[Draft] Management of Pediatric Malignancies

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Disclosure

• I am employed by the University of Washington
• My sites of practice include the University of Washington Medical Center, Seattle Children’s Hospital and the Seattle Cancer Care Alliance Proton Therapy Center
• I have no conflicts of interest to disclose.
Learning Objectives

Upon completion of this activity, attendees should be able to:

• List the most common pediatric malignancies treated with radiation therapy

• Describe workup, target volumes and doses for common central nervous system pediatric malignancies, and common non-central nervous system such as Ewing Sarcoma, Wilms Tumor, rhabdomyosarcoma, and neuroblastoma

• Outline potential benefits and limitations of proton therapy in managing pediatric malignancies
• For the purposes of education, several open clinical trials are described.
• Providers should not treat patients with experimental schema without the patients being enrolled on study.
Where do pediatric cancers fit into overall picture of Cancer in the United States? Incidence.

Pediatric cancers: 12,500 cases in patients up to 15 years old

CA Cancer J Clin 2017; 67:7-30
What cancers do children get?

Li. Pediatrics. 2008
Trends in Outcomes for Pediatric Oncology

Declining Use of Radiotherapy in Management of Pediatric Malignancies

Declining Use of Radiotherapy in Management of Pediatric Malignancies

Outline for Remainder of Presentation

- Non-Central Nervous System Malignancies
  - Wilms Tumor
  - Neuroblastoma
  - Hodgkin Disease
  - Rhabdomyosarcoma
  - Ewing Sarcoma

- Central Nervous System Malignancies
  - Medulloblastoma
  - Ependymoma
  - Germ cell tumors
  - Craniopharyngioma, *if time allows*
  - Diffuse Intrinsic Pontine Glioma, *if time allows*
  - Pilocytic Astrocytoma, *if time allows*

- Protons
Wilms Tumor (Nephroblastoma)

• Most common abdominal tumor of childhood

• 6% of childhood cancers, approximately 650 cases/year

• Median age of unilateral presentation: 41.5 mo in boys, 46.9 mo in girls; younger in bilateral presentation

• Common presentation: painless abdominal mass; less commonly nausea, abdominal pain, fever or hematuria
Wilms Tumor-Associated Anomalies

• Congenital anomalies in 10-13%: aniridia, GU, hemihypertrophy

• Syndromes
  • WAGR: Wilms’ Tumor, Aniridia, Genitourinary abnormalities, and Mental Retardation
  • Denys-Drash: Mutation of WT1, and 90% incidence of Wilms Tumor
  • Beckwith-Wiedemann Syndrome: gigantism, umbilical herniation, macroglossia, GU anomalies, hemihypertrophy
Wilms Tumor Histologies

• Wilms tumor is a triphasic embryonal neoplasm that includes at least one or combinations of:
  - Blastemal (39%)
  - Epithelial (Tubules, 18%)
  - Stromal (1%)

• Mixed histology is the most common (41%).

• Three entities have traditionally been grouped under the general term *unfavorable histology*:
  - Anaplastic Wilms tumor (4-5% of cases)
  - Clear cell sarcoma of the kidney (CCSK)
  - Rhabdoid tumor of the kidney (RTK)

• LOH at 1p & 16q are associated with increased risk of relapse and death. Grundy. JCO. 2005
Wilms Tumor Workup

• History and Physical
• Ultrasound
• Urinalysis
• CBC and complete metabolic panel
• CT abdomen
• Chest imaging
• Bone scan in CCSK
• MRI Brain in CCSK and RTK
• ECG and Echocardiogram
Wilms Tumor Staging

• Stage I Completely resected tumor limited to the kidney

• Stage II Completely resected tumor regionally extended (i.e., into renal sinus, blood vessels extending from kidney)
Wilms Tumor Staging

• Stage III
  • Spillage
  • Lymph Nodes
  • Unresectable
  • Residual disease
  • Peritoneal implants

• Stage IV Hematogenenous Metastases beyond the abdomen

• Stage V Bilateral Disease
## NWTS 5 Wilms Tumor Outcomes FH and Anaplasia

<table>
<thead>
<tr>
<th>Histology and stage</th>
<th>4-year relapse-free survival rate (%)</th>
<th>4-year overall survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (&lt;24 months/tumor weight &lt;550g, nephrectomy only)(^a)</td>
<td>84</td>
<td>98</td>
</tr>
<tr>
<td>I/II, no LOH</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>I/II, LOH 1p and 16q</td>
<td>75</td>
<td>91</td>
</tr>
<tr>
<td>III/IV, no LOH</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>III/IV, LOH 1p and 16q</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td>V, any LOH</td>
<td>61</td>
<td>81</td>
</tr>
<tr>
<td>Diffuse anaplastic histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>II</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>III</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>IV</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>V</td>
<td>25</td>
<td>42</td>
</tr>
</tbody>
</table>

\(^a\) Dome. PBC. 2013
Children’s Oncology Group (COG) vs. International Society of Paediatric Oncology (SIOP) Approaches

• COG. Local therapy -> systemic therapy
• SIOP. Biopsy -> systemic therapy -> local therapy

• Today I am only covering COG approach
Wilms Tumor Chemotherapy

- Almost all regimens include vincristine and dactinomycin
  - These two drugs alone (Regimen EE4A) are used with lowest risk patients
- Doxorubicin added with some increased risk, such as FH with lung metastases (Regimen DD4A)
- Other drugs sometimes used include Cyclophosphamide and Etoposide
Wilms Tumor Radiation Volumes and Fields

• Non-contrast simulation, often under anesthesia

• 3D planning can be used, but 2D principles still acceptable
  • IMRT and protons described

• Flank radiation: Encompasses pre-resection volume of tumor (including in ureter) with 1 cm margin
  • Avoid splitting vertebral bodies
  • Avoid crossing extending beyond 1 cm into contralateral kidney
  • If LN involved, include para-Aortics up to crus of diaphragm

• Whole Abdomen Radiation
  • Include the diaphragm
  • Shield the femoral heads
  • Inferiorly extend fields at least to inferior pubic ramus

Examples from Halperin, et al Pediatric Radiation Oncology 2010
Wilms Tumor Radiation Therapy

• No RT for Stage I or II Favorable Histology

• RT for all stages if focal and diffuse anaplasia, CCSK, or RTK

• Flank RT to 10.8 Gy/6 fxs for Stage III FH, Stage I-III focal anaplasia, Stage I-II diffuse anaplasia, Stage I-III CCSK
  • Boost gross residual disease by 10.8 Gy

• Flank RT to 19.8 Gy for Stage III diffuse anaplasia

• Whole abdomen RT 10.5 Gy/7 fxs for positive cytology, tumor spill or peritoneal seeding.
  • Boost residual disease by 10.5 Gy/7 fxs
Wilms Tumor Radiation Therapy

• Whole lung RT 12 Gy/8 fxs (or 10.5 Gy/7 fxs if <1 yr)

• Whole brain radiation 21.6 Gy in 12 fxs

• Focal liver 19.8 Gy in 11 fxs

• Bone metastases 25.2 Gy<16 years, 30.6 Gy if >15yrs

• Lymph nodes resected 10.8 Gy and unresected 19.8 Gy

Start radiation no later than 10-14 days after surgery (NWTS-1)
Two Evolving Issues in Wilms Tumor Radiation

- **IMRT for Whole Lung Irradiation**
  - Cardiac sparing IMRT feasible for WLI. Kalapurakal IJROBP 2013

- **Deferring Whole Lung Irradiation in FH pts. (AREN0533)**
  - If lung mets resolve with upfront chemotherapy, no lung radiation
  - Results presented *in abstract* at ASCO 2015: modest decrease in 4y EFS with no difference in 4y OS. (but some question of CIs)
  - Farooqi. Peds Blood Cancer. 2014. If Abd and whole lung fields treated separately, potentially higher pulmonary and cardiac dose and risks
Take Home Messages for Wilms Tumor

- Radiation (when indicated) usually begins within 10-14 days of surgery
- RT fields continue to be designed based on 2D planning principles
  - Examples: flank, whole abdomen, whole lung
  - IMRT of whole lung is becoming more standard
- Wilms is a very radiosensitive tumor, with doses typically ranging from 10.5-21 Gy
- Expect publication soon on whether whole lung radiation can be omitted in FH patients with lung mets ca with CR after 6 weeks of chemotherapy
Neuroblastoma

• 2nd most common abdominal tumor of childhood, and most common abdominal tumor in children < 18 mo
• Arise from Neurocrest cells/sympathetic nervous system tissue
• In contrast to Wilms Tumor patients, NB patients tend to present younger and more acutely ill
• Primary site location distribution (Halperin. 2010):
  • Adrenal gland 35%
  • Posterior mediastinum 20%
  • Paraspinal ganglion in low thorax, abdomen, or pelvis 32%
  • Cervical sympathetic ganglion 1%
  • Other 12%
Neuroblastoma Workup

• CBC and Complete metabolic panel
• CT chest/abdomen/pelvis
• Urine catecholamines
• Bone marrow biopsies
• ECG and MUGA/Echocardiogram
• Audiogram or BAERS
• MIBG scan
• Tumor resection or biopsy
Neuroblastoma **Old** Staging System: INSS

- Stage I. Localized tumor with R0 or R1 resection with negative lymph nodes
- Stage 2A. Localized tumor with residual disease after resection, negative lymph nodes
- Stage 2B. Localized tumor with residual disease after resection, negative lymph nodes
- Stage 3. Unresectable, unilateral and crossing midline, +/- LN; unilateral tumor with contralateral +LN
- Stage 4. Distant Metastases
- Stage 4S. Localized tumor in patient <1 yo with dissemination limited to skin, liver, and bone marrow without gross bone metastases.
Neuroblastoma New Staging System: International Neuroblastoma Risk Group (INRG)

• L1. Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
• L2. Locoregional tumor with presence of one or more image-defined risk factors
• M. Distant metastatic disease (except MS)
• MS. Localized tumor in patient <18 mo with dissemination limited to skin, liver, and bone marrow
Neuroblastoma Risk Factors

• MYCN amplification
• Diploid
• Older age (>11 or >17 months)
• LOH 1p or 11q
• Grade of Tumor Differentiation
### Neuroblastoma Risk Stratification: A Reference Table, Not To Be Memorized

#### Table 1. International Neuroblastoma Risk Group Pretreatment Classification Schema

<table>
<thead>
<tr>
<th>INRG Stage</th>
<th>Age (months)</th>
<th>Histologic Category</th>
<th>Grade of Tumor Differentiation</th>
<th>MYCN</th>
<th>11q Aberration</th>
<th>Ploidy</th>
<th>Pretreatment Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1/L2</td>
<td></td>
<td>GN maturing, GNB intermixed</td>
<td></td>
<td>NA</td>
<td></td>
<td>A (very low)</td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td></td>
<td>Any, except GN maturing or GNB intermixed</td>
<td></td>
<td>Amplified</td>
<td>No</td>
<td></td>
<td>B (very low)</td>
</tr>
<tr>
<td>L2</td>
<td>&lt; 18</td>
<td>Any, except GN maturing or GNB intermixed</td>
<td>Differentiating</td>
<td>NA</td>
<td>No</td>
<td>D (low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 18</td>
<td>GNB nodular neuroblastoma</td>
<td>Poorly differentiated or undifferentiated</td>
<td>NA</td>
<td>Yes</td>
<td>G (intermediate)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>&lt; 18</td>
<td></td>
<td></td>
<td>Amplified</td>
<td></td>
<td>E (low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F (low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 to &lt; 18</td>
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<td></td>
<td></td>
<td></td>
<td>I (intermediate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>J (intermediate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 18</td>
<td></td>
<td></td>
<td>Amplified</td>
<td></td>
<td>O (high)</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>&lt; 18</td>
<td></td>
<td></td>
<td>Amplified</td>
<td>No</td>
<td>C (very low)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** GN, ganglioneuroma; GNB, ganglioneuroblastoma; INRG, International Neuroblastoma Risk Group; NA, not amplified.

Pinto. JCO. 2015
High Risk Neuroblastoma Treatment Standard of Care

**Induction**
- Surgery
- Chemotherapy
  - Stem-cell harvest

**Consolidation**
- Myeloablative chemotherapy
- XRT
  - Stem-cell infusion

**Post-Consolidation**
- Immunotherapy and cytokines plus isotretinoin

### Induction Chemotherapy Agents
- Cisplatin
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Topotecan
- Vincristine

### Myeloablative regimens
- Cisplatin/etoposide/melphalan
- Busulfan/melphalan
- Thiotepa/cyclophosphamide plus cisplatin/etoposide/melphalan

### Immunotherapy Regimens
- ch 14.18 mAB + subq GM-CSF / ch 14.18 mAB + IV IL-2
- ch 14.18/CHO mAB + subq IL-2

ANBL0531 presented at ASCO 2016: Tandem ASCT better than single ASCT for most patients.
High Risk Neuroblastoma Outcomes are Improving

Pinto. JCO. 2015
Critical Features of Radiation Therapy for High Risk Neuroblastoma

• Radiation rarely used in Low or Intermediate Risk patients

• On CCG-3891 patients received 10 Gy to gross disease, then were randomized for conditioning for auto stem cell transplant with either chemotherapy or 10 Gy TBI conditioning.
  • TBI conditioning vs non-TBI conditioning, 20% vs. 50% local failure rates, p = 0.022
  • Haas-Kogan. IJROBP. 2003.

• The initial target volume (GTV) is the **extent of disease at the time of surgery**, whenever surgery occurs
  • Typically induction chemotherapy provides a dramatic response in these tumors that can occupy much of the abdomen
  • If the tumor is resected before induction chemotherapy, the initial target volume will be larger
High Risk Neuroblastoma Radiation Treatment Details

• Patients often treated under anesthesia
• 4D planning CTs can be employed to minimize PTV expansions

• GTV1 = extent of tumor at time of surgery, including involved lymph nodes
• CTV1 = GTV1 + 1.5 cm, anatomically-confined

• GTV2 = residual disease > 1 cm³
• CTV2 = GTV2 + 1 cm, anatomically-confined
High Risk Neuroblastoma Radiation Treatment Details

- PTV1 treated to 21.6 Gy in 12 fractions
- PTV2 treated to 14.4 Gy in 8 fractions (on protocol ANBL0532)

- RT for metastatic disease is controversial
  - often reserved for functionally active residual metastases after surgery

- Recent high risk studies
  - ANBL09P1 examines use of therapeutic $^{131}$I-MIBG in induction chemotherapy
  - ANBL12P1 examines use of Busulfan and Melphalan in chemotherapy consolisation
High Risk Neuroblastoma Organs at Risk

• Chemotherapy includes doxorubicin, so heart doses must be low.
• High risk of sinusoidal obstructive syndrome so liver doses must be low.
• ANBL0532 AOR constraints (in setting of prescriptions to 21.6 or 36 Gy)
  • Ipsilateral kidney: V19.8<50%, V14.4<100%
  • Contralateral kidney: V12<20%, V8<50%
  • Liver: V9<50%, V18<25%
  • Lungs: V15<33%
  • These can be very difficult to achieve and maintain target coverage.
  • They are very conservative. Kandula, et al, found virtually no renal or hepatic toxicity with these constraints, or even when they are exceeded. Peds Blood Cancer. 2015.
• Vertebral body axial dose uniformity drives dose into the contralateral kidney
# High Risk Neuroblastoma Organs at Risk: ANBL 1531 proposed OAR/Target Volume Coverage

<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Kidney</td>
<td>&lt;75%</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mean dose ≤ 18 Gy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;100%</td>
<td>14.4</td>
</tr>
<tr>
<td>Contralateral Kidney</td>
<td>&lt;25%</td>
<td>18</td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td>&lt;30%</td>
<td>20</td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td>&lt;10%</td>
<td>20</td>
</tr>
<tr>
<td>B/L Lung</td>
<td>&lt;30%</td>
<td>20</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;15%</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean &lt; 15 Gy</td>
<td></td>
</tr>
<tr>
<td>Vertebral Bodies</td>
<td>If vertebral body requires treatment, the entire vertebral body and posterior elements mean dose should be &gt;18 Gy.</td>
<td>Mean dose &gt;18 Gy</td>
</tr>
<tr>
<td>CTVs</td>
<td>&gt;99% receives 95% of prescribed dose</td>
<td></td>
</tr>
<tr>
<td>PTVs</td>
<td>&gt;90% receives 95% of prescribed dose</td>
<td></td>
</tr>
</tbody>
</table>
Neuroblastoma Take Home Points

• Radiation plays critical role in local control of high risk neuroblastoma
• Radiation takes place after induction chemotherapy, tumor resection, and myeloablative chemotherapy/stem cell rescue
• The GTV is the extent of primary disease and involved LN at the time of resection, whenever that occurs
• OAR planning dose constraints are very low
Hodgkin Lymphoma

- Ann Arbor staging (and assess for bulk)
- Historically treated with total lymphoid irradiation
- 44 Gy with associated severe late effects
Historic Late Mortality Risks of HD Treatment

Reduced dose RT also Associated with SMN

- Median follow up 20 years
- 15-25 Gy with possible 10 Gy boosts
- Radiation volumes “tailored to the involved nodal station with appropriate margins—mantle, minimantle, or hemimantle for disease above the diaphragm and modified spade, para-aortic, or inverted Y fields for infradiaphragmatic disease.”
- SMN rate 17%: breast, thyroid, sarcoma, leukemia
Breast Cancer Risk Varies by Target Volume

- Mantle->mediastinal fields reduced incidence of secondary breast cancer
- Also found that decreased breast cancer risk was associated with decreased duration of ovarian function
Common Hodgkin Disease Chemotherapy

• A. Adriamycin
• B. Bleomycin
• V. Vincristine
• E. Etoposide
• P. Prednisone
• C. Cyclophosphamide
Recent COG Risk Stratification

• Low risk: Stage IA and IIA without Bulk
• Intermediate Risk: I-IIA with bulk, I-IIAE, I-IIB, and IIIA and IVA
• High risk: Stage IIIB and IVB
Low Risk: Lymphocyte Predominant Hodgkin Disease AHOD03P1

- Stage I and II non-bulky LPHD
- 183 pts, 178 evaluable
- Surgery only for single LN involvement (52 pts)
- Others 135 (including 9 with surgery-only then relapsed) received AV-PE x 3. If CR->No RT
- 5 y EFS 89% (95%CI, 82%-93%), 5 y OS 100%
Low Risk Hodgkin Disease

- Most recent study is AHOD0431
- Only presented in abstract
- Response based radiation therapy: patients received 3 cycles of AV-PC; those with radiographic CR did not receive radiation
- An amendment was added to recommend radiation to patients with positive PET scans after 1 cycle of chemotherapy
- No peer reviewed final report
AHOD0031: Intermediate Risk HL Trial 2002-2010 with 1712 patients

- IFRT 1.5 Gy x 14

>60% reduction of product of perpendicular diameters (PPD) of 5 largest nodal sites

>80% reduction of PPD of 5 largest nodal sites (or WNL), and PET/gallium negative
AHOD0031: Intermediate Risk HL trial: Excellent Outcomes

- **Overall**
  - OS 97.8%
  - EFS 85%

- **EFS**
  - RER 86.9%
  - SER 77.4%

- **RER/CR EFS**
  - + IFRT 87.9%
  - - IFRT 84.3%
  - Difference in patients with LMA

Pts who seem to benefit from IFRT had anemia and Stage I/II disease bulk. Carpentier. IJROBP. 2016.

Friedman, et al. JCO. 2014
Relapses rarely occur solely in new sites and/or out of field. In irradiated patients, relapses rarely occur solely out of field. Dharmarajan, et al. IJROBP. 92:60-66. 2015.
AHOD0031: Relapses Occur in both bulk and nonbulk sites

- Suggests concern about only treating bulky disease sites
AHOD0031: Childhood Hodgkin International Prognostic Score (CHIPS)

- Retrospective analysis of AHOD0031
- One point for each of:
  - Fever
  - Stage IV disease
  - Large mediastinal Adenopathy
  - Albumin <3.5

- CHIPS was highly predictive of EFS,
  - identifying a subset (with CHIPS 2 or 3) that comprises 27% of intermediate-risk patients
  - have a 4-year EFS of <80%
  - may benefit from early therapeutic augmentation.

High Risk Disease

• AHOD0831 attempted to employ a risk adapted RT based on response
  • 5 cycles of ABVE-PC
  • If RER, then only to initial bulky disease
  • If SER, only PET avid sites and sites with >2.5 cm of residual disease
  • RT 21 Gy in 14 fractions of involved field radiation.

• Results not published, but did not meet goal of 95% EFS
AHOD1331: High Risk HL RCT with Brentuximab Vedotin in which ISRT is employed

- Radiation (21 Gy/14 fractions) will be based on bulk and SER vs. RER by PET
- A boost (9 Gy/6 fractions) is determined by end of chemotherapy PET
- IMRT and Protons allowed
- No RT study questions, yet ...

- This radiation varies from established patterns of care and is for research purposes, and only on-study.
International Lymphoma Radiation Oncology Group Guidelines for Pediatric HD

• Target original extent of disease. Effectively describe ISRT without explicitly endorsing it

• Suggested dose limitations
  • Heart mean <15 Gy
  • Lung V20< 37%
  • Mean lung dose < 12

Hodgson. Practical Radiation Oncology. 5:85-92. 2015
ILROPG suggestions

• Bone growth affected starting at 8 Gy
• Breast tissue growth and development affected at 5-10 Gy
• Thyroid. >15 Gy associated with 30% risk of thyroid insufficiency
• Soft tissue growth and development affected at 25-30 Gy

Hodgson. Practical Radiation Oncology. 5:85-92. 2015
Hodgkin Lymphoma Take Home Points

• Radiosensitive disease in which doses and target volumes have been reduced over decades because of concern for late MORTALITY

• Radiation remains a part of therapy for many pediatric patients with HL

• AHOD 0031 confirms adjuvant IFRT can be omitted intermediate risk patients who are RERs and achieve radiographic CR, although questions remain about patients with large mediastinal adenopathy.
  • Those that do not achieve RER and CR should receive adjuvant (ISRT?) 21 Gy/14 fx
  • In spite of excellent outcomes, relapse tend to be in-field

• ISRT **becoming** standard
Rhabdomyosarcoma

- A radiosensitive sarcoma
- Most common soft tissue sarcoma of childhood
  - 350 cases per year in US

Figure courtesy of Doug Hawkins, MD, Seattle Children’s Hospital
Rhabdomyosarcoma Site Distribution

- G-U
- Extremity
- Other
- Orbit
- Parameningeal
- Other Head/Neck
- Other Head/Neck

C/o Doug Hawkins, MD
Rhabdomyosarcoma Histologic Subtypes

• Favorable
  • Embryonal, botryoid, and spindle cell
  • Embryonal patients typically younger
  • Vast majority of RMS patients
  • Typically F0X01 fusion negative

• Unfavorable
  • Alveolar
  • Often older (adolescent patients)
  • Minority of RMS patients
  • F0X01 fusion positive
Rhabdomyosarcoma: Does Histology or FOX01 status matter more? FOX01 status

Patterns of Spread

• Lymph node involvement varies widely by primary site
  • Orbit 0-1%
  • Extremity 10-15%
  • Paratesticular 25-30%

• Metastases
  • Bone
  • Lung
  • Bone Marrow
Rhabdomyosarcoma Workup

• History and Physical
• CBC and CMP
• CT and/or MRI of primary site
• Biopsy/Resection
• CT of chest/abdomen and pelvis
• Bone Marrow Biopsy
• PET/CT (recommended but not required)
• If parameningeal primary, then CSF cytology and MRI imaging of neuroaxis
• Urinalysis
Rhabdomyosarcoma: A Nuanced Approach to Workup

## Rhabdomyosarcoma: Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>Size</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit/Eyelid, Head and Neck (excluding parameningeal (PM)), Non-bladder/Non-prostate GU</td>
<td>Any</td>
<td>Any</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Bladder/Prostate, Extremity, PM, Other (trunk, retroperitoneal, etc)</td>
<td>&lt;5 cm</td>
<td>N0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Bladder/Prostate, Extremity, PM, Other</td>
<td>&lt;5 cm</td>
<td>N1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other (trunk, retroperitoneal, etc)</td>
<td>≥5 cm</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Any Distant Metastases</td>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
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</table>
Intergroup Rhabdomyosarcoma Grouping System. **AT TIME OF DIAGNOSIS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Localized disease, completely resected</td>
</tr>
</tbody>
</table>
| II    | Gross total resection with  
a. Microscopic positive margins  
b. Regional Lymph Node involvement and resected  
c. Both |
| III   | Incomplete resection of gross disease |
| IV    | Metastatic Disease |
# Rhabdomyosarcoma Risk Stratification

<table>
<thead>
<tr>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Localized, EMBRYONAL, Any resected site (Group II or III) or favorable sites Group III</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Any localized ALVEOLAR (Group I-III) or any unfavorable site Group III</td>
</tr>
<tr>
<td>High</td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>
### TABLE I. Children’s Oncology Group Rhabdomyosarcoma Prognostic Groups [5,12]

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Stage</th>
<th>Group</th>
<th>Histology</th>
<th>Approximate % of RMS</th>
<th>Long-term EFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, subset 1</td>
<td>1</td>
<td>I-II</td>
<td>ERMS</td>
<td>27%</td>
<td>85–95%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>III (orbit)</td>
<td>ERMS</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>I-II</td>
<td>ERMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low, subset 2</td>
<td>1</td>
<td>III (non-orbit)</td>
<td>ERMS</td>
<td>5%</td>
<td>70–85%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I-II</td>
<td>ERMS</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>2–3</td>
<td>III</td>
<td>ERMS</td>
<td>27%</td>
<td>73%</td>
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<tr>
<td></td>
<td>1–3</td>
<td>I–III</td>
<td>ARMS</td>
<td>25%</td>
<td>65%</td>
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<tr>
<td>High</td>
<td>4</td>
<td>IV</td>
<td>ERMS</td>
<td>8%</td>
<td>35%</td>
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<tr>
<td></td>
<td>4</td>
<td>IV</td>
<td>ARMS</td>
<td>8%</td>
<td>15%</td>
</tr>
</tbody>
</table>

RMS, rhabdomyosarcoma; ERMS, embryonal RMS; ARMS, alveolar RMS; EFS, event-free survival.

Hawkins. Peds Blood Cancer. 2013
IRS IV: The Gold Standard for Local Control

• Last trial with a major radiation question
• Treated with very intense chemotherapy including VAC (C = cyclophosphamide 26.4 G/m²)
• RT Dose
  • Group I, Stage 1/2: No RT
  • Group I-II, stage 3: 41.4 Gy
  • Group III Randomization:
    • Conventional Fractionation (50.4 Gy, 1.8 Gy daily, 28 fractions)
    • Hyperfractionation 59.4 Gy (1.1 Gy BID, in 54 fractions)
• Volume GTV + 2 cm
Rhabdomyosarcoma: IRS-IV local control
Outcomes

5 year local control for Group III RMS

- Extremity  96%
- Orbit      95%
- Bladder/Prostate  90%
- Head and Neck    88%
- Parameningeal    84%
- Other         90%

Crist. JCO. 2001
Donaldson. IJROBP. 2001
IRS IV: No Advantage to Hyperfractionation

Fig. 3. FFS for patients who actually received the CFRT or HFRT to which they were randomized.

Log Rank Test: p=0.67
Rhabdomyosarcoma  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: 41.4 Gy
• Group III Non-orbit 50.4 Gy
• Whole lung 15 Gy in 10 fractions (12 Gy in 8 fractions if <7 yo)

* If patient has had an amputation and margins are clearly negative then no adjuvant radiation
Target Volumes

- Typically GTV is pre-chemotherapy extent of disease, accounting for pushing margins.
  - Infiltrating margins that recede should be included in GTV
- CTV = GTV + 1.5 cm
- PTV site specific

- ARST0531 employed cone down after 36 Gy to post-chemo extent of disease (but including infiltrating extent of disease)
  - Reports from that study not available yet
Many “Rules of Thumb” in RMS: Some examples

• Confine orbital CTV to orbit unless tumor extended beyond the orbit

• Boys ≥ 10 years old with paratesticular rhabdomyosarcoma should have “aggressive lymph node sampling” even if clinically negative, and boys of all ages should have LND if clinically involved regional lymph nodes

• Treat only regionally-involved nodal basins

• Have a low threshold for treating regionally involved nodal basins in patients with RMS of perineal and peri-anal regions (Wolden, et al, IJROBP. 2014)

• Radiation typically given with concurrent chemotherapy, most commonly Vincristine/Cyclophosphamide alone or alternating with Vincristine/Irenotecan
Orbital ERMS: Is 45 Gy Enough?  Chemotherapy and RT dependent

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Dose (Gy)</th>
<th>Chemotherapy¹</th>
<th>Timing of RT (Week)</th>
<th>5 year local failure rate</th>
<th>5 year failure-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS-III (n=71)</td>
<td>41.4-50.4</td>
<td>VA</td>
<td>2 or 6²</td>
<td>16%</td>
<td>79%</td>
</tr>
<tr>
<td>IRS-IV (n=50)</td>
<td>50.4-59.4</td>
<td>VAC (26.4 g/m²)/VAI/VIE</td>
<td>9</td>
<td>4%</td>
<td>94%</td>
</tr>
<tr>
<td>D9602 (n=77)</td>
<td>45</td>
<td>VA</td>
<td>3</td>
<td>14%</td>
<td>86%</td>
</tr>
<tr>
<td>ARST0331³</td>
<td>45</td>
<td>VAC (4.8 g/m²)</td>
<td>13</td>
<td>13%</td>
<td>87%</td>
</tr>
</tbody>
</table>

ARST0331 Regimen of modest dose Cyclophosphamide and 45 Gy RT associated with suboptimal local control in patients with < CR to induction chemo

Overall (n=62⁴)
- Week 12 CR (n=15)
  - 13%
  - 0%
  - 87%
  - 100%
- Week 12 PR/SD (n = 38)
  - 16%
  - 84%

¹Cumulative dose of cyclophosphamide shown in parentheses
²Patients less than 6 years old with tumors less than 5 cm received radiation at week 2, others received radiation at week 6
³Only ARST0331 assessed response to induction chemotherapy.
⁴Includes 2 patients with progressive disease at the end of induction chemotherapy and 7 patients with unknown disease status at week 13 or incomplete information.

Abbreviations: ERMS = Embryonal Rhabdomyosarcoma; IRS = Intergroup Rhabdomyosarcoma Study; VA = vincristine, dactinomycin; VAC = vincristine, dactinomycin, cyclophosphamide; VAI = vincristine, dactinomycin, ifosfamide; VIE = vincristine, ifosfamide, etoposide

Ermoian, et al. Ped Blood Cancer. Accepted for pub
Modest Dose Cyclophosphamide also a Concern with other Rhabdomyosarcoma Patients

Reduction of Cyclophosphamide Dose for Patients With Subset 2 Low-Risk Rhabdomyosarcoma Is Associated With an Increased Risk of Recurrence: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group

David O. Walterhouse, MD1; Alberto S. Pappo, MD2; Jane L. Meza, PhD3; John C. Breneman, MD4; Andrea Hayes-Jordan, MD5; David M. Parham, MD6; Timothy P. Cripe, MD, PhD7; James R. Anderson, PhD8; William H. Meyer, MD9; and Douglas S. Hawkins, MD10

• Expected 10 failures in 66 patients; had 20 failures
• Attributed to lower cyclophosphamide dose and omission of local therapy in vaginal RMS patients with CR
• Cancer. Ahead of print. 2017
Rhabdomyosarcoma: Timing of Radiation

Get the chemo in first, if you can ...

• RT is myelosuppressive in patients who need count-dependent chemotherapy

• When patients with parameningeal disease with high risk features are excluded, early treatment failures are rare. (Minn. JCO. 2010)

• Most recent COG protocols place local therapy after week 12 in most cases
Rhabdomyosarcoma: Intermediate Risk
Treatment Local Therapy Can Start at Week 12

Log-Rank, p=0.65

Proportion With Local Failure

D9803
IRS-IV

Week 12
Week 4

Spauding. IJROBP. 2013
Rhabdomyosarcoma Metastases: Should they be treated? Perhaps, if feasible

- On IRS-IV better control (80 vs 56%) of lung mets if patients treated with whole lung irradiation. (Rodeberg. J Ped Surg. 2005)

- Liu, et al, showed that among 13 patients with Ewing Sarcoma (ES) and rhabdomyosarcoma (RMS) metastases, all but 1 treated site was controlled with definitive doses of RT (Ped Blood Cancer. 2011)

- Casey, et al, showed that ES and RMS bone metastases were controlled in 43 of 49 patients treated with definitive doses of RT (Ped Blood Cancer. 2015)

- On metastatic study ARST08P1, even when directed to treat metastases, many Rad Oncs did not
Omit local therapy?

- **MMT 89: 1989-95**
  - 503 non-metastatic RMS patients treated 1989-95
  - Goal to avoid radiotherapy with chemotherapy regimens
  - 5 year OS 71%, EFS 57%
  - 49% cured without local therapy

Stevens. JCO. 2005
There is a **mortality** cost to omitting local therapy

<table>
<thead>
<tr>
<th></th>
<th>MMT 89 5 year % rate</th>
<th>IRS IV 5 year % rate</th>
</tr>
</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>
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<tr>
<td>Embryonal</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Orbit</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>64</td>
<td>35</td>
</tr>
<tr>
<td>Extremity</td>
<td>46</td>
<td>35</td>
</tr>
</tbody>
</table>

Donaldson. JCO. 2005
Rhabdomyosarcoma Take-Home Points

• Very radiosensitive tumor histology
• Radiation continues to play an essential role in local therapy of most rhabdomyosarcoma cases
• Radiation therapy is associated with late morbidity, but its omission is also associated with higher mortality risk
• 50.4 Gy remains the definitive dose for treating gross disease in most cases
• If feasible, treating metastases can be locally effective
Ewing Sarcoma

- 300 cases per year in the US
- Can arise in bone or soft tissue
- Associate with classic t(11,22) EWS-FLI1
- Fairly radiosensitive
- “small round blue cell tumor” with “onion skinning”

Arndt. CAS. NRJM. 341-352. 1999
Ewing sarcoma: Age, gender distribution

Hawkins DS, Principles and Practice of Pediatric Oncology, 2011.
Ewing Sarcoma: Sites of Disease

Hawkins DS, Principles and Practice of Pediatric Oncology, 2011.
Ewing Sarcoma: Pre-chemotherapy Evaluation

• Primary Site: plain film, MRI and CT, biopsy
• Chest CT
• Urinalysis
• CBC and CMP
• Bilateral bone marrow aspiration, biopsy
• Echocardiogram, ECG
• Bone scan/PET scan
Outline of Ewing Sarcoma Treatment Regimen

Prognostic factors
- SR localized
- HR localized
- Mets (lung only)
- Mets (other)

Primary local control
- Neoadjuvant chemotherapy
- Early metastasis prophylaxis
- to facilitate conservative surgery

Maintenance chemotherapy
- Metastasis prophylaxis

Surgery

Radiotherapy

Metastasis local control

Gaspar. JCO 33:3036-3046. 2015
Ewing Sarcoma Chemotherapy: INT-0091 1988-92

- VACA +/- IE
- 17 chemo courses
- Local therapy
  - Surgery only: 34%
  - Radiation only: 39%
  - Combined: 22%

Grier HE, NEJM 2003; 348:694-701
Ewing Sarcoma Chemotherapy: The most recent clinical trial

- AEWS-1031
  - Standard therapy arm: Vincristine, Doxorubicin, Cyclophosphamide (VDC) alternating with Ifosfamide and Etoposide (IE), total of 17 cycles, with 6 cycles before local therapy
  
  - Experimental arm: Adding Vincristine, Topotecan and Cyclophosphamide (VTC) to standard therapy

- Study closed; no reports yet
Histologic Response to Induction Chemotherapy Matters


  - CESS 81
  - CESS 86
  - EICESS 92

- Patients treated with surgery only with wide margins:
  - Wide resection, poor histologic response => 12% local failure rate
  - Wide resection, good histologic response => 1% local failure rate
Functional Imaging Response Matters

- 24 patients with localized ES, 1995-2002 SCH, UWMC
- Treated with chemo
- Median 4 courses
- Range, 2-7 courses

Hawkins DS JCO 2005 23:8828-8834
Ewing Sarcoma Local Therapy

• No randomized studies to guide surgery, RT or Surgery + RT

• Surgery alone often preferred and is chosen in a majority of ES cases.
  • “Expendable bones” include ribs, fibula, clavicle

• On AEWS 1031 all of the following 4 options were allowed at the discretion of the treating physicians:
  • RT alone
  • Surgery alone
  • Surgery + post-op RT
  • ***Pre-op RT (36 Gy) ->Surgery-> post-op RT (if necessary)
Three options for local control:

- Surgery alone
- 50.4 Gy/ 28 fxs post-op if margins < 5 mm
- 55.8 Gy/ 31 fxs definitive RT
- CTV margins have decreased from whole bone or muscle bundle to 2 cm
INT-0091 Local Failure by Local Therapy Modality

• All site local only failure rate
  • Surgery alone 5.1 %
  • Radiation alone 9.2 %
  • Surgery plus radiation 2.0 %
  • p=0.16

• Pelvic tumor subset failure rate
  • Yock, et al. JCO 24:3838. 2006
  • Surgery alone 25%
  • Radiation alone 25%
  • Surgery + radiation 10.5%
  • p = 0.46
  • EFS also not significantly different
Ewing Sarcoma Patterns of Failure: Mostly Systemic

- GPOH trials 1980-1998
- 1549 patients (both localized, metastatic)
- 714 relapses
- 72% within 2 years after diagnosis
- Systemic relapse most common, usually lung

Stahl M, Ped Blood Cancer 2011; 23:8828-8834
Metastatic Ewing Sarcoma: What to treat?

- Prior references in Rhabdomyosarcoma section
- Haeusler, et al, showed that when patients with metastatic disease receive local therapy, they have better EFS. Cancer 2010; 116:443-50.
  - Review of 120 patients with metastases on EURO-EWING 99 trial treated at Muenster between 1998 and 2006

<table>
<thead>
<tr>
<th>Local therapy delivered to:</th>
<th>Percent of patients receiving this therapy</th>
<th>3 year Event free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither primary site nor metastases</td>
<td>27%</td>
<td>14%</td>
</tr>
<tr>
<td>Only primary site or metastases</td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td>Both primary and metastases</td>
<td>39%</td>
<td>39%</td>
</tr>
</tbody>
</table>

- Absence of local treatment is EFS risk \( p=0.027 \)
 Radiation Details

• All patients should have all local and distant disease addressed with an appropriate local control modality.

• Definitive local therapy (surgery, SBRT, EBRT) is recommended to all metastatic sites documented at the time of diagnosis.

• SBRT is recommended to all bone metastatic sites < 5 cm in maximal dimension (based upon maximal dimension at diagnosis) if not treated surgically.

• Optimal local control will be determined by the treating institution
Current Target Volume and Dose Recommendations: RT alone

- MRI essential for defining initial extent of disease, including all T2/FLAIR changes
- GTV1 includes pre-chemo extent of disease in soft tissue and bone
- CTV1 = GTV1 + 1-2 cm, with high threshold to reduce the volume for pushing margin
- GTV2 includes pre-chemo extent of disease in bone and post-chemo extent of disease in soft tissue.
- CTV2 = GTV2 + 1 cm
- PTV expansion site- and institution- specific
- Dose
  - PTV1 45 Gy in 25 fractions
  - PTV2 10.8 Gy in 6 fractions (0-5.4 Gy/3 fx if vertebral body lesion)
- Concurrent chemotherapy
ES Post-operative Radiation

• Threshold for radiation:
  • Positive margins (<5 mm)
  • <90% necrosis of tumor

• Dose:
  • If gross residual disease, treat to 55.8 Gy like in RT alone
  • 50.4 to PTV1 if <90% necrosis (+/- microscopically positive margin)
  • 50.4 Gy to PTV2 if microscopic+ and > 90% necrosis

• Post-operative target volumes
  • GTV1 and CTV1 are the same
  • GTV2 is the residual bone, microscopic margin soft tissue abnormality
  • CTV2 = GTV2 + 1

• Concurrent chemotherapy
Take Home Points for Ewing Sarcoma

• Local therapy often occurs after induction chemotherapy
• No randomized trials to show preferred local therapy modality
  • Analyses suggesting best local therapy is surgery + radiation may reflect selection bias
• Systemic recurrences remains the principle concern in many patients
• There is a strong rationale for treating metastases for durable control at those sites, and perhaps for EFS benefit
Brain Tumors

• Embryonal Tumors including Medulloblastoma
• Ependymoma
• Germ cell tumors
• Craniopharyngiomas
• Diffuse Intrinsic Pontine Gliomas
• Pilocytic Astrocytomas
Embryonal Tumors: PNETs went away in 2016!

And Medulloblastomas defined either histologically or genetically

<table>
<thead>
<tr>
<th>Embryonal tumours</th>
<th>9475/3*</th>
<th>9476/3*</th>
<th>9471/3</th>
<th>9477/3*</th>
<th>9470/3</th>
<th>9471/3</th>
<th>9471/3</th>
<th>9474/3</th>
<th>9470/3</th>
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<tbody>
<tr>
<td>Medulloblastomas, genetically defined</td>
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<tr>
<td>Medulloblastoma, WNT-activated</td>
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<td>Medulloblastoma, SHH-activated and TP53-mutant</td>
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<td>Medulloblastoma, SHH-activated and TP53-wildtype</td>
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<tr>
<td>Medulloblastoma, non-WNT/non-SHH</td>
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<td>Medulloblastomas, histologically defined</td>
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<td>Medulloblastoma, classic</td>
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<td>Medulloblastoma with extensive nodularity</td>
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<tr>
<td>Embryonal tumour with multilayered rosettes, C19MC-altered</td>
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<td>Embryonal tumour with multilayered rosettes, NOS</td>
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<tr>
<td>CNS neuroblastoma</td>
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<td>CNS ganglioneuroblastoma</td>
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<tr>
<td>Atypical teratoid/rhabdoid tumour</td>
<td>9508/3</td>
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<tr>
<td>CNS embryonal tumour with rhabdoid features</td>
<td>9508/3</td>
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</table>

Medulloblastoma

- 500-600 cases per year in the US
- Arises in the posterior fossa
- High potential for CSF dissemination
- Median age at presentation: 5-6 years

Medulloblastoma Rule of 20s

- Brain Tumors = 20% of childhood malignancy
- Medulloblastoma = 20% of childhood brain tumors
- Only 20% of children recently diagnosed with medulloblastoma still die from their disease (less with Av Risk, more with High Risk)
- Only 20% of medulloblastoma occurs in patients over 14

Sarah Leary, MD, Seattle Children’s Hospital, personal communication
Medulloblastoma Workup

- (Preferably) MRI brain and Spine prior to resection
  - To avoid artifacts from peri-resection blood
  - If disseminated disease, this may guide this surgeon regarding how aggressive to be
- Maximal safe resection
- Post-operative MRI brain
- *CSF specimen 10-14 days post-surgery*

- Metastases staging:
  - M0 No disease beyond primary site
  - M1 CSF positive
  - M2 Intracranial tumor beyond primary site
  - M3 Gross nodular seeding in spinal subarachnoid space
  - M4 Metastases beyond the cerebrospinal axis
Risk Stratification

• **Average** Risk: ≥ 3 years old, M0, no less than 1.5 cm² of residual disease
  - 5 year EFS 83%
  - 5 year EFS 73% with anaplasia

• **High** Risk: M+ or residual disease, or diffuse anaplasia (on most recent COG ACNS 0332 protocol)
  - 5 year EFS 65%

• Infants: less than 3 years old
  - 5 year EFS 65%
Posterior Fossa Syndrome

• Occurs in 15-25% of patients
• Can include
  • Mutism
  • Dysphagia
  • Truncal ataxia
  • Hypotonia
  • Increased mood lability
  • Gaze palsy
  • Occasionally respiratory failure
Treatment Regimen for Average Risk Medulloblastoma

• CCG-9892 established equivalency of reduced dose craniospinal irradiation (CSI, 23.4 Gy) with adjuvant CCNU, vincristine and cisplatin compare to CSI full dose CSI (36 Gy)

• Craniospinal Irradiation to 23.4 Gy in 13 fractions starting no later than 31 days after surgery

• Followed by boost to resection bed plus margin to 54 Gy with an additional 30.6 Gy in 17 fractions

• Radiation is typically delivered with weekly vincristine
• Boost
  • 30.6 Gy in 17 fractions
  • Resection bed plus 1.5 cm CTV margin, and whole posterior fossa are associated with EFS and OS
    • Use resection bed plus margin

• Craniospinal Irradiation
  • 18 Gy is inferior to 23.4 Gy
  • 18 Gy associated with 10% decrement in 5y EFS and 7% decrement in 5y OS
Example of tumor bed boost

• Example from Wolden, et al. (JCO 21:3079-3083. 2003)
Craniospinal Irradiation

- Includes whole brain and entire CSF space including the nerve roots and through bottom of thecal sac
- Bottom of thecal sac best seen on sagittal MRI imaging that includes the sacral spine
- Consider:
  - Lateral border at least 1 cm lateral to vertebral bodies
  - Inferior border at least 2 cm below bottom of thecal sac, at least at S2-S3 interspace
- Particular attention needs to be paid around the cribiform plate, where autocontouring tools often will not capture the inferior extent of the CSF space
- Start when feasible, but not more than 28-31 days after surgery
Prone Craniospinal Technique

- Set inferior edge
- Match opposed lateral brain field to spine field
  - Rotate the columnator to match the divergence of the spine field
  - Kick the couch so the brain field inferior edge matches the superior edge of the spine field
- Use 2 spine fields if necessary
- Cold spine match preferred over hot
  - Set brain-spine to avoid exit into shoulders and mandible
  - Feather the junction(s) or junction shift q5 fxs
Alternative Craniospinal Techniques

• Supine: easier for patient, easier if require anesthesia, but cannot visualize the match lines

• IMRT: more conformal with respect to high dose, but larger region receives low dose radiation.

• Proton radiation. Will discuss later.
A cautionary article about craniospinal irradiation: tomotherapy versus 3d CRT

<table>
<thead>
<tr>
<th>Organ</th>
<th>Excess absolute risk of radiation-induced cancer (cases/100 irradiated patients)</th>
<th>Absolute difference (tomo - conv)</th>
<th>Relative risk ratio (tomo/conv)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Tomo CSI 5.6</td>
<td>Conv CSI 4.3</td>
<td>1.3</td>
<td>1.3</td>
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<tr>
<td>Breast</td>
<td>Tomo CSI 15.7</td>
<td>Conv CSI 7.5</td>
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<td>Conv CSI 0.2</td>
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<tr>
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<td>Conv CSI 0.8</td>
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<tr>
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<td>Conv CSI 1.9</td>
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<tr>
<td>Thyroid</td>
<td>Tomo CSI 0.54</td>
<td>Conv CSI 2.4</td>
<td>-1.9</td>
<td>0.23</td>
</tr>
</tbody>
</table>

CSI, craniospinal irradiation; SMN, secondary malignancy. Bold values indicate statistically significant differences.
High Risk Medulloblastoma

- Craniospinal dose at least 36 Gy
  - Spine 39.6 if diffuse gross disease
  - Or focal boosts to spine to 45 Gy

- Boost whole posterior fossa to 55.8 Gy

- The current COG ACNS0332 trial includes the following features:
  - Radiation boost is to whole posterior fossa, even if M1 or M0 and diffuse anaplasia
  - Randomization to ± concurrent DAILY carboplatin during radiation
  - Randomization to ± Isotretinoin during and after maintenance
  - Patients with supratentorial PNET tumors recently no longer allowed on study
  - Study continues to enroll
Future Directions: Molecular Profiling of Medulloblastoma

Late Morbidity of Treating Medulloblastoma, as an example of late side effects and risks of CNS radiation

- Neurocognitive
- Secondary Malignancy
- Late Vascular Events
- Pituitary dysfunction
- Hearing loss
- Cataracts
- Decreased bone growth
- Hypothyroidism
- Hypothalamic dysfunction
- Dry eyes
- Pulmonary complications
- Heart disease
- Infertility
- Vision Loss
- Radiation Necrosis/Myelitis
Neurocognitive Effects of Treating Very Young Patients

• Fouladi. JCO. 23:7152-7160. 2005
• Patient with brain tumors and <4 years old
• Important differences between patients who received no RT, focal RT, and CSI

Baseline less than 100. Tumor and surgery effects.
Ependymoma

- Median age 5-6, but frequently present under 3 years old
- Approximately 300 cases per year
- 2/3 infratentorial, 1/3 supratentorial
- Infrequently present with CSF dissemination
- Frequently extend through Foramen of Magendie or Foramen of Luschka
Ependymoma

• Workup same as medulloblastoma

• Histology

• Grade I Myxopapillary most frequently seen in spine; usually surgically-managed, role of radiation therapy very controversial

• Grade II (Classic) and Grade III (Anaplastic) are usually intracranial

• Most important prognostic factors is extent of resection
  • 7 year EFS GTR vs STR : 77% vs 34%

• Grade has a smaller predictive effects
  • 7 year EFS Grade II vs. Grade III: 79% vs 61%
Ependymoma Treatment Algorithm

- Radiation therapy is local unless documented metastatic disease (in which patient receives CSI 36 Gy if ≥3 yo)

- Mainstay of therapy are surgery followed by radiation
  - The role of chemotherapy is not well established and is the subject of clinical trials
Ependymoma Treatment Algorithm

• GTR must be defined with great care
  • Ependymomas can be very invasive, not just extending through foramen of Magendie and Luschka, but sometimes into jugular foramen, internal acoustic canal, and even cavernous sinus
  • Must review pre-operative imaging (which hopefully includes fine cut MRI), operative note, post-operative imaging; as well as discuss with the surgeon

• CTV is typically GTV +1 cm

• PTV 0.3-0.5 cm
Radiation Dose

• Patterns of practice vary between 54 and 59.4 Gy

• Merchant. JCO. 22:3156-3162. 2004
  • Phase II trial to patients with localized ependymoma, age 1-22 years
  • 74/88 patients had GTR
  • 59.4 Gy to 73 patients or 54 Gy to 15 patients mostly under 18 months
  • 75% 3 year PFS; 8 of 20 recurrences were local-only
Ependymoma: Brainstem recovery after RT to 59.4 Gy

• Merchant, et al. IJROBP 76:496-503. 2010
• Reviewed 68 patients to assess recovery from deficits
  • 17 started with no deficits and developed no deficits
  • Risk factors for poor brainstem recovery: surgical morbidity and initial extent of the tumor
  • 4 developed progressive deficits at any time between 1 and 5 years
Ependymoma: Current protocol ACNS0831

• Examining roles of second look surgery, chemotherapy
• Omitting RT for patients with GTR of grade II supratentorial ependymoma
• Radiation: small margins, high doses
  • CTV1 = residual tumor and resection bed + 0.5 cm
  • CTV2 = residual tumor and resection bed, above the cord
  • Dose: 54 Gy to PTV1, 5.4 Gy to PTV2
Intracranial Germ Cell Tumors

• 2-4% of pediatric brain tumors in US and Europe
  • Up to 11% of pediatric brain tumors in Japan and Taiwan
  • Usually they arise from suprasellar and pineal regions
• 60% of germinomas are diagnosed in second decade
• M>F in pineal region
• F>M in suprasellar region
Presenting Symptoms and Differential Diagnosis of Tumors in Suprasellar and Pineal regions

Signs and Symptoms

- **Suprasellar**
  - Diabetes Insipidus (DI)
  - Neuroendocrine anomalies
  - Visual deficits

- **Pineal region**
  - Hydrocephalus (nausea/headaches)
  - Parinaud’s syndrome (decreased upward gaze, Argyll-Robertson pupil, and convergence nystagmus)

Differential Diagnosis

- **Pineal region**: GCT, pineoblastoma, pineocytoma, teratoma, glioma

- **Suprasellar region**: GCT, craniopharyngioma, teratoma, histiocytoma

- **Tumor markers**: CSF > serum
  - B-hCG and AFP
Workup

• Serum and CSF tumor cell markers
• MRI brain and spine
• Ophthalmologic evaluation
• Hypothalamic and pituitary function evaluation
Interpretation of Tumor Markers

• Germinomas. 60% of tumors.
  • MAY have elevated B-hCG (up to 50-75 IU/L) but B-hCG may also be normal.
  • However, AFP is always WNL

• Non-germinomatous GCT (40%)
  • Choriocarcinoma (markedly elevated B-hCG)
  • Yolk sac tumors (elevated AFP)
  • Embryonal carcinoma (may have elevated markers)
GCT: May be multifocal

- 5-10% of germinomas are multifocal
- Not necessarily treated at metastatic disease. Current COG ACNS1123 localized germ cell tumor treats such patients as non-metastatic
Biopsy/resection

• Surgery can be associated with morbidity, particularly in the pineal region; therefore role of surgery/resection is controversial

• For germinomas
  • Biopsy is preferred
  • COG ACNS1123 allows enrollment without a biopsy
  • Tumors respond to chemotherapy and radiation so well that extent of resection is not important

• For NGGCT
  • Biopsy is preferred
  •Extent of resection is important
Management of Pure Germinomas

• Historically, CSI (24-36 Gy) with boost to primary site to 45-50 Gy yielded 90-100% DFS (Bamberg. JCO. 1999; Maity. IJROBP. 2004)

• However, combined modality therapy was introduced to reduce late morbidity

• For localized disease, induction chemo (such as 4 cycles carbo/etop) followed by whole ventricular radiation

• WV Atlas at [www.qarc.org](http://www.qarc.org)
Localized CNS Germinomas Management

• Whole ventricle 24 Gy in 1.5 Gy fractions
• Boost to 30-36 Gy in 1.5 Gy fractions depending on whether CR is achieved
• ACNS1123 is examining reducing the WV dose to 18 Gy in patients with CR
• If metastatic, CSI

MacDonald. IJROBP. 2011
NGGCT Management

- Resection
- Chemotherapy such as 6 cycles of alternating carbo/etoposide and ifos/etoposide
- Then CSI 36 Gy (1.8 Gy fxs) followed by primary site boost to 54 Gy

- ACNS 1123 Stratum 1 (NGGCT) examined reducing the target volume from craniospinal to whole ventricle
  - This stratum closed early because of higher than anticipated relapses
Craniopharyngioma

- Similar presentation as suprasellar GCT
- Arise from remnants of Rathke pouch
- Radiographically often distinct due to cysts and calcifications
Craniopharyngioma Management

• GTR associated with 70-85 % DFS

• However, there can be tremendous morbidity associated with GTR: neuroendocrine dysfunction including DI, vision loss, and hypothalamic dysfunction

• STR + RT also associated with 85-90% DFS
Craniopharyngioma RT Details

• Target volume:
  • GTV = residual disease including cysts
  • CTV = GTV + 0.5-1 cm
  • PTV = CTV + 0.3-0.5 cm

• Dose: 54 Gy in conventional fractionation

• Dose limiting OARs include brainstem, optic nerves, hippocampi, and temporal lobes
  • Pituitary dysfunction is very likely

• Cyst and tumor swelling during and after radiation can threaten adequacy of target volumes and vision loss
  • Should obtain multiple MRI studies while on treatment to confirm target volumes
Pilocytic Astrocytoma

• Low grade glioma
• Typically contrast enhancing, with cysts
• Characterized by Rosenthal fibers, but Rosenthal fibers are not unique to PA

O’brien. AOCR. 2013
Wippold. AJNR. 2006
Pilocytic Astrocytoma Management

• Management is primarily surgical

• Patterns of practice vary, but RT increasingly reserved for symptomatic unresectable tumors, often after chemotherapy proven ineffective

• Radiation Therapy is effective for durable control of the tumor
  • Early RT associated with better EFS (90%) but equivalent OS
  • However, there are late recurrences
  • A growing body of literature surrounding late effects of radiation

• Chemotherapy can delay and possibly avert the need for radiation

• ACNS0221 has been closed for 4 years; it examined margins (0.5 cm CTV) used for radiotherapy for patients who progressed on chemotherapy

• Standard RT is typically 50.4-54 Gy in 1.8 Gy fractions to lesion + 1 cm CTV + 0.3-0.5 cm PTV
Diffuse Intrinsic Pontine Glioma

- Functionally a GBM of the brainstem
- Biopsy can be associated with severe injury and so the diagnosis can be made by imaging. Very important that the lesion not be mistaken for LGG
- Radiation is the only proven means of extending survival
- Median survival is 9-12 months
DIPG Radiation Guidelines

• Start radiation promptly
• Typical regimen is 54 Gy in 30 fractions to MRI extent of disease plus 1 cm expansion for CTV (anatomically confined) and 0.3-0.5 cm PTV expansion
• Patients often clinically improve before succumbing to their disease
Take Home Notes: CNS tumors

• Radiation therapy remains effective and often essential for effective clinical outcome in brain tumors, including in young children

• Recent efforts to de-escalate craniospinal dose in Av Risk Medullo and field size in NGGCT have NOT been successful.

• It is associated with critical late effects that impact patients for the rest of their lives
Protons: The Bragg Peak

Figure ES1. Dose distribution by tissue depth for proton and photon radiation.

(A) proton RT plan and (B) intensity-modulated RT plan for infratentorial ependymoma.

MacDonald. Neuro-Oncology. 2013

Promise of Proton Therapy

• Anticipate improved late effects with respect to neuroendocrine, hearing loss, neurocognitive effects, hypothyroidism, infertility, secondary malignancy, etc.
• Many single institution retrospective and some Phase II studies.
• Equivalent disease control and favorable side effect profiles.
• Multiple studies show expected **cost benefits** due to decreased late effects.
• COG trials agnostic to the type of radiation for **most** diseases including Ewing Sarcoma, Rhabdomyosarcoma, most brain tumors, and Hodgkin Lymphoma.
• Photon therapy remains viable treatment for nearly all pediatric malignancies.
Proton Example: Infratentorial Ependymoma

Massachusetts General Hospital Experience

• 70 patients, mean age 38 months @ dx
• Median follow-up of 46 months,
• 3-year
  • local control 83%,
  • progression-free survival 76%
  • overall survival 95%
• Two of 42 required growth hormone replacement

• Two of 23 patients with auditory records had hearing loss
• No secondary malignancies
• No change in intelligence measurements, albeit with short follow up in young patients

MacDonald. Neuro-Oncology. 2013
Challenges of Proton Therapy

• No randomized studies in pediatric patients (although no RCTs for IMRT, etc)

• Accessing proton therapy in timely manner for patients requiring travel and time-sensitive RT (like medulloblastoma)

• Coordinating care with Referring Institutions

• Logistical challenges for families

• ?Insurance authorization

• Radiobiologic Effectiveness questions
Proton Brainstem Side Effects in Pediatric Patients: Identifying the Risk Factors


303 Patients

11 cases of symptomatic brainstem injury

Risk factors include:
• Max dose >60 Gy
• V52.4>50%

Figure 1. A comprehensive dose-volume histogram (DVH) including each patient’s DVH curve. The colored curves correspond with the 11 patients who experienced toxicities outlined in Table III as follows: ● 1; 2; ● 3; ●4; ●5; ●6; ●7; ●8; ●9; ●10; ●11. The inset provides a magnified view of the high-dose range.
Thank you!

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