Pediatric Low Grade Gliomas

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Adult Brain Tumors

* LGG are proportionately more common in children

Pediatric Brain Tumors

CBTRUS Neuro-Oncol 2015
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

<table>
<thead>
<tr>
<th>Type 1 (von Recklinghausen)</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:3000</td>
<td>1:50,000</td>
</tr>
<tr>
<td>Optic pathway gliomas</td>
<td>Bilateral acoustic neuroma</td>
</tr>
<tr>
<td>Lisch Nodules</td>
<td>Meningioma</td>
</tr>
<tr>
<td>Axillary/inguinal freckles</td>
<td>Spinal cord ependymoma</td>
</tr>
<tr>
<td>Mental delay</td>
<td>Childhood cataracts</td>
</tr>
<tr>
<td>Sphenoid dysplasia</td>
<td></td>
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<tr>
<td>Pheochromocytoma</td>
<td></td>
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<tr>
<td>Renal artery stenosis</td>
<td></td>
</tr>
</tbody>
</table>
For NF-1 patients, keep in mind:

- 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
Surgery
Children’s Cancer Group 9891
Pediatric Oncology Group 9130

• Largest Prospective study of surgery for all low grade gliomas in children
• n=660
• Post op RT allowed (if ≥ 1.5 cc residual)
  – (RT not detailed)
CCG 9891 / POG 9130

PFS based on surgery extent:

Fig. 9. Progression-free survival curves by extent of surgical resection for the Children’s Cancer Group and Pediatric Oncology Group Study (from Sanford et al., 2002)

Sanford et al (Abstr), 2002
Surgery

• Gross Total Resection is curative usually
• Subtotal resection has an increased risk of progression, though substantial numbers of patients will be progression-free.
Chemotherapy
24 Children – median age 1.6 yrs
3 patients with Neurofibromatosis
Progressive Hypothalamic or Optic pathway tumors
Biopsy not mandatory
Accrual 1977 – 1987
Actinomycin D and vincristine x 6 cycles
- Median f/u 4.3 years
- Of those getting RT salvage, median age was 4.5 years
- Neuropsych testing in 15 patients:
  - 1 pt severely impaired
  - 14 had mean IQ of 103
- Chemo Toxicity: 2 pts required admission, some mild paresthesias

Chemotherapy has reasonable activity
Potential to delay the RT with chemotherapy

Children’s Oncology Group Approach

Age-specific protocol treatment <10 years?

YES → Chemo A9953

NO → Radiation 0221
COG A9952

- Initial Chemotherapy for patients < 10 yr old
- CV vs TPCV
- All low grade gliomas
- n=274
- No NF patients
- Median f/u 5 yrs
- **PFS 39 vs 52%**

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

Ater JCO 30:2641, 2012
COG ACNS 0223

- A pilot study to test feasibility of
  - Vincristine, Carboplatin, AND Temozolomide (alternating)
- 60 children ≤ 10 yrs (median 4.6 yrs) with unresectable and symptomatic or progressive LGG --grade 1(majority) and 2
- NF1 patients excluded

Chintagumpala et al Neuro-Oncology 17:1132, 2015
COG ACNS 0223

- Grade 3 or higher neutropenia in 50%
- Met feasibility endpoints
- 5 yr EFS 46%

Fig. 1. Event-free and overall survival of all eligible patients on the study.
Radiation Therapy
35 children with unresectable pilocytic astrocytoma (Grade 1)
1982-2009
RT alone
Median dose 54 Gy
Typically 2 cm margin
Median f/u 5 years
No NF patients

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>35</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>31</td>
</tr>
<tr>
<td>African-American</td>
<td>4</td>
</tr>
<tr>
<td>Central nervous system site</td>
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</tr>
<tr>
<td>Supratentorial</td>
<td>20</td>
</tr>
<tr>
<td>Optic pathway</td>
<td>3</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>11</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>1</td>
</tr>
<tr>
<td>Surgery extent</td>
<td></td>
</tr>
<tr>
<td>Biopsy only</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal</td>
<td>23</td>
</tr>
<tr>
<td>Radiotherapy timing</td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>16</td>
</tr>
<tr>
<td>Delayed (after progression after observation, or chemotherapy)</td>
<td>19</td>
</tr>
<tr>
<td>Radiotherapy modality</td>
<td></td>
</tr>
<tr>
<td>External beam only</td>
<td>29</td>
</tr>
<tr>
<td>Radiosurgery only</td>
<td>5</td>
</tr>
<tr>
<td>External beam and radiosurgery</td>
<td>1</td>
</tr>
</tbody>
</table>

Mansur et al, IJROBP, 79:829, 2011
Overall survival 100%
5 year PFS 68%
8/9 patients who progressed did within the irradiated volume

Fig. 1. Progression-free survival for all patients.

Mansur et al IJROBP 79:829, 2011
Washington University
St. Louis Children’s Hospital

• Pattern of failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at RT (y)</th>
<th>Tumor location</th>
<th>Surgery extent</th>
<th>RT timing</th>
<th>RT dose (Gy)</th>
<th>Failure-free interval (y)</th>
<th>Pattern of failure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Female</td>
<td>5</td>
<td>Supra</td>
<td>Sub</td>
<td>Im</td>
<td>54</td>
<td>2.5</td>
<td>Local</td>
<td>Symptomatic increase in size, rebiopsy (+)</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>15</td>
<td>Supra</td>
<td>Sub</td>
<td>Del</td>
<td>54</td>
<td>0.7</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
</tr>
<tr>
<td>18</td>
<td>Male</td>
<td>20</td>
<td>Supra</td>
<td>Sub</td>
<td>Im</td>
<td>54</td>
<td>2.5</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
</tr>
<tr>
<td>20</td>
<td>Female</td>
<td>18</td>
<td>Spine</td>
<td>Biopsy</td>
<td>Im</td>
<td>50,4</td>
<td>1.3</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
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<tr>
<td>24</td>
<td>Male</td>
<td>12</td>
<td>Supra</td>
<td>Biopsy</td>
<td>Im</td>
<td>54</td>
<td>0.5</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
</tr>
<tr>
<td>25</td>
<td>Female</td>
<td>9</td>
<td>Supra</td>
<td>Sub</td>
<td>Del</td>
<td>54</td>
<td>3.8</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
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<tr>
<td>27</td>
<td>Male</td>
<td>7</td>
<td>Optic</td>
<td>Sub</td>
<td>Del</td>
<td>54</td>
<td>2.0</td>
<td>Distant</td>
<td>Disseminated disease after conformal RT</td>
</tr>
<tr>
<td>29</td>
<td>Female</td>
<td>15</td>
<td>Optic</td>
<td>Biopsy</td>
<td>Del</td>
<td>52,2</td>
<td>1.1</td>
<td>Vision</td>
<td>Progressive vision loss despite RT</td>
</tr>
<tr>
<td>39</td>
<td>Male</td>
<td>8</td>
<td>Supra</td>
<td>Sub</td>
<td>Del</td>
<td>52,2</td>
<td>0.4</td>
<td>Local</td>
<td>Symptomatic increase in size, repeat surgery (+)</td>
</tr>
</tbody>
</table>

*Abbreviations: supra = supratentorial; sub = subtotal resection; im = immediate; del = delayed; RS = radiosurgery; RT = radiotherapy.*
Pseudoprogression occurs in a minority of patients
German (GPOH)

- German (GPOH) HIT-LGG 1996
- 117 children
- 10 had NF
- Median age 9 yrs
- Pilocytic astrocytoma
- RT as first or 2nd line treatment
- Median dose 54Gy
- 1-2 cm margins
- 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
St. Jude Children’s – 1 cm margin to CTV

Fig 1. Event-free survival (EFS; gold line) and overall survival (OS; blue line) for pediatric patients with low-grade glioma. Numbers indicate patients at risk. CRT, conformal radiation therapy.

Merchant et al JCO 27:3589, 2009
COG ACNS 0221

- Conformal RT for all unresectable LGG
- Children 10 yrs and over or younger if progressive after chemotherapy
- 3DCRT, IMRT, protons
- MRI (3 mm) co-registration required
- Pre-treatment central review
- CTV = GTV + 5 mm
- 54 Gy
- Opened in 2005
- Study amended to decrease target accrual to 75
- Closed to accrual 2010........
Chemo-RT?
Children’s Cancer Group - 945

- 70 patients with LGG:
  - 44 Grade II
  - 19 pilocytic,
  - 2 ganglioglioma
  - 7 unspecified low grade
- Originally diagnosed as high grade
  Median f/u 10 years

**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
CCG – 945 progression-free surv

63% PFS at 5 years

Low Grade

High Grade

p=0.0001

Fouladi Cancer 98:1243, 2003
CCG – 945 progression-free surv

Pilocytics
Fibrillary

p=0.04

Fouladi  Cancer 98:1243, 2003
Management Conclusions

• Gross Total Resection is usually curative
• Subtotal resection has an increased risk of progression, though substantial numbers of patients will be progression-free.
• Progressive unresectable disease is an indication for additional treatments
• PFS for chemotherapy is 40-50%, benefit of adding Temodar not clear
• PFS for RT is 70-80%, but this is preferred modality either in older children or those with progression after initial chemotherapy.
• CTV = 1.0 cm expansion (pending 0221 results)
• Pseudoprogression can make interpreting post RT scans difficult
• Combined modality does not appear to improve outcome over RT alone but no randomized data. How to reconcile with recent RTOG 9802 data with PCV is not clear.