<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade Oligodendroglioma</td>
<td>~120</td>
</tr>
<tr>
<td>Low Grade Astrocytoma</td>
<td>~60</td>
</tr>
<tr>
<td>Anaplastic Oligodendroglioma</td>
<td>~60</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma</td>
<td>~36</td>
</tr>
<tr>
<td>Glioblastoma Multiforme</td>
<td>&lt;12</td>
</tr>
</tbody>
</table>
Malignant Glioma: Facts & Challenges

- 1-2% of all cancer
- Most common malignant primary brain tumours in adults
- Yearly incidence 5/100,000
  - India: 50,000 patients per year
  - Mumbai: 500 pts (TMH:100-120)
Multimodality management of Malignant Gliomas

- Age, Performance Status, Logistics, Cost
  - Maximal Safe Surgery
  - Focal Radiotherapy
  - +/- Chemotherapy
High grade Gliomas: Prognostic Groups

Prognostic factors:
- Age (<50 vs more),
- Grade (III vs IV),
- Resection status (Total vs biopsy)
- Performance status (Good vs Poor)

- MRC prognostic groups
  - Age, resection, WHO Performance Status, Seizures

- RTOG- RPA groups (6 classes)
  - Age, resection, Grade, Mental Status, KPS, RT dose
# High grade Gliomas

## Effect of Extent of surgery

<table>
<thead>
<tr>
<th>Surgical Extent</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resection</td>
<td>11.3 months</td>
</tr>
<tr>
<td>Partial Resection</td>
<td>10.4 months</td>
</tr>
<tr>
<td>Only biopsy</td>
<td>6.6 months</td>
</tr>
</tbody>
</table>

MDAH retrospective series of 416 GBM patients *(Lecroix, JNS 2001)*

Med survival 13 mths vs 9 months for > or < 98% resection
Brain Tumour Study Group (BTSG) trial

Walker J Neurosurg 1978;49:333-343

303 patients

A: Surgery → Supportive care
B: Chemotherapy (BCNU)
C: Radiotherapy
D: RT+ BCNU
High Grade Gliomas

Whole brain RT (WBRT) versus Partial Brain RT (PBRT)

**Autopsy studies** reveal that microscopic tumour within 2cm of enhancing margins on scan in 90% and only 3% multicentric *(Hochberg, Neurol 1980)*

**Failure pattern after partial brain RT** *(enhancing tumour + 2cm)*
Vast majority of recurrences (86%) were infield *(Hess, Radioth. Oncol)*

**RCT** *(n=303)* of WBRT-60Gy vs WBRT -43Gy + PBRT boost-17Gy
No difference in outcome *(Shapiro, J Neurosurg, 1989)*

**RCT** of WBRT - 44Gy vs PBRT - 53Gy
Med surv. WBRT - 8.5 mths vs PBRT 11.5 mths *(Ramsey, J Neurosurg, 1973)*

**STANDARD OF CARE** - PBRT ENCOMPASSING THE ENHANCING TUMOUR + 2-3 CM MARGINS
## MRC Randomised Trial

**RT dose (45 Gy Vs 60 Gy)**

<table>
<thead>
<tr>
<th>Months</th>
<th>45 Gy (n=144)</th>
<th>60 Gy (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>
RT Dose escalation in malignant gliomas

Implant (brachytherapy)
Gliasite: MRI and Treatment Plan

Target area receives at least 100% of the prescribed dose. Typically 40-60 Gy.

Rapid dose drop-off outside the target volume due to low energy photons of I-125.

Dosimetry issues; clinical data not encouraging
Phase III randomised trial of dose escalation

Steroid use double in Brachytherapy arm

BTCG-8701 randomised trial of RT Vs RT + boost; Median Survival 68 vs 58 weeks (p=0.1)

Laperriere. IJROBP 1998;41:1005-1011

Selker, Neurosurg 2002
STEREOTACTIC IRRADIATION

Advantages

- Relatively more homogenous dose distribution in the target volume - less toxicity
- Deep seated tumours also treated
- Wider application
- Non invasive, no risk of hemorrhage, infection
RISK OF REOPERATION

Brachytherapy

SRS

Time (months)
Phase III Randomised Trial of SRS boost
RTOG 9305

- 203 patients with GBM
- Conv RT60 Gy +/- SRS boost (15-24 Gy)
- Median f/u 44 months
- Median Survival: 14.1 Vs 13.7 months
- 2 year survival: 22 Vs 18%
- 3 year survival: 16 Vs 8%
- 18% pts in SRS arm had significant toxicity

RADIOSURGERY Contraindicated
Magnetic Resonance Spectroscopy
FDG PET/CT-PET
11C Methionine PET

Any attempt for dose escalation has to be done utilising biological target volume

Grosu IJROBP 2005
TMH RT protocol for HGG

- **Radiotherapy technique**
  Focal radiotherapy (GTV + 2.0-3cm margin) with 2-4 fields; Energy -6 MV photons or Cobalt-60

- **Dose and fractionation**
  Conventional schedule
  - 60Gy/30#, 2Gy daily over 6weeks
  
  Hypo-fractionated schedules
  - 35Gy/7#, 5Gy weekly over 7 weeks
  - 45Gy/18, 2.5Gy daily over 3.5 weeks
Fig 1. Overall survival from randomization by treatment group. There was no difference in the overall survival between the standard 6-week (thick line) versus abbreviated 3-week (thin line) course of radiation therapy (Log-rank test, $P = .57$).
TMH data of Overall survival in Prognostic groups in HGG (n=270)

Favourable Group
- 6 months 91.2%
- 12 months 50.4%
- Median 12.34 months

Poor-prognosis Group
- 6 months 60%
- 12 months 18%
- Median 6.7 months

(P=0.0001)
Adjuvant chemotherapy in malignant gliomas

GMT Lancet 2002; 359:1011-18

MRC JCO 2001; 19:509-18
Temozolomide (TMZ)

- Oral administration
- Excellent concentration in CNS
- Encouraging antitumour activity
- Favourable toxicity profile
- Synergism with radiotherapy and other agents

[Graph showing plasma concentration over time for IV and PO (capsules)]

Plasma-CSF: 30-40%
$^{11}$C-Temozolomide

PET Scan.

Time Activity Curve.

- bloodpool
- tumour
- contralateral brain
Concomitant + adjuvant TMZ-RT

Median survival = 16 months
One year survival = 58%
Two year survival = 28%

Stupp JCO 2002 20: 1375-82
EORTC 26981/22981

Phase III (target accrual 520)

Newly diagnosed GBM
stratification: age; Bx vs complete resection; ECOG PS 0,1 vs 2; institution
Written informed consent

TMZ 200 mg/m² od x 5 day repeat every 28 days

TMZ 75mg/m² od x 6-7 wks

Focal Radiotherapy (60 Gy)
Tumour volume with 2-3 cm margin

weeks
Concomitant + adjuvant TMZ-RT in adult gliomas—EORTC

Design (phase III, n = 570):
Newly diagnosed GBM
- RT (n= 286) Vs RT+ TMZ (n=287)

RESULTS
- 2 year survival: 8% Vs 26% (p<0.0001)
- Median survival: 12 months Vs 15 months (p<0.0001)
Temozolomide + RT in newly diagnosed GBM

NEW STANDARD OF CARE

Throughout the world
Results

- Median Age 56 yrs
- Debulking surgery in 84% of patients
- On central review, diagnosis of GBM confirmed in 93% of cases
- Interruptions due to toxicity of Rx in 3% and 4% in RT and RT + Tem
- 87% of patients completed concomitant temozolomide
- 78% started adjuvant tem and 47% completed 6 cycles
- At progression or at 2 yr FU, salvage chemotherapy at investigator’s discretion
Progression free survival  
Overall survival

Stupp NEJM March 2005
MGMT (Methylguanine DNA methyltransferase) and TMZ Resistance

![Bar chart showing mean MGMT activity (%)](image)

- Pretreatment
- Day 8
- Day 15
- Day 22

*Statistically significant change
†Significant change compared to pretreatment
MGMT (Methylguanine DNA methyltransferase) and TMZ Resistance

- 573 specimens
- 307 Methylation specific PCR.
- 206/307 paraffin blocks could be studied adequately.
- Studied in two groups as original design of EORTC and NCIC study (Stuup et al)

Hegi et al NEJM, 2005
<table>
<thead>
<tr>
<th>Promoter Status and Outcome</th>
<th>Radiotherapy (N=100)</th>
<th>Temozolomide plus Radiotherapy (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylated MGMT promoter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mo)</td>
<td>5.9 (5.3–7.7)</td>
<td>10.3 (6.5–14.0)</td>
</tr>
<tr>
<td>Rate at 6 mo (%)</td>
<td>47.8 (33.4–62.3)</td>
<td>68.9 (55.4–82.4)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.00</td>
<td>0.48 (0.31–0.75)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mo)</td>
<td>15.3 (13.0–20.9)</td>
<td>21.7 (17.4–30.4)</td>
</tr>
<tr>
<td>Rate at 2 yr (%)</td>
<td>22.7 (10.3–35.1)</td>
<td>46.0 (31.2–60.8)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.00</td>
<td>0.51 (0.31–0.84)</td>
</tr>
<tr>
<td><strong>Unmethylated MGMT promoter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mo)</td>
<td>4.4 (3.1–6.0)</td>
<td>5.3 (5.0–7.6)</td>
</tr>
<tr>
<td>Rate at 6 mo (%)</td>
<td>35.2 (22.5–47.9)</td>
<td>40.0 (27.6–52.4)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.00</td>
<td>0.62 (0.42–0.92)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mo)</td>
<td>11.8 (9.7–14.1)</td>
<td>12.7 (11.6–14.4)</td>
</tr>
<tr>
<td>Rate at 2 yr (%)</td>
<td>&lt;2†</td>
<td>13.8 (4.8–22.7)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.00</td>
<td>0.69 (0.47–1.02)</td>
</tr>
</tbody>
</table>
TMZ protocol

- Concomitant TMZ at 75 mg/m² 20-30 min before RT, every day for 42 days (including weekends)
- 4 hours fasting
- Adjuvant TMZ 150-200 mg/m² x 6 cycles, 4 weeks apart

All patients on prophylactic antiemetics and PCP prophylaxis (cotrimaxazole 1 tab bd x42 days)
1 and 2 year overall survival: 72% and 31%
Median survival: 24 months at mean fu of 11.4 months (range 2-60 months)