Pediatric Tumors: ASTRO Refresher Course

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Conflicts of Interest

- Principal investigator of Elekta-funded grant sponsoring a pediatric research consortium
Learning Objectives

- Demonstrate current standard of care therapy for common pediatric malignancies
- Discuss ongoing large-scale studies investigating radiotherapy questions for common pediatric tumors
- Discuss target volume delineation and radiation approach in the treatment of common pediatric tumors
**Distribution of common pediatric malignancies**

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

Embryonal  Alveolar
RMS – Histologic Subtypes

- **Embryonal**
  - 75% of cases
  - Less aggressive
  - Younger patients (2-6 years old)
  - Classic, botryoid, and spindle cell

- **Alveolar**
  - 25% of cases
  - More aggressive
  - Older patients (15-19 years old)
  - \(t(2;13)\) translocation (70%)
    - Fusion of PAX3 gene with FKHD
  - \(t(1;13)\) translocation (20%)
    - Fusion of PAX7 and FOXO1 fusion
Distribution of Primary Site

- Head and Neck (10%)
- Parameningeal (16%)
- Genitourinary (24%)
- Extremities (19%)
- Other (22%)
- Orbit (9%)
RMS Staging Workup

- History and Physical Exam
- CT and MRI of primary site
- Biopsy
- CT of the Chest, Abdomen, and Pelvis
- Bone Marrow Biopsy
- Bone Scan
- PET/CT (recommended but not required)
- If parameningeal, then CSF cytology and craniospinal axis MRI
RMS: Patterns of spread

- Distant metastases, < ¼ at presentation
  - lungs, bone marrow, and bone

- Regional lymph node involvement varies by primary site
  - 0-1% for orbit
  - 20-30% for paratesticular and extremity

Lawrence et al. Cancer 60:910, 1987
### IRS Clinical Group Staging System for Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Description</th>
</tr>
</thead>
</table>
| I             | A. Tumor localized to site of origin, complete resection  
B. Tumor localized but invading beyond site of origin, complete resection |
| II            | A. Localized tumor, gross total resection, microscopic residual disease  
B. Locally extensive (regional lymph node spread), complete resection  
C. Locally extensive (regional lymph node spread), gross total resection, microscopic residual disease |
| III           | A. Localized or locally extensive, gross residual disease after biopsy only  
B. Localized or locally extensive, gross residual disease after >50% debulking at surgery |
| IV            | Any size, with or without regionaly lymph nodes, distant metastases, surgical approach or resection does not matter |
## 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>≤5cm</td>
<td>N0</td>
</tr>
<tr>
<td>3</td>
<td>B/P, Extremity, PM, Other</td>
<td>≤5cm</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5cm</td>
<td>N0 or N1</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>
Risk Stratification

- Low risk: localized, embryonal, any resected site (group I/II) and favorable sites group III

- Intermediate risk: any localized alveolar (group I-III) or unfavorable embryonal site (stage II&III)

- High risk: Any metastasis
IRS IV (1991-1997)

- Radiation Guidelines:
  - Dose:
    - Group I, Stage 1/2: no RT.
    - Group I-II, Stage 3: 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+
D9602 – Low Risk Protocol

- Subgroup A: ERMS, Stage 1 group I/IIA, Stage 1 group III orbit, Stage 2 group I received VA.

- Subgroup B: ERMS, Stage 1 group IIB/C, Stage I group III nonorbit, Stage 2 group II, Stage 3 group I/II received VAC

- Outcomes
  - Subgroup A: 5-year FFS: 89%
  - Subgroup B: 5-year FFS: 85%

- Cumulative incidence of local/regional failure was 15% in patients with microscopic involved margins without cyclophosphamide (C) and 0% with cyclophosphamide (C)

Raney, JCO 2011
D9602 – Low Risk Protocol

- Orbital patients received VA + 45 Gy RT
  - IRS III, FFS/OS: 79%/95%
  - IRS IV, FFS/OS: 94%/100%
  - D9602, FFS/OS: 86%/96%
- Local-only failure on D9602 was 14% vs. 4% on IRS IV
- Improved results on IRS-IV may be due to VAC or combination of VAC with higher RT dose

Raney, JCO 2011
D9803 – Intermediate Risk Protocol

- Study evaluated the outcome of patients receiving standard VAC compared to VAC alternating with VTC.
- Local therapy after week 12.
- Median follow-up of 4.3 years:
  - 4-year FFS of 73% VAC and 68% VAC/VTC.

Arndt, JCO 2009
D9803 Outcomes

A

Failure-Free Survival (probability)

Time (years)

Log-rank P = .3

B

Overall Survival (probability)

Time (years)

Log-rank P = .9

Arndt, JCO 2009
D9803 Outcomes by Group

![Graph showing failure-free survival by group with different markers and lines representing different groups with failure-free survival over time.](image)

- Alv/UDS Stage 1 or Group I (n = 106)
- Emb Stage 2/3 Group III (n = 205)
- PM + ICE (n = 101)
- Alv/UDS Stage 2/3 & Group II/III (n = 168)
- Emb Group IV age < 10 (n = 37)

Log-rank P = .001
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
503 nonmetastatic RMS patients treated 1989-95

Goal to avoid radiotherapy

Variety of 1st and 2nd line chemotherapy regimens

OS = 71%

EFS=57%

49% cured without significant local therapy

Stevens et al. JCO 23:2618, 2005
## MMT 89 vs. IRS IV

<table>
<thead>
<tr>
<th></th>
<th>MMT 89 5 year % rate</th>
<th>IRS IV 5 year % rate</th>
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</thead>
<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>
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<tr>
<td>Orbit</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>64</td>
<td>35</td>
</tr>
<tr>
<td>Extremity</td>
<td>46</td>
<td>35</td>
</tr>
</tbody>
</table>

Donaldson et al. JCO 23:2586, 2005
Dose Guidelines and Timing

- Low Risk: Week 13
- Intermediate Risk: Week 4
  - Potentially will go back to week 12
- High Risk: Week 20 (primary) and end of chemotherapy (metastasis)
Radiation Dose Guidelines

- Group I Embryonal: 0 Gy
- Group I (Alveolar), Group II (microscopic disease) and after delayed primary resection of embryonal tumor (completely resected after chemotherapy and microscopic margins): 36 Gy
- Resected node positive disease or biopsy proven CR to chemotherapy (gross nodes get 50.4 Gy): 41.4 Gy
- Group III orbit: 45 Gy + VAC chemotherapy or 50.4 Gy without cytoxan
- Group III disease non-orbit: 50.4 Gy
Non-rhabdo soft tissue sarcomas (NRSTS)

- 550-600 cases/yr (61%)
- ~350 cases/yr (39%)

- RMS
- NRSTS
NRSTS predominates in older kids
Management

- Limb-sparing surgery and adjuvant radiation is considered standard for large, high grade tumors.

- Negative surgical margins is the goal of surgical treatment.

- Pre- or post-op radiation particularly in close proximity to neurovascular structures.
# Pre- vs. Post-op RT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pre-op</th>
<th>Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Volume</td>
<td>Smaller</td>
<td>Larger</td>
</tr>
<tr>
<td>Improved Resectability</td>
<td>Possible</td>
<td>N/A</td>
</tr>
<tr>
<td>Local Control</td>
<td>Equivalent</td>
<td></td>
</tr>
<tr>
<td>Wound Complications</td>
<td>35%</td>
<td>17%</td>
</tr>
<tr>
<td>Grade $\geq 2$ Fibrosis</td>
<td>31.5%</td>
<td>48.2%</td>
</tr>
</tbody>
</table>
Many histologic subtypes
Poor understanding of NRSTS biology
Limited data on prognostic features in children
Grading and staging systems not validated in pediatrics
Difficult to prove benefit of chemotherapy
Morbidity of therapy in children alters risk: benefit ratio of treatments proven efficacious in adults
ARST0332 STS Schema

Non-metastatic

Grossly Resected

Tumor Grade

Low

- Microscopic margins
  - Microscopic
  - Microscopic†

<5cm

- Microscopic margins
  - Microscopic
  - Microscopic†

>5cm

- Microscopic margins
  - Microscopic
  - Microscopic†

Maximal Tumor Diameter

All Disease Resected?

Yes

No

- Microscopic margins
  - Microscopic
  - Microscopic†

Metastatic to lymph nodes and/or distant sites

Tumor Grade

Low

- All Disease Resected?
  - Yes
  - No

High

- Metastatic
  - Grossly resected
  - Unresected

Unresected*

(Unresectable or high grade tumor >5cm where delayed resection planned)

Arm A

Observation

Arm B

Adjuvant radiotherapy

Arm C

Adjuvant chemo + RT

Arm D

Neoadjuvant chemoradiotherapy

Low Risk

Intermediate Risk

High Risk
COG High Grade Schema

Definitive surgical resection

Tumor ≤ 5cm

- Microscopic margins positive
  - no
    - No RT
  - yes
    - RT 55.8 Gy

Tumor > 5cm

- RT 55.8 Gy + Ifos/Doxo x5
Unresected Tumors
(Unresectable tumors or high grade tumors >5 cm where delayed resection planned)

⇒

Neoadjuvant chemo-radiation
RT 45 Gy

COG schema for Unresected NRSTS
Outcomes of ARST0332

- 551 eligible patients were enrolled
- Most common subtypes were synovial sarcoma (149), malignant peripheral nerve sheath tumor (60), and undifferentiated sarcoma (48)
- Tumors were 53% extremity, 72% high grade, 76% > 5 cm, and 14% metastatic
- Median follow-up of 2.6 years
- Estimated 3-year event-free survival:
  - A 91%, B 79%, C 68%, D 52%
- Estimated 3-year overall survival: was:
  - A 99%, B 100%, C 81%, D 66%

Spunt, ASCO 2014
ARST 1221
in collaboration with RTOG 1208

Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib
Rationale for Pazopanib

- Survival rates for intermediate and high-risk NRSTS are approximately 50% and 15%, respectively.
- Response rate to standard backbone chemotherapy (AI) is only 35-40% and outcomes poor for intermediate and high-risk NRSTS.
- Extreme biological heterogeneity across each subtype and involvement of multiple signaling pathways.
- Pazopanib: oral, multi-receptor tyrosine kinase inhibitor
  - Tyrosine kinases have been found to be expressed and dysregulated in NRSTS.
- Protocol builds on ARST0332 and RTOG 0630 by adding pazopanib to standard chemotherapy and RT.
Study Entry and Randomization

Regimen C

**INDUCTION**
Pazopanib daily Weeks 1-9 + Radiation Therapy

Evaluation (Week 10)

Primary Site Surgery

**CONTINUATION**
Pazopanib daily Weeks 13-25 + Postoperative Boost Radiotherapy**

Surgery/Radiotherapy to metastatic sites at completion of and recovery from assigned therapy

End of Protocol Therapy

Regimen D

**INDUCTION**
Radiation Therapy Alone

Evaluation (Week 10)

Primary Site Surgery

**CONTINUATION**
Postoperative Boost Radiotherapy**
### Volume Definition: Adult vs. Pediatric

<table>
<thead>
<tr>
<th>RTOG: Age &gt; 18</th>
<th>COG: Age &lt; 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>- GTV = gross tumor on MRI T1 post contrast</td>
<td>- GTV = gross tumor on MRI T1 post-contrast</td>
</tr>
<tr>
<td>- CTV = GTV plus 3 cm in the <strong>longitudinal</strong> direction</td>
<td>- CTV = GTV + 1.5 cm <strong>radially</strong> and <strong>longitudinally</strong> respecting intact fascia, bone, or skin</td>
</tr>
<tr>
<td>- Suspicious edema defined by MRI T2 images</td>
<td>- Suspicious edema defined by MRI T2 images</td>
</tr>
<tr>
<td>- Field shortened if CTV extends beyond the compartment</td>
<td>- Field shortened if it extends beyond compartment</td>
</tr>
<tr>
<td>- CTV = 1.5 cm <strong>radially</strong> respecting intact fascia, bone, or skin</td>
<td></td>
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</table>
# Radiation Dose

<table>
<thead>
<tr>
<th>Chemotherapy Cohort</th>
<th>Target Dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Cumulative Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative RT</td>
<td>45</td>
<td>1.8</td>
<td>45</td>
</tr>
<tr>
<td>Postoperative RT</td>
<td>16.2</td>
<td>1.8</td>
<td>61.2</td>
</tr>
<tr>
<td>Positive microscopic margins (optional)</td>
<td>21.6</td>
<td>1.8</td>
<td>66.2</td>
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<tr>
<td>Gross residual disease (required)</td>
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<tr>
<td>Non-Chemotherapy Cohort</td>
<td></td>
<td></td>
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<tr>
<td>Preoperative RT</td>
<td>50</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Postoperative RT</td>
<td>16</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>Positive microscopic margins (optional)</td>
<td>20</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>Gross residual disease (required)</td>
<td></td>
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</table>
Image Guidance

- IGRT studied on recent adult phase II RTOG 0630 study
  - IGRT defined as DAILY image guidance (MV, KV, CBCT)
  - PTV margin of 5 mm used with daily image guidance
  - If not using daily IGRT, 1 cm PTV margin
  - For children, contact Radiation PI if daily image guidance cannot be used
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
Pathology

- Small round blue cell tumor
  - Sheets of cells with hyperchromatic nuclei and little cytoplasm

- Origin from epithelial and neuronal elements

*Medullo, RMS, Lymphoma, Ewings, AML, Rb, Neuroblastoma, SCLC*
Ewing’s Staging Workup

- CT and MRI of Primary
- CT of chest
- Bone Scan
- Bone Marrow Biopsy
- Labs (ESR/LDH)
- Biopsy
- PET Scan recommended but not required
"Onion skin" periosteal reaction on AP and lateral views of the distal femur in a 15-year-old girl with Ewing's sarcoma.
Imaging - MRI

- **T1-weighted coronal MRI image** of the showing extensive destruction of the entire mid femur by tumor (arrows)

- **T1- axial MRI image** through the proximal femur w/ gadolinium and fat saturation. The tumor appears hyperintense relative to the surrounding tissues (arrows)
Ewing’s sarcoma should be treated as a systemic disease
• Most patients have micrometastastic disease at diagnosis
• Historical series – local control alone cures only 10%

Treatment paradigm
• Upfront Chemo (CTX) → Local Therapy → Consolidation Chemo (CTX)
Treatment Principles: Local Therapy

- No prospective randomized data comparing surgery to radiation
- Selection bias confounds the data
  - Central and larger tumors with poorer prognosis more likely to receive RT
  - Local failure after RT alone 20% or more
  - Some data favors surgery due to inadequate RT doses or lack of QA in RT planning
Treatment Principles: Local Therapy

- Surgery more feasible in small lesions in “expendable” bones
  - Hands, feet, fibula, lower sacrum, ribs, clavicle, scapula
- Innovative surgical techniques and cytoreductive CTX allowing for more resections
- Consider risk of second CA after RT and age of pt
- Consider functional deficits and psychological impacts of each type of therapy
Chemotherapy
- Alkylating agents + anthracyclines
- DFS correlates with response to CTX
  - Surgical specimens with gross disease
    - 5yr DFS 34%
  - Surgical specimens with necrosis
    - 5yr DFS 95%
Intergroup Ewing sarcoma studies (IESS)

- Three options for local control:
  - Surgery alone if margins negative
  - 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%
To determine whether additional CTX agents could improve outcomes
- Randomized, prospective trial, 1988-1992
- 518 pts, 398 pts with localized disease only
- Treatment arms
  - VACAdr
  - VACAdr + IE (alternating courses)*
- CTX given q3wk, 17 cycles, 49 weeks
- Local therapy at wk 12: surgery +/- RT or RT alone

*VACAdr = Vincristine, Dactinomycin, Cyclophosphamide, and Adriamycin; IE = Ifosfamide and Etoposide
Localized disease:

- **5yr OS:**
  - VACA-IE: 72%
  - VACA: 61%  \( p=0.01 \)

- **5yr EFS:**
  - VACA-IE: 69%
  - VACA: 54%  \( p=0.005 \)

- **Local failure:**
  - VACA-IE: 5%
  - VACA: 15%  \( p\leq0.001 \)
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

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’s sarcoma study (CESS 81, 86, EICESS 92)

- Local control best with surgery >90%
  - Plus radiotherapy when indicated
    - Pre-op to avoid incomplete resection
    - Post-op for positive margins or poor histologic response

- Definitive RT local control 74%
  - Very negatively selected group
  - No benefit to hyperfractionated split course

Cooperative Ewing sarcoma study (CESS 81, 86, EICESS 92)

- Equivalent EFS, OS

Post-op RT improved LC over surgery alone if:
  • Intralesional resection
  • Wide resection and poor histologic response

LC comparable for definitive RT and post-op RT after intralesional resections
  • Therefore, avoid surgery and give RT alone if incomplete resection anticipated
RT Volumes

- Originally encompassed entire medullary cavity: whole bone + boost to primary
- Later data showed comparable results with tailored fields
- Volume issues important for LC
  - Poor rates in CESS-1 due to lack of quality control
14 alternating cycles of:
- Vincristine, cyclophosphamide, and MESNA +/- doxorubicin
- Ifosfamide, etoposide, and MESNA
- Compressed treatment had an improved 3-year EFS (76% vs. 65%, $P = .028$).
- No increase in toxicity

Womer, JCO 2008
Randomly assigning patients with newly diagnosed nonmetastatic ESFT to either:

- Standard interval-compressed VDC/IE
- Interval-compressed therapy with the addition of vincristine, cyclophosphamide, and topotecan (VTC) [VTC/VDC/IE]}

Primary objective

- Evaluate effect of treatment regimen on EFS and OS
Use MRI to identify extent of bony and soft tissue disease

GTV takes into account pre-chemo extent of disease

CTV 1.0-1.5cm margin, plus PTV margin
  • Except for large soft tissue mass extending into a body cavity which responds to CTX and allows normal tissues to shift back into position

Post-op RT
  • Not as well defined
  • Pre-op tumor bed with margins, c/d to any residual
GTV1, CTV1, and PTV1 are defined
- 45 Gy in 1.8 Gy are delivered based on pre-chemo extent

GTV2 defined as residual visible or palpable tumor by imaging or physical exam
- For unresected or partially resected tumors, GTV2 includes pre-treatment abnormalities in bone and gross tumor in soft tissue post-chemo
- CTV2=GTv2 + 1 cm
- PTV2 = 10.8 Gy for total of 55.8 Gy

Post-op RT: 50.4 Gy for R1 and 55.8 Gy for R2
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
Pediatric Hodgkin Lymphoma
Evolution of the Treatment of Pediatric Hodgkin Lymphoma

1901 - RT alone

1960 - Advent of combined modality therapy

1970 - 1981
MOPP + 15-35Gy IFRT (Stanford)

1980 - 1990
MOPP/ABVD vs. ABVD + 21Gy IFRT (CCG 521)

1982-1990
MOPP/ABVD + 15-25Gy IFRT (Stanford)

1987-1992
MOPP/ABVD + /- 21Gy TLI (POG 8725)

1990-2000
VAMP + response-based IFRT (Stanford/St. Jude/Dana-Farber)

1995-1998
COPP/ABV + response-based IFRT (CCG5942)

1990-2000
VAMP + response-based IFRT (Stanford/St. Jude/Dana-Farber)

2000 - AHOD0031

2009 - AHOD0031

Slide courtesy of K. Dharmarajan
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 2\textsuperscript{nd} cancers for early mortality
Total Lymphoid Irradiation: 44 Gy
Standard for most teens until 1990’s
Late Effects

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

Tucker et al. NEJM 318:76, 1988
Excess cancers per 100 patients followed 20 years

- Males: 8.8
- Females: 15.6
- Breast: 8.9
- Sarcoma: 2.2
- NHL: 0.8
- Leukemia: 1.5

Wolden et al. JCO 16:536, 1998
Volume Effects
Relative Risk of Breast Cancer by Age

Hancock et al, JNCI 85:1, 1993
Wolden et al. JCO16:536, 1998
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></th>
<th>N</th>
<th>SIR</th>
<th>AER</th>
</tr>
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<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>
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</tr>
<tr>
<td>Breast</td>
<td>6</td>
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<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%
COG HD Stratification

- **HIGH**: IIIB, IVB
- **LOW**: IA, IIA no bulk
- **INTERMEDIATE**: All Others
- **LP**: Low/LP: minimal therapy
- **High**: response based, slow response augmented by new regimens from COG Phase II studies

Primary Approaches:

- **Low/LP**: minimal therapy
- **Intermediate**: evaluate dose dense, response based paradigm

Accrual: > 450 HD patients/year in COG

*Figure courtesy of S. Constine, MD*
CCG 5942

- 1995-1998
- 829 patients
- 501 with CR

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

PR

LD-IFRT

No LD-IFRT

Treatment Failure

Physician Choice

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

10 yr OS = 92.5%
10 yr EFS = 83.5%

Wolden et al. JCO 30:26, 2012
CCG 5942 – Long-term Results

EFS 91% vs 83%, p=0.004

OS 97% vs 96%, p=0.5

Wolden et al. JCO 30:26, 2012
Recent COG Protocols

- **AHOD0431**: Low Risk Study - Closed
  - Early response-based treatment
  - PET after 1 cycle of AV-PC may predict need for RT

- **AHOD0031**: Intermediate Risk Study - Closed
  - Early response-based treatment
  - Largest study of ped HL (n>1700)

- **AHOD0831**: High Risk Study – Recently closed
  - Use of risk-adapted RT
AHOD0031: A Phase III Study of Dose-Intensive Therapy for Intermediate Risk Hodgkin Lymphoma: A Report From the Children’s Oncology Group

Debra Friedman, Suzanne Wolden, Louis Constine, Lu Chen, Kathleen McCartney, TJ Fitzgerald, Pedro De Alarcon, Allen Chen, Robert Hutchison, Peter Ehrlich, Nathan Kobrinsky, Meghan Higman, Shirley Hogan, Lorna Roll, Tanya Trippett, Cindy Schwartz
AHOD0031 Schema

RER → ABVE-PCX2

CR

< CR

ABVE-PCX2

SER

RANDOMIZE

IFRT
(Standard arm)

No IFRT
(Reduced therapy arm)

IFRT

ABVE-PCX2 + DECAX2 + IFRT
(Augmented therapy arm)

ABVE-PCX2 + IFRT
(Standard arm)
Treatment Response Definition

- Response assessed after 2 and 4 cycles

- Rapid Early Response - “RER”
  - ≥ 60% reduction in product of perpendicular diameters (PPD) of each lesion on CT imaging

- Slow Early Response – “SER”
  - < 60% reduction in PPD of each lesion on CT imaging

- Complete Response – “CR”
  - ≥ 80% reduction in PPD of each lesion on CT
  - AND negative PET or Gallium scan

- Response assessed in real-time at QARC
Newly diagnosed Hodgkin Lymphoma
  • all histologies

Ages 0 – 21 years

All Stages except
  • Stage IA, IIA – no bulk
  • Stage IIIB, IVB


1712 eligible patients
AHOD0031

<table>
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<tr>
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<th>Entire Cohort</th>
<th>RER*</th>
<th>SER*</th>
<th>p Value</th>
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<tr>
<td>EFS 4-year</td>
<td>85.0%</td>
<td>86.9%</td>
<td>77.4%</td>
<td>P&lt;.001</td>
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<tr>
<td>OS 4-year</td>
<td>97.8%</td>
<td>98.5%</td>
<td>95.3%</td>
<td>P&lt;.001</td>
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<table>
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<tr>
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<th>No IFRT</th>
<th>+ IFRT</th>
<th>p Value</th>
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<tbody>
<tr>
<td>RER</td>
<td>87.3%</td>
<td>86.7%</td>
<td>0.87</td>
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</table>

Friedman D, JCO 2014
Future of Study of RT for Pediatrics

- Early response to chemotherapy suggests:
  - Therapy can be limited for RER
  - Intensification of therapy may be necessary for SER
- Using an early response paradigm, dose dense chemotherapy can lead to efficacy and reduced toxicity
- Involved site RT and response-based RT
- Allowance of IMRT and proton therapy on study
Solid Abdominal Tumors
Wilms Tumor - Histology

- Favorable Histology
- Focal Anaplasia
- Diffuse Anaplasia
- Clear Cell Sarcoma of the Kidney
- Rhabdoid Tumor of the Kidney
Wilms Tumor - Staging

- Stage I: Tumor limited to capsule and completely resected
- Stage II: Tumor beyond kidney and completely resected
  - Penetrates kidney capsule
  - Lymphatics or veins of renal sinus
  - Tumor in renal vein
Wilms Tumor Staging

- Stage III
  - SLURPP
    - Spillage (localized and diffuse)
    - Lymph Nodes
    - Unresectable
    - Residual
    - Peritoneal Implants
    - Prior Biopsy
  *** NWTS-5 – localized spillage and biopsy now stage III

- Stage IV – Hematogenous Mets or spread beyond abdomen

- Stage V – Bilateral Disease
Clinical Syndromes
- WAGR (Wilms tumor, aniridia, GU malformations, mental retardation)
  - WT1 - 11p13
- Denys-Drash syndrome (pseudohermaphroditism, mesangial sclerosis, renal failure, Wilms Tumor)
  - WT1
- Beckwith-Wiedmann syndrome (gigantism, omphalocele, macroglossia, GU abnormalities, ear creases, hypoglycemia, hemihypertrophy, Wilms tumor)
  - WT2 – 11p15
Wilms Tumor – RT Considerations

- No RT for Stage I or II, Favorable Histology
- RT for all focal and diffuse anaplasia, CCSK, rhabdoid
- Flank to 10.8 Gy Stage III FH, Stage I-III focal anaplasia, Stage I-II diffuse anaplasia, Stage I-III CCSK
- Flank to 19.8 Gy for Stage III diffuse anaplasia
  - 10.8 for any residual disease
- Whole abdominal RT to 10.5 Gy for positive cytology, abdominal tumor spill, peritoneal seeding
Wilms Tumor – RT Considerations

- Whole lung RT: 10.5 Gy (<12 mo) and 12 Gy (>12 mo)
- Whole brain: 21.6 Gy
- Focal liver: 19.8 Gy
- Bone mets: 25.2 Gy < 16 years; 30.6 Gy > 16 years
- Resected LN 10.8 Gy and not resected 19.8 Gy
Wilms Tumor - Chemotherapy

- VAA – Vincristine, Actinomycin D, Adriamycin
  - VA only for early stage FH
- CAVE for clear cell – Cytoxan, Adriamycin, Vincristine, Etoposide
- CEC for rhabdoid – Carboplatin, Etoposide, Cytoxan
Neuroblastoma – General Principles

- Most common malignancy in infants < 18 months
- Develops from neural crest tissue/sympathetic nervous system
- Negative Prognostic factors include:
  - Age
  - Diploid
  - Unfavorable Shimada histology
  - MYCN amplification
  - LOH 1p or 11q
Neuroblastoma - Workup

- CT and/or MRI of primary site (generally adrenal but often paraspinal)
- CT of chest, abdomen, and pelvis
- Bone marrow biopsy
- MIBG scan
- Urine catecholamines (VMA and HVA)
Neuroblastoma – Staging INSS

- 1 – Localized and completely resected, N0
- 2A – Localized and incompletely resected, N0
- 2B – Localized (complete or incomplete resection) + ipsilateral LN
- 3 – Unresectable, unilateral and crossing midline +/- LN; unilateral tumor with contralateral + LN
- 4 – Distant metastasis
- 4S – Localized primary tumor (1, 2, 2A) in patient < 1 year old with skin, liver, bone marrow involvement
High-risk neuroblastoma
- Phase III COG trial examining intensified chemotherapy
- Randomization to 1 or 2 transplants

INSS Stage 4 with unfavorable features
- MYCN amplification
- > 18 months
- Age 12-18 months with any of the following: MYCN amplification, unfavorable pathology, and/or DNA index = 1
ANBL0532 – Eligibility continued

- INSS Stage 3:
  - MYCN amplification
  - Age > 18 months with unfavorably pathology, regardless of MYCN status

- INSS Stage 2a/2b
  - MYCN amplification

- INSS Stage 4S with MYCN amplification
Neuroblastoma – Radiation Principles

- Primary site post-induction chemotherapy volume and prior to surgery – 21.6 Gy
  - Boost to gross residual disease after induction chemotherapy and surgery
    - Additional 14.4 Gy for total of 36 Gy
- Any metastatic site still MIBG positive after induction chemotherapy – 21.6 Gy
Neuroblastoma – Respiratory Compromise

- Classic scenario in 4S disease associated with massive liver disease
- Chemotherapy initiation is an option
- Radiation using 1.5 Gy x 3 fractions
Pediatric Brain Tumors
Epidemiological data

- German pediatric brain tumor population-based data (Cancer 2001; 92:3155)
  - Excludes germ cell tumors
- Incidence: 2.6 per 100,000 children < 15 yo
  - About 1/2500 children
- About 3000 cases/year in USA (age 1 to 19)
- Increasing incidence noted may be due to introduction of MRI
Children versus adults

- Primary brain tumors, not metastases
- Infratentorial > supratentorial
- Long-term survivors
- Quality of life concerns
  - Neuropsychological sequelae
  - Neuroendocrine sequelae
Posterior Fossa Differential Diagnosis

- Juvenile Pilocytic Astrocytoma
- Medulloblastoma
- ATRT (Atypical Teratoid Rhabdoid Tumor)
- Ependymoma
Medulloblastoma
MRI scan
Medulloblastoma – General Workup

- Embryonal tumor of the posterior fossa with high potential for spread through CSF
- Goal for surgery to achieve < 1.5 cm² residual tumor
  - Maximal safe resection
- Tumors are Grade IV
  - Desmoplastic, Classic, Anaplastic
- Workup
  - Postoperative MRI (within 48 hours of surgery)
  - MRI spine (10-14 days post-surgery)
  - CSF (10-14 days post-surgery)
Homer-Wright Rosette
Risk groups

- Standard risk: > 3 yo, M-0, less than 1.5 cm$^2$ post-operative residual tumor
- High risk: M1+ and/or greater than 1.5 cm$^2$ post-operative residual tumor, non-cerebellar primaries
- Infants: Considered separately due to desire to avoid RT
Chang Staging

○ **T Stage**
  ○ T1 - tumor <3 cm in diameter
  ○ T2 - tumor ≥3 cm in diameter
  ○ T3a - tumor >3 cm and with extension into Aqueduct of Sylvius or foramen of Luschka
  ○ T3b - tumor >3 cm and with unequivocal extension into brainstem
  ○ T4 - tumor >3 cm with extension past Aqueduct of Sylvius or down past foramen magnum

○ **M Stage**
  ○ M0 - No evidence of gross subarachnoid or hematogenous metastasis
  ○ M1 - microscopic tumors cells found in CSF
  ○ M2 - gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space or in third or lateral ventricle)
  ○ M3 - gross nodular seeding in spinal subarachnoid space
  ○ M4 - metastasis outside cerebrospinal axis
4 variants of MB

Embryonal
  ↓
Medulloblastoma
  ↓
Classic
  ↓
Desmoplastic

PNET
  ↓
Large cell/Anaplastic
  ↓
Nodular

ATRT
Desmoplastic Variant
*Histology is prognostic*

- 10-20% of cases of medulloblastoma
  - Older age at dx
- Located in cerebellar hemispheres
- Assoc. w mutations in SHH-PTCH pathway
- **Better prognosis**

Rutkowski S et al NEJM 2005
Variant Features

- Large cell/anaplastic
  - Nuclear pleomorphism, high mitotic rate
  - 17p-, MYC amplification
  - Aggressive
  - Increased propensity for CSF dissemination
  - Poorer prognosis
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<tr>
<th>Clinical features</th>
<th>WNT (~10%)</th>
<th>SHH (~30%)</th>
<th>Group 3 (~25%)</th>
<th>Group 4 (~35%)</th>
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<td>Gender ratio (M/F)</td>
<td>~1/1</td>
<td>~1.5/1</td>
<td>~2/1</td>
<td>~3/1</td>
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<td>Age distribution</td>
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<th>Histology</th>
<th>Classic; very rare LCA</th>
<th>Classic &gt; desmoplastic/nodular &gt; LCA &gt; MBEN</th>
<th>Classic &gt; LCA</th>
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<td>Metastasis at diagnosis</td>
<td>~5–10%</td>
<td>~15–20%</td>
<td>~40–45%</td>
<td>~35–40%</td>
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<td>Overall survival (5 years)</td>
<td>~95%</td>
<td>~75%</td>
<td>~50%</td>
<td>~75%</td>
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<td>Proposed cell of origin</td>
<td>Lower rhombic lip progenitor cells</td>
<td>CGNPs of the EGL and cochlear nucleus; neural stem cells of the SVZ</td>
<td>Prominin 1⁺, lineage⁻ neural stem cells; CGNPs of the EGL</td>
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<td>Driver genes†</td>
<td>CTNNB1 (90.6%)</td>
<td>PTCH1 (28%)</td>
<td>MYC (16.7%)</td>
<td>KDM6A (13%)</td>
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<td>DDX3X (50%)</td>
<td>TP53 (13.6%)</td>
<td>PVT1 (11.9%)</td>
<td>SNCA (10.4%)</td>
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<td>SMARCA4 (26.3%)</td>
<td>MLL2 (12.9%)</td>
<td>SMARCA4 (10.5%)</td>
<td>MYCN (6.3%)</td>
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<td>MLL2 (12.5%)</td>
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<td>OTX2 (7.7%)</td>
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<td>MLL2 (4%)</td>
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<td>TCF4 (5.5%)</td>
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<td>GLI2 (5.2%)</td>
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<th>Expression signature</th>
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<td>Retinal signature</td>
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UptoDate, 2015
What are the risks of aggressive surgery?

Typical Neurosurgery Risks
- Meningitis
- CSF leak
- Pseudomeningocele

Posterior Fossa Mutism Syndrome in 15-25%
- MUTISM
- Dysphagia
- Truncal ataxia
- Hypotonia
- Increased mood lability
- Less often respiratory failure
Posterior Fossa Mutism Syndrome

- Proposed mechanism
  - Disruption of dentatrubrothalamic pathways to the supplementary motor cortex
  - Occurs 12-24 hrs after surgery, may take months to improve
Historical standard therapy (standard-risk disease)

- The 5-year event-free survival of patients treated with standard RT only or RT + non-cisplatin containing chemotherapy is ~ 60%

- Standard RT was 3600 cGy craniospinal + boost to 5580 cGy to whole posterior fossa
Medulloblastoma

- Deutch (PedNeurosurg 1996) then updated by Thomas (JCO 2000)
  - RCT POG/CCG investigating reduced dose CSI for standard risk medullo
  - Surgery then randomized to 36Gy vs 23.4Gy CSI
    - 54Gy PF boost in both arms
    - No chemotherapy
  - Closed early when interim analysis showed 5/63 relapses in standard arm vs 17/60 in reduced dose arm (p=0.0025)
  - 5 yr EFS was 67% vs 52% (p=0.08)
  - Concluded that when using RT alone, reduced dose should not be used
Medulloblastoma

- Packer (JCO 1999) (CCG)
  - 65 patients, ages 3-21, average risk prospective phase II trial investigating reduced dose CSI with chemo
  - 23.4Gy with concurrent weekly vincristine, 55.8Gy to entire PF, then eight cycles of vincristine, CCNU and cisplatin
  - 5 yr PFS: 80%
  - Compared favorably to previous RT alone results of 60% at 5 yrs
Current standard therapy

- The addition of cisplatin chemotherapy is associated with improved 5-year EFS to ~ 80%.
- The dose of craniospinal RT can safely be decreased from 3600 cGy to 2340 cGy in association with such chemotherapy.
- Weekly vincristine followed by 8 cycles of vincristine, cisplatin, CCNU OR alternating AAB, AAB, AAB
  - A – Cisplatin, Lomustine (CCNU), Vincristine
  - B – Cyclophosphamide, Vincristine, MESNA
Medulloblastoma - Boost

- Wolden (JCO 2003)
  - 32 patients (27 average risk, 5 high risk)
  - 23.4-39.6Gy CSI and 54-59.4Gy primary tumor bed boost (PF boost eliminated)
  - 5 yr DFS and OS: 84% and 85%
  - 5 and 10 yr FF posterior fossa failure: 100% and 86%
  - Decreased dose to cochlea, temporal lobes, parotid glands, pituitary and hypothalamus
Medulloblastoma - Boost

- Merchant et al. (IJROBP 2007)
  - Multi-institutional phase II, prospective trial investigating reduced dose CSI and conformal boost with adjuvant chemotherapy (cyclophosphamide, cisplatin and vincristine)
  - PTV for primary boost is postop cavity +2.5cm margin
  - 86 patients (ages 3-21)
  - 61 month followup
  - Surgery -> RT -> chemo
  - 5 yr EFS: 83%
  - Reduced dose to cochlea, temporal lobes, and hypothalamus
ACNS0331

- Children less than age < 8 were randomized to 18 Gy CSI compared to 23.4 Gy CSI.
- For all patients, boost randomization to involved field versus whole posterior fossa.
- Weekly vincristine during radiation.
- Cisplatin-based chemotherapy after radiation.
Craniospinal Technique

- Patient placed prone with mask
- Spine: Define spine field first
  - Inferior border: Bottom of the thecal sac with margin. Thecal sac determined by MRI spine sagittal view, generally S2
  - Superior border: C5-6 (Defined as low as possible while still clearing shoulders so that when you feather, you won’t diverge through mouth or brain)
  - Lateral border: 1 cm lateral to vertebral body and coverage of sacral nerve roots inferiorly may be wider
Craniospinal Technique

- WBRT Field setup
  - 2 angles
    - Rotate collimator to match the divergence of the spine field (\(\arctan(L/2)/SSD\))
    - Kick the coach toward the beam to avoid divergence of the WBRT field into the spine field (\(\arctan(L/2)/SAD\))
  - Angle WBRT gantry to avoid contralateral retina/lens
Craniospinal Technique

- If the spine field is too long, can use extended distance
- If spine field is too long with extended distance, can split spine field into two fields with gap that is also feathered
- Feather all matches
  - Weekly (every 9 Gy)
Craniospinal Technique
Craniospinal Technique

Matched
Craniospinal Technique

- Match spine fields anterior to the cord to avoid a hot spot.
- Cold spot is preferred to avoid toxicity.
- Therapists place marker on skin to check gap.

Figure 1: Craniospinal Irradiation Technique—The patient is placed in a prone position. The lateral brain fields are angled to match the divergence of the beam from the upper posterior spine fields. The angle $\theta$ depends on the length of the upper spinal field. When two posterior spine fields are used, a skin gap(s) is utilized to account for the divergence of the two fields and to prevent overdosing of the spinal cord at the junction(s).
Craniospinal Technique

- Kick the couch so feet rotate towards the gantry of brain field being treated.

- Without table correction, there is a hot spot at junction of cranial and spinal fields.
Craniospinal Summary
Craniospinal – Spinal Column

Posterior Fossa Boost Volume Definition

Posterior Fossa Definition:

- CTV
  - Inferior margin: C1
  - Superior margin: Tentorium
  - Lateral margin: Bones of occiput and temporal bones
  - Posterior fossa atlas available at QARC

- PTV
  - 3-5 mm margin: should extend to posterior clinoid and C1/C2
Involved Field Definition

- Tumor Bed Definition
  - Preoperative tumor contoured but modified to account for changes in normal anatomy resection cavity
  - CTV – 1.5 cm margin (excluding bone and tentorium)
  - PTV – 3-5 mm margin
Toxicities

- Neuropsychological:
  - Learning, memory, school performance

- Neuroendocrine:
  - GH deficiency, hypothyroidism

- Growth:
  - Impaired spinal growth

- Audiometric:
  - Ototoxicity due to RT and/or cisplatin
High-risk Medulloblastoma

- Treatment with 36 Gy CSI with posterior fossa boost to 54 Gy
- For spinal nodules, boost to 45 Gy
- Supratentorial PNET and pineoblastoma treated as high-risk medulloblastoma
Age 3-21 years

Concurrent VCR with RT

Concurrent VCR and Carbo with RT

CT alone

CT + isotretinoin

CT alone

CT + isotretinoin
Medulloblastoma - Infants

- Duffner (NEJM 1993)
  - 198 patients < 3yo with malignant brain tumors treated with chemo alone until progression or 3yo
  - 31% medullo
  - PFS of about 40% at 2yrs
  - Outcomes compared favorably to surgery + RT
  - Patients with GTR had nearly 90% 1 yr PFS
  - Age < 2yr vs>2yr – EFS 12% vs 55%
  - Normal neurocognitive development
  - Conclusion: chemo in children <3 can delay the use of RT
Medulloblastoma - Infants

- Rutkowski (NEJM 2005)
  - 43 patients, age <3, prospectively enrolled on chemo alone protocol after surgery
  - Chemo: cyclophosphamide, vincristine, MTX, carbo, etoposide and IT MTX
  - 5yr PFS and OS: 58% and 66%
    - Complete resection (17): 82% and 93%
    - Residual tumor (14): 50% and 56%
    - M0/M1 (31): 68% and 77%
    - M2 or M3 disease (12): 33% and 38%
Medulloblastoma - Outcomes

- Standard Risk Medulloblastoma
  - 5 year EFS 83%, no anaplasia
  - 5 year EFS 73% with anaplasia

- High Risk Medulloblastoma
  - 5 year EFS 67%

- Supratentorial PNET
  - 5 year EFS 50-68%

- Infant Medulloblastoma
  - 5 year EFS approximately 50%
Atypical Rhabdoid Tumor

- Loss of INI-1 tumor suppressor gene
- Worked up as medulloblastoma
- Occurs in younger children
- Poor prognosis but curable when disease is localized
- Focal disease treated with high dose chemotherapy and 54 Gy local treatment
- CSI considered for older patients with localized disease and metastatic disease
Ependymoma - Presentation
Ependymoma

- Median age 5-6 years
- Infratentorial location (2/3) and Supratentorial (1/3)
- Workup is the same as medulloblastoma
- Prognostic Factors
  - Maximal safe resection to GTR
  - Histology
    - Classic (WHO Grade II) or Anaplastic (WHO Grade III)
    - Myxopapillary (WHO Grade I) seen in lumbar spine most frequently
Ependymoma – Radiation Considerations

- Radiation to the involved field to 54 – 59.4 Gy
- If metastatic disease to spine, CSI to 36 Gy for children > 3 years with involved field boost
- The benefit of the chemotherapy is unproven but chemotherapy is used on some protocols

Outcomes
- 7 year EFS grade II, grade III – 79% and 61%
- 7 year EFS GTR, STR – 77% and 34%
- 7 year OS GTR, STR - 88% and 52%
MacDonald et al. (2014)
- 70 patients with localized disease tx with protons
- 3 year LC – 83%
- 3 year PFS – 76%
- 3 year OS – 95%
- STR was significantly associated with reduced PFS, 54% (STR) vs. 88% (GTR)
- STR was significantly associated with OS with reduced 90% (STR) vs. 97 % (GTR)
Juvenile pilocytic astrocytoma: MRI
PILOCYTIC ASTROCYTOMA
Rosenthal Fibers
Juvenile pilocytic astrocytoma

- Occur at various sites
  - hypothalamus-chiasm
  - cerebellum
- NF-1 association
- Grade I astrocytoma, but no malignant progression to higher grades
Juvenile pilocytic astrocytoma: Treatment

- Surgically curable, but not hypothalamic location
- Incomplete resection + RT
- Chemotherapy in younger patients
  - vincristine & carboplatin
  - TPCV (UCSF regimen)
ACNS 0221 LGG Study

- Patients 3-21 years with progressive LGG
  - Patients < 10 years old must have had 1 or more trials with chemotherapy

- Measure PFS and OS of patients treated to conformal therapy to 54 Gy

- RT Guidelines:
  - GTV – Visible tumor on MRI (T1 post-gad and T2/Flair)
  - CTV – 5 mm margin
  - PTV – 3-5 mm margin
Hypothalamic Astrocytoma
Treatment Recommendations

- Biopsy (more difficult to biopsy optic glioma or tectal glioma)
- Surgery or shunt/3rd ventriculostomy to relieve symptoms
- Chemotherapy to delay RT (should always be discussed in tumor board, typical for patients under the age of 10, preferred for NF1 patients under the age of 5)
  - Carboplatin and vincristine are first line regimens
- Most patients ultimately require RT
High Grade Glioma RT

- Standard of care is maximal safe resection and radiation
- The role of chemotherapy is less clear than in adults although often given
- Temozolomide and CCNU appears equivalent to VCR/CCNU/Prednisone
- 3 year EFS for AA and GBM is 13% and 7%
High Grade Glioma RT

- Radiation dose to 54 Gy – 59.4 Gy depending on location
- T2 flair with margin to 45 Gy
- T1 post-contrast to a total of 54-59.4 Gy
Brainstem Glioma presentation

- 6 yo boy
- Woke with facial droop and double vision
- Mom very concerned and brought him to ED
- PE: Right CN VI and VII palsy
Diffuse intrinsic pontine glioma (DIPG)
DIPG
DIPG Workup

- Generally a radiographic diagnosis
- Do not need to biopsy
- There is a trend towards getting tissue (active clinical trials) for molecular information for development of targeted agents
- Biopsy if looks atypical (e.g. dorsally exophytic)
DIPG management

- Radiation treatment is standard of care (generally with steroids)
  - RT dose of 54 Gy
  - Tumors respond in 70% of patients with improvement in symptoms
  - Most recur in 6-12 months
  - Median OS is 1 year

- CCG-9882: Increased doses (7200 & 7800 cGy hyperfractionated) were not beneficial

- Chemotherapy: no proven benefit

- Trials for targeted agents in early phase

Cancer 1993;72:1414 & 1994;74:1827
Atypical brainstem tumors

- Pontine focal tumors
- Pontine dorsally exophytic tumors
- Midbrain or medulla tumors
- Tumors in patients with NF-1
- Long history
- Suggest better prognosis
No biopsy performed. Received RT (5400 cGy) involved-field.

Clinical improvement, no radiographic response, unable to wean completely off-steroids.

Disease progression noted 6 months post-dx and pt died shortly afterwards.
Intracranial Germ Cell Tumors (GCT)

- Intracranial germ cell tumors (GCT) comprise 3-5% of primary brain tumors in children and young adults
  - 50-60% of these are germinoma

- Decreased incidence in Western hemisphere compared to Japan and Far East

- 60% of germinomas are diagnosed between 10-20 years of age
  - Males > Females in pineal region
  - Females > Males in suprasellar region

Packer, R, Oncologist; 2000
Location

- Most frequently in the pineal and suprasellar region
Pineal vs. Suprasellar mass
Diagnosis

- Pineal region
  - GCT, pineoblastomas, pineocytomas, teratoma or glioma

- Suprasellar region
  - GCT, glioma, craniopharyngioma, teratoma or histiocytoma

- Tumor markers - CSF > serum
  - ß-HCG
  - AFP

Hoffman H, J Neurosurg; 1991
GCT - Symptoms

- Suprasellar
  - Diabetes Insipidus
  - GH Abnormality
  - Other hormonal abnormality
  - Visual deficit

- Pineal
  - Hydrocephalus
  - Parinaud’s syndrome (paralysis of upward gaze, convergence-retraction nystagmus, eyelid retraction)
    - Compression to dorsal midbrain
    - Do not react to light (similar to Argyll Robertson pupil)
Clinical Groups of GCTs

- Germinoma (60%)
  - No elevation AFP
  - HCG < 50 mIU/ml in serum and CSF (may change to < 100)

- Non-germinoma germ cell tumors (40%)
  - Embryonal carcinoma (bHCG+ AFP)
  - Endodermal sinus tumor (yolk sac) (AFP)
  - Choriocarcinoma (bHCG)
  - Immature teratoma

- Mature teratoma (1%)
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>β-HCG</th>
<th>AFP</th>
</tr>
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<tbody>
<tr>
<td>Germinoma</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Mixed germ cell</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Teratoma</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Hoffman H, J Neurosurg; 1991
- 5-10% are multifocal (not considered metastatic)
- Unclear if this is discontiguous spread of tumor within the brain vs. 2 simultaneous primaries
- Intracranial GCT’s in general tend to arise in the midline
- Treatment of spinal involvement is craniospinal RT
GCT Workup

- MRI of brain and spine
- Serum and CSF HCG and AFP
- Biopsy unless markers are positive
- Occasionally require procedure to relieve hydrocephalus upfront
Pure Germinoma Management

- Resection generally not done excellent response to other therapies
- Whole ventricle radiation (24 Gy) + boost (to 45 Gy) has been standard therapy
- 10 year survival with RT alone $\geq 85\%-95\%$
**GCT Management**

- Reduce morbidity of RT by combining neoadjuvant chemotherapy and reduced radiation dose
- Standard chemo is 2-4 cycles of carbo/etoposide
- If CR to chemo, reduced dose radiation with 21 Gy to whole ventricles and 9 Gy boost
- Involved field RT only associated with increased ventricle relapse
- For disseminated disease, CSI and boost
Whole Ventricle Atlas – ACNS1123
NGGCT Management

- Standard is chemotherapy and radiation with or without surgical resection
- Chemotherapy combined craniospinal RT and boost
  - CSI is 36 Gy followed by 54 Gy boost
  - Common chemo is 6 cycles of alternative carbo/etoposide and ifos/etoposide
Craniopharyngioma – Symptoms

- Patient presentation
  - Visual deficits
  - Diabetes insipidus
  - Increased ICP
  - MRI may demonstrate cystic changes associated with calcifications
Craniopharyngioma - Management

- Generally, first approach involves surgical management
- High potential surgical morbidity and ideally, should be discussed upfront to determine best morbidity profile
  - Endocrinopathies
  - Vision loss
  - Vasculopathy
  - Hypothalamic dysfunction
  - Memory loss
Craniopharyngioma – RT Principles

- Difficult to obtain true gross total resection
- Reasonable approach in the very young patient is resection followed by observation until growth of residual
- Radiation delivered to 54 Gy (50.4 - 54 Gy) to residual tumor, tumor bed with an additional 5-8 mm margin
- Cystic changes during the course of RT and up to 9 months post-RT
  - Recommend obtaining MRIs during RT to assess for re-planning
- Local control – STR + RT is approximately 90%
Retinoblastoma - Workup

- Workup includes exam under anesthesia
- MRI of orbits and brain
  - Rule out trilateral retinoblastoma (pineal region mass)
- High risk features include:
  - Bone scan
  - Bone marrow biopsy
  - CSF
Retinoblastoma – Treatment options

- Enucleation
- Exenteration
- Chemotherapy (carboplatin-based regimens)
- Local therapies:
  - Cryotherapy
  - Photocoagulation
  - Laser hyperthermia
  - Radioactive plaque therapy
- EBRT (generally tx focused on delaying EBRT)
EBRT Indications

- Preservation of vision
- Tumor too extensive for successful focal therapy
- Bilateral advanced intraocular disease
- Tumor in macula
- Salvage
- Treatment of metastatic or extraocular disease

- Most common indications:
  - Vitreous seeding
  - High risk features post-enucleation (positive optic nerve margin)
  - Large tumor in macula (consolidation post-chemo)
RT Approach

- Radiation dose is 45 Gy in 1.8 Gy fractions
- Consider proton therapy
- 5 year survival in US > 90%
- Increased risk of secondary tumors with germline RB mutation
  - High risk in RT field and higher mortality for 2\textsuperscript{nd} tumors
  - Sarcomas most common
- Preservation of eye with EBRT
  - 95% Stage I
  - 50% Stage IV-V
Leukemia

- Cranial radiation 12-18 Gy for high risk features in 1.5-1.8 Gy fractions
- T cell disease and WBC (>50 K)
- Age > 10
- CNS3 disease (> 5 WBC/ul in CSF and blasts)
  - 18 Gy

- Cranial RT is standard for CNS relapse (up to 24 Gy)
  - Consider CSI
Langerhans cell histiocytosis

- Clonal proliferation of langerhans cells – abnormal cells in the bone marrow

- Hand-Schuler-Christian
  - > 2 years
  - Exophthalmos, skull/bone, DI
  - Good prognosis

- Letterer-Siwe Disease
  - <2 years old
  - Splenomegaly, hepatomegaly, anemia, lymphadenopathy
  - Poor prognosis
Langerhans Cell Histiocytosis

- Surgical stabilization depending on site
- Chemotherapy for multi-organ system disease
- Steroids
- Can be observed if asymptomatic
- Radiation for symptomatic lesions (skull base and spine)
- Young children, dose is 5-10 Gy in 3-5 fractions
- In young adults, higher doses with 18-20 Gy used
Conclusions

- Approaches to management of pediatric tumors differ from that of adults.
- Treatment decisions more frequently involve balancing toxicities with efficacy.
- Decisions to delay radiation or reduce radiotherapy fields are made with the goal of reducing late toxicities that can impact survivorship and mortality.
Thank You