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
References to Open Studies

• 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.

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>226,870</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,470</td>
<td>109,690</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73,420</td>
<td>70,040</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>55,600</td>
<td>47,130</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>44,250</td>
<td>43,210</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,250</td>
<td>32,000</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,160</td>
<td>31,970</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>28,540</td>
<td>24,520</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,830</td>
<td>22,280</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,090</td>
<td>21,830</td>
</tr>
<tr>
<td>All Sites</td>
<td>848,170</td>
<td>790,740</td>
</tr>
</tbody>
</table>

Pediatric cancers: 12,500 cases in patients up to 15 years old
Where do pediatric cancers fit into overall picture of Cancer in the United States?

Deaths

1,284 children (age 0-14) died of cancer in 2008

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2012. Estimates are rounded to the nearest 10 and exclude basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.
What cancers do children get?

Li. Pediatrics. 2008

- I Leukemias: 26.25%
- II Lymphomas: 14.57%
- III CNS neoplasms: 17.57%
- IV Neuroblastomas: 5.01%
- V Retinoblastoma: 1.81%
- VI Renal tumors: 3.99%
- VII Hepatic tumors: 1.16%
- VIII Malignant bone tumors: 5.39%
- IX Soft tissue sarcomas: 7.15%
- X Germ cell neoplasms: 6.49%
- XI Other epithelial neoplasms: 10.15%
- XII Other and unspecified malignant neoplasms: 0.46%

Cases = 36,446
Rate = 165.92 per million
Trends in Outcome 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
  • Diffuse Intrinsic Pontine Glioma
  • Pilocytic Astrocytoma

• Protons
Wilms Tumor

• Most common abdominal tumor of childhood

• 6% of childhood cancers, approximately 500 cases/year

• Male: Female is 0.92 for unilateral disease, 0.6 for bilateral disease; bilateral disease presents earlier; Bilateral presentation 4-8%

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

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

• Associated with congenital anomalies in 10-13% of cases
  • Aniridia
  • Genitourinary Disorders: fused kidney, hypospadism, double collecting system
  • Hemihypertrophy
Wilms Tumor-Associated Anomalies

- **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 any one of the following elements or a combination thereof:
  - 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)
Wilms Tumor Workup

- Ultrasound
- CBC and complete metabolic panel
- CT abdomen
- Chest imaging
- Bone scan in CCSK and RTK
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 Hematogenous Metastases beyond the abdomen

• Stage V Bilateral Disease
Wilms Tumor Radiation Therapy

- No RT for Stage I or II Favorable Histology

- RT for all focal and diffuse anaplasia, CCSK, or RTK

- Flank RT to 10.8 Gy/6 fx 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 fx for positive cytology, tumor spill or peritoneal seeding.
  
  • Boost residual disease by 10.5 Gy/7 fx
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 unresected 10.8 Gy and not resected 19.8 Gy

Start radiation no greater than 10-14 days after surgery
Wilms Tumor Radiation Volumes and Fields

• 3D planning can be used, but 2D principles still acceptable

• Flank radiation: Encompasses pre-resection volume of tumor 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
Two Evolving Issues in Wilms Tumor Radiation

- IMRT for Whole Lung Irradiation
  - Kalapurakal IJROBP 2013 show cardiac sparing feasible with IMRT for WLI

- Deferring Whole Lung Irradiation in FH pts to see if mets resolve with upfront chemotherapy?
  - AREN0533 closed
  - Results presented in abstract at ASCO 2015: modest increase in EFS with no difference in OS
  - Farooqi. Peds Blood Cancer. 2014. If Abd and whole lung fields treated separately, potentially higher pulmonary and cardiac risks
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 acute 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 CMP
- CT chest/abdomen/pelvis
- Tumor resection or biopsy
- Urine catecholamines
- Bone marrow biopsies
- MIBG scans
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
• 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>NA</td>
<td>NA</td>
<td></td>
<td>A</td>
<td>(very low)</td>
</tr>
<tr>
<td>L1</td>
<td></td>
<td>Any, except GN maturing or GNB intermixed</td>
<td>NA</td>
<td>Amplified</td>
<td></td>
<td>B</td>
<td>(very low)</td>
</tr>
<tr>
<td>L2 &lt; 18</td>
<td></td>
<td>Any, except GN maturing or GNB intermixed</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>D</td>
<td>(low)</td>
</tr>
<tr>
<td>L2 ≥ 18</td>
<td></td>
<td>GNB nodular neuroblastoma</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>E</td>
<td>(low)</td>
</tr>
<tr>
<td>M &lt; 18</td>
<td></td>
<td>NA</td>
<td>Amplified</td>
<td>Hyperdiploid</td>
<td></td>
<td>F</td>
<td>(low)</td>
</tr>
<tr>
<td>M &lt; 12</td>
<td></td>
<td>NA</td>
<td>Diploid</td>
<td>J (intermediate)</td>
<td></td>
<td>G</td>
<td>(intermediate)</td>
</tr>
<tr>
<td>M 12 to &lt; 18</td>
<td></td>
<td>NA</td>
<td>Diploid</td>
<td>J (intermediate)</td>
<td></td>
<td>I</td>
<td>(intermediate)</td>
</tr>
<tr>
<td>M ≥ 18</td>
<td></td>
<td>NA</td>
<td>Amplified</td>
<td></td>
<td></td>
<td>P</td>
<td>(high)</td>
</tr>
<tr>
<td>MS &lt; 18</td>
<td></td>
<td>NA</td>
<td>No</td>
<td>Q (high)</td>
<td></td>
<td>R</td>
<td>(high)</td>
</tr>
</tbody>
</table>

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

Pinto. JCO. 2015
Rationale for Radiation Therapy

• 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.
  • If TBI conditioning, 20% local failure
  • If chemotherapy conditioning, local control was 50
  • $P = 0.022$
  • Haas-Kogan. IJROBP. 2003.
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

Pinto. JCO. 2015
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

• Sequence of High Risk therapy usually includes staging including biopsy->induction chemotherapy->resection-> myeloablative chemotherapy and stem cell rescue->THEN RT ->Then post-consolidation chemotherapy

• The initial target volume 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

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

• GTV2 = residual disease > 1 cm³
  • CTV2 = GTV2 + 1 cm

• Patients often treated under anesthesia

• 4D planning CTs can be employed to minimize PTV expansions
High Risk Neuroblastoma Radiation Treatment Details

• PTV1 treated to 21.6 Gy in 12 fractions
• PTV2 treated to 14.4 Gy in 8 fractions

• Treatment of metastatic disease is controversial, and often reserved for functionally active residual metastases after surgery
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.
Neuroblastoma Take Home Points

• Radiation plays critical role in treating high risk neuroblastoma
• Radiation takes place after induction chemotherapy, tumor resection, and myeloablative chemotherapy
• The GTV is the extent of primary disease and draining LN at the time of resection, whenever that occurs
• AOR planning dose limits are very low
Hodgkin Lymphoma

• Ann Arbor staging (and assess for bulk)
• Historically treated with total lymphoid irradiation
• 44 Gy
• Terrible late effects
  • Cardiac/vascular
  • Secondary malignancies
  • Hypothyroidism
  • Sterility
  • Musculoskeletal anomalies
One imagine that captures the challenge of curing this disease

Types of secondary Malignancies

- Stanford Experience
  - 694 patients followed for 1-31 years
  - Nearly half receive total lymphoid irradiation
  - 59 secondary malignancies in 56 patients
Reduced dose 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


• Also found that decrease breast cancer risk was associated with decreased duration of ovarian function
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 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

Fig. 1. Treatment protocol. ABVE-PC = doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; RER = rapid early response; SER = slow early response; CR = complete response; IFRT = involved field radiation therapy; DECA = dexamethasone, etoposide, cisplatin, cytarabine.
AHOD0031: Intermediate Risk HL trial 2002-2010 with 1712 patients

- Overall
  - OS 97.8%
  - EFS 85%

- EFS
  - RER 86.9%
  - SER 77.4%

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

Friedman, et al. JCO. 2014
Relapse patterns on AHOD0031

- Relapses rarely occur solely in new sites
- In irradiated patients, relapses rarely occur solely out of field

AHOD0031: Relapses Occur in both bulk and nonbulk sites

- Suggests concern about only treating bulky disease sites
High Risk Disease

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

• Results not published
AHOD1331: RCT for high risk patients of 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
- This radiation varies from established patterns of care and is for research purposes, and only on study.
Take Home Points

• Although Hodgkin Lymphoma is very radiosensitive, doses and target volumes have steadily come down over decades because of concern for late effects

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

• AHOD 0031 is a landmark study that justifies not using adjuvant radiation in intermediate patients who are rapid early responders and achieve complete response, although questions remain about patients with LMA
Rhabdomyosarcoma

• A radiosensitive sarcoma
• Most common soft tissue sarcoma of childhood
  • 350 cases per year in US
Rhabdomyosarcoma Age Distribution

c/o Doug Hawkins, MD
Rhabdomyosarcoma Site Distribution

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

C/o Doug Hawkins, MD
Rhabdomyosarcoma Histologic Subtypes

• Favorable
  • Embryonal, botryoid, and spindle cell
  • Embryonal patients typically younger
  • Vast majority of RMS patients
  • Typically FOXO1 fusion negative

• Unfavorable
  • Alveolar
  • Often older (adolescent patients)
  • Minority of RMS patients
  • FOXO1 fusion positive
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
• 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
Rhabdomyosarcoma: A more 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>
</tr>
</tbody>
</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>
## Risk Stratification Translates to Outcomes

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Stage</th>
<th>Group</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, subset 1</td>
<td>1</td>
<td>I–II</td>
<td>ERMS</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>III (orbit)</td>
<td>ERMS</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I–II</td>
<td>ERMS</td>
</tr>
<tr>
<td>Low, subset 2</td>
<td>1</td>
<td>III (non-orbit)</td>
<td>ERMS</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I–II</td>
<td>ERMS</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2–3</td>
<td>III</td>
<td>ERMS</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>I–III</td>
<td>ARMS</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>IV</td>
<td>ERMS</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IV</td>
<td>ARMS</td>
</tr>
</tbody>
</table>

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/m^2)

• 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.
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 very site specific

• ARST0531 employed cond 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 Rhabdomyosarcoma: 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 if involved

• 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)
Orbital ERMS: Is 45 Gy enough?

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Dose (Gy)</th>
<th>Chemotherapy*</th>
<th>5 year local failure rate</th>
<th>5 year FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS-III (n=71)</td>
<td>41.4-50.4</td>
<td>VA</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/VAE</td>
<td>4%</td>
<td>94%</td>
</tr>
<tr>
<td>D9602 (n=77)</td>
<td>45</td>
<td>VA</td>
<td>14%</td>
<td>86%</td>
</tr>
<tr>
<td>ARST0331 Overall (n=53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 CR (n=15)</td>
<td>45</td>
<td>VAC (4.8 g/m²)</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Week 12 PR/SD (n = 38)</td>
<td>45</td>
<td>VAC (4.8 g/m²)</td>
<td>17%</td>
<td>81%</td>
</tr>
</tbody>
</table>

*Cumulative dose of cyclophosphamide shown in parentheses

Abbreviations: ERMS = Embryonal Rhabdomyosarcoma; IRS = Intergroup Rhabdomyosarcoma Study; VA = vincristine, dactinomycin; VAC = vincristine, dactinomycin, cyclophosphamide; VAI = vincristine, dactinomycin, ifosfamide; VAE = vincristine, dactinomycin, etoposide;
Orbital ERMS: Is 45 Gy enough?

COG Soft Tissue Committee is proposing (manuscript not accepted by peer-reviewed journal yet)

• With ASRT0331 Chemotherapy (including lower dose cyclophosphamide) Group 3 ERMS of the orbit should be treated with 50.4 Gy if not a complete response (CR)
• No position on dose for patients who achieve a CR
Rhabdomyosarcoma: Timing or Radiation

• Low risk: Week 12

• High risk: Week 20

• Intermediate Risk:
  • Week 4 or Week 12?
Rhabdomyosarcoma: Intermediate Risk
Treatment Local Therapy Can Start at Week 12

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

- On IRS-IV 80% control of lung metastases treated with radiotherapy compared to 56% to patients not receiving lung radiation (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 avoiding 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>
</tr>
<tr>
<td>Embryonal</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Orbit</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>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
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
- SRBC tumor with “onion skinning”

Arndt. CAS. NRJM. 341-352. 1999
MRI Imaging of Ewing Sarcoma

• T1 with contrast and STIR or T2 necessary to define the tumor
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
• Bone scan
• Chest CT
• Bilateral bone marrow aspiration, biopsy
• Echocardiogram
• Renal function assessment
• 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


• Combined results of three trials (1981–1999):
  • 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 chose a majority of the time in ES cases.
• 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)
RT Intergroup Ewing Sarcoma Studies

• Three options for local control
  • Surgery alone
  • 50.4 Gy/ 28 fx post-op if margins < 5 mm
  • 55.8 Gy/ 31 fx definitive RT
  • 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
  - Surgery alone 25%
  - Radiation alone 25%
  - Surgery + radiation 10.5%
  - P = 0.46
  - EFS also not significantly different
Cooperative Ewing Sarcoma Study (CESS 81, 86, EICESS 92)

• Local control best with surgery (with radiation as indicated) >90%
  • Pre-op RT 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
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

Slide c/o Doug Hawkins, MD
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
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 + 1-1.5 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
- PTV1 45 Gy in 25 fractions
- PTV2 10.8 Gy in 6 fractions (0-5.4 Gy/3 fxs if vertebral body lesion)
ES Post-operative Radiation

- Not as clearly defined at definitive radiation
- Threshold for radiation:
  - Negative margins (5 mm)
  - <90% necrosis of tumor
- Post-operative target volumes
  - GTV1 and CTV1 are the same
  - GTV2 is the residual bone, microscopic margin soft tissue abnormality
  - CTV2 = GTV2 + 1
- Dose:
  - If gross residual disease, treat to 55.8 Gy like in RT alone
  - 50.4 to PTV1 if microscopic+ and <90% necrosis
  - 50.4 Gy/ 28 fx to PTV2 if microscopic+ and > 90% necrosis
Take Home Points for Rhabdomyosarcoma

• Both tumors are radiosensitive
• Radiation continues to play an essential role in management of many cases, and is associated with excellent local control
• Systemic recurrences remain a great concern in many patients
• Local therapy almost always occurs after induction chemotherapy
• There is a strong rationale for treating metastases for durable control at those sites, and perhaps for EFS
Brain Tumors

- Embryonal Tumors including Medulloblastoma
- Ependymoma
- Germ cell tumors
- Craniopharyngiomas
- Diffuse Intrinsic Pontine Gliomas
- Pilocytic Astrocytomomas
Brain Tumors: Children Compared to Adults

• In children
  • Much more likely to be primary brain tumors rather than metastases
  • Much more likely to be infratentorial than supratentorial
  • Patients are often long term survivors but more sensitive to late effects
  • Heightened concern about neuroendocrine, neurocognitive, auditory, late vascular, and other risks
Embryonal Tumors

• Medulloblastoma
• Primitive Neuroectodermal Tumor
• Atypical Teratoid/Rhabdoid Tumor
• Pineoblastoma
Medulloblastoma

• 500-600 cases per year in the United States

• By definition, medulloblastoma 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 (actually closer to 15% now)
• 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
Posterior Fossa Syndrome

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

• **Average** Risk: ≥ 3 years old, M0, no residual disease and >1.5 cm^2

• **High** Risk: M+ or residual disease, or diffuse anaplasia (on most recent COG ACNS 0332 protocol)

• Infants: less than 3 years old
Treatment Regimen for Average Risk Medulloblastoma

• CCG-9892 established equivalency of reduced dose craniospinal irradiation (CSI, 23.4 Gy) with adjuvant CCNU, vincristine and 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 or posterior fossa to 54 Gy with an additional 30.6 Gy in 17 fractions

• Radiation is delivered with weekly vincristine
What is the target for the boost?

• ACNS0331 is examining boosts of whole posterior fossa vs. resection bed plus 1.5 CTV expansion. The study is closed to accrual (July 2015) and results not reported.

• Merchant et al. (IJROBP 70:782-787. 2008) showed in a 4 institution Phase II study excellent outcomes with resection bed + 2 cm.

• Wolden, et al. (JCO 21:3079-3083. 2003) showed similar recurrence pattern with tumor bed (+ 1-2 cm) compared to series with whole posterior fossa

• Growing consensus to use CTV = resection bed plus 1.5 – 2 cm expansion confined by tentorium and bones
Example of tumor bed boost

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 fx s
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.
ACNS0331: Trial closed and results are pending

• Average Risk study

• Patients age 3-7 yo randomized to CSI 18 Gy vs 23.4 Gy (all older patients receive CSI 23.4 Gy)
  • THIS IS A STUDY QUESTION

• All patients randomized to whole posterior fossa radiation vs. resection bed plus margin
High Risk Medulloblastoma

- Craniospinal dose at least 36 Gy
  - 39.6 if diffuse gross disease
  - Or focal boosts to spine to 45 Gy
- Boost primary site 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 carboplatin during radiation
  - Randomization to ± Isotretinoin during and after maintenance
  - Patients with supratentorial PNET tumors recently no longer allowed on study
Future Directions: Molecular Profiling of Medulloblastoma

Desmoplastic Histology

- Older patients
- 10-20% of cases
- Usually in cerebellar hemispheres
- Associated with mutations in SHH-PTCH pathway
- Better prognosis
  - Whether can omit RT all together is a subject of clinical trials
Late Morbidity of Treating Medulloblastoma, as an example of late 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 <4 years old
- Important differences between patients who received no RT, focal RT, and CSI
Medulloblastoma Outcomes

• Standard Risk Medulloblastoma
  • 5 year EFS 83%
  • 5 year EFS 73% with anaplasia

• High Risk Medulloblastoma
  • 5 year EFS 65%

• Infant Medulloblastoma
  • 5 year EFS approximately 50%
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
  • 4 developed progressive deficits at any time between 1 and 5 years
  • Risk factors for poor brainstem recovery: surgical morbidity and initial extent of the tumor
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
  • 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 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
  • 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
Localized Germinomas

• Whole ventricle 21-24 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 boost to 54 Gy
• ACNS 1123 is examining changing radiation to 30.6 WV with boost to primary site
  • THIS IS A MAJOR STUDY QUESTION
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 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 Brainstem 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.

• It is associated with critical late effects that impact patients for the rest of their lives.

• Researchers are seeking to delay or avoid RT in diseases such as low grade glioma, some ependymomas, and subsets of medulloblastoma.
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.

Promise of Proton Therapy

• With lack of exit dose, 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 (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

Thank you!