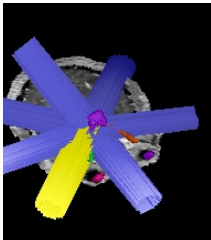




# Hypofractionated stereotactic radiotherapy and continuous low-dose temozolomide in patients with recurrent or progressive malignant gliomas

*Reirradiazione con radioterapia stereotassica ipofrazionata e temozolomide a bassa dose continuativa in pazienti con glioma maligno recidivante o in progressione*



C. Scaringi, E. Clarke, G. Minniti, T. Falco, V. De Sanctis, M. Valeriani, M. Luciani, S. Narici, R. Maurizi Enrici

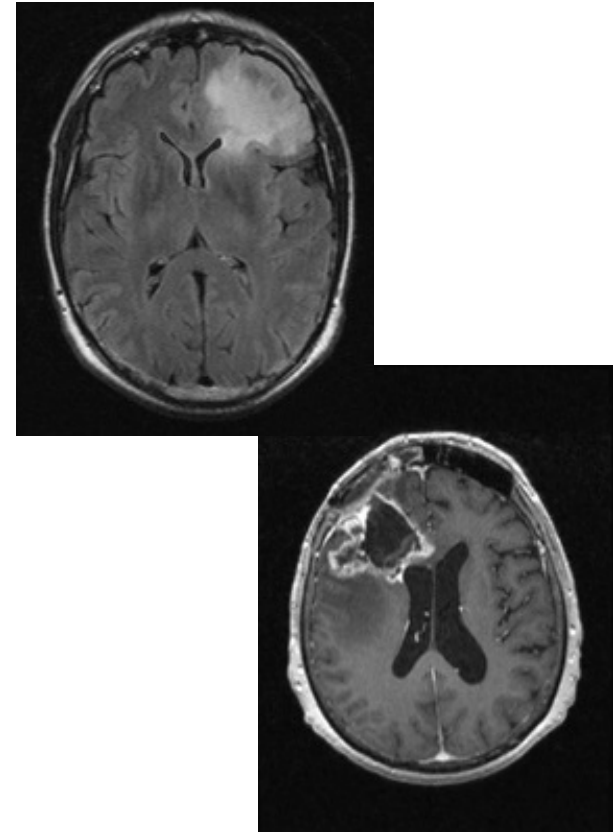
S Andrea Hospital, University “La Sapienza”, Rome;  
Neuromed Institute, Pozzilli (IS);Italy.



Associazione  
Italiana  
Radioterapia  
Oncologica

# Background

- Tumor control and survival in patients with malignant gliomas is limited, and almost all patients recur at the site of primary tumor within 1–3 years of initial standard chemotherapy
- Chemotherapy is the most frequent salvage treatment for recurrent malignant gliomas, with survival rates in the range of 7–11 months
- A surgical approach can be employed in selected patients, but optimal resection is very difficult because of the infiltrative nature of disease and may be associated with a high risk of morbidity



# Background

- Different Radiation schedules alone or in association with chemotherapy have been employed reporting a survival time of 6–15 months with acceptable toxicity
- Hypofractionated stereotactic radiotherapy given in 5–15 fractions of 2.5–6 Gy (HSRT) enables the precision and accuracy of SRS, while maintaining the radiobiological advantages of fractionation in terms of tumor control and protection of surrounding normal brain tissue.

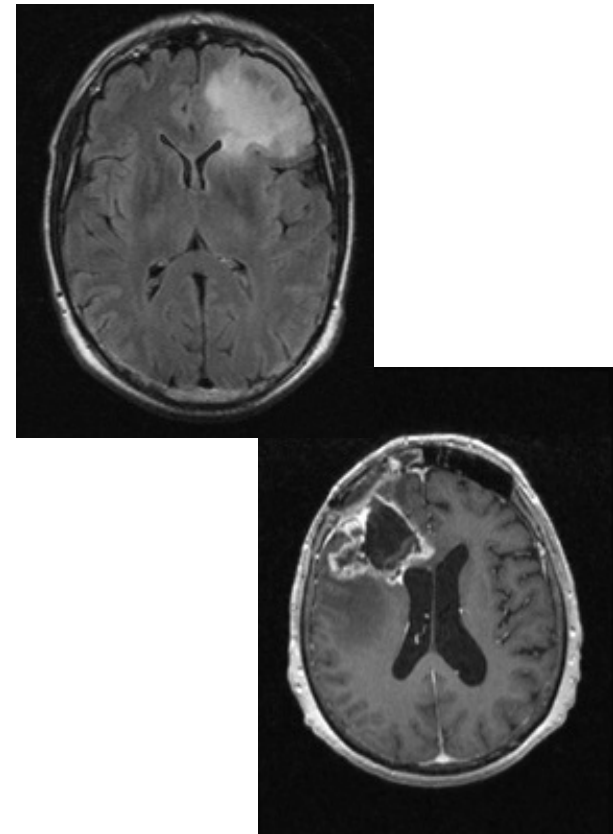


## Aim of the study

We have examined the safety and efficacy of salvage HSRT in combination with systemic therapy in a series of patients with recurrent malignant gliomas

The treatment consisted of:

- HSRT (30 Gy in 6–Gy fractions)
- plus concomitant TMZ (75 mg/m<sup>2</sup> / day)
- followed by continuous TMZ at 50 mg/m<sup>2</sup> everyday up to 1 year or until progression



# Aim of the study

## Endpoints:

OS

PFS

## Inclusion criteria:

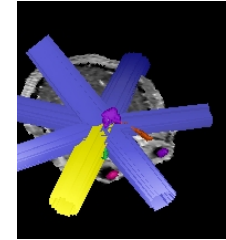
- maximal tumor size 4 cm
- KPS  $\geq$  60
- previously treated with standard conformal RT (60 Gy) with concomitant and adjuvant TMZ
- recurrent malignant glioma(WHO grade 3/4) as showed at 18 F-FDOPA PET and/or MRI or histologically proven, occurring at least 6 months after the initial diagnosis



Patient characteristics	
Age (years) Median (Range)	52 (30–72)
Sex	
Male	32
Female	22
WHO grade	
III	16
IV	38
Karnofsky performance status (KPS) Median (Range)	80 (60–100)
Resection	
Yes	12
Not	42
MGMT methylation status	
Methylated	26
Unmethylated	28
Number of cycles with Temozolomide	
<6 cycles	5
6 cycles	22
>6 cycles	27
Interval between primary radiation and reirradiation Median (Range) (months)	15.5 (6–108)
Salvage chemotherapy before reirradiation	
Yes	4
No	50
Recurrence volume (cm <sup>3</sup> ) Median (Range)	9.7 (3.1–32.3)
PTV (cm <sup>3</sup> ) Median (Range)	30.3 (12.3–53.4)

54 pts

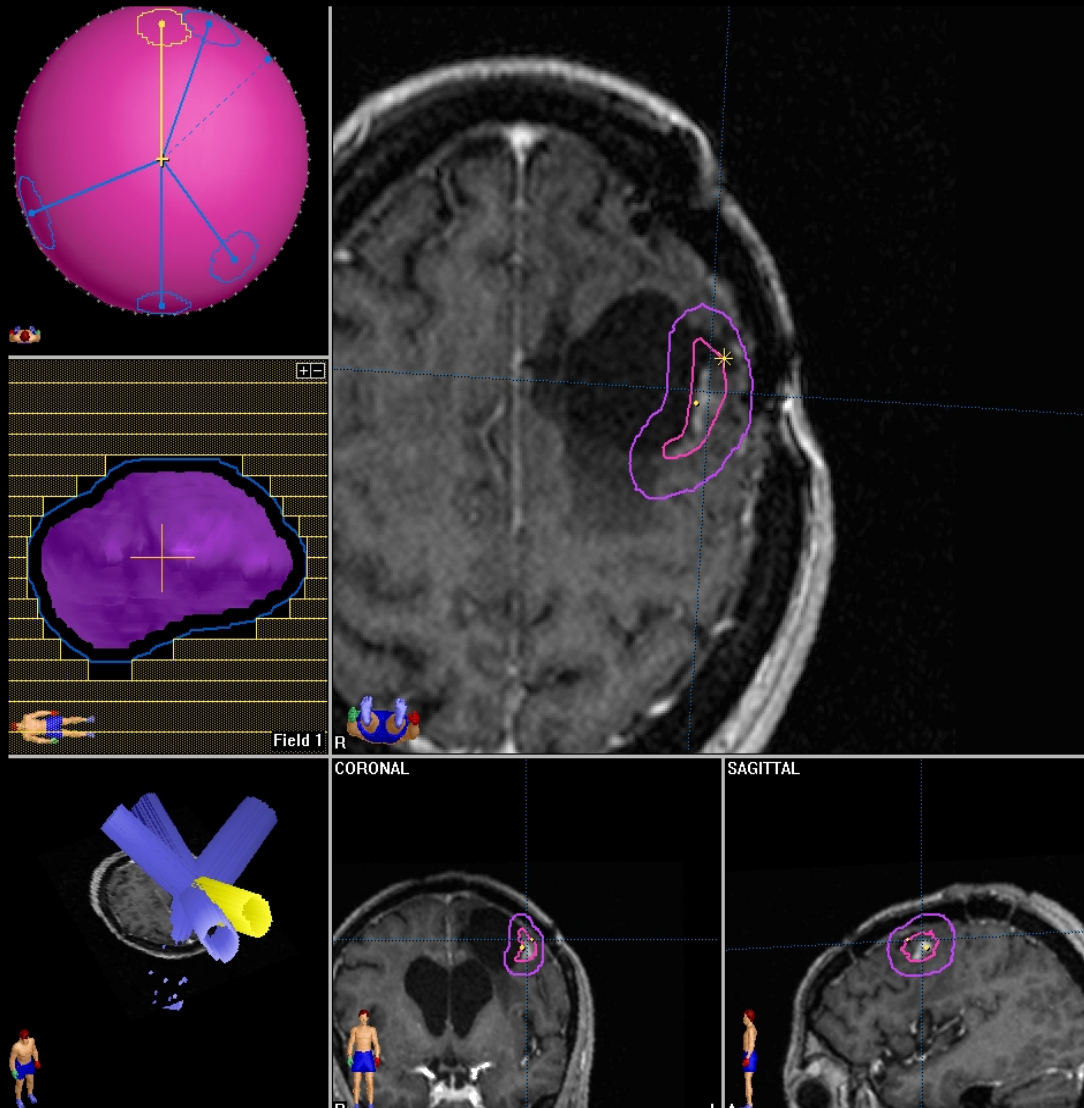
# Patients and methods



- 54 pts between May 2006 and December 2011
- median PTV (GTV + 5/7mm) 30.3cc
- 4-10 noncoplanar conformal fixed fields  
or 3-6 dynamic arcs

## Dose:

- 30 Gy (6Gy x 5)
- PTV encompassed by the 90% isodose line



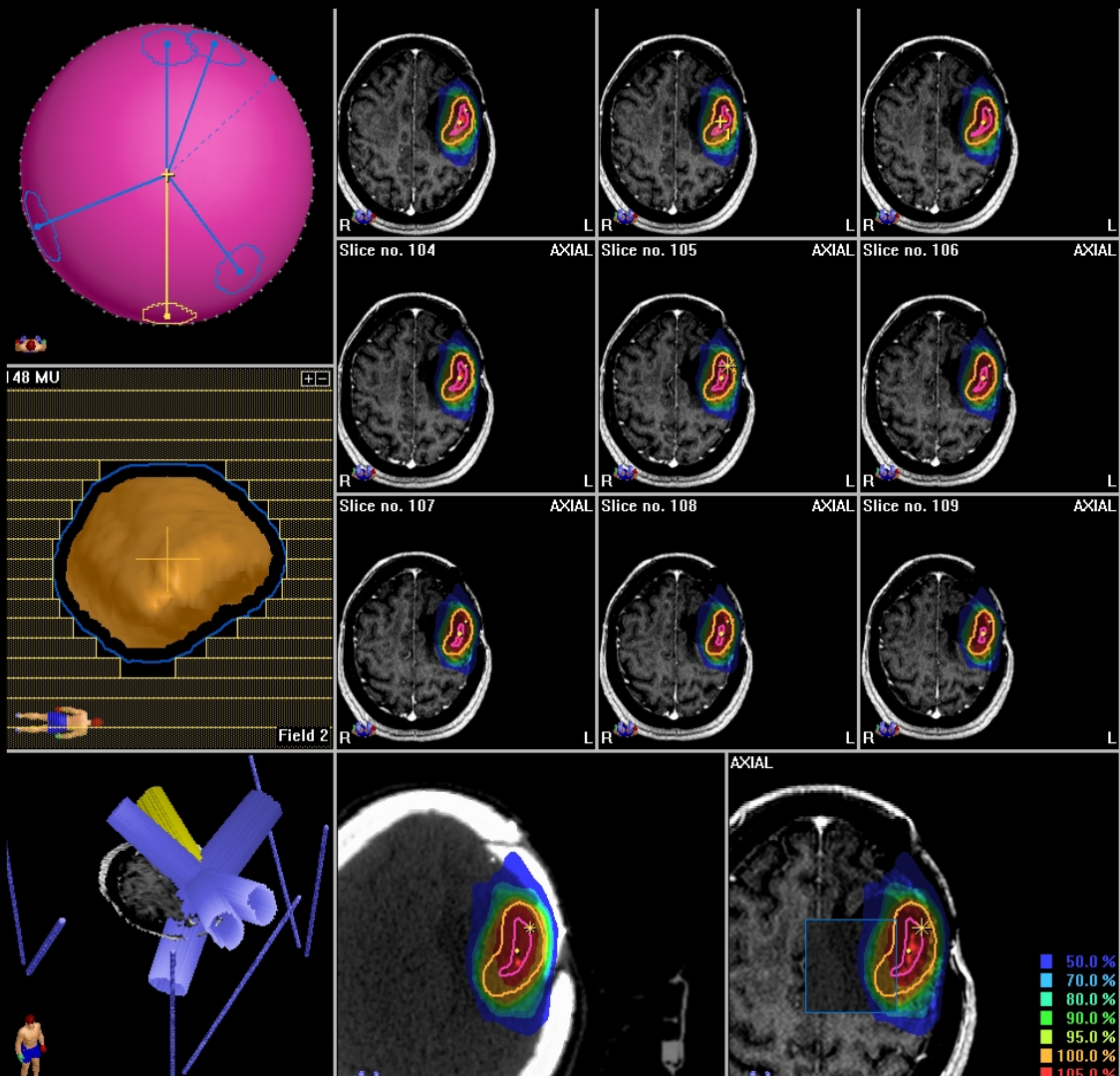
*GTV (T1 after contrast)*

*CTV = GTV + 5 mm*

*PTV = CTV + 2 mm*

*Recurrent glioma treated with HSRT*





*Recurrent glioma treated with HSRT*

Se:6  
Im:101

[AH]

R.ASSUNTA  
Study Date:28/07/2...  
Study Time:14.03.11  
MRN:

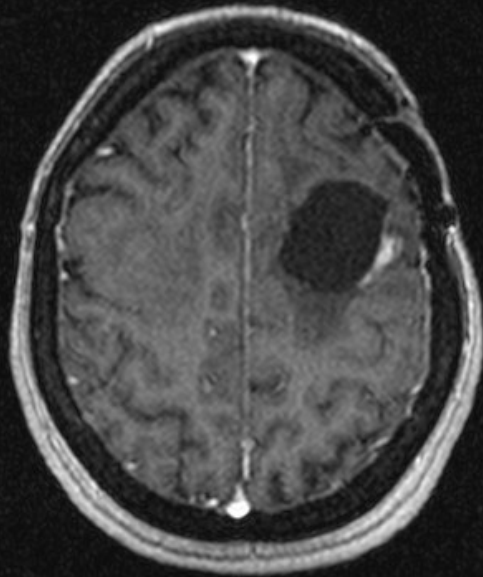
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MRN:

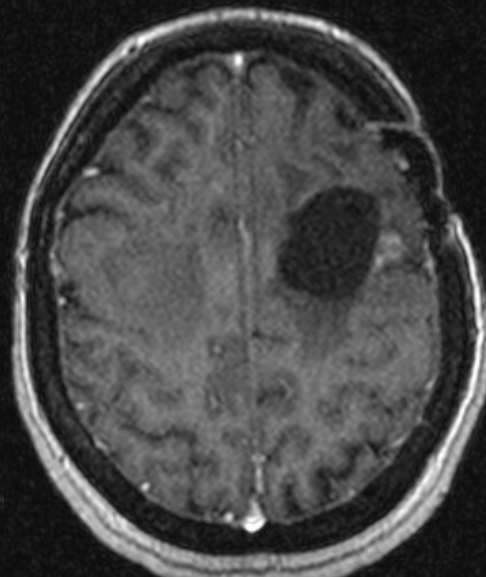
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Study Time:16.36.56  
MRN:

[R]

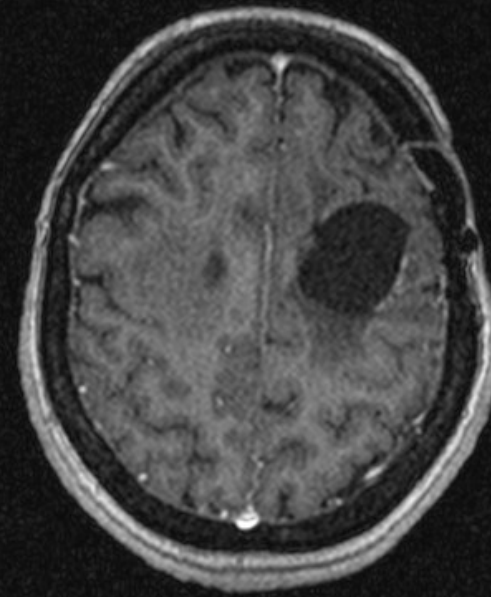


[L]



3 months

[L]



[L]

6 months

with contrast

[PF]

C351  
W771 ntrast

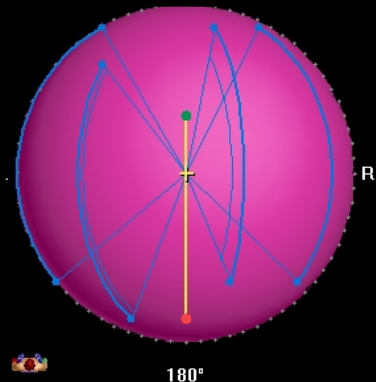
[P]

C346  
W762 contrast

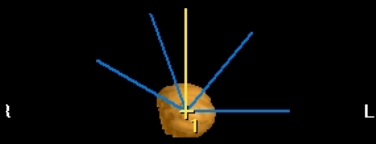
[P]

C321  
W702

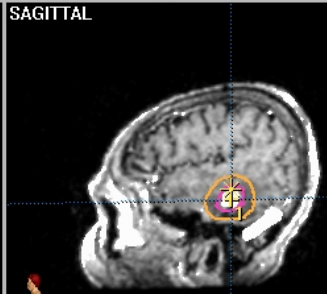
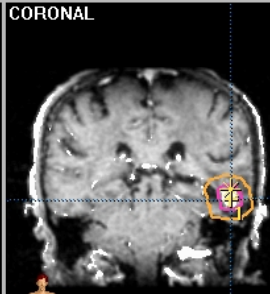
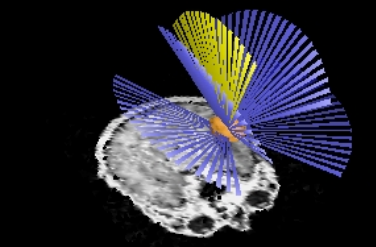
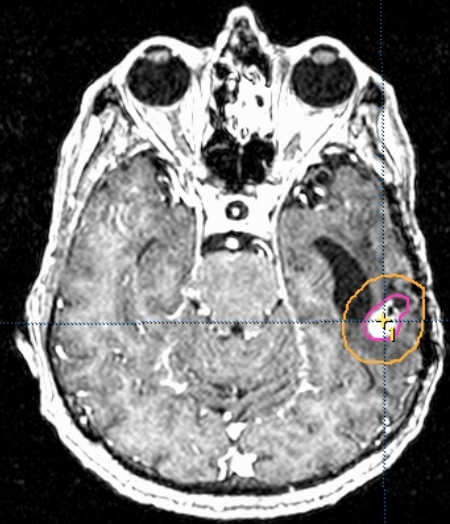
# Recurrent GBM



CORONAL



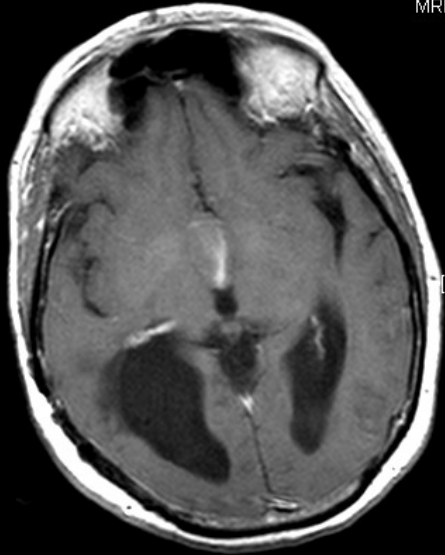
Arc 1



Se:5  
Im:9

[AH]

R.FRANCA  
Study Date:27/10/...  
Study Time:18.01.20  
MRN:



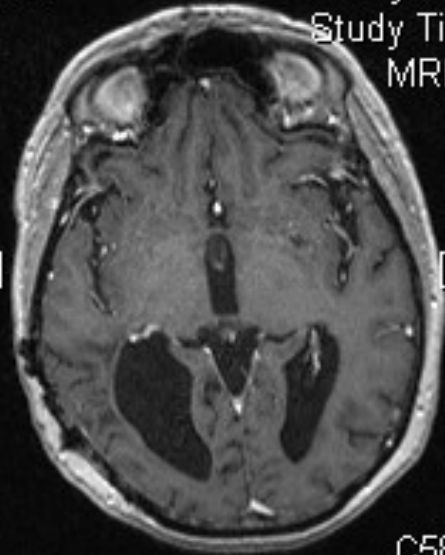
[R]

[L]

Se:5  
Im:61

[AH]

R.FRAN...  
Study D...  
Study Ti...  
MRN:



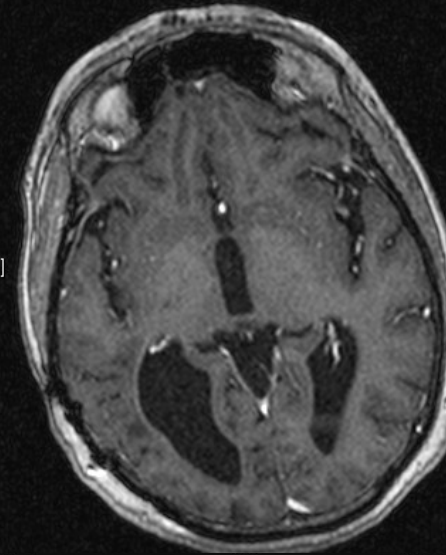
[R]

[L]

Se:7  
Im:62

[AH]

R.FRANCA  
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Study Time:14.32.13  
MRN:



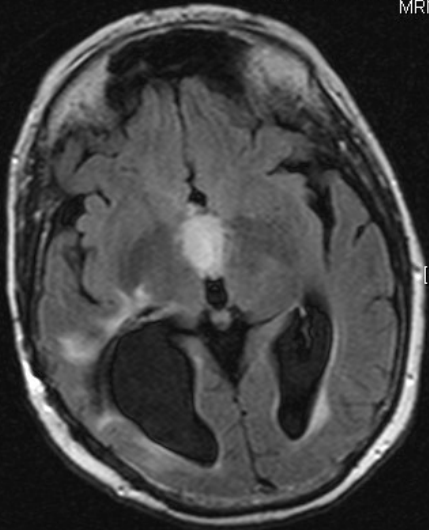
[RF]

[LH]

Se:2  
w Im:9

[AH]

R.FRANCA  
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Study Time:18.01.20  
MRN:



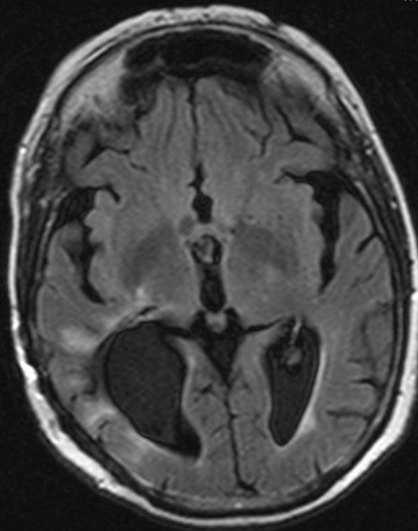
[R]

[L]

Se:2  
Im:9

[AH]

R.FRANCA  
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MRN:



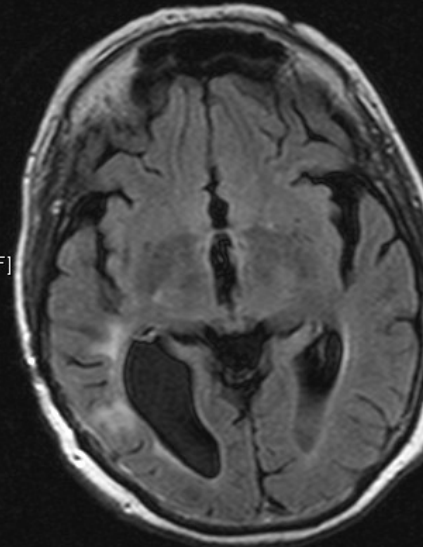
[R]

[L]

Se:2  
Im:10

[AH]

R.FRANCA  
Study Date:08/04/...  
Study Time:14.32.13  
MRN:



[RF]

[LH]

3 months

6 months

C582

C363  
W799

C348  
W775

C66  
W765

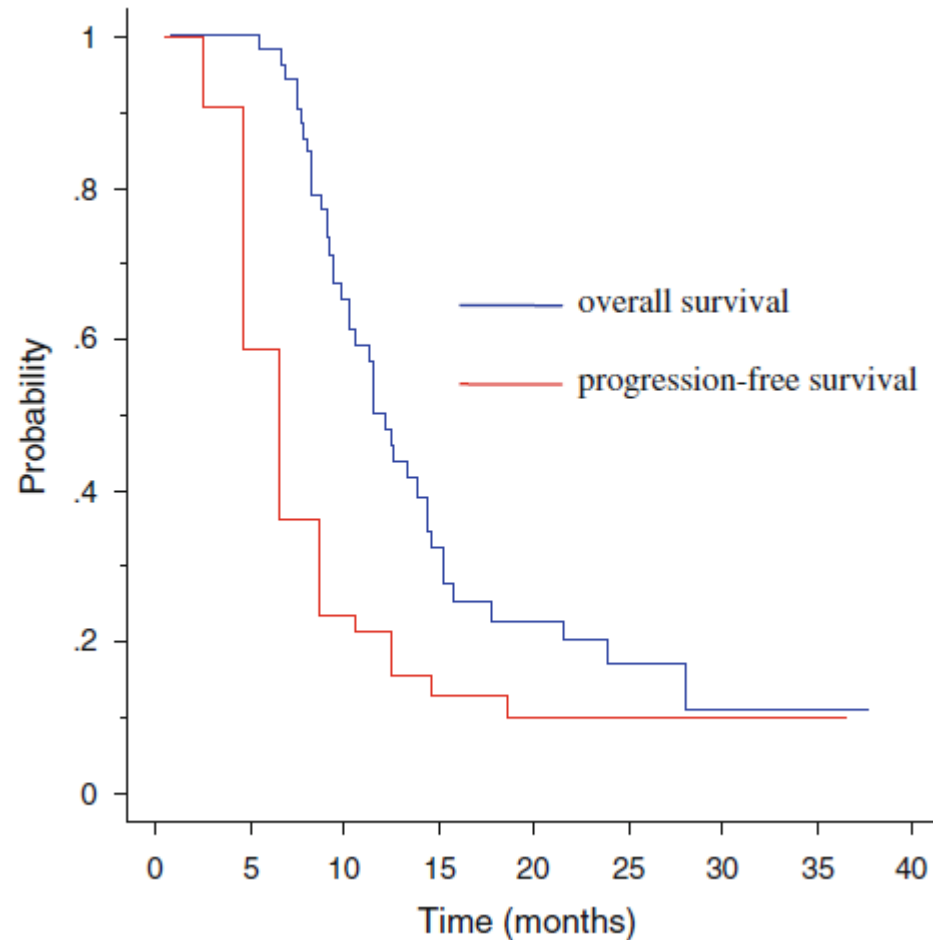
Recurrent GBM

# Outcome

Median OS after HSRT  
12.4 months

12-month survival rate 53%  
24-month survival rate 16 %

median survival from the time of  
initial treatment 27.9 months



# Outcome

median PFS 6 months

12-month PFS rate 24%

24-month PFS rate 10 %

complete response 4 pts (7 %)

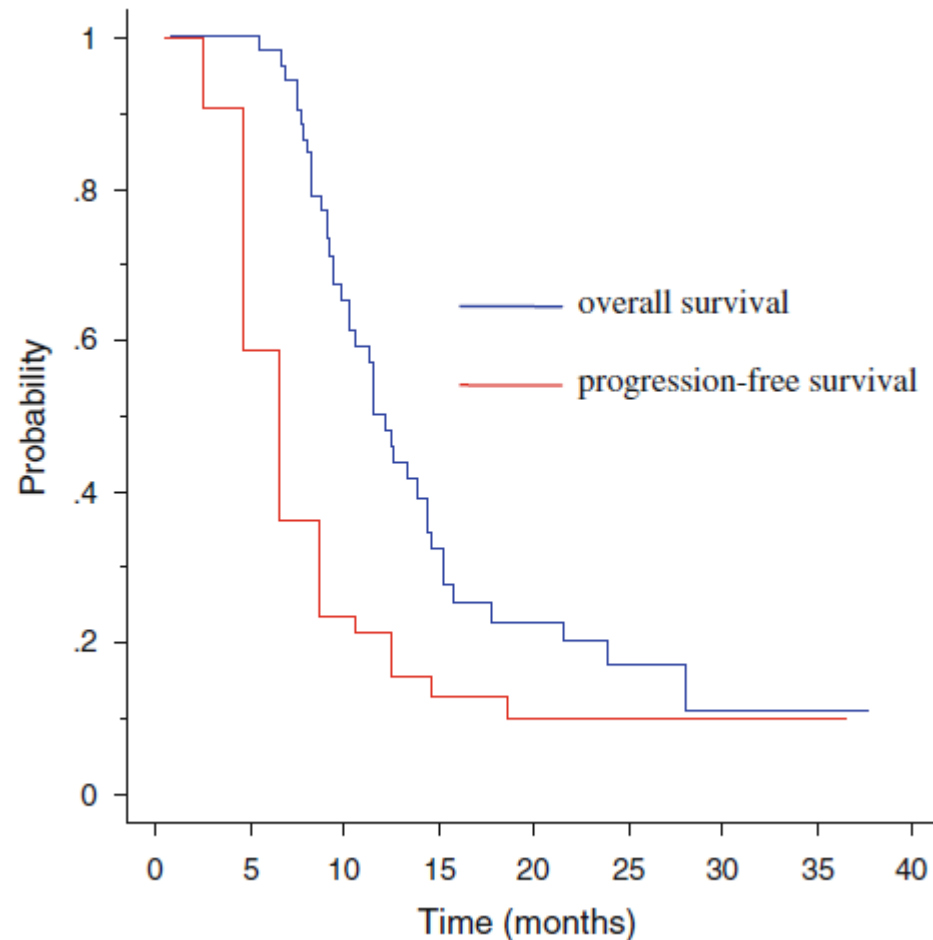
partial response 14 (26 %)

Progression in-field (within the prescription isodose) in 18 patients

marginal (outside of the prescription isodose) in 12 patients

both in 8 patients

and distant in 7 patients

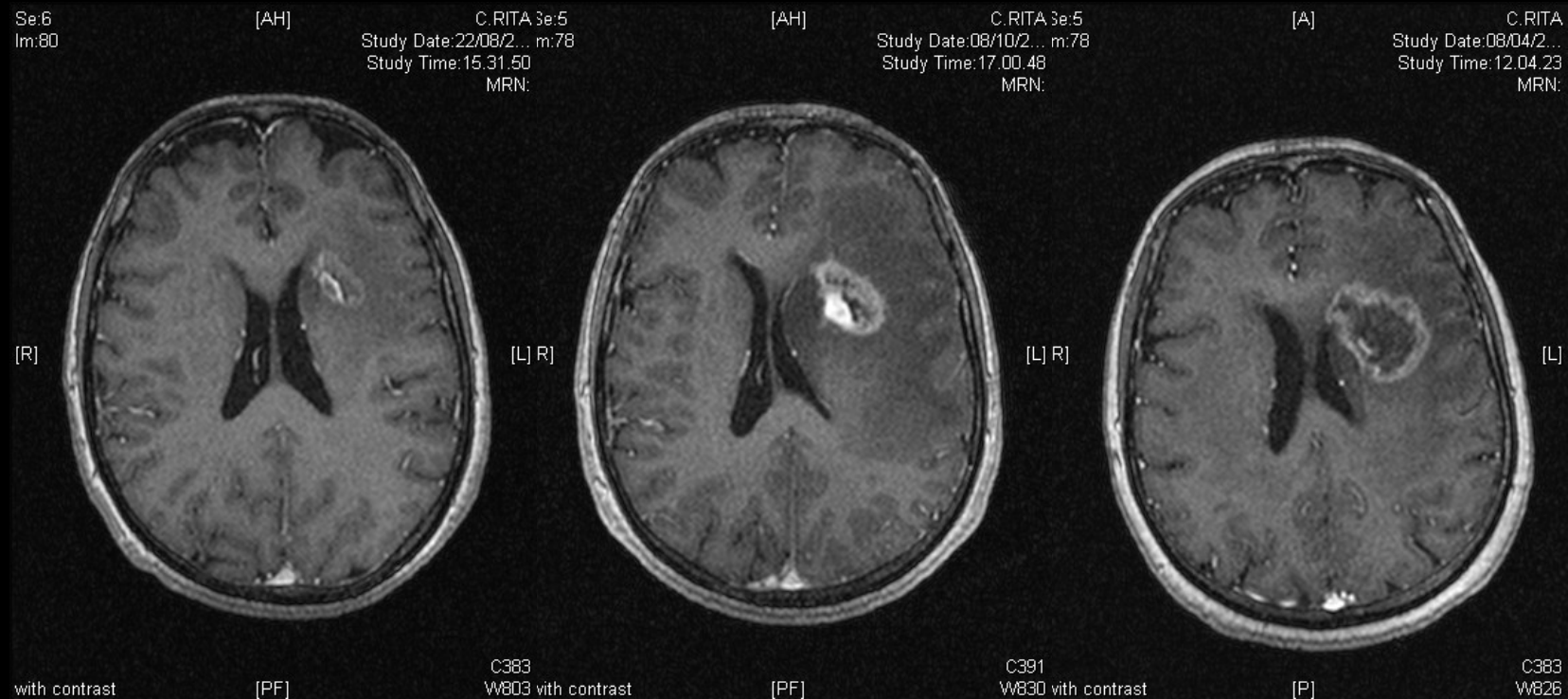


# Outcome

## Multivariate survival and progression-free survival analysis

Factor	Hazard ratio (95 % CI)	<i>P</i> value
Risk of death		
KPS >70	0.42 (0.22–0.78)	0.01
Grade 3	0.18 (0.07–0.45)	0.0002
MGMT methylation status	0.61 (0.35–1.09)	0.08
Interval from initial treatment	0.97 (0.93–1.02)	0.4
Risk of progression		
Grade 3	0.32 (0.15–0.68)	0.003
MGMT methylation status	0.64 (0.34–1.18)	0.15

## Radionecrosis after HSRT in a GBM



**Grade 3 neurological deterioration attributable to radiation-induced necrosis occurred in four patients (7 %) at 2 (n = 2), 4 and 10 (n = 2) months after HSRT, and was managed successfully with high dose dexamethasone and/or surgery**



# Complications

Hematologic and nonhematologic toxicities  
according to common toxicity criteria

Event	Grade 2	Grade 3	Grade 4
<b>Hematologic</b>			
Trombocytopenia	3 (5 %)	2 (4 %)	0
Anemia	2 (4 %)	0	0
Neutropenia	3 (5 %)	2 (4 %)	0
Lymphocytopenia	9 (15 %)	7 (4 %)	3 (5 %)
<b>Nonhematologic</b>			
Nausea/vomiting	3 (5 %)	1 (2 %)	0
Dermatologic/skin	1 (2 %)	0	0
Neurologic	3 (5 %)	4 (7 %)	0
Liver enzymes	2 (4 %)	1 (2 %)	0
Fatigue	7 (13 %)	4 (7 %)	0

## Main published series on stereotactic reirradiation plus chemotherapy for recurrent malignant gliomas

Authors	Patients	Treatment	Radiation dose (Gy)	Chemotherapy	Interval	Volume (cm <sup>3</sup> )	KPS	Median PFS (months)	Median OS (months)	Radiation necrosis
Lederman et al. [33]	18	HSRT	24/4 fr	Paclitaxel	7.8	32.7	70	NR	7 (17 % at 12 months)	0 %
Arcicasa et al. [34]	31	FSRT	34.5/23 fr	Concomitant/adjuvant CCNU	14	NR	70	NR	13.7 (53 % at 12 months)	0 %
Minniti et al. [27]	36	HSRT	37.5/15 fr	Concomitant TMZ	14	13.1	70	5	9.4 (33 % at 12 months)	8 %
Combs et al. [25]	25*	FSRT	36/18 fr	Concomitant TMZ	36	NR	70	5	8 (25 % at 12 months)	
Grosu et al. [24]	44*	HSRT	30/6 fr	Concomitant TMZ (29 pts) HSRT alone (15 pts)	NR	15	NR	NR	11 (HSRT + TMZ) 6 (HSRT alone)	7 %
Gutin et al. [26]	25*	HSRT	30/5 fr	BVZ	15	34**	80	7.3	12.5 (54 % at 12 months)	0 %
Cuneo et al. [28]	49*	SRS	15	BVZ (33 pts) SRS alone (16 pts)	21	4.5	80	5.2 2.1	11.9 (50 % at 12 months) 3.9 (20 % at 12 months)	10 %
Park et al. [30]	11	SRS	16	BVZ	17.2	13.6	90	14.9	17.9 (73 % at 12 months)	9 %
Niyazi et al. [29]	30*	FSRT	36/18 fr	BVZ (20 pts) FSRT alone (10 pts)	NR	NR	80	8 5	12 <sup>a</sup> (67 % at 12 months) 6 <sup>a</sup> (0 % at 12 months)	0 %
Current study	54*	HSRT	30/5 fr	Concomitant/adjuvant TMZ	15.5	9.8	80	6	12.4 (54 % at 12 months)	7 %

# Conclusions

- In conclusion, HSRT plus concomitant TMZ followed by continuous dose-intense TMZ for patients with recurrent malignant gliomas is a feasible treatment associated with survival benefit and relatively low toxicity.
- The potential advantages of combined chemoradiation schedules to further improve outcome in patients with recurrent malignant gliomas need to be explored in future studies.