Management of Pediatric Malignancies

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Disclosure

• I have no conflicts of interest to disclose.
Learning Objectives

• Define the current standard of care for pediatric brain tumors and sarcomas.
• Describe the controversies in the management of Hodgkin lymphoma, Wilms tumor and neuroblastoma.
• Interpret the risks and benefits of radiotherapy in the treatment of retinoblastoma.
Distribution of common pediatric malignancies

- Leukemia: 31%
- Wilms' Tumor: 6%
- Lymphoma: 14%
- Neuroblastoma: 7%
- Germ Cell: 3%
- Central Nervous System: 18%
- Soft Tissue: 6%
- Other: 7%
- Bone: 5%
- Eye: 3%
- Other: 7%
Pediatric Cancer Cure Rates

The graph illustrates the cure rates for different types of cancers in the 1960s and 1990s. The categories include All cancers, Bone sarcomas, and Soft tissue sarcomas. The bars show a significant increase in cure rates for all categories, particularly for Bone sarcomas and Soft tissue sarcomas, indicating improved treatment outcomes over the decades.
Medulloblastoma

- 10-20% of pediatric brain tumors
- ~300 patients diagnosed annually in U.S.
- Peak incidence 5 to 7 years
- 2:1 male-to-female ratio
- Usually arises in midline of cerebellar vermis and grows anteriorly into 4th ventricle
Medulloblastoma pathology

- Classic
- Large cell anaplastic
- Desmoplastic nodular
Molecular genetics

- SHH activation
  - Cerebellar hemisphere
  - DN & LCA histology
  - Infants
- WNT mutations
  - Dorsal brainstem
  - Classic histology

Gibson et al. Nature 2010; 468:1095
Presentation

- Vomiting (67%), headache (60%), ataxia (40%), and nausea (39%)
- 80% have hydrocephalus due to obstruction of 4th ventricle
- 30% disseminated disease at diagnosis (incidence higher in children < 3 years); usually involves spinal subarachnoid space
Medulloblastoma work-up

- MRI with contrast of entire neural axis
- Lumbar puncture
Staging

- **Chang “M” stage**
  - **0**: no dissemination
  - **1**: positive cytology
  - **2**: intracranial nodules
  - **3**: spinal nodules
  - **4**: extra-neural disease

- **Average risk**:
  - age $\geq$ 3 years
  - $< 1.5 \text{ cm}^2$ residual
  - M0 stage

- **High risk**:
  - age $\leq$ 3 years
  - $\geq 1.5 \text{ cm}^2$ residual
  - M+ stage
Old standard: surgery + RT

- 36 Gy craniospinal + posterior fossa boost to 55.8 Gy
- 5 year EFS for standard risk patients treated with RT alone or RT + non-cisplatin chemotherapy ~ 60%
- Survivors have high risk of late effects due to RT: growth, neurocognitive, endocrine, 2nd cancers
- Risk highly correlated to patient age and RT dose
Can you decrease CSI dose?  
CCG-923

- 1986-90, 81 average risk patients
- 23.4 Gy vs 36 Gy CSI alone
- closed early due to relapses in 23.4 Gy arm
- 5-year EFS 67% vs 52% (P=0.08)

Thomas et al. JCO 2000;18:3004
Packer regimen: single arm trial

- 1983-93, 63 patients age 2-21
- Sub-total resection (19), brainstem inv (42), and/or M-1+(15)
- CSI (36 Gy, 23.4 Gy if < 5 years) + PF boost
- Add vincristine, cisplatin, lomustine
- 5 yr PFS 83% (M-0 90% vs M-1+ 67%)

CCG-9961 phase III trial

- 379 patients 3-21 yo, < 1.5 cm², M-0
- 23.4 Gy CSI + PF boost to 55.8 Gy
- Weekly vincristine, then:
  - Randomized: vincristine-cisplatin-lomustine vs vincristine-cisplatin-cyclophosphamide
  - No difference in chemo regimens
- 5 year EFS = 81%, survival = 86%

Packer et al. JCO 2006;24:4202
Current standard of care

Surgery

< 3 yo

High dose CT

~ 50% EFS

> 3 yo

Average-risk
- M0, and
- < 1.5 cm² residual

23.4/55.8 CSI + CT

~ 80% EFS

High-risk
- M+, or
- ≥ 1.5 cm² residual

36/55.8 CSI + CT

~ 65% EFS
Can we reduce boost volume?

Severe ototoxicity 25-50% due to cisplatin + RT

- 32 consecutive MKSCC patients (5 high risk)
- Boost to tumor bed plus 1.5 cm margin
- 28 received chemotherapy
- 20 treated with 3D RT, 12 with IMRT
- 5 year EFS 84%
- One isolated PF failure outside boost field

Wolden et al. JCO 2003;21:3079
Whole posterior fossa

Tumor bed
## Normal tissue sparing

<table>
<thead>
<tr>
<th></th>
<th>Lateral fields treating posterior fossa</th>
<th>Conformal therapy treating tumor bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning target volume</td>
<td>102%</td>
<td>105%</td>
</tr>
<tr>
<td>Cochlea</td>
<td>104%</td>
<td>43%</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>84%</td>
<td>48%</td>
</tr>
<tr>
<td>Parotid glands</td>
<td>71%</td>
<td>10%</td>
</tr>
<tr>
<td>Pituitary &amp; hypothalamus</td>
<td>35%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Boost techniques

2D

3D

IMRT
Dose volume histogram for cochlea

Anat:EARIN_L
Proton therapy
IMRT Update

- 33 consecutive patients
  - Standard-risk
    23.4 Gy CSI w/ boost to 55.8 Gy, or
    IT $^{131}$I-3F8, 18 Gy CSI w/ boost to 54 Gy
  - High-risk
    36 or 39.6 Gy CSI w/ boost to 55.8 Gy
- Concurrent vincristine, then standard cisplatin-based chemotherapy
- Pre- and post-treatment audiograms available for 31 patients

Polkinghorn et al. IJROBP 2011;81:e15
Patterns of Failure

- Posterior fossa failure w/in boost field, n=2
- Distant failure, n=2
- Combined PF and distant failure, n=3

_No isolated posterior fossa failures outside of the boost volume_
## Cochlear Dosimetry

<table>
<thead>
<tr>
<th>Cohort Group</th>
<th>Mean dose (Gy)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Risk (18.0/54.0 Gy)</td>
<td>38.6</td>
<td>± 3.1</td>
</tr>
<tr>
<td>Standard Risk (23.4/55.8 Gy)</td>
<td>40.6</td>
<td>± 4.7</td>
</tr>
<tr>
<td>High Risk (36 or 39.6/5580 Gy)</td>
<td>49.1</td>
<td>± 4.6</td>
</tr>
</tbody>
</table>
Ototoxicity

Grade 3: 6%
Grade 4: 0
Median f/u: 19 mo
Current COG Study: Average Risk MB

Children, ages 3-7:
- Randomize #
  - Reduced-Dose Craniospinal Radiation
    - Randomize #
      - Smaller Volume Boost (Radiation to tumor Bed)
        - Maintenance Chemotherapy 9 Cycles
  - Standard Volume Boost (Radiation to the entire posterior fossa)

Children, age 8 and older:
- Randomize #
  - Standard-Dose Craniospinal Radiation
CNS germ cell tumors

- In West, 3-11% of pediatric brain tumors
  - Higher incidence in Japan and Far East
- Most common in 2\textsuperscript{nd} - 3\textsuperscript{rd} decade of life
- Male : female ratio 2:1
- Primary sites: Pineal and suprasellar region
  - 5-10% of GCT present in both sites
Pineal germinoma
Suprasellar non-germinoma GCT
Classification of Intracranial GCT

- Germinoma
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma
- Teratoma
  - Immature
  - Mature
- Mixed Germ Cell

Most common: 2/3 of cases

Non-germinoma GCT
1/3 of cases
Diagnosis

Parinaud’s syndrome, diabetes insipidus, elevated ICP

Historically, patients received empirical trial of radiotherapy

Modern techniques now allow safe biopsy

MRI brain + spine; CSF cytology

Tumor markers: serum & CSF

<table>
<thead>
<tr>
<th>Table 2. Cerebrospinal fluid markers in germ cell tumors</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Germinoma (Pure)</td>
</tr>
<tr>
<td>Germinoma (syncytiotrophoblastic)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Mixed germ cell</td>
</tr>
<tr>
<td>Endodermal sinuia</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
</tbody>
</table>

Legend β-HCG= beta-human-chorionic gonadotropin
α-FP= alpha-fetoprotein
PLAP= placental alkaline-phosphatase

Packer et al. Oncologist, 2000; 5312.
Parinaud Syndrome

- Paralysis of upward gaze
- Convergence nystagmus
- Light-near pupil dissociation
- Lid retraction (Collier’s sign)
Management of CNS Germinoma

- Radiation alone is gold-standard
- 5-yr PFS 85-95%; OS 90-98%
- CSI not necessary for isolated disease
- Whole ventricle prophylaxis is!
- High dose chemotherapy: 50% fail
- No clear role for chemotherapy
- Recommendation:
  - 25 Gy whole ventricle (CSI if CSF+)
  - 45 Gy to gross disease

Haas-Kogan et al. IJROBP, 2003; 56(2)511.
Non-germinoma germ cell tumors

- Poor prognosis: 5 year PFS 50-60%; OS 60-70%

- Require intensive chemotherapy, surgery and RT
  - Local failure common: second look surgery recommended

- RT fields controversial: CSI versus whole ventricle
  - Pattern of failure same as germinoma: favors whole ventricle
  - COG protocol ACNS0122: 36 Gy CSI, boost to 54 Gy
Craniopharyngioma

- 6-9% of pediatric brain tumors, peak age 10
- Benign, arises from pharyngeal cell rests
- Presentation:
  - Short stature, hydrocephalus, vision loss, *not* DI
- Best treatment: subtotal resection + 54 Gy
  - Results in control rate of 75-80%
  - Total resection associated with increased late morbidity and equivalent control rates
  - May treat post-operative GTV + margin
Craniopharyngioma
**Common pediatric sarcomas**

- Rhabdomyosarcoma
- Non-rhabdo soft tissue sarcomas
  - Synovial most common
- Ewing sarcoma
- Osteosarcoma
- Desmoplastic small round cell tumor
Rhabdomyosarcoma

- The most radiosensitive sarcoma
- 350 cases annually in the U.S
  - Two-thirds of cases are in children under age 7
- Majority of patients receive RT
RMS: molecular biology

Gene Fusions with Novel Chimeric Protein Products

\[
\text{t}(2;13)(q35;q14)
\]

Activation of aberrant gene program

Chromosome 2

Chromosome 13

(or pax7 chr 1)

Malignant transformation

• Embryonal tumors may have LOH at 11p15, encodes for IGF II

Distribution by primary site

- Head and Neck (10%)
- Parameningeal (16%)
- Genitourinary (24%)
- Extremities (19%)
- Other (22%)
- Orbit (9%)
RMS: Patterns of spread

• Distant metastases, $<\frac{1}{4}$ at presentation
  – lungs, bone marrow, and bone

• Regional lymph nodes varies by site
  – 0-1% for orbit
  – 30% for paratesticular and extremity

Lawrence et al. Cancer 60:910, 1987
IRSG post-surgical grouping

- Group I: Localized disease, completely resected
- Group II: Positive microscopic margins or resected regional disease
- Group III: Gross residual disease
- Group IV: Distant metastases
# RMS: pretreatment staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>Size</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit, H/N (not PM), GU (not B/P)</td>
<td>all</td>
<td>N0 or N1</td>
</tr>
<tr>
<td>2</td>
<td>B/P, Extremity, PM, Other</td>
<td>&lt;5cm</td>
<td>N0</td>
</tr>
<tr>
<td>3</td>
<td>B/P, Extremity, PM, Other</td>
<td>&lt;5cm &gt;5cm</td>
<td>N1 N0 or N1</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>any</td>
<td>M1</td>
</tr>
</tbody>
</table>
Survival by treatment era

- 1960's: 20%
- IRS-I: 50%
- IRS-II: 60%
- IRS-III: 70%
- IRS-IV: 80%
IRS IV (1991-1997)

• Radiation Guidelines:
  – Dose:
    • Group I, Stage 1/2: no RT. Group I, Stage 3 / II: 41.4 Gy
    • Group III randomized to 50.4 Gy CRT vs 59.4 Gy HRT (1.1 Gy BID)
  – Volume: GTV + 2cm
  – Timing: Day 0 PM with CN palsy, BOS erosion, ICE. Week 12 for others
Failure-free survival of patients with local/regional RMS on IRS-IV by chemotherapy regimen

Log Rank Test: p=0.52
Failure-free survival of patients with Group III tumors by radiation schedule

Log Rank Test: p=0.76
Failure-free survival for local/regional tumors by primary site

Log Rank Test: p<0.001
IRS IV (1991-1997)

• 5-yr local control for Group III RMS
  – Extremity 96%
  – Orbit 95%
  – Bladder/prostate 90%
  – Head and neck 88%
  – Parameningeal 84%
  – Other 90%.

Crist et al. JCO 19:3091, 2001
Donaldson et al. IJROBP 51:718, 2001
IRS V (1999-2004)

- Experimental dose reductions:
  - Group I alveolar/undifferentiated 36 Gy
  - Group II N0: 36 Gy
  - Group III orbit/eyelid: 45 Gy
  - Group III second look surgery
    - negative margins: 36 Gy
    - microscopically + margins: 41.4 Gy
  - Group III requiring 50.4: volume reduction to initial GTV + 5 mm at 36 Gy if N0, and at 41.4 Gy if N+
COG Int risk: ARST0531 (ongoing)

- Randomized VAC vs VAC / V + Irinotecan
- Early radiotherapy for all patients at week 4
  - attempt to improve local & possibly distant control
  - allow radiotherapy deviation for infants < 2 years
- Concurrent Irinotecan with radiotherapy
  - potential for radiosensitization
  - pilot data from ongoing MSKCC trial
- PET scans for staging and response evaluation
COG ARST0531: V/CPT-11 arm:

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</table>

Radiotherapy

<table>
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<th>Week</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
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<td>A</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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</tbody>
</table>

EVAL
# Dose according to Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Localized disease, completely resected with negative margins</td>
<td>36</td>
</tr>
<tr>
<td>II</td>
<td>Positive microscopic margins or resected regional disease</td>
<td>36 (N0) 41.4 (N+)</td>
</tr>
<tr>
<td>III</td>
<td>Gross residual disease</td>
<td>50.4</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>As above</td>
</tr>
</tbody>
</table>
SIOP Experience: MMT 89

- 503 nonmetastatic RMS patients treated 1989-95
- Goal to avoid radiotherapy
- Variety of 1\textsuperscript{st} and 2\textsuperscript{nd} line chemotherapy regimens
- OS = 71%
- EFS 57%
- 49% cured without significant local therapy

Stevens et al. JCO 23:2618, 2005
<table>
<thead>
<tr>
<th></th>
<th>MMT 89 5 year % rate</th>
<th>IRS IV 5 year % rate</th>
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<tbody>
<tr>
<td></td>
<td>OS</td>
<td>EFS</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>57</td>
</tr>
<tr>
<td>Alveolar</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Embryonal</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Orbit</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>64</td>
<td>35</td>
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<tr>
<td>Extremity</td>
<td>46</td>
<td>35</td>
</tr>
</tbody>
</table>

Donaldson et al. JCO 23:2586, 2005
FDG-PET scan staging
MSKCC experience

- All primary tumors PET positive
  - SUV 4.0 - 12.7
- For all sites:
  - sensitivity 81%
  - specificity 97%
- Therapy altered in 14% cases
  - LN + detected only on PET

Pre-treatment PET scan
Local Control by Pre-RT PET

- PET Negative
  - LC = 97%
- PET Positive
  - LC = 81%

$p = 0.06$
Local Control by First Post-RT PET

- PET Negative
  - LC = 94%
- PET Positive
  - LC = 75%

\[ p = 0.02 \]
Infratemporal fossa with PM extension
Parameningeal RMS: Dose Comparison (IMRT v Protons)  
(Kozak, Yock, *IJROBP*)

Results:

- Improved dose conformality of protons spared most normal tissues examined except for a few ipsilateral structures such as the parotid and cochlea.
Interstitial tongue brachytherapy
Electron for eyelid RMS
Non-rhabdo soft tissue sarcomas (NRSTS) are more common in children and adolescents

550-600 cases/yr (61%)

~350 cases/yr (39%)

SEER Program 1975-1995, NCI
NRSTS predominates in older pediatric age groups

SEER Program 1975-1995, NCI
COG ARST0032: low grade NRSTS

Definitive surgical resection

Clinical Group I

No RT

Clinical Group II

Would local recurrence result in significant morbidity?

No

No RT

Yes

RT 55.8 Gy
COG ARST0032: high grade NRSTS

Definitive surgical resection

Tumor ≤ 5cm

Margins ≥ 1 cm or unbroken fascial plane?

yes → No RT

no → RT 55.8 Gy

Tumor > 5cm

RT 55.8 Gy + Ifos/Doxo x5
Ewing sarcoma family of tumors

- 300 cases per year in U.S.
  - Most common in second decade (10-20 years)
  - Arises from bone or soft tissue
  - Classic EWS-FLI1, t(11;22)
  - Extremely rare in children of African or Chinese ethnicity
- Relatively radiosensitive
- Role of RT not as well studied as in RMS
- Patients may have surgery, RT or a combination
Radiation therapy for Ewing sarcoma
MSKCC results 1990-2004

• 60 patients received primary site RT
  – 31 RT alone
  – 26 Post-op RT
  – 3 Pre-op RT

• All had VACIE (EFT chemotherapy regimen)
• Median age 16 (2-40) years
• Median follow-up 41 months

La, Wolden et al. IJROBP 64:544, 2006
Local control: localized vs. metastatic disease

![Graph showing probability vs. years for localized and metastatic disease](image)

- Localized: $p = 0.036$
- Metastatic: $p = 0.036$

The graph illustrates the difference in probability of local control between localized and metastatic disease, with a statistically significant difference at $p = 0.036$.
Disease free survival by tumor size

![Graph showing disease free survival by tumor size. The graph compares survival rates for tumors less than 8 cm and 8 cm or greater. The survival rates are significantly different with a p-value of less than 0.001.](image-url)
Survival with localized vs. metastatic disease

![Graph showing survival probabilities for localized and metastatic diseases. The graph indicates a significant difference in survival probability with p < 0.001.](image-url)
Intergroup Ewing sarcoma studies (IESS)

- Three options for local control:
  - Surgery alone if margins negative
  - 45-50.4 Gy post-op if margins are <5mm
  - 55.8 Gy definitive RT
    - Margins have decreased from whole bone or muscle bundle to 5cm and now to 2 cm
- Local failure is approximately 10%
Local progression in pelvic Ewing sarcoma by surgery, RT, or both

Fig 1. Cumulative incidence of local progression by the surgery alone, radiation alone, and combined surgery plus radiation.

Yock et al, JCO 24:3838, 2006
Event free survival in pelvic Ewing sarcoma by surgery, RT, or both

Fig 2. Event-free survival in patients by surgery alone, radiation alone, and surgery and radiation combined.

Yock et al, JCO 24:3838, 2006
Cooperative Ewing sarcoma study (CESS 81, 86, EICESS 92)

- Local control best with surgery >90%
- RT local control 74% - NEGATIVELY SELECTED!
- Equivalent EFS, OS

Ewing Sarcoma: Askim Tumor + Whole Lung IMRT
Osteosarcoma

- Relatively radioresistant: requires high dose

- RT for unresectable osteosarcoma at MGH
  - 56% received protons with doses up to 80 Gy
  - 5 year LC = 78% after incomplete resection
  - 5 year LC = 40% after biopsy only

DeLaney et al. IJROBP 61(2):492, 2005
Desmoplastic small round cell tumor (DSRCT)

- Aggressive abdominal tumor in young men
- Peritoneal seeding, similar to ovarian cancer
DSRCT Histology

H & E

Vimentin

Cytokeratin

Desmin
Molecular Genetics

• Specific recurrent chromosomal abnormality

• t(11;22)(p13;q12)

• Translocation of 2 genes associated with other malignancies
Multimodality Treatment Results

- Intensive P6 chemotherapy
- Maximal surgical debulking
- +/- Stem cell transplant
- WAPRT: 30Gy in 1.5Gy fractions

- 20 patients 1992-2000
- Median age 17; 95% male

Disease Free Survival

4-year DFS = 14%
Median time to relapse = 21 mos
Whole abdomen-pelvis IMRT
Pediatric sarcoma conclusions

• Radiation plays a critical role: maximize cure with preservation of form and function
• Future challenges for radiation oncology
  – further improvement in local control
  – reduction of late-effects
  – prevent nodal and distant metastases
• Radiation therapy must be individualized
  – new technologies promising but not always better
Neuroblastoma

- Arises from embryonal neuroblasts of sympathetic peripheral nervous system
- Adrenal/abdomen most common site
- 7.2% (SEER); ~650 cases per year
- 10.2 per million children <15yrs
- Most common malignancy < 1yr
- Male = Female
Neuroblastoma
# Metastatic sites

## Stage 4

<table>
<thead>
<tr>
<th>Disease localization</th>
<th>Initial</th>
<th>1st recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>bone marrow</td>
<td>87.3</td>
<td>35.2</td>
</tr>
<tr>
<td>bone</td>
<td>66.1</td>
<td>46.6</td>
</tr>
<tr>
<td>lymph nodes</td>
<td>18.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Liver</td>
<td>17.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Skin</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial/cerebral</td>
<td>9.1</td>
<td>19.0</td>
</tr>
<tr>
<td>lung/pleura</td>
<td>4.7</td>
<td>3.1</td>
</tr>
<tr>
<td>paratesticular</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.3</td>
<td>0</td>
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<tr>
<td>Isolated local recurrence</td>
<td></td>
<td>17.0</td>
</tr>
<tr>
<td>Isolated metastatic recurrence</td>
<td></td>
<td>58.1</td>
</tr>
<tr>
<td>Combined local and metastatic</td>
<td></td>
<td>24.9</td>
</tr>
</tbody>
</table>
MIBG (I-131-meta-iodobenzylguanidine) scan
## Staging (INSS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Stage 1** | Localized tumor confined to the area of origin.  
GTR +/- microscopic residual disease;  
Regional LN negative (ipsilateral and contralateral)  
Adherent removed LN can be positive |
| **Stage 2A** | Unilateral with incomplete gross resection  
LN negative (ipsilateral and contralateral) |
| **Stage 2B** | Unilateral with complete or incomplete gross resection  
ipsilateral LN positive but contralateral LN negative |
| **Stage 3** | Tumor infiltrating across midline +/- LN or  
unilateral tumor with contralateral LN involvement or  
midline tumor with bilateral LN involvement |
| **Stage 4** | Dissemination of tumor to distant lymph nodes, bone marrow, liver, or other organs except as defined in stage 4S. |
| **Stage 4S** | Localized primary tumor as defined for stage 1 or 2  
with dissemination limited to liver, skin and bone marrow (< 10 % of nucleated marrow cells are tumor cells). |
Stage 4S

1.5 Gy x 3 if life-threatening liver distention
Prognosis

- Stage (4 versus LR/4s)
- MYCN amplification
- Age (infants, 12-18 months, >18 months, adolescents, adults)
- LN only versus bone +/- marrow
- LDH
  - Histology (Shimada)
  - Ferritin
  - 1p36 deletion
  - VMA/HVA
  - Symptomatic
Clinical Stages of Neuroblastoma

- 4s
- 1,2,3
- 4

Stages:
- 4s: Spontaneous cure
- 1,2,3: Surgery
- 4: ???
High risk NB: stage 4, >1 y Age

**Bulk disease**
- Dose intensity
- Surgical debulking

**Minimal Residual Disease**
- Local radiation
- Radioimmunotherapy
- Targeted immunotherapy
- Differentiation therapy
Radiation for high risk NB

- 21 Gy to primary tumor bed after GTR
  - 90% local control
  - 36 Gy boost to gross residual – not effective?
    - Recommended in current COG trial
- RT to residual MIBG + or initially bulky mets
- CSI + boost with RIT for CNS relapse
- Extremely effective palliation of bone disease

Wolden et al, IJROBP 46:969, 2000
Croog et al, IJROBP 78:849, 2010
Stage 4 NB >1y age: outcome

Children’s Oncology Group study 3891

- Autologous SCT
- Cis-retinoic acid

Matthay et al; NEJM. 341: 1165, 1999
Pediatric Hodgkin lymphoma

We have come a long way in the last century.

Where do we go from here?

Photo from Reed et al, 1902
Why do we use lower radiation doses in children?
Late effects

- Growth deficits
  - Clinically nonsignificant with low dose RT
    - Willman et al. IJROBP 28:85, 1994

- Thyroid abnormalities
  - RR hypothyroidism = 17, hyperthyroidism = 8, nodules = 27
    - Sklar et al. J Clin Endocrinol Metab 85:4441, 2000

- Second cancers

- Cardiovascular and Pulmonary Toxicity
  - Outranks 2nd cancers for early mortality
Total Lymphoid Irradiation: 44 Gy standard for most teens until 1990’s
Risk of Congestive Heart Failure Multivariate Analysis

- **Sex:** M (Male), F (Female)
- **Age at Diagnosis:** ≤4, 5-9, 10-14, 15-20
- **Cardiac RT dose (Gy):** 0, 1-5, 6-15, ≥15
- ** Anthracycline (mg/m²):** <250, ≥250

* Adjusted for race, BMI, income, education, smoking, treatment era

Mulrooney BMJ 2009
Risk of Valvular Disease Multivariate Analysis

- Sex
- Age at Diagnosis (yrs)
- Cardiac RT dose (Gy)
- Anthracycline (mg/m²)

P <0.05 * Adjusted for race, BMI, income, education, smoking, treatment era

Mulrooney BMJ 2009
Second cancers
Stanford data 1968-84 (n=1510)

- All Cancers (17.6%)
- Solid Tumors (13.2%)
- Leukemia (3.3%)
- Lymphoma (1.6%)

Tucker et al. NEJM 318:76, 1988
Breast cancer risk by attained age after HD

Bhatia et al, NEJM 334:12, 1996
Excess cancers per 100 patients followed 20 years

Wolden et al. JCO 16:536, 1998
Relative risk of breast cancer by age

Hancock et al, JNCI 85:1, 1993
Wolden et al. JCO16:536, 1998
Do the data support efficacy of lower radiation doses in children?
Stanford, St Jude, Dana-Farber

- Stage I-II favorable
- VAMP x 4

- Response based IFRT
  - Assessed after cycle 2
  - CR: 15 Gy (7%)
  - PR: 25.5 Gy (92%)

- Results
  - 5 year EFS 93%
  - 5 year OS 99%

Donaldson et al. JCO 20:3081, 2002
Do lower doses reduce risk of SMN?

110 patients received 15-25 Gy 1970-90
- 18 developed SMN: cumulative incidence 17%

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>SIR</th>
<th>AER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>4</td>
<td>91</td>
<td>19</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>53</td>
<td>23</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4</td>
<td>89</td>
<td>19</td>
</tr>
</tbody>
</table>

O'Brien et al. JCO 28:1232, 2010
SMN after Low Dose RT (15-25 Gy)

Any SMN

Solid tumor
5 year OS = 85%

Leukemia
5 year OS = 0%

O'Brien et al. JCO 28:1232, 2010
Is radiotherapy necessary in all patients?
German GPOH-HD 95 trial

- 1018 Patients
- OPPA (OEPA) / COPP
- 20-35 Gy IFRT for <CR

- Lowest risk group
  - DFS 94% / OS 99%
  - CR no RT = PR + RT

- Int / high risk groups
  - No difference in survival
  - DFS 69% no RT vs 91% with RT (p = 0.0001)

CCG 5942
829 patients
501 with CR
1995-98

Clinical-Group-Specific Chemotherapy
Group 1: COPP/ABV x 4 courses
Group 2: COPP/ABV x 6 courses
Group 3: Cycle A/Cycle B/Cycle C x 2 courses

Response Evaluation

CR
Randomize
LD-IFRT
No LD-IFRT

PR
Treatment Failure

Physician Choice

Nachman et al. JCO 20:3765, 2002
CCG 5942 Long-term results

EFS 91% vs 83%, p=0.004

OS 97% vs 96%, p=0.5

Wolden et al. JCO (in press), 2012
COG AHOD0431: Low Risk HL

AV-PC* q3 weeks

1 AV-PC* → PET → 2 AV-PC*

CR → No RT → IV-DECA/RT

PR → 21 Gy

relapse → SCT

Eligibility:
• Age ≤21 years
• CS IA-IIA
• No bulk disease or LPHL

Keller, ASH abstract 2010
AHOD0431
Early Stage Favorable HL

- 275 subjects evaluable between 2/2006 and 12/2008
- CR rate after 3 cycles of AVPC = 63.6% (lower than expected)
- Medium follow-up 25 months

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>CR (no IFRT)</th>
<th>PR (+ IFRT)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year EFS</td>
<td>84%</td>
<td>80%**</td>
<td>88%</td>
<td>0.11</td>
</tr>
<tr>
<td>2 year OS</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Study closed by DSMC**
AHOD0431
2 year EFS

- 227 subjects had evaluable PET results after 1 cycle (3 weeks) of chemotherapy (PET1)

<table>
<thead>
<tr>
<th></th>
<th>CR (no IFRT)</th>
<th>p Value</th>
<th>PR (+ IFRT)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET1+</td>
<td>65%**</td>
<td></td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>PET1-</td>
<td>87%</td>
<td>0.005</td>
<td>96%</td>
<td>0.047</td>
</tr>
</tbody>
</table>

** CR patients with positive or equivocal PET1 called back for IFRT if within one year of completing chemotherapy
Should early response determine therapy?
AHOD0031: Intermediate Risk HL

- Test the paradigm of response-based therapy
  - to decrease therapy for rapid early responders
  - to augment therapy for slow early responders
- All histologies, ages 0-21 years
- All Stages except
  - Stage IA, IIA – no bulk
  - Stage IIIB, IVB

Friedman, ASH abstract 2010
IFRT: 21 Gy (standard arm)

No IFRT (reduced therapy arm)

ABVE-PCX2 + DECA X2 + IFRT: 21 Gy (augmented therapy arm)

ABVE-PCX2 + IFRT: 21 Gy (standard arm)
Response criteria

*Real – Time Central review by QARC*

• Rapid early response
  – >60% reduction in the product of the perpendicular diameters of each lesion *by CT scan*

• Complete response
  – >80% reduction in the product of the perpendicular diameters of each lesion *by CT scan*  
  **PLUS**
  – Negative functional imaging study
  – No extra-mediastinal residual lymph aggregate > 2cm
<table>
<thead>
<tr>
<th>Study participants (N = 1712)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>IA bulk</td>
</tr>
<tr>
<td>IIA bulk</td>
</tr>
<tr>
<td>IAE, IIAE</td>
</tr>
<tr>
<td>IB</td>
</tr>
<tr>
<td>IIB</td>
</tr>
<tr>
<td>IIIA</td>
</tr>
<tr>
<td>IVA</td>
</tr>
</tbody>
</table>

81% (716) RER and 19% (305) SER randomized
RER vs. SER

RER 3 YR EFS = 87.3%
SER 3 YR EFS = 77.9%

P = 0.0001
IFRT vs. no IFRT**

**IFRT** 
3 YR EFS = 87.9%

No IFRT  
3 YR EFS = 85.4%

P = 0.07**
DECA vs. no DECA

DECA
3 YR EFS = 80.2%

No DECA
3 YR EFS = 75.6%

P = 0.16
Role of PET

• PET superior to gallium
  – For staging
  – Response evaluation
  – RT field design
  – Can PET response determine need for RT?

• Further study needed
  – Standardized values
  – Bone lesions
  – Utility for follow-up

Esiashvili et al. ASTRO, 2008
Is involved node therapy adequate?

- Total Lymphoid Irradiation (TLI)
- Involved-Field Radiation (IFRT)
- Involved Node Radiation (INRT)
Current study: high risk HD (IIIIB, IVB) COG AHOD0831

Risk Adapted RT: 21 Gy

Modified IFRT: 21 Gy

*Only if PET-1 positive
IFRT in high risk study

Sites of RT for RER patients:
- **Initial bulky disease**: MMR > 1/3, nodal masses >6 cm and macroscopic splenic nodules
- Non-bulky areas that are PET2 negative will not be targeted for RT

Sites of RT for SER patients:
- **Initial bulky disease**
- Slow responding non-bulky disease (PET2+)
- Residual disease > 2.5 cm at end of chemotherapy
Wilms Tumor

• Approximately 450-500 cases annually in U.S.

• 5th most common pediatric malignancy

• Median age: 3.5 years for unilateral tumor
  2.5 years for bilateral tumors (6%)

• Common signs/symptoms:
  – Abdominal mass/distension (83%)
  – Abdominal pain (37%)
  – Fever/Malaise (23%)
  – Hematuria (21% usually microscopic)
  – Hypertension (25%)
Wilms Tumor Pathogenesis

- Abnormal proliferation of metanephric blastema
- 1–2% with family history, majority are sporadic
- Associated with congenital anomalies in 10–13% of cases

Wilms tumor gene WT1 (located at 11p13) tumor suppressor gene specific for kidney development. 20% of all Wilms tumors carry WT1 mutations.
- **WAGR syndrome (WT1)**
  - Wilms tumor, aniridia, genitourinary malformations, and mental retardation
- **Denys-Drash syndrome (WT1)**
  - Wilms tumor, pseudohermaphroditism, and glomerulopathy

Wilms tumor gene WT2 (11p15) proto-oncogene associated with IGF2
- **Beckwith-Wiedemann syndrome (WT2)**
  - Macroglossia, hemihypertrophy, gigantism, and umbilical hernia
Wilms Tumor
# 2007 AREN Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>10 yr OS (FH*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to kidney, completely resected. Renal capsule intact. Tumor not ruptured or biopsied prior to resection. Vessels of renal sinus not involved or &lt;2 mm. Negative margins</td>
<td>97%</td>
</tr>
<tr>
<td>II</td>
<td>Extends beyond kidney but completely excised. Regional extension (e.g. penetration of renal capsule or blood vessels &gt;2mm); blood vessels outside renal parenchyma contain tumor. Negative margins.</td>
<td>93%</td>
</tr>
</tbody>
</table>
| III   | S: Spillage, including local  
L: Lymph nodes involved  
U: Unresectable  
R: Rupture  
P: Peritoneal implants or positive margins | 90% |
| IV    | Distant metastases | 80% |
| V     | Bilateral | 78% |

Favorable Histology (not anaplastic, clear cell, rhabdoid) accounts for 90% of cases  
Anaplastic 10 year OS: Stage I-III: 49%, Stage IV: 18%
# Treatment Recommendations

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I –II FH I Anaplasia</td>
<td>Nephrectomy → vincristine/dactinomycin pulse intensive (18 wks) No RT</td>
</tr>
<tr>
<td>III-IV FH II-IV Focal Anaplasia</td>
<td>Nephrectomy → RT → chemotherapy vincristine/dactinomycin/adriamycin (24 wks)</td>
</tr>
<tr>
<td>II-IV Diffuse Anaplasia I-IV Clear Cell Sarcoma</td>
<td>Nephrectomy → RT → chemotherapy vincristine/adriamycin/etoposide/cyclophosphamide (24 wks)</td>
</tr>
<tr>
<td>I-IV Rhabdoid tumor</td>
<td>Nephrectomy → RT → chemotherapy carboplatin/etoposide/cyclophosphamide (24 wks)</td>
</tr>
<tr>
<td>Bilateral Wilms</td>
<td>Biopsy and stage each kidney → give chemo for highest stage then evaluate response at 5 wks. If possible to leave &gt;2/3 each kidney after resection → surgery. RT for Stage III/IV FH, III/IV anaplasia, clear cell, rhabdoid.</td>
</tr>
</tbody>
</table>
Wilms RT

- Start RT by day 9 post-op; AP/PA fields
- 10.8 Gy to pre-op kidney + tumor + 1cm margin + PA nodes
- Peritoneal seeding/rupture: whole abdomen/pelvis RT to 10.5 Gy
- Lung Metastases: whole lung RT: 12 Gy

- Current investigational protocols:
  - Stratifying risk based on LOH in chromosome 1p and 16q (poor prognosis)
  - Elimination of WLRT for patients with CR by week 6 (no 1p / 16q loss)
  - Highest risk: 19.8 Gy for rhabdoid tumors and stage III diffuse anaplasia
  - IMRT for whole lung radiation
Retinoblastoma (RB): Epidemiology

- 200 patients annually in U.S
- Median age = 2 years
  - Hereditary cases earlier than sporadic
- Male = Female
- Unilateral 75%
  - 15% multifocal
- Bilateral 25%
  - 100% multifocal (2-20 tumors)
Genetics

• Autosomal dominant inheritance pattern
  – nearly complete penetrance: 45%

• Autosomal recessive gene: RB1
  – located on chromosome 13
  – tumor suppressor gene
Two-hit hypothesis

1\textsuperscript{st} hit

2\textsuperscript{nd} hit

proliferation
Stained section
RB: Clinical presentation

- Most are intraocular in U.S
  - Late diagnosis is common in developing countries
- Leukocoria: “cat’s eye reflex”
  - Large visible tumor or retinal detachment
- Strabismus: esotropia or exotropia
  - Macular involvement with loss of central vision
- Screening of children with family history
Patterns of Spread

• Arises in the retina and proliferates rapidly
  – Endophytic or exophytic growth
  – May “seed” the vitreous and fill the globe
  – Spreads along optic nerve toward brain
  – May extend outside the globe, into the orbit
  – Extra-orbital spread in the CNS or bone marrow

• “Trilateral” RB: involvement of the pineal gland
  – Rare (6%) hereditary form with poor prognosis
Vitreous seeding
Work-up

• Diagnosis made by ophthalmologic exam
  – Pathologic confirmation not required
  – Fundus diagram and/or photos taken

• Ancillary tests
  – Ultrasound helpful when fundus not seen well
  – CT and MRI scan less useful
    • Not reliable for spread along nerve
    • Calcifications may or may not be present & can cause artifact
Indirect ophthalmoscopy view
Reese-Ellsworth staging classification

- Group I
  - \( \leq 4 \) disk diameters, at or behind equator
- Group II
  - 4-10 disk diameters, at or behind equator
- Group III
  - Anterior to equator or solitary tumor >10 disk diameters behind equator
- Group IV
  - Multiple tumors >10 disk diameters or extending anterior to ora serrata
- Group V
  - Tumors involving more than half of the retina or vitreous seeding
Treatment considerations

Goals
1. Curing patient of retinoblastoma
2. Preserving vision
3. Minimizing risk of 2\textsuperscript{nd} cancer
4. Cosmesis
Treatment Options

• Enucleation: removal of the eye
• Cryotherapy or laser photocoagulation
• Chemotherapy: systemic or intra-arterial
• External beam indications:
  – Preservation vision; tumor in macula
  – Tumor too extensive for focal therapy
  – Salvage after failure of focal therapy
  – Extraocular or metastatic disease
Episceral plaque brachytherapy

- Iodine-125: apical dose 40-42.5 Gy
  - Cobalt and other sources used historically
  - Sutured to sclera by ophthalmologist

- Complications rare
  - Cataracts for anterior tumors
  - Second malignancy/ optic neuropathy risk negligible

External beam: 45 Gy

- Opposed lateral D-shape fields for bilateral RB
  - Cover entire retina, vitreous & 1cm of optic nerve
  - Isocenter at fleshy canthus (posterior lens)
  - “Beam-split” to reduce risk of cataract
  - Protons

- Superior/inferior oblique for unilateral RB
  - Local control 84% (Group I-III) at MSKCC, n=182 eyes*
  - IMRT or protons

Blach et al. IJROBP 35:45, 1996
External beam RT results

- Five year survival is >90% in the U.S.
- Preservation of eye with EBRT*
  - 95% for stage I-III
  - 50% for stage IV-V
- Acuity is excellent (20/40) in most patients**
  - Poor if macula involved

*Blach et al. IJROBP 35:45, 1995
Complications

• Cataract formation
  – Threshold is 10-20 Gy fractionated
  – Long term incidence 22% at MSKCC

• Dry eye
  – Uncommon if conjunctiva and lacrimal glands spared

• Retinopathy
  – Low risk with doses ≤ 45 Gy

• Bone growth abnormalities
  – Occur with EBRT or enucleation
Second Cancers

• Increased risk with germline RB mutation
  – Increased risk regardless of RT
  – Higher risk in RT field
  – Higher mortality for in-field sarcomas
  – Sarcomas most common (bone and soft tissue)
  – Higher mortality from 2\textsuperscript{nd} tumors than RB in U.S.
RT & Second cancers

![Graph showing cumulative mortality over time after diagnosis for children with bilateral retinoblastoma treated with or without radiotherapy. The graph indicates a higher cumulative mortality for those treated with radiotherapy compared to those not treated. The data points are as follows:

- Radiotherapy: 835, 593, 359, 134, 25
- No Radiotherapy: 84, 70, 45, 27, 11

The graph is based on data from Eng et al., J Natl Cancer Inst 1993; 85:1121.](image-url)
Second Cancers

- Hereditary RB
  - Cumulative incidence 51% at 50 years
  - Higher risk for patients <1 vs >1 year (p=.004)
  - 10-year incidence of 3\textsuperscript{rd} cancer is 22%

- Nonhereditary RB
  - Cumulative incidence 5% at 50 years

Wong et al. JAMA 278:1284-5, 1997