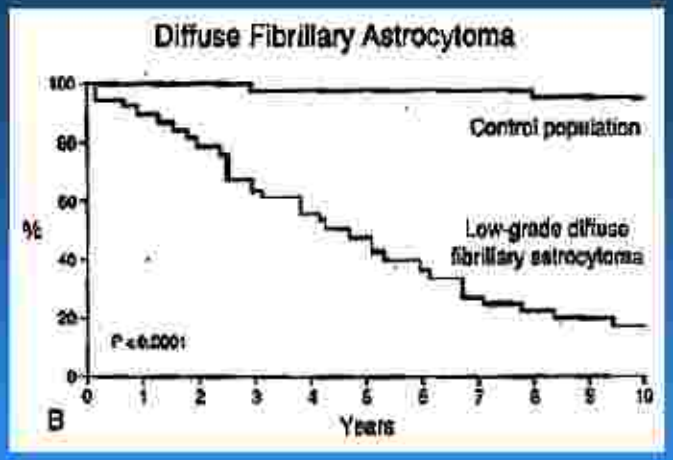
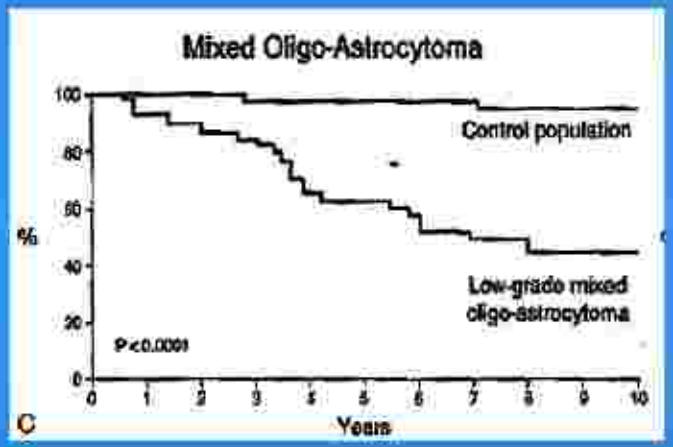
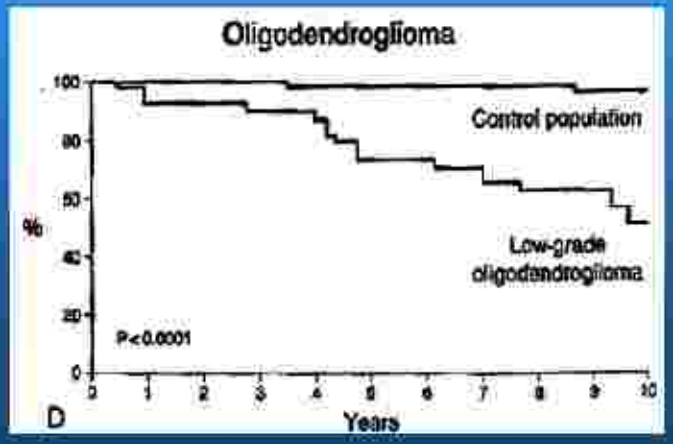
LGG-the spectrum

Survival Astrocytomas	Oligo-Astros	Oligodendrogliomas
Median (yr) 4.7	7.1	9.8
2-yr (%) 80	89	93
5-yr (%) 46	63	73
10-yr (%) 17	33	49
15-yr (%) 17	17	49



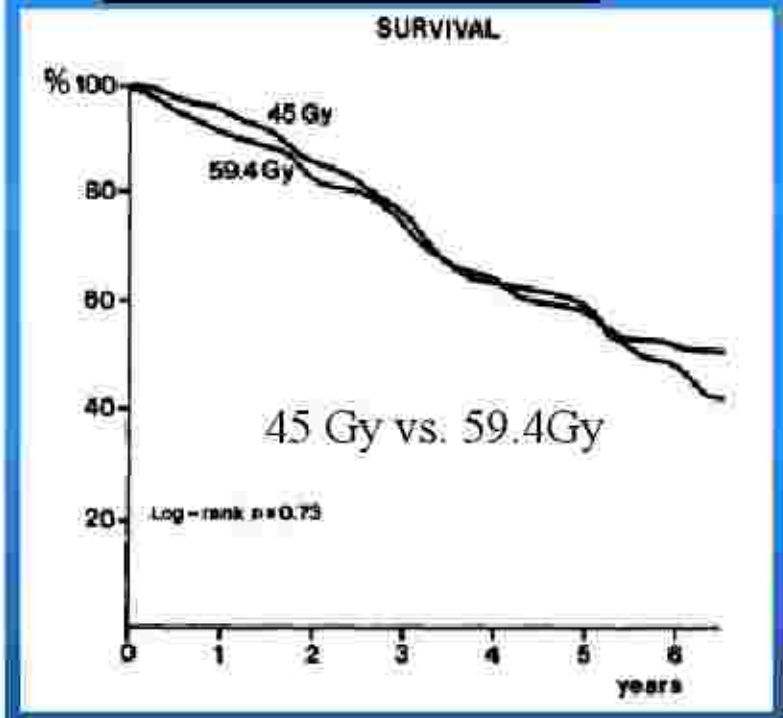


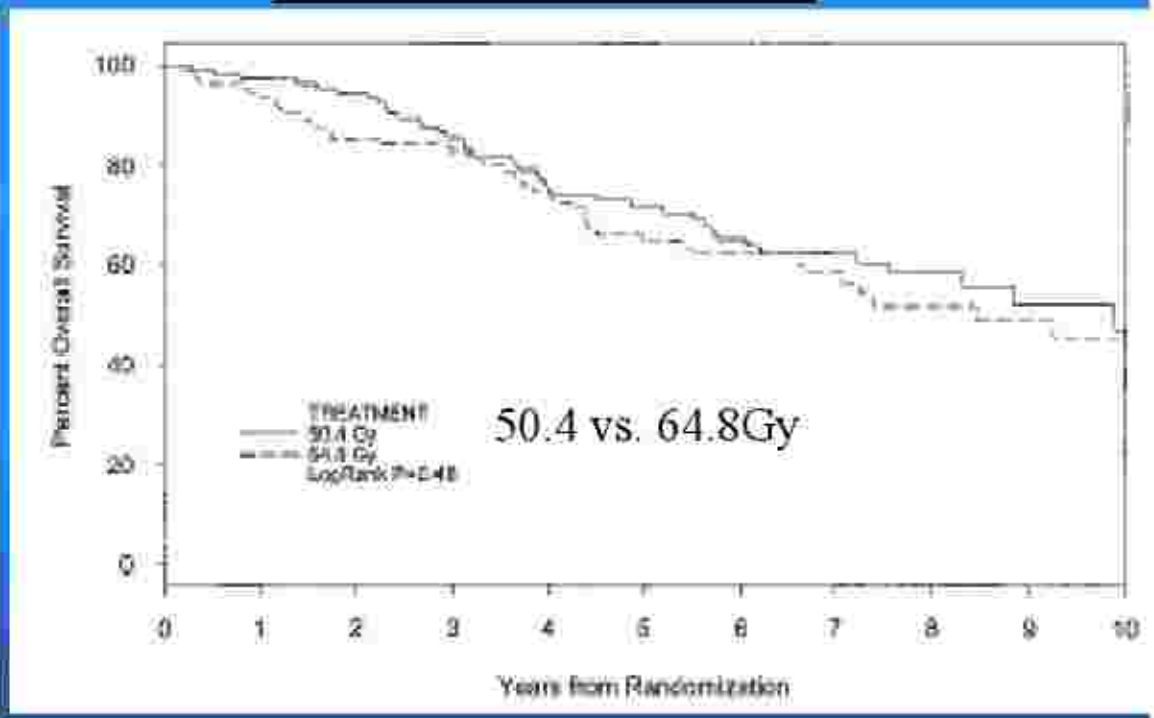


Traditionally RT is offered
What is the appropriate dose?

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 30fractions 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 45-50.4Gy

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

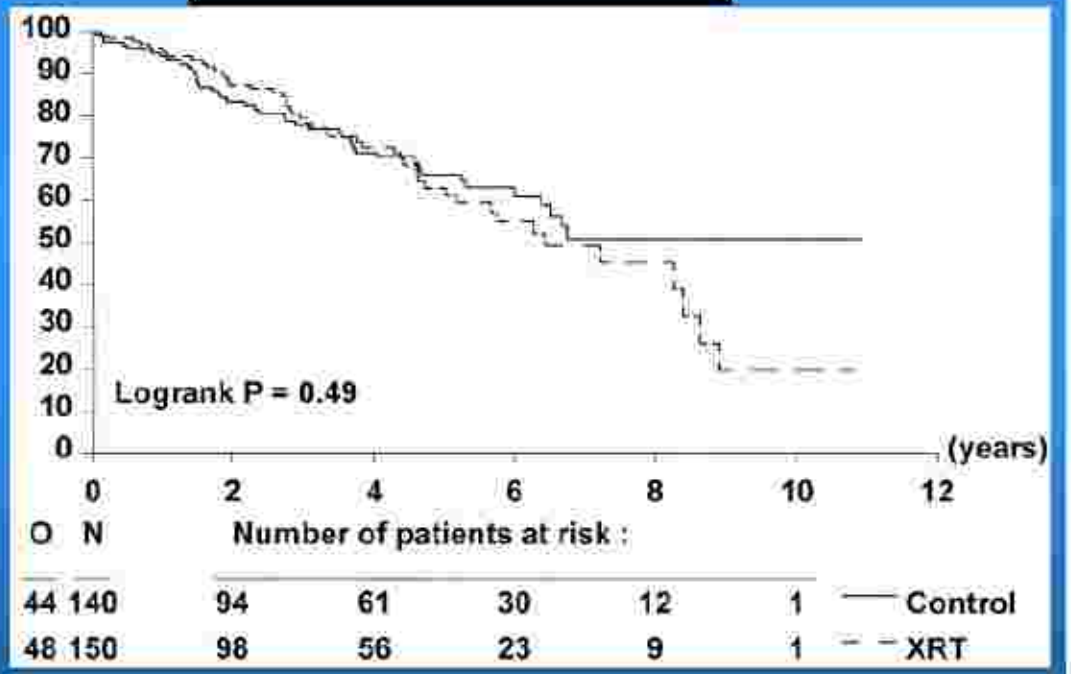
- 10/11 patients of Grade II glioma with recurrence were located within the boost volume.

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



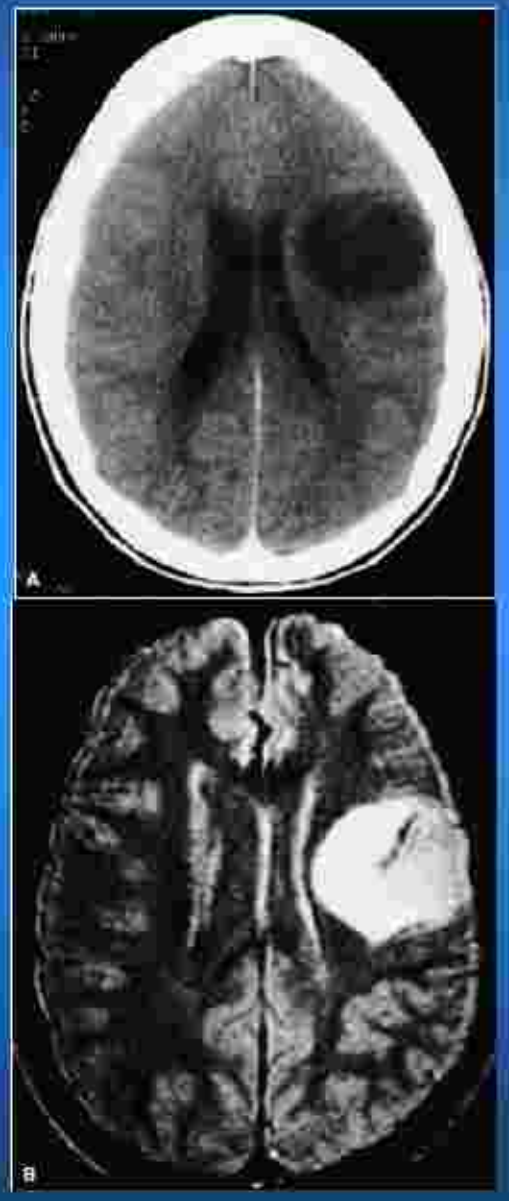
Observation *vs.* Sx as initial strategy in LGG?

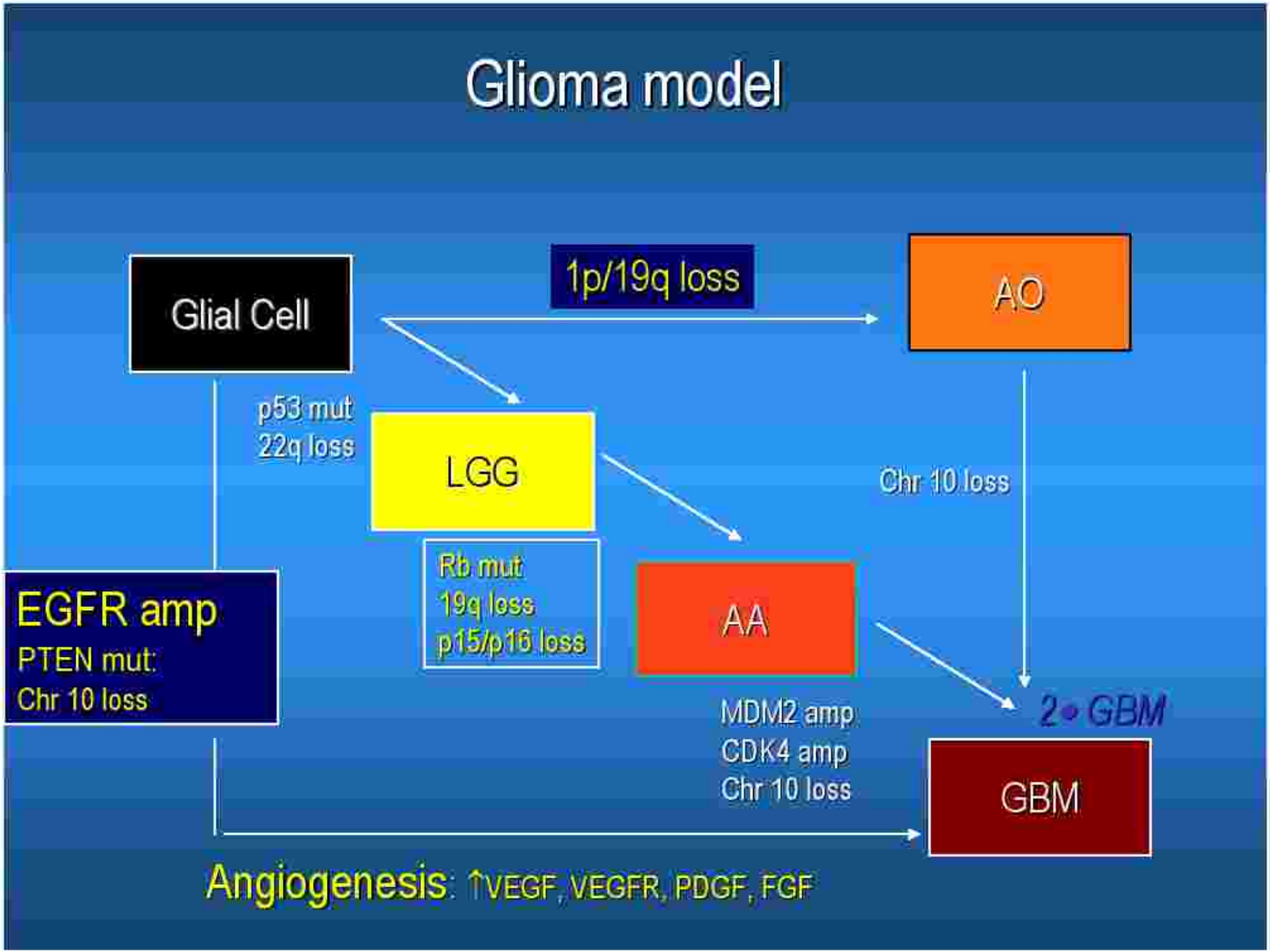
Pros:

- If symptoms uncontrolled medically, then benefits of Sx on seizures / raised ICT are fairly dramatic
- Imaging misleading upto 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
1p/19q loss
AO
p53 mut
22q loss
LGG
Chr 10 loss
Rb mut
19q loss
p15/p16 loss
AA
EGFR amp
PTEN mut
Chr 10 loss
2° GBM
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
  - Tm 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

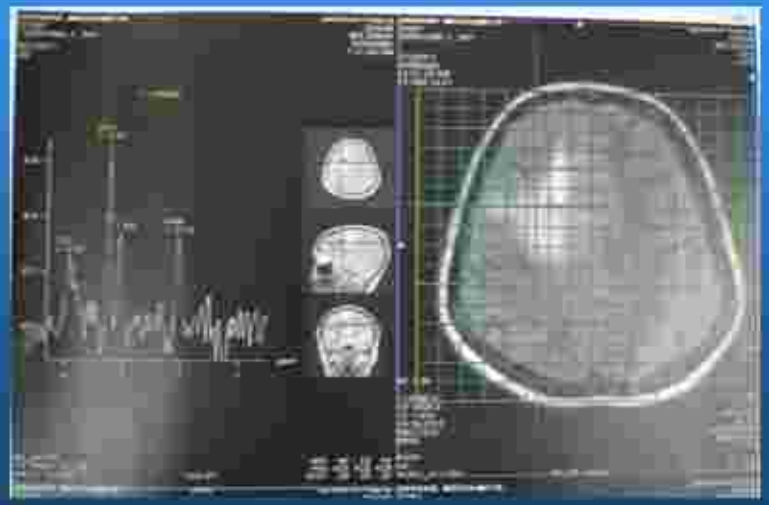
Treatment - dependent factors

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

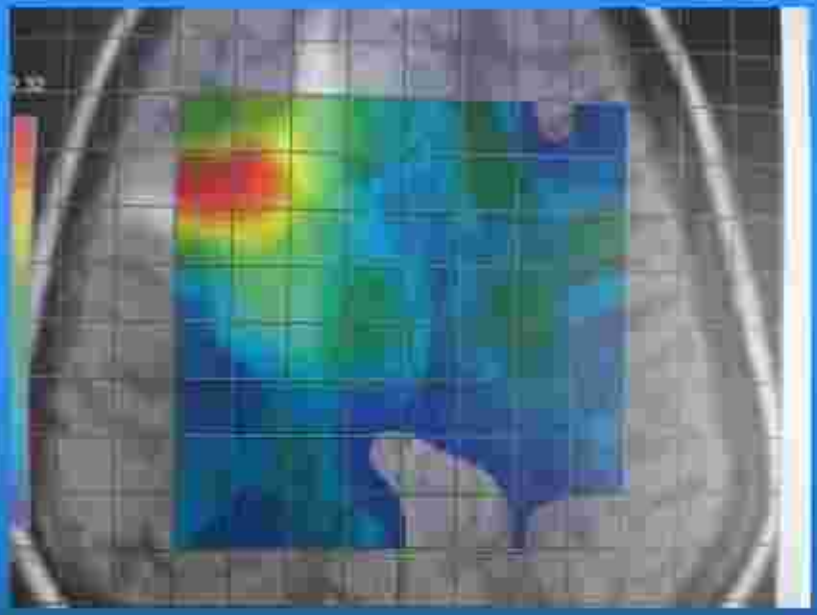
- Radiotherapy
  - For dose levels, 2 RCTs : 45Gy = 59.4Gy and 50.4Gy = 64.8Gy
  - Immediate *vs.* deferred RT, 1RCT: Equivalence of outcome

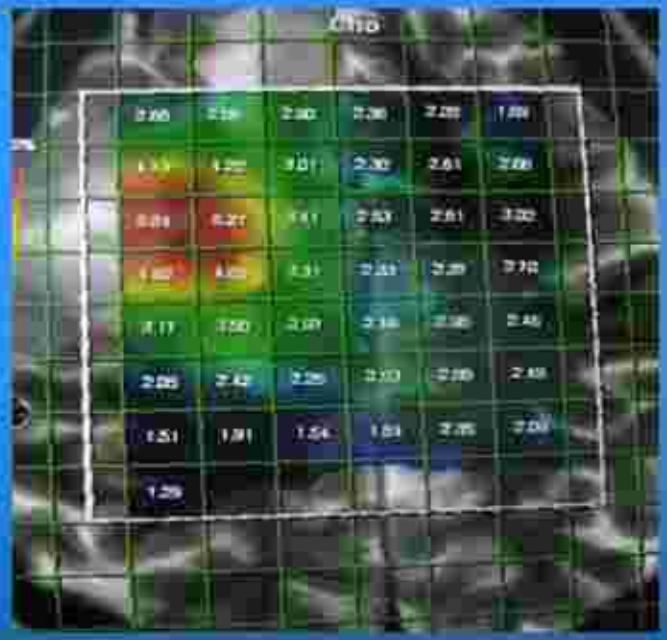
Low grade Gliomas – Imaging

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

Prognostic factor	*HR*	*p value*
Age at randomisation		
< 40 years	1	0.007
≥ 40 years	1.26	
Largest diameter of tumor		
< 6 cm	1	0.000
≥ 6 cm	1.39	
Tumor crossing midline		
No	1	0.000
Yes	1.37	
Histology type		
Oligo / mixed	1	0.005
Astrocytoma	1.30	
Neurologic deficit		
Absent	1	0.001
Present	1.35	

Low risk 0-2 7.72 yr

High risk 3-5 3.20 yr

Role of chemotherapy

- Temozolamide in 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% ENHANCING on CT / MR
- MR every 8 weeks, Macdonald's criteria

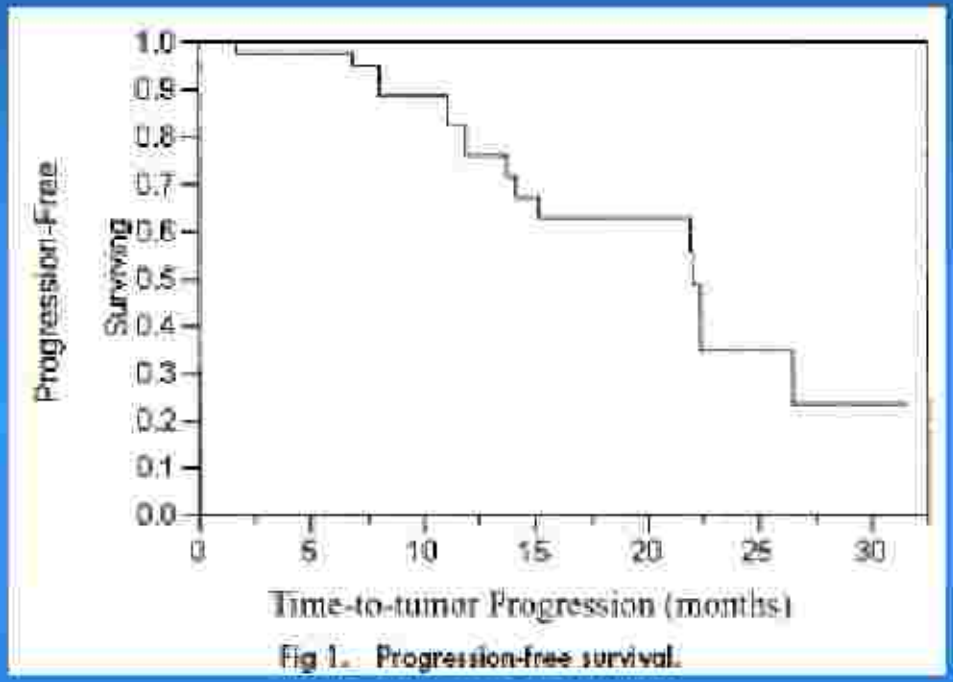
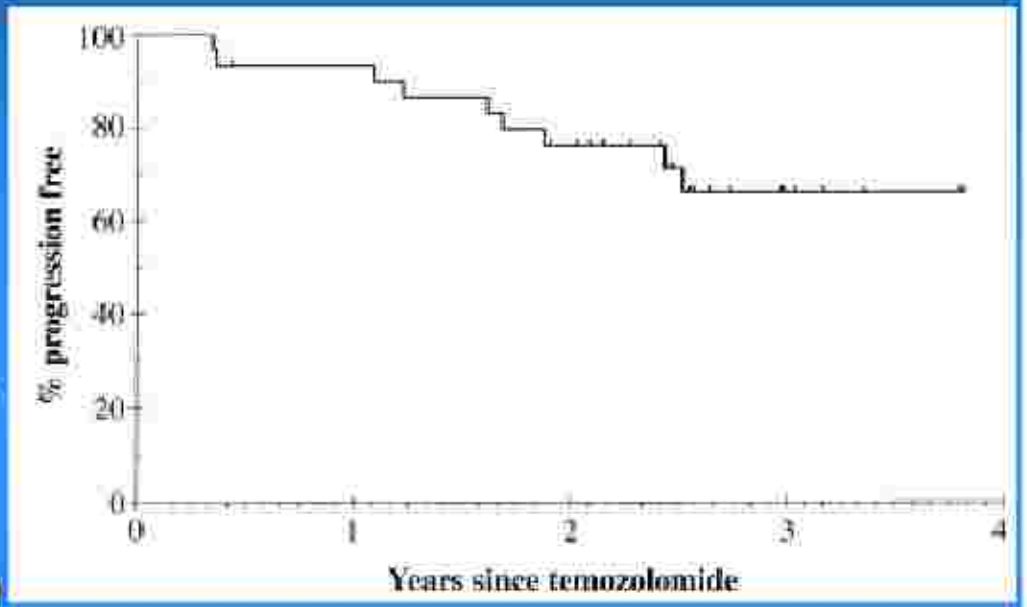


Fig 1. Progression-free survival.

Overall Median PFS 22 months, 12 mo PFS 73% for astrocytoma
Overall CR = 24% (31% for astrocytoma)
Overall PR = 37% (38% for astrocytoma)
Overall CR + PR = 61% (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/m^2/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