Pediatric Radiation Oncology Update 2018

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Disclosures

No disclosures directly related to this presentation

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Consultant: Myriad, Genome DX, Medivation, Johnson & Johnson, and Augmenix

Research Grants: Novartis & Augmenix
Learning Objectives

1. To be familiar with the role of radiotherapy and the genetic cross-section of ependymomas and how that might influence the use of radiotherapy as well as long-term prognosis.

2. To be familiar with the changing role of molecular profiling and risk stratification as well as their impact upon treatment for patients with medulloblastoma.

3. To gain an understanding of the scope, role, clinical data, and potential benefits of proton therapy in treating pediatric patients.
Outline

• Overview of Pediatric Radiation Oncology
• CNS Tumors
  • Medulloblastoma
  • Ependymoma
• Late Effects and the role of Proton Therapy
  • Introduction to proton physics and biology
  • Clinical data
  • Consensus and patterns of care
Overview of Pediatric Radiation Oncology
Pediatric Cancer Survival is Increasing
Pediatric Radiation Therapy: The Paradox

- Radiation is an important part of curative therapy for many pediatric patients with tumors...... But

- Ionizing radiation even at low doses for young children may have late side effects years or decades after treatment

  - Second cancers
  - Growth disturbances
  - Decreased functional outcomes
    - Hearing
    - Vision
    - Neurocognitive
    - Vascular Anomalies
    - Endocrine
  - Cosmesis
What Is the Risk of 2\textsuperscript{nd} Malignancies After Treatment for Pediatric Cancers?

- Childhood cancer survivors cohort
- 20,000 pts treated from 1970-1986
- 14,358 included in analysis of second malignancies
Radiation Therapy Use Dramatically Impacts 2\textsuperscript{nd} Malignancy Rates

No Previous RT

Previous RT

\begin{tabular}{|c|c|c|c|}
\hline
\text{Age (years)} & \text{Cumulative Incidence} & \text{No Previous RT} & \text{Previous RT} \\
\hline
40 & 10 & 52 & 400 \\
45 & 20 & 26 & 120 \\
50 & 30 & 4 & 25 \\
55 & 40 & 1 & 5 \\
\hline
\end{tabular}
Risk Factors for Increased Risk of 2nd Malignancy

• Use of RT
• Younger Age at Diagnosis
• Female Gender
• Positive Family history of Malignancy
• Initial diagnosis
Risk of Glioma and Meningioma By RT exposure and dose

- Adjusted odds ratio for
  - Glioma was 6.8x
  - Meningioma was 9.9x

![Graph showing relative risk vs dose with lines indicating fitted models for Glioma and Meningioma]
How Relevant are these 2<sup>nd</sup> Malignancies?

- In an assessment of 5-years survivors in CCSS
- This excluded patients who died within the first 5-years
  - 13.8% had died
    - 67% of these from initial diagnosis
    - 19% from second malignancies
- At 20 years death due to 2<sup>nd</sup> malignancies was the most common cause of death
  - Albeit being alive to 5-years necessary to be included in analysis
- **As a result second malignancy after pediatric cancer treatment is a serious concern**
CNS Tumors
Medulloblastoma
Medulloblastoma

• Primitive cerebellar tumor of neuroectodermal origin.
• Small round blue cell tumor
• 20% of pediatric CNS tumors
  • 400 cases/yr in the USA
• Median age at diagnosis is 5-6 yrs.
  • 70% are diagnosed before age 20
  • 20% present in infants < 2 yrs
• Outcome: 5 year OS 80-85% for standard risk

Images courtesy Wikipedia
Medulloblastoma
Risk stratification - Previous

- **Standard risk (all 3 criteria present)**
  - > 3 yrs old
  - GTR or STR with <1.5 cm² residual
  - M₀
- **High risk**
  - < 3 yrs old
  - > 1.5 cm² residual on early imaging
  - M(+)
Evolution of radiation therapy for medulloblastoma

Classic treatment entailed treatment to the whole Spine and brain followed by a boost to the brain

Spine: 36 Gy (in absence of chemotherapy)

Brain: 54 Gy (to whole posterior fossa)
Improved Outcomes with Chemotherapy

Greater benefit in higher risk disease
- Sub-total resection (p=0.007)
- Brainstem involvement (p=0.001)
- T3-T4 (p=0.002)

Treatment of Children With Medulloblastomas With Reduced-Dose Craniospinal Radiation Therapy and Adjuvant Chemotherapy: A Children’s Cancer Group Study

- CCG 9892
- N= 65
- 23.4 Gy CSI
  - PF 55.2
- 8 cycles of chemotherapy
  - Vincristine
  - CCNU
  - Cisplatinum

Reduced dose (23.4 Gy CSI) + Chemotherapy became standard of care

Packard et al, J Clin Oncol 1999, 17:2127-2136
Why treat the entire posterior fossa?

1) Because you can see it on plain x-rays
2) Tradition
Patterns of failure: Posterior Fossa

- Retrospective study from UM/CHOP analyzing pattern of recurrence
  - 27 pts who recurred after CSI followed by boost to entire PF
- Isolated tumor bed recurrence is rare (2 out of 27 pts)
- Isolated failures in the PF but outside the tumor bed is rare (1 out of 27 pts)
- Conclusion: Limited PF boost may be reasonable

<table>
<thead>
<tr>
<th>Site of first failure</th>
<th>Only site of failure</th>
<th>Any component of failure</th>
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</thead>
<tbody>
<tr>
<td>Tumor bed</td>
<td>2 (7%)</td>
<td>14 (52%)</td>
</tr>
<tr>
<td>PF outside TB</td>
<td>1 (3%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Spine</td>
<td>5 (19%)</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>2 (7%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Extraneural</td>
<td>2 (7%)</td>
<td>3 (11%)</td>
</tr>
</tbody>
</table>

Patterns of Failure with 18 Gy CSI

• A total of 17 patients reported in literature with 18 Gy CSI
  • 10: Upenn Goldwein IJROBP 1996
  • 7: Pittsburgh Jacacki IJROBP 2004
• Of these 6 (35%) had failure
  • All failures involved CSI component
• Most recent COG trial with 23.4 Gy
  • EFS 5 years = 19%
  • Two-thirds of failures include CSI component → 13%
A Phase III Trial of Involved Field Radiotherapy (IFRT) and Low Dose Craniospinal Irradiation (LD-CSI) with Chemotherapy in Average Risk Medulloblastoma

COG ACNS0331
A Report from the Children’s Oncology Group

Jeff Michalski¹, Gilbert Vezina², Peter Burger³, Amar Gajjar⁴, Ian Pollack⁵, Thomas Merchant⁴, T.J. Fitzgerald⁶, Timothy Booth⁷, Nancy Tarbell⁸, Ingrid Sheih⁹, Chris Williams-Hughes¹⁰, Yimei Li⁴, Catherine Billups⁴, Roger Packer², Anna Janss¹¹

¹Washington University School of Medicine; ²Children’s National Medical Center; ³Johns Hopkins University; ⁴St. Jude’s Children’s Research Hospital; ⁵Children’s Hospital of Pittsburgh of UPMC; ⁶Quality Assurance Review Center; ⁷UT Southwestern/Simmons Cancer Center; ⁸Massachusetts General Hospital Cancer Center; ¹⁰Childrens Oncology Group; ¹¹Children’s Healthcare of Atlanta

NCTN Operations Center Grant U10CA180886, COG Chairs Grant U10CA098543, NCTN Statistics & Data Center U10CA098413, U10CA180899, QARC U10 CA29511, IROC U24 CA180803
ACNS0331
Experimental Design Schema

Children ages 3-7

RANDOMIZE#1

Reduced-Dose Craniospinal Radiation

RANDOMIZE#2

Children ages 8 and older

Standard-Dose Craniospinal Radiation

Smaller Volume Boost (Radiation to Tumor Bed)*

Standard Volume Boost (Radiation to Entire PF)

Maintenance Chemotherapy 9 Cycles

*Patients 3-7 randomized to reduced dose receive 5.4Gy to PF before IFRT
#Both randomizations occur at the time of study enrollment
Medulloblastoma ACNS0331 Limited Target Volume Boost 54Gy

- PTV = CTV + 0.3 to 0.5 cm
- CTV = GTV + 1.5 cm (Within Posterior fossa)
- “Tumor bed” + GTV
- If 18 Gy CSI dose to PF 23.4

CTV = GTV + 1.5 cm (Within Posterior fossa)
# 4.0 TREATMENT PLAN

## Surgical Resection

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<tr>
<th>Day</th>
<th>Week</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>V</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>V</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>V</td>
</tr>
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<td>22</td>
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<td>29</td>
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<td>36</td>
<td>5</td>
<td>V</td>
</tr>
<tr>
<td>43</td>
<td>6</td>
<td>V</td>
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## XRT Starts

- **31 days**

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<th>4 Weeks</th>
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<td>7</td>
<td>49</td>
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<tr>
<td>8</td>
<td>55</td>
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</tbody>
</table>

## XRT Ends

- **4 Weeks**

## Chemotherapy

- **V** - Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV push weekly X6 during radiation

## XRT

### Age 3 to 7
- 18.00 vs 23.40 Gy CSRT *(randomized)*
- 5.40 Gy Posterior fossa *(if 18.00 Gy CSRT)*
- 30.60 Gy Local vs Posterior fossa boost *(randomized)*

### Age 8 to 21
- 23.40 Gy CSRT
- 30.60 Gy Local vs Posterior fossa boost *(randomized)*

## A
- Cisplatin (75 mg/m^2) IV over 8 hours on Day 1
- Lomustine (CCNU) (75 mg/m^2) orally on Day 1
- Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV Days 1, 8, and 15

## B
- Cyclophosphamide (1000 mg/m^2) IV over 1 hour daily with MESNA (360 mg/m^2) Days 1 and 2
- Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV push on Days 1 and 8
- MESNA (360 mg/m^2/dose) IV push 15 minutes prior to Cyclophosphamide and repeated at 3 and 6 hours.
Results for eligible patients without evidence of excess residual disease or anaplastic histology by treatment regimen (IFRT vs. PFRT)

Five year OS estimates
84.1\% \pm 2.8\% \text{ IFRT (n=227)}
85.2\% \pm 2.6\% \text{ PFRT (n=237)}

Five year EFS estimates
82.2\% \pm 2.9\% \text{ IFRT (n=227)}
80.8\% \pm 3.0\% \text{ PFRT (n=237)}

EFS: The one-sided 94\% upper confidence limit of the hazard ratio (based on a stratified approach) was 1.3. Since this confidence limit is lower than 1.6, IFRT is deemed to be non-inferior compared with PFRT.
Results for eligible patients 3-7 years of age without evidence of excess residual disease or anaplastic histology by CSI group (LDCSI vs. SDCSI)

Five year EFS estimates
82.6% ± 4.2% SDCSI (n=110)
72.1% ± 4.8% LDCSI (n=116)

Five year OS estimates
85.9% ± 3.8% SDCSI (n=110)
78.1% ± 4.4% LDCSI (n=116)
(p=0.058 stratified by RT group)

Goldstein et al 65% @ 3-years

EFS: The one-sided 80% upper confidence limit of the hazard ratio (based on a stratified approach) was 1.9. Since this confidence limit is larger than 1.6, LDCSI cannot be deemed to be noninferior compared with SDCSI.
Cumulative incidence of **isolated local failure** by RT group
(IFRT vs. PFRT)
(p=0.178 stratified by age and CSI group)

**Five year ILF estimates**
- 1.9% ± 1.0% IFRT (n=224)
- 3.7% ± 1.3% PFRT (n=235)

None of the IFRT PF failures occurred outside the boost volume
Cumulative incidence of isolated distant failure by CSI group (LDCSI vs. SDCSI) patients 3-7 years of age

Five year IDF estimates
12.8% ± 3.2% LDCSI (n=115)
8.2% ± 2.8% SDCSI (n=108)
10 cases with SMNs identified*
7 in SDCSI, 3 in LDCSI
- 6 Glioblastoma
- 2 MDS
- 2 AML
- 1 Anaplastic Astrocytoma
- 1 Meningioma
- 1 Parosteal osteosarcoma

*One patient had MDS, AML, GBM
*One patient had MDS, AML

Do difference in 2\textsuperscript{nd} malignancies Between arms.
Smaller number of patients randomized To low dose CSI (only those 3-7 years of age)
Grade 3,4 Toxicity by CSI dose and RT boost group

- After correcting for age, there are **no differences** in incidences of grade 3 or 4 CTC-AE toxicity by either CSI dose or Boost volume
Conclusions to ACNS 0331

• In Pediatric Average Risk Medulloblastoma…
• An involved field boost volume is **non-inferior** to whole posterior fossa irradiation
• A reduction in CSI dose to 18Gy is **worse** than 23.4Gy in children ages 3-7 years
Medulloblastoma

Updates in Risk Stratification
Medulloblastoma Risk stratification - Previous

• **Standard risk (all 3 criteria present)**
  • > 3 yrs old
  • GTR or STR with <1.5 cm\(^2\) residual
  • M\(_0\)

• **High risk**
  • < 3 yrs old
  • > 1.5 cm\(^2\) residual on early imaging
  • M(+)

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Large Cell / Anaplastic Histology Results in Worse Overall Survival

POG 7909, 8631, 8633, 8695, 9031, 9233

Legend:
- Large cell / Anaplastic
- Control

Brown et al. J. Exp Neuropath 2000
SJMB-96: Histology Matters More than Stage

Gajar et al *Lancet Oncology* 2006
Risk stratification - Current

• **Standard risk** (all 4 criteria present)
  • > 3 yrs old
  • GTR or STR with <1.5 cm² residual
  • M₀
  • **No diffuse anaplasia**

• **High risk**
  • < 3 yrs old
  • > 1.5 cm² residual on early imaging
  • M(+)  
  • **Diffuse anaplasia**
Can Daily Carboplatin with RT Improve Disease Control?

• 161 patients
• **All with metastatic disease**
• CSI = 36 Gy
• Carboplatin escalated to a dose of 30 mg/m²/dose x 30 doses daily with RT
• Adjuvant chemotherapy per standard
Result COG Phase II Daily Carbo + RT
All Met (+) Patients

Survival (probability)

Time From Study Entry (years)

No. at risk
M1  18  16  16  15  15  14  13  8  7  4  2
M2  10  9   7  7   6  5   3  2  1  1  1  1
M3  49  47  41  39  37  35  28  19  13  6  3  1

P = .4
Result COG Phase II Daily Carbo + RT
All Met (+) Patients

Jacacki et al. *J Clin Oncol* 2012

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Atypical teratoid rhabdoid tumor

Embryonal tumor with abundant neuropil and true rosettes
Molecular Subgroups of Medulloblastoma

**CONSENSUS**

Cho (2010)
Northcott (2010)
Kool (2008)
Thompson (2006)

**DEMOGRAPHICS**

Age Group:  
- Infant
- Child
- Adult

Gender:  
- Female
- Male

**CLINICAL FEATURES**

- Histology
- Metastasis
- Prognosis

**GENE EXPRESSION**

- WNT signaling: MYC +
- SHH signaling: MYCN +

**WNT**

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<th>C6</th>
<th>WNT</th>
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**SHH**

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<th>SHH</th>
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**Group 3**

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<td>A</td>
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<td>B</td>
<td>E</td>
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**Group 4**

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<td>A</td>
<td>Group D</td>
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<tr>
<td>B</td>
<td>E, A</td>
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</table>

**Classifications**

- **WNT**: rare, rarely LCA; rarely M+, very good
- **SHH**: desmoplastic/nodular, classic, LCA; uncommonly M+, infants good, others intermediate
- **Group 3**: classic, LCA; very frequently M+, poor
- **Group 4**: classic, LCA; frequently M+, intermediate

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Outcome by Molecular Group

Localized Disease - EFS

Metastatic Disease - OS


Treatment Recommendations Medulloblastoma (Off Protocol)

**Standard Risk**
- CSI 23.4 Gy in 1.8 Gy
- Boost to PF resection cavity to total of 54 Gy
  - GTV = Cavity
  - CTV = Cavity + 1-1.5 cm – anatomically constrained within PF
  - PTV = 3-5 mm
- Adjuvant chemotherapy for 9 cycles

**High Risk**
- CSI 36 Gy in 1.8 Gy fractions
- Boost to (whole) PF to 54 Gy total
- Adjuvant chemotherapy for 9 cycles
Assessment Question #1

Children’s Oncology Group trial ACNS0331 was a Phase III trial for average risk medulloblastoma that evaluated chemotherapy along with two randomizations: 1) The role of involved field radiotherapy (IFRT) for the posterior fossa boost as compared to whole posterior fossa RT and 2) low dose (18 Gy) cranial spinal RT (LD-CSI) as compared to conventional dose CSI (23.4 Gy). This trial found:

A) No difference in any outcome between randomized arms.
B) Increased local failure in the posterior fossa with IFRT.
C) Decreased event free and overall survival with LD-CSI as compared to standard dose CSI.
D) Lower toxicity with LD-CSI compared to conventional dose CSI.
Ependyoma
Ependymoma

• 8-10% of childhood CNS tumors
  • ~170 cases/year in US
• Mean age at diagnosis ~5 years
  • ~30% in children <3
• Survival has been disappointing with 5-yr EFS 23-45% and OS 50-64%
  • Most failures local
  • ~20% with isolated systemic failures
• Standard of care has been surgical resection followed by adjuvant RT
  • Role of chemotherapy is evolving

Images courtesy Wikipedia
Background

Age < 3 years

Chemotherapy

5YR EFS: 24% ± 5%
5YR OS: 43% ± 5%

Neuro Oncol 2014 16:457-65
Study Dates 1992-1997

Age > 3 years

Radiation Therapy

5YR EFS: 57% ± 6%
5YR OS: 71% ± 6%

Study Dates 1995-1999
What is value of Resection and RT in <3 yr old SEER analysis 1973-2013

Best outcomes with maximal surgical resection and adjuvant RT
A Phase II Trial of Conformal Radiation Therapy for Pediatric Patients with Localized Ependymoma, Chemotherapy Prior to Second Surgery for Incompletely Resected Ependymoma, and Observation for Completely Resected, Differentiated, Supratentorial Ependymoma (ACNS0121)

Thomas E. Merchant, Anne E. Bendel, Noah D. Sabin, Dennis W. Shaw, Shengjie Wu, James M. Boyett, Robert A. Sanford, and other co-investigators

Thanks to Tom Merchant for Providing Slides
Breakthrough

Conformal and Intensity-Modulated RT

J Clin Oncol. 2004 Aug 1;22(15):3156-62

3YR PFS 74.7% ± 5.7%

Cognitive Preservation

Survival Probability

Time (months)

Patients at risk

88
88
81
57
42
22
6
1

IQ

Time (months)

Age > 3 yrs
Age < 3 yrs

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## Study Design

<table>
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<tr>
<th>Stratum</th>
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<tr>
<td>Surgery</td>
<td>GTR1</td>
<td>STR</td>
<td>NTR/GTR2</td>
<td>GTR1</td>
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<td>II</td>
<td>II-III</td>
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<tr>
<td>Site</td>
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<td>Any</td>
<td>Supratentorial III Infratentorial II-III</td>
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<tr>
<td>Treatment</td>
<td>Observation</td>
<td>Chemotherapy ↓ ± 2nd Surgery ↓ Radiation Therapy</td>
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<td>Radiation Therapy</td>
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### Eligibility: Age ≥ 12 months, < 56 days from initial surgery, intracranial primary
Event-Free and Overall Survival

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<tr>
<th>Years from study entry</th>
<th>Event-Free Survival</th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td>3 year</td>
<td>68.8% ± 2.5%</td>
<td>89.3% ± 1.7%</td>
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<tr>
<td>5 year</td>
<td>62.7% ± 2.7%</td>
<td>83.8% ± 2.1%</td>
</tr>
<tr>
<td>7 year</td>
<td>60.4% ± 3.0%</td>
<td>77.4% ± 2.6%</td>
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<tr>
<td>10 year</td>
<td>55.6% ± 9.6%</td>
<td>71.2% ± 9.3%</td>
</tr>
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</table>

356 eligible patients
Event-Free Survival By Stratum

- GTR/nGTR with RT did best
  - Stratum’s 3 and 4
- STR with chemotherapy and adjuvant RT the worst
  - Stratum 2
- Best Prognostic Group
  - Stratum 1
  - Supratentorial
  - Grade 2 only (no grade 3)
  - GTR
  - Observation
  - 5 year EFS: 61% ± 14%
Event-Free Survival Stratum 3 By Central Pathology
Central Pathology Significantly Impacted EFS

3-year EFS by Review Diagnosis

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<td>44 ± 8</td>
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<tr>
<td>All</td>
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<td>215</td>
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Substantial discordance between local pathology and central pathology review
## Comparison of Outcomes

### Age < 3 years

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<th>ACNS0121 (2003-07)</th>
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<td>All Patients</td>
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<tr>
<td>5 year EFS</td>
<td>24%</td>
<td>57%</td>
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<td>5 year OS</td>
<td>43%</td>
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</tr>
<tr>
<td>5 year EFS</td>
<td>57%</td>
<td>65%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>71%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Molecular Sub-type and Outcome in Ependymoma

PFS

OS


ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 • REFRESHER18
Impact of Radiotherapy


**Table A2.** Multivariable Cox Proportional Hazards Regression Model of 10-Year Progression-Free and Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free survival (n = 777)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.97 to 1.00</td>
<td>.09</td>
</tr>
<tr>
<td>Male</td>
<td>1.25</td>
<td>1.01 to 1.54</td>
<td>.04</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>1.88</td>
<td>1.51 to 2.33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjuvant first-line radiation</td>
<td>0.63</td>
<td>0.50 to 0.81</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjuvant first-line chemotherapy</td>
<td>1.02</td>
<td>0.79 to 1.32</td>
<td>.87</td>
</tr>
<tr>
<td>EPN_PFA subgroup</td>
<td>2.18</td>
<td>1.31 to 3.62</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Overall survival (n = 778)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96 to 1.00</td>
<td>.13</td>
</tr>
<tr>
<td>Male</td>
<td>1.40</td>
<td>1.06 to 1.84</td>
<td>.02</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>2.14</td>
<td>1.61 to 2.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjuvant first-line radiation</td>
<td>0.52</td>
<td>0.38 to 0.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjuvant first-line chemotherapy</td>
<td>0.91</td>
<td>0.66 to 1.27</td>
<td>.6</td>
</tr>
<tr>
<td>EPN_PFA Subgroup</td>
<td>4.27</td>
<td>1.86 to 9.81</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Consensus Statement on Molecular Classification and Ependymoma

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

<table>
<thead>
<tr>
<th>Molecular subgroup</th>
<th>Tumor Location</th>
<th>Genetics</th>
<th>Age Distribution (yrs)</th>
<th>Gender Distribution</th>
<th>Survival (OS:months)</th>
<th>Subgroup-specific consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-EPN-REL A</td>
<td></td>
<td>Ablation 11q</td>
<td>4 &gt; 8 &lt; 60</td>
<td>男女比</td>
<td>120</td>
<td>There is not enough evidence to recommend distinct treatment approaches. Outcome should be further validated in prospective and retrospective studies.</td>
</tr>
<tr>
<td>ST-EPN-YAP 1</td>
<td></td>
<td>Ablation 11q</td>
<td>4 &gt; 8 &lt; 60</td>
<td>男女比</td>
<td>120</td>
<td>It should be rapidly determined whether the YAP1 subgroup is associated with favorable clinical outcome.</td>
</tr>
<tr>
<td>PF-EPN-A</td>
<td></td>
<td>Balanced</td>
<td>4 &gt; 8 &lt; 60</td>
<td>男女比</td>
<td>120</td>
<td>Outside of clinical trials, in patients &gt; 12 months of age, maximal safe resection and focal radiotherapy is the standard of care.</td>
</tr>
<tr>
<td>PF-EPN-B</td>
<td></td>
<td>Chromosomal instability</td>
<td>4 &gt; 8 &lt; 60</td>
<td>男女比</td>
<td>120</td>
<td>An observation only clinical trial will be implemented to determine the opportunity of de-escalating therapy.</td>
</tr>
</tbody>
</table>

Ependymoma Treatment Recommendations (Off Protocol)

• Maximal Safe resection / re-resection if needed

• Treatment volumes
  • GTV = post-op resection cavity
  • CTV = GTV + 0.5 cm
  • PTV = CTV + 3-5 mm

• Dose : 59.4 / 1.8 Gy
  • 54 Gy for 12-36 months
  • Consider 54 Gy with proton therapy
Assessment Question #2

ACNS 0121 was a multi-center phase II trial performed by the COG for localized ependymoma. Which of the following was true based upon this study?

A) There is little additional benefit from aggressive surgery so biopsy or subtotal resection is appropriate followed by definitive radiotherapy.

B) In low-risk disease, defined as WHO grade 2, supratentorial location, and gross total resection there was excellent event free survival, and, therefore, in these cases observation should be the standard of care.

C) Radiotherapy following surgical resection appeared to provide excellent local control even in children as young as one year of age.

D) Adjuvant chemotherapy following surgery and RT provided a substantial benefit and should be routinely offered to all children with localized ependymoma.
Late Effects and the Role of Proton Therapy
Protons
Introduction to Physics and Biology of Proton Therapy
Can we do better than X-rays?

Proton is hydrogen atom without electron

(Heavy particle)
X-rays pass through tissue

Protons STOP

Penetration Depth (cm)

Radiation Dose

Conventional X-rays

Protons

Bragg Peak

Tumor

100%

0%

0 10 20 30 40
Typically compensators and range modifiers used to passively scatter beam and spread it out for both width and depth these are beam line and patient specific.
Clinical Proton Beam: The Spread-Out-Bragg-Peak (Passive Scattering)

Range Modulator Wheel
- rapidly spinning wheel
- arc = mod

Target (depth modulation)

Percent Dose

Depth
Where do the Protons Come From?

hydrogen gas + heat → plasma + electrostatic force → free proton (H⁺)
Cyclotron accelerates protons to ~ 2/3 light speed.

Protons travel over 300,000 miles before reaching the patient (traveling around the world more than 12 times).
Cyclotron
Using electric fields, the cyclotron can accelerate hydrogen protons to two-thirds the speed of light.

Electromagnets
Magnets focus and steer proton beam to gantries.

Gantry
Giant gantries provide the beam pathway to treatment nozzle, utilizing series of steering and focusing magnets.
Gantry

Diameter ~ 33 feet
Weight ~ 128 tons

(equivalent to Boeing 757 with passengers and cargo)
1946: Harvard (700 tons)
1996: IBA/Sumitomo (220 tons)
2000: Varian/Accel (90 tons)
2012: Mevion Medical Systems (<20 tons)

IBA (50 tons)
ProteusOne
Clinical Protons
Types of proton therapy delivery

- Passive scattered (most common)
- Spot-scanning (pencil-beam scanning)
- Intensity modulated proton therapy (IMPT)
Spot scanning (pencil-beam scanning)
“Conventional” proton therapy
(Right lateral beam’s eye view)
The pencil-beam scanning mode of proton beam delivery

Spot scanning

- Multiple “spots” are used to cover the target
- Prostate = 1800 spots and 24 layers
- Delivered in 68 seconds

Source: Pedroni, PSI
Energy deposited in and near DNA

Ionizing radiation produces discrete energy deposition events in time and space.

DNA is damaged directly and indirectly by generation of reactive species mainly produced by radiolysis of water.
Low-LET radiation can produce localized cluster of ionizations within single electron track

High-LET radiation produces somewhat larger number of ionizations that are closer together

As protons decrease speed near the end of the Bragg peak they deposit energy more densely increasing the LET

- This extends the biologic effectiveness of the Bragg peak by a few microns to a few mm
The Relative Biological Effectiveness (RBE) of Protons Compared to X-rays using biological (cell survival) assays

\[ RBE = 1.1 \text{ for protons (general consensus)} \]

\[ 1.07 \pm 0.12 \]

RBE Changes Across Range of Proton Bragg Peak or SOBP with a higher RBE at tail of Peak (60 MeV)

Physical Dose in SOBP

LET 2.2x at end of SOBP

CFA At Different Depths

Fibroblasts

Glioma

RBE Varies as a Function of Depth and Dose (Cell Kill)
Greater Cell Survival = Greater Variation in RBE
“You can only kill a cell once”
Implications of RBE Effects

• Biologic dose at end of Bragg peak may be substantially higher than anticipated based upon simple RBE of 1.1
  • This could have implications for toxicity at end of Bragg peak
  • Brain stem necrosis has been a concern
• Biologic dose even more complicated when considering IMPT with multiple small beamlets
• Dose optimization based upon alternative BED models are being formulated but are not at present part of the standard of care
Protons

Clinical Data
Craniopharyngioma and Proton Therapy

Protons Offer the Benefits of Proven Therapy With Decreased Risk of Side Effects By Minimizing Unnecessary RT

**Mean Dose Whole Brain**
- IMRT: 13 Gy
- 3D Protons: 9 Gy
- IMPT: 6 Gy

**Mean Dose Temporal Lobes**
- IMRT: 16 Gy
- 3D Protons: 4 Gy
- IMPT: 2 Gy

**Mean Dose Tumor**
- IMRT: 57 Gy
- 3D Protons: 57 Gy
- IMPT: 57 Gy
Medulloblastoma: Cranial Spinal Radiation

X-rays

Exit dose ~ 50%

Protons

No exit dose
Is it Effective?
How do results Compare to X-Ray Based Treatment?

Patterns of Failure

<table>
<thead>
<tr>
<th>Failure</th>
<th>Current</th>
<th>Previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>50%</td>
<td>14-69%</td>
</tr>
<tr>
<td>Spine</td>
<td>71%</td>
<td>34-70%</td>
</tr>
<tr>
<td>PF</td>
<td>43%</td>
<td>17-52%</td>
</tr>
<tr>
<td>SupTent</td>
<td>50%</td>
<td>17-69%</td>
</tr>
</tbody>
</table>

Impact of Age and Radiation Dose on Neurocognitive Function – St Jude X-rays

**Age Most Important**

**Modified by Dose and Volume**
These are models of what might be achieved with proton therapy. Does clinical data support this improvement?
Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors

Cognitive Functioning: Baseline and Follow-Up (N=60)

Int J Radiat Oncol Biol Phys. 2015 Oct 1;93(2):400-7
Other Selected Late Effects of LOW dose RT

- **Fertility**
  - Testis 2-3 Gy permanent azospermia
  - Ovaries 12-15 Gy difficult fertility

- **Cardiovascular**
  - Heart 2.5-3 Gy increased CAD
  - Vascular 1-4 Gy stroke & heart disease

- **Vision**
  - Eye 0.5-2 Gy Cataract
  - Eye 5-12 Gy Double vision, dry eye

Shimizu et al, BMJ 2010;340:b5349
Carr et al, IJROBP 2005 842-850
St Jude Long-Term Follow-up. Pituitary Dysfunction as a Factor of RT Dose

% With Deficiency

Growth Hormone

LH

TSHD

ACTHD

<21.9 Gy

<30 Gy

>30 Gy
Growth Hormone Secretion After Conformal Radiation Therapy As A Function of Hypothalamic RT Dose
Radiation Dose to Endocrine Structures: Proton vs. X-ray in Medulloblastoma

Vatner et al ASTRO 2015
Hormone Deficiency Post Radiation for Medulloblastoma: Proton vs. X-ray

**OR: 3.9 (95%CI:1.3-11.6)**  
*p=0.013*

**OR: 6.9 (95%CI:2.5-19.2)**  
*p<0.001*

Vatner et al ASTRO 2015
Does Proton Therapy Result in Better Patient / Parent Reported Quality of Life at 3-years?

Cross-sectional analysis of patient & parent reported QOL using the PedsQL general instrument at 2 different institutions and compared to normative age population

<table>
<thead>
<tr>
<th></th>
<th>MGH</th>
<th>Stanford</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
<td>Proton</td>
<td>Photon</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>57</td>
<td>63</td>
<td>0.6</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>3.0</td>
<td>2.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84%</td>
<td>51%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>5%</td>
<td>16%</td>
<td>0.06</td>
</tr>
<tr>
<td>Posterior Fossa</td>
<td>47%</td>
<td>65%</td>
<td>0.05</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>53%</td>
<td>70%</td>
<td>0.05</td>
</tr>
<tr>
<td>RT &gt;49 Gy</td>
<td>89%</td>
<td>76%</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Quality of Life On Average 3-years Following Protons, X-rays, or Age-Matched Controls For Brain Tumor Patients Demonstrates Advantages with Protons

Proton therapy group statistically lower than controls for all domains, but better than x-rays for all domains except School performance where the difference was not significant.
Protons may reduce second cancers risks and have other benefits

Source: MDACC
Physiologic Observance of Dose Distribution of Protons

14 year-old female whole spine not treated

Krejcarek 2007, IJROBP
Physiologic Observance of Dose Distribution of Protons

7-year old male whole spine treated

Krejcarek 2007, IJROBP
What Are The Predicted Risk of Second Malignancies Based Upon Photon or Proton CSI?

Zhang et al 2013 Phys Med Biol
What Are The Predicted Risk of Second Malignancies Based Upon Photon of Proton CSI?

<table>
<thead>
<tr>
<th>Study/Method</th>
<th>Photon</th>
<th>Proton</th>
<th>RLAR</th>
<th>R_{rel}</th>
<th>e</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miralbell et al (2002)</td>
<td>35.6</td>
<td>2.4</td>
<td>-</td>
<td>14.8</td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>Newhauser et al (2009)</td>
<td>35.6^a</td>
<td>3.3</td>
<td>-</td>
<td>10.8</td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>This work</td>
<td>138</td>
<td>24.6</td>
<td>5.6</td>
<td>-</td>
<td>4</td>
<td>100</td>
</tr>
</tbody>
</table>

Zhang et al 2013 Phys Med Biol
How Does The Relative Impact of Neutrons Influence These Predictions?

- Relative Risk Reduction of SMN Risk Protons vs. X-rays
- Predict an 80% reduction in SMN with Protons based upon current recommended neutron predictions
- Neutron predictions would have to be off by 2 orders of magnitude to overcome benefit

Zhang et al 2013 Phys Med Biol
How Do Different 2\textsuperscript{nd} Malignancy Models Impact this Outcome?

<table>
<thead>
<tr>
<th>Dose–risk model</th>
<th>Proton ((H = 0.39 \text{ Sv}))</th>
<th>Photon ((H = 10.85 \text{ Sv}))</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNT</td>
<td>2.78</td>
<td>50.81</td>
<td>0.055</td>
</tr>
<tr>
<td>LEXP (5)</td>
<td>2.78</td>
<td>7.65</td>
<td>0.36</td>
</tr>
<tr>
<td>LEXP (15)</td>
<td>2.78</td>
<td>22.79</td>
<td>0.12</td>
</tr>
<tr>
<td>LEXP (25)</td>
<td>2.78</td>
<td>30.89</td>
<td>0.09</td>
</tr>
<tr>
<td>LEXP (35)</td>
<td>2.78</td>
<td>35.24</td>
<td>0.079</td>
</tr>
<tr>
<td>LPLAT (5)</td>
<td>2.78</td>
<td>8.63</td>
<td>0.32</td>
</tr>
<tr>
<td>LPLAT (15)</td>
<td>2.78</td>
<td>20.31</td>
<td>0.14</td>
</tr>
<tr>
<td>LPLAT (25)</td>
<td>2.78</td>
<td>26.33</td>
<td>0.11</td>
</tr>
<tr>
<td>LPLAT (35)</td>
<td>2.78</td>
<td>29.10</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Zhang et al 2013 Phys Med Biol
Observational Data
Protons reduce second cancers by ~50%

- MGH report spanning 26 years (1974-2001)

- Matched 558 patients treated with protons
  - vs. X-ray patients from SEER registry
  - Most also received some X-rays (about 20% of total dose)
  - CNS 32%, HN 24%, prostate 33%, sarcoma 7.8% (no ocular)

- Observed second cancer rates were 6.9 vs. 10.3 (per 1000 person-years) for protons vs. XRT, respectively a 35% reduction

- Adjusted for sex, age, primary site, and year of diagnosis
  - Hazard Ratio 0.52 (95%CI:0.32-0.85, p=0.009)

Chung et al., Int J Radiat Oncol Biol Phys 87, 2013
Craniopharyngioma
Craniopharyngioma

- Benign tumors found near pituitary gland
- Derive from epithelium from Rathke’s pouch
- Most common in children (<7 yrs) and then in adults (>50 yrs)
- Typically mixture of solid and cystic components
- Given location although “benign” can have profound endocrine, neurologic, and developmental effects
- Treatment with RT can produce long-term cures even with minimal surgery (biopsy only)
Cysts Can Expand During and After Treatment & Adaptive RT Associated with Decreased Progression

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Early Cyst Growth</th>
<th>Surgical Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory</td>
<td>21</td>
<td>52% (11)</td>
<td>18% (2)</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>52</td>
<td>33% (17)*</td>
<td>17% (3)</td>
</tr>
<tr>
<td>Rochester</td>
<td>11</td>
<td>36% (4)</td>
<td>0%</td>
</tr>
<tr>
<td>St Jude</td>
<td>88</td>
<td>25% (22)</td>
<td>15% (13)**</td>
</tr>
<tr>
<td>TOTAL</td>
<td>172</td>
<td>32% (54)</td>
<td>33% (18)</td>
</tr>
</tbody>
</table>

**St Jude all interventions were during RT

**Following RT cyst expansion is common followed by later shrinkage. Supportive care with minimal interventions (such as cyst drainage) preferred over more aggressive treatments

Comparison of Academic Achievement Scores after Proton and Photon Therapy in Children and Young Adults with Craniopharyngioma

Thomas E. Merchant, Danny J. Indelicato, Chia-ho Hua,
Shengjie Wu, Heather M. Conklin

SIOP 2017
Washington, DC

Thanks to Tom Merchant for Providing Slides
Dosimetry: Proton vs. Photon Therapy

IMRT

Proton Therapy

axial | coronal | sagittal
Comparing Photon and DS Proton
Mean ± SD Proton (solid) vs. Photon (dashed) cDVH

Brain

Left Temporal Lobe
Methods

• Phase II trial 9/19/2011 – 2/22/2016
  • 94 children and young adults with craniopharyngioma
  • Median age 9.4 years (2-20.2 years)

• Targeting (St. Jude → UFHPTI)
  • GTV_PREOP = Cystic and solid tumor present at the time of diagnosis
  • GTV = residual tumor and post-operative tumor bed
  • CTV = anatomically constrained CTV 5mm margin surrounding the GTV
  • PTV = 3mm geometric expansion

• Proton Therapy (UFHPTI)
  • Prescribed dose 54CGE in 30 fractions
  • Minimum 95% coverage
  • Median elapsed days 43 (range 40-50)
  • Weekly monitoring - non-contrast MR
## Results – Disease Control

Progression-Free Survival

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Patients</th>
<th>3 Year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>94</td>
<td>98.1% ± 1.9%</td>
</tr>
<tr>
<td>Photon</td>
<td>101</td>
<td>96.0% ± 1.9%</td>
</tr>
</tbody>
</table>


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Results - Complications

Cumulative Incidence of Necrosis

Vasculopathy

Permanent Neurologic Deficits

Progression-Free Survival after Proton Therapy for Childhood Craniopharyngioma: Early Results From a Prospective Trial.
Results

• Tests of academic achievement (reading and math) were administered before and after treatment

• Patients were included that had at least two evaluations

• Test scores were modeled with normal tissue dose variables to compare scores by modality
Results

• Fifty-two patients treated with proton therapy were compared to 70 patients treated with photon therapy.

• The median dose (range) to the whole brain was 7.63 CGE (0.25-16.40CGE) and 17.34Gy (10.99-27.55Gy), respectively.
Normal Tissue Dosimetry

Normal Tissue Dose Means (±SD)

Dose CGE/cGy

- Cerebellum
- Brain
- Temporal Left
- Temporal Right
- Supratentorial

Proton
Photon
Results

- Comparison by modality
  - No difference comparing reading or math scores based on treatment modality
  - No adjustment for volume of radiated tissue between groups / size of tumor

<table>
<thead>
<tr>
<th></th>
<th>Reading Scores</th>
<th>Math Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>36 months</td>
</tr>
<tr>
<td>Proton</td>
<td>103.1</td>
<td>103.1</td>
</tr>
<tr>
<td>Photon</td>
<td>100.6</td>
<td>96.7</td>
</tr>
</tbody>
</table>

Not Significant
Academic Achievement Scores: Proton vs Photon

Reading Scores

Baseline
36 months

Proton
Photon

Math Scores

Baseline
36 months

Proton
Photon

N=52 Proton  +0.001274 points/CGE/mo
N=70 Photon  -0.1020 points/Gy/mo (p=0.0018)

N=52 Proton  +0.000614 points/CGE/mo
N=70 Photon  -0.08266 points/Gy/mo (p=0.0263)
Craniopharyngioma Treatment Recommendations (Off Protocol)

• Maximal safe surgical resection
  • Biopsy or cyst decompression only often preferable

• Treatment Volumes
  • GTV_PREOP = Cystic and solid tumor present at the time of diagnosis
  • GTV = residual tumor and post-operative tumor bed
  • CTV =
    • CTV 5mm margin *anatomically constrained* surrounding the GTV with MRI 4+ times during treatment
    • CTV 10 mm margin *anatomically constrained* surrounding the GTV without MRI during treatment
  • PTV = 3-5 mm geometric expansion with daily imaging

• Dose
  • 54 Gy in 1.8 Gy
Assessment Question #3

In regards to the treatment of pediatric craniopharyngioma which one of the following is true?

A) Given its solid and cystic nature there is no role for proton therapy in the treatment of craniopharyngioma.

B) Best clinical outcomes are observed with maximal surgical resection followed by adjuvant radiotherapy.

C) Intra-cystic $^{32}$P should be administered as earlier as possible after external beam radiotherapy to maximize the change of synergistic shrinkage of the cyst.

D) Best clinical outcomes appear to occur with adaptive radiotherapy with frequent intratreament MRIs to account for changes in cyst size.
In Which Pediatric Patients Getting Radiotherapy Does is Make Sense to Use Protons?

• Consensus conference held in Stockholm in 2015 on role of proton therapy in pediatric RT
• 24 pediatric radiation oncologist
• Consensus that most (50-90%) of children getting RT should be offered protons
• Significant variation by disease type
Patterns of Care: Age of Treatment for Pediatric Proton Therapy in US From 2010-2013

Total 2494

42% required anesthesia

Year 2010 2011 2012 2013
Patients 465 613 694 722

Courtesy Pediatric Proton Foundation

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Most Commonly Treated Diagnoses

- Ependymoma
- Medulloblastoma
- Glioma, Low Grade
- Rhabdomyosarcoma
- Ewing Sarcoma
- Craniopharyngioma
- ATRT
- Neuroblastoma
- Other Sarcoma, High Grade
- Chordoma/Oncodermatoma
- Lymphoma, Hodgkin’s
- Glioblastoma, PNET
- Carcinoma, Non-CNS

[Graph showing the most commonly treated diagnoses for CNS (Cerebral Nervous System) disorders over the years 2010, 2011, and 2012.]
Conclusions To Patterns of Care Study

- Number of children treated at US proton centers continues to increase, rising 36% since 2010

- Average patient continues to be
  - A child <10 years old
  - Curable
  - Brain tumor or axial sarcoma,
  - But many different tumor types and locations being treated

- Access to a multidisciplinary pediatric team remains critical
  - ½ of the top six tumors require concurrent chemotherapy
  - ½ of patients require anesthesia support
Assessment Question #4

The Stockholm Pediatric Proton Therapy Conference on the role of proton therapy in pediatric radiation oncology found in a consensus statement that:

A) Proton therapy is likely appropriate in 50-90% of pediatric patients scheduled to receive radiotherapy.

B) Given their high curability with conventional x-rays there is no role for proton therapy in low-grade glioma.

C) Given their poor outcome with conventional x-rays dose-escalated proton therapy should be utilized in patients with high-grade glioma.

D) Given the large volume of normal tissue radiated newly diagnosed high-risk neuroblastoma should be treated with proton therapy for local control of the primary site and metastatic lesions.
Assessment Question #5

Proton therapy is being more commonly utilized to treat children with cancer who require radiotherapy. Which of the following is true about the current state of proton therapy?

A) Randomized results from St Jude and the University of Florida support similar disease control but less neurocognitive decline when using proton therapy as compared to IMRT to treat craniopharyngioma.

B) Growth hormone decline after hypothalamic RT appears to have a dose-response with a plateau at 20 Gy below which there is no significant risk of decline.

C) Based upon parallel cohort analysis it appears that children with brain tumors treated with radiotherapy have clinically significant less decline in health related quality of life if protons are used as compared to those treated with x-rays.

D) Radiation dose to the temporal lobes is the strongest predictor of decline in neurocognitive function following RT.
Improving Therapeutic Index In Pediatric Radiation Oncology

- Radiation therapy continues to play an important role in the curative treatment of many pediatric malignancies

- Given the risks of late effects pediatric RT is being adapted by
  - Treating less patients / selecting patients appropriately
    - Histologic and genetic sub-types
  - Decreasing treated volume
  - Decreasing treated dose
  - Decreasing normal tissues exposed
    - Image guidance
    - 3D conformal therapy / IMRT
    - Proton therapy
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