Brain stem glioma

- 20% of childhood and 5% of adult CNS tumours.
- Most frequently in children between 3 and 10 years.
- Tissue confirmation is frequently not feasible with infiltrating, except in expansile tumors.
- 60-80% of patients do not have a histological diagnosis.
- Universally associated with dismal prognosis.
- Historically, regarded as a single entity.
Clinical presentation

- Insidious/sudden onset
- Cranial nerve palsies
- Long tract signs (hemiparesis)
- Cerebellar signs (ataxia)
- Long history – better prognosis
Types

- Focal: 5-10%
- Dorsal exophytic: 10-20%
- Cervicomedullary: 5-10%
- Diffuse intrinsic: 75-85%
Focal tumors

- Surgery should be attempted
- Most are JPA
- If fear of morbidity, RT
- Favourable prognosis

Abbott Ped Neurosurg 1991
Dorsal exophytic tumors

- Insidious onset
- Surgery should be attempted
- Most are JPA, low-grade
- Favourable prognosis
- RT for residual/progressive disease

Fig 4 - A large exophytic tumor of the pons in a 6-year-old boy who presented with ataxia as seen on sagittal T1 weighted MRI after contrast administration.

Cervico-medullary tumours

- Typically present with Cr N palsies, long tract signs
- Surgery treatment of choice (GTR achieved in 75% of cases)
- Most are JPA/low-grade
- RT not given routinely except for residual/progressive disease

Epstein J Neurosurg 1986
Diffuse pontine tumours

Major therapeutic challenge

- Typically present with short history
- Surgery (including biopsy) not feasible
- Most are fibrillary, but on autopsy high-grade
- Direct RT in view of typical clinico-radiological picture
- MRS/perfusion/PET could be complementary
Diffuse pontine gliomas

Literally everything tried, but nothing has really changed the outcome of these tumours

Frustrating
# RT Dose Escalation/Hyperfractionation

**POG# 8495**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose</th>
<th>Median PFS (mths)</th>
<th>Median OS (mths)</th>
<th>1 YS</th>
<th>2 YS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34</td>
<td>66Gy/1.1BID</td>
<td>6.5</td>
<td>11</td>
<td>47%</td>
<td>6.3%</td>
</tr>
<tr>
<td>II</td>
<td>57</td>
<td>70.2Gy/1.17BID</td>
<td>6</td>
<td>10</td>
<td>39.6%</td>
<td>23%</td>
</tr>
<tr>
<td>III</td>
<td>39</td>
<td>75.6Gy/1.26BID</td>
<td>7</td>
<td>10</td>
<td>39.9%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Increased toxicities with 75.6 Gy**

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid use &gt; 3 mths</td>
<td>62</td>
</tr>
<tr>
<td>Intrallesional necrosis</td>
<td>45</td>
</tr>
<tr>
<td>Otitis media/externa</td>
<td>26</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>21</td>
</tr>
</tbody>
</table>

*Freeman et al., IJROBP, 1993: 27(2)*
Randomised trial

POG #9239:

Arm 1: 66 pts
54Gy/1.8
+ Cisplatin 100mg/m² (120hr cont infusion)

Arm 2: 64 pts
HFT: 70.2Gy/1.7Gy BID
+ Cisplatin 100mg/m² (120hr cont infusion)

132 pts between 6/92 and 3/96
Survival

Median 8.5 months for 54 Gy
8 months for 70.2 Gy
Chemotherapy
Randomised trial (n=74)

- RT alone (50-60Gy)
- RT + chemo (CCNU, vincristine, prednisone)

- RT alone $\rightarrow$ 5 yr survival was 17%; median time to relapse - 8 ms
- RT + chemo $\rightarrow$ 5 yr survival was 23% (p=0.56); median time to relapse 7 mths.

Chemotherapy
cisplatin based

Compared 57 patients treated with 70.2 Gy (POG #8495) to 64 pts treated with identical RT + cisplatinum (POG 9239)

“Identical cohort, non-randomised”

No difference in outcome

Freeman IJORBP 2000, 47(3).
A DETRIMENTAL EFFECT OF A COMBINED CHEMOTHERAPY–RADIOThERAPY APPROACH IN CHILDREN WITH DIFFUSE INTRINSIC BRAIN STEM GLIOMAS?

CAROLYN R. FREEMAN, M.B., B.S., FRCP(C),* JIM KEPNER, PH.D.,†
LARRY E. KUN, M.D., § ROBERT A. SANFORD, M.D., ‡ RICHARD KADOTA, M.D., ¶
LYNDA MANDELL, M.D., ‡ AND HENRY FRIEDMAN, M.D. #

*McGill University, Montreal, PQ, Canada; §Pediatric Oncology Group Statistical Office, Gainesville, FL; ‡St. Jude Children’s Research Hospital and the University of Tennessee College of Medicine, Memphis, TN; ¶Semmes Murphy Clinic, Memphis, TN; #Children’s Hospital and Health Center, University of California, San Diego Medical Center, San Diego, CA; *Mount Sinai, School of Medicine, New York, NY; and ‡Duke University Medical Center, Durham, NC
Radiotherapy

FS a little generous as kids could be uncooperative

Conventional Cobalt/6 MV

No great benefit of hi-fi techniques

Beneficial in focal tumours (conformal/stereotactic/IMRT)

54-60 Gy/30#
Recurrent brain stem gliomas

- Individualise, symptomatic care/steriods
- Re-irradiation rarely ever possible/helpful
- Chemo largely ineffective
- Temozolomide, Tamoxifen, interferons, Iressa, etc - several small phase II studies - investigational

Large study material – learnt what does not work
Something very original/innovative needed
10% of all childhood CNS tumours
90% are intracranial; 2/3 within the posterior fossa
50% of pts are < 5yrs old, 25% are less than 2
Difficult to treat, perplexing tumours
Ependymoma

Haemorrhage, calcification
Cellular, with rosettes/pseudorosettes
Anaplastic: 10-30%
Spinal mets: 10-15%
Ependymoblastoma (PNET)
Spinal MRI/CSF for post fossa/anaplastic tumours
Surgery treatment of choice and the most important prognostic factor

- Gross tumour resection (GTR) - 50-75% long term control
- Subtotal resection (STR) - 0-30% GTR possible in only 50% cases, aggressive debulking/2nd look

Van Veelan JNS 2002
Schild IJROBP 1998
Radiotherapy

- No randomised trial of RT vs no RT, but large data about efficacy of RT
- CSI - in 1970’s and 80’s, but does not influence local control/survival
- Present recommendations - local RT (even in anaplastic)
- CSI - if spinal mets (CSF or MRI)
- Unresolved questions – a) RT in completely resected tumours
  b) can we avoid RT in very young children

Merchant IJROBP 2002;53:51-7
Vanuytsel IJROBP 1992;23:313-9
Radiotherapy

- Traditionally post fossa irradiation, cover inferiorly upto C3-C4
- Local RT = GTV + margin (2 cms)
- Conformal (3D CRT, Stereotactic RT with lesser margins)
Stereotactic conformal RT is an attractive option for minimizing treatment-related toxicity and dose escalation. The 6-field noncoplanar technique is the most optimal.
Chemotherapy

- Role unknown
- Randomised trial of RT Vs RT + adj V, CCNU & P – no benefit (MPO 1996;27:8-14)
- CCG trial – V, CCNU, P Vs 8-in-1 chemo: no difference (JNS 1999;88:695-03)
- Could consider for children < 5 years with 40% not requiring RT for 2 years (JCO 2001)
- Role needs to be crystallised
Benign/low-grade with indolent behaviour
Surgery treatment of choice
completely excised/small residual - observe
excellent cure rates

Fernandez Neurosurg 2003;53:544
Pilocytic astrocytoma

- Chemotherapy (baby brain protocol, Carboplatin + VCR) for very young children to avoid/defer RT

- RT – only for large residual, near brain stem or progressive

- Local RT (preferably with conformal RT to 50-54 Gy/30 #)
Conformal therapy
phase II data

- 102 children (64 EP, 38 LGA)
- PTV = GTV + 1.0 cm CTV + 0.5 cm
- Localised fields with conformal RT to 54 – 59 Gy
- median follow up of 17 months (3 - 43)
- 92 patients controlled
- 6 pts with EP failed (5 local, 1 disseminated)
- 4 pts with LGA failed (3 within CTV)
- Encouraging prelim results with narrow margins

Merchant IJROBP 2002;52:325-32
High precision conformal radiotherapy employing conservative margins in childhood benign and low-grade brain tumours

Rakesh Jalali, Ashwini Budrukkar, Rajiv Sarin, Dayananda S. Sharma

*Department of Radiation Oncology, 113 Tata Memorial Hospital, Parel, Mumbai, India
*Department of Medical Physics, Tata Memorial Hospital, Parel, Mumbai, India

- 26 children (benign and low-grade brain tumours)
- Localised fields with conformal RT to 54 Gy
- median follow up of 25 months (12 - 47)
- 25 patients controlled; Cognition maintained
Baseline score of Full Scale IQ for patients treated with SCRT (n=20)

<table>
<thead>
<tr>
<th>Class</th>
<th>IQ Limits</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective</td>
<td>69 &amp; below</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>70-79</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Dull-normal</td>
<td>80-89</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Average</td>
<td>90-109</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Bright-normal</td>
<td>110-119</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Superior</td>
<td>120-129</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Very Superior</td>
<td>130 &amp; above</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

14/20 patients have below avg IQ
# Neuropsychological profile in children treated with SCRT

<table>
<thead>
<tr>
<th>Significance</th>
<th>Baseline before SCRT</th>
<th>6 months after SCRT</th>
<th>24 months after SCRT</th>
<th>Statistical (baseline vs 24 months)</th>
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</thead>
<tbody>
<tr>
<td>Verbal IQ</td>
<td>84 (41-99)</td>
<td>85 (66-110)</td>
<td>88 (74-117)</td>
<td>NS^Ⅲ</td>
</tr>
<tr>
<td>No. of patients 14</td>
<td>13</td>
<td>7</td>
<td></td>
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<tr>
<td>Performance IQ</td>
<td>87 (61-111)</td>
<td>89 (61-106)</td>
<td>96 (82-117)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients 12</td>
<td>12</td>
<td>7</td>
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<tr>
<td>Full Scale IQ</td>
<td>82 (33-105)</td>
<td>86 (66-108)</td>
<td>89 (81-118)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients 14</td>
<td>14</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAIC^*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>48 (27-78)</td>
<td>32 (4-64)</td>
<td>30 (20-38)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>No. of patients 12</td>
<td>12</td>
<td>11</td>
<td>6</td>
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</tr>
<tr>
<td>C2</td>
<td>40 (15-72)</td>
<td>25 (4-57)</td>
<td>26 (24-30)</td>
<td>NS</td>
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<td>No. of patients 12</td>
<td>12</td>
<td>11</td>
<td>6</td>
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<tr>
<td>LOTCA^§</td>
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<td>No. of patients</td>
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<td>10</td>
<td>7</td>
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<tr>
<td>Vithoba Paknikar</td>
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<tr>
<td>Performance Test</td>
<td>89 (90-104)</td>
<td>92 (80-104)</td>
<td>83 (77-88)</td>
<td>NS</td>
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<tr>
<td>No. of patients</td>
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<td>2</td>
<td>2</td>
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</tr>
</tbody>
</table>

Jalali IJROBP 2006 (in press)
High-grade hemispheric gliomas

Relatively rare

Somewhat better outcome than adults but long-term cure still rare

Overexp of p53 strong prognostic factor (NEJM 2002)

Surgery, conv RT std of care as in adults

Role of chemo not fully evolved
High-grade hemispheric gliomas

- Randomised trial of RT + adj pCV Vs RT alone (n=58): 5yr DFS of 46% Vs 18% (CCG 943)
- Results never duplicated (38 % slides reviewed were not high-grade, Boyett 1998)
- Intensive/pre irradiation chemo: no major impact
- Currently several regimens being tested (TMZ, thalidomide, carboplatin, topotecan, etc)