

Reirradiation of gliomas



I declare no conflict of interest



SAPIENZA
UNIVERSITÀ DI ROMA

Cattedra di Radioterapia



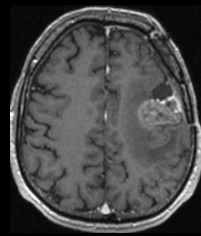
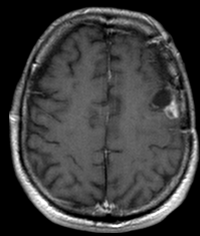
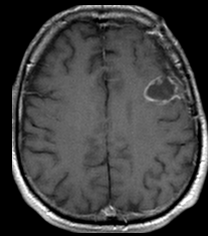
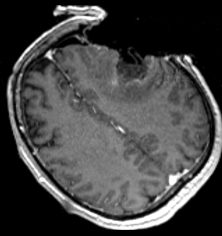
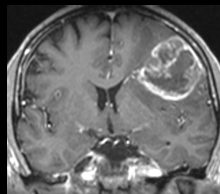
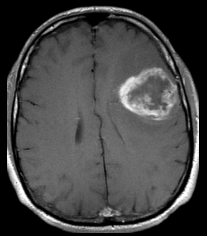
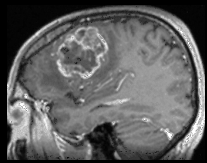
Brescia, 4/10/2013

man 47 years old, GBM

Diagnosis
2/2010

IMRT + TMZ
4/2010

Recurrent GBM
3/2011

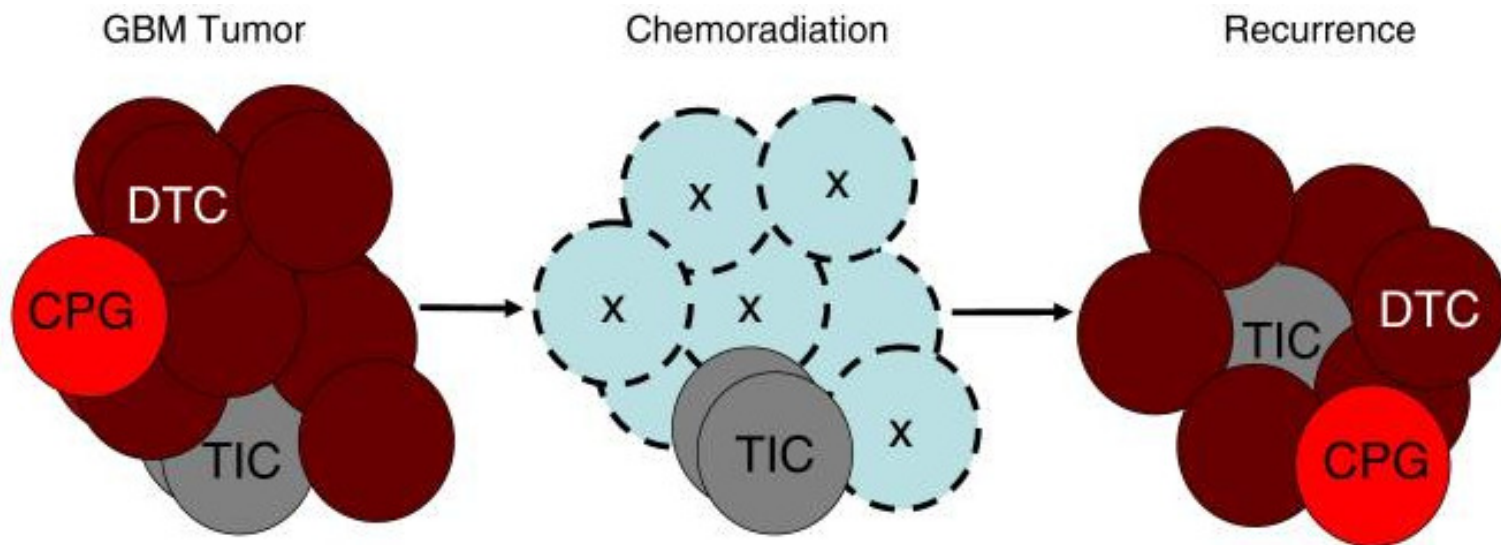
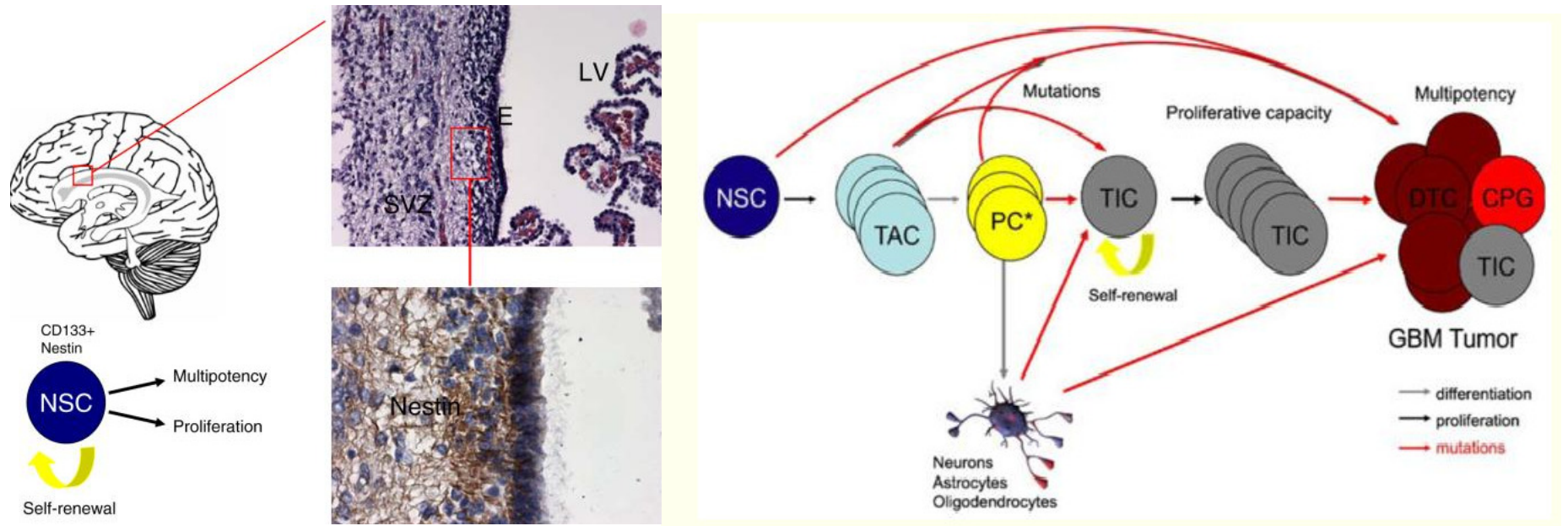


Surgery
3/2010

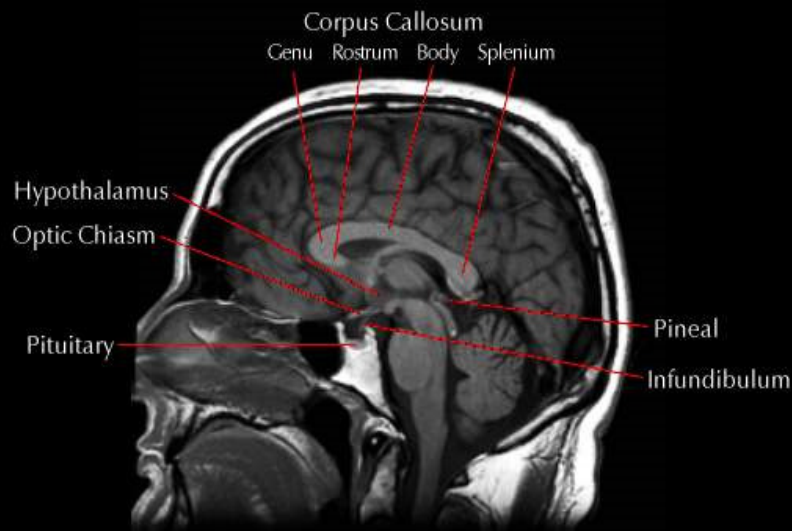
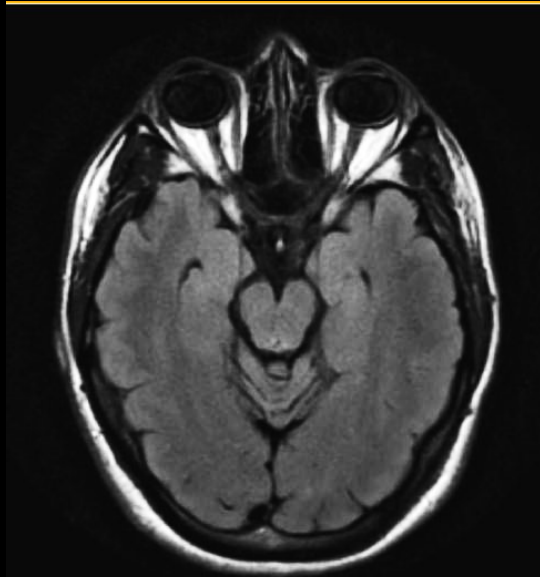
Adjuvant TMZ
6 cycles

- *What is the rationale for reirradiating recurrent or progressive gliomas ?*
- *Radiation therapy as first line treatment has already failed to control the tumor growth*
- *the high risk of brain radionecrosis that carries with cumulative radiation doses of the two treatments is unacceptable*

Possible mechanisms of resistance to radiation treatment in GBM



Normal tolerance of NCS to conventional RT



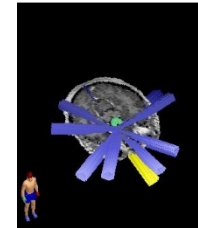
- *optic nerve (55-60 Gy)*
- *optic chiasm (55 Gy)*
- *brainstem (63 Gy/ 54Gy)*
- *lens (8-10 Gy)*
- *temporal lobe (30-40 Gy)*
- *Hyppocampus (?)*

Reirradiation of malignant gliomas

- *Conventional radiotherapy*
- *Stereotactic conformal fractionated radiotherapy*
- *Radiosurgery*



Brain tumors reirradiation in GBMs



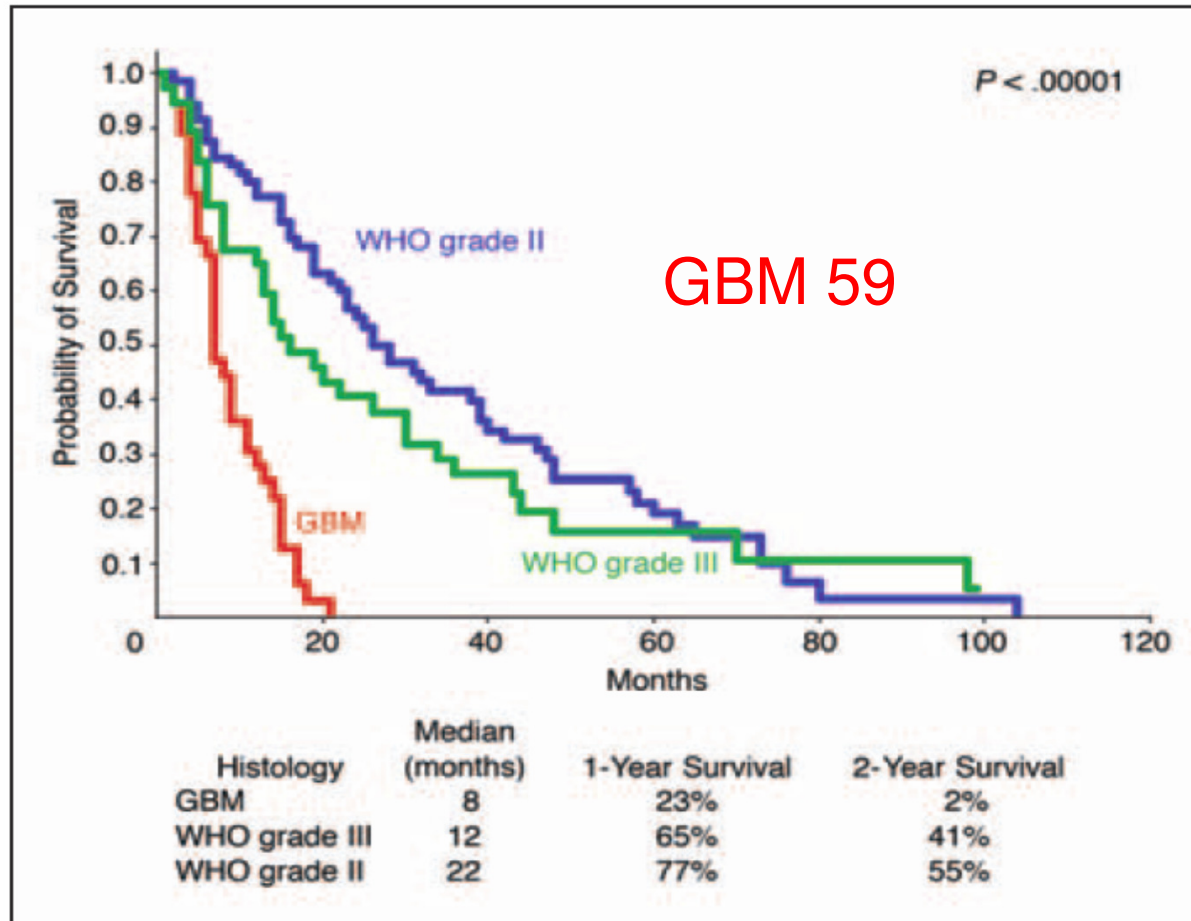
➤ FSRT

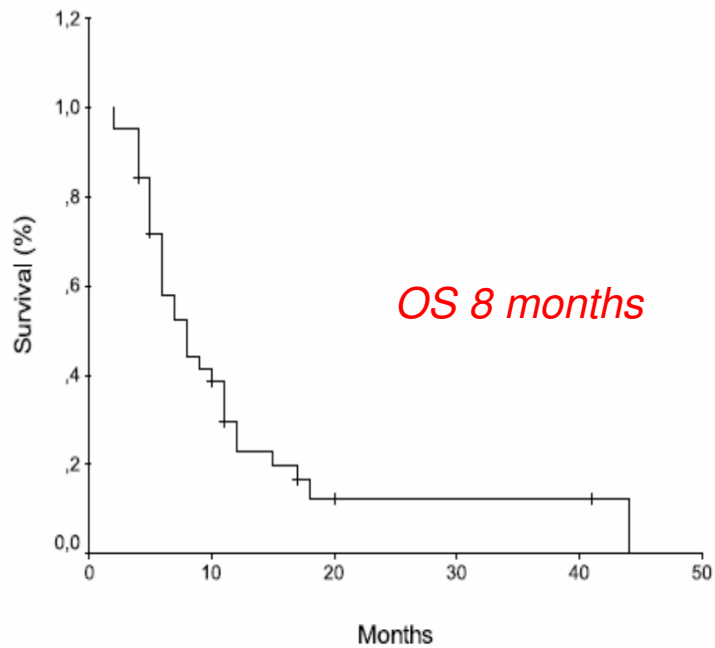
Author	Pts Number	Interval (months)	Dose (Gy)	Volume (cc)	Cumulative BED	OS months	Toxicity
Combs (2005)	42 Gr.III	34.5	36 Gy	56.2	190.8	16	Not severe
	59 GBM	10		49	186	8	
Grosu (2005)	44 (Grade III/IV)	16	30 Gy	18	219-255	8	13%
Combs (2008)	25 *	36	36 Gy **	50	192	8	Not severe
Cho (1999)	25 (Grade III/IV)	19	37,5 Gy	25	198.4	12	4%

*8 GBM, 10 grade III, 7 low grade

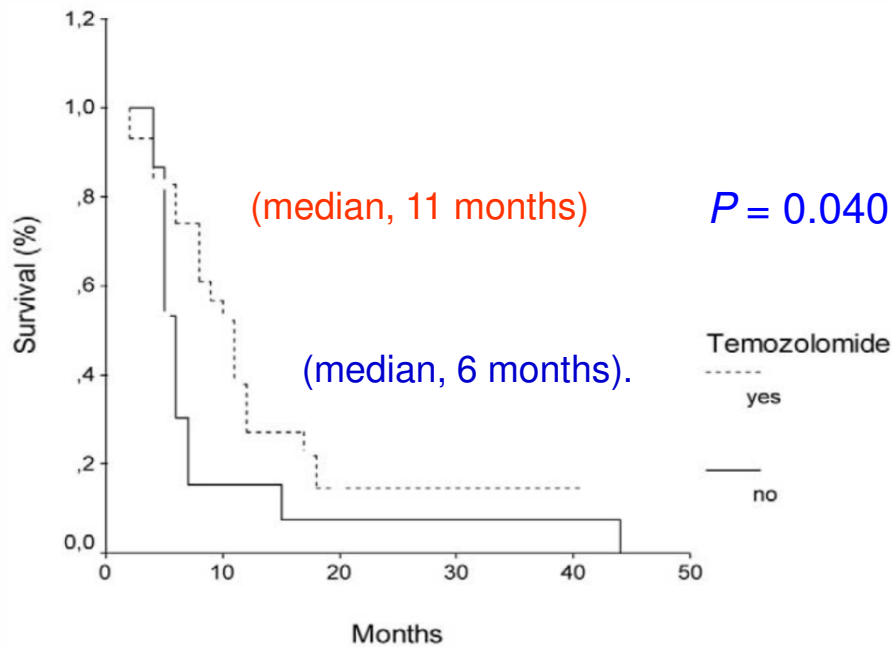
**concomitant temozolomide chemotherapy

Survival after reirradiation of 172 patients treated with FSRT





Kaplan-Meier survival curve for 44 patients with recurrent high-grade glioma treated with fractionated stereotactic RT and TMZ

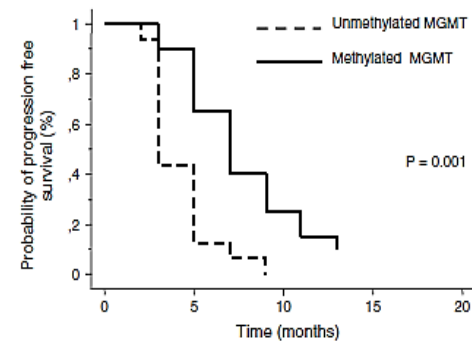
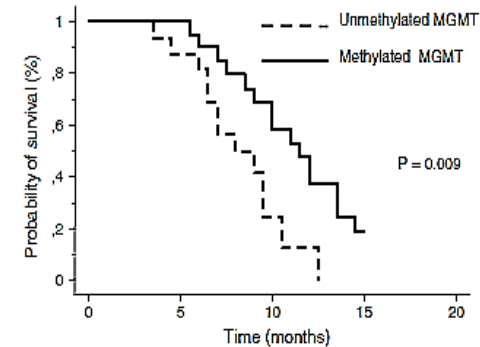
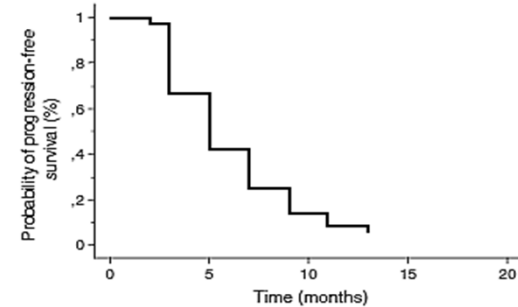
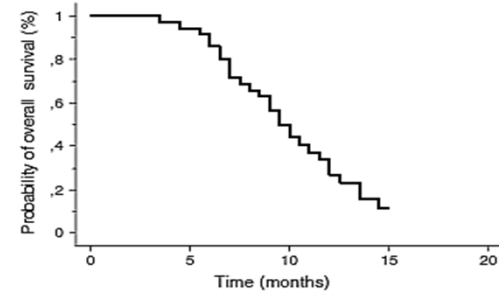


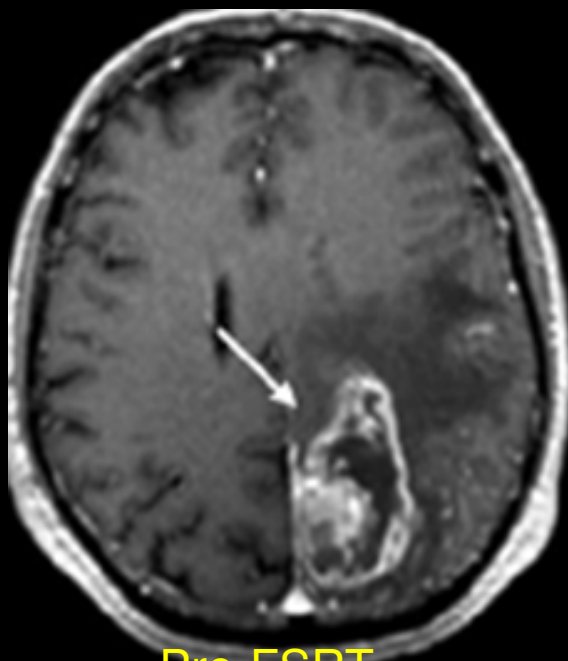
Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma

G. Minniti · V. Armosini · M. Salvati ·
 G. Lanzetta · P. Caporello · M. Mei ·
 M. F. Osti · R. Enrici Maurizi

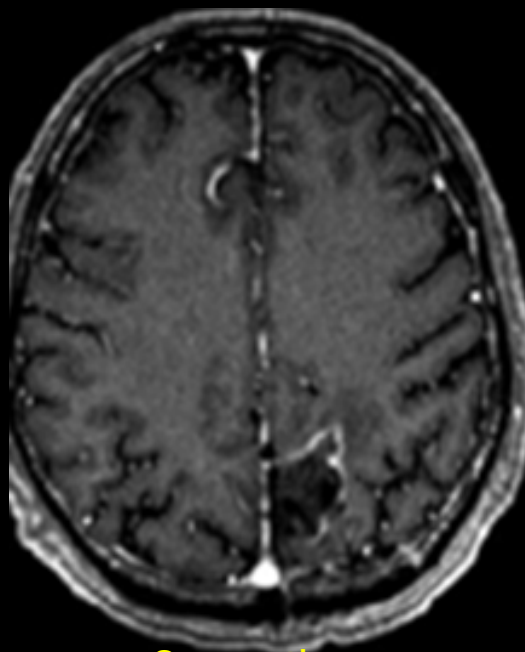
Table 1 Characteristics of 36 patients with recurrent glioblastoma

Characteristics	
Age (years)	
Median	56
Range	34–72
Sex	
Male	22
Female	14
Karnofsky performance status	
Median	70
Range	60–100
Site of tumor	
Temporal	11
Frontal	12
Parietal	7
Occipital	6
Extension of resection	
Total	17
Partial/subtotal	19
MGMT methylation status	
Methylated	20
Unmethylated	16
Number of cycles with temozolomide	
6 cycles	29
12 cycles	7
Interval between primary radiation and reirradiation	
Median (months)	14
Range (months)	9–39
Recurrence volume (cm³)	
Median	13.1
Range 2	1–35.3
Planning target volume (cm³)	
Median	32.1
Range	12.3–72.4

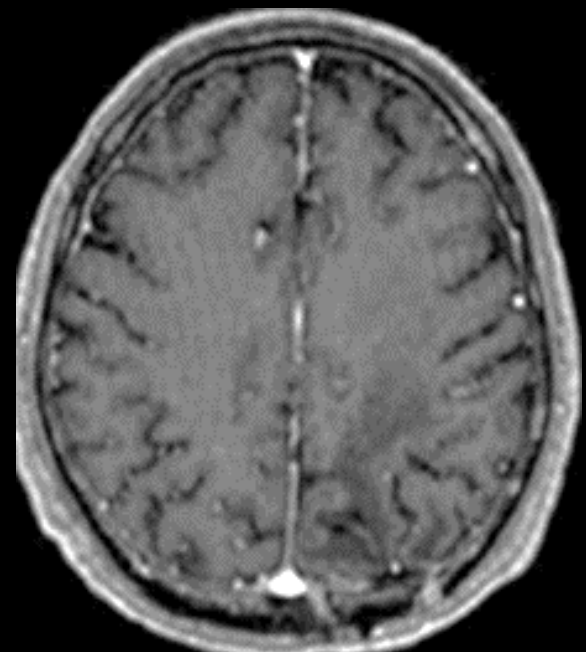




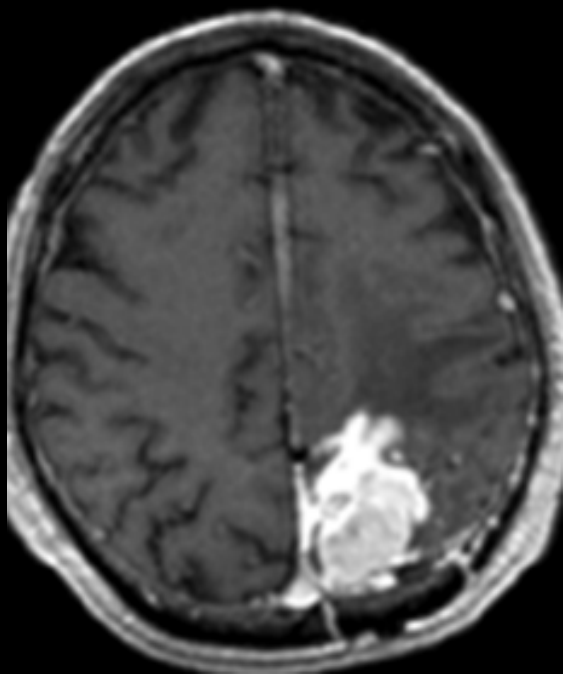
Pre-FSRT



3 months

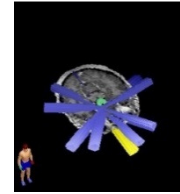


6 months



Recurrent GBM

✓ Brain tumors reirradiation in GBMs



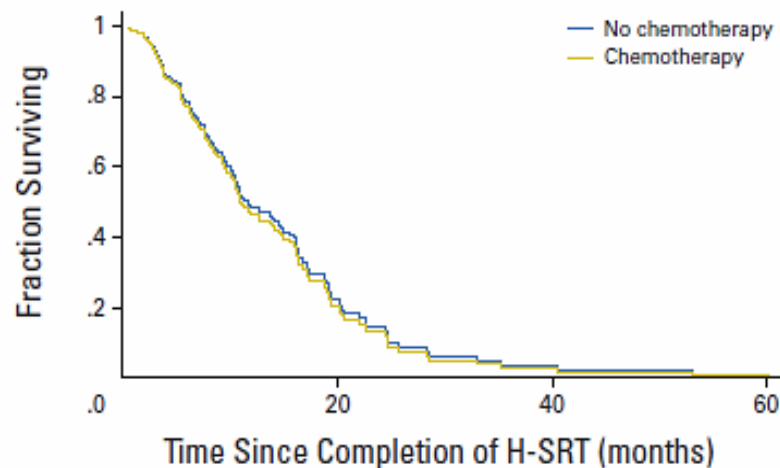
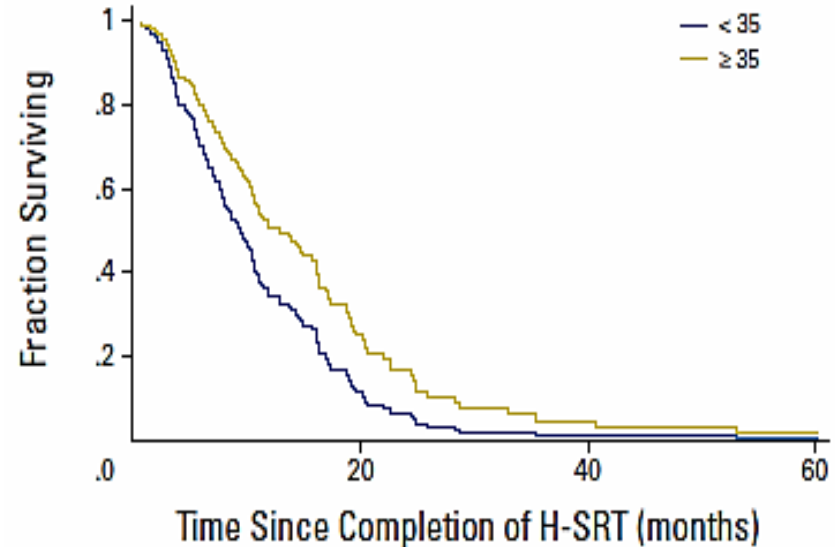
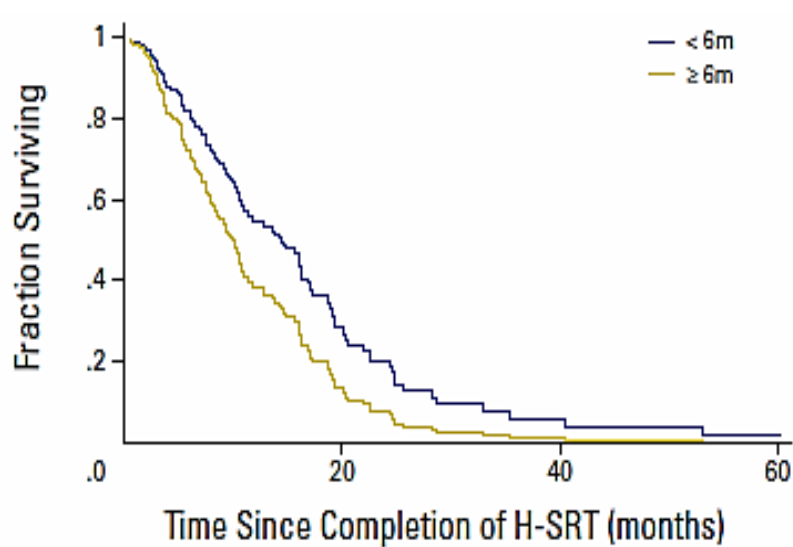
➤ HSRT

Author	Pts GBM	Interval months	Dose (Gy)	Volume (cc)	Cumulative BED	OS months	Toxicity
Shepherd (1997)	36 *	29	20-50	24	226.8	11	12 %
Selch (2000)	21 (Grade III/IV)	20	25	12	207.5	6	Not severe
Lederman (1998)	14	6.3	24	32.7	210	14.2	8%
Hudes (1999)	20	3	24-35	13	210	10.5	Not severe

*32 grade III/IV

Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas

Shannon E. Fogh, David W. Andrews, Jon Glass, Walter Curran, Charles Glass, Colin Champ, James J. Evans, Terry Hyslop, Edward Pequignot, Beverly Downes, Eileen Comber, Mitchell Maltenfort, Adam P. Dicker, and Maria Werner-Wasik

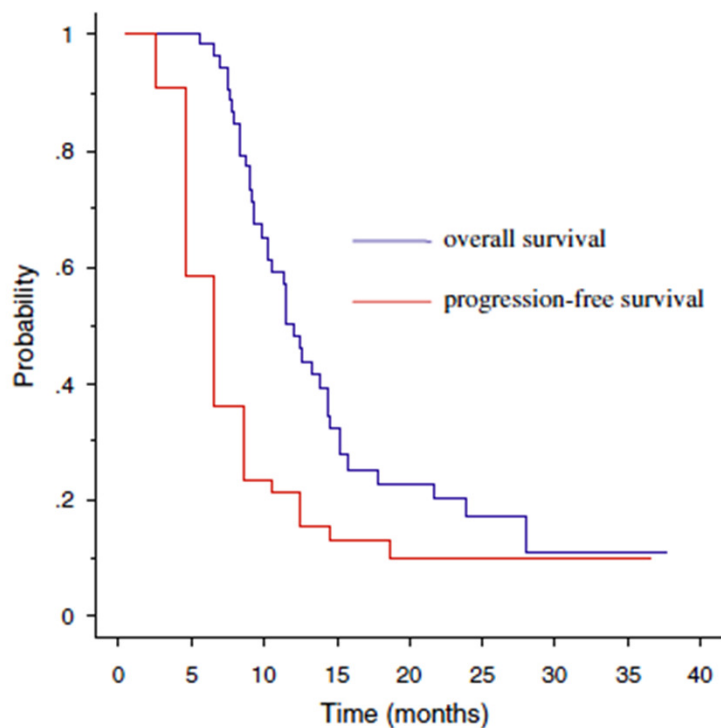


147 pts
35 Gy in 10 fractions

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

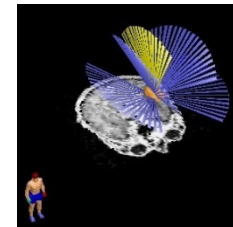
Giuseppe Minniti · Claudia Scaringi · Vitaliana De Sanctis · Gaetano Lanzetta · Teresa Falco · Domenica Di Stefano · Vincenzo esposito · Riccardo Maurizi Enrici

Characteristic	
Age (years)	
Median	52
Range	30–72
Sex	
Male	32
Female	22
WHO grade	
III	16
IV	38
Karnofsky performance status (KPS)	
Median	80
Range	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 (months)	15.5
Range (months)	6–108
Salvage chemotherapy before reirradiation	
Yes	4
No	50
Recurrence volume (cm ³)	
Median	9.7
Range	3.1–32.3
Planning target volume volume (cm ³)	
Median	30.3
Range	12.3–53.4



Factor	Hazard ratio (95 % CI)	P 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

Brain tumors reirradiation in GBMs




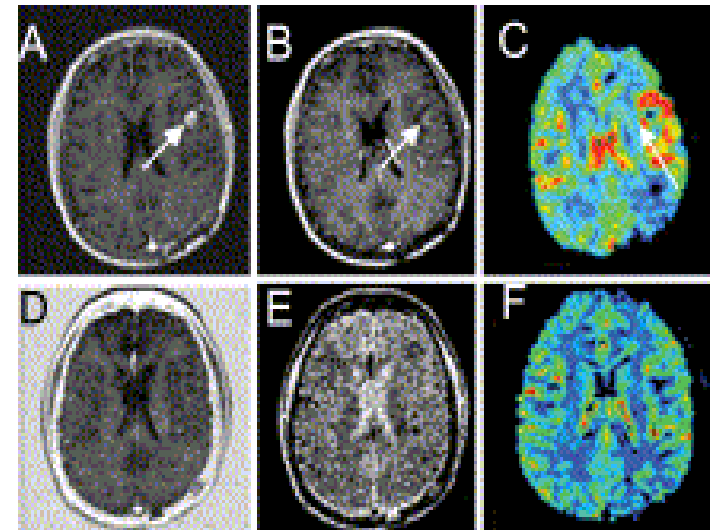
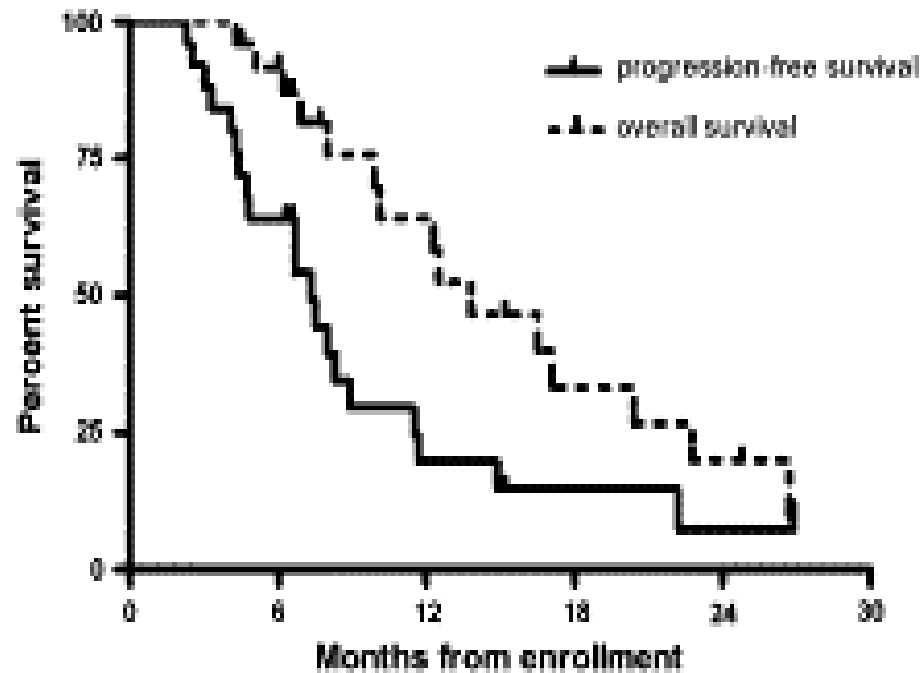
➤ Radiosurgery

Author	Pts (n)	Interval months	Dose (Gy)	Volume (cc)	Cumulative BED	OS months	Toxicity
Kong (2008)	49 (Gr. III)	11.0	16 Gy	10.6	266	26	24.4 %
	65 (GBM)	4.3				13	
Combs (2005)	32 GBM	10	15 Gy	10	235.5	10	0%
Cho (1999)	46 (Grade III/IV)	10	17 Gy	30	274.4	11	17%

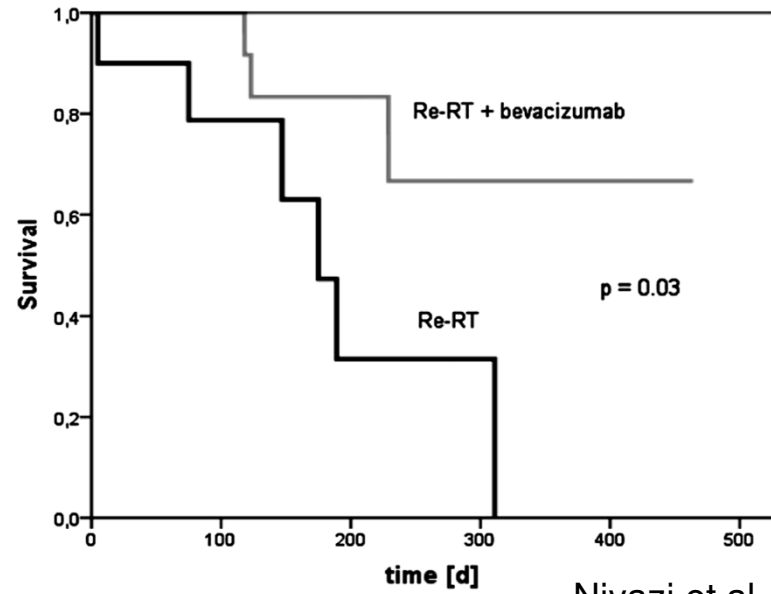
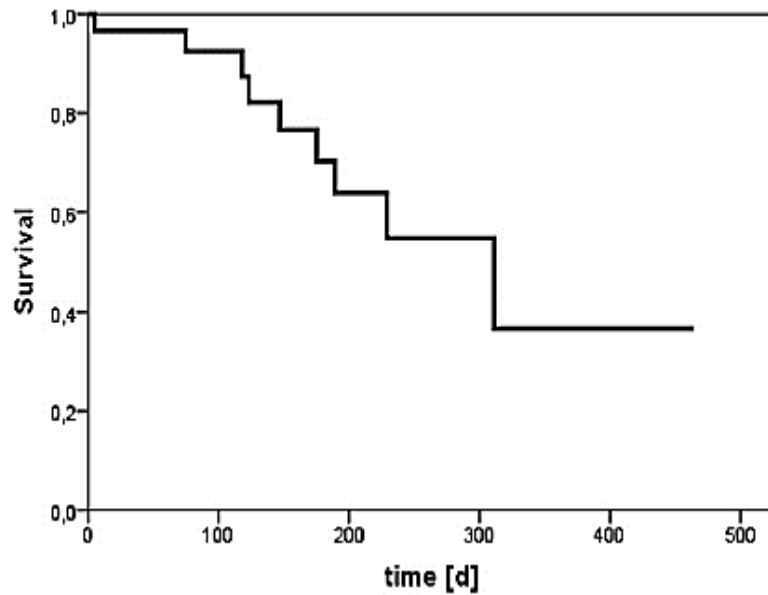
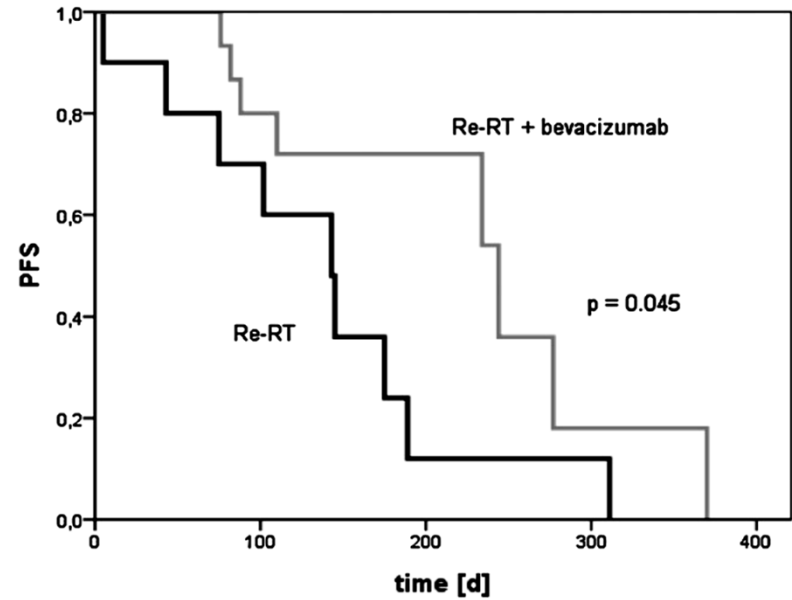
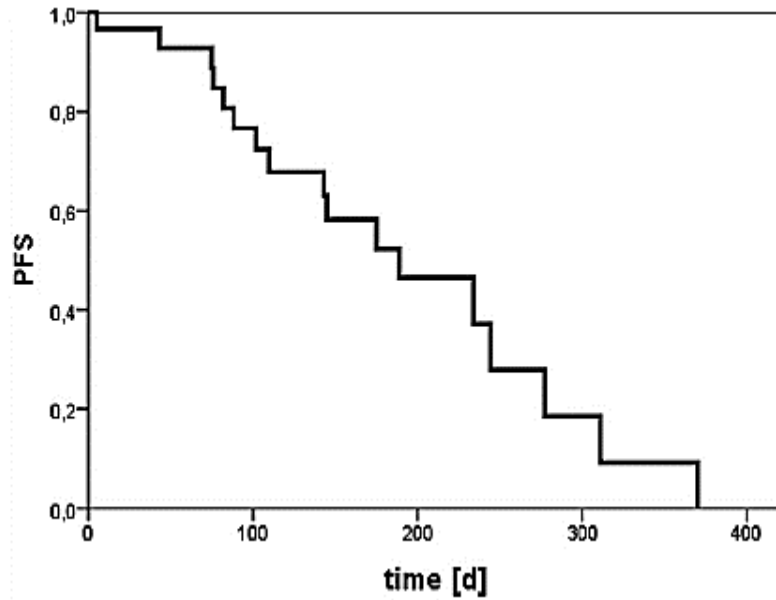
Clinical Investigation

Safety and Efficacy of Bevacizumab With Hypofractionated Stereotactic Irradiation for Recurrent Malignant Gliomas

Philip H. Gutin, M.D.^{*,†,††},  Fabio M. Iwamoto, M.D.^{*,‡}, Kathryn Beal, M.D.^{*,¶}, Nimish A. Mohile, M.D.[‡], Sasan Karimi, M.D.^{*,§}, Bob L. Hou, Ph.D.^{*,§,¶¶}, Stella Lymberis, M.D.[¶], Yoshiya Yamada, M.D., FRCPC.^{*,¶}, Jenghwa Chang, Ph.D.[¶], Lauren E. Abrey, M.D.^{*,‡}





✓ **Recurrent gliomas:** 30 pts (FSRT reirradiation 36 Gy in 18 fr)

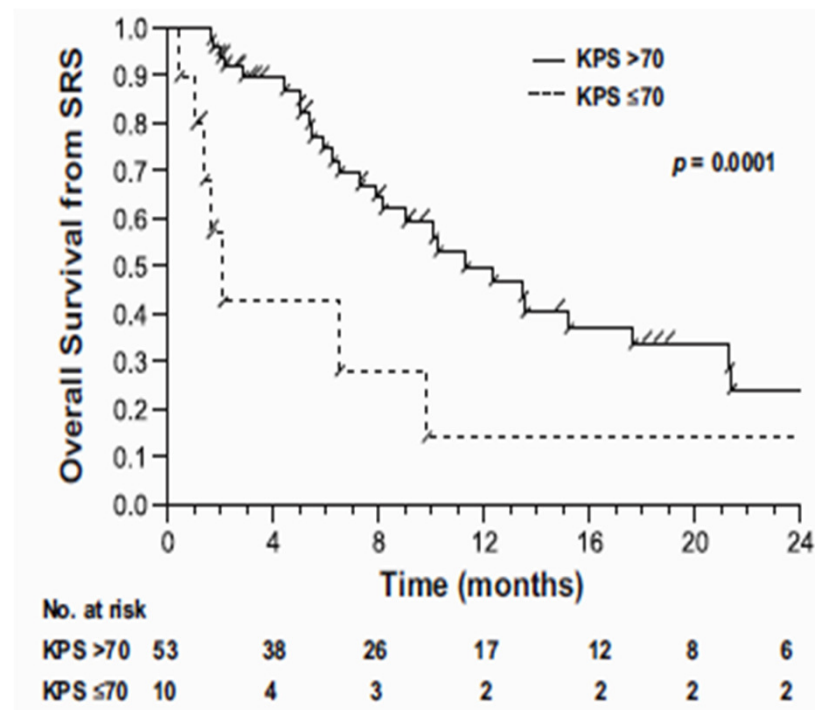
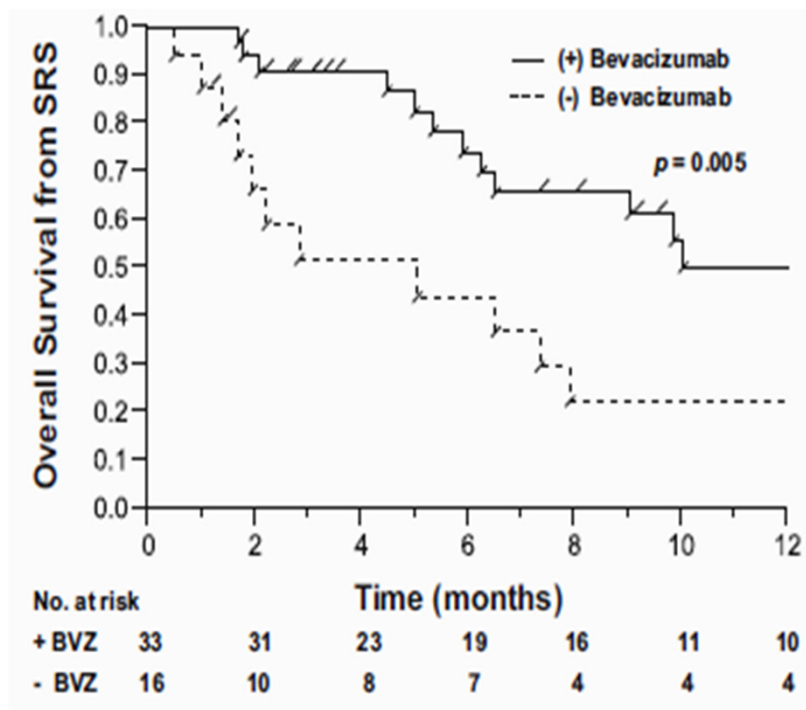


Clinical Investigation

Safety and Efficacy of Stereotactic Radiosurgery and Adjuvant Bevacizumab in Patients With Recurrent Malignant Gliomas

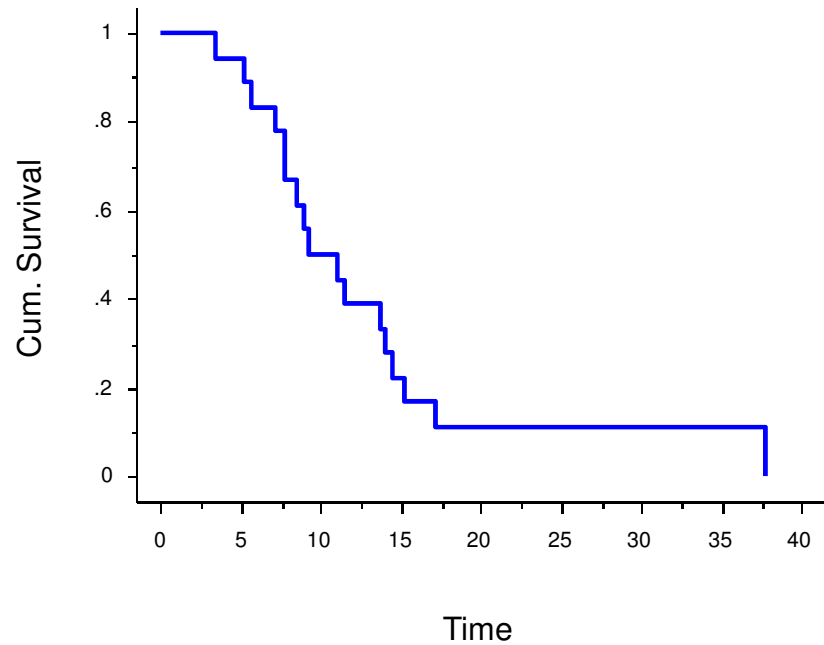
Presented at the 51st Annual Meeting of the American Society for Radiation Oncology, Chicago, IL, November 1–5, 2009.

Kyle C. Cuneo, M.D.[†], James J. Vredenburg, M.D.^{†,‡}, John H. Sampson, M.D., Ph.D.^{†,‡}, David A. Reardon, M.D.^{†,‡}, Annick Desjardins, M.D.^{†,‡}, Katherine B. Peters, M.D., Ph.D.^{†,‡}, Henry S. Friedman, M.D.^{†,‡}, Christopher G. Willett, M.D.[†], John P. Kirkpatrick, M.D., Ph.D.^{†,‡}  

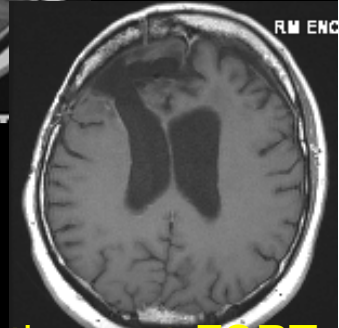
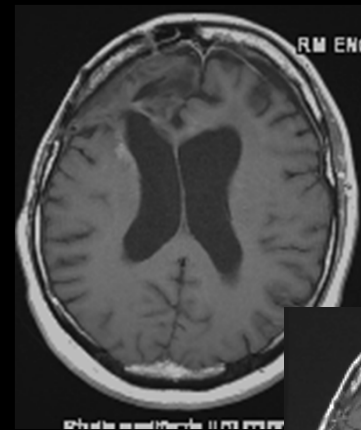
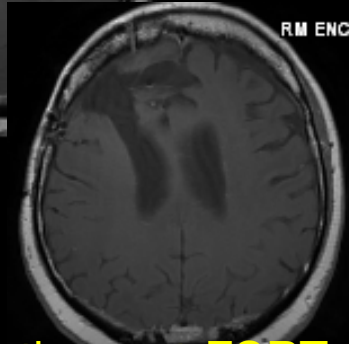
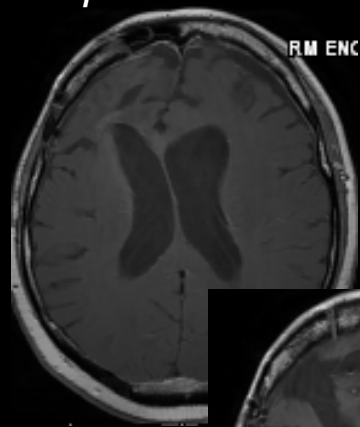
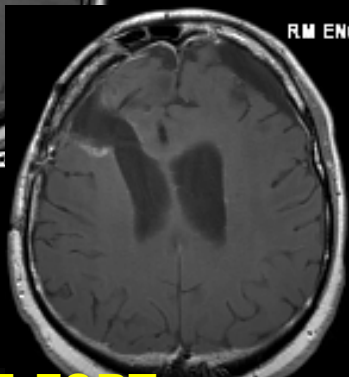
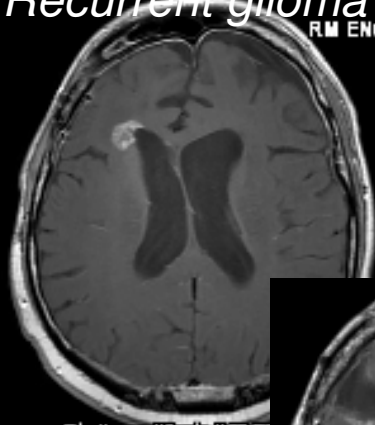


Reirradiation with bevacizumab in patients with progressive/recurrent high grade glioma treated at Sant'Andrea Hospital

SRT plus TMZ (42)
SRT plus bevacizumab (18)



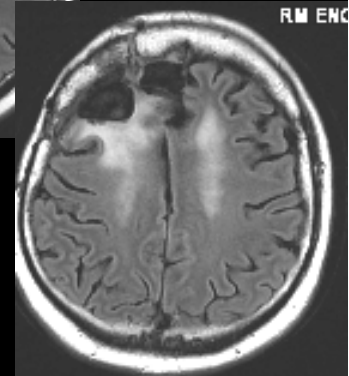
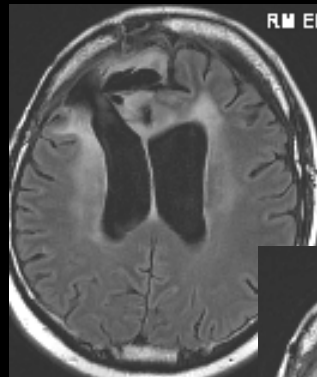
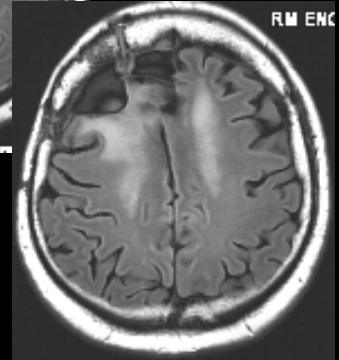
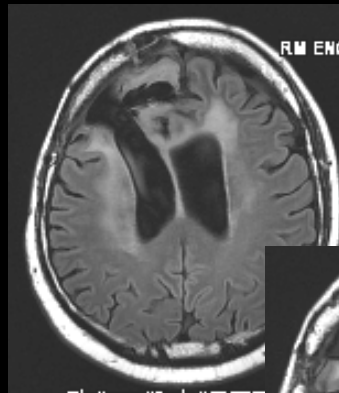
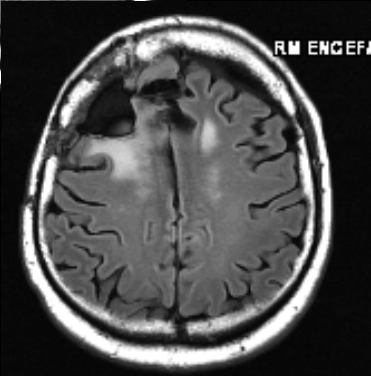
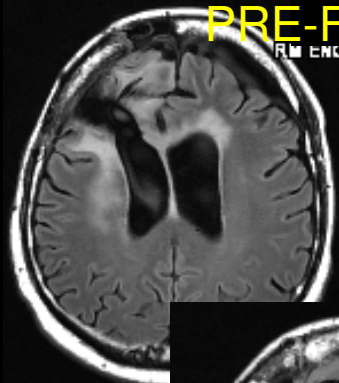
Recurrent glioma treated with FSRT plus bevacizumab



PRE-FSRT

12 months post-FSRT

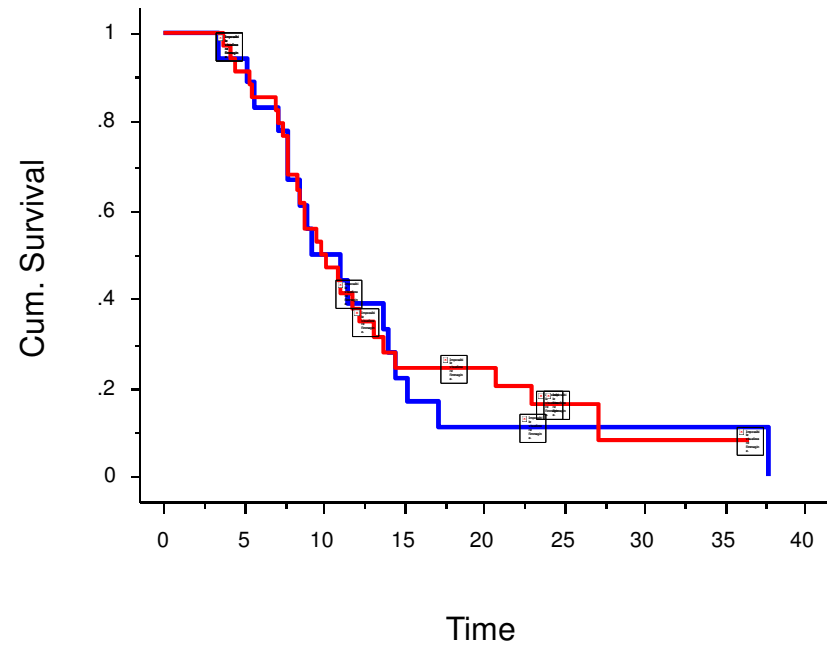
36 months post-FSRT



Reirradiation with and without bevacizumab in patients with progressive/recurrent high grade gliomas treated at Sant'Andrea Hospital

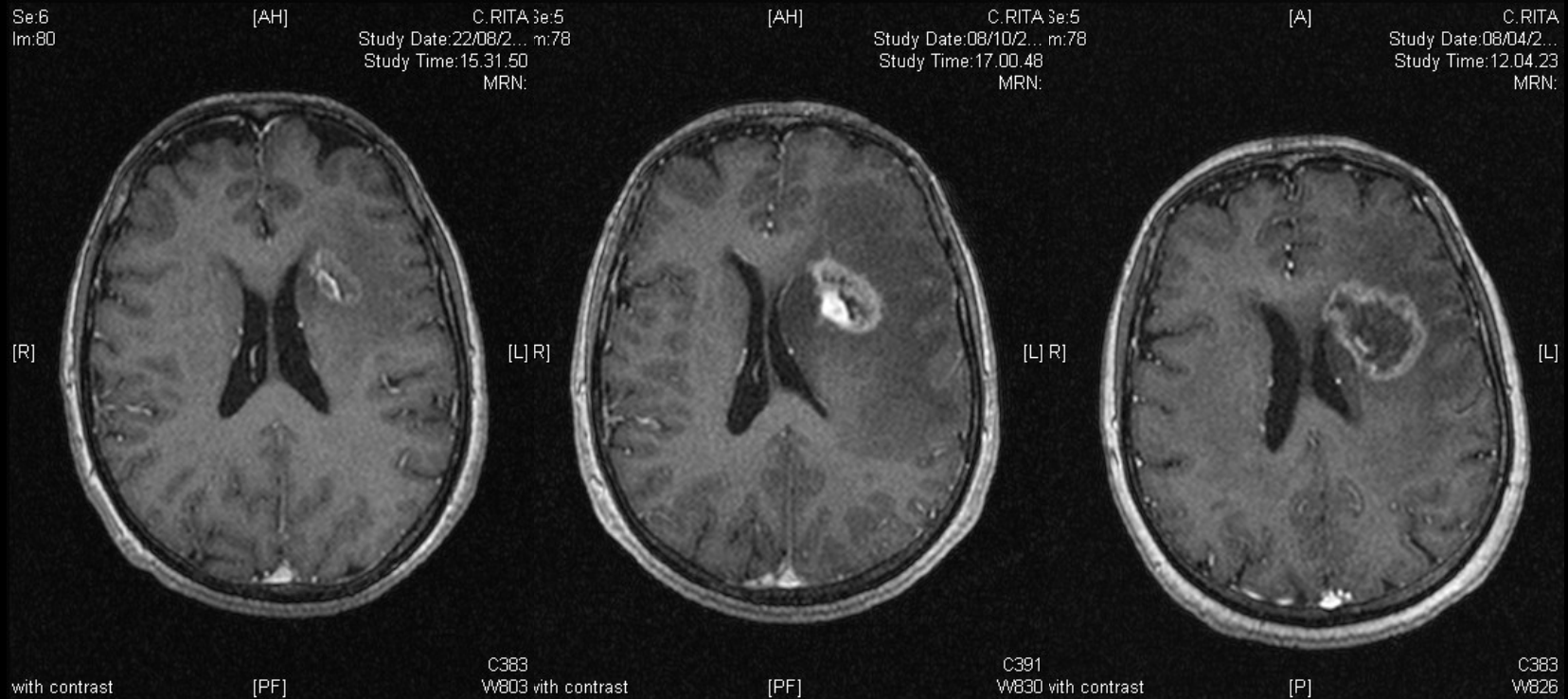
SRT plus bevacizumab (18)

SRT plus TMZ (42)

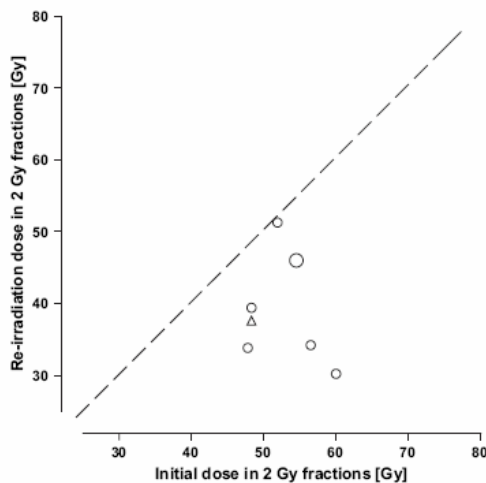


— Cum. Survival (BEVA)
— Cum. Survival (TMZ)

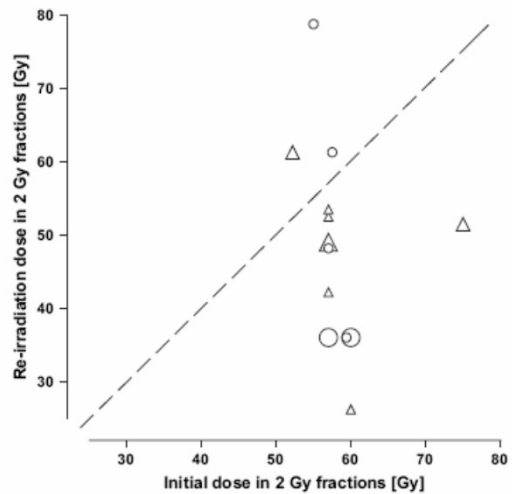
Radionecrosis after SRS in a GBM



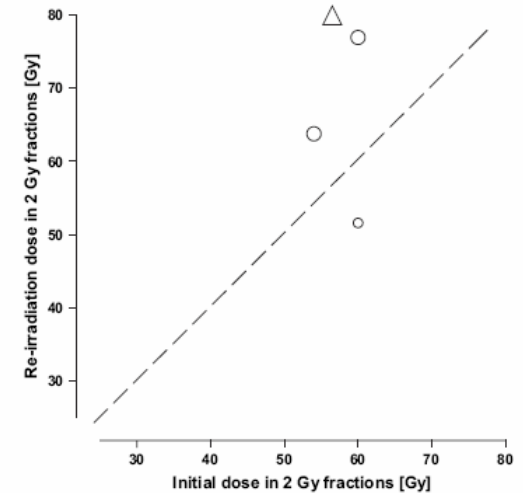
Correlation between the initial dose of the normalized total dose (NTD_{initial}) and the normalized total dose of reirradiation (NTD_{reirradiation}) in patients who underwent reirradiation



FSRT



HSRT



SRS



no brain necrosis



patient(s) with radionecrosis in the study

small symbols indicate <25 patients

medium symbols 26 to 50 patients

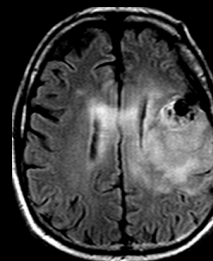
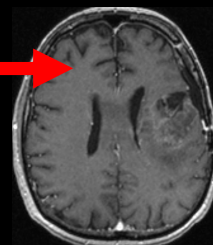
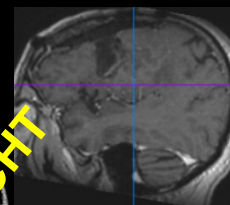
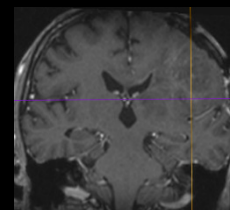
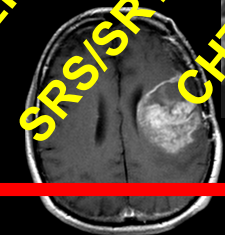
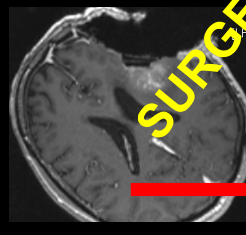
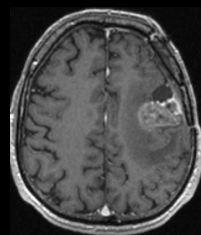
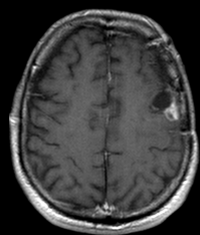
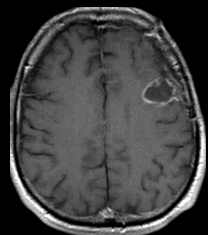
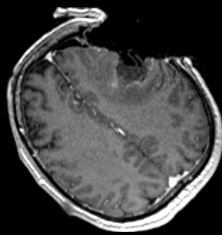
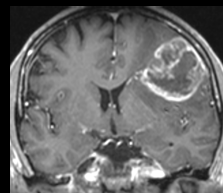
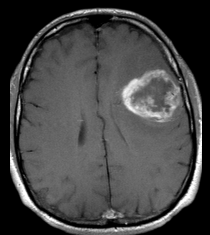
large symbols >50 patients

Diagnosis
2/2010

IMRT + TMZ
4/2010

Recurrent GBM
3/2011

SRT + Beva
6/2011



Surgery
3/2010

Adjuvant TMZ
6 cycles

2° Surgery
4/2011

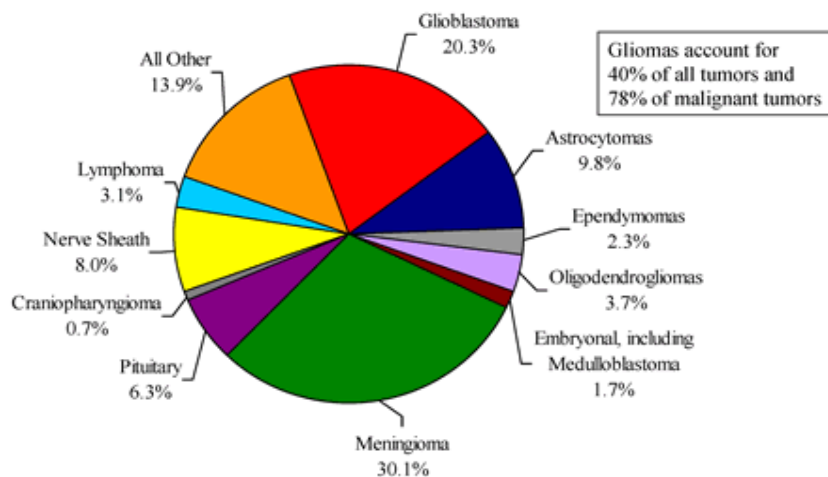
12/2011

(†1/2012)

man 47 years old, GBM

SURGERY
SRS/SRT
CHT

Summary



- *Reirradiation is a feasible option for patients with high grade gliomas;*
- *However results are modest; better with chemoradiation (bevacizumab, temozolomide?)*
- *Toxicity remains of concern for volumes > 35 ml in previously irradiated brain areas. A maximum cumulative BED of 200 is recommended.*

....thank you for your attention



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