Radiotherapy for Infant Brain Tumors

Panel 15: The Changing Role of Radiotherapy In Childhood Cancer

Anita Mahajan MD
MD Anderson Cancer Center
ASTRO, Boston September 27, 2016
Incidence of Primary Brain Tumors in Young Children

Tumor Histologies

<1 y.o.

1-4 y.o.
<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>% of All Tumors</th>
<th>Median Age</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliomas</td>
<td>8,487</td>
<td>52.9%</td>
<td>6.0</td>
<td>2.78</td>
</tr>
<tr>
<td><em>Pilocytic astrocytoma</em></td>
<td>2,821</td>
<td>17.6%</td>
<td>7.0</td>
<td>0.93</td>
</tr>
<tr>
<td><em>Other low grade glioma</em></td>
<td>2,296</td>
<td>14.3%</td>
<td>6.0</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>High grade glioma</strong></td>
<td>1,784</td>
<td>11.1%</td>
<td><strong>7.0</strong></td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Ependymal tumors</strong></td>
<td>879</td>
<td>5.5%</td>
<td><strong>4.0</strong></td>
<td>0.29</td>
</tr>
<tr>
<td><em>Other glioma</em></td>
<td>707</td>
<td>4.4%</td>
<td>7.0</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Choroid plexus tumors</strong></td>
<td>362</td>
<td>2.3%</td>
<td>1.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Tumors of the pineal region</td>
<td>701</td>
<td>4.4%</td>
<td>6.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Neuronal and mixed neuronal-glial tumors</td>
<td>140</td>
<td>0.9%</td>
<td>9.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Embryonal tumors</td>
<td>2,413</td>
<td>15.0%</td>
<td>4.0</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Medulloblastoma</strong></td>
<td>1,494</td>
<td>9.3%</td>
<td>6.0</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Primitive neuroectodermal tumor</strong></td>
<td>360</td>
<td>2.2%</td>
<td><strong>3.5</strong></td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Atypical teratoid/rhabdoid tumor</strong></td>
<td>363</td>
<td>2.3%</td>
<td><strong>1.0</strong></td>
<td>0.12</td>
</tr>
<tr>
<td><em>Other embryonal tumors</em></td>
<td>196</td>
<td>1.2%</td>
<td>1.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Tumors of cranial and spinal nerves</td>
<td>758</td>
<td>4.7%</td>
<td>7.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Tumors of meninges</td>
<td>458</td>
<td>2.9%</td>
<td>9.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Lymphomas and hematopoietic neoplasms</td>
<td>70</td>
<td>0.4%</td>
<td>6.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>590</td>
<td>3.7%</td>
<td>9.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Tumors of the pituitary</td>
<td>625</td>
<td>3.9%</td>
<td>12.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Craniosphenoidioma</td>
<td>648</td>
<td>4.0%</td>
<td>8.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Other/unclassified tumors</td>
<td>792</td>
<td>4.9%</td>
<td>9.0</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>16,044</td>
<td>100.0%</td>
<td>7.0</td>
<td>5.26</td>
</tr>
</tbody>
</table>
5 Y OS by histology & age of diagnosis
Why poorer survival?

• Parents chose to withhold treatment
• Toxicity
  – Neurotoxicity
  – Growth failure
  – Leukoencephalopathy
• Radiotherapy has been associated with significant toxicities and is avoided in young patients (even if better tumor control).
<table>
<thead>
<tr>
<th>STUDY</th>
<th>Concept</th>
<th>N</th>
<th>yrs</th>
<th>Histologies</th>
<th>Primary Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delay CSI- 1980’s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby POG 1 (8633/34)</td>
<td></td>
<td>198</td>
<td>86-90</td>
<td>MB, PNET, E, HGG, BSG, CPC</td>
<td>Can delay RT. Elim RT in CR, GTR’s. 30% 5yPFS, 39% 5yOS</td>
</tr>
<tr>
<td>HIT-SKK 87</td>
<td>IT MTX</td>
<td>30</td>
<td>87-92</td>
<td>Malig brain tumors</td>
<td>5y OS 50%</td>
</tr>
<tr>
<td><strong>Avoid RT- Salvage with CSI – 1990’s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby POG 2: (9233/34)</td>
<td>CT (std vs dose intense)</td>
<td>330</td>
<td>92-00</td>
<td>MB, PNET, E, HGG, BSG, CPC, ATRT, GCT, CNS Sarc</td>
<td></td>
</tr>
<tr>
<td>CCG 9921:</td>
<td>CT</td>
<td>299</td>
<td>93-97</td>
<td>MB, PNET, E, HGG, BSG, CPC, ATRT, GCT, CNS Sarc</td>
<td>M+, PR, PD=&gt; RT@36mo. PD =&gt;RT. M0/CR-GTR =&gt; no RT. 5y efs 27%, 5y OS 43%</td>
</tr>
<tr>
<td>HIT-SKK 92:</td>
<td>CT, IT MTX</td>
<td>43</td>
<td>92-97</td>
<td>MB</td>
<td>5y PFS 58% 5y OS 66%</td>
</tr>
<tr>
<td>Headstart:</td>
<td>CT +HDSCRT</td>
<td>62</td>
<td>91-95</td>
<td>MB, PNET, E, HGG, BSG, CPC</td>
<td>19 pt had RT, 17 for PD. 3y efs 25%, 3 y OS 40%</td>
</tr>
<tr>
<td>CCG 99703:</td>
<td>CT +HDSCRT</td>
<td>92</td>
<td>98-04</td>
<td>MB, PNET, E, HGG, BSG, CPC</td>
<td>GTR was sig better. 5y efs 44%, 5y Os 64%</td>
</tr>
</tbody>
</table>
MDA Tumor Registry
- <4 yo
- Pt’s with CNS tumor
- 497 patients
MDA Experience

- ATRT
- PNET
- Epend
- Glioma

Bar charts showing the percentage of cases by decade from 1970 to 2010.
MDA Experience

- <1970
- 1970's
- 1980's
- 1990's
- 2000's
- 2010's

Legend:
- Other
- Epend
- Glioma
- ATRT
- MB/PNET
Figure 3. Overall Survival in Children with Medulloblastomas, Ependymomas, Malignant Gliomas, or Primitive Neuroectodermal Tumors. The differences between groups were significant (P<0.001).
Recent Studies-Separate Histologies

- Medulloblastoma
- Ependymoma
- ATRT
RT Advances over last 40 years

- 3D CRT
- MRI planning, staging, evaluation
- IMRT
- IGRT
- Proton Therapy
Medulloblastoma
Table 1. Results of multicenter trials for infant medulloblastoma

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>CT</th>
<th>RT</th>
<th>5-Yr EFS/PFS (±SE)</th>
<th>5-Yr OS (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby POG1 [28]</td>
<td>62</td>
<td>Conventional</td>
<td>Delayed adjuvant CSI</td>
<td>31.8% (±8.3%)</td>
<td>39.7% (±6.9%)</td>
</tr>
<tr>
<td>CCG 9921 [31]</td>
<td>92</td>
<td>Conventional</td>
<td>Delayed adjuvant for residual disease or salvage</td>
<td>32% (±5%)</td>
<td>43% (±5%)</td>
</tr>
<tr>
<td>BB SFOP [32]</td>
<td>79</td>
<td>Conventional</td>
<td>Salvage</td>
<td>R0M0, 29%; R1M0, 6%; M+, 13%</td>
<td>R0M0, 73%; R1M0, 41%; M+, 13%</td>
</tr>
<tr>
<td>HIT-SKK92 [34]</td>
<td>43</td>
<td>Conventional with HD MTX + intraventricular MTX</td>
<td>None</td>
<td>58% (±9%); R0M0, 82% (±9%); R1M0, 50% (±13%); M+, 33% (±14%)</td>
<td>66% (±7%); R0M0, 93% (±6%); R1M0, 56% (±14%); M+, 38% (±15%)</td>
</tr>
<tr>
<td>Head Start I and II [45]</td>
<td>21 M0</td>
<td>Induction CT + (HDC&amp;SCR) × 1</td>
<td>Salvage</td>
<td>52% (±11%)</td>
<td>70% (±10%)</td>
</tr>
<tr>
<td>Head Start II [17]</td>
<td>21 M+</td>
<td>Induction CT with HD MTX + (HDC&amp;SCR) × 1</td>
<td>&gt;6 yrs old or residual disease</td>
<td>49%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>P9934 [37]</td>
<td>78</td>
<td>Conventional</td>
<td>Early adjuvant focal</td>
<td>58% (±6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66% (±6%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>At 3 years.
BABY POG 1

• The single most important predictor of survival was the degree of surgical resection
• 57 GTR 5 yr OS: 62%
• 113 < GTR: 31%
• GTR + M0 (44 patients), the OS was 65%
• Progression tended to occur very early within the first 3-6 months and failures beyond 2 years were uncommon

Courtesy of M. Chintagumpala
Primary objective:

- To prospectively determine the outcome of patients randomized to standard or dose-intensive chemotherapy, with restricted use of RT

  - Standard Dose: Regimen A
  - Dose-Intensive: Regimen B

=> RT only for those with M+ disease at dx and those with residual M0 disease at end of chemotherapy
Summary for 9233

• As in Baby POG 1, some infants with MB cured with S & CT
  – M0: 40% survived with no RT, 36% with RT
  => RT not necessary for all, but not curative for all who need it
• More irradiated children survive (~42% vs ~31%)
• Factors?
  – Large cell/anaplastic variant; M+ disease: bad
  – Need biologic correlative studies which are now happening

Courtesy of M. Chintagumpala
Late Effects of Survivors, No RT

- Targeted late effect **reporting was voluntary**
- Non-RT vs radiated survivors late effect reporting:
  - Having “none” reported more often
  - **More hearing loss**
  - Fewer & **less severe developmental delays** and need for special education
  - **No endocrine problems** vs. GH, thyroid, adrenal deficiencies reported with RT

Courtesy of M. Chintagumpala
Infant M0 Medulloblastoma Strategies

1. Residual disease is associated with higher rate of progression
2. Failures are both local & metastatic
3. Possible increased survival with HDSCRT
4. Possible increased survival with IT/IV methotrexate
ACNS 0334

- SPNET & HR MB <36 mo randomized to HDSCRT +/- MTX
- 5/14 to 3/16 suspended, 91 accrued
- RT not mandated, only at MD discretion
  - Tumor bed only or CSI
- No results yet
PBTC 026

• 2mo-4yo MB
• Induction => Consolidation (HDSCRT) => RT for M0
  => SAHA/isotretinoin
• M0 Pt get RT, others at MD discretion
• Closed, no results
ACNS 1221

- Phase II M0 desmoplastic MB in <4yo
- Induction chemo (cpm, vcr, carbo, vp16, HD MTX) x 3 cycles
  - => CR: end of tx
  - => PR: SLO then 2 cycles chemo, then end
- NO RT for this study
- Open 12/13, temporary closed 7/16, 37 of 42 accrued
Infant MB RT Thoughts

• GTR is advantageous

• M0: may do local field only but consider salvage issues of CSI needed later

• M+:
  – CSI, try to delay to >3yo
  – Dose: lower dose if CR is being explored
EPENDYMOMA
BABY POG 1: Ependymoma

- 48 children with ependymoma
- GTR: 66%
- Subtotal: 25%
  - 2 yr Chemo (0-24 mo) 5 yr S: 26%
  - 1 yr Chemo (24-36 mo) 5 yr S: 63%

Courtesy of M. Chintagumpala
Ependymoma Prognostic Factors

• Multivariate Analysis independent for poor risk
  – WHO grade III, male, age, intracranial location, no surgery
  – With STR: no RT associated with poor outcome HR 1.748, P=0.024

Rodriguez et al, j of surg res, vol 156 (2) 340-351, 2009
COG ACNS 0121

1) Evaluation of chemo after STR in an effort to improve resectablity
2) Evaluation of observation after microscopic GTR for grade 2 supratentorial ependymoma
3) All others RT after GTR or 2\textsuperscript{nd} resection evaluation post-chemo
4) RT dose 59.4Gy/33 fractions
5) Anaplastic ependymomas stratified
Event-Free Survival by Strata

Stratum 1: Supratentorial GTR1
Stratum 2: STR - any grade or site
Stratum 3: <5mm resid or macroscopic GTR, any grade or site
Stratum 4: GTR1 & anaplastic or GTR with infratentorial

ACNS0121 Children’s Oncology Group
EFS – Stratum 3+4 by Tumor Grade

<table>
<thead>
<tr>
<th>Years</th>
<th>Grade II (EP)</th>
<th>Grade III (AEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5YR</td>
<td>74.6% ± 3.6%</td>
<td>60.7% ± 4.7%</td>
</tr>
<tr>
<td>10YR</td>
<td>68.8% ± 11.1%</td>
<td>49.8% ± 20.4%</td>
</tr>
</tbody>
</table>

log-rank: p=0.0044

ACNS0121 Children’s Oncology Group
EFS and OS – Stratum 3+4 by Age

- Log-rank: p=0.2295
  - 5YR EFS
    - Age < 3yrs: 62.9% ± 5.6%
    - Age ≥ 3yrs: 70.5% ± 3.4%

- Log-rank: p=0.6904
  - 5YR OS
    - Age < 3yrs: 87.4% ± 4.0%
    - Age ≥ 3yrs: 85.8% ± 2.6%

ACNS0121 Children’s Oncology Group
Role of adjuvant chemo after surgery & RT

- Opened 3/2010
- 347 of 400 patient accrual goal as of 9/26/16
ACNS 0121 & 0831

- GTV 1= post op resection margin + gross disease based on pre & post op MRI
- GTV 2= GTV 1 – off spinal cord and/or OC
- CTV= GTV + 0.5mm (anatomically adjusted)
- PTV = CTV + 3mm (IGRT) or 5mm

Total Dose 59.4Gy/33 fractions
- 54 Gy to PTV 1
- 5.4 Gy boost to PTV 2
- 500 samples
- Molecular classification by DNA methylation profiling
- 9 subtypes
- Can differentiate b/w grade II/III PF and ST tumors

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Age</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-SE</td>
<td>I</td>
<td>◾️</td>
</tr>
<tr>
<td>Subependymoma Balanced Genome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-EPN-YAP1 (Anaplastic) Ependymoma YAP1-fusion</td>
<td>II / III</td>
<td>◾️</td>
</tr>
<tr>
<td>ST-EPN-RELA (Anaplastic) Ependymoma Chromothripsis: RELA-fusion</td>
<td>II / III</td>
<td>◾️</td>
</tr>
<tr>
<td>PF-SE</td>
<td>I</td>
<td>◾️</td>
</tr>
<tr>
<td>Subependymoma Balanced Genome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-EPN-A (Anaplastic) Ependymoma Balanced Genome</td>
<td>II / III</td>
<td>◾️</td>
</tr>
<tr>
<td>PF-EPN-B (Anaplastic) Ependymoma Chromosomal Instability</td>
<td>II / III</td>
<td>◾️</td>
</tr>
<tr>
<td>SP-SE</td>
<td>I</td>
<td>◾️</td>
</tr>
<tr>
<td>Subependymoma 6q deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP-MPE</td>
<td>I</td>
<td>◾️</td>
</tr>
<tr>
<td>Myxopapillary Ependymoma Chromosomal Instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP-EPN</td>
<td>II / III</td>
<td>◾️</td>
</tr>
<tr>
<td>(Anaplastic) Ependymoma NF2 mutation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pajtler et al, Cancer Cell 27, 728-43, 2015
ATRT
• First described in 1987 by Rorke et al
  – Previously dx as MB, PNET, CPC
  – US incidence $3 \times 10^6$ children = approx 3% of pediatric CNS tumors
• Poor prognosis, most die of disease

Table 6. Comparative features of CNS atypical teratoid/rhabdoid and primitive neuroectodermal tumors of childhood

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATTRhT</td>
</tr>
<tr>
<td>Age</td>
<td>17.5 months</td>
</tr>
<tr>
<td>Posterior fossa location</td>
<td>65%</td>
</tr>
<tr>
<td>Initial response to therapy</td>
<td>12%</td>
</tr>
</tbody>
</table>

Rorke et al, J Neuro-Oncol 24, 1995
ATRT Primary Site

- 50-60% posterior fossa
- 30-40% supratentorial
- 2% spinal
- 2% multifocal

Normal staining in non-tumor cells, (control)

INI 1 protein staining absent in tumor cells
ATRT outcomes - historical

• POG 9923: 36 patients
  – 69% PD by 3-6 mo on therapy
  – 83% PD by 12 mo
  – Med OS 193 d (Strother et al)
  – Most failures in primary site, all died of disease

• CCG 9921: 28 patients
  – EFS 32% at 1 yr, 14% at 2 y (Geyer et al)
  – Failure: local 45%, local & met 29%
ATRT - Surgery

• Surgery for diagnosis
• Registry data: degree of surgery may affect survival
  – 20 GTR EFS 12.5 mo
  – 22 STR EFS 9.25 mo
  – 10/14 long term survivors had GTR
  – ? Role of second look surgery
Chemotherapy – IRS III

- **RT, IT MTX, Ara C, hydrocortisone, multi-agent chemo**
  - All 3 pt responded, 1/3 had prolonged survival
- **CHOP: similar approach**
  - 2 Y EFS 33% (Janss)
- **Boston:**
  - IRS III in 2 pt with relapsed ATRT, alive at 30 mo (Kieran)
High dose chemo with SCT

- ATRT registry 13 pt
  - 4/13 pt alive at last evaluation: **2/4 had RT**
- HS II: HDSCR + MTX, no RT:
  - 3/6 pt NED at 12, 34, 46 mo from dx
  - 1 pt salvaged w RT and chemo
- HS I: No MTX: 6/6 ATRT pt died
ATRT-Boston experience

- 2004-06: 20 pt
  - med age 26 mo
  - 14 M0, 5 M3
  - 15 pt RT: 11 CRT, 4 CSI
- 2y PFS & OS: 53% & 70%.
- Local RT for M0

Chi et al, JCO, 27 385-389, 2008
ATRT- Radiotherapy

• ATRT registry: 42 pt
  – 13 pt received RT as part of primary therapy
    • 9 RT to primary site
    • 4 RT to CSI + primary site
    • Median OS 48 mo vs. 16.7 mo for all pt on registry
    • Of the 14 long term survivors on registry, 7 had RT

• St Judes:
  – 22 pt <3 y at dx: chemo alone=> 3 y EFS 11%
  – 9 pt >3 y at dx: CSI +chemo => 3 y EFS 58%
ATRT SJMB 03 - 9/04-11/09

- 17 pts, mean age 5.7 y (3.1-12.1)
  - ST 8, PF 7, spinal cord 2
  - 9 AR, 8 HR (M+ 6)
  - 10/17 GTR or NTR

- Treatment regimen
  - 23.4 Gy or 36-39.6 Gy CSI + boost to 55.8Gy
  - 4 cycles cyclo based intense chemo

- Results at median f/u 12 mo (3-64mo):
  - 16 pt received median of 4 cycles of chemo
  - 10 pt alive NED, 7 pt DOD
  - 5Y EFS 54%, 5Y OS 52%  
  - 5Y OS AR vs HR: 87.5 vs 15%

SNO 2010 PC-03 abstract: Gajjar et al
ATRT – Overall Data Summary

• Retrospective studies: median OS +/-1 yr
• Data suggest:
  – Std & intensive chemo: good response, but high recurrence
  – Early RT may be associated with survival
  – CT with PBSCT may have higher control rates
  – MTX (HSII and IRS III) may be useful
MANDATORY PATHOLOGY RAPID CENTRAL REVIEW AND MANDATORY BIOLOGY TISSUE SUBMISSION
SEE SECTIONS 3.1.6 & 3.1.7

**ACNS- 0333**

Younger or M+

Older or M0

**INDUCTION (2 CYCLES)**
**PBSC HARVEST**
Methotrexate, Vincristine, Etoposide, Cyclophosphamide, Cisplatin

Infratentorial M₀ (Age <6 months)†
Supratentorial M₀ (Age <12 months)†
Disseminated Disease M₅ (Any site, Any Age)

NO RESECTABLE DISEASE
CONSIDER SECOND SURGERY
CONSOLIDATION (3 CYCLES)
Thiotepa, Carboplatin PBSC Rescue

M₀ – FOCAL IRRADIATION
M₅ – AGE-ADJUSTED CRANIOSPINAL IRRADIATION*

RESECTABLE DISEASE

Infratentorial M₀ (Age ≥ 6 months)†
Supratentorial M₀ (Age ≥12 months)†

NO RESECTABLE DISEASE
CONSIDER SECOND SURGERY

RESECTABLE DISEASE
FOCAL IRRADIATION
CONSOLIDATION (3 CYCLES)
Thiotepa, Carboplatin PBSC Rescue

*Craniospinal irradiation is recommended but not mandated for patients with disseminated disease at the time of enrollment.
M₀ = no evidence of metastatic disease at the time of enrollment.
M₅ = evidence of metastatic disease at the time of enrollment.
ACNS 0333 continued

- Opened 12/08 closed 2/14
- Accrued 70 patients

<table>
<thead>
<tr>
<th>Age @ RT</th>
<th>M Stage</th>
<th>Primary</th>
<th>Volume</th>
<th>CSI</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-36 mo</td>
<td>M0</td>
<td>IT</td>
<td>Focal</td>
<td>0</td>
<td>50.4</td>
</tr>
<tr>
<td>&gt;36 mo</td>
<td>M0</td>
<td>IT/ST</td>
<td>Focal</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>&lt;36 mo</td>
<td>M+</td>
<td>IT/ST</td>
<td>Focal+CSI</td>
<td>23.4</td>
<td>27</td>
</tr>
<tr>
<td>&gt;36 mo</td>
<td>M+</td>
<td>IT/ST</td>
<td>Focal+CSI</td>
<td>36</td>
<td>18</td>
</tr>
</tbody>
</table>

Failure pattern will be studied to determine need for CSI
• So far 24 mo:
  - All: EFS 43% OS 52%
  - <36 mo: EFS 39% OS 48% (p<0.025)

⇒ ACNS 0333 better for <36 mo pt
⇒ Order of therapy not important
⇒ Further intensification not possible
⇒ Molecular stratification may be helpful
ATRT

• ATRT is a devastating disease
• Aggressive multimodality therapy appears to be necessary even for very young children
• Early radiotherapy advocated for all children with non-disseminated disease
• Biology of ATRT will need more study
Late Effects with Advanced RT Techniques

• Study for St. Jude's suggests very young children with PF tumors and local RT do well with respect to cognitive function.
• MDA ATRT study did not indicate significant late effects, but more follow up needed.
Proton Therapy – just a word!
### MDA Proton Therapy in <4yo Pt’s

<table>
<thead>
<tr>
<th>Decade</th>
<th>Total</th>
<th>N malign</th>
<th>% Malig</th>
<th>N RT (X/P)</th>
<th>% RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1970</td>
<td>18</td>
<td>17</td>
<td>0.94</td>
<td>4</td>
<td>0.78</td>
</tr>
<tr>
<td>1970's</td>
<td>28</td>
<td>27</td>
<td>0.96</td>
<td>13</td>
<td>0.75</td>
</tr>
<tr>
<td>1980's</td>
<td>61</td>
<td>58</td>
<td>0.95</td>
<td>15</td>
<td>0.31</td>
</tr>
<tr>
<td>1990's</td>
<td>86</td>
<td>81</td>
<td>0.94</td>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>2000's</td>
<td>133</td>
<td>125</td>
<td>0.94</td>
<td><strong>74 (39/35)</strong></td>
<td>0.54</td>
</tr>
<tr>
<td>2010's</td>
<td>170</td>
<td>165</td>
<td>0.97</td>
<td><strong>139 (37/102)</strong></td>
<td>0.79</td>
</tr>
</tbody>
</table>
US Pediatric PRT Trends 2010-13

Total 2494

2010 465
2011 613
2012 694
2013 722

Courtesy of PPF
Summary

• Management of malignant infant brain tumors requires multidisciplinary approach
• Radiotherapy has made a “come back” and requires consideration of all normal tissues, MRI based planning, highly conformal dosimetry to CTV
• Continue accrual on protocols to improve outcomes further
• Follow patients to study incidence of late effects.