSKCC (Dalbagni 1999): T2-T4, 36 pts, surgery only 5 yr DFS 45%

Female
- After pelvic exenteration: 5 yr OS 20%, LF 66%
- RT alone: 5 yr OS 75% early stage, 34% advanced stage (Kreig 1999)
- RT alone approach: 50-60Gy brachy alone or EBRT (45Gy) + 20-25 Gy brachy

Concurrent chemo
- Only case reports, consider 5FU/mitoC, 5FU/cisplatin, carbo/taxol (Eng 2003)

NCCN
- Tis/Ta: TUR
- T1-2: surgery +/- PORT or chemoRT (66-70 Gy)
- T3-T4 or N+: chemoRT
Testicular Cancer\textsuperscript{1-5,340-342}

- **T1** – testis, epididymis, no LVSI, no vaginalis
- **T2** – T1 + LVSI or vaginalis
- **T3** – spermatic cord
- **T4** – scrotum

- **N1** – N+, all ≤2cm (path ≤5 nodes)
- **N2** – N+, all 2-5cm (path >5 nodes or ECE)
- **N3** – N+, >5cm

- **M1a** – nonregional nodes or lung mets
- **M1b** – distant

- **S0** – normal serum markers (ALL POST ORCHIECTOMY)
- **S1** - LDH < 1.5 ULN AND hCG < 5000 AND AFP < 1000
- **S2** – LDH 1.5 - 10 ULN OR hCG 5000-50,000 OR AFP 1000-10,000
- **S3** – LDH > 10 ULN OR hCG >50,000 OR AFP > 10,000

**Overview**
- Lymph flows to PA nodes (left vein drains to renal vein)
- 95% GCTs (seminomas/NSGCTs)
- Seminoma: bHcG can be ↑ (15%) but NEVER AFP
- NSGCTs
  - embryonal carcinoma (most common)
  - yolk sac (↑AFP, Schiller Duval bodies)
  - choriocarcinoma (↑bHcG)
  - teratoma
  - mixed (60%)
  - others
  - sertoli cell: ↑estrogen
  - leydig cell: ↑androgens
  - lymphomas, sarcomas
- Risk factors: cryptorchidism, first born, polyvinyl chloride, Downs, Klinefelter’s, HIV
- bHcG half life: 24 hrs
- AFP half life: 5 days

**Stage I Seminoma**
- RT field: MRC (Fossa 1999): stage I seminoma comparing dogleg vs PA only. 3 yr RFS/OS same (~98%) and PA better tolerated
- RT dose: MRC (Jones 2005): stage I seminoma, 20/10 vs 30/15. Mostly PA only.5 yr RFS same (~97%)
- Chemo: MRC (Oliver 2005): carbo x 1c vs RT. RFS same (~95%). Relapse location varied but chemo better tolerated

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>10 yr RFS</th>
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<tr>
<td>N0</td>
<td>IA (S0)</td>
<td>IB (S0)</td>
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<td>98%</td>
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<tr>
<td>N1</td>
<td>II (S0-1)</td>
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<tr>
<td>N2</td>
<td>II (S0-1)</td>
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<td>86%</td>
</tr>
<tr>
<td>N3</td>
<td>II (S0-1)</td>
<td></td>
<td></td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>M1a</td>
<td>IIIA (S0-1, any N)</td>
<td></td>
<td></td>
<td></td>
<td>90% OS</td>
</tr>
<tr>
<td>S2</td>
<td>IIIB</td>
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<td>80% OS</td>
</tr>
<tr>
<td>S3</td>
<td>IIIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- S0 - normal serum markers (ALL POST ORCHIECTOMY)
- S1 - LDH < 1.5 ULN AND hCG < 5000 AND AFP < 1000
- S2 – LDH 1.5 - 10 ULN OR hCG 5000-50,000 OR AFP 1000-10,000
- S3 – LDH > 10 ULN OR hCG >50,000 OR AFP > 10,000

**Technique**
- Sperm bank?
- Supine, clamshell other testicle, move penis
- PA: T11/12 to L5/S1, laterally through transverse process (2cm margin on nodes). For left sided tumors include left renal hilum)
- Dogleg: PA field but down to top of acetabulum
- 20/10, boost IIA nodes to 30 Gy, IIB nodes to 36 Gy
- Do not use IMRT
- 2cm margin on GTV nodes to block edge
- Dose limits
  - 50 cGy: transient azospermia
  - 2 Gy causes sterilization
  - 30% of patients are fertile after RT
  - Kidneys: D50%< 8 Gy

**NCCN**
- *All patients: radical transinguinal orchiectomy with high ligation of the spermatic cord (never biopsy), then repeat tumor markers*
- Adjuvant Seminoma
  - I: obs* (16% LRF) or 20 Gy PA or carboplatin
  - II: 20 Gy* (dogleg+boost GTV to 30) or cis/etop x4c
  - IIIB: cis/etop x4c or 20 Gy (dogleg+boost GTV to 36)
  - IIC-III: chemo (cis/etop +/- bleo)
- Adjuvant NSGCT: RT palliative only
  - I: obs (30% LRF) vs RP-LND (30% path +) vs cis/etop/bleo
  - Positive tumor markers after surgery → chemo
- Follow up depends on tx, but generally labs/CT Q3m for 2 years then Q6m for 2 years, then Qyear
Penile Cancer

- **Tis, Ta**: CIS, noninvasive verrucous
- **T1**
  - T1a – subepithelial, no LVSI, no G3-4
  - T1b – subepithelial, +LVSI or G3-4
- **T2** – spongiosum or cavernosum
- **T3** – urethra
- **T4** – adj structures (inc prostate)

- **N1** – unilateral inguinal
- **N2** – multiple or bilateral inguinal
- **N3** – fixed or pelvic (ECE)

### Overview
- **cN0** → 20% pN+
- **cN+** → 30-50% pN0
- **Risk factors**: uncircumcised, phimosis, poor hygiene, HPV 16, 18
- **Inguinal node borders**:
  - superior: inguinal ligament
  - interior: fossa ovalis
  - lateral: sartorious
  - medially: adductor longus
- **Workup**: H&P, sperm banking?, EUA if advanced, ultrasound or MRI, CT for nodes, CXR, biopsy
- **No randomized trials**, mostly extracted from vulvar data
- **Need 5cm for sexual intercourse**
- **Need 3 cm to urinate standing**

### Early Stage EBRT
- **Grabstald & Kelly (1980)**: 10 pts, stage I-II: 90% LC
- **McLean 1993**: 26 pts, stage I-II: mostly 50/20: 5 yr DFS 50%

### Early Stage Brachy
- **Crook 2005**: 49 pts, T1-3, Ir-192 to 55-65 Gy. 5 yr LC 85%, OS 78%, penile preservation 86%
- **Mazeron 1984**: T1-3 Ir-192 to ~65Gy, LC 78%, penile preservation 74%

### Locally Advanced
- **Krieg 1981**: 17 pts stage I-IV, surgery+/-LND +/-RT, but 88% of pts without nodal treatment failed in nodes

### Risk Group

<table>
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<tr>
<th>Risk Group</th>
<th>Stage &amp; Grade</th>
<th>LN (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>T1 G1</td>
<td>0%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T1 G2-3, T2 G1</td>
<td>33%</td>
</tr>
<tr>
<td>High</td>
<td>T2 G2-3, T3 G1-3</td>
<td>83%</td>
</tr>
</tbody>
</table>

- **Sarin 1997**: 101 pts stage I-IV, mixed treatments, 10 yr OS 39%, LC 55%, validated use of RT with surgical salvage. 2 pts attempted suicide after penectomy

### Technique
- **Sim supine, foley, suspend penis, bolus, frog leg**
- **Tape up if treating pelvis**
- **Brachytherapy mold (tube loaded with Ir-192)**
- **Interstitial**: 1cm spacing, Ir-192
- **Dose limits**:
  - Urethra 60 Gy
  - Testes 3 Gy

### NCCN
- **Tis**: resection, imiquimod, topical 5FU
- **T1-2**:
  - partial vs radical penectomy (need 1-2cm margin)
  -inguinal node dissection if T1b+
  - pelvic dissection if ≥2 inguinal nodes
  - **Circumcision** with brachy (<4cm)
  - 65 Gy HDR interstitial (preferred)
  - 60 Gy mold
  - **Circumcision** with 65-70 Gy with 2cm margin
  - chemoRT (category 3)
- **Locally Advanced**:
  - Neoadj chemo for N2+, >4cm nodes, T4
  - Paclitaxel/ifosfamide/cisplatin
  - ChemoRT: 50 Gy WPRT + 10-20 Gy boost
  - Radical penectomy + LND +/- post op RT (same doses as head and neck)
Gynecologic
Cervical Cancer\textsuperscript{1-5,349-355}

- **T1**
  - T1a (\textit{IA}) – micro
  - T1a1 (\textit{IA1}) – <3mm DOI, \(\leq 7\)mm wide
  - T1a2 (\textit{IA2}) – 3-5mm DOI, \(\leq 7\)mm wide
  - T1b (\textit{IB}) – macro
  - T1b1 (\textit{IB1}) – \(\leq 4\)cm
  - T1b2 (\textit{IB2}) – >4cm

- **T2**
  - T2a (\textit{II}) – upper 2/3 vagina
  - T2a1 (\textit{IIA1}) – \(\leq 4\)cm
  - T2a2 (\textit{IIA2}) – >4cm
  - T2b (\textit{IIB}) – parametrium

Overview
- HPV types 16 and 18
- ASCUS: 2/3 resolve, repeat pap 6m
- LGSIL: 1/2 resolve, repeat pap 6m
- HGSIL: 1/3 resolve, colposcopy & biopsy
- Workup: history, EUA, pap smear, colposcopy? Sigmoidoscopy?, labs, PETCT, MRI

Surgery
- Class I: extrafascial TAH
- Class II: modified radical hysterectomy (extended to ureters)
- Class III: radical abdominal hysterectomy (to sidewall)
- Class IV: extended radical hysterectomy (bladder + excision)

Postop RT and Chemo
- GOG 92 (Sedlis): 277 pts IB-IIA → RadHys +/- WPRT. Had to have 2 of (>4cm, LVSI, middle/deep stroma invasion). PORT ↓LF, ↓mets, ↑PFS (65→78%)
- GOG 109 (Peters): 243 pts IB-IIA → RadHys, RT +/- cis/5FU. Had to have either (+margin, +LN, +parametrium). CRT improved 4 yr PFS (63→80%) and OS (71→81%)

Definitive RT and CRT
- Landoni 1997: 343 pts IB-IIA → RT vs RadHyst. Adjuvant RT given for stage >IIA. Unchanged OS, DFS, but morbidity worse in surgery arm (28 vs 12%)
- RTOG 90-01: 386 pts IIB-IVA, >5cm or LN+ → EFRT vs WPRT+cis/5FU. All pts got brachy. CRT won. 8yr OS 41→67%, LRF 35→18%, DM 35→20%
- GOG 120: 526 pts, IIB-IVA → RT with (cis vs cis/FU/hydroxyurea vs hydroxyurea). Cisplatin containing arms won
- NCIC: 353 pts → CRT with LDR (35Gy) vs HDR (8x3). No difference in 5 yr OS
- GOG 71: 282 pts IB2 → RT +/- adjuvant hysterectomy. No difference in OS, more LF in RT arm

Technique
- WPRT borders: L5/S1→obturator canal, 2cm lateral to pelvic brim, public symphysis to sacral hollow. 45 Gy in 25 fx
- Boost gross nodes to 60 Gy with IMRT
- Boost sidewall 10 Gy for +parametria
- T&O: 6 Gy in 5 fractions
- Dose constraints (EQD2)
  - Vagina: 120 Gy
  - Rectum: 75 Gy
  - Bladder: 85 Gy

NCCN
- IA1, IA2, IB1, IIA1: Surgery +/- PORT +/- chemo
- Incidental IA1 after TAH
  - No LVSI or 3Ps: observe
  - +LVSI or 3Ps: completion RadHys or RT
- IB1: definitive RT
- IB2-IVA: chemoRT

- **T3**
  - T3a (\textit{IIIA}) – lower 1/3 vagina
  - T3b (\textit{IIIB}) – pelvic wall or hydro
  - T4 (\textit{IVA}) – bladder or rectum

- **N1** – regional (up to common iliac)

- **M1** (\textit{IVB}) - distant
Endometrial Cancer

- T1
  - T1a (IA) – < ½ myometrium
  - T1b (IB) – ≥ ½ myometrium
- T2 (II) – cervical stroma
- T3
  - T3a (IIIA) – serosa/adnexa
  - T3b (IIIB) – vagina/parametrium
- T4 (IVA) – bladder or rectum
- N1 (IIIC1) – regional (up to common iliac)
- N2 (IIIC2) – paraaortic nodes
- M1 (IVB) – distant

FIGO 1971 (inoperable endometrial cancer staging)
I - Confined to corpus
  IA - Length of uterine cavity 8 cm or less
  IB - Length of uterine cavity > 8 cm
II - Involves corpus and cervix, but no extension beyond the uterus
III - Extends outside uterus but not outside true pelvis
IV - Outside the true pelvis or involves bladder or rectum
  IVA - Involves bladder, rectum, sigmoid, or small bowel
  IVB - Distant mets

Overview
- Risk factors: esotrogen, nulliparity, obesity, tamoxifen
- Simple hyperplasia → cancer (<2%)
- Complex hyperplasia → cancer (40%)
- Pathology: endometrioid adenocarcinoma, UPSC, clear cell, mucinous, sarcomas
- Lynch Syndrome: microsat instability, uterine + colon ca
  + pelvic nodes → 33% chance of + PA nodes
- Workup: H&P, labs, CA-125 (for trending in III/IV), Endometrial biopsy, imaging/scopes for symptoms

Surgery
- All patients go for surgery if able: TAH/BSO, peritoneal inspection, fluid cytology, +/- LND (usually for grade 2/3), rad hys if cervical involvement
- ASTEC trial 2009: stage I dz: TAH/BSO +/- LND: no difference, but some high risk patients got WPRT

Adjuvant RT
- GOG 99: old IB+IC+IIA: TAH/BSO+LND +/-50.4 Gy WPRT: RT won. LRR 12→3%, OS 86→92% NSS. Mostly benefited high risk patients
- PORTEC-1: old IB+IC: TAH/BSO +/-46 Gy WPRT (no LND required). RT won. LRR 14→4%, 75% of failures in cuff. OS unchanged (~85%). Better for high risk pts.
- Aalders 1980: old IB+IC: TAH/BSO + VC +/- 40 Gy WPRT (no LND). WPRT ↓LRR (7→2%), unchanged OS
- PORTEC-2: old IB+IC+IIA: 46 Gy WPRT vs 21/3 VC. Similar results except that WPRT reduced pelvic failure (3.6→0.7%) and ↑QOL

Adjuvant Chemo
- RTOG 9708: phase II: high risk early stage: WPRT + concurrent cisplatin, Q3wk. 4 yr OS 85%, low failures
- GOG 122: stage III/IV: debulking, then WART+boost vs chemo only (doxorubicin+cisplatin). Chemo won. OS 42→55%, DFS 38→50%, but ↑toxicity

Technique
- WPRT borders: L5/S1→obtruator canal, 2cm lateral to pelvic brim, public symphysis to split sacrum (include sacral hollow for stage II+). 45 Gy in 25 fx
  - Boost gross nodes to 60 Gy with IMRT
  - VC: target usually upper 2/3 vagina, to 5mm depth. 21 Gy in fx HDR (eval for vaginal extension).
  - If WPRT+VC: lower VC dose to 4-6 Gy in 2-3 fx
  - Y-app: 21/3 to uterine serosa (~2cm)

NCCN/ASTRO guidelines (Klopp 2014)
- Surgery if able with RT as below within 12 wks, LND for high risk
- Stage III/IV: postop chemoRT
- Fertility-sparing options as appropriate
- Inoperable: 45 Gy WPRT + Y-app (8.5 x2) or just Y-app 8.5x4
- Dilator at 2-4 wks post-RT → indefinitely
- Risk factors: age>60, LVSI, tumor>2cm, +cervical gland, ↑grade

G1
- Observe
  - Adverse risk factors present
  - Adverse risk factors not present

G2
- Observe or Vaginal brachytherapy
  - Observe or Vaginal brachytherapy and/or Pelvic RT (category 2B for pelvic RT)
  - Observe or Vaginal brachytherapy and/or Pelvic RT

G3
- Observe or Vaginal brachytherapy
  - Observe or Vaginal brachytherapy and/or Pelvic RT
  - Vaginal brachytherapy and/or Pelvic RT or Observe (category 2B for observation)

Y-app: 21/3 to uterine serosa (~2cm)

Surgically staged: Stage I

Surgically staged: Stage II

Surgically staged: Stage III

Surgically staged: Stage IV
Uterine Sarcoma Cancer

Leiomyosarcoma and Endometrial Stromal Sarcoma

- **T1**
  - T1a (*IA*) – ≤5cm
  - T1b (*IB*) – >5cm
- **T2**
  - T2a (*IIA*) – adenexa
  - T2b (*IIB*) – pelvic tissues
- **T3** – invades abdominal tissues
  - T3a (*IIIA*) – one site
  - T3b (*IIIB*) – multiple sites
- **T4** (*IVA*) – bladder or rectum
- **N1** (*IIIC*) – nodes
- **M1** (*IVB*) - distant

### Overview
- 4% of uterine malignancies
- Carcinosarcoma (MMMT) staged like plain EndoCa
- ESS is less aggressive, can respond to hormone therapy

### Trials
- EORTC 55874: stage I-II sarcomas (41% carcino)→surgery +/- WPRT. RT improved LC, but not OS. No benefit for LMS.

Adenosarcoma

- **T1**
  - T1a (*IA*) – endometrium only
  - T1b (*IB*) – ≤½ myometrium
  - T1c (*IC*) – >½ myometrium
- **T2**
  - T2a (*IIA*) – adenexa
  - T2b (*IIB*) – pelvic tissues
- **T3** – invades abdominal tissues
  - T3a (*IIIA*) – one site
  - T3b (*IIIB*) – multiple sites
- **T4** (*IVA*) – bladder or rectum
- **N1** (*IIIC*) – nodes
- **M1** (*IVB*) - distant

- Wright 2008: SEER database. Showed PORT improves OS for MMMT but not LMS.
- Mayo clinic: retrospective LMS. WPRT did not change OS but ↓LC
- GOG 150: carcinocarcoma→ WART vs chemo. No difference but WART had ↑tox

### NCCN
- Basically the same as endometrial cancer
Vulvar Cancer

- **Tis** – CIS
- **T1**
  - T1a (*IA*) – ≤2cm and ≤1mm DOI
  - T1b (*IB*) – >2cm or >1mm DOI
- **T2** (*II*) – ↓1/3 urethra, ↓1/3 vagina, or anus

- **N1** (*IIIA*)
  - N1a – 1-2 LNs, each <5mm
  - N1b – 1 LN, ≥5mm
- **N2**
  - N2a (*IIIB*) – 3+ LNs, each <5mm
  - N2b (*IIIB*) – 2+ LN ≥5mm
  - N2c (*IIIC*) – ECE
- **N3** (*IVA*) – fixed/ulcerated LN

**Overview**
- 3,500 dx/yr in US, 5% GYN malig, 1% female malig
- Risk factors: ↑age, HPV (# 6, 16, 18, 33), VIN, Bowens/Pagets, vaginitis, smoking laundry facilities
- Subsites: labia majora/minora, mons pubis, clitoris, vestibule, perineal body, posterior forchette, Bartholins
- LN spread: superficial inguinoabdominal → deep inguinofemoral → ext iliac (clitoris can spread straight to deep)
  - Cloquet’s node: superior deep femoral node
- Workup: H&P, CBC, UA, HIV, EUA/PAP/DRE, CT C/A/P vs PET vs MRI based on size/stage

**Surgery**
- Lymphadenectomy for DOI>1mm or G3 or LVSI (all stage IB+ pts)
  - 2cm margin is goal
  - PORT for +margin, close margin (8mm fixed, 1cm frozen), LVSI, DOI>5mm
  - GROINSS-V:T1-T2→SLNBx→no LND if neg. 3yr regional failure 2.3%.

**Nodal RT**
- GOG 37: WLE with ILND → PLND vs RT (pelv +groin); RT won; 2 yr LRR 24→5%, OS 54→68%
  - No benefit for only 1 node (similar to H&N sites)
- GOG 88: cN0 with WLE → RT vs ILND+PORT. LR, PFS and OS favored ILND+PORT
  - Criticisms: no CT staging, 50 Gy mixed beam to 3cm depth (inadeq dose and coverage for gross disease)
  - Koh 1993: mean inguinofemoral depth 6.1cm, failures in GOG88 <47Gy
- Katz 2003: modern RT techniques; LC with RT ~90%

**Neoadj CRT for unresectable disease**
- GOG 101: advanced primary or nodes→cisplatin/5FU + RT; 47.6 Gy BID; 97% were converted to resectable (31% pCR)
- GOG 205: phase II, T3-4 unresectable→inguinal LND→ preop CRT (cisplatin + 57.6Gy/32fx). 45 Gy AP/PA pelvis, 12.6 Gy boost. 50% pCR, 40% 2yr OS.
  - Improved results compared to GOG101

**Technique**
- Sim Frog-leg +/- bolus
  - 3D-CRT: “pair of paints”
    - 1 PA beam: pelvis only
    - 3 AP fields: ‘pelvic, R/L inguinal

**ACR Consensus Guidelines (no NCCN)**
- Chemos: cisplatin +/- 5FU, mitomycin C
- RT alone: 45-50.4 Gy @ 1.8 + 14-24 Gy boost (brachy vs EBRRT)
- Neoadj CRT: 57.6 Gy @ 1.8 (GOG205)
- Definitive CRT: no dose given (~60 Gy?)
- Vulva + BL nodes if cN0
Vaginal Cancer\textsuperscript{1-5,371-374}

- Tis – CIS
- T1 (I) – vagina only
- T2 (II) – paravaginal tissue
- T3 (III) – pelvic wall
- T4 (IVA) – bladder or rectum

- N1 (III) – pelvic/inguinal (up to common iliac)
- M1 (IVB) - distant

<table>
<thead>
<tr>
<th>Stage</th>
<th>Lian 2008 5 yr DFS</th>
<th>Crevoisier 2007 5 yr DFS</th>
<th>Frank 2005 5 yr DFS</th>
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<tbody>
<tr>
<td>I</td>
<td>90%</td>
<td>83%</td>
<td>85%</td>
</tr>
<tr>
<td>II</td>
<td>87%</td>
<td>76%</td>
<td>78%</td>
</tr>
<tr>
<td>III</td>
<td>32%</td>
<td>52%</td>
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<tr>
<td>IV</td>
<td>26%</td>
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<td>83%</td>
</tr>
</tbody>
</table>

Overview
- Risk factors: CIS, HPV, irritation, ↑sex, DES
- Prognostic factors: >60 yo, lower location size, anemia
- Workup: exam, biopsy, labs, CT/MRI, +/- PET
- Risk of nodal involvement
  - I: 5%
  - II: 25%
  - III: 75%
  - IV: 85%

Nodal RT
- RT techniques; LC with RT ~90%

Neoadj CRT for unresectable disease
- GOG 101: aresults compared to GOG101

Technique
- Sim Frog- fields: ‘pelvic, R/L inguinal

Hanson and Roach Guidelines
- CIS: WLE, laser, 5FU, Ve cuff
- I: surgery or cuff to 65Gy
  - If >5mm deep, >2cm or G3: add LND or WPRT
- II+: WPRT to 45 Gy + brachy to 75 Gy (6x3 HDR)

Ovarian Cancer and Fallopian Tube Cancer\textsuperscript{1-5,375-378}

- T1
  - T1a (IA) – one ovary, capsule intact
  - T1b (IB) – both ovaries capsule intact
  - T1c (IC) – capsule ruptured or +washings
- T2 – pelvic extension
  - T2a (IIA) – implants on uterus/tube, -wash
  - T2b (IIB) – implants in pelvis, -wash
  - T2c (IIC) – implants with +wash
- T3
  - T3a (IIIA) – micro peritoneal implants
  - T3b (IIIB) – macro peritoneal implants <2cm
  - T3c (IIIC) – macro peritoneal implants ≥2cm
- N1 (IIIC) – intraabd/inguinal nodes
- M1 (IV) - distant

Overview
- BRCA1: 45% risk, BRCA2 25% risk (also HNPCC)
- Epithelial 65%, germcell 25%, sex cord stromal 5%, mets 5%
- Workup: H&P, gyn exam, labs, CA125, AFP/bHcG
- Ultrasound, CT C/A/P
- Surgical staging and debulking

Trials
- GOG 111: cis/paclitxel improved OS
- GOG 158: carb/paclitxel less toxic
- GOG 172: intraperitoneal chemo toxic but effective
- Smith 1975: WART vs old chemo. Same results but more tox with WART (WART is 30 Gy at 1.5/fx)

NCCN
- RT only for local recurrence of palliation
Hematologic
Hodgkin’s Disease

Overview
- 8,200 cases/USyr, 1,300 deaths
- Classical: CD 15+, 30+, 45-, 20-
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte depleted
  - Lymphocyte rich
- Nonclassical: CD 15-, 30-, 45+, 20+
  - Nodular lymphocyte predominant HL
  - B-symptoms
    - Temp > 38°C
    - > 10% weight loss in last 6m
    - Drenching night sweats
  - Bulky disease
    - >1/3 mid-thoracic diameter (~T5/6 on PA CXR)
    - 5cm or 10cm (depends on trial)
- Workup
  - CBC w/diff, CMP, ESR, LDH, albumin, alk phos, Hep B, BHcG
  - PET-CT, PFTs (bleo), echocardiogram (adria)
  - BM Bx if: B-sympx, Stage III/IV, bulky, >2 sites, recurrence
  - Staging laparotomy not needed with STNI or chemo (EORTC H6F)
- Grouped nodes:
  - Waldeyer’s: Palantine, pharyngeal, lingual tonsils
  - Cervical/supraclav/occipital/preauricular
  - Epitrochlear/brachial
  - Inguinal/femoral
  - German unfav has different nodal grouping

Chemotherapy
- ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
- Stanford V: mechlorethamine, oncovorin, prednisone, etoposide, adriamycin, bleomycin, vinblastine (MOPE-ABV, needs RT)
- BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, oncovorine, procarbazine, prednisone

RT vs CRT
- 4 trials showed improvement with CRT, one with OS improvement (H8F): EORTC H7F, H8F, German HD7, SWOG S9133

Chemo +/- RT
- NCI: unfav I-II, nonbulky: ABVD x4-6c vs ABVD x2c + STNI: 5 yr PFS initially favored CRT (88→95%), same OS; 12 yr f/u showed ↓OS in chemoRT arm (94% vs 87%) (RT and nonRT related deaths in RT arm)
- Laskar: very mixed group: 6c ABVD with CR→ IFRT vs obs. RT won: 8yr EFS 76→88%, OS 89→100%
- Aleman: III-IV→ 4-6c MOPP-ABV w/ CR→ IFRT vs obs. Same EFS and OS

Deauville PET criteria
- 1: no uptake
- 2: uptake < mediastinum
- 3: mediastinum < uptake < liver
- 4: ↑moderately compared to liver
- 5a: ↑markedly compared to liver
- 5b: new FDG avid site

Technique
- Mantle: inf border at T10/11
- TLI: mantle + inv-Y + spleen
- STLTI: TLI –inv-Y
  - Block larynx ≤ 20 Gy
  - Block heart ≤ 30 Gy

Deauville PET criteria
- 1: no uptake
- 2: uptake < mediastinum
- 3: mediastinum < uptake < liver
- 4: ↑moderately compared to liver
- 5a: ↑markedly compared to liver
- 5b: new FDG avid site

NCCN
- Classical
  - IA-IIB: ISRT 30 Gy (20 Gy if qual for HD10)
  - IB-IIB: chemo then RT (30 Gy; 36 for bulk)
- Nonclassical
  - IA-IIB: ISRT: 30 Gy, 25-30 to adjacent nodes
  - IB-IIB: chemo then RT (30 Gy; 36 for bulk, ABVD or R-CHOP)
- III-IV: chemo +/- RT

International Prognostic Score (IPI: WALSHAM)

<table>
<thead>
<tr>
<th>WBC &gt; 15k</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb &lt;4</td>
<td>Hgb &lt;10.5</td>
</tr>
<tr>
<td>Lymph &lt;600</td>
<td>Age&gt;45, male</td>
</tr>
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</table>

Examples of Unfavorable Risk Factors for Stage III Hodgkin Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCIC</th>
<th>NCCN</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>MC or LD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms</td>
<td>&gt;50 if A: &gt;30 if F</td>
<td>&gt;50 if A: &gt;30 if B</td>
<td>&gt;50 or any B sx</td>
<td>&gt;50 or any B sx</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt;33</td>
<td>MTR &gt;35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt;2</td>
<td>&gt;3</td>
<td>&gt;3</td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td>E lesion</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td></td>
<td></td>
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</tbody>
</table>

69
Non-Hodgkin’s Lymphoma 1-5,388-390

a. Overview
   i. Categories
      1. Low grade NHL: follicular (G1,G2), CLL, MALT, mucosis fungoides
      2. Intermediate grade NHL: follicular (G3), mantle cell, DLBCL, T/NK cell, peripheral T cell, anaplastic large cell
      3. High grade NHL: Burkitt’s, lymphoblastic
   ii. Genetics
      1. Follicular: t(11,18)→ ↑bcl-2
      2. SLL/CLL: del13, t(14,19), tri12
      3. MALT: t(11,18), tri3
      4. Richter syndrome: SLL/CLL → DLBCL transformation (5%)
   iii. Workup
      1. CBC w/diff, CMP, LDH, B2micro, SPE, HIV, HepB, HepC
      2. BM Bx for most
      3. LP for CNS, testicular, paranasal sinus, immunodeficient
      4. PET-CT for all, MRI if getting LP
   iv. GELF-Criteria
      1. ≥3 nodal sites (each >3cm), mass ≥7cm, B-sympx, splenomegaly, effusion/ascites, cytopenia, leukemia

b. Chemotherapy

<table>
<thead>
<tr>
<th>International prognostic Index (IPI) (APLES)</th>
<th>Revised IPI (ritux)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
<td>5yr OS</td>
</tr>
<tr>
<td>ECOG ≥2</td>
<td>5yr OS</td>
</tr>
<tr>
<td>LDH &gt; ULN</td>
<td></td>
</tr>
<tr>
<td>&gt;1 extranodal</td>
<td>73%</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>94%</td>
</tr>
<tr>
<td>≥5 extranodal</td>
<td>51%</td>
</tr>
<tr>
<td>FL International prognostic Index (FLIPI)</td>
<td>43%</td>
</tr>
<tr>
<td>(HASSL): separate nodal groups</td>
<td>26%</td>
</tr>
<tr>
<td>Hgb &lt; 12</td>
<td></td>
</tr>
<tr>
<td>Age ≥60</td>
<td>10yr OS</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td></td>
</tr>
<tr>
<td>≥5 extranodal</td>
<td>71%</td>
</tr>
<tr>
<td>LDH &gt; ULN</td>
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</tbody>
</table>

i. R-CHOP: rituximab, cyclophosphamide, hydroxydaunomycin (adria), oncovorin (vincristine), prednisone

<table>
<thead>
<tr>
<th>Intermediate Grade Trials</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>i. SWOG 8736: 1-IIIE int grade NHL: CHOPx8c vs CHOP x3c +IFRT (40-55 Gy): 5 yr results favored CRT, but 7 yr results overlapped</td>
<td></td>
</tr>
<tr>
<td>ii. ECOG E1484: 1-IIIE, int grade NHL: CHOPx8c with CR→IFRT vs obs: RT won. 6 yr DFS 56→73%, OS same</td>
<td></td>
</tr>
<tr>
<td>iii. GELA LNH-93-4: &gt;60 y/o, low risk: CHOPx4c vs CHOPx4c + IFRT (40Gy): 5 yr EFS and OS same</td>
<td></td>
</tr>
</tbody>
</table>

d. NCCN
   i. Follicular Lymphoma
      1. Low grade localized FL: 24-30 Gy only
      2. III/IV: palliative (>20 Gy or 2x2 Gy)
   ii. DLBCL
      1. I-II: RCHOP x3-6c +/- RT (40-50 Gy for PR)
      2. III/IV: palliative
      3. Testicle: 25-30 Gy
   iii. Mantle cell: I-II: chemo +/-RT
   iv. SLL: palliation
   v. Marginal zone: palliation

General Dose Guidelines:
- Localized CLL/SLL: 24-30 Gy
- Follicular lymphoma: 24-30 Gy
- Marginal zone lymphoma:
  - Gastric: 30 Gy
  - Other extranodal sites: 24-30 Gy
  - Nodal MZL: 24-30 Gy
- Early-stage mantle cell lymphoma: 30-36 Gy
- Mini-dose RT (2 Gy x 2 may be repeated) for palliation/local control of SLL, FL, MZL, MCL

• Diffuse large cell lymphoma or PTCL
  - Consolidation after chemotherapy CR: 30-36 Gy
  - Complimentary after PR: 40-50 Gy
  - RT as primary treatment for refractory or noncandidates for chemotherapy: 45-55 Gy
  - Salvage pre- or post-stem cell transplantation: 30-40 Gy
• Primary cutaneous anaplastic large cell lymphoma: 30-36 Gy
MALT Lymphoma

1. Overview
   a. Arises from Peyer’s patches, marginal zone
   b. t(11:18), tri3, CD 20+, 35+, 5-, 10-
   c. Workup: T&P, CBC w/diff, CMP, LDH CXR, CT A/P, EGD/EUS, BM Bx for advanced
   d. Use FLIPI (HASSL)
   e. Ann Arbor or Lugano staging

2. RT indications
   a. H. Pylori negative
   b. t(11,18) → (<5% respond to abx)
   c. invasion past submucosa
   d. progression on abx
   e. failure after 2 courses of abx
   f. rapid/symptomatic progression

3. Site Specific recommendations
   a. Gastric MALT
      i. Commonly caused by H. pylori (abx: triple therapy)
      ii. Tx strategy
         1. Rapid urease test on biopsy
         2. Triple therapy (clarithromycin/flagyl/PPI)
         3. Urea breath test 1m after abx
         4. EGD w/ bx Q3m
         5. Secondary abx if persistent dz
         6. IFRT vs chemo for persistence/progression
      iii. Note: DLBCL of stomach → RCHOP +IFRT
      iv. Technique
         1. Sim fasting with PO contrast, 4D
         2. Cover whole stomach + perigastric nodes +/- celiac
         3. 2cm margin
         4. 4-field to 30 Gy in 20 fx (boost residual to 36 Gy)
         5. Kidney mean <20 Gy, liver V25<50%
      v. 10 yr LC 95%, DFS 50%
   b. Orbital MALT
      i. Commonly caused by Chlamydia psittaci (abx: doxycycline)
      ii. Treat whole orbit
      iii. 25-30 Gy in 10-20fx (can dose reduce for low grade to 19.5-24 Gy)
      iv. 95% local control (↑distant failure)
   c. Salivary MALT
      i. Commonly caused by Sjogeren’s syndrome
      ii. (Thyroid caused by Hashimoto thyroiditis)
      iii. Treat whole gland
      iv. 30 Gy in 20 fx
      v. Cervical nodes if involved
   d. Skin MALT
      i. Commonly caused by Borrelia burgdorferi (abx: doxycycline)
      ii. Surgery vs electrons
      iii. 30 Gy in 20 fx
   e. Lung MALT
      i. Early stage → surgery with PORT for +margin or mediastinal nodes
      ii. Advanced stage → chemo +/- IFRT

Lugano Staging

<table>
<thead>
<tr>
<th>IE1</th>
<th>Mucosa/submucosa</th>
</tr>
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<tbody>
<tr>
<td>IE2</td>
<td>Into muscularis/seroa</td>
</tr>
<tr>
<td>IIIE</td>
<td>Perigastric LNs</td>
</tr>
<tr>
<td>IIIE</td>
<td>Distant abd LNs</td>
</tr>
<tr>
<td>IIIE</td>
<td>Into adventitia</td>
</tr>
<tr>
<td>IVE</td>
<td>Across diaphragm</td>
</tr>
</tbody>
</table>
Plasmacytoma/Multiple Myeloma

1. Overview
   a. 15,000 cases/yr in UA
   b. Solitary extramedullary plasmacytoma (SEP)→MM (25% @10yrs)
   c. Solitary bone plasmacytoma (SBP)→MM (75% @10yrs)
   d. CRAB: ↑calcium, renal failure, anemia, bone lesions
   e. POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-spike, skin changes (POEMS patients respond well to RT)
   f. Workup: H&P, CBC w/ diff, CMP, LDH, Ca/albumin, B2micro, SPEP, UPEP, skeletal survey, unilateral BMbx
   g. PET-CT can be helpful but no bone scan (lytic lesions)

<table>
<thead>
<tr>
<th>International Staging System (ISS)</th>
</tr>
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<tbody>
<tr>
<td>B2-micro</td>
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<tr>
<td>&lt;3.5 mg/L</td>
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<tr>
<td>Albumin</td>
</tr>
<tr>
<td>MS</td>
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</tbody>
</table>

   Note: also Durie-Salmon criteria staging (more involved)

2. Dx Criteria for MGUS (all required)
   a. SPEP M-spike < 3g/dL
   b. BM plasma cells < 10%
   c. No end organ damage

3. Dx Criteria for Solitary Plasmacytoma (all required)
   a. Single bone/extracranial lesion by skeletal survey
   b. Plasmacytoma by biopsy
   c. <5% plasma cells by BM bx
   d. No end organ damage

4. Dx Criteria for MM (all required)
   a. Clonal plasma cells (≥10% BM bx)
   b. M-spike on SPEP or UPEP
   c. End organ damage: CRAB
      i. Ca >11.5 mg/dL
      ii. Cr >2mg/dL
      iii. Hgb <10g/dL
      iv. Bone lesions
   d. Note: only a+b is “smoldering MM”

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>i. Bisphosphonates (skeletal events 41→24%)</td>
</tr>
<tr>
<td>ii. Chemotherapy (lots of options)</td>
</tr>
<tr>
<td>1. Boprtezomib/dexamethasone</td>
</tr>
<tr>
<td>2. Add melphan if no transplant planned</td>
</tr>
<tr>
<td>3. Maintenance with bortezomib or thalidomide</td>
</tr>
<tr>
<td>iii. Bone marrow transplant</td>
</tr>
<tr>
<td>1. Condition with high dose melphalan</td>
</tr>
<tr>
<td>iv. Palliative RT</td>
</tr>
<tr>
<td>1. 20-36 Gy @ 1.5-2 Gy/fx</td>
</tr>
</tbody>
</table>

5. SEP
   a. Tournier-Rangeard, 2006: SEP retrospective
      i. 5 yr LC: 100% if ≥45 Gy, 50% if <45 Gy
      ii. 5 yr DFS: 81% among all doses
   b. Technique
      i. Mass + primary LNs
      ii. ≥45 Gy
      iii. Then restage

6. SBP
   a. Tsang, 2001: mostly SBP (also some SEP)
      i. 8 yr LC: 83%
      ii. 8 yr OS: 65%
      iii. 8 yr DFS 44%
      iv. Freedom from MM: 50%
   b. Technique
      i. Bone with 2-3cm margin
      ii. Spine: 2 above and 2 below
      iii. ≥45 Gy
      iv. Then restage
Sarcoma
Osteosarcoma, Chondrosarcoma, Chordoma

- T1 - ≤8cm
- T2 - >8cm
- T3 – discontinuous tumors
- N1 – nodes
- M1a - lung
- M1b - other

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
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<tbody>
<tr>
<td>N0</td>
<td>IA (G1)</td>
<td>IIA (G3)</td>
<td>IB (G1)</td>
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<td></td>
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<td>IIB (G2)</td>
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<td></td>
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<td>III (G3)</td>
</tr>
<tr>
<td>N1</td>
<td></td>
<td></td>
<td>IVB</td>
</tr>
<tr>
<td>M1a</td>
<td></td>
<td></td>
<td>IVA</td>
</tr>
<tr>
<td>M1b</td>
<td></td>
<td></td>
<td>IVB</td>
</tr>
</tbody>
</table>

Overview
- Prevalence:
  - osteosarcoma>chondrosarcoma>ewings>MFH
- Physaliferous cell: chordoma
- Onion skin: ewings (lytic, diaphysis)
- Sunburst: osteosarcoma (sclerotic, metaphysis)
- Workup: H&P, labs, alkphos, ESR, plain films, CT primary+chest, bone scan
- Biopsy after images. Need to excise biopsy site

Osteosarcoma
- Neoadj and adj chemo ↓LF (Link 1986, Eilber 1987)
- Ozaki 2003: retrospec. RT improved OS for R1 or R2

Technique
- Spare 2cm skin
- CTV is surgical bed + scar + 2cm

NCCN
- Resect if possible otherwise RT
- Osteosarcoma needs neoadj and adj chemo (cat 1)
Soft Tissue Sarcoma

<table>
<thead>
<tr>
<th>TNM</th>
<th>G</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>T1</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
</tr>
<tr>
<td>III</td>
<td>T2 or N1</td>
</tr>
<tr>
<td>IV</td>
<td>M1</td>
</tr>
</tbody>
</table>

Overview
- 11,000 cases/yr, 4,400 deaths/yr
- Histology
  - Undiff pleomorphic sarcoma (MFH) 25%
  - Liposarcoma 15%
  - Leiomyosarcoma 10%
  - Synovial sarcoma 5% [t(x,18)]
  - MPNST (5%)
  - Clear cell <5% [t(11,22)]
  - Grade based on diff, necrosis, mitosis
  - Stewart-Treves syndrome: lymphangiosarcoma from lymphedema
  - ↑LN+: SCARE [synovial, clear cell, angio, rhabdo, epitheliod]
  - Workup: H&P, Xray, CT, MRI, CT chest, bx
  - Biopsy incision should be excised

Karposi Sarcoma
- AIDS assoc and non-AIDS assoc
- HHV8 infection
- Kirova 1998: 30 Gy (15-10 for face/groins). 92% response

Surgery & Chemo
- Goal is >1cm in all directions
- Pervaz 2008: metaanalysis for chemo (doxorubicin-based). Chemo improved LC 4% and OS 6%
- Harvard study: retrospective 48 pts with neoadj CRT (MAID +44/22 split course) with boost postop if R1. 5 yr LC 92%, OS 87%
- RTOG 9514: used Harvard neoadj CRT with 64 pts. showed similar results (OS 71%), but toxic

Postop RT
- Rosenberg 1982: G3→amputation vs WLE+RT (boost to 60-70Gy). No difference in LC or OS.
- Pisters 1996: WLW+/-brachy (45Gy LDR). Brachy →↑LC for G3, but not for G1-2
- Yang 1998: WLE +/-EBRT (63Gy). G3 tumors got chemo. RT improved LC for all grades, but no change in OS.

Preop vs Postop RT
- Pollack 1998: preop (50Gy) vs postop (60-66Gy). Same LC (81%)
- O’Sullivan 2002: preop (50Gy) vs postop (66Gy). If +margin, preop got 16Gy boost. Same LC (93%) and DM(25%). No difference in OS. More temporary wound healing problems with preop (35 vs 15%), but more late fibrosis with postop.

Retroperitoneal sarcoma
- Mendenhall 2005: review of lit. GRT in ~50%, but close margins. Most faily locally. 5 yr LC 50%, OS 50%.

Technique
- Postop (3-8wks postop)
  - CTV is tumor bed, edema, and scar (3-6cm longitudinally and 2cm radially) to 50 Gy
  - Boost tumor bed +2cm
    - 60-66Gy for R0
    - 66-68Gy for R1
    - 70-76Gy for R2
- Preop (3-6 weeks preop)
  - 50 Gy to large volume
  - 16-18 Gy PORT for R1
  - 20-26 Gy PORT for R2
- Unresectable disease to 75Gy
- No ENI

NCCN
- Stage I: surgery alone, consider RT for +margin (cat 2b)
- Stage II-III:
  - Surgery + PORT
  - PreopRT + surgery
  - Preopchemo cat 2b
- Retroperitoneal sarcoma: surgery+PORT (cat 2b for preopRT), same doses
Desmoid Tumor

Overview
- 900 cases/yr
- Benign, fibroblastic neoplasms
- Don’t metastasize
- Assoc with APC gene mutation
- More common in women, abdominal wall
- Workup: H&P, MRI, bx to rule out STS
- Eval for Gardner’s syndrome or FAP

Surgery
- Goal is 2cm margin
- R0: 15% LR
- R1: 26% LR
- Crago 2013: R1 resection → observed. Did well.

RT dose
- RT alone: 22% LR (Nuyttens 2000)
- Nuyttens 2000: dose >50Gy (50-56) for GTV, post op
- Margin similar to STS

Medical options
- Tamoxifen, NSAIDs, MTX, imatinib

NCCN
- Observe
- Resect
  - R0: observe
  - R1: observe (Crago 2013) or reresect
  - R2: reresect or RT (50 Gy) or obs
- RT (56-58Gy) or systemic therapy

Notes
Palliative
Brain Metastases

- **Background**
  - Most common brain tumor (30% of cancer pts)
  - Solitary vs single
  - Lung>breast>melanoma>others
  - Hemorrhagic: RCC, choriocarcinoma, melanoma

- **Workup**
  - H&P, MRI, rule out infection, steroids for neuro sympx (4mg Q6H)
  - Only anticonvulsants if seizure (Glantz 2000 guidelines)
  - Identify primary (CT C/A/P), KPS

- **WBRT+Surgery?**
  - Patchell #1 (1990): solitary brain mets: 36/12 WBRT +/- preRT surgery. Surgery+RT won. ↑survival, ↑LC, ↓neurologic death, ↑functional status. 6 out of 60 patients were excluded (noncancerous tumor)
  - EORTC 22952: surgery or SRS +/- 30/10 WBRT: similar findings to Patchell #2

- **WBRT+SRS?**
  - Andrews 2004: 1-3 mets, KPS>70: 37.5/15 WBRT +/- SRS (15-24 Gy): same findings as Patchell #1 (↑survival, ↑KPS, ↑LC)
  - RTOG 9508: 1-3 mets, <4cm: WBRT +/- SRS boost: SRS ↑ OS (4.9→6.5m) for single met, but not for >1 met

- **SRS alone**
  - JROSG 99-1: 1-4 mets, KPS>70: SRS +/- 30/10 WBRT: same findings as Patchell #2
  - Chang 2009: 1-3 mets, KPS>70, STS +/- 30/12 WBRT: whole brain ↑LRC, but ↓neurocognitive and ↓OS (15.2→5.7 months)

- **Fractionation**
  - RTOG whole brain fractionation papers (6901, 7361): outcomes were the same for 30-40/20-15, worse for 10/1 and 15/2
  - RTOG 7606, 9104: WBRT escalation to ~50 Gy provided no benefit
  - NCCN WBRT: 30-45 Gy in 1.8-3 Gy/fx (20/5 for ↓KPS)
  - WBRT reirradiation: 20/5
  - SRS fractionation: RTOG 9005 (Shaw):
    - ≤20mm → 24 Gy
    - 21-30mm → 18 Gy
    - 31-40mm → 15 Gy

- **Sim/planning**
  - Supine, short mask, opposed laterals, flash skin
  - Block: orbits, nasal cavity, C2 (include temporal fossa)
  - 5% risk of symptomatic necrosis with SRS
  - 50% of neurocognitive dysfunction with WBRT by formal testing

- **NCCN**
  - 1-3 mets:
    - Surgery +WBRT (category 1, can do SRS if single met)
    - Surgery + SRS boost
    - SRS +/- WBRT (category 2b)
    - WBRT alone for ↓KPS for disseminated systemic disease
  - 4+ mets:
    - WBRT +/- SRS
    - SRS +/- WBRT for ↑KPS
Cord Compression1-5,417-421

- **Background**
  - Usually lung, breast, prostate, RCC, lymphoma, myeloma
  - Batson venous plexus: drains from pelvis directly into spine
  - Epidural vs intradural vs intramedullary

- **Workup**
  - H&P, sensation, motor, bowel/bladder, gait
  - Steroids (dexamethasone 10mg IVx1 then 4-6mg Q6H)
  - Surgical consult for stability, possible debulking/fixation
  - MRI C/T/L spine (20% have additional tumors), bx if needed
  - CT if concern for bony retropulsion
  - CT myelogram if MRI contraindicated
  - Surgery = 360 degree decompression with stabilization (not laminectomy)

- **Steroids**
  - Vecht 1989: loading dose 10mg IV vs 100mg IV. Both went on to 16mg daily. No difference

- **Trials**
  - Patchell 2005: 30Gy vs surgery + 30Gy. All +steroids, one lesion, no cauda equine, >3m life expectancy, paralyzed<48 hrs, not radiosensitive. Stopped early, surgery won. Regained ambulation 19→62%, sustained ambulation 13→122 days, OS 100→126 days
  - Rades 2005: retrospective. 8/1 vs 30/10 (no surgery). No differences in motor fxn or stability. 34% regained ambulation
  - Rades 2009: nonrandomized. 1-5 fx vs 10-20 fx. Long course won. 1 yr LC 61→81%. Motor function and OS unchanged overall, but improved for ↑KPS, ↓disease
  - Rades 2008: retrospective: reirradiation for cord compression: no myelopathy if BED<100Gy total

- **SBRT for vertebral body mets (not cord compression)**
  - Gerzsten: 12.5-25Gy x1. Mostly reirradiations. 86% improvement in pain, LC 90%

- **Sim/planning**
  - Cervical: laterals. Others: usually AP/PA
  - +/- 1 vertebral body
  - 30/10, 20/5, 8/1

- **NCCN**
  - Dexamethasone 4mg Q6H minimum
  - Debulking/fixation if solitary site with >3m life expectancy, paraplegia < 24 hrs, not hematologic cancer, or if unstable
  - Postop RT 1-3 weeks postop
  - Chemo for hematologic cancers
  - Consider SBRT if no cord compression

Bone Metastases1-5,422-428

**Overview**
- Sites: spine > pelvis > ribs > femur > skull

**Surgery**
- Mirels 1989: scoring system for fx
- VanderLinden 2004: femur cortical involvement >30mm and/or circumferential >50% predict for fx

**EBRT**
- RTOG 9714: breast and prostate bone mets → 8x1 vs 30/10. Pain CR/PR same (15%/50%). More tox with 30/10, more retreatment with 8x1 (9 vs 18%)
- Bone pain trial working party: 8x1 vs 20/5 vs 30/10. Same effectiveness. More reRT with 8x1 (23 vs 10%)
- Chow 2007: metaanalysis. No differences except 2.5x increase in retreatment if 8x1

**Radiopharmaceuticals**
- Radium-223 (α):
  - ALSYMPCA: Ra223 improved OS (11→14.9m) over placebo

**PORT**
- Townsend 1994: PORT reduced need for 2nd surgery (15→2%) and improved faster

**SRS**
- Gerstzen 2007: retrospective, median 20Gy x1. Improved pain in 86%, LC 90%
Physics and Radiobiology
Physics
## Brachytherapy Sources

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$\tau$</th>
<th>Energy</th>
<th>Decay Mechanism</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{103}$Pd</td>
<td>17 days</td>
<td>21 keV photons (avg)</td>
<td>Electron capture</td>
<td>Prostate LDR</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>60 days</td>
<td>28 keV photons (avg)</td>
<td>Electron capture</td>
<td>Prostate LDR, Eye plaque</td>
</tr>
<tr>
<td>$^{131}$Cs</td>
<td>9.7 days</td>
<td>30 keV photons (avg)</td>
<td>Electron capture</td>
<td>Prostate LDR</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>6 hrs</td>
<td>140 keV photons</td>
<td>Gamma</td>
<td>SPECT, Bone scan</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8 days</td>
<td>364 keV photons (avg)</td>
<td>Beta -</td>
<td>Thyroid ablation</td>
</tr>
<tr>
<td>$^{192}$Ir</td>
<td>74 days</td>
<td>380 keV photons (avg)</td>
<td>Beta -</td>
<td>HDR or LDR</td>
</tr>
<tr>
<td>$^{198}$Au</td>
<td>2.7 days</td>
<td>412 keV photons</td>
<td>Beta -</td>
<td>Prostate LDR, Eye plaque (Historical)</td>
</tr>
<tr>
<td>$^{90}$Sr</td>
<td>28 yrs</td>
<td>$546$ keV $\beta$ (max, mean $\sim 1/3$)</td>
<td>Beta -</td>
<td>Source of $^{90}$Y, Opthalmic applicator, Intravascular</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 min</td>
<td>633 keV positrons</td>
<td>Beta +</td>
<td>PET, annihilation 511 keV photons x 2</td>
</tr>
<tr>
<td>$^{137}$Cs</td>
<td>30 yrs</td>
<td>660 keV photons</td>
<td>Beta -</td>
<td>GYN Brachy, LDR</td>
</tr>
<tr>
<td>$^{226}$Ra</td>
<td>1622 yrs</td>
<td>830 keV photons (avg)</td>
<td>Alpha</td>
<td>GYN Brachy, LDR (Historical)</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>11.4 days</td>
<td>5.8 MeV $\alpha$</td>
<td>Alpha</td>
<td>Xofigo</td>
</tr>
<tr>
<td>$^{222}$Rn</td>
<td>3.8 days</td>
<td>830 keV photons (avg)</td>
<td>Alpha</td>
<td>Environmental hazard, Radium daughter</td>
</tr>
<tr>
<td>$^{5.5}$MeV alpha</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{60}$Co</td>
<td>5.3 yrs</td>
<td>1.25 MeV photons (avg)</td>
<td>Beta -</td>
<td>Teletherapy</td>
</tr>
<tr>
<td>$^{40}$K</td>
<td>$10^9$ yrs</td>
<td>1.3 MeV $\beta$ (max, mean $\sim 1/3$)</td>
<td>Beta -</td>
<td>Small ams commonly found in nature, animals, bananas, etc.</td>
</tr>
<tr>
<td>$^{89}$Sr</td>
<td>50 days</td>
<td>1.5 MeV $\beta$ (max, mean $\sim 1/3$)</td>
<td>Beta -</td>
<td>IV tx of bone mets</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>14.3 days</td>
<td>1.7 MeV $\beta$ (max, mean $\sim 1/3$)</td>
<td>Beta -</td>
<td>IV tx of bone mets, Polycythemia vera, Intravascular</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>2.7 days</td>
<td>2.3 MeV $\beta$ (max, mean $\sim 1/3$)</td>
<td>Beta -</td>
<td>Theraspheres, SIR-Spheres</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Release with instructions if activity $&lt;$</th>
<th>Release with instructions if dose rate at 1m $&lt;$</th>
<th>Release without instructions if activity $&lt;$</th>
<th>Release without instructions if dose rate at 1m $&lt;$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{125}$I</td>
<td>9 mCi</td>
<td>0.01 mSv/h</td>
<td>2 mCi</td>
<td>0.002 mSv/h</td>
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<tr>
<td>$^{103}$Pd</td>
<td>40 mCi</td>
<td>0.03 mSv/h</td>
<td>8 mCi</td>
<td>0.007 mSv/h</td>
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<tr>
<td>$^{192}$Ir</td>
<td>2 mCi</td>
<td>0.008 mSv/h</td>
<td>0.3 mCi</td>
<td>0.002 mSv/h</td>
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<tr>
<td>$^{131}$I</td>
<td>33 mCi</td>
<td>0.07 mSv/h</td>
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</table>
### Radiobiology

<table>
<thead>
<tr>
<th>Marker</th>
<th>Classic association</th>
<th>Also seen in</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>HCC, NSGCTs</td>
<td>GI, pregnancy, cirrhosis</td>
</tr>
<tr>
<td>β2microglob</td>
<td>Myeloma</td>
<td>Bcell, lung, breast, bone dz</td>
</tr>
<tr>
<td>CA-125</td>
<td>Ovarian</td>
<td>GYN, breast, lung, abdominal</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Breast</td>
<td>Ovary, lung prostate</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreas, bile duct</td>
<td>Abdominal</td>
</tr>
<tr>
<td>CA 27.29</td>
<td>Breast</td>
<td>Various</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Medullary duct</td>
<td>Various</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal</td>
<td>Various</td>
</tr>
<tr>
<td>Neuron-enolase</td>
<td>Neuroblastoma, SCLC</td>
<td>Wilms, melanoma, thyroid, testicle, Merkel cell</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate</td>
<td>Benign GU</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Thyroid (non-MTC)</td>
<td>Benign thyroid</td>
</tr>
<tr>
<td>βHcG</td>
<td>NSGCTs</td>
<td>pregnancy</td>
</tr>
</tbody>
</table>

#### Dose Limits (1rem = 0.01mSv)

<table>
<thead>
<tr>
<th></th>
<th>Per year</th>
<th>Per hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occupational</strong></td>
<td>50 mSv</td>
<td>0.02mSv</td>
</tr>
<tr>
<td><strong>Fetus</strong></td>
<td>0.5 mSv/month</td>
<td></td>
</tr>
<tr>
<td><strong>Public cont exposure</strong></td>
<td>1 mSv</td>
<td></td>
</tr>
<tr>
<td><strong>Public intermittent exposure</strong></td>
<td>5 mSv</td>
<td></td>
</tr>
</tbody>
</table>

Background radiation: 2.5 mSv/yr

#### Acute TBI

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>Observe</td>
</tr>
<tr>
<td>2-5</td>
<td>Prodrome, latency, cytopenias?</td>
</tr>
<tr>
<td>5-10</td>
<td>Hospitalize, hypotension?</td>
</tr>
<tr>
<td>10-20</td>
<td>GI syndrome, FATAL</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Cerebrovasc syndrome, FATAL</td>
</tr>
</tbody>
</table>

#### Translocation and Cancer

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(2:13)</td>
<td>Alveolar Rhabdo</td>
</tr>
<tr>
<td>t(8:14)</td>
<td>Burkitts, Bcell ALL</td>
</tr>
<tr>
<td>t(11:14)</td>
<td>Mantle cell (BCL1, cyclin D1)</td>
</tr>
<tr>
<td>t(11:22)</td>
<td>Ewings, PPNET</td>
</tr>
<tr>
<td>t(12:22)</td>
<td>Clear cell sarcoma</td>
</tr>
<tr>
<td>t(14:18)</td>
<td>Follicular, DLBCL (BCL2)</td>
</tr>
<tr>
<td>t(14:19)</td>
<td>CLL (BCL3)</td>
</tr>
<tr>
<td>t(X:18)</td>
<td>Synovial cell sarcoma</td>
</tr>
</tbody>
</table>

#### Radiation LET (keV/µm)

<table>
<thead>
<tr>
<th>Radiation Type</th>
<th>LET (keV/µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 MeV α</td>
<td>150</td>
</tr>
<tr>
<td>1 GeV Fe ions</td>
<td>150</td>
</tr>
<tr>
<td>14 MeV neutrons</td>
<td>100</td>
</tr>
<tr>
<td>250 kV Xrays</td>
<td>2</td>
</tr>
<tr>
<td>150 MeV protons</td>
<td>0.5</td>
</tr>
<tr>
<td>²⁶Co γ</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Statistics


99. Chen AM, Bucci MK, Quivey JM, Garcia J, Eisele DW, Fu KK. Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinoma.


PL03.05 An intergroup randomized phase III comparison of standard-dose (60 Gy) vs high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (cetux) for stage III non-small cell lung cancer (NSCLC): results on cetux from RT06 0161. *Clin Adv Hematol Oncol.* 2014;12(1 Suppl 1):2-4.


286. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-


