Radiation Therapy for Pediatric Brain Tumors

David B. Mansur, M.D.

Associate Professor of Radiation Oncology and Pediatrics
Vice Chair and Director Proton Therapy Center
Case Western Reserve University School of Medicine
Cleveland, OH, USA
Disclosures

• No conflict of interests
Overview

• Surgery
• Post operative staging and work up
• Management of Specific Tumors
  – Low Grade Glioma
  – High Grade Glioma
  – Ependymoma
  – Embryonal Tumors / Medulloblastoma
• Radiation Therapy Techniques
• Neurocognitive Late Effects
Surgery
Surgery Extent

- No Surgery
- Gross Total Resection
Surgery Extent

No Surgery

- Optic pathway glioma
- Diffuse intrinsic pontine glioma (DIPG)

Gross Total Resection
Surgery Extent

No Surgery

- Optic pathway glioma
- Diffuse intrinsic pontine glioma (DIPG)

Gross Total Resection

- Lymphoma
- Germinoma
Surgery Extent

No Surgery

- Optic pathway glioma
- Diffuse intrinsic pontine glioma (DIPG)
- Lymphoma
- Germinoma

Gross Total Resection

- Gliomas
- Ependymoma
- Embryonal Tumors (medulloblastoma, PNET)
- Everything else
Surgery Extent

No Surgery

- Optic pathway glioma
- Diffuse intrinsic pontine glioma (DIPG)
- Lymphoma
- Germinoma

Gross Total Resection

- Gliomas
- Ependymoma
- Embryonal Tumors (medulloblastoma, PNET)
- Everything else

• Not fully resectable due to tumor location
Post-operative Imaging

- Verify extent of resection
- Determine if spinal dissemination is present
Extent of Resection
Extent of Resection

24 hours post-op
Extent of Resection

24 hours post-op

3 weeks post-op
## Spinal Dissemination

<table>
<thead>
<tr>
<th>Tumor</th>
<th>% with spinal dissemination at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioma</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>10-15</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>30</td>
</tr>
<tr>
<td>Embryonal tumor (medulloblastoma, PNET, etc)</td>
<td>30</td>
</tr>
</tbody>
</table>
R/O Dissemination

• Wait >10 Days **post-op**: Because debris and blood products can mimic drop metastases. Then:
  – MRI spine
  – Lumbar puncture for cytology
Radiation Therapy Considerations

- Surgery Extent
- *To Irradiate or not?*
- Radiation Volume
- Radiation Dose
- Chemotherapy?
The decision to use radiation therapy is a balancing act.
Maximize survival AND quality of life
Predisposing Syndromes

• Tuberous Sclerosis, von Hippel Lindau, Gorlin
• Neurofibromatosis “NF”
  – A group of syndromes with neuro-cutaneous manifestations
  – Autosomal Dominant
  – Multiple Café au Lait spots
  – Neurofibromas
  – Brain Tumors
Neurofibromatosis

• **Type 1** (von Recklinghausen)
  – 1:3000
  – Optic pathway gliomas
  – Lisch Nodules
  – Axillary/inguinal freckles
  – Mental delay
  – Sphenoid dysplasia
  – Pheochromocytoma
  – Renal artery stenosis

• **Type 2**
  – 1:50,000
  – Bilateral acoustic neuroma
  – Meningioma
  – Spinal cord ependymoma
  – Childhood cataracts
For NF-1 patients...

- Tumors tend to be low grade and slowly growing

- RT complication risk is higher
  - 3x risk of vasculopathy and occlusion of the Circle of Willis: “moyamoya” syndrome
  - 3x increase risk of radiation-induced second malignancies
Low Grade Glioma
Surgery: CCG 9891 POG 9130

- Prospective study of surgery for all low grade gliomas in children
- n=660

Progression-Free Based on Surgery extent:
Chemotherapy COG A9952

- Initial Chemotherapy
- CV vs TPCV
- All low grade gliomas
- Patients < 10 years old
- n=274
- No NF patients
- Median f/u 5 yrs
- **Overall PFS 45-50%**

*Patients with neurofibromatosis (NF) will be non-randomly assigned to Regimen A*

TPCV = Thioguanine, Procarbazine, CCNU, Vincristine

CV = Carboplatin, VCR = Vincristine

Ater JCO 30:2641, 2012
Radiation Therapy

- 35 children with unresectable pilocytic astrocytoma (Grade 1)
- RT alone
- Median dose 54 Gy
- Median f/u 5 years
- No NF patients
- **5 yr PFS 68%**
- 8/9 patients who progressed did within the irradiated volume

Radiation Therapy

- German (HIT-LGG 1996)
- 117 children
- 10 had NF
- Median age 9 yrs
- Pilocytic astrocytoma
- RT as first or 2nd line treatment
- Median dose 54Gy
- Median f/u 8 yrs
- 5 yr PFS 77%

Muller et al, Strahlenther Onkol 189:647, 2013
Radiation Therapy Dose

Muller et al, Strahlenther Onkol 189:647, 2013
Chemotherapy And Radiation?

- Children’s Cancer Group 945
- Trial for High Grade Glioma, but
- 70 patients with LGG:
- Originally diagnosed as high grade

**FIGURE 1.** Schema for the Children’s Cancer Group (CCG) high-grade glioma protocol (CCG-945). Control regimen A consisted of vincristine (V) 1.5 mg/m², lomustine (C) 100 mg/m², and prednisone (P) 40 mg/m² per day for 14 days. Experimental regimen B consisted of vincristine 1.5 mg/m², lomustine 100 mg/m², procarbazine 75 mg/m², hydroxyurea 3000 mg/m², cisplatin 90 mg/m², mannitol 12 gm/m², cytarabine 300 mg/m², dacarbazine 150 mg/m², and methylprednisolone 300 mg/m² for 3 doses.

Fouladi  Cancer 98:1243, 2003
Chemo/RT: CCG – 945

Pilocytics

Fibrillary

\[ p = 0.04 \]

Fouladi  Cancer 98:1243, 2003
Low Grade Astrocytoma

- Extent of surgery is prognostic and GTR is usually curative
- PFS with chemotherapy is 45-50%
- PFS with RT is 70%
- Appears to be no benefit for the addition of chemotherapy compared to RT
- Conformal RT and dose of 50.4 Gy
- Approach to each patient must be individualized:
High Grade Astrocytoma
Glioblastoma

- An adult tumor, median age 60 yrs
- Only 6% of Childhood brain tumors are high grade gliomas (Anaplastic Astrocytoma and Glioblastoma)

From Ohgaki and Kleihues  J Neuropath Exp Neurol 64:479, 2005
Childrens Cancer Group 943

- First systematic use of chemotherapy for children with high grade astrocytomas
- 1976-81
- Randomized comparison:

\[
\begin{align*}
\text{54 Gy “regional”} & \quad \text{vs} \quad \text{54 Gy “regional”} \\
& + \\
& \text{Prednisone} \\
& \text{CCNU (Lomustine)} \\
& \text{Vincristine}
\end{align*}
\]

Fig. 4. Survival (in years) by randomized treatment assignment.
Single Institution Glioblastoma

- 24 children since 1970
- Median age 11 yrs
- 58% had chemotherapy
- Median follow up 12.5 months

EORTC 26981

- RT alone vs RT + Temozolomide
  - 75mg/m2 daily
  - 150-200 mg/m2 x5d x6mo
- 96% GB
- 573 pts
- Median age 57

Children’s Oncology Group
ACNS 0126

- Temodar 90mg/m² daily + 54/59.4 Gy
- Maintenance Temodar 200mg/m² x5d monthly x 10 cycles
- Phase II 107 patients 2002-2005
Children’s Oncology Group
ACNS 0822

Surgery

Study Entry and Randomization

Arm A
Chemoradiotherapy
Vorinostat 230mg/m²/day (determined from the feasibility study)
5 days/week for 6 weeks
And
Radiation Therapy for 6 weeks and 4 week rest

Arm B
Chemoradiotherapy
Temozolomide 90mg/m²/dose
Daily for 42 days
And
Radiation Therapy for 6 weeks and 4 week rest

Arm C
Chemoradiotherapy
Bevacizumab 10mg/kg/dose
Days 22 and 36 During RT
And
Radiation Therapy for 6 weeks and 4 week rest

Maintenance Chemotherapy
Bevacizumab 10mg/kg/dose every 2 weeks
And
Temozolomide 200mg/m²/dose Days 1-5
(for up to 12 cycles in the absence of Progressive Disease and unacceptable toxicities)
High Grade Astrocytoma

- Poor outcome
- RT: Total dose 59.4 Gy

*All patients treated with chemotherapy* in addition to RT

- Results with Temozolomide less encouraging than in adults
- Optimal chemotherapy still to be determined
Ependymoma
Ependymoma Classification 2007

- Subependymoma: Grade I
- Myxopapillary ependymoma
- Ependymoma
  - Cellular: Grade II
  - Papillary
  - Clear Cell
  - Tanycytic
- Anaplastic Ependymoma: Grade III
Ependymoma Classification 2007

- Subependymoma  
  Grade I
- Myxopapillary ependymoma
- Ependymoma
  - Cellular  
  - Papillary  
  - Clear Cell  
  - Tanycytic  
  Grade II
- Anaplastic Ependymoma  
  Grade III
Surgery Alone For Ependymoma?

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>F/U yrs</th>
<th>% Progression free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awaad (1996)</td>
<td>7</td>
<td>3.6</td>
<td>71</td>
</tr>
<tr>
<td>Venkatramani (2012)</td>
<td>6</td>
<td>--</td>
<td>50</td>
</tr>
<tr>
<td>Palma (2000)</td>
<td>7</td>
<td>--</td>
<td>42</td>
</tr>
<tr>
<td>Hukin (1998)</td>
<td>10</td>
<td>4</td>
<td>70</td>
</tr>
</tbody>
</table>
Chemotherapy?  CCG - 942

- Children’s Cancer Group – 942
- Medulloblastoma trial 1975-1981
- Included infratentorial ependymoma
- 80% Grade II, median age 5,

Evans et al/ Med Ped Onc 27:8, 1996
CCG - 942

10 year f/u
Overall survival 39%
No difference between treatment arms
# Chemotherapy to Delay RT?

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Age (years)</th>
<th>GTR (%)</th>
<th>Grade III (%)</th>
<th>Agents</th>
<th>Response rate (%)</th>
<th>PFS (%)</th>
<th>OS (%)</th>
<th>Role of RT</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massimino et al.</td>
<td>41</td>
<td>&lt;3</td>
<td>54</td>
<td>39</td>
<td>VCR/HD MTX, cyclophosphamide, cisplatin, etoposide</td>
<td>–</td>
<td>27</td>
<td>37</td>
<td>Planned if residual disease after chemotherapy or to salvage progressive disease</td>
<td>[52]</td>
</tr>
<tr>
<td>Grill et al.</td>
<td>73</td>
<td>&lt;5</td>
<td>60</td>
<td>88</td>
<td>Procarbazine, carboplatin, cisplatin/etoposide, VCR/cyclophosphamide</td>
<td>0</td>
<td>22</td>
<td>59</td>
<td>None planned. To salvage progressive disease only</td>
<td>[19]</td>
</tr>
<tr>
<td>Grundy et al.</td>
<td>80</td>
<td>&lt;3</td>
<td>50</td>
<td>33</td>
<td>Carboplatin/VCR, MTX/cyclophosphamide/cisplatin</td>
<td>–</td>
<td>42</td>
<td>63</td>
<td>None planned. To salvage progressive disease only</td>
<td>[11]</td>
</tr>
<tr>
<td>Timmermann et al.</td>
<td>34</td>
<td>&lt;3</td>
<td>53</td>
<td>100</td>
<td>Procarbazine/MTX/VCR, ifosfamide, etoposide, cisplatin, cytarabine, cyclophosphamide IV/MTX/cisplatin</td>
<td>–</td>
<td>27</td>
<td>56</td>
<td>Planned at age 3 years or to salvage progressive disease</td>
<td>[35]</td>
</tr>
<tr>
<td>Duffner et al.</td>
<td>48</td>
<td>&lt;3</td>
<td>40</td>
<td>29</td>
<td>VCR/cyclophosphamide, cisplatin/etoposide</td>
<td>–</td>
<td>27</td>
<td>41</td>
<td>Planned after 1 year if &gt;2 years old, and after 2 years if &lt;2 years old, or as salvage for progression</td>
<td>[10]</td>
</tr>
<tr>
<td>Geyer et al.</td>
<td>74</td>
<td>&lt;3</td>
<td>81% (&gt;90% resected)</td>
<td>44</td>
<td>VCR/etoposide, cisplatin/ cyclophosphamide, carboplatin/ifosfamide</td>
<td>44</td>
<td>32</td>
<td>59</td>
<td>None planned if no residual or metastatic disease. Only to salvage progressive disease</td>
<td>[53]</td>
</tr>
</tbody>
</table>

GTR: Gross total resection; HD: High dose; IV: Intraventricular; MTX: Methotrexate; OS: Overall survival; PFS: Progression-free survival; RT: Radiation therapy; VCR: Vincristine.
Role of Post Operative Radiation Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>F/U yrs</th>
<th>n -RT / +RT</th>
<th>%PFS -RT / +RT</th>
<th>%OS -RT / +RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perilongo (1997)</td>
<td>3</td>
<td>16 / 76</td>
<td>20 / 41</td>
<td>52 / 58</td>
</tr>
<tr>
<td>Rogers (2005)</td>
<td>5.5</td>
<td>19/13</td>
<td>50 / 100</td>
<td>67 / 83</td>
</tr>
<tr>
<td>GTR only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metellus (2010)</td>
<td>6</td>
<td>79/35</td>
<td>36 / 86</td>
<td>58 / 95</td>
</tr>
<tr>
<td>STR only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollack 1995</td>
<td>--</td>
<td>10 / 27</td>
<td>13 / 70</td>
<td>40 / 88</td>
</tr>
<tr>
<td>Rousseau (1994)</td>
<td>4.5</td>
<td>15 / 65</td>
<td>0 / 45</td>
<td>23 / 63</td>
</tr>
<tr>
<td>Koshy (2011) All &lt; 3 yrs old</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>56 / 81</td>
</tr>
</tbody>
</table>

Post Operative RT established as standard of care in the US
## Disseminated Disease at Diagnosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Institution</th>
<th>n</th>
<th>Grade</th>
<th>% +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson</td>
<td>CCG-921</td>
<td>32</td>
<td>II/III</td>
<td>9.4 all grade II</td>
</tr>
<tr>
<td>Horn</td>
<td>Multi-Insti</td>
<td>72</td>
<td>II/III</td>
<td>15</td>
</tr>
<tr>
<td>Timmerman</td>
<td>German</td>
<td>55</td>
<td>III</td>
<td>9</td>
</tr>
<tr>
<td>Pollack</td>
<td>Pittsburgh</td>
<td>31</td>
<td>II/III</td>
<td>21 (8% supra, 28% infra)</td>
</tr>
<tr>
<td>Perilongo</td>
<td>Italian</td>
<td>29</td>
<td>II/III</td>
<td>7</td>
</tr>
<tr>
<td>Rousseau</td>
<td>IGR</td>
<td>69</td>
<td>II/III</td>
<td>6</td>
</tr>
</tbody>
</table>

Disseminated disease requires craniospinal RT, localized disease does not!
## Ependymoma Pattern of Relapse

<table>
<thead>
<tr>
<th>Study</th>
<th>% of patients with isolated out-of-field recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollack (U. Pittsburgh)</td>
<td>5</td>
</tr>
<tr>
<td>Carrie (Lyon)</td>
<td>3</td>
</tr>
<tr>
<td>Merchant (MSK)</td>
<td>0</td>
</tr>
<tr>
<td>Rousseau (IGR)</td>
<td>12.5</td>
</tr>
<tr>
<td>Merchant (St. Jude)</td>
<td>3</td>
</tr>
<tr>
<td>Mansur (Wash. U)</td>
<td>0</td>
</tr>
</tbody>
</table>
Dose Response in Ependymoma

<table>
<thead>
<tr>
<th>Author (Institution)</th>
<th>Dose Response</th>
<th>Dose Level (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldwein (CHOP)</td>
<td>Yes</td>
<td>&gt; 45</td>
</tr>
<tr>
<td>Carrie (Lyon)</td>
<td>No</td>
<td>+/- 50</td>
</tr>
<tr>
<td>Kim (U. Michigan)</td>
<td>Yes</td>
<td>&gt; 45</td>
</tr>
<tr>
<td>Merchant (MSK)</td>
<td>Yes</td>
<td>Continuous Variable to 59.4</td>
</tr>
<tr>
<td>Rousseau (IGR)</td>
<td>No</td>
<td>+/- 50</td>
</tr>
<tr>
<td>Stuben (Germany)</td>
<td>Yes</td>
<td>&gt; 45</td>
</tr>
<tr>
<td>Mansur (Wash U)</td>
<td>Yes</td>
<td>&gt; 54</td>
</tr>
</tbody>
</table>

Current recommendations: 54-59.4 Gy
## Radiosurgery for Ependymoma

### Table 2. Results with stereotactic radiosurgery for intracranial ependymoma.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Age range (years)</th>
<th>Grade III (%)</th>
<th>Median dose (Gy)</th>
<th>Median follow-up (months)</th>
<th>PFS (%)</th>
<th>OS (%)</th>
<th>Symptomatic complications (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgson et al. (2001)</td>
<td>25 salvage 3 initial</td>
<td>1.4–21.4</td>
<td>–</td>
<td>12.5</td>
<td>24</td>
<td>22</td>
<td>–</td>
<td>26</td>
<td>[42]</td>
</tr>
<tr>
<td>Jawahar et al. (1999)</td>
<td>22 salvage</td>
<td>1.5–65</td>
<td>100</td>
<td>16.1</td>
<td>21</td>
<td>32</td>
<td>50</td>
<td>4.5</td>
<td>[43]</td>
</tr>
<tr>
<td>Stafford et al. (2000)</td>
<td>12 salvage</td>
<td>5–56</td>
<td>--</td>
<td>18</td>
<td>22</td>
<td>68</td>
<td>–</td>
<td>17</td>
<td>[44]</td>
</tr>
<tr>
<td>Aggarwal et al. (1997)</td>
<td>4 salvage* 1 initial</td>
<td>1.3–12.4</td>
<td>20</td>
<td>10</td>
<td>24</td>
<td>80</td>
<td>80</td>
<td>20</td>
<td>[45]</td>
</tr>
<tr>
<td>Mansur et al. (2004)</td>
<td>5 salvage 4 initial</td>
<td>3–72</td>
<td>22</td>
<td>16</td>
<td>28</td>
<td>56</td>
<td>71</td>
<td>22</td>
<td>[46]</td>
</tr>
<tr>
<td>Lo et al. (2006)</td>
<td>5 salvage 3 initial</td>
<td>1.3–34.9</td>
<td>12.5</td>
<td>14</td>
<td>30</td>
<td>50</td>
<td>–</td>
<td>25</td>
<td>[47]</td>
</tr>
<tr>
<td>Kano et al. (2010)</td>
<td>21 salvage</td>
<td>2.9–17.2</td>
<td>43</td>
<td>15</td>
<td>28</td>
<td>42</td>
<td>23</td>
<td>4</td>
<td>[48]</td>
</tr>
<tr>
<td>Stauder et al. (2012)</td>
<td>26 salvage</td>
<td>1.4–69.6</td>
<td>34</td>
<td>18</td>
<td>37</td>
<td>66</td>
<td>69</td>
<td>8</td>
<td>[49]</td>
</tr>
</tbody>
</table>

*Four patients progressed on chemotherapy and were treated with planned external-beam and stereotactic radiosurgery boost. OS: Overall survival; PFS: Progression-free survival.
Ependymoma

• Post op RT is standard of care in USA
  – Local conformal volume if no dissemination
  – Craniospinal RT if disseminated disease is present

• Many questions remain (role of chemotherapy?, role of surgery alone?, best incorporated into clinical trials....)
Ependymoma -- COG 0831

Supratentorial Grade II GTR

STR

chemo

Everybody Else

CR

2nd Look Surgery

GTR

Observation

Conformal RT to 59.4 Gy

0.5 cm CTV, 3-5 mm PTV

Randomized

Maintenance chemo
Embryonal Tumors
Embryonal Tumor Classification

- Medulloblastoma
- Primitive Neuroectodermal Tumors
  - CNS neuroblastoma, ependymoblastoma, medulloepithelioma
- Atypical Teratoid Rhabdoid Tumor
- Pineoblastoma
Embryonal Tumors

- High grade tumors (all Grade 4 in W.H.O)
- High rate of cerebrospinal fluid dissemination
- Careful work up of spine
- Craniospinal RT required with boost to primary site and possibly metastatic deposits
- Poor prognosis, except for medulloblastoma
Medulloblastoma

**Average Risk**
- Age $\geq$ 3 years
  - AND
  - $\leq$ 1.5 cm² residual
  - AND
  - No Dissemination

**High Risk**
- Age $<$ 3 years
  - or
  - $>1.5$ cm² residual
  - or
  - Disseminated tumor
  - or
  - Anaplastic Histology

PFS: 80% vs 30-60%*
Medulloblastoma

**Average Risk**
- Age $\geq$ 3 years
- AND
- $\leq$ 1.5 cm$^2$ residual
- AND
- No Dissemination

**High Risk**
- Age $<$ 3 years
  - or
- $>1.5$ cm$^2$ residual
  - or
- Disseminated tumor
  - or
- Anaplastic Histology

- Reduced intensity RT
- Lower CSI dose
- Smaller boost volume

- Standard dose and volume of RT
- Intensified chemotherapy
- Treated with other embryonal tumors
Average Risk Medulloblastoma
COG 0331

Children ages 3-7

Reduced-dose craniospinal radiation

18 Gy

Smaller volume boost (radiation to tumor bed)*

Randomize#

Maintenance Chemotherapy
9 Cycles
(Cisplatin, VCR, CCNU, Cytoxan)

Children 8 and older

As of Amendment #5, the children 8 and older Arm was completed.

Standard-dose craniospinal radiation

23.4 Gy

Standard volume boost (radiation to the entire posterior fossa)

Randomize#
High Risk Medullo and Other Embryonal Tumors: COG 0332

RT:
CSI 36 Gy
Boost to 55.8 Gy

(Cisplat, VCR, Cytoxan)
Radiation Therapy Techniques
Simulation
Image Fusion For Contouring

CT Simulation

Diagnostic MRI
Image Fusion For Contouring

Diagnostic MRI

CT simulation image
# Summary of Volume, Dose, and Chemotherapy for Pediatric Brain Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Volume (CTV in cm) and Dose (Gy)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local Field</td>
<td>Whole Ventricle +Boost</td>
</tr>
<tr>
<td>Low Grade Glioma</td>
<td>1 cm 50.4-54</td>
<td>---</td>
</tr>
<tr>
<td>Ependymoma Localized</td>
<td>1 cm 54-59.4</td>
<td>---</td>
</tr>
<tr>
<td>Ependymoma Disseminated</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>High Grade Glioma</td>
<td>2-3 cm</td>
<td>---</td>
</tr>
<tr>
<td>Average Risk Medulloblastoma</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>All other Embryonal tumors</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>0.5-1 cm 50-54 Gy</td>
<td>---</td>
</tr>
<tr>
<td>Pure Germinoma (Localized)</td>
<td>---</td>
<td>24 Gy Boost to 45-50</td>
</tr>
<tr>
<td>Pure Germinoma (Disseminated)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Mixed Germ Cell tumor (Localized)</td>
<td>---</td>
<td>30 Gy Boost to 54</td>
</tr>
<tr>
<td>Mixed Germ Cell Tumor (Disseminated)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
Ependymoma

**GTV**

**CTV**: 1 cm

**PTV**: 0.5 cm
High Grade Astrocytoma

**Initial volume**
T2 signal + 2-3 cm
45-50.4 Gy

**Boost volume**
T1 signal and/or tumor cavity + 1-2 cm

**Total Dose 59.4**
Embryonal Tumors: Craniospinal Technique
Technical Challenge – Craniospinal RT
Cribriform Plate
Cribriform Plate
Cribriform Plate
Helical Tomotherapy
Tomotherapy Craniospinal

- Avoids matching of fields
- More conformal prescription isodoses
- More low dose spread to other tissues.
Posterior Fossa Boost
Posterior Fossa Boost
Conventional Fields

- Draw a line from posterior clinoid (A) to the internal occipital protuberance (B)
- Draw a line bisecting and perpendicular to AB (DE)
- Tentorial apex (C) is $\frac{1}{2}$ the distance between D-E.

Drayer et al IJROBP 41:625, 1998
Posterior Fossa Boost
Conventional Fields

- Draw a line from posterior clinoid (A) to the internal occipital protuberance (B)
- Draw a line bisecting and perpendicular to AB (DE)
- Tentorial apex © is ½ the distance from E-D
- Draw lateral portal with 1-2 cm margin
- Not as accurate for children < 1 yr of age

Drayer et al IJROBP 41:625, 1998
Posterior Fossa Boost
Conventional Fields

Conventional lateral view
Posterior Fossa Boost
Conformal Technique
Posterior Fossa Boost
Conformal Technique
IMRT Posterior Fossa Boost
Proton Beam For Pediatric Brain Tumors
Photons vs Protons
Depth Dose Curve
5 Field IMRT

1 Field Proton

Courtesy Beth Pierburg, CMD
Pseudoprogression
Pseudoprogression
Neurocognitive Toxicity
Neurocognitive Toxicity -- Surgery
CCG 9891 / POG 9130

• Prospective protocol of Low Grade Glioma patients age 3-18 treated with surgery alone between 1991-1996
• Neuro-cognitive testing within a year of surgery.
Posterior Fossa Tumors  \( n=103 \)

Supratentorial Tumors  \( n=93 \)

Ris JCO 26:4765, 2008  Beebe JCO 23:5198, 2005
Neurocognitive Toxicities -- RT
Radiation Induced Cognitive Decline

- RT Dose
- RT Volume
- Age at RT
IQ following RT for infant medulloblastoma – 35 Gy Craniospinal
CCG 9892 -- 23.4 Gy Craniospinal

Change in Mean Full-Scale Intelligence Quotient

n = 43

Ris et al  JCO 19:3470, 2001
CCG 9892 -- 23.4 Gy Craniospinal

Change in Mean Non-Verbal IQ by Patient Age

Ris et al  JCO 19:3470, 2001
Mean IQ Decline After RT

Mean IQ Decline With Time After RT

* Influence of DOSE and AGE

Courtesy Gisele Pereira
Hoppe-Hirsch et al 1995

**Ependymoma** Posterior Fossa only 50 Gy

**vs Medulloblastoma** whole brain 25-35 + PF boost to 50 Gy

IQ: no sig. Differences at 1 year. At 10 years, only 10% of medullo kids had IQ > 90

School Performance:
St. Jude – Neurocognitive Testing after conformal RT

Ependymoma patients
>12 months old
High dose 54-59.4 Gy conformal RT
Tumor/cavity + 1 cm
Median f/u 60 months
IQ stable, however modest decline in reading function observed
* Influence of VOUME

Fig 1. Relationships among reading, intellectual functioning (IQ), and parent reported school problems. Linear models of Wechsler Individual Achievement Test (WIAT) reading, IQ, and Achenbach Child Behavior Checklist (CBCL) School Problems. The WIAT reading and IQ are on the primary vertical axis, and CBCL School Problems is on the secondary axis.

Conklin JCO 26:3965, 2008
Neurocognitive Decline

• Multi-factorial
  – Damage from the tumor
  – Surgery
  – Chemotherapy esp. methotrexate
  – RT

• RT effects result from 3 variables:
  – Dose
  – Volume
  – Age of child
Obrigado