LGG - the spectrum

<table>
<thead>
<tr>
<th>Survival Astrocytomas</th>
<th>Oligo-Astros</th>
<th>Oligodendroglomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (yr)</td>
<td>4.7</td>
<td>7.1</td>
</tr>
<tr>
<td>2-yr (%)</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>5-yr (%)</td>
<td>46</td>
<td>63</td>
</tr>
<tr>
<td>10-yr (%)</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>15-yr (%)</td>
<td>17</td>
<td>17</td>
</tr>
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</table>
Traditionally RT is offered
What is the appropriate dose?

EORTC 22844
379 randomised
April’85-Sept’91
Med FU 74 mo

NCCT/RTOG/ECOG
203 randomised
May’86-Dec’94
Med FU 6.4 yrs

54 Gy in 30 fractions is a good compromise
What is the appropriate volume of treatment?

- With conformal RT, the T2-signal abnormality was treated with a 1-3 cm 3-D expansion for initial 45-50.4 Gy

followed by 0-2 cm margin to a total dose of 54-59.4 Gy

- 10/11 patients of Grade II glioma with recurrence were located within the boost volume.
Timing of radiotherapy?

Arguments for immediate RT:
- LGG respond to RT
- Tumors often display aggressive behavior and transform
- Patients with high risk profile will benefit
- Modern focal RT is far less toxic than older high risk regimens
- RT may be more effective earlier with lower tumor burden

EORTC 22845
311 randomised
March’86-Sept’97
RT dose=54Gy
Median FU=60mo
Observation vs. Sx as initial strategy in LGG?

Pros:
- If symptoms uncontrolled medically, then benefits of Sx on seizures / raised ICT are fairly dramatic
- Imaging misleading up to 40%
- Early Sx delays reappearance of symptoms and tm growth
- Survival advantage to gross resection in retrospective literature

Cons:
- Possibility of complications in a minimally symptomatic person
Glioma model

- **Glial Cell**
  - p53 mut
  - 22q loss

- **LGG**
  - Rb mut
  - 19q loss
  - p15/p16 loss

- **AO**
  - Chr 10 loss

- **AA**
  - MDM2 amp
  - CDK4 amp
  - Chr 10 loss

- **GBM**

**Angiogenesis:** ↑VEGF, VEGFR, PDGF, FGF
Who can be observed?
The prognostic factors

- **Tumor dependent**
  - Histology: Oligo vs. Oligo-astro vs. fibrillary astro
  - Molecular markers: p53, MIB-1
  - Contrast enhancement
  - Size > 5 cm
  - Tumor crossing midline

- **Patient dependent**
  - Age < 40
  - PS
  - Neurologic function
  - Seizures as initial symptoms
  - Corticosteroid dependency

- **Treatment dependent**
  - Radical Sx
  - RT at diagnosis
  - Chemo at diagnosis
Tumor-dependent factors

- Presence of p53 mutation and high proliferation index (MIB-1 >5%) associated with slightly more rapid transformation to HGG and worse prognosis

- Contrast uptake (=disrupted BBB or increased vascularity) freq associated with transformation to higher grade (and worse survival in age >40 and good PS). Methionine uptake on PET is of negative prognostic value

- Large Tm, crossing midline, rarely resectable, rapidly symptomatic, shorter survival
Patient-dependent factors

- Age: under 40 favourable
- PS: performance status and neurologic function depend upon tumor size and location. KPS <70 consistently unfavourable
- Seizures: significant on univariate, not on MV
Treatment - dependent factors

- Radical surgery: Median TTP correlated with post-operative volume (<50% resection = 24mo) vs. (50-89% resection = 36mo)

- Radiotherapy
  - For dose levels, 2 RCTs: 45Gy = 59.4Gy and 50.4Gy = 64.8Gy
  - Immediate vs. deferred RT, 1 RCT: Equivalence of outcome
Low grade Gliomas - Imaging
Low grade Gliomas – Imaging
Biological Imaging: Perfusion/Angiogenesis

Relative Cerebral Blood volume (rCBV) values: mL/100 gms of brain tissue
### Prognostic score: LGG

322 pts from EORTC 22844

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>1</td>
<td>0.007</td>
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<tr>
<td>≥ 40 years</td>
<td>1.26</td>
<td></td>
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<tr>
<td>Largest diameter of tumor</td>
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<td></td>
</tr>
<tr>
<td>&lt; 6 cm</td>
<td>1</td>
<td>0.000</td>
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<tr>
<td>≥ 6 cm</td>
<td>1.39</td>
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<tr>
<td>Tumor crossing midline</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.000</td>
</tr>
<tr>
<td>Yes</td>
<td>1.37</td>
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</tr>
<tr>
<td>Histology type</td>
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<tr>
<td>Oligo / mixed</td>
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<td>0.005</td>
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<tr>
<td>Astrocytoma</td>
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<tr>
<td>Neurologic deficit</td>
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<tr>
<td>Absent</td>
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<td>0.001</td>
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<tr>
<td>Present</td>
<td>1.35</td>
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Low risk 0-2 7.72 yr

High risk 3-5 3.20 yr
Role of chemotherapy

- Temozolamide in \textit{progressive} LGG
- \( n = 41 \) (16 = 35\% astrocytomas)
- newly diagnosed or previously Rx (52\% resected, 22\% prior chemo, 15\% prior RT)
- 200mg/m\(^2\)/day x 5days q28 days x 12 cs
- 70\% \textit{ENHANCING} on CT / MR
- MR every 8 weeks, Macdonald's criteria

\textbf{Overall Median PFS} 22 months, 12 mo PFS 73\% for astrocytoma

Overall CR = 24\%  \hspace{1cm} (31\% for astrocytoma)

Overall PR = 37\%  \hspace{1cm} (38\% for astrocytoma)

Overall CR + PR = 61\%  \hspace{1cm} (69\% for astrocytoma)
Role of chemotherapy

- Temozolamide in stable or progressive LGG
- n=30 (19 = 63% astrocytomas/mixed)
- 60% resected, no prior chemo or RT
- 200mg/m²/day x 5days q28 days x 12 cs
- NO ENHANCEMENT on CT / MR
- MR every 3 months, Macdonald’s criteria

Overall Median PFS not reached, 3 yr PFS = 66%
Overall CR = Nil
Overall PR = 10% (5% for astrocytoma/mixed)
Overall MR = 48% (58% for astrocytoma/mixed)
Suggested management

- For favourable prognosis patients, attentive watchful waiting is justified.
- Decision to use surgery with or without RT should be based on an appraisal of risk of relapse, and in patients with progression.
- Conformation in 3-D is highly desirable to reduce the potential for late morbidity in adult LGG.
- Molecular markers will help.
- Chemo (TMZ) being tested in large EORTC/RTOG trials.