

# *Reirradiazione dei tumori cerebrali*



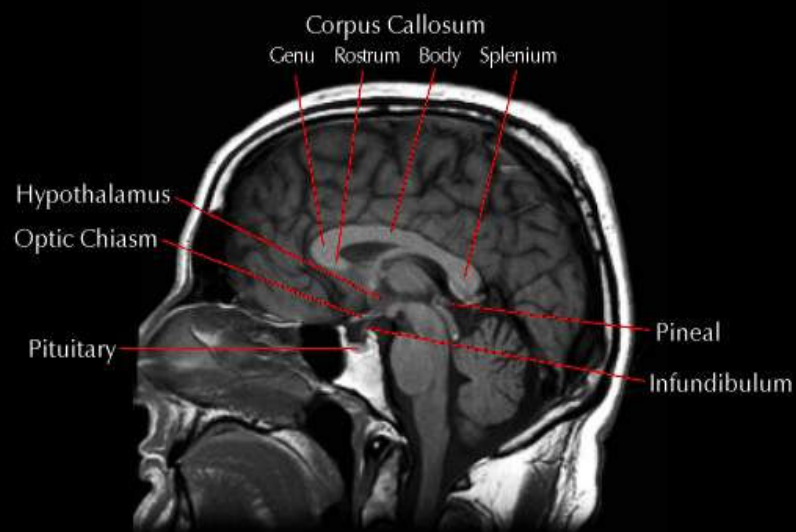
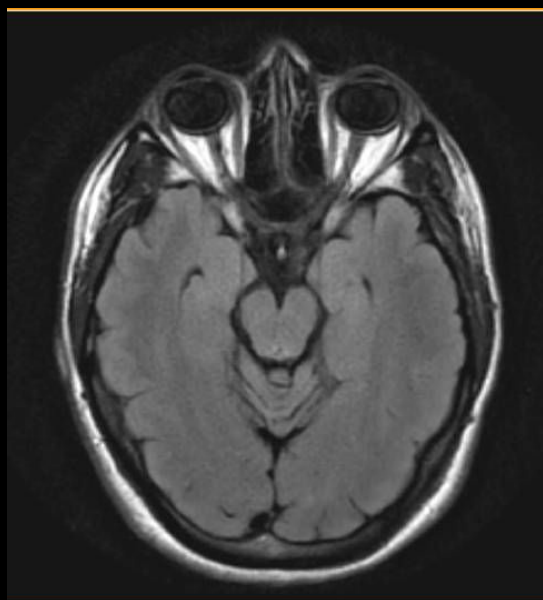
SAPIENZA  
UNIVERSITÀ DI ROMA

**Cattedra di Radioterapia**



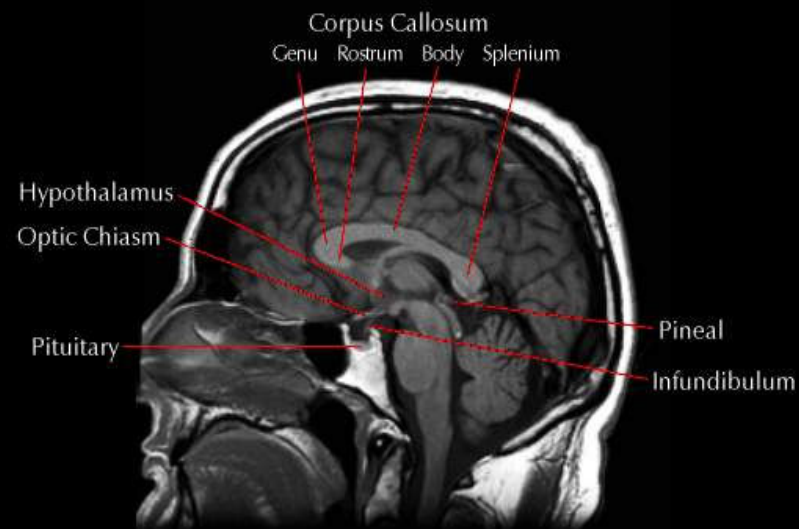
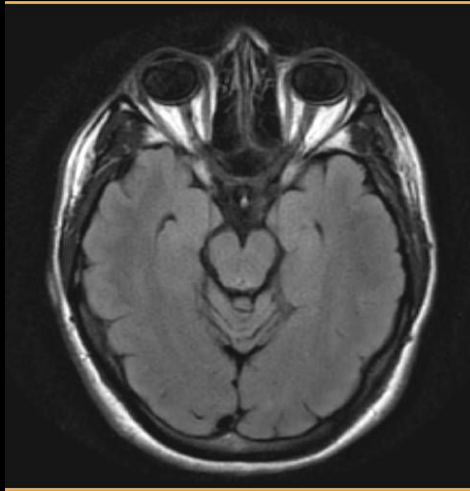
Roma, 17 Aprile 2012

## Normale tolleranza del SNC alla RT convenzionale



- Nervo ottico (55-60 Gy)
- Chiasma ottico (55 Gy)
- Tronco 63 Gy/ 54Gy
- Cristallino (8-10 Gy)
- Lobi temporali (30-40 Gy)
- ippocampo (?)

## Tolerance of brain structures to SRS



- Nervo ottico (12 Gy)
- Chiasma ottico (10 Gy)
- Tronco 12 - 15
- Normal brain (?)

# Reirradiation of malignant gliomas

## Conventional radiotherapy

- Stereotactic conformal fractionated radiotherapy
- radiosurgery



# Brain tumors reirradiation in GBMs

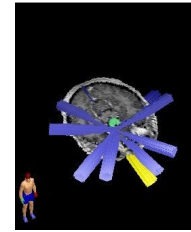


## Conventional RT

Author	Pts (n)	Interval months	Dose (Gy)	Cumulative BED	OS (months)	Toxicity
Veninga (2001)	29*	33	46	197.5	10.9	9%
Bauman (1996)	34**	16.3	30-40	160	8.3	29%

- \*10 GBM, 3 Grade III, 15 Grade II, 1 Grade I
- \*\*10 Grade III gliomas

# Brain tumors reirradiation in GBMs



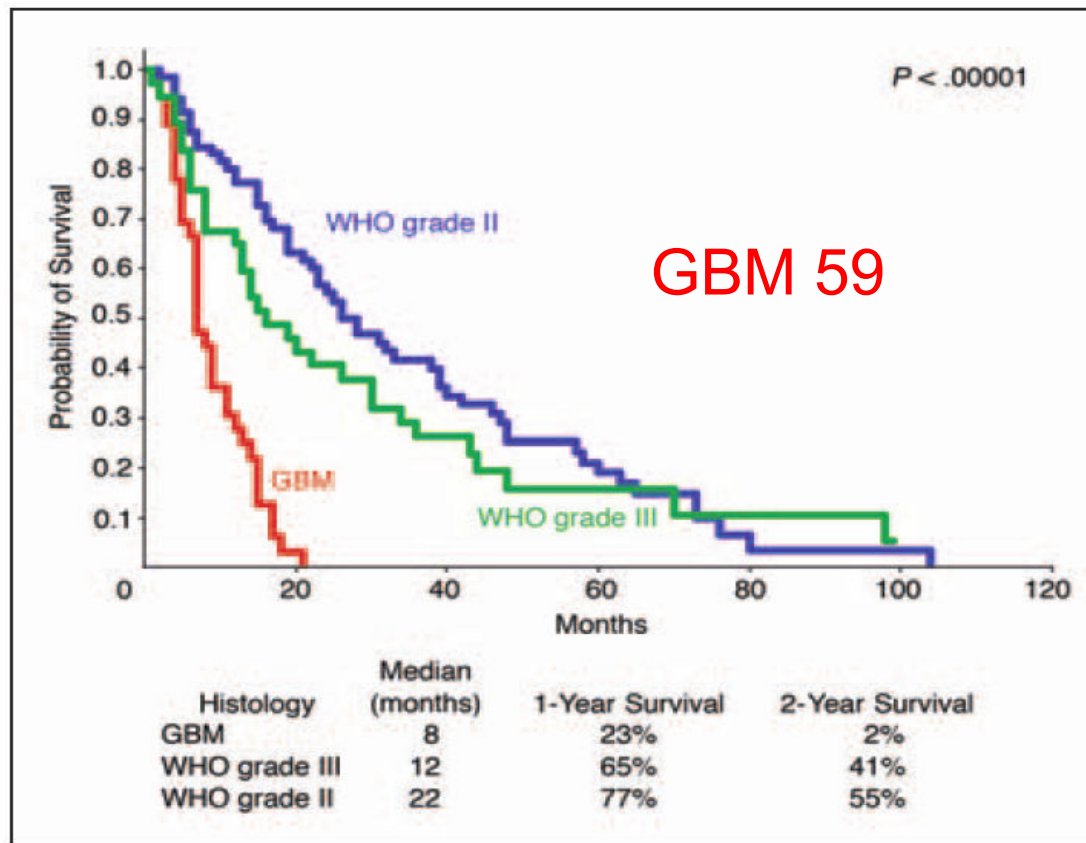
## FSRT

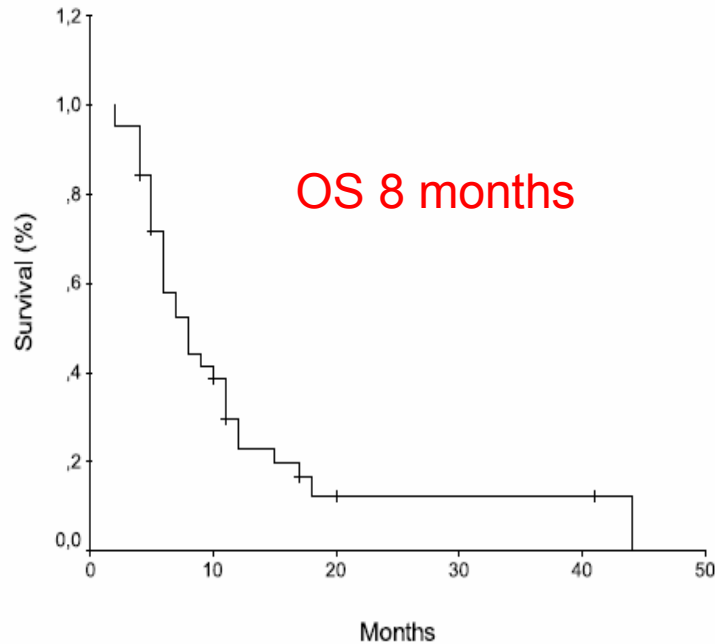
Author	Pts Number	Interval (months)	Dose (Gy)	Volume (cc)	Cumulative BED	OS months	Toxicity
Combs (2005)	42 Gr.III	34.5	36 Gy	56.2	190.8	16	Not severe
	59 GBM	10		49	186	8	
Grosu (2005)	44 (Grade III/IV)	16	30 Gy	18	219-255	8	13%
Combs (2008)	25 *	36	36 Gy **	50	192	8	Not severe
Cho (1999)	25 (Grade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

\*8 GBM, 10 grade III, 7 low grade

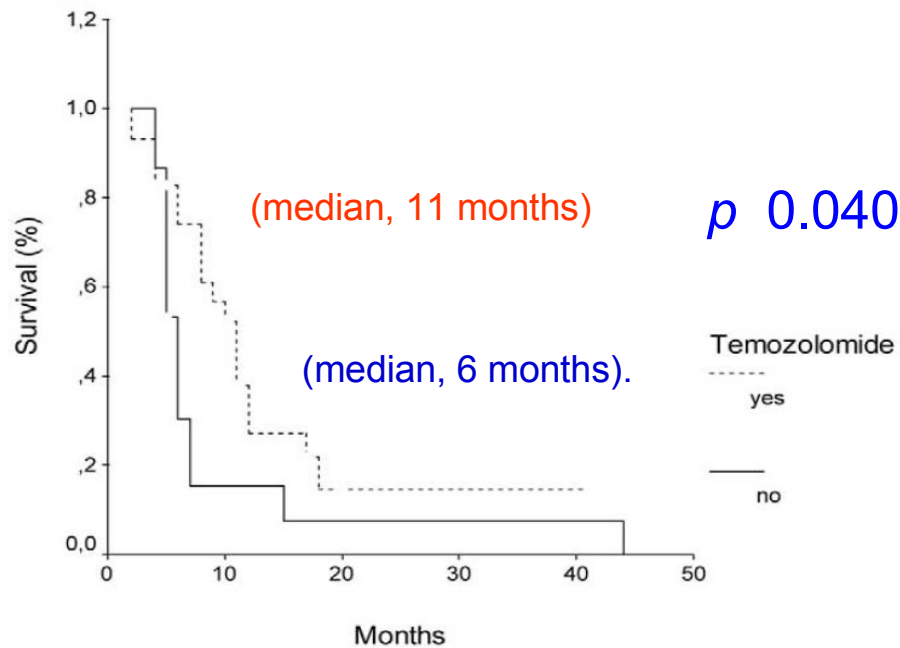
\*\*concomitant temozolomide chemotherapy

# Survival after reirradiation of 172 patients treated with FSRT

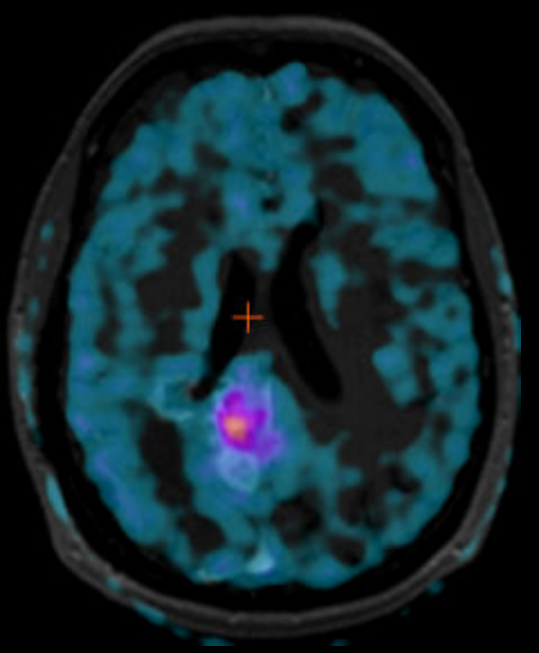
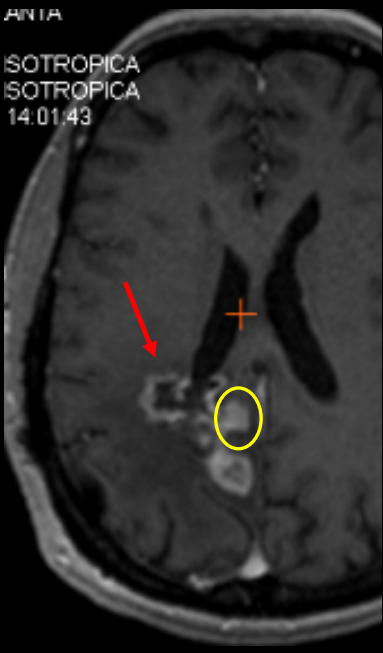
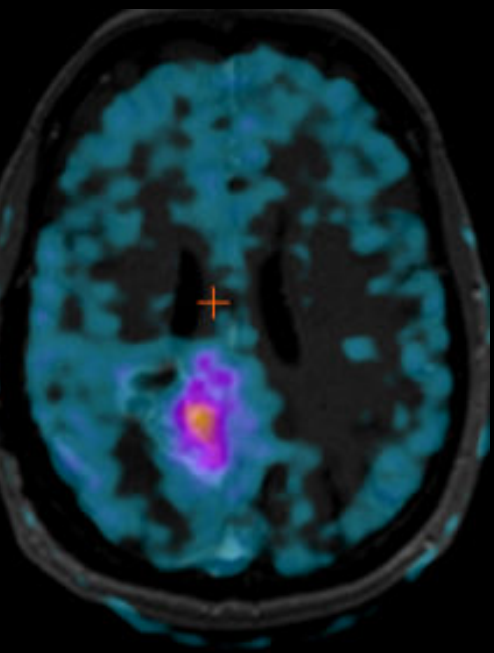
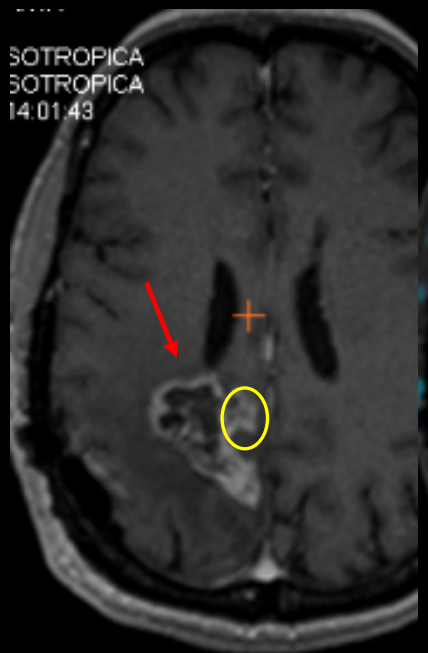
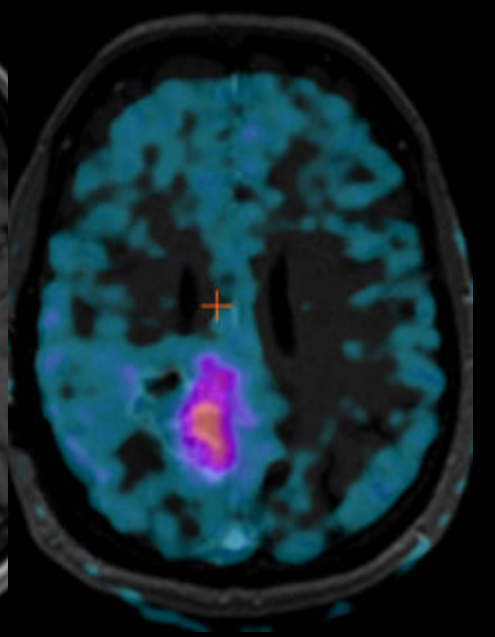
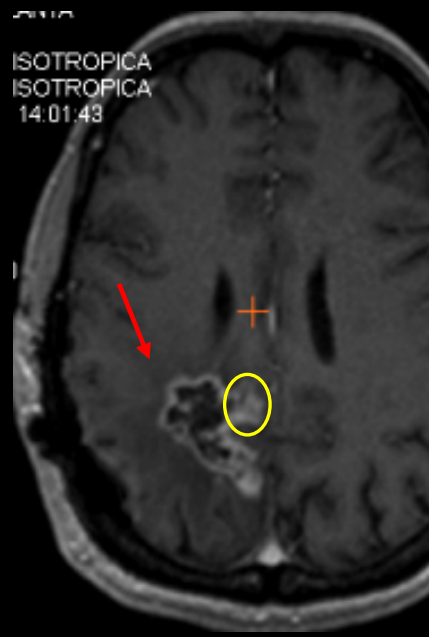
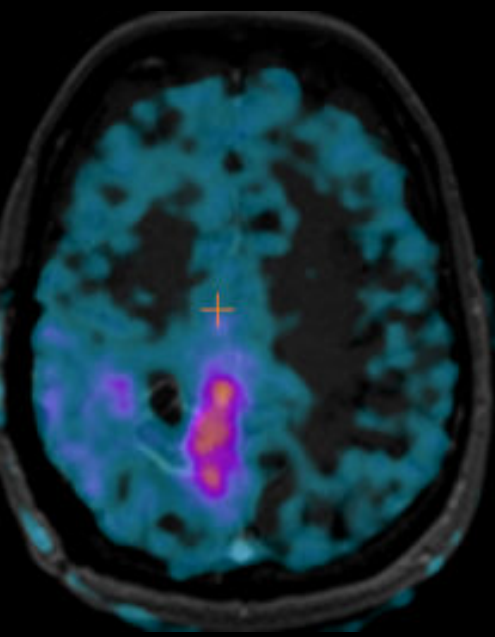
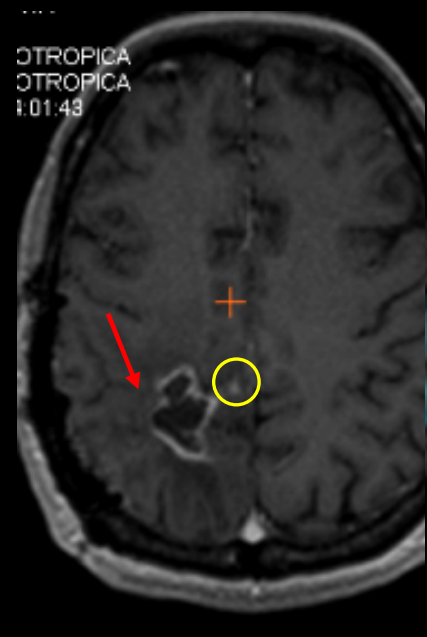




Kaplan-Meier survival curve for 44 patients with recurrent high-grade glioma treated with fractionated stereotactic RT and TMZ





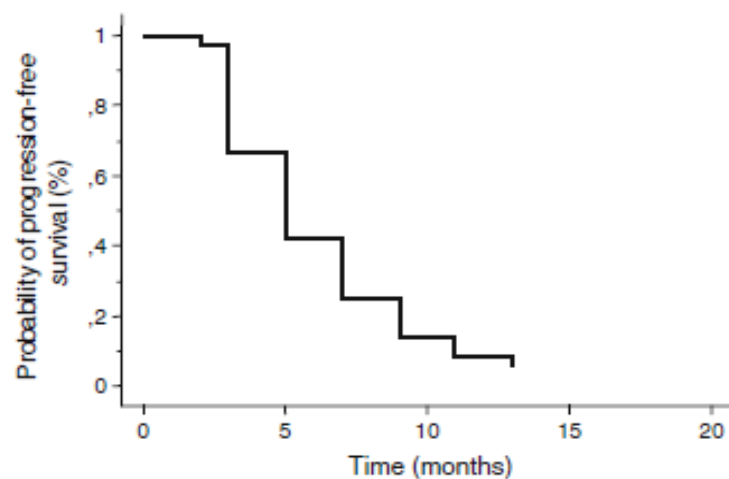
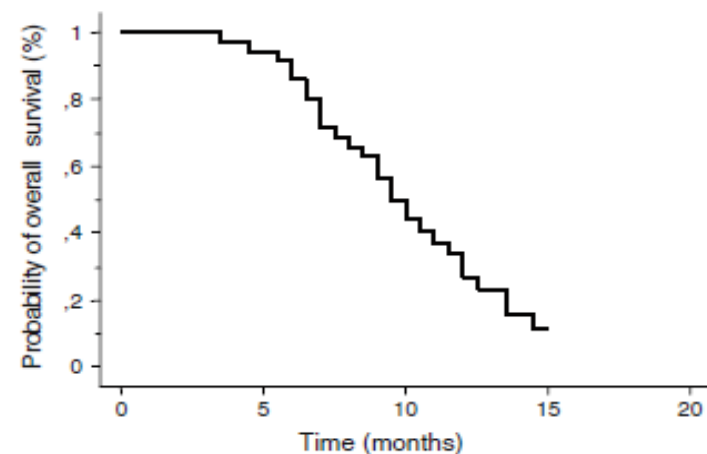


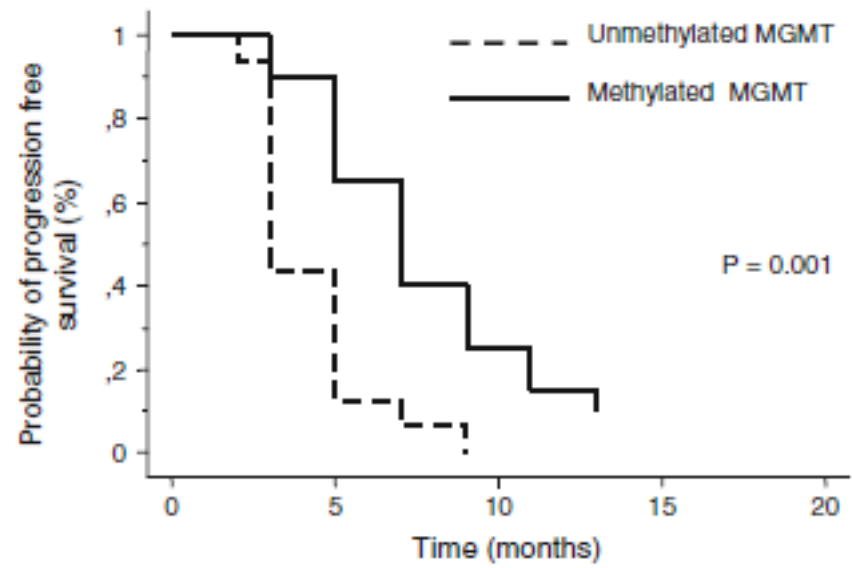
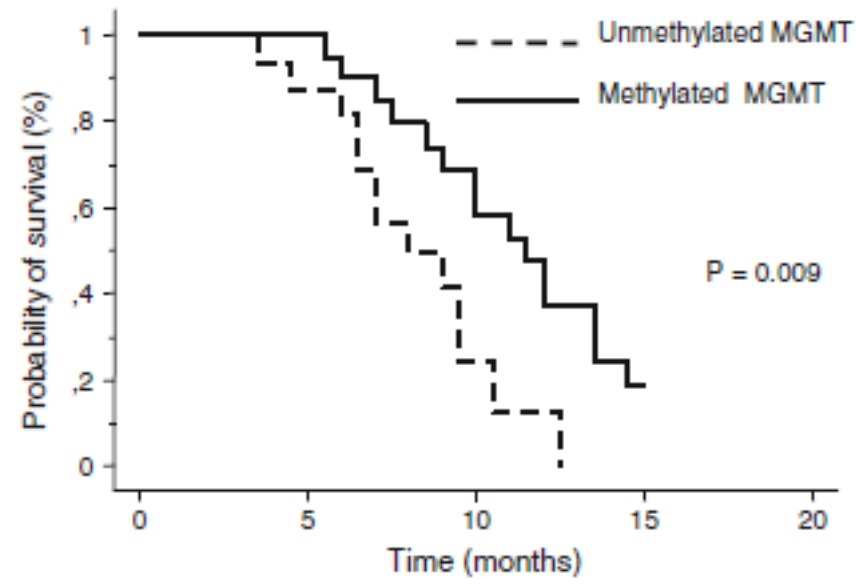
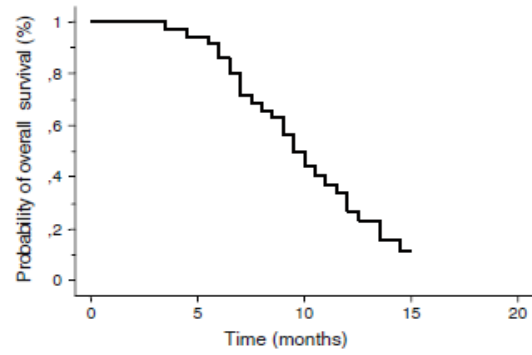
## Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma

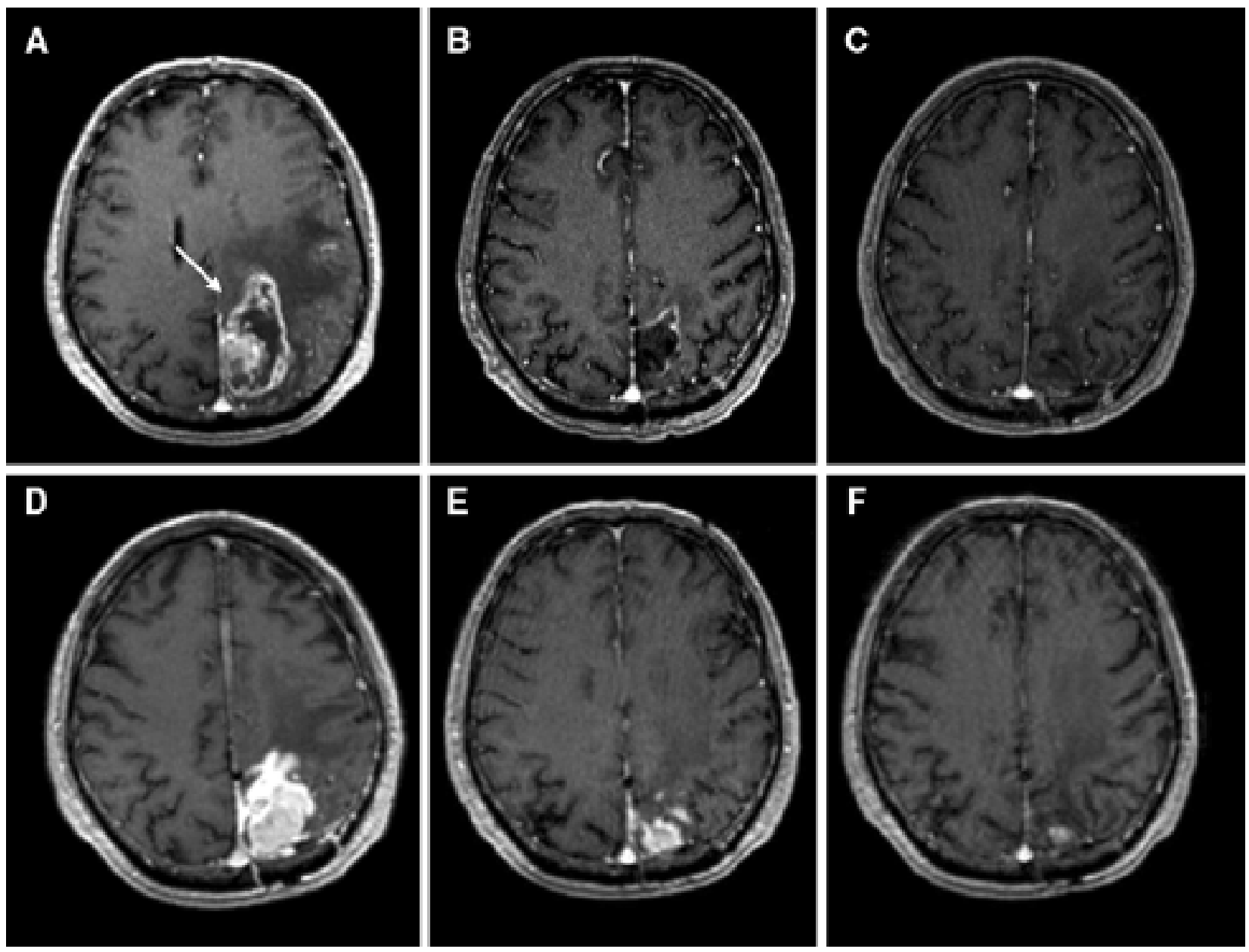
G. Minniti · V. Armosini · M. Salvati ·  
G. Lanzetta · P. Caporello · M. Mei ·  
M. F. Osti · R. Enrici Maurizi

**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 (cm <sup>3</sup> )	
Median	13.1
Range	1–35.3
Planning target volume (cm <sup>3</sup> )	
Median	32.1
Range	12.3–72.4





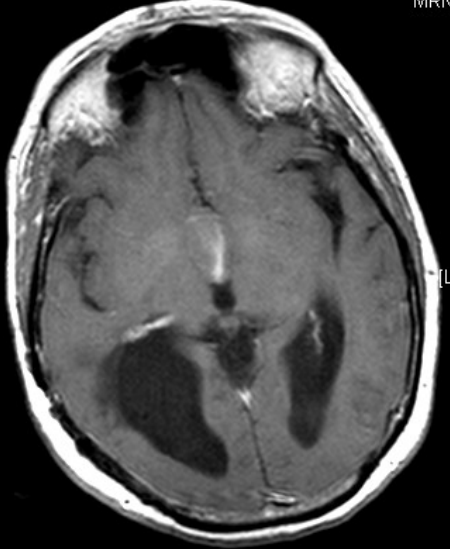


6 months post re-FSRT

Se:5  
Im:9

[AH]

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



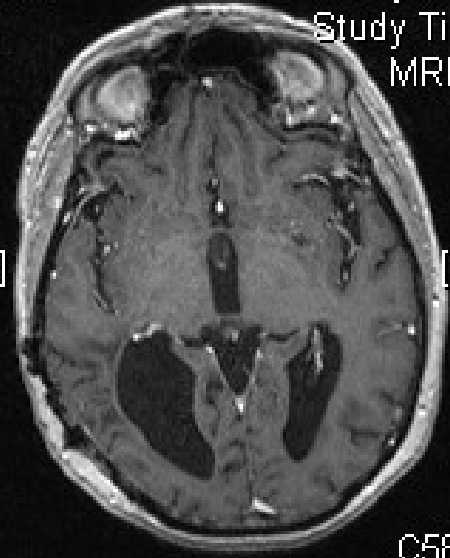
[R]

[L]

Se:5  
Im:61

[AH]

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



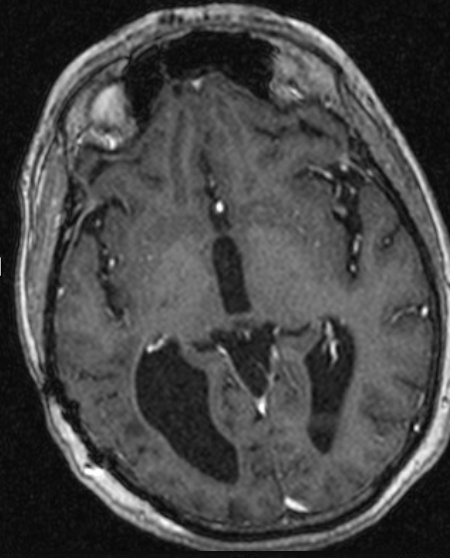
[R]

[L]

Se:7  
Im:62

[AH]

R.FRANCA  
Study Date:08/04/2...  
Study Time:14.32.13  
MRN:



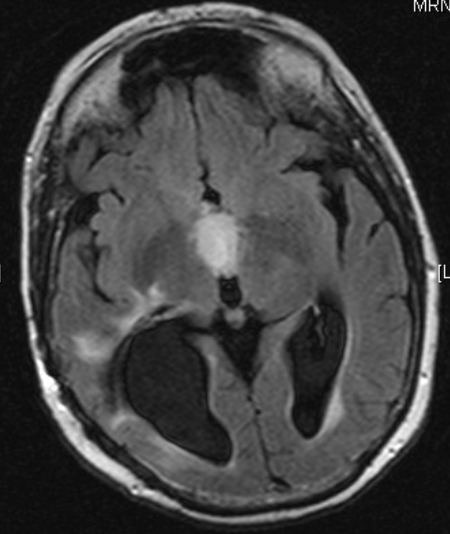
[RF]

[LH]

Se:2  
w/Im:9

[AH]

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



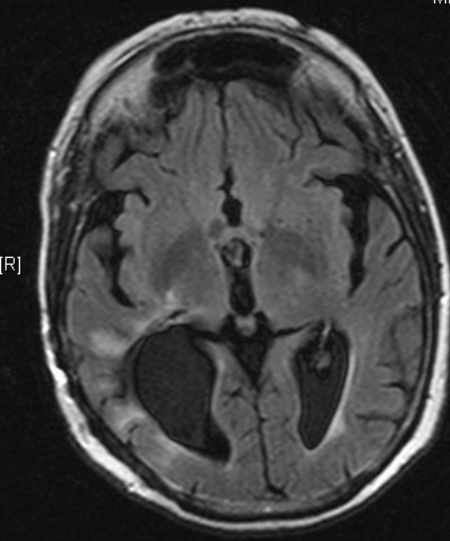
[R]

[L]

Se:2  
Im:9

[AH]

R.FRANCA  
Study Date:09/01/...  
Study Time:18.42.40  
MRN:



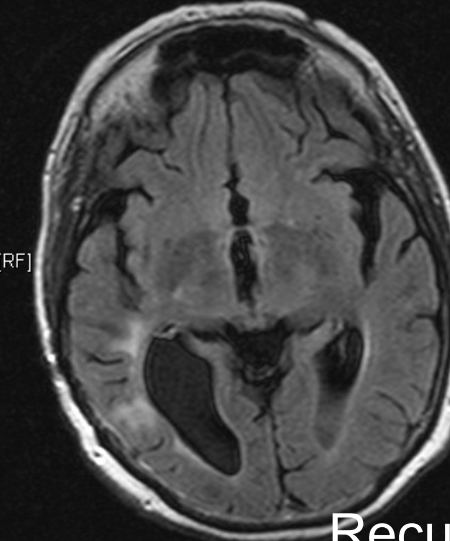
[R]

[L]

Se:2  
Im:10

[AH]

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



[RF]

[LH]

C582  
3 months

6 months

Recurrent GBM

C363  
W799

C348  
W775

C343  
W765

[PF]

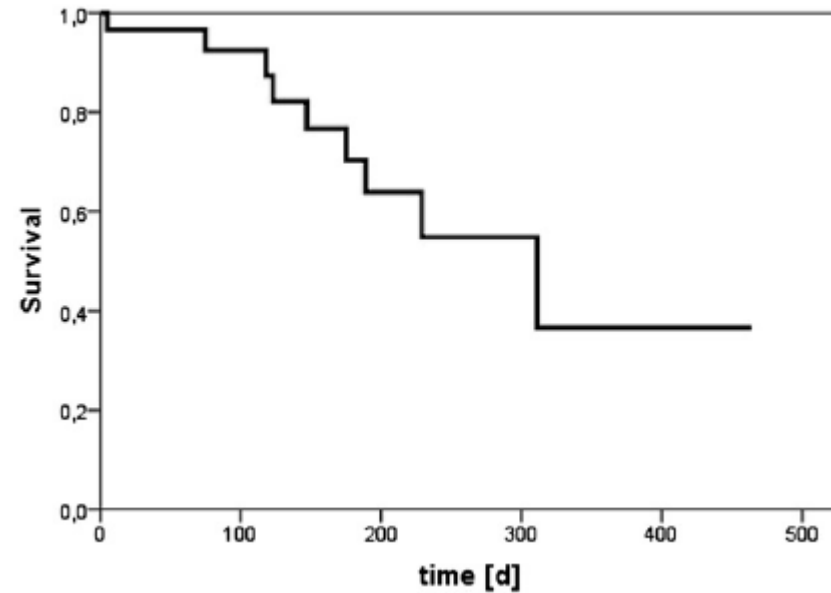
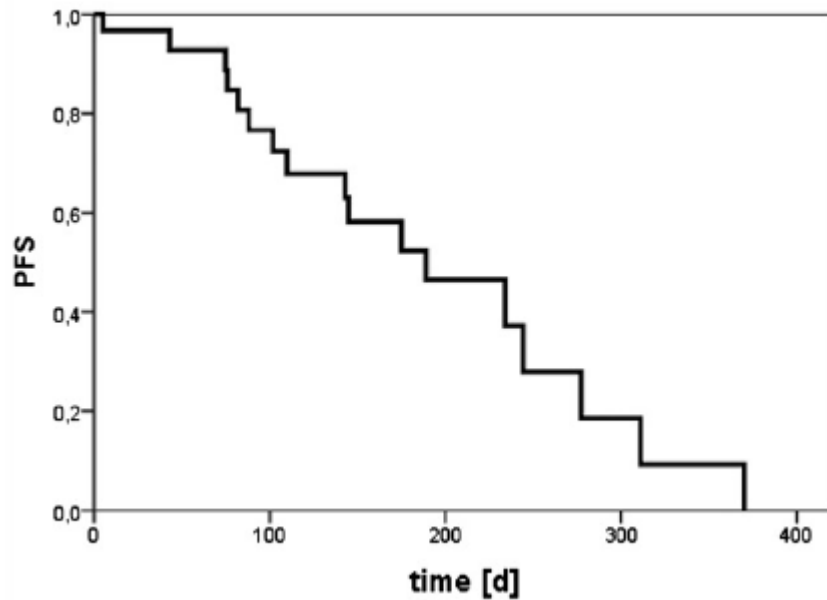
[PF]

[PF]

## IRRADIATION AND BEVACIZUMAB IN HIGH-GRADE GLIOMA RETREATMENT SETTINGS

MAXIMILIAN NIYAZI, M.D., M.Sc.,\* UTE GANSWINDT, M.D.,\* SILKE BIRGIT SCHWARZ, M.D.,\*  
FRIEDRICH-WILHELM KRETH, M.D., PH.D.,† JÖRG-CHRISTIAN TONN, M.D., PH.D.,† JULIA GEISLER, M.D.,‡  
CHRISTIAN LA FOUÛÈRE, M.D.,‡ LORENZ ERTL, M.D.,§ JENNIFER LINN, M.D.,§ AXEL SIEFERT, M.D.,\*  
AND CLAUS BELKA, M.D., PH.D.\*

Departments of \*Radiation Oncology, †Neurosurgery, ‡Nuclear Medicine, and §Neuroradiology, Ludwig-Maximilians-University  
Munich, Munich, Germany



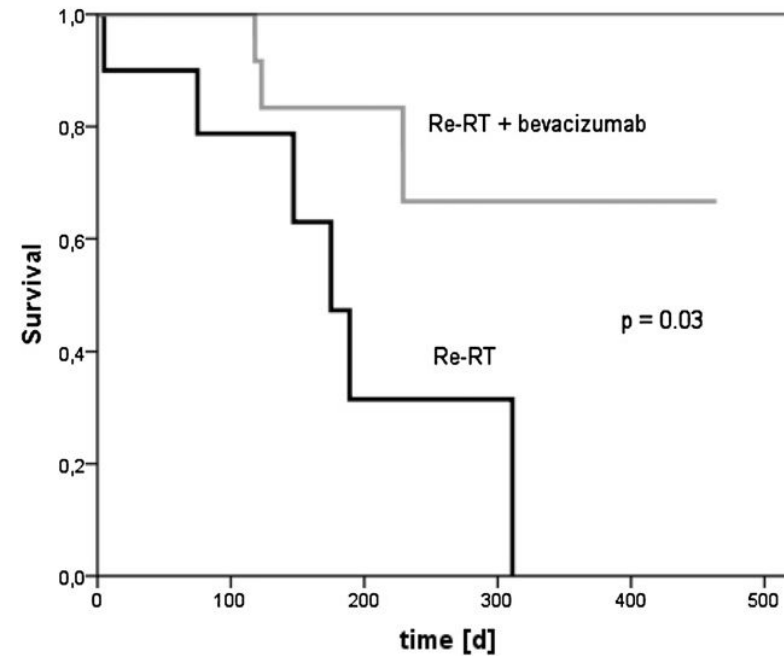
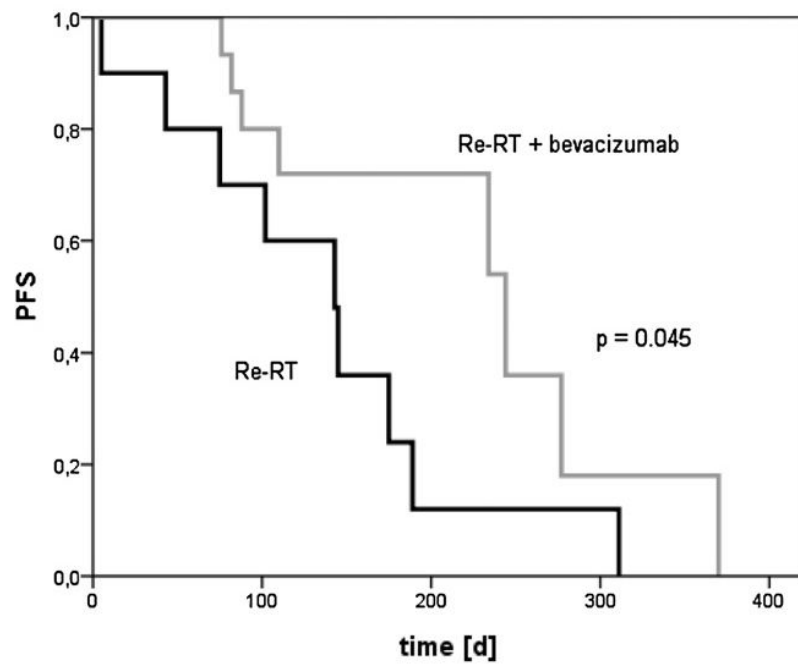
30 pts  
36 Gy in 18 fr



## IRRADIATION AND BEVACIZUMAB IN HIGH-GRADE GLIOMA RETREATMENT SETTINGS

MAXIMILIAN NIYAZI, M.D., M.Sc.,\* UTE GANSWINDT, M.D.,\* SILKE BIRGIT SCHWARZ, M.D.,\*  
FRIEDRICH-WILHELM KRETH, M.D., PH.D.,† JÖRG-CHRISTIAN TONN, M.D., PH.D.,† JULIA GEISLER, M.D.,‡  
CHRISTIAN LA FOUÛERE, M.D.,‡ LORENZ ERTL, M.D.,§ JENNIFER LINN, M.D.,§ AXEL SIEFERT, M.D.,\*  
AND CLAUS BELKA, M.D., PH.D.\*

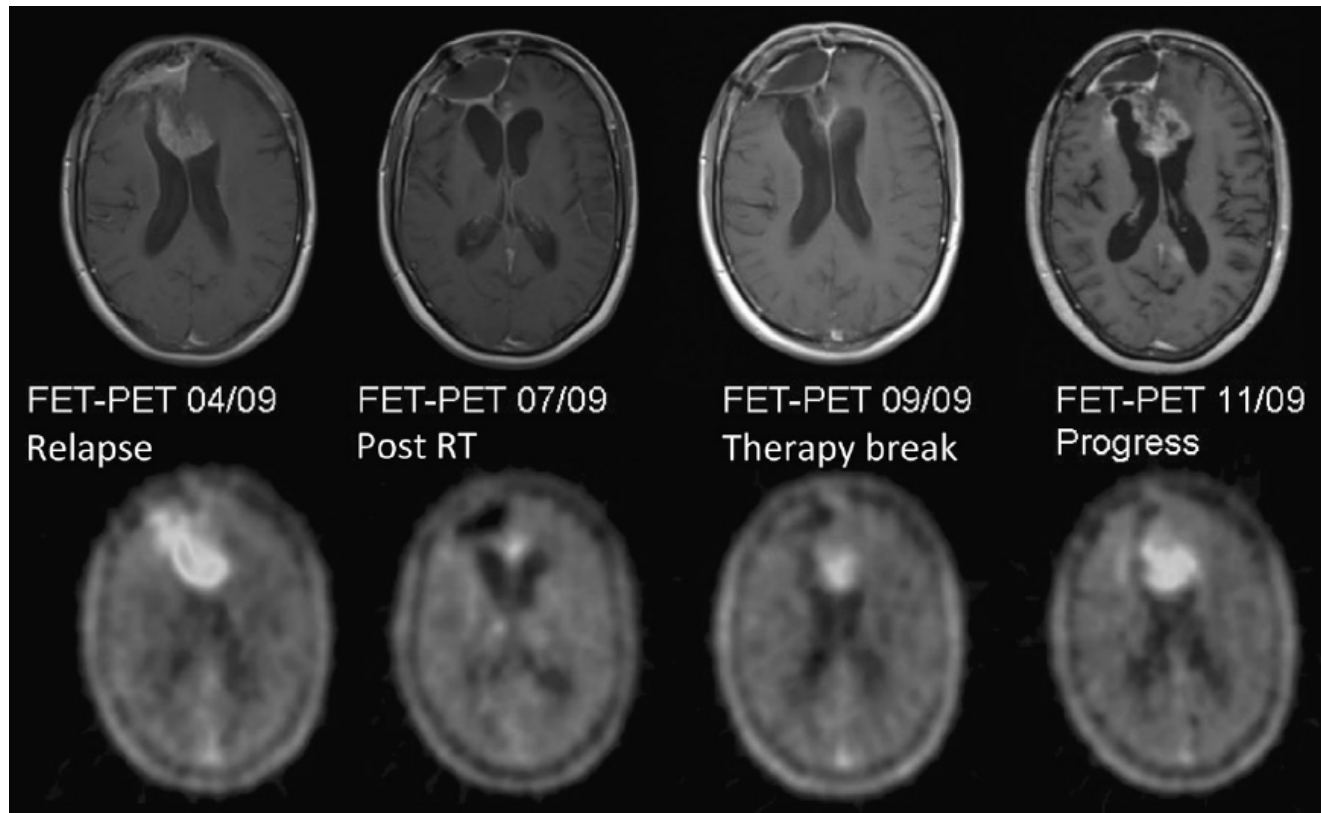
Departments of \*Radiation Oncology, †Neurosurgery, ‡Nuclear Medicine, and §Neuroradiology, Ludwig-Maximilians-University  
Munich, Munich, Germany



## IRRADIATION AND BEVACIZUMAB IN HIGH-GRADE GLIOMA RETREATMENT SETTINGS

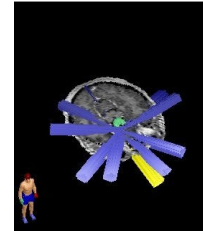
MAXIMILIAN NIYAZI, M.D., M.Sc.,\* UTE GANSWINDT, M.D.,\* SILKE BIRGIT SCHWARZ, M.D.,\*  
FRIEDRICH-WILHELM KRETH, M.D., PH.D.,† JÖRG-CHRISTIAN TONN, M.D., PH.D.,† JULIA GEISLER, M.D.,‡  
CHRISTIAN LA FOUÛERE, M.D.,‡ LORENZ ERTL, M.D.,§ JENNIFER LINN, M.D.,§ AXEL SIEFERT, M.D.,\*  
AND CLAUS BELKA, M.D., PH.D.\*

Departments of \*Radiation Oncology, †Neurosurgery, ‡Nuclear Medicine, and §Neuroradiology, Ludwig-Maximilians-University  
Munich, Munich, Germany





# Brain tumors reirradiation in GBMs



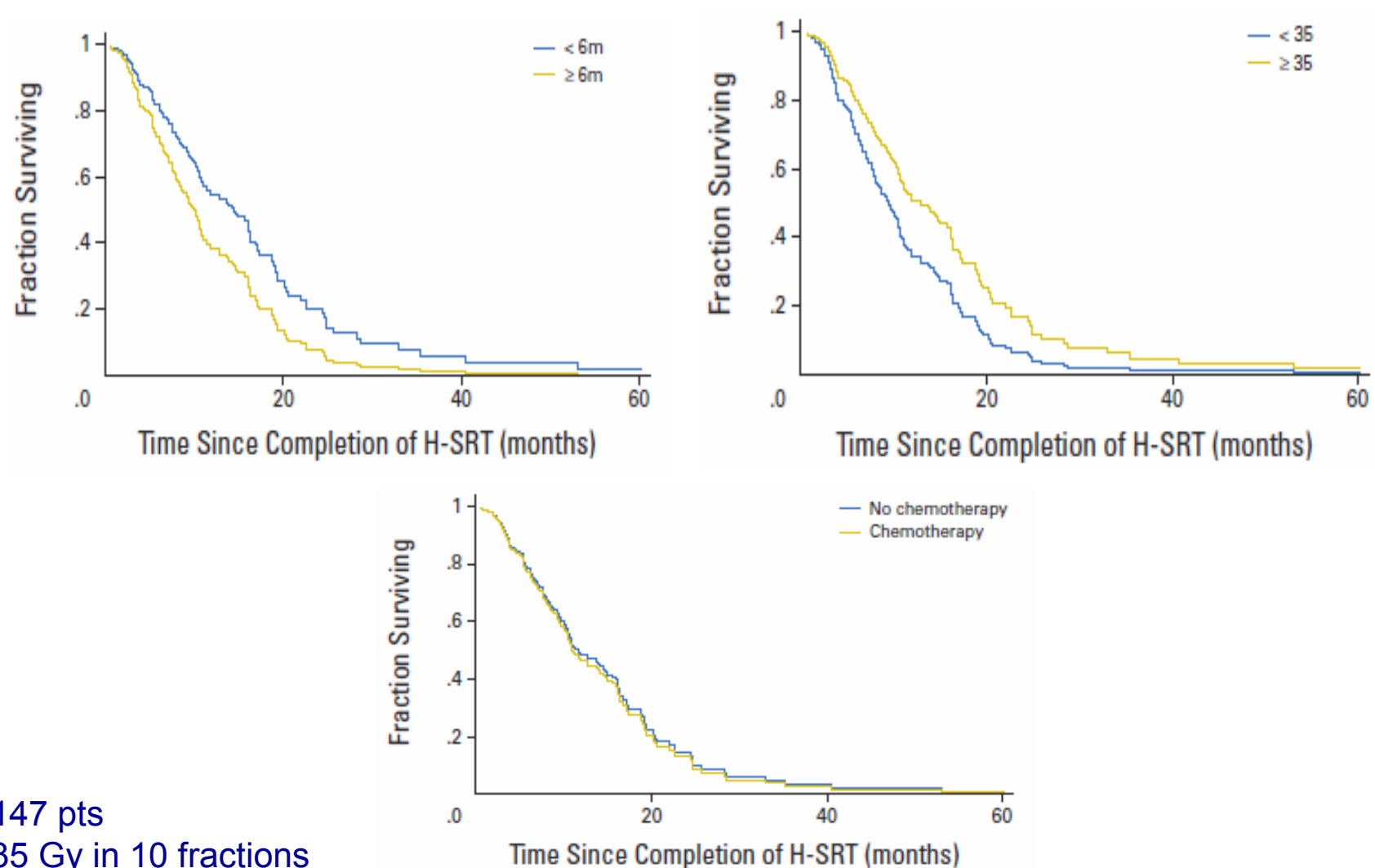
## HSRT

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 max	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

# Reirradiation for recurrent GBM



*Good KPS ( > 70)*

*Six months from previous RT*

*Volume < 25 ml*

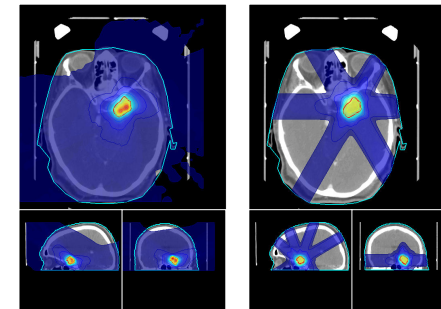
*FSRT*

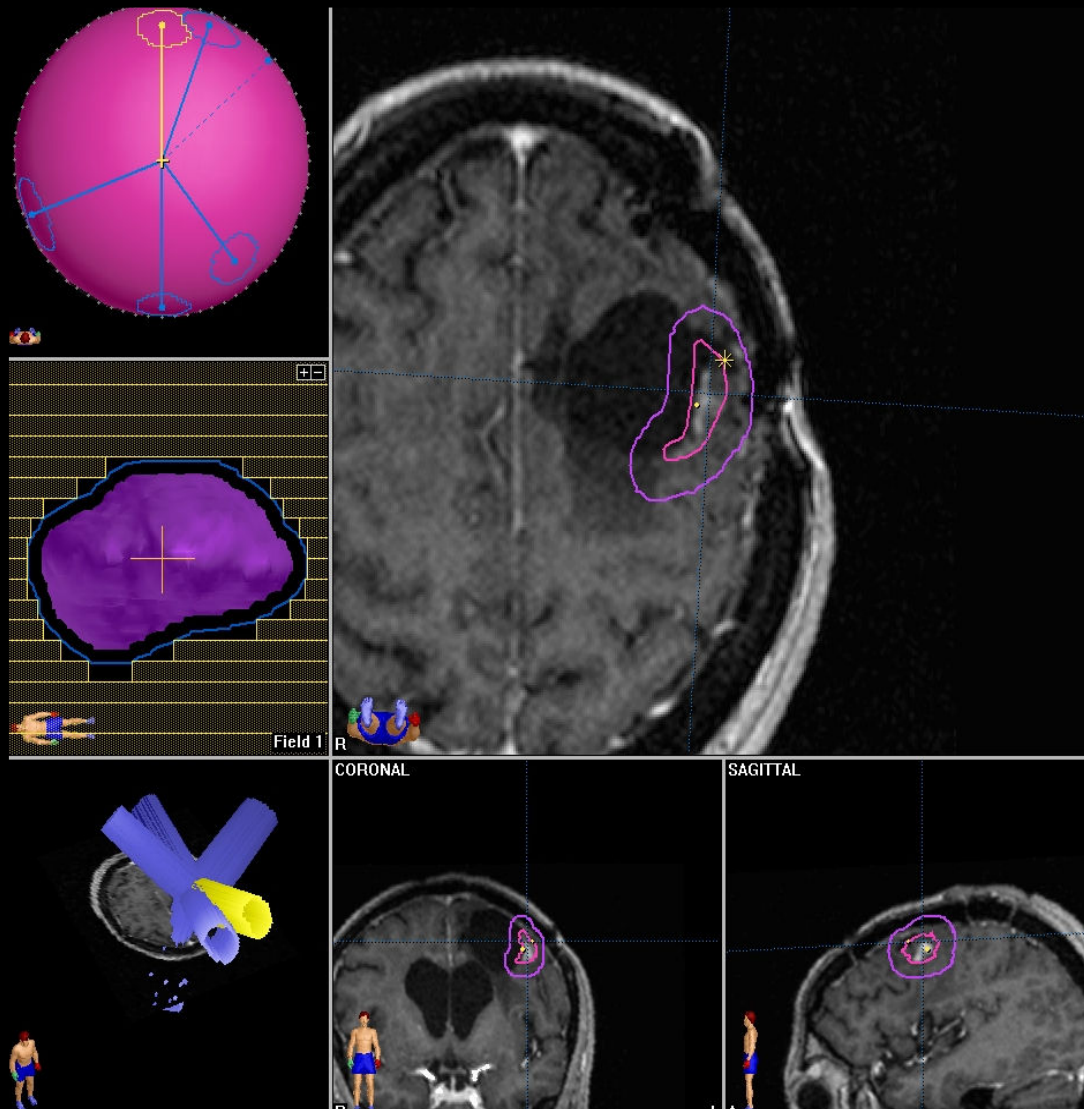
***30 Gy in 5 fractions (37 pts)***

*37.5 Gy in 15 fractions*

*Radiosurgery*

*14-16 Gy (6 pts)*



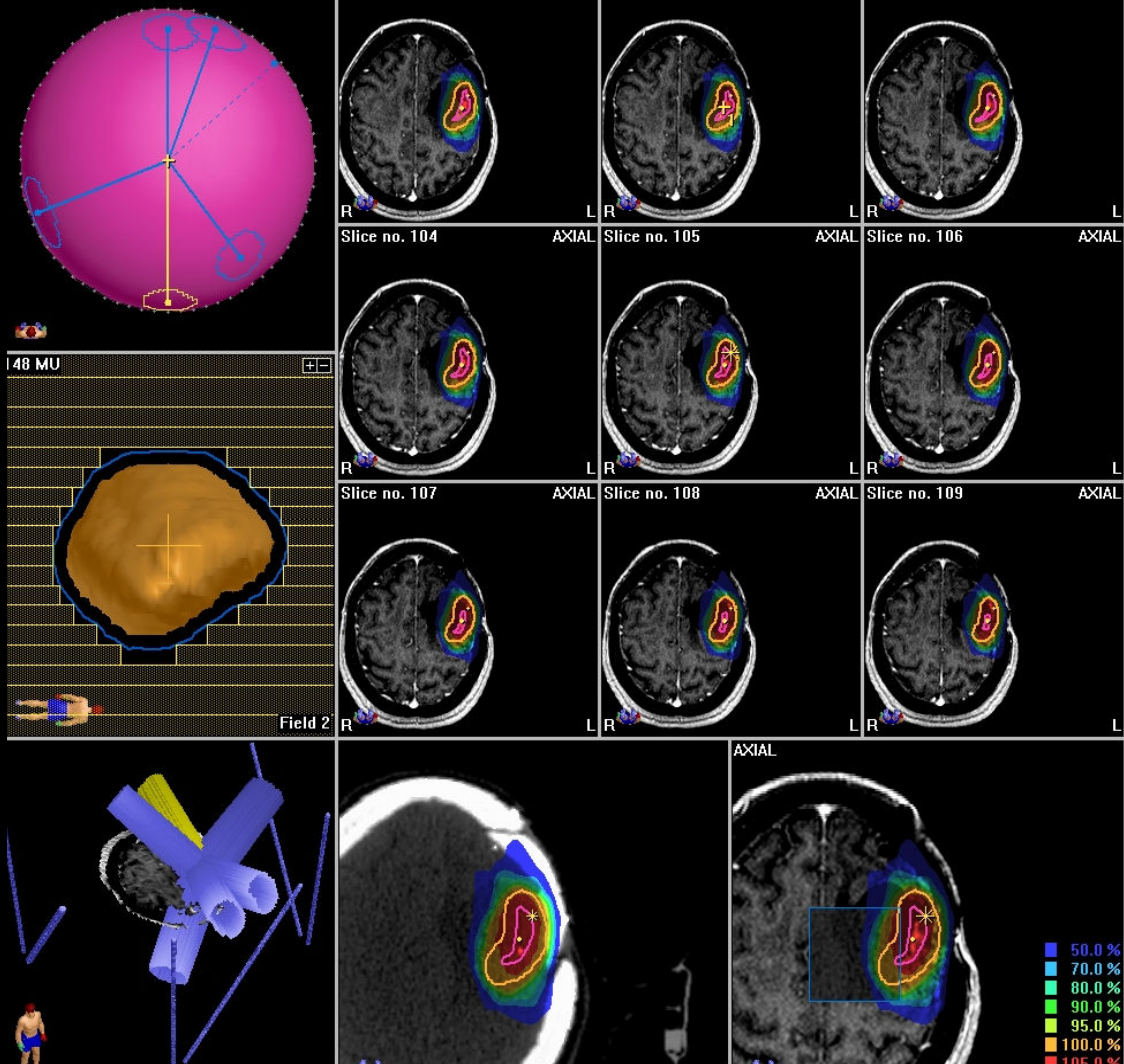


*GTV (T1 after contrast)*

*CTV = GTV + 3-5 mm*

*PTV = CTV + 2 mm*

*Recurrent glioma treated with FSRT*



***Recurrent glioma treated with FSRT***



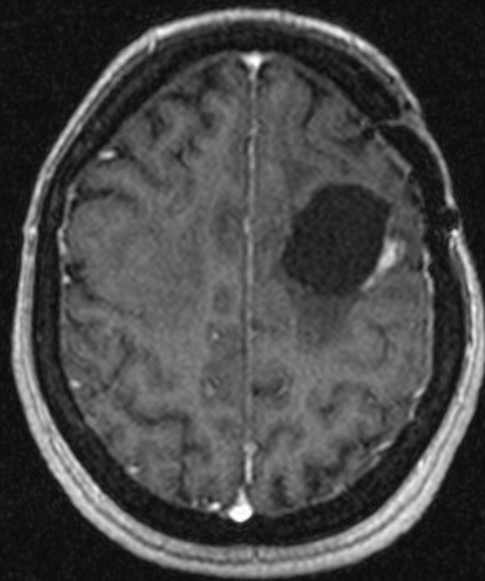
Se:6  
Im:101

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

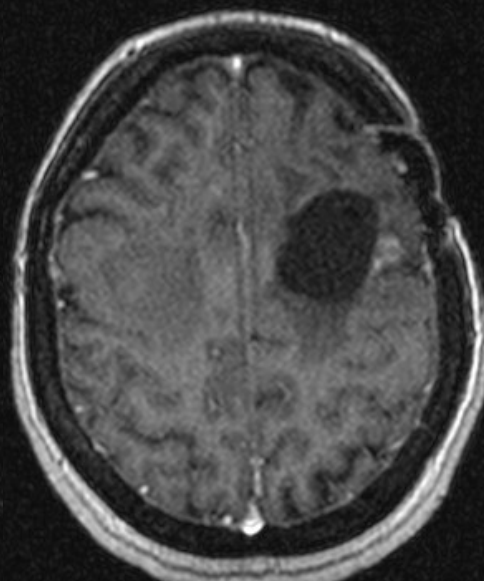
[A] R.ASSUNTA ;  
Study Date:15/10/2... 00  
Study Time:19.57.37  
MRN:

[A] R.ASSUNTA  
Study Date:09/02/2...  
Study Time:16.36.56  
MRN:

[R]

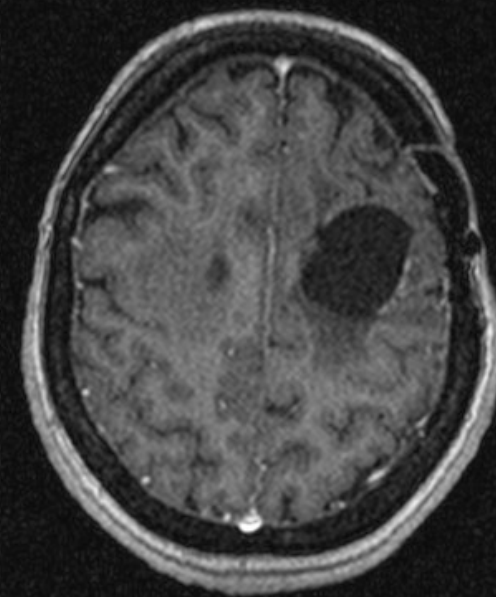


[L]



3 months

[L]



6 months

[L]

with contrast

[PF]

C351  
W771 ntrast

[P]

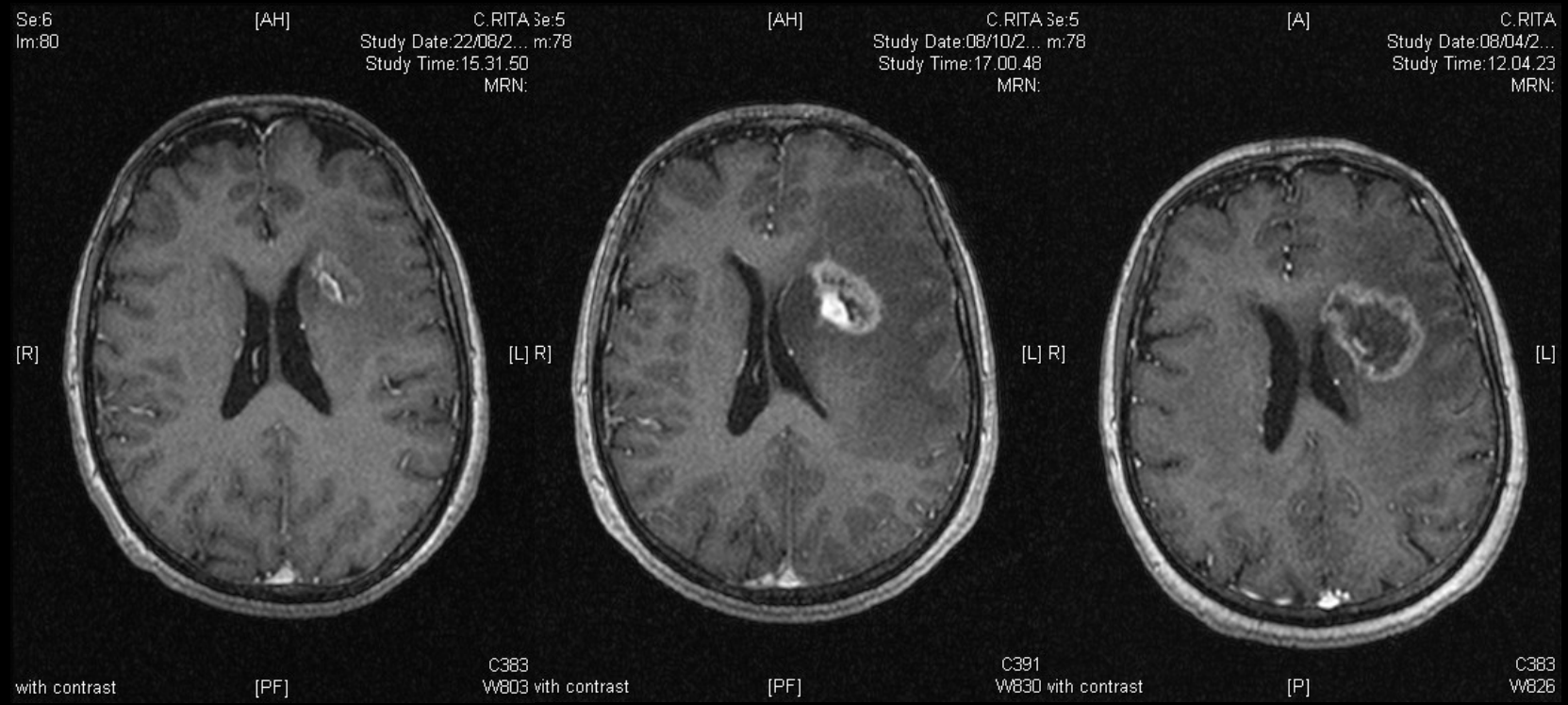
C346  
W762 contrast

[P]

C321  
W702



***Recurrent glioma treated with FSRT***

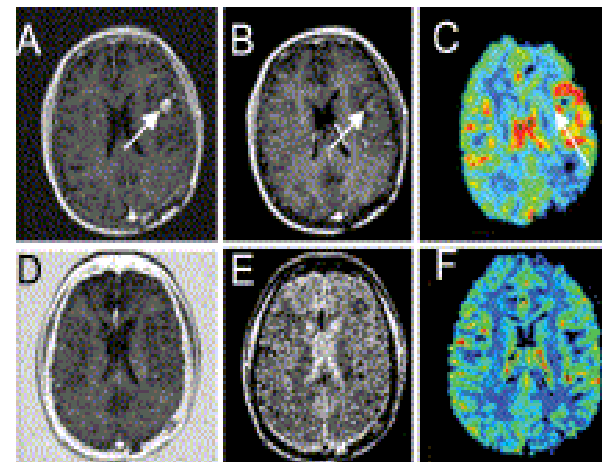
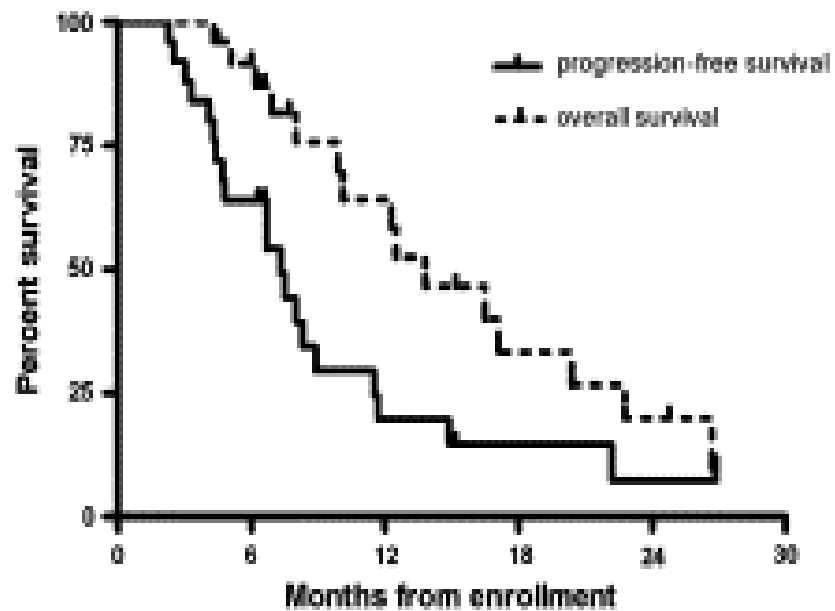
# Radionecrosis after SRS in a GBM



Clinical Investigation

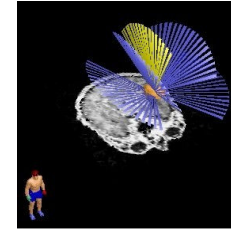
## Safety and Efficacy of Bevacizumab With Hypofractionated Stereotactic Irradiation for Recurrent Malignant Gliomas

Philip H. Gutin, M.D.<sup>\*,†,††</sup>,  , Fabio M. Iwamoto, M.D.<sup>\*,‡</sup>, Kathryn Beal, M.D.<sup>\*,¶</sup>, Nimish A. Mohile, M.D.<sup>‡</sup>, Sasan Karimi, M.D.<sup>\*,§</sup>, Bob L. Hou, Ph.D.<sup>\*,§,\*\*</sup>, Stella Lymberis, M.D.<sup>¶</sup>, Yoshiya Yamada, M.D., FRCPC.<sup>\*,¶</sup>, Jenghwa Chang, Ph.D.<sup>\*\*</sup>, Lauren E. Abrey, M.D.<sup>\*,‡</sup>





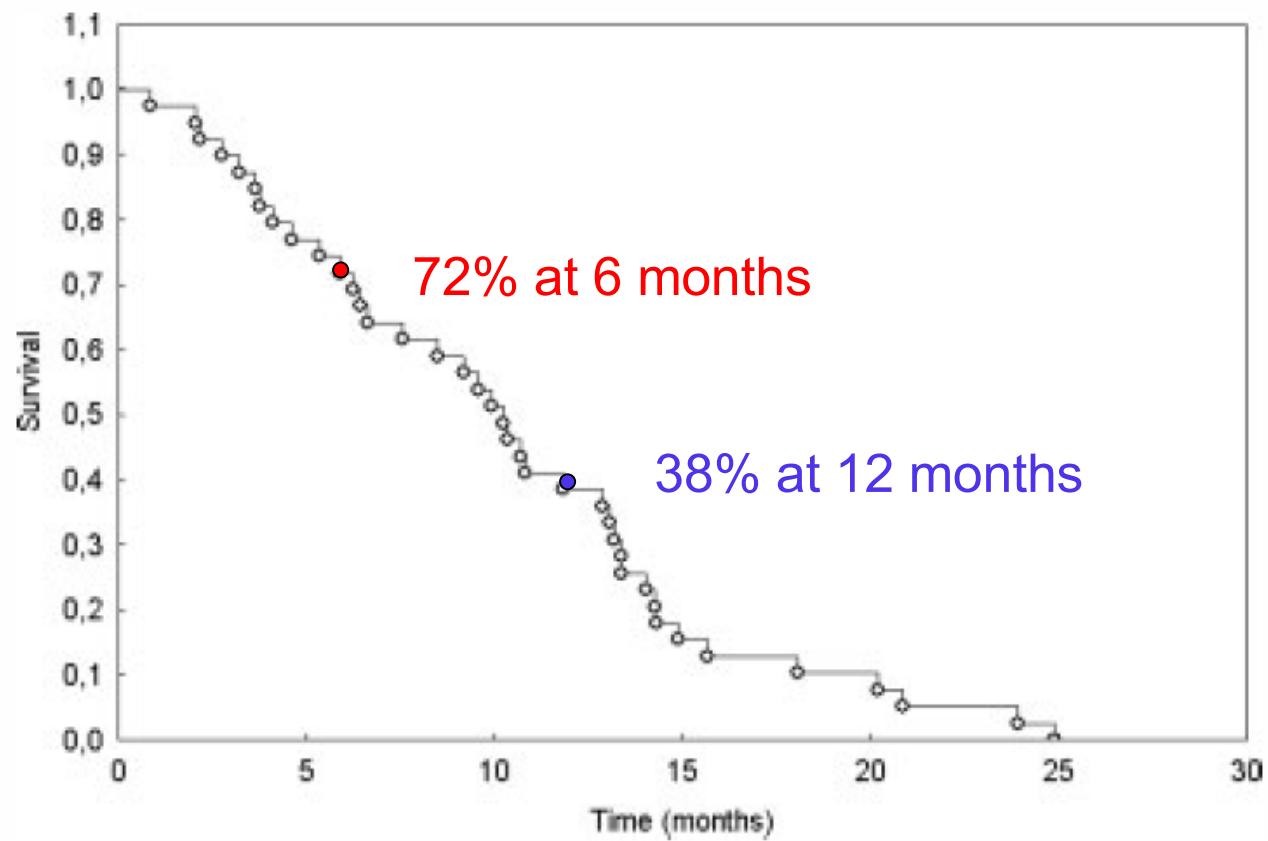
# Brain tumors reirradiation in GBMs



## Radisurgery

Author	Pts (n)	Interval months	Dose (Gy)	Volume (cc)	Cumulative BED	OS months	Toxicity
Kong (2008)	49 (Gr. III) 65 (GBM)	11.0 4.3	16 Gy	10.6	266	26 13	24.4 %
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%

## Overall survival after SRS





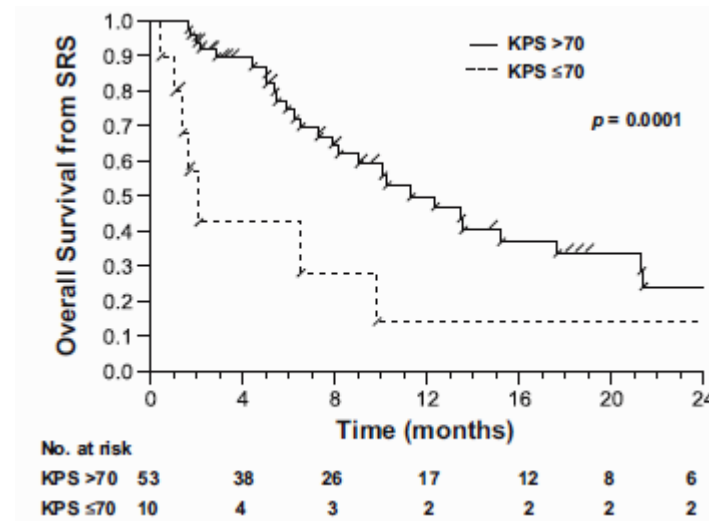
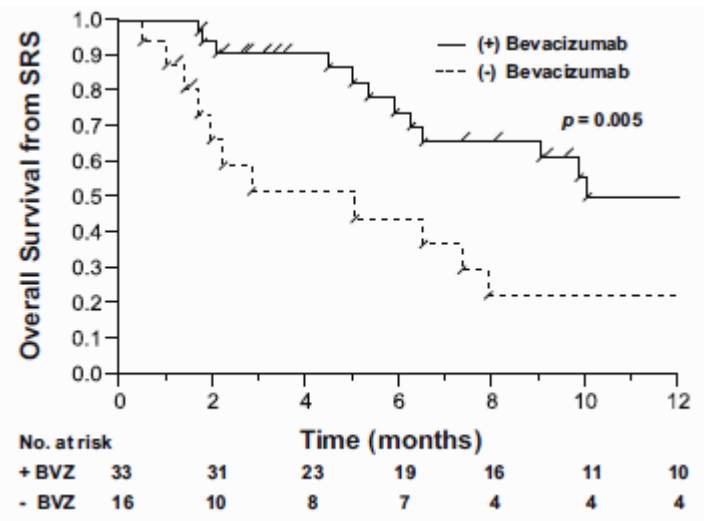


Clinical Investigation

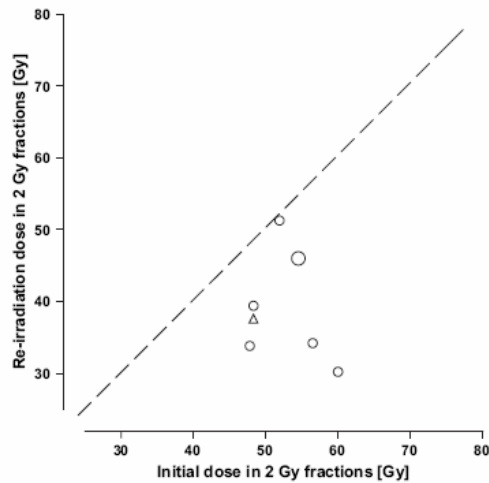
## Safety and Efficacy of Stereotactic Radiosurgery and Adjuvant Bevacizumab in Patients With Recurrent Malignant Gliomas

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

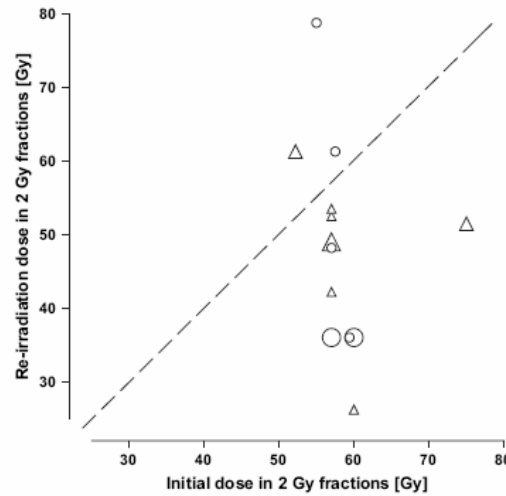
Kyle C. Cuneo, M.D.<sup>\*</sup>, James J. Vredenburg, M.D.<sup>†,‡</sup>, John H. Sampson, M.D., Ph.D.<sup>†,‡</sup>, David A. Reardon, M.D.<sup>†,‡</sup>, Annick Desjardins, M.D.<sup>†,‡</sup>, Katherine B. Peters, M.D., Ph.D.<sup>†,‡</sup>, Henry S. Friedman, M.D.<sup>†,‡</sup>, Christopher G. Willett, M.D.<sup>\*</sup>, John P. Kirkpatrick, M.D., Ph.D.<sup>\*,‡</sup>  



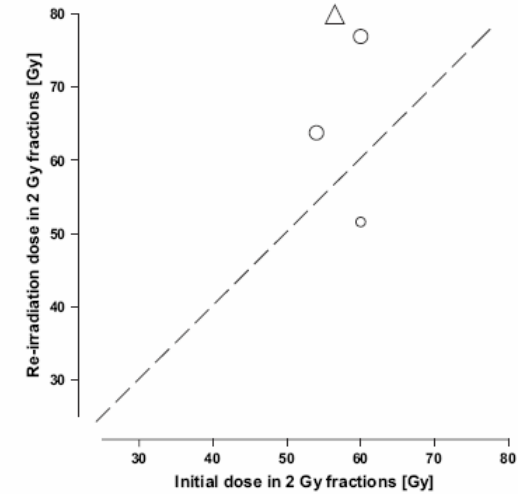
Correlation between the initial dose of the normalized total dose (NTD<sub>initial</sub>) and the normalized total dose of reirradiation (NTD<sub>reirradiation</sub>) in patients who underwent reirradiation



conventional RT



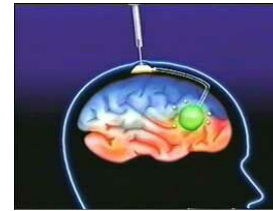
FSRT



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

# Brain tumors reirradiation in GBMs

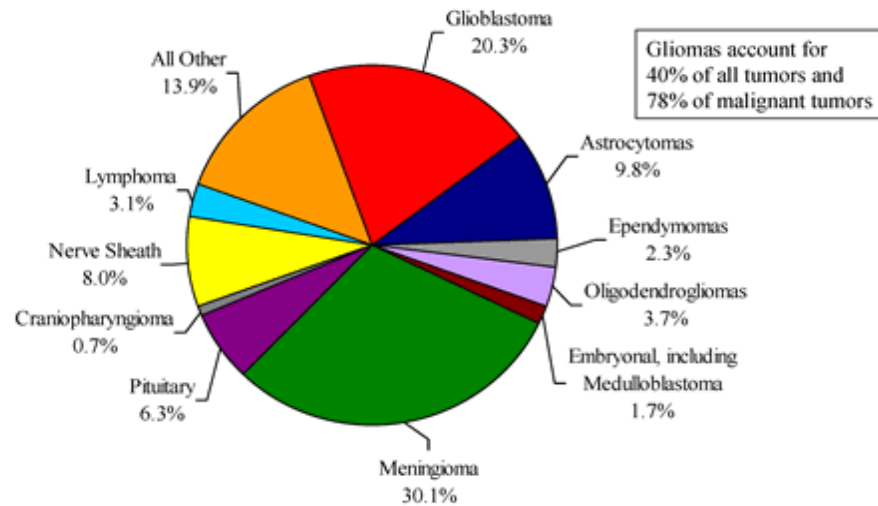


## Brachytherapy

Table 4: Series of patients with recurrent gliomas treated with I-125 seed implants.

Author	Pt. Number	Histology	(Median) Dose (Gy)	Median survival (months)	Rate of Severe Toxicity/Reoperation rate (%)
<i>Permanent Brachytherapy</i>					
Gaspar et al., 1999	37 (22)	GBM (AA)	100	10.5	44%
Halligan et al., 1996	22(4)	GBM (AA)	-	16	5%
Larson et al., 2004	38	GBM	150-500	12.0	10%
Patel et al., 2000	40	GBM	120-160	11.8	0%
<i>Temporary Brachytherapy</i>					
Gutin et al., 1987	18	GBM	-	13	41%
Leibel et al., 1989	45	GBM	70	12.5	49%
Leibel et al., 1989	50	AA	70	18.7	
Shrivastava et al., 1995	32	GBM	50	11.5	44%
Simon et al., 2002	42	GBM	40-60	12.5	24%
Sneed et al., 1997	45	AA	64	12.3	53%
Sneed et al., 1997	66	GBM	64	11.7	46%
<i>Glia Site Temporary Brachytherapy</i>					
Chan et al., 2005	24	GBM	53	9.1	33%
Gabayan et al., 2006	80	GBM	60 Gy	8.9	2%
Gabayan et al., 2006	15	Non-GBM	60 Gy	10.9	

# Summary



- Reirradiation is a feasible option for patients with high grade gliomas;

However results are modest;

Toxicity remains of concern for volumes > 35 ml in previously irradiated brain areas.

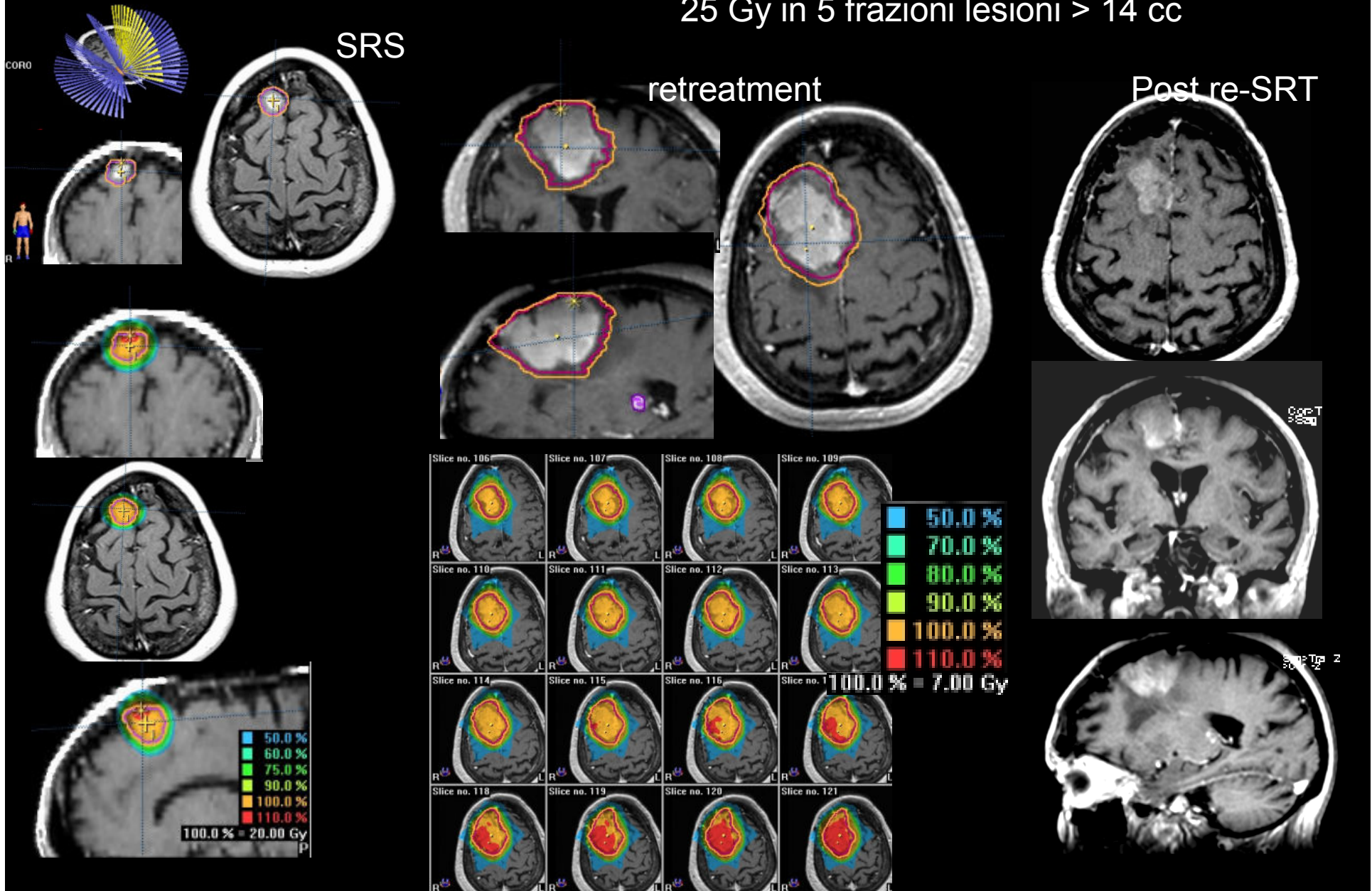
## Reirradiation of brain metastases

### The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline

First author (Year)	Study design/evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/progression after retreatment	Median time to recurrence/progression after retreatment
Chen [13] (2000)	Case series Evidence class III	SRS (n = 45)	Recurrent/progressive BM Initial BM treatment included SRS ± WBRT	28 weeks	Local control (by lesion for 84% of lesions with data) 90% 1 year freedom from tumor progression: 94%	NR
Kwon [18] (2007)	Case series Evidence class III	SRS (n = 43)	Recurrent/progressive BM Initial BM treatment included SRS	32 weeks	6 month local control rate: 91% 6 month overall brain control rate: 86%	NR
Shuto [23] (2004)	Case series Evidence class III	SRS (n = 16)	Recurrent/progressive BM Initial BM treatment included SRS	22.4 months (from 1st SRS treatment)	Tumor response: [Of 173/242 (72%) lesions with data]: Complete response 121/173 (70%) Partial response or no change 47/173 (27%) Progression 5/173 (3%)	NR
Yamanaka [24] (1999)	Case series Evidence class III	SRS (n = 41)	Recurrent/progressive BM Initial BM treatment included SRS	15 months (from first SRS treatment)	Overall local control rate after 2nd SRS (by lesion): 93% Response after 2nd SRS [Of 61 lesions evaluable]: Disappeared 16/61 (26%) Decreased 40/61 (66%) Unchanged 1/61 (2%) Increased 4/61 (7%)	NR

# Reirradiation of brain metastases

16 Gy in frazione singola lesioni < 4.3 cc  
21 Gy in 3 frazioni lesioni < 14 cc  
25 Gy in 5 frazioni lesioni > 14 cc

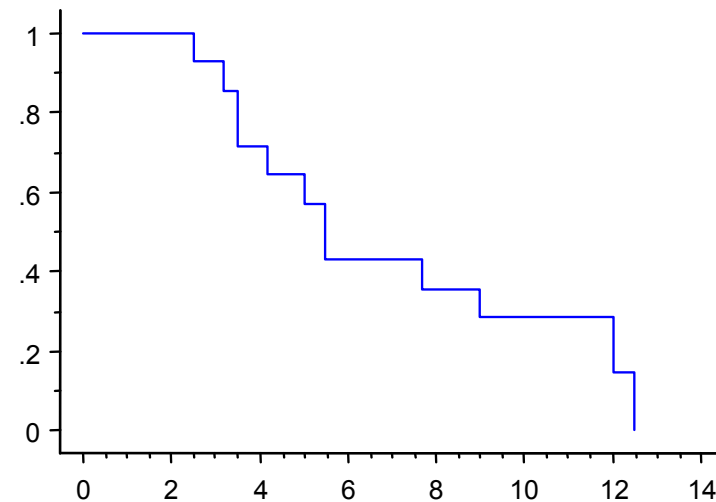




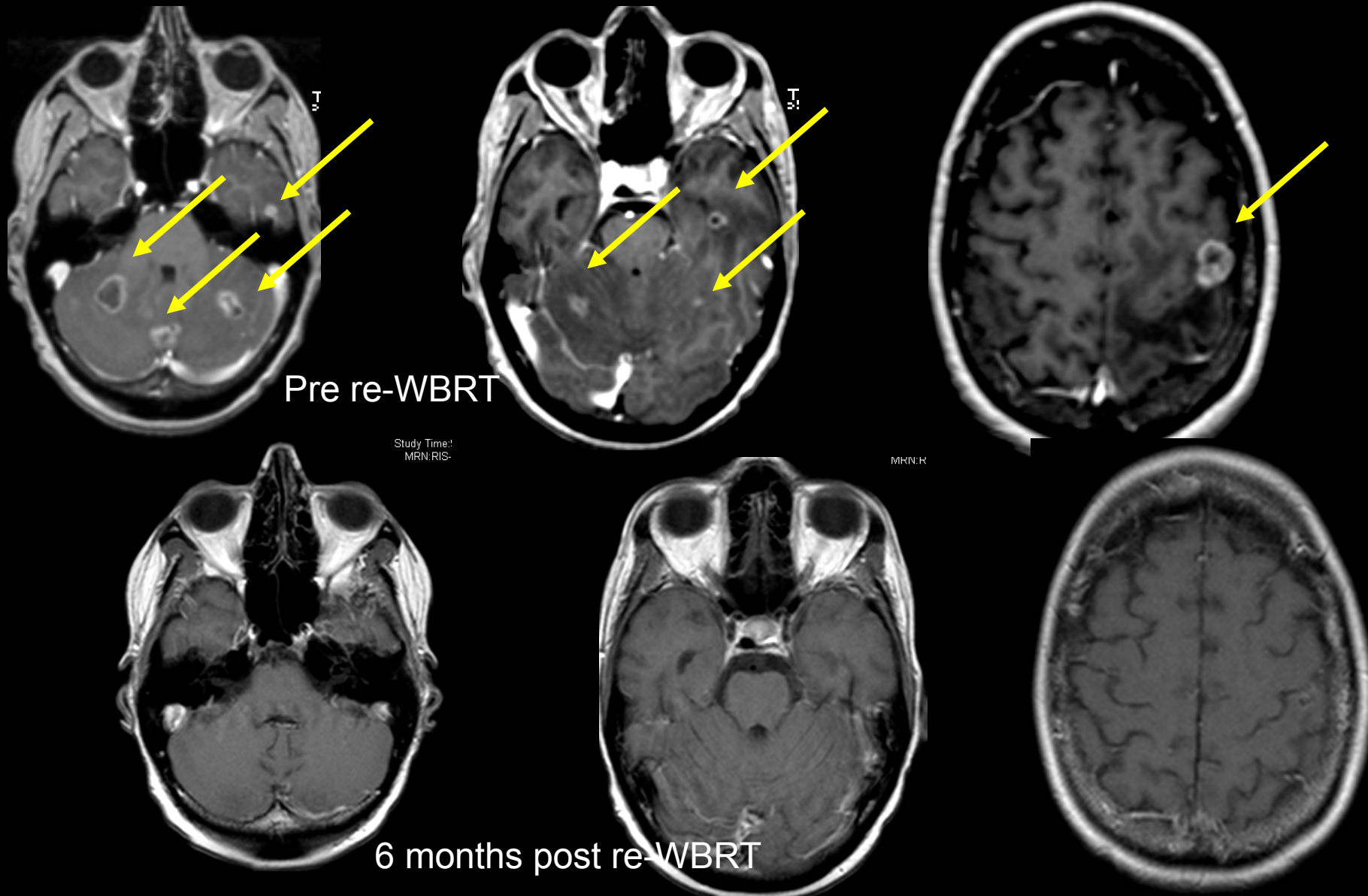
## WB reirradiation of brain metastases

16 patients presenting with intracranial progression after SRS and/or WBRT

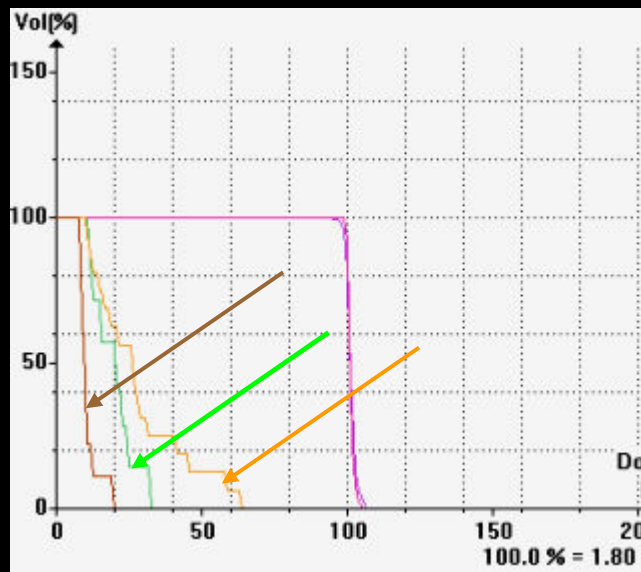
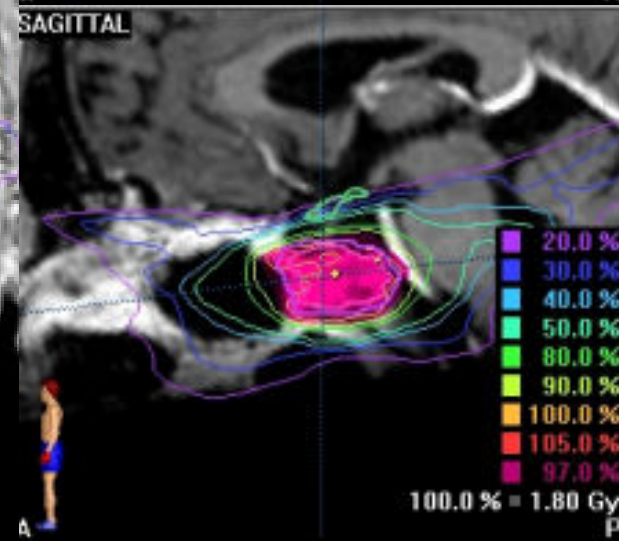
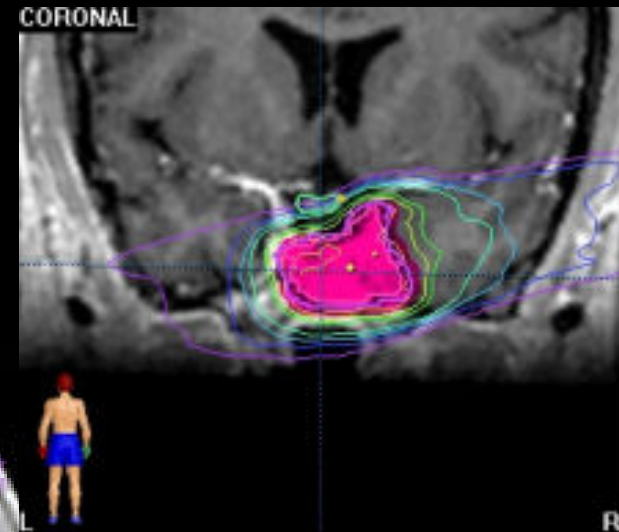
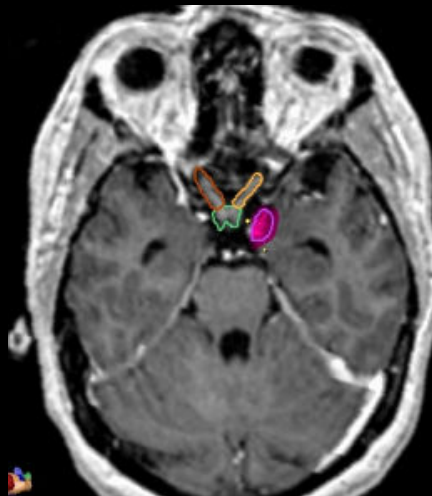
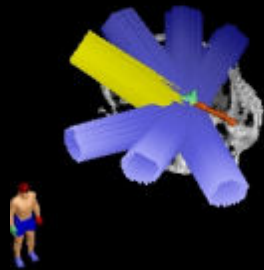
- 3 new/progressive lesions
- KPS > 60
- Median age 56 years
- 25 Gy in 10 frazioni in associazione a TMZ
- Median survival 5.5 months
- 6-month survival 42%
- 12-month survival 15%



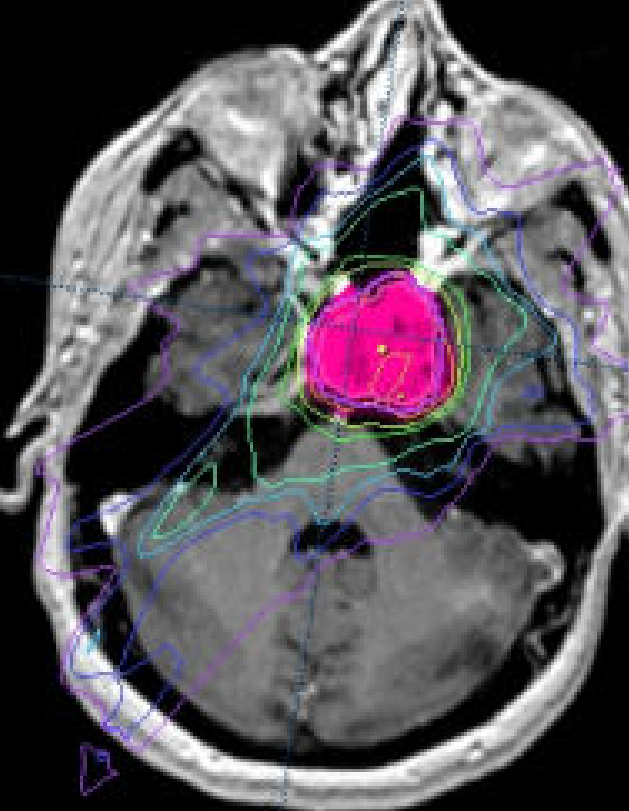
# WB reirradiation of brain metastases



# SRT reirradiation of a prolactinoma



Optic chiasm  
Right optic nerve  
Left optic nerve



*....Grazie per l'attenzione*



**SAPIENZA**  
UNIVERSITÀ DI ROMA

Ospedale Sant'Andrea