

# GLIOMAS

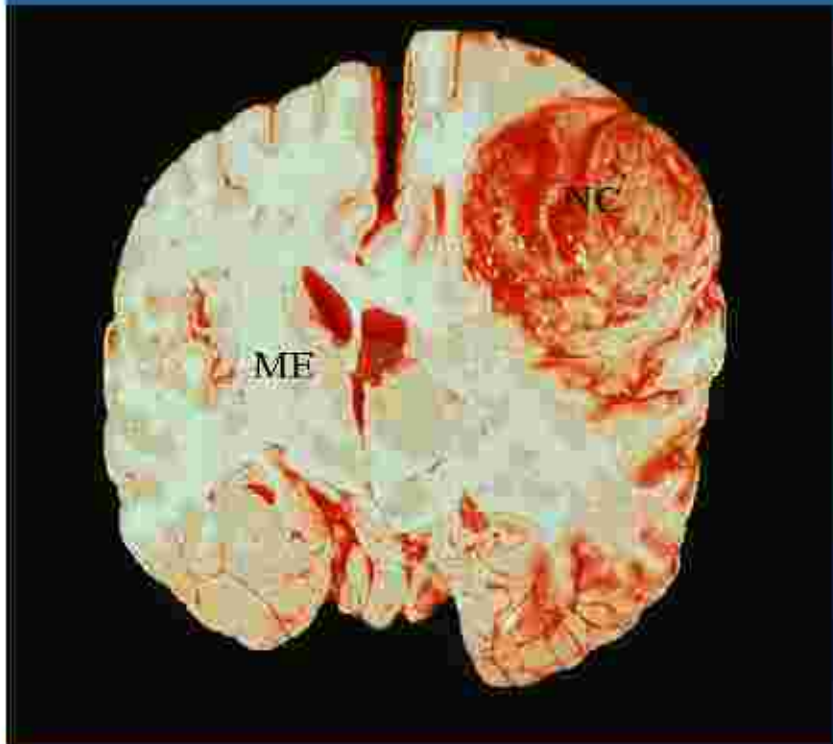


## Tumour Type-median survival (months)

- Low Grade Oligodendroglioma ~120
- Low Grade Astrocytoma ~ 60
  
- Anaplastic Oligodendroglioma ~ 60
- Anaplastic Astrocytoma ~ 36
  
- Glioblastoma Multiforme < 12



# 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

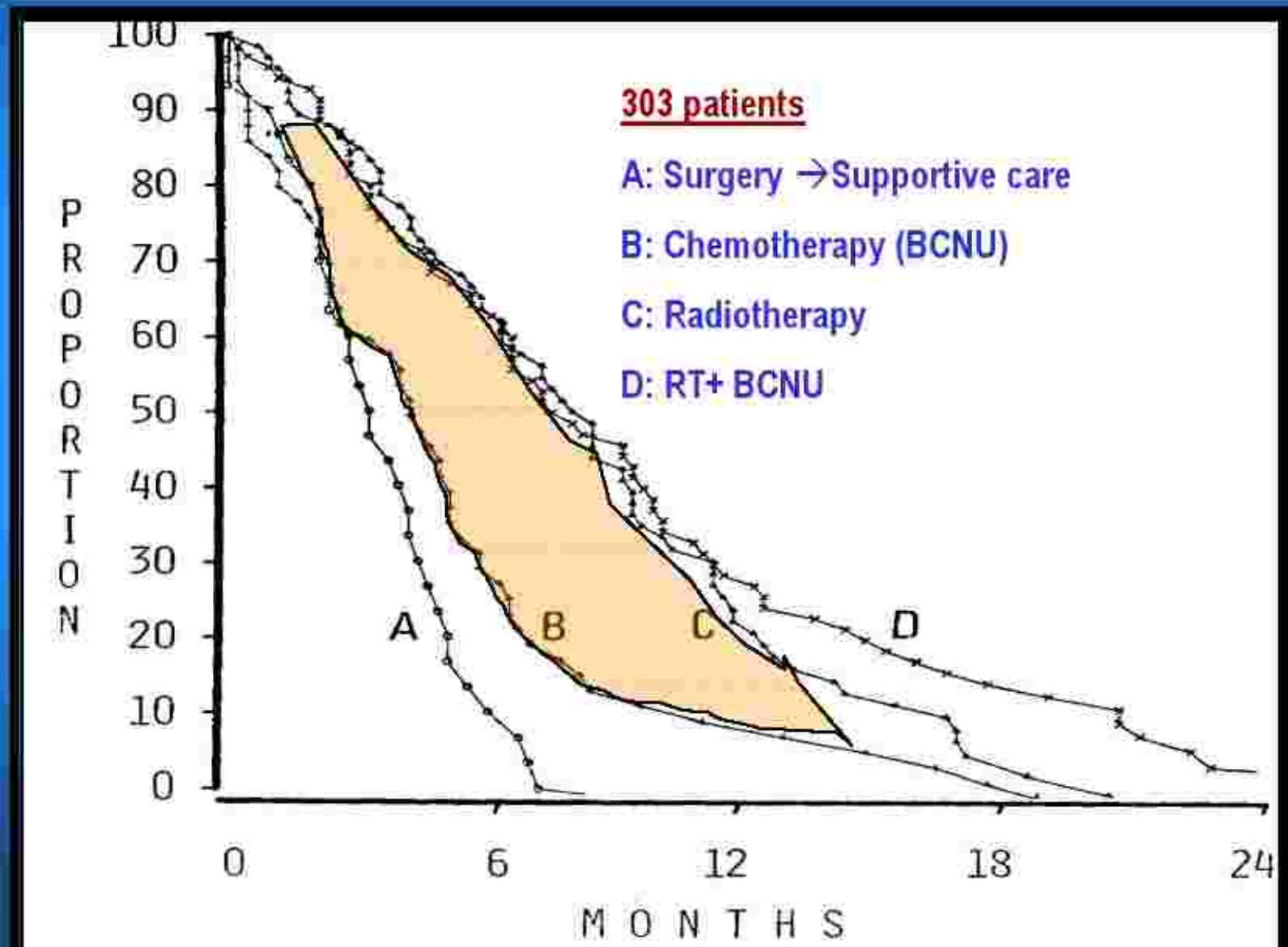
Surgical Extent	Median Survival
Complete resection	11.3 months
Partial Resection	10.4 months
Only biopsy	6.6 months

**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



# 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  $\pm$  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 mnths vs PBRT 11.5 mnths (*Ramsey, J Neurosurg, 1973*)

**STANDARD OF CARE - PBRT ENCOMPASSING THE  
ENHANCING TUMOUR + 2-3 CM MARGINS**

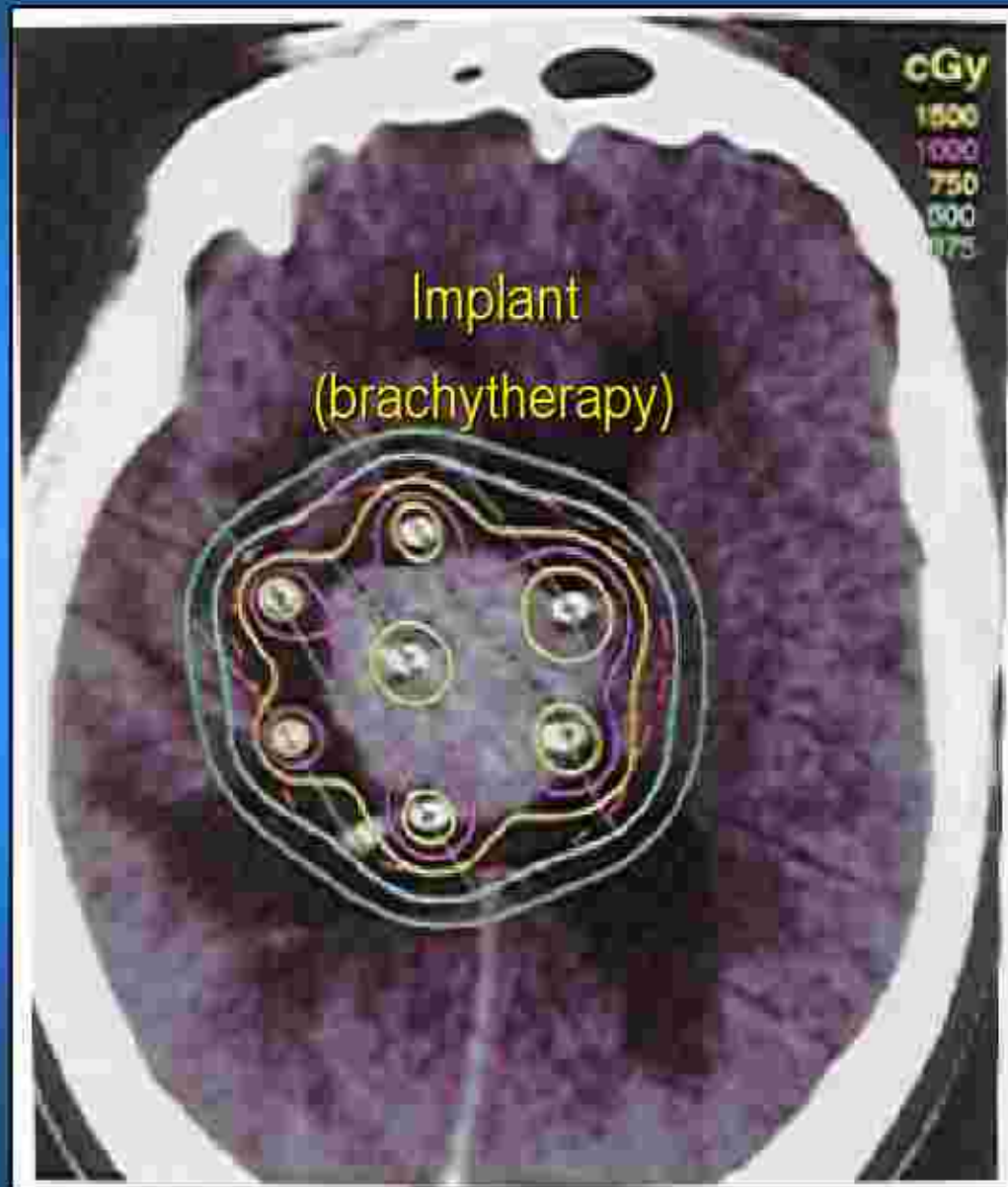
# MRC Randomised Trial

## RT dose (45 Gy Vs 60 Gy)

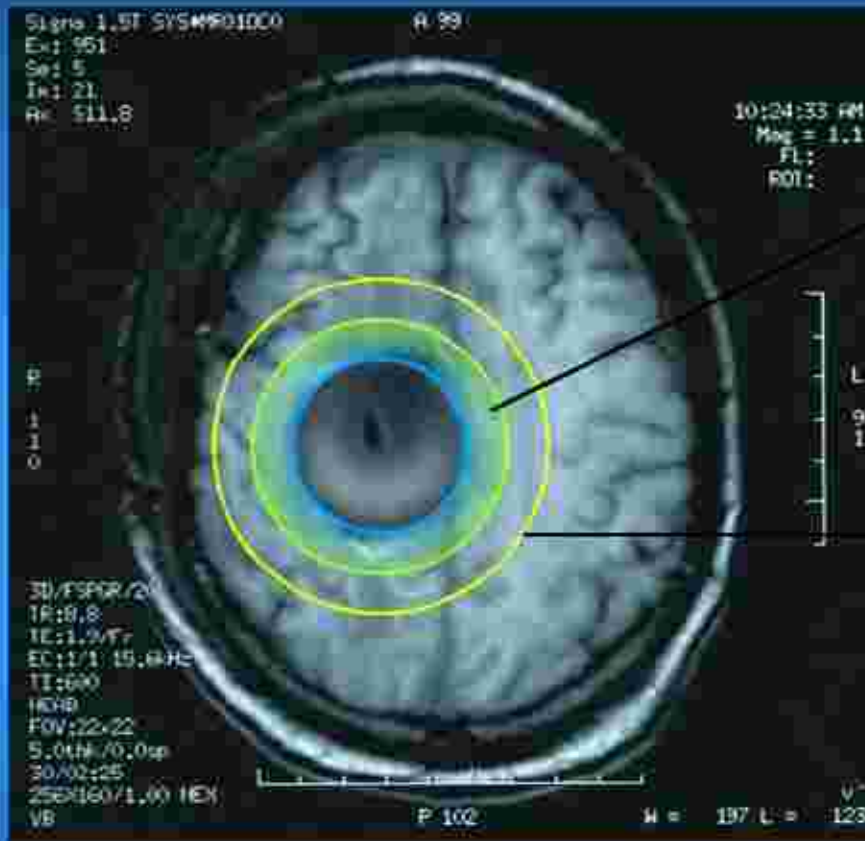
Survival rate (%)		
Months	45 Gy (n=144)	60 Gy (n=299)
0	100	100
6	69	74
12	29	39
18	11	18
24	8	12
30	5	8



# RT Dose escalation in malignant gliomas



# Gliasite: MRI and Treatment Plan



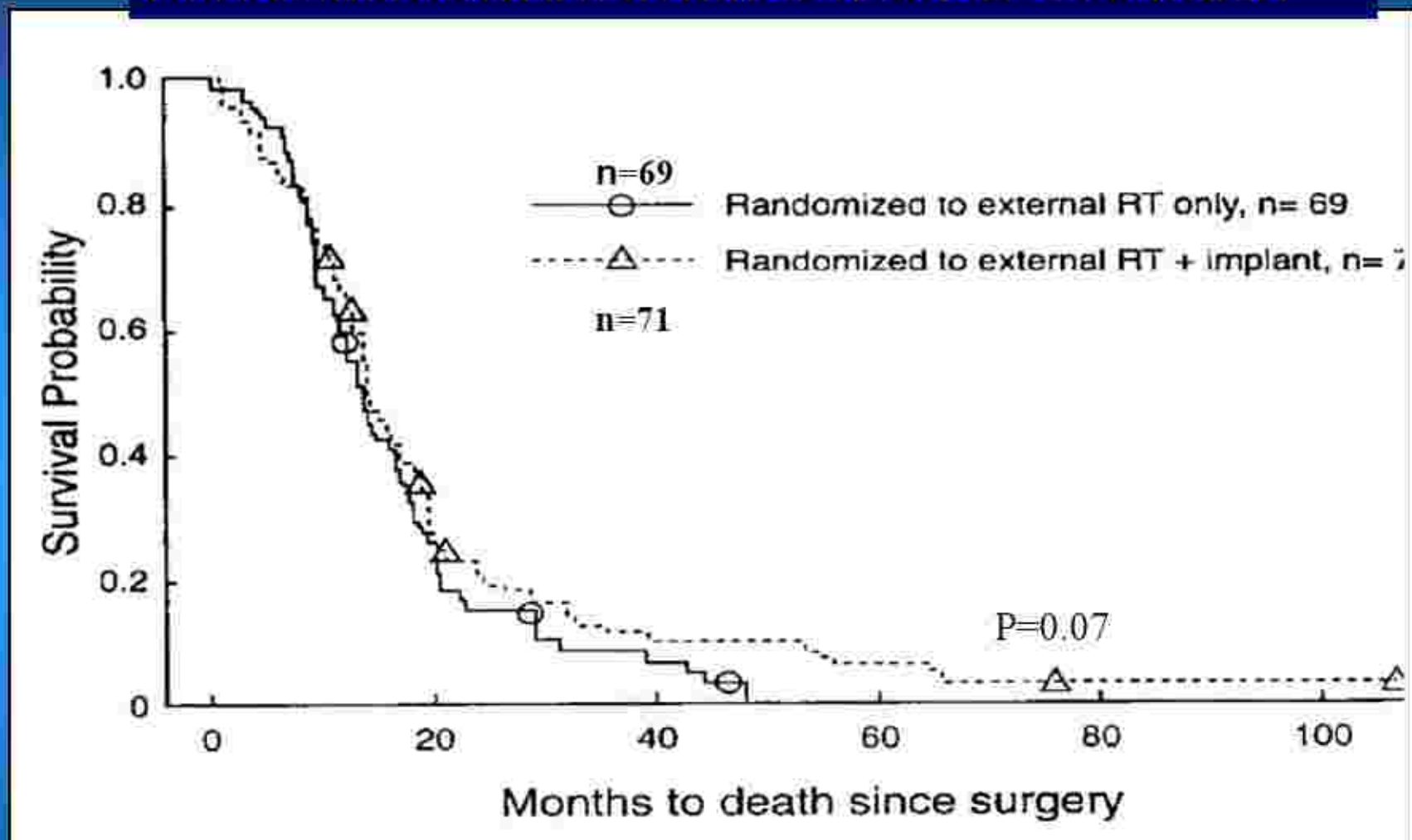
Target area receives at least 100% of the prescribed dose. Typically 40-60 Gy.

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

1.

Dosimetry issues, clinical data not encouraging

## Phase III randomised trial of dose escalation



Steroid use double in Brachytherapy arm

Laperriere. *IJROBP* 1998;41:1005-1011

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

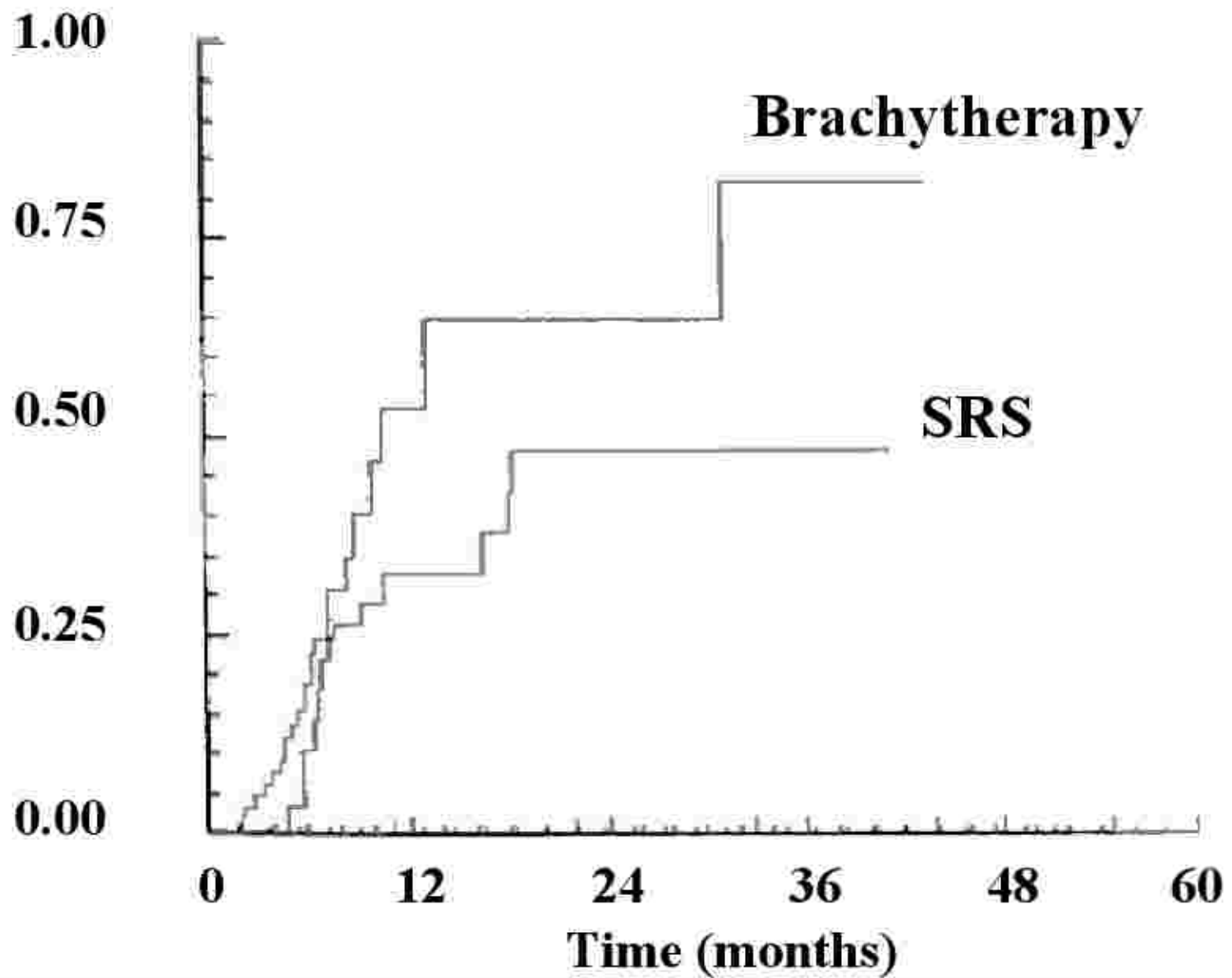
Selker, *Neurosurg* 2002

# 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



# Phase III Randomised Trial of SRS boost

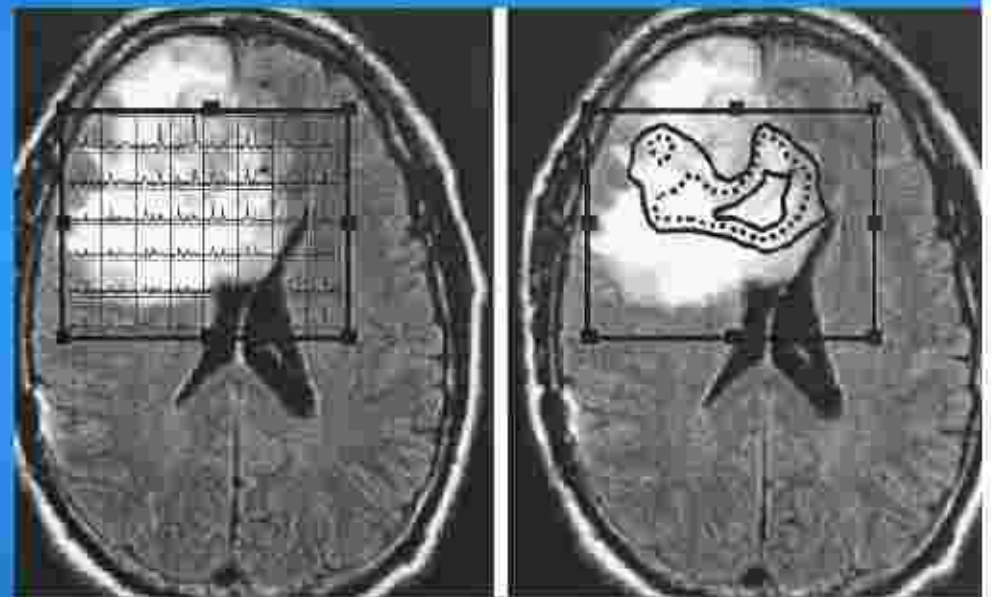
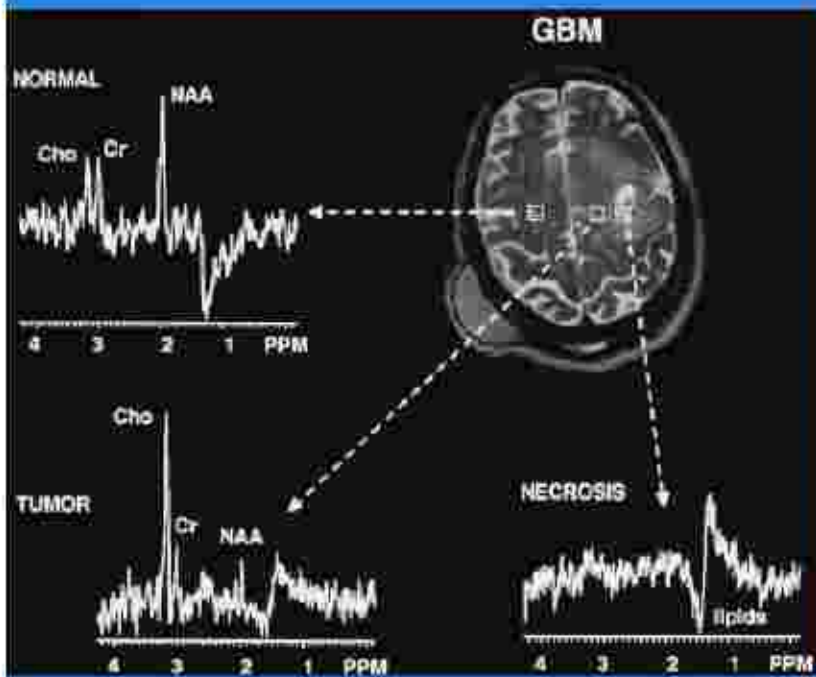
RTOG 9305



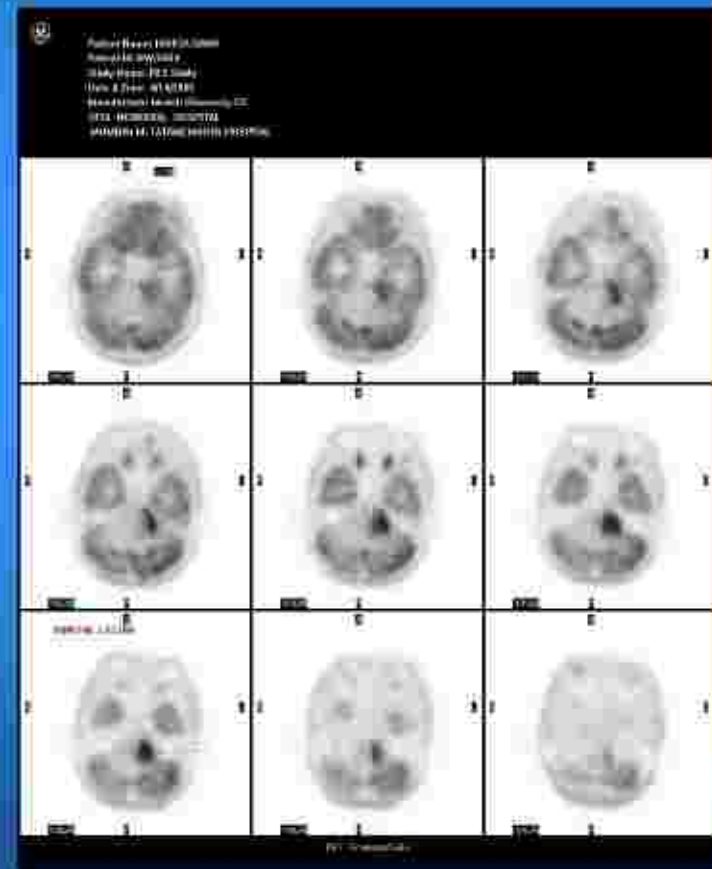
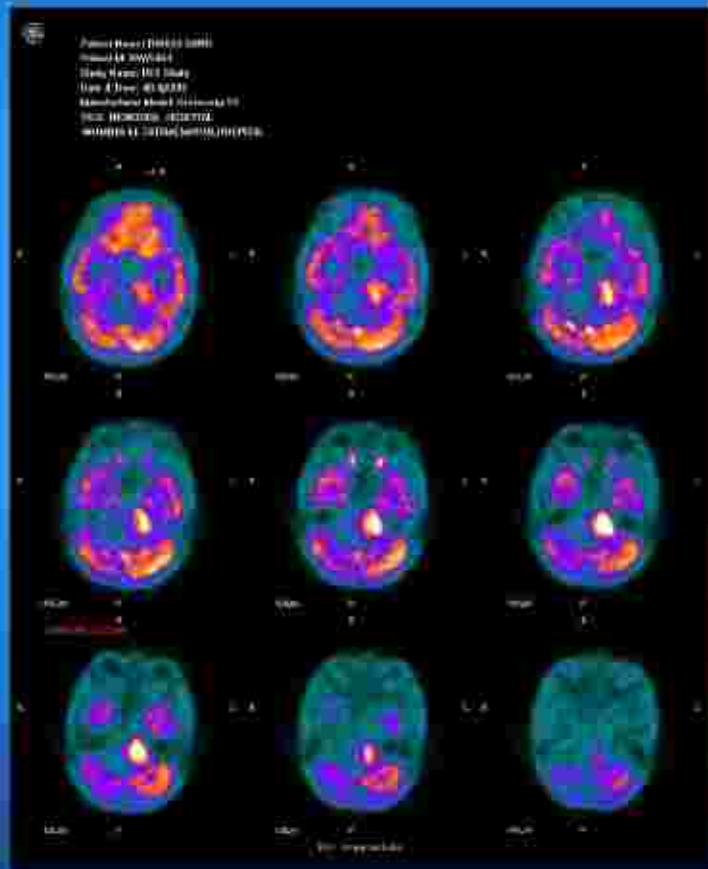
- 203 patients with GBM
- Conv RT60 Gy +/- SRS boost (15-24 Gy)
- Median f/u 44 months
- Median Survival : 14.1 Vs 13.7 months
- 2 year survival: 22 Vs 18%
- 3 year survival: 16 Vs 8%
- 18% pts in SRS arm had significant toxicity

**RADIOSURGERY Contraindicated**

# Magnetic Resonance Spectroscopy



# FDG PET/CT-PET





# $^{11}\text{C}$ Methionine PET



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

# 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

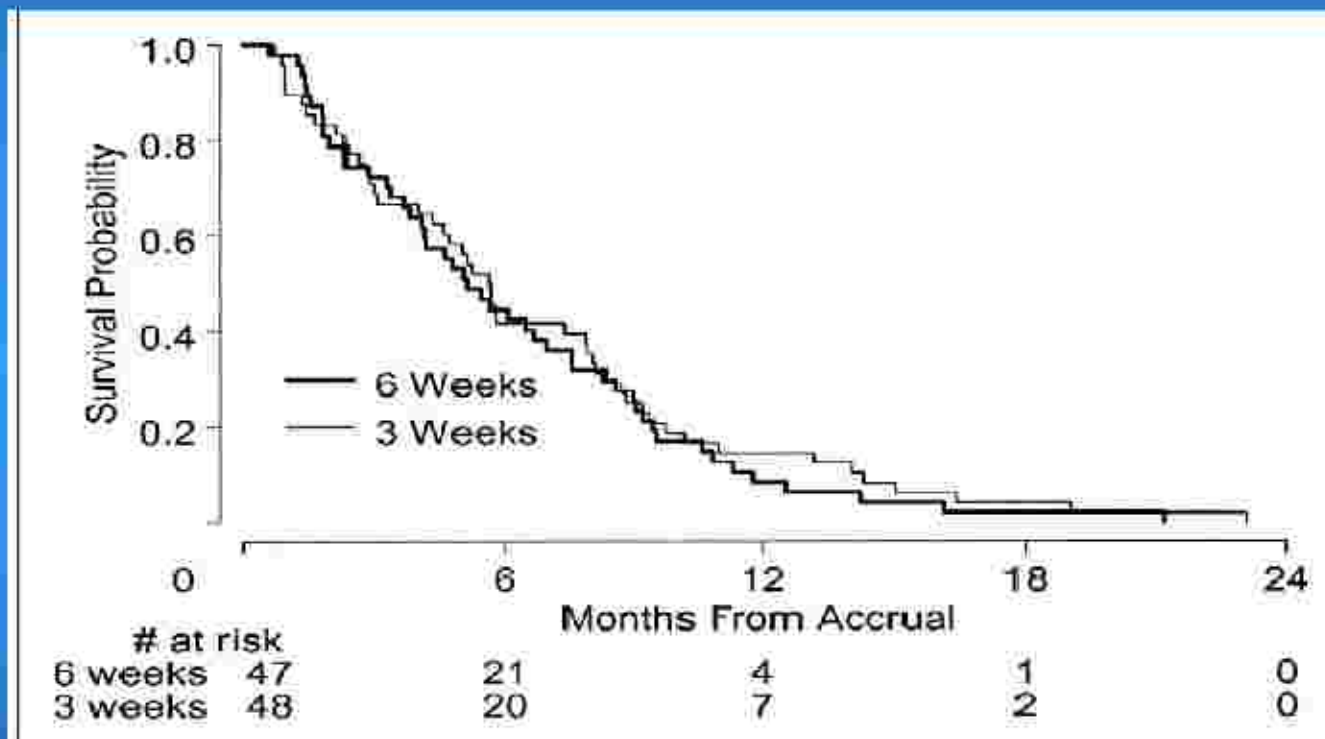
60Gy/30#, 2Gy daily over 6weeks

***Hypo-fractionated schedules***

35Gy/7#, 5Gy weekly over 7 weeks

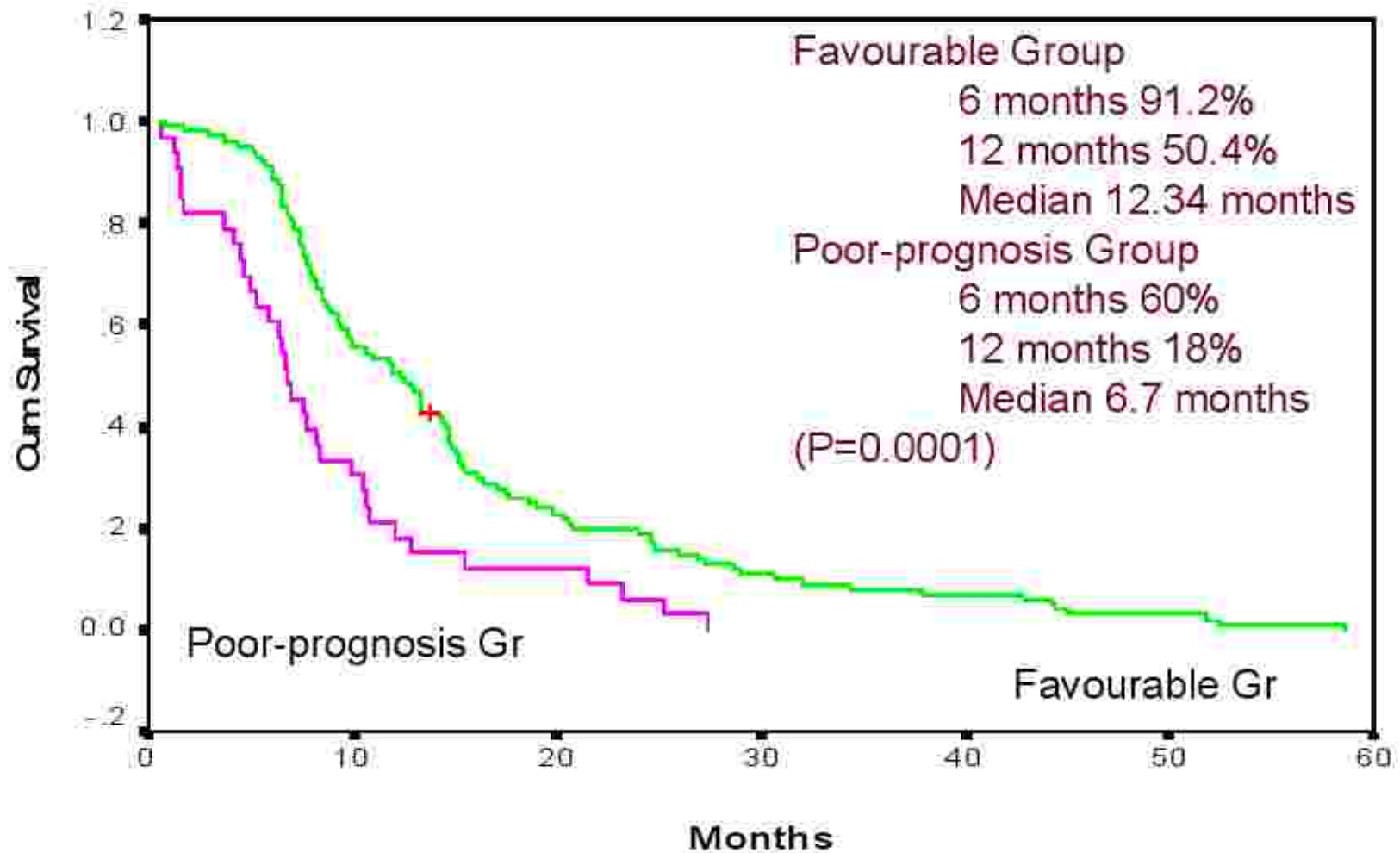
45Gy/18, 2.5Gy daily over 3.5weeks

# Hypofractionated RT for poor prognosis patients

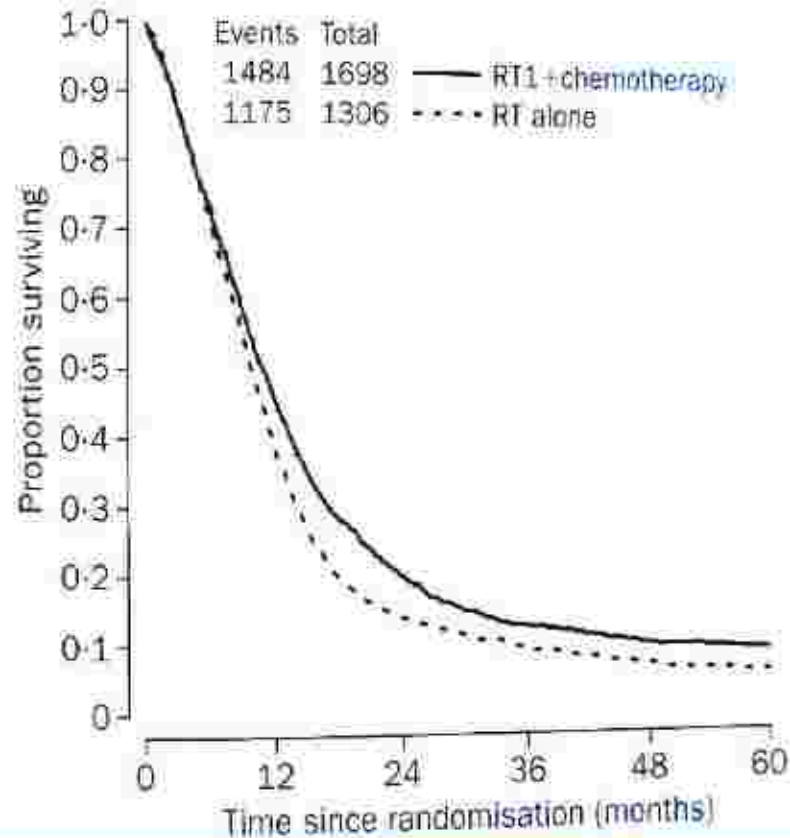


**Fig 1.** Overall survival from randomization by treatment group. There was no difference in the overall survival between the standard 6-week (thick line) versus abbreviated 3-week (thin line) course of radiation therapy (Log-rank test,  $P = .57$ ).

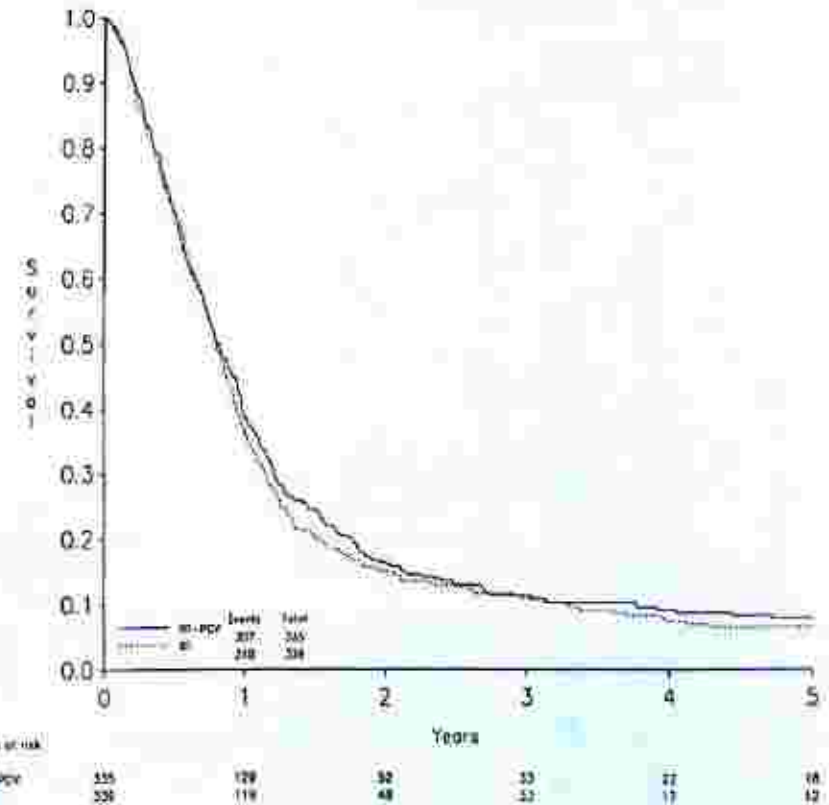
# TMH data of Overall survival in Prognostic groups in HGG (n=270)



# Adjuvant chemotherapy in malignant gliomas



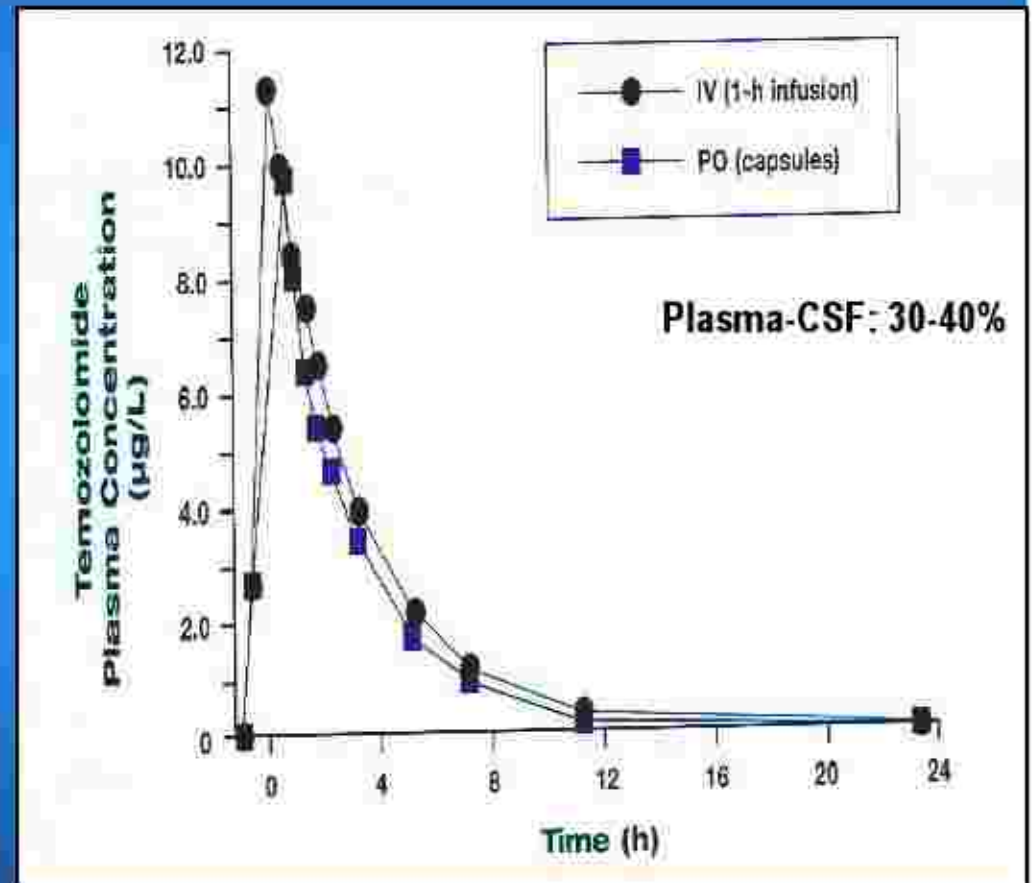
GMT Lancet 2002; 359:1011-18



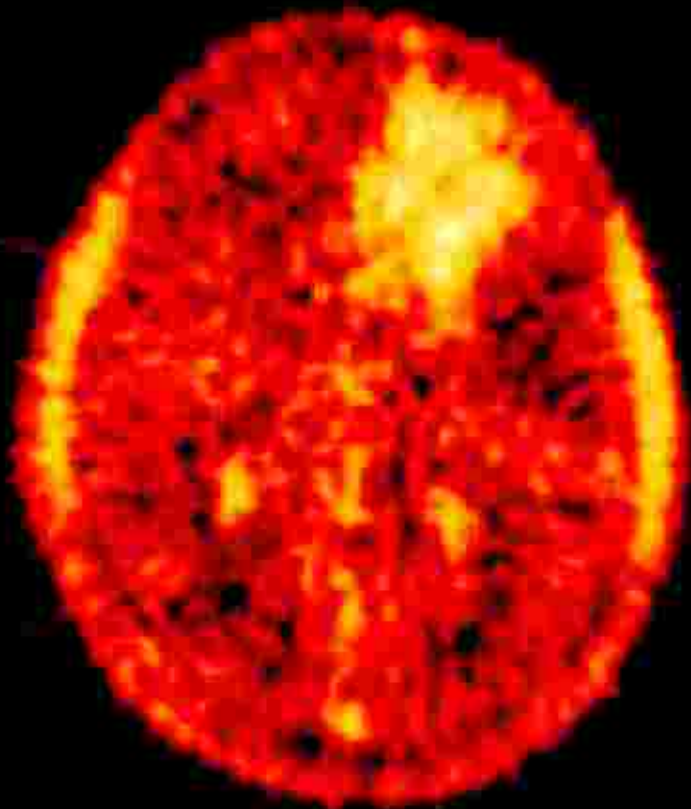
MRC JCO 2001;19:509-18

# Temozolomide (TMZ)

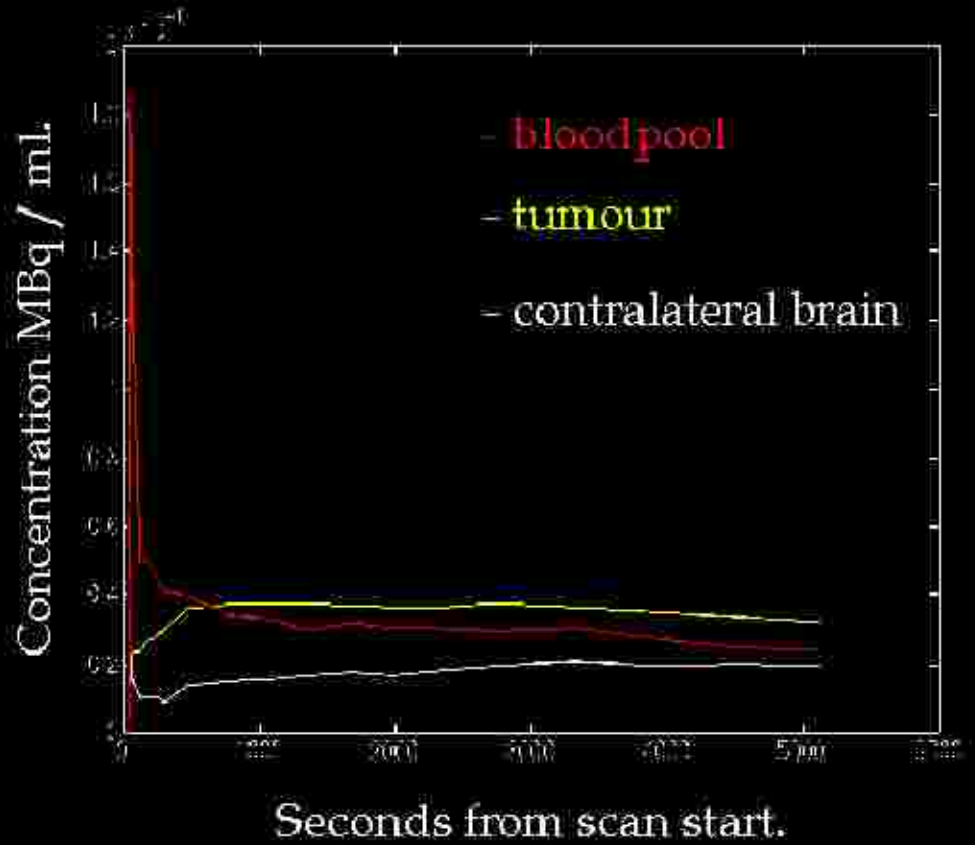
- Oral administration
- excellent concentration in CNS
- encouraging antitumour activity
- favourable toxicity profile
- synergism with radiotherapy and other agents



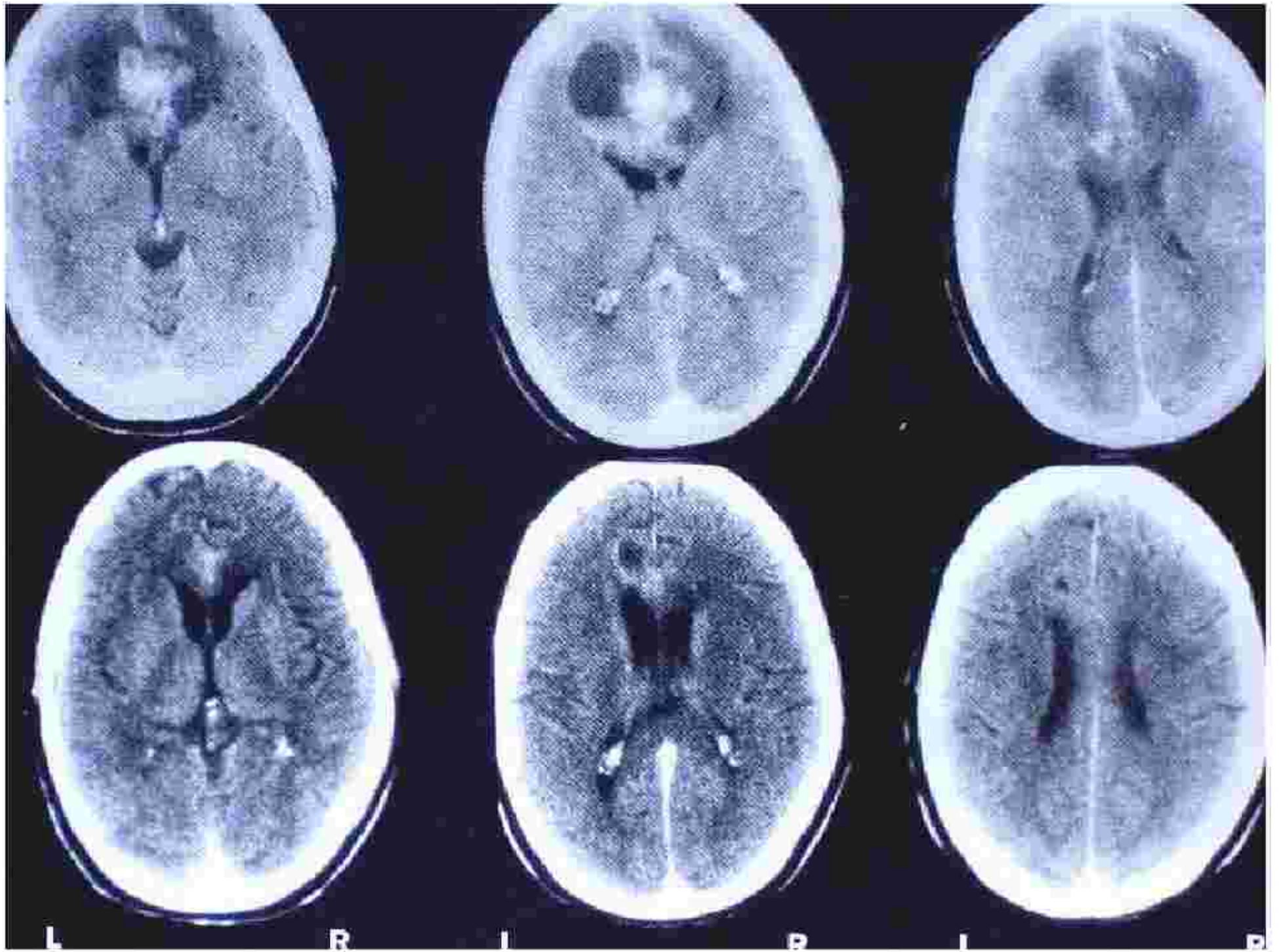
# $^{11}\text{C}$ -Temozolomide



PET Scan.

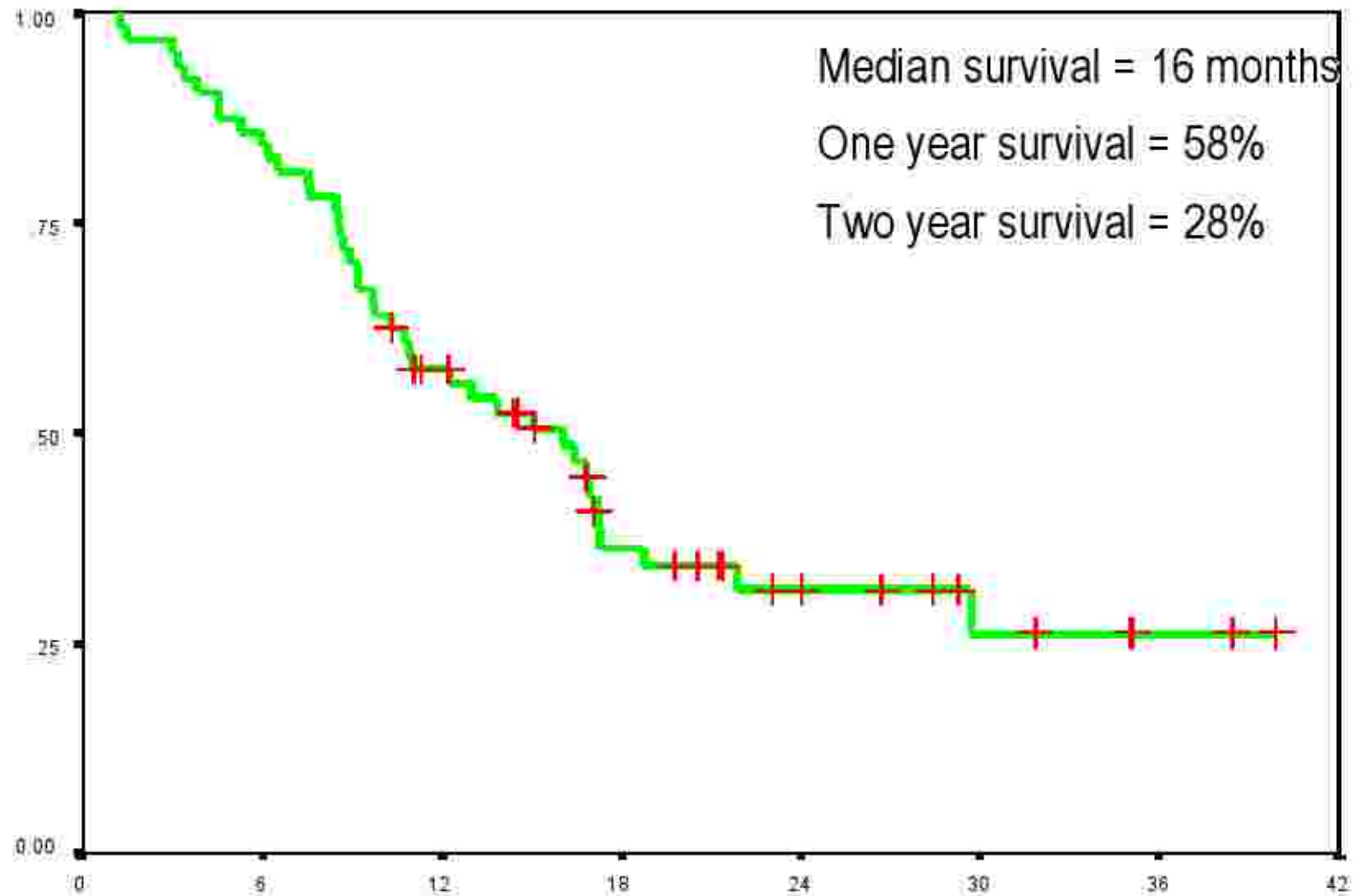


Time Activity Curve.





# Concomitant + adjuvant TMZ-RT



# 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/m<sup>2</sup> od x 5 day  
repeat every 28 days

x 6 cycles

TMZ 75mg/m<sup>2</sup> od x 6-7 wks



# 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**

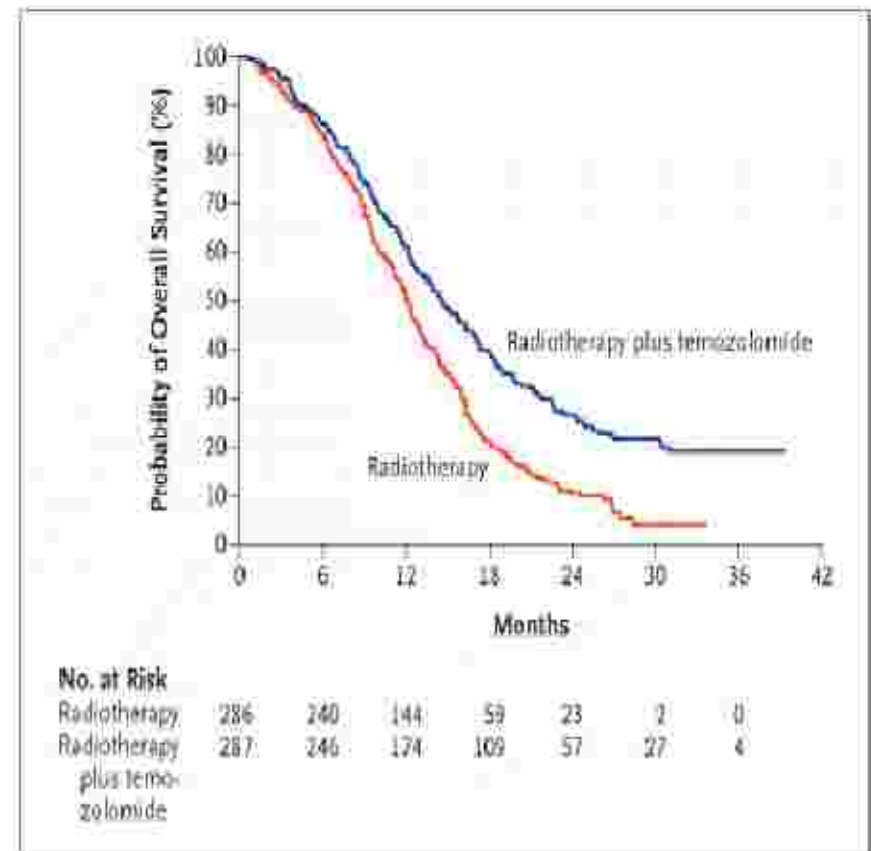
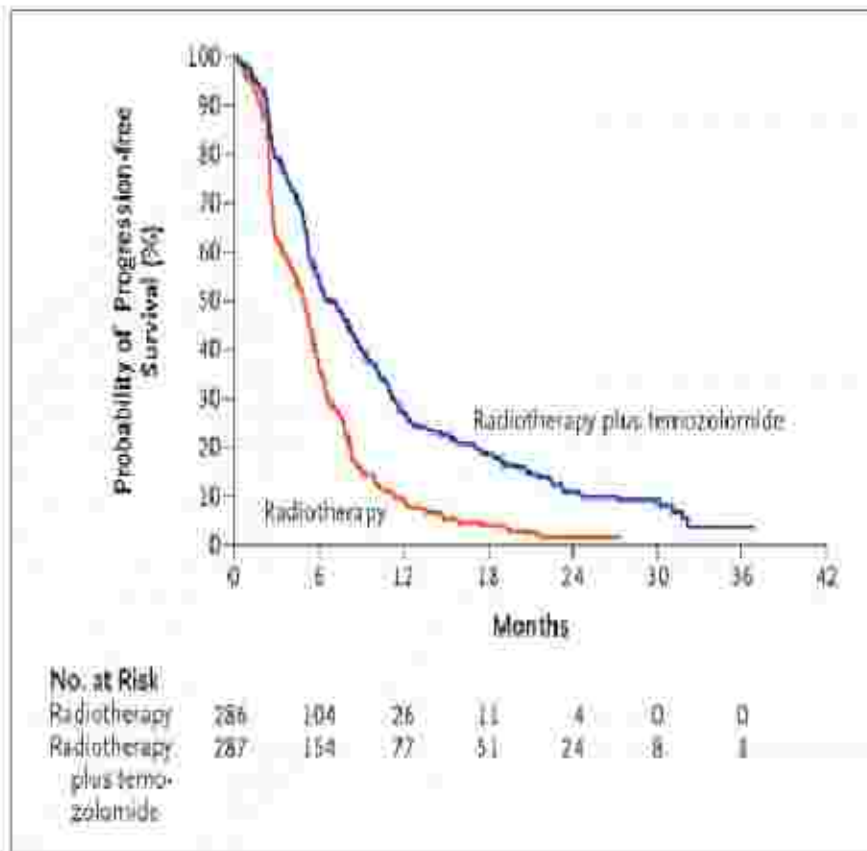
**Throughout the world**

# Results

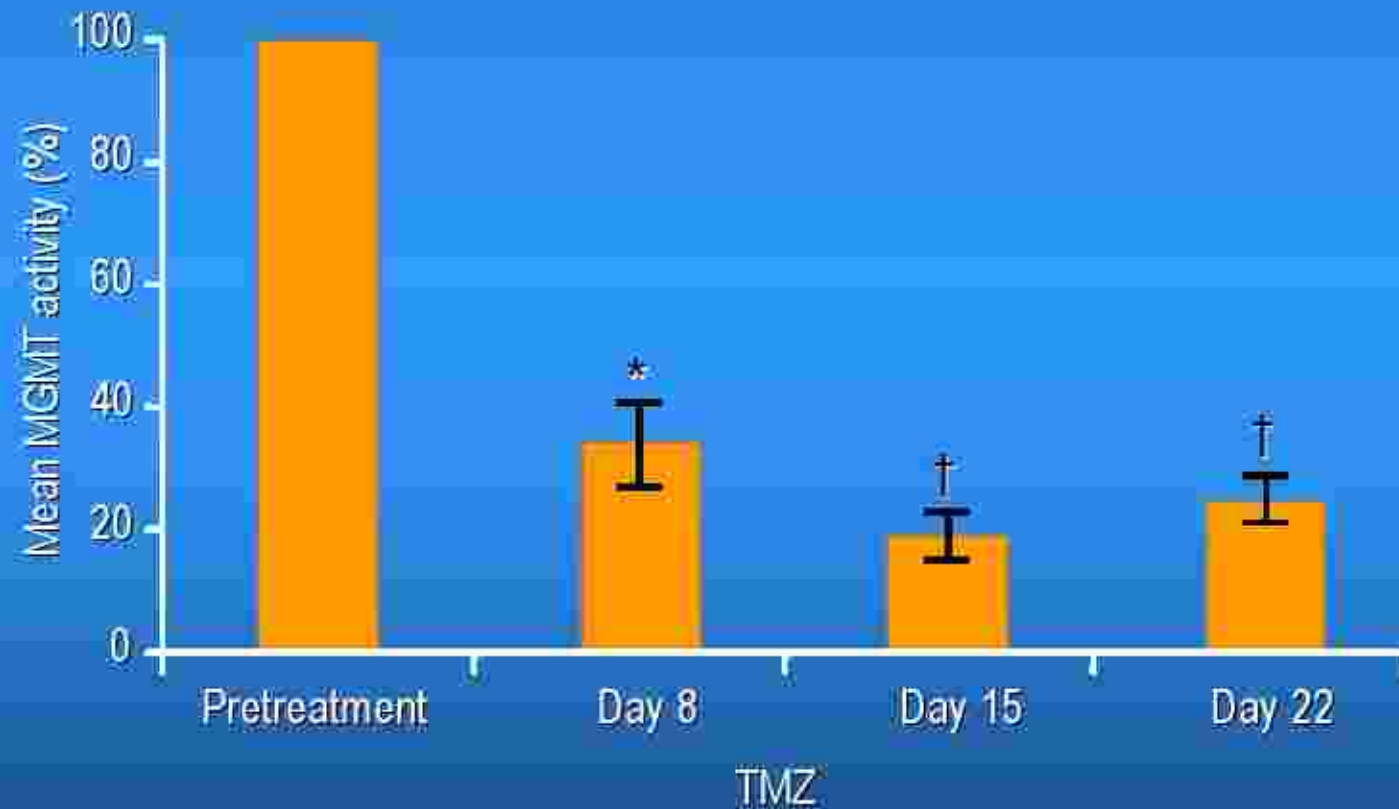
- Median Age 56 yrs
- Debulking surgery in 84% of patients
- On central review, diagnosis of GBM confirmed in 93% of cases
- Interruptions due to toxicity of Rx in 3% and 4% in RT and RT + Tem
- 87% of patients completed concomitant temozolomide
- 78% started adjuvant tem and 47% completed 6 cycles
-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

## Progression free survival

## Overall survival

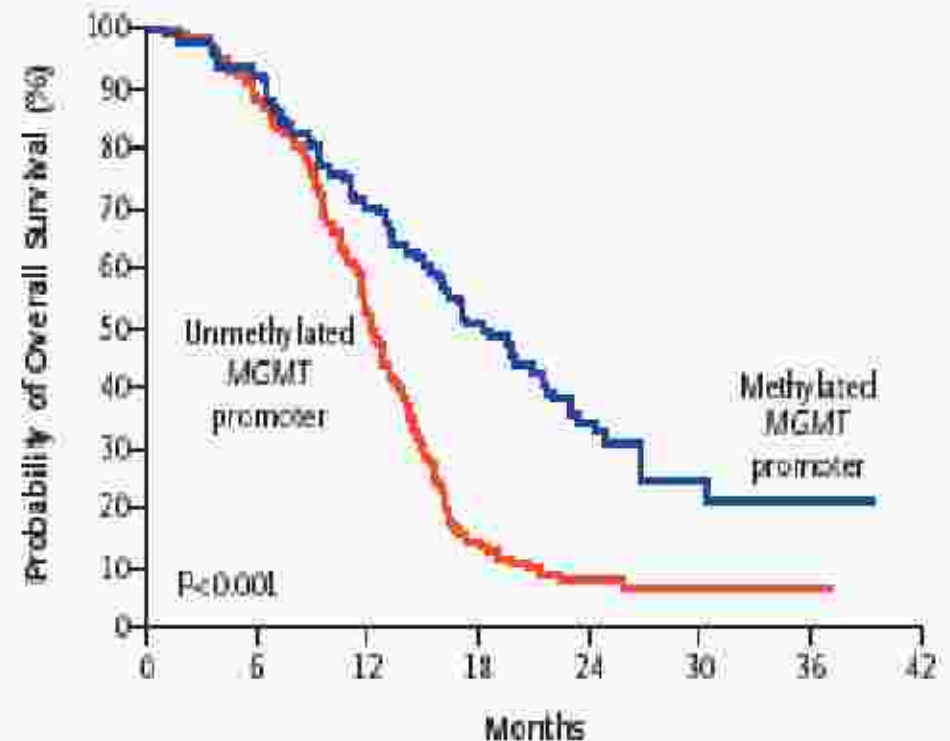


# MGMT (Methylguanine DNA methyltransferase) and TMZ Resistance



# 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)



No. at Risk	0	6	12	18	24	30	36
Unmethylated	114	100	59	16	7	4	1
Methylated	92	84	64	46	24	7	1



**Table 1.** Effect of MGMT Promoter Methylation Status on Survival, According to Random Treatment Assignment.<sup>a</sup>

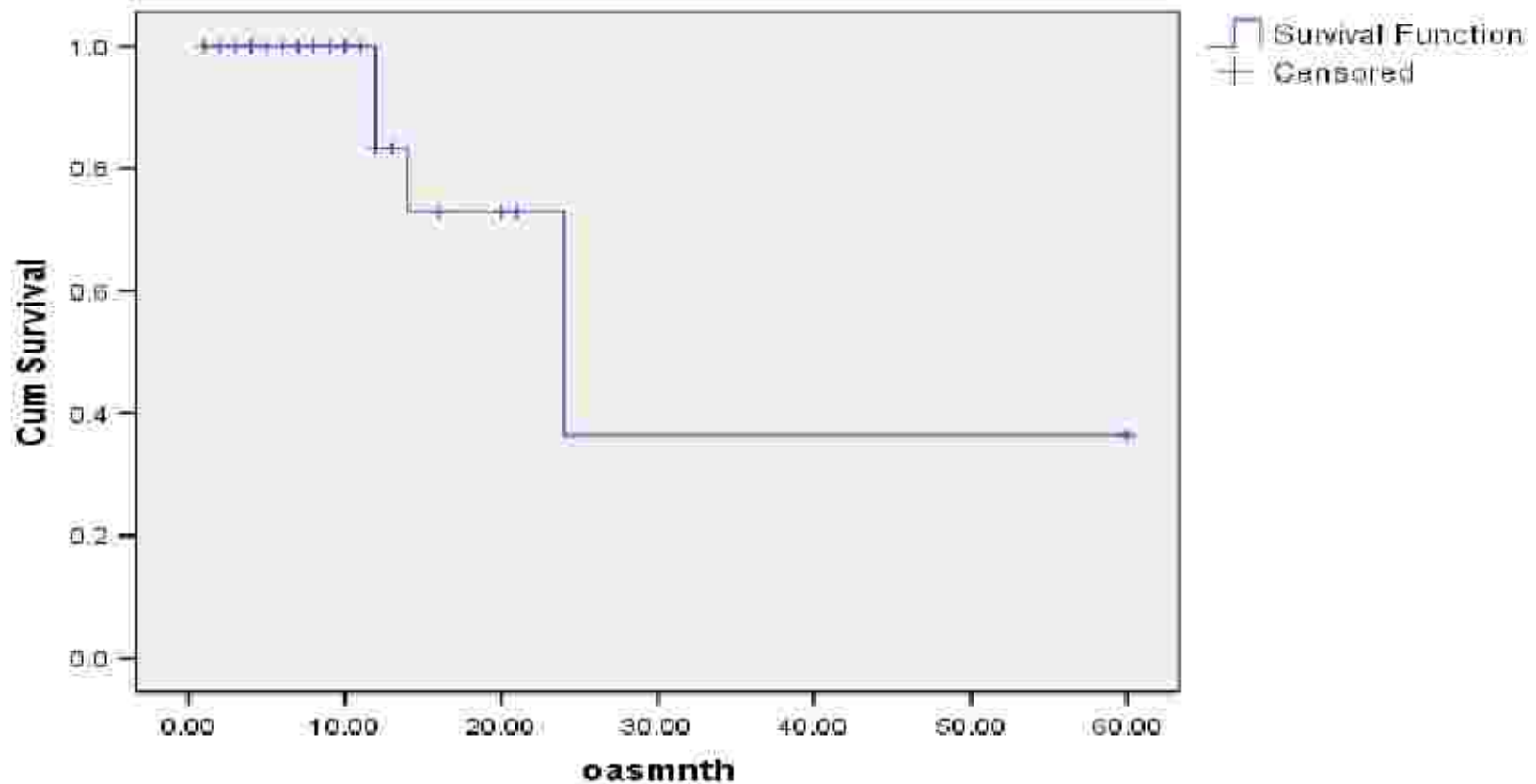
Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
<b>Methylated MGMT promoter</b>		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00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

# TMZ protocol

- concomitant TMZ at 75 mg/m<sup>2</sup> 20-30 min before RT, every day for 42 days (including weekends)
- 4 hours fasting
- adjuvant TMZ 150-200 mg/m<sup>2</sup> x 6 cycles, 4 weeks apart

*all patients on prophylactic antiemetics and PCP prophylaxis (cotrimaxazole 1 tab bd x42 days)*

### Survival Function



1 and 2 year overall survival : 72% and 31%

Median survival: 24 months at mean fu of 11.4 months (range 2-60 months)

