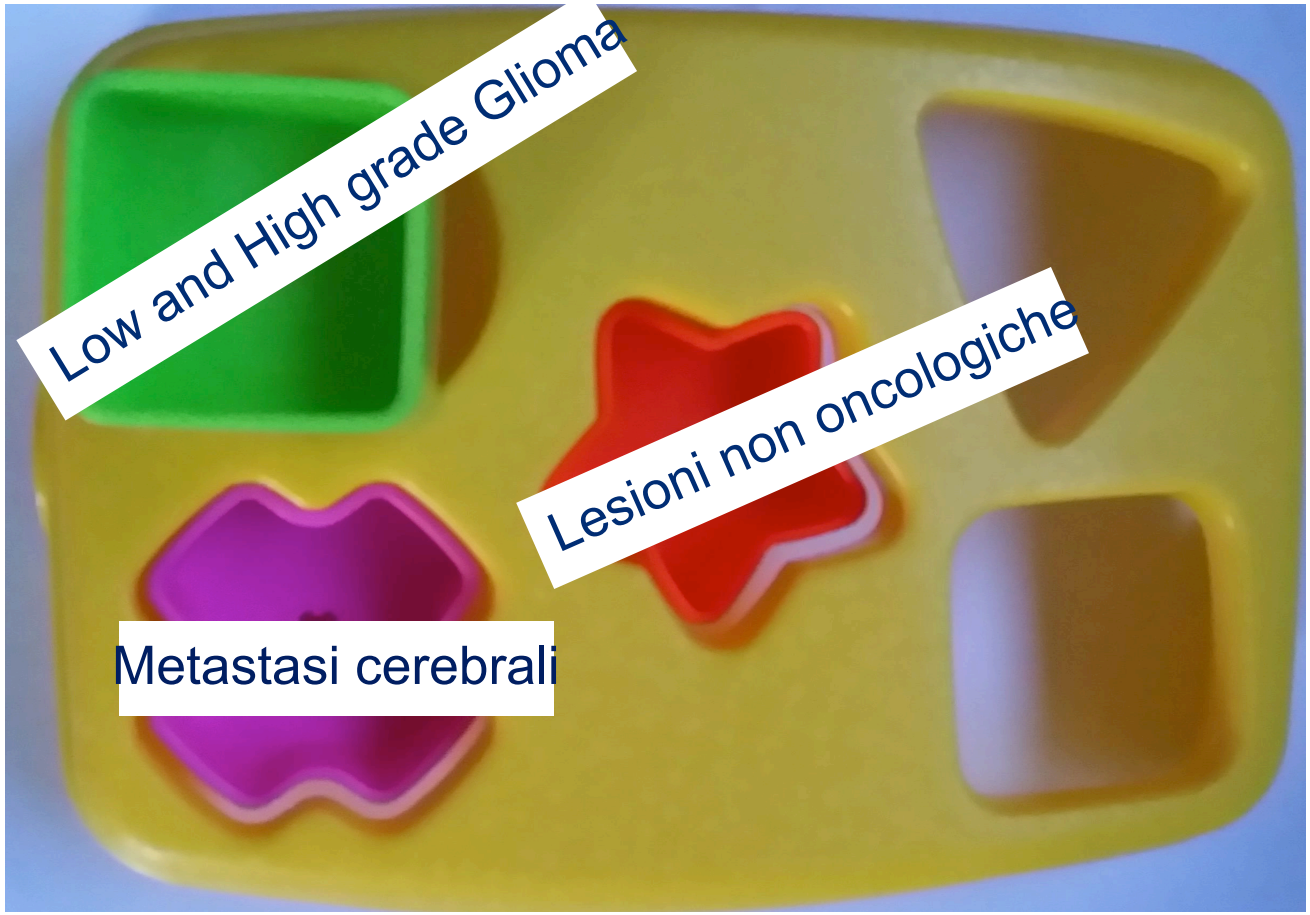
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

LA RADIOTERAPIA STEREOTASSICA ABLATIVA: High and Low Grade Glioma

Silvia Chiesa

Gemelli ART
ADVANCED RADIATION THERAPY


Low and High grade Glioma
Lesioni non oncologiche
Metastasi cerebrali

The RSSearchTM Registry: patterns of care and outcomes research on patients treated with stereotactic radiosurgery and stereotactic body radiotherapy

Table 3 Lesion characteristics and most common lesion location and histology

Variable (N)	N (%)
All lesions – lesion type (11154)	
Arterio-venous malformation	92 (0.8%)
Benign tumor	1218 (10.9%)
Malignant primary tumor	3668 (32.9%)
Metastatic tumor	4639 (41.6%)
Recurrent primary tumor	1050 (9.4%)
Functional disease	485 (4.3%)
Intracranial lesions (5441)	
Benign lesions	1176 (21.6%)
Acoustic neuroma	321 (5.9%)
Meningioma	360 (6.7%)
Benign, NOS	155 (2.9%)
Pituitary adenoma	88 (1.6%)
Primary malignant	226 (4.2%)
Astrocytoma	29 (0.6%)
Glioblastoma	76 (1.4%)
Glioma	8 (0.2%)
Meningioma, malignant	44 (0.8%)
Metastatic	2917 (53.6%)
Brain/cranial nerve/spinal cord	2867 (52.7%)
Meninges	4 (0.8%)
Recurrent	263 (4.8%)
Astrocytoma	19 (0.4%)
Glioblastoma	87 (1.6%)
Glioma	8 (0.2%)
Pituitary adenoma	16 (0.3%)
Functional disease	485 (9%)
Trigeminal neuralgia – typical	364 (6.7%)
Trigeminal neuralgia – atypical	99 (1.8%)
Trigeminal neuralgia- MS	13 (0.3%)

Radiation Oncology 2013, **8**:275

Bullet Points

- SRT in Low Grade Gliomas
  - at the diagnosis

RT Dose?

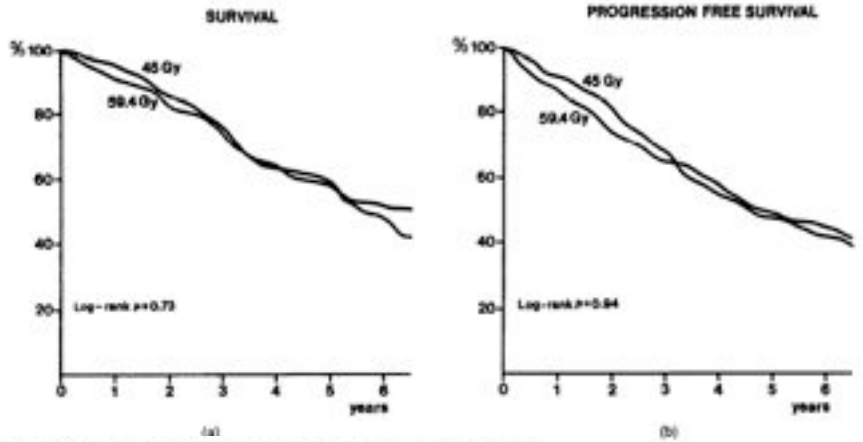
EORTC 22844

EORTC NCCTG-RTOG-ECOG

● *Clinical Original Contribution*

A RANDOMIZED TRIAL ON DOSE–RESPONSE IN RADIATION THERAPY OF LOW-GRADE CEREBRAL GLIOMA: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) STUDY 22844

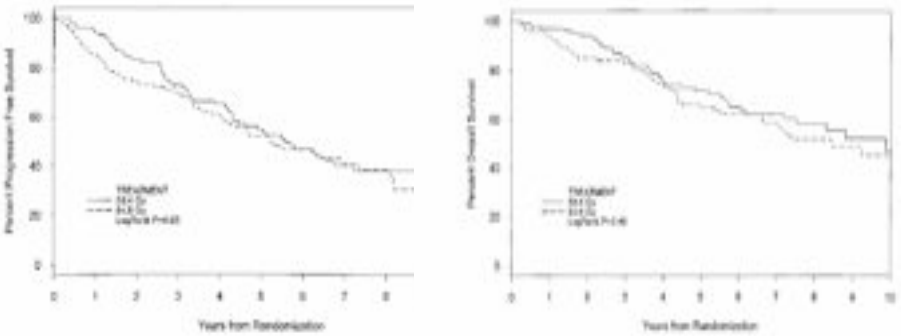
ABUL B. M. F. KARIM, M.D., PH.D.,* BEN MAAT, M.D.,† REIDULV HATLEVOLL, M.D.,‡ JOHAN MENTEN, M.D.,§ EWALD H. J. M. RUTTEN, M.D.,‖ DAVID G. T. THOMAS, M.D., PH.D.,¶ FRANCISCO MASCARENHAS, M.D.,# JEAN C. HORIOT, M.D., PH.D.,‖ LEENA M. PARVINEN,** MATTHIJS VAN REIJN, M.D.,** JOS J. JAGER, M.D.,†† MARIA G. FABRINI, M.D.,‡‡ AUGUST M. VAN ALPHEN, M.D., PH.D.,§§ HAN P. HAMERS, M.D., PH.D.,‖‖ LUIS GASPAR, M.D.,¶¶ EVA NOORDMAN, M.D., PH.D.,## MARIANNE PIERART, M.SC.‖‖ AND MARTINE VAN GLABBEKE, M.SC.‖‖



Int. J. Radiation Oncology Biol. Phys., Vol. 36, No. 3, pp. 549–556, 1996

Prospective Randomized Trial of Low- Versus High-Dose Radiation Therapy in Adults With Supratentorial Low-Grade Glioma: Initial Report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study

By E. Shaw, R. Arusell, B. Scheithauer, J. O'Fallon, B. O'Neill, R. Dinapoli, D. Nelson, J. Earle, C. Jones, T. Cascino, D. Nichols, R. Ivnik, R. Hellman, W. Curran, and R. Abrams



J Clin Oncol 20:2267-2276

50-54 Gy in 1,8Gy/fr

EORTC 22845

RT Timing?

Lancet 2005; 366: 985–90

Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial

M J van den Bent, D Afra, O de Witte, M Ben Hassel, S Schraub, K Hoang-Xuan, P-O Malmström, L Collette, M Piérart, R Mirimanoff, A B M F Karim, for the EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council

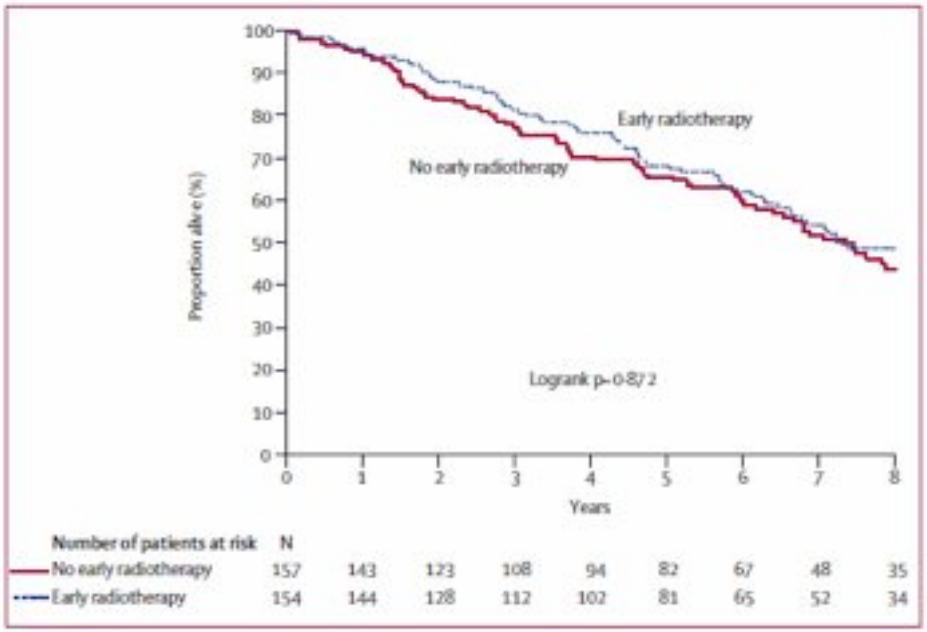


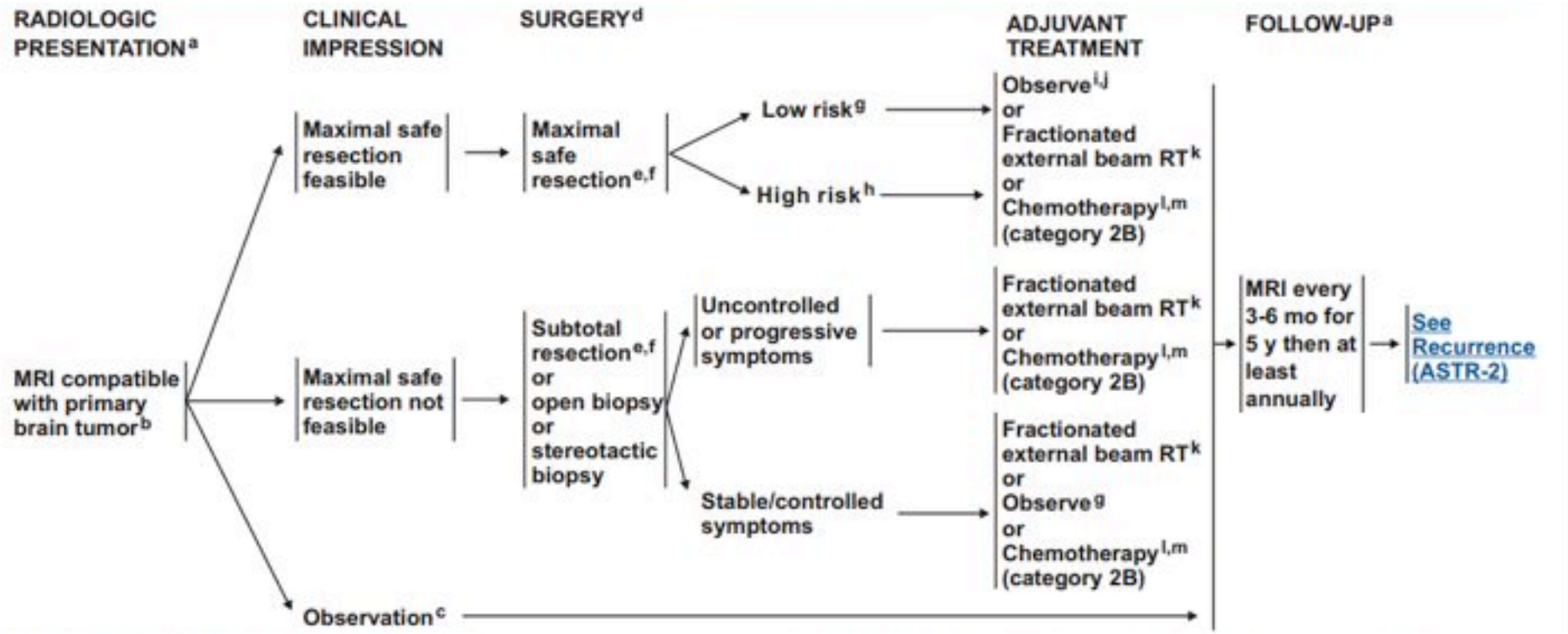
Figure 2: Overall survival by intention-to-treat analysis
Number of events: 0=80 for control group; 0=76 for early radiotherapy group

	No early radiotherapy (n=157)	Early radiotherapy (n=154)	Hazard ratio (95% CI)
Overall survival			
Median years (95% CI)	7·4 (6·1–8·9)	7·2 (6·4–8·6)	0·97 (0·71–1·34)
Proportion alive at 5 years	65·7% (57·8–73·5)	68·4% (60·7–76·2)	
Progression-free survival			
Median years (95% CI)	3·4 (2·9–4·4)	5·3 (4·6–6·3)	0·59 (0·45–0·77)
Proportion free from progression at 5 years	34·6% (26·7–42·5)	55·0% (46·7–63·3)	

Table 2: Survival and progression-free survival

Early radiotherapy after surgery lengthens the period without progression but does not affect overall survival.
Radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored

NCCN Guidelines Version 1.2014
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)



[g]Low-risk features: Oligodendroglioma or mixed oligoastrocytoma, <40 y, KPS ≥ 70, tumor dimension < 6 cm, minor or no neurological deficit, 1p and 19q codeleted, IDH1 or 2 mutated.

[h]High-risk features: 3 or more of: Astrocytoma, Age ≥40 y, KPS < 70, tumor dimension ≥6 cm, tumor crossing midline, preoperative neurological deficit of more than minor degree. One or no deletions on 1p and 19q, IDH1 or 2 not mutated, increased perfusion on imaging are also adverse factors that may be considered.

SRS or FSRT?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)

Low Grade Gliomas (Grades I/II)

- Tumor volumes are best defined using pre- and postoperative imaging, usually FLAIR and or T2 signal abnormality on MRI for GTV. CTV (GTV plus 1-2 cm margin) should receive 45-54 Gy in 1.8-2.0 Gy fractions.
- SRS has not been established to have a role in the management of low grade gliomas. Phase I trials using SRS do not support its role as initial treatment.

No Evidence

Technol Cancer Res Treat. 2006 Feb;5(1):1-8.

Hypofractionated stereotactic radiotherapy for low grade glioma at McGill University: long-term follow-up.

Roberge D[1], Souhami L, Olivier A, Leblanc R, Podgorsak E.

21 pts; < 4cm; 42 Gy /6 fr

Radiology. 1989 May;171(2):565-9.

Low-grade astrocytomas: treatment with unconventionally fractionated external beam stereotactic radiation therapy.

Pozza F[1], Colombo F, Chierego G, Avanzo RC, Marchetti C, Benedetti A, Casentini L, Danieli D.

14 pts; 16-50Gy/1-2fr/8 days apart

Cancer. 1991 Nov 15;68(10):2101-8.

Fractionated stereotactic radiation therapy for intracranial tumors.

Souhami L[1], Olivier A, Podgorsak EB, Villemure JG, Pla M, Sadikot AF.

15 pts; 42/6fr

Enthusiasm for SRS in low grade gliomas has wanted due to insufficient evidence for therapeutic advantage

Bullet Points

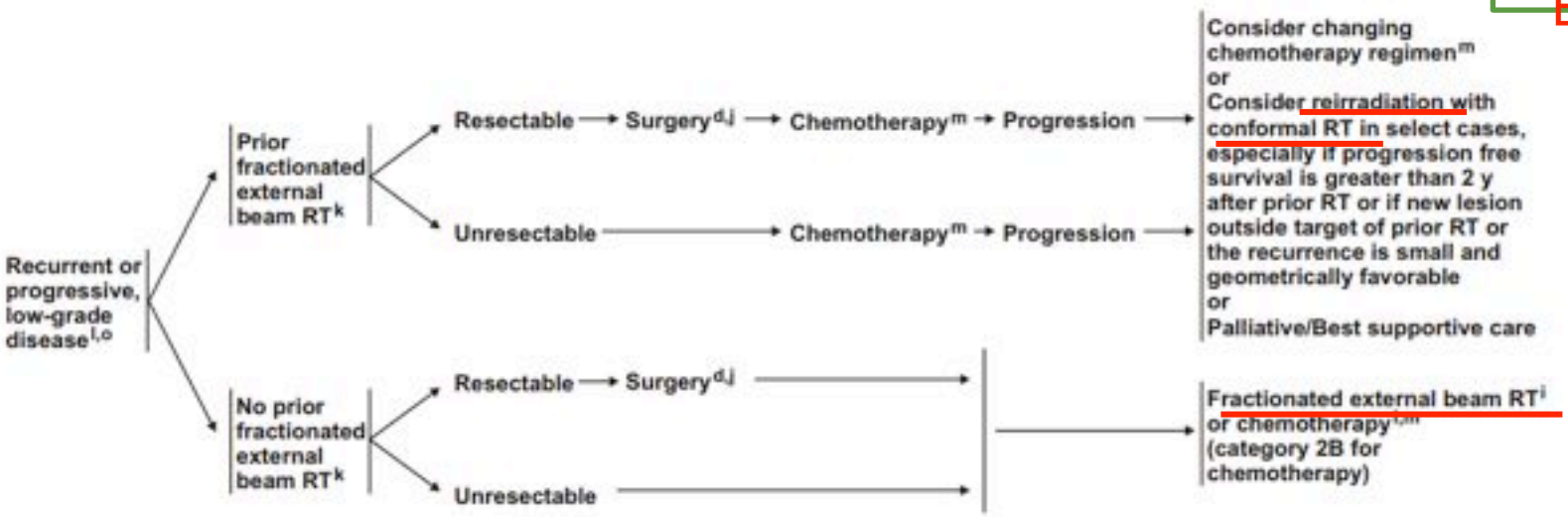
- SRT in Low Grade Gliomas
  - at the diagnosis
  - at recurrence

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma)

RECURRENCE[n]

No Evidence



Retrospective

Recurrent low-grade gliomas: the role of fractionated stereotactic re-irradiation

S.E. Combs[1,2], R. Ahmadi[3], D. Schulz-Ertner[1,2], C. Thilmann[1,2] and J. Debus[1,2]
[1]*Department of Radiation Oncology German Cancer Research Center (DKFZ) INF 280;* [2]*Department of Radiation Oncology;* [3]*Department of Neurosurgery, University of Heidelberg, INF 400 Heidelberg, Germany*

Journal of Neuro-Oncology (2005) 71: 319–323

Stereotactically guided fractionated re-irradiation in recurrent glioma represents an effective treatment option with good results and few complications. However, further investigation is warranted

Summary

	Primary	Recurrent/Re-irradiation
Low Grade Glioma	SRS has not been established to have a role in the management of low grade glioma	effective treatment option with good results and few complications.

Bullet Points

- SRS in Low Grade Gliomas
  - at the diagnosis
  - at recurrence

- High Grade Gliomas
  - at the diagnosis: SRS

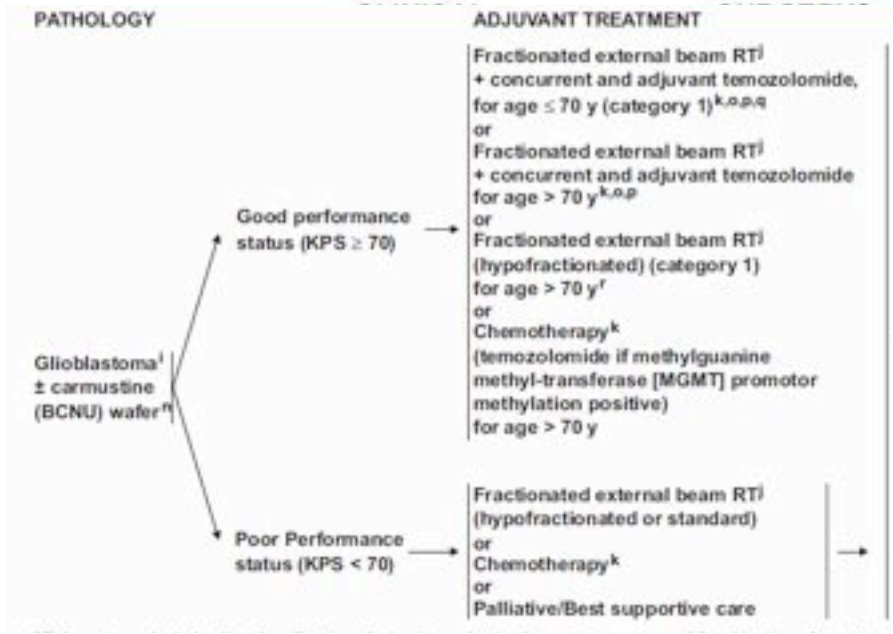
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

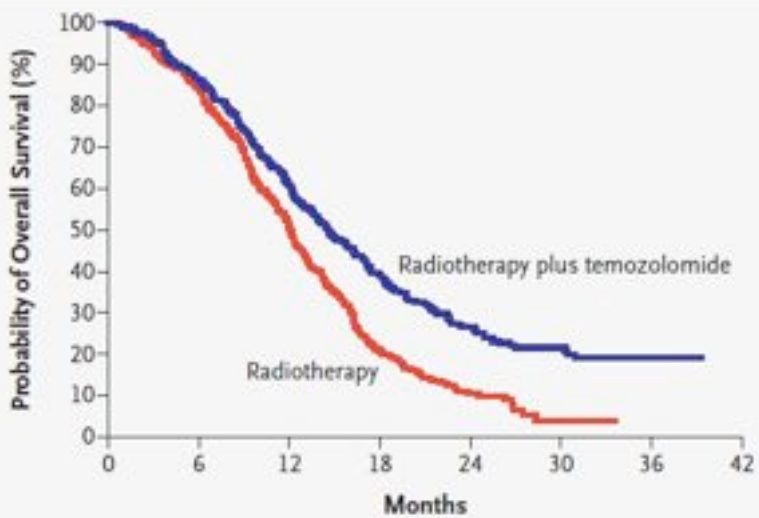
Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

N Engl J Med 2005;352:987-96.

SRS or FSRT?

NCCN Guidelines Version 2.2013
Anaplastic Gliomas/Glioblastoma[a]





No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

pre

Retrospective

Int. J. Radiation Oncology Biol. Phys., Vol. 32, No. 4, pp. 931–941, 1995

RADIOSURGERY IN THE INITIAL MANAGEMENT OF MALIGNANT GLIOMAS: SURVIVAL COMPARISON WITH THE RTOG RECURSIVE PARTITIONING ANALYSIS

JANN N. SARKARIA, M.D.,* MINESH P. MEHTA, M.D.,* JAY S. LOEFFLER, M.D.,† JOHN M. BUATTI, M.D.,‡ RICHARD J. CHAPPELL, PH.D.,§ ALLAN B. LEVIN, M.D.,¶ EBEN ALEXANDER III, M.D.,# WILLIAM A. FRIEDMAN, M.D.** AND TIMOTHY J. KINSELLA, M.D.*

*Departments of Human Oncology, †Biostatistics, and ¶Neurosurgery, University of Wisconsin School of Medicine, Madison, WI, Joint Center for Radiation Therapy, Departments of ‡Radiation Oncology and #Neurosurgery, Harvard Medical School, Boston, MA, Departments of §Radiation Oncology and **Neurosurgery, University of Florida School of Medicine, Gainesville, FL

- At the diagnosis
- SRS

115 pts
3 institutions: Wisconsin, Harvard Boston, Florida

CTV + 2- 40mm or no margin)

Table 2. Radiotherapy technique

	UW	JCRT	UF
EBRT dose, Gy median (range)	54.0 (0–66.0)	59.4 (54–60.2)	60.0 (54.0–60.0)
SR minimum tumor dose, Gy median (range)	12.0 (10.0–20.0)	12.0 (6.0–20.0)	13.8 (10.0–15.0)
Number of patients with single isocenter (%)	17 (57%)	70 (93%)	9 (90%)
Number of patients with multiple isocenters (%)	13 (43%)	5 (7%)	1 (10%)

Retrospective

Int. J. Radiation Oncology Biol. Phys., Vol. 32, No. 4, pp. 931–941, 1995

RADIOSURGERY IN THE INITIAL MANAGEMENT OF MALIGNANT GLIOMAS: SURVIVAL COMPARISON WITH THE RTOG RECURSIVE PARTITIONING ANALYSIS

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*Departments of Human Oncology, †Biostatistics, and ¶Neurosurgery, University of Wisconsin School of Medicine, Madison, WI, Joint Center for Radiation Therapy, Departments of †Radiation Oncology and #Neurosurgery, Harvard Medical School, Boston, MA, Departments of ‡Radiation Oncology and **Neurosurgery, University of Florida School of Medicine, Gainesville, FL

- At the diagnosis
- SRS

115 pts
3 institutions: Wisconsin, Harvard Boston, Florida

CTV + 2- 40mm or none margin)

Table 5. Survival stratified by prognostic class

	Present study			RTOG		
Class	MST (months)	2-year survival (%)	*n*	MST (months)	2-year survival (%)	*n*
1	—*	81†	17†	58.6	76	139
2				[illegible]	[illegible]	34
3	38.1	75	24	17.9	35	175
4	19.6	34	35	11.1	15	457
5	13.1‡	21‡	43‡	8.9	6	395
6				4.6	4	263

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 853–860, 2004 Brain

RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL

RTOG 93-05

Randomized

Luis Souhami, M.D.,* Wendy Seiferheld, M.S.,† David Brachman, M.D.,‡ Ervin B. Podgorsak, Ph.D.,* Maria Werner-Wasik, M.D.,§ Robert Lustig, M.D.,‖ Christopher J. Schultz, M.D.,¶ William Sause, M.D.,# Paul Okunieff, M.D.,** Jan Buckner, M.D.,†† Lucia Zamorano, M.D.,‡‡ Minesh P. Mehta, M.D.,§§ and Walter J. Curran, Jr., M.D.§

- At the diagnosis
- SRS

GBM <40 mm → R

- **SRS** 15-24 Gy **+ EBRT** (60 Gy) **+ BCNU** (80 mg/m2 Day 1-3 every 8 weeks for 6 cycles)
- **EBRT** (60 Gy) **+ BCNU** (80 mg/m2 Day 1-3 every 8 weeks for 6 cycles)

RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL

RTOG 93-05

- At the diagnosis
- SRS

Table 3. Patterns of failure

	Radiation therapy (n = 96)	Stereotactic radiosurgery + radiation therapy (n = 89)
Local only	51 (67%)	42 (58%)
Adjacent only	4 (5%)	2 (3%)
Local + adjacent	16 (21%)	18 (25%)
Nonadjacent only	0	1 (1%)
Local + nonadjacent	2 (3%)	1 (1%)
Local + adjacent + nonadjacent	3 (4%)	5 (7%)
Unknown	0	4 (5%)
No failure	20	16

Table 4. End of RT measures

End of RT	RT	SRS + RT
Spitzer Quality of Life Index		
n	62	49
Decline	26 (42%)	24 (49%)
Stable	15 (24%)	9 (18%)
Improve	21 (34%)	16 (33%)
p value	0.699	
Mini-Mental Status Exam		
n	59	49
Decline	19 (32%)	14 (29%)
Stable	19 (32%)	14 (29%)
Improve	21 (36%)	21 (43%)
p value	0.706	

Abbreviations: RT = radiation therapy; SRS = stereotactic radiosurgery.

Table 5. Late toxicities

	Radiation therapy (n = 87) Grade			Stereotactic radiosurgery + radiation therapy (n = 80) Grade		
	1	2	3	1	2	3
Ototoxicity	2	0	0	1	1	0
Skin	10	5	0	14	4	0
Neurologic	7	1	0	3	6	3
Other	13	5	1	10	7	1
Maximum toxicity reported per patient	17	6	0	10	9	4

Table 6. Salvage therapy*

	RT (n = 96)	SRS+RT (n = 89)
Surgery	34 (35%)	29 (33%)
Partial resection	16	14
Total resection	15	14
Shunt + total	1	1
Other type	5	7
Unknown type	3	0
Non-protocol RT	6 (6%)	6 (7%)
Non-protocol RS	18 (19%)	5 (6%)
Non-protocol chemotherapy	54 (56%)	47 (53%)

Abbreviations: RT = radiation therapy; SRS = stereotactic radiosurgery; RS = radiosurgery.

* These categories are not mutually exclusive. Some patients received more than 1 salvage therapy.

NO DIFFERENCE

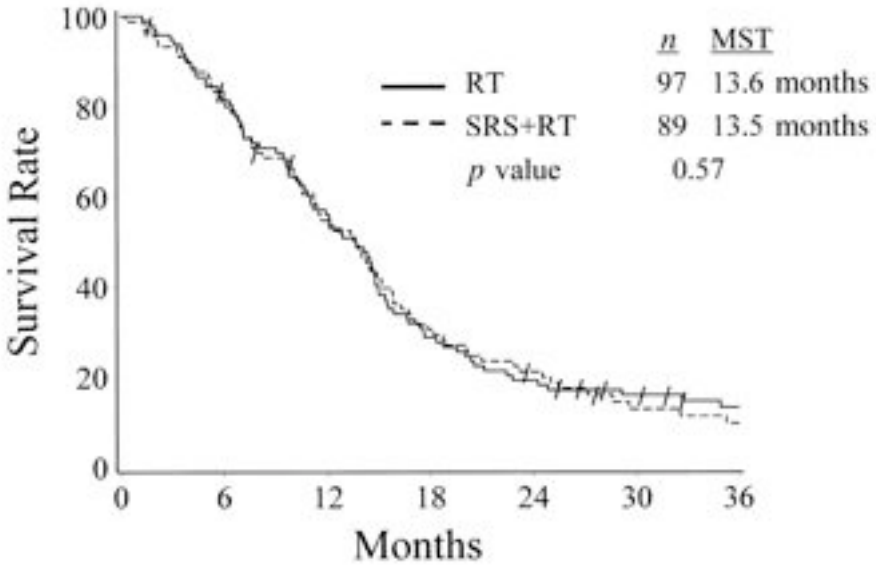
CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 853–860, 2004 Brain

RTOG 93-05

RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL

- At the diagnosis
- SRS

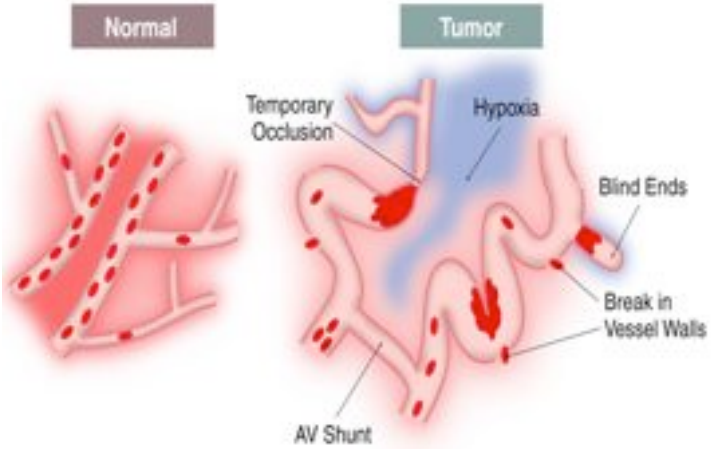
Luis Souhami, M.D.,* Wendy Seiferheld, M.S.,† David Brachman, M.D.,‡ Ervin B. Podgorsak, Ph.D.,* Maria Werner-Wasik, M.D.,§ Robert Lustig, M.D.,‖ Christopher J. Schultz, M.D.,¶ William Sause, M.D.,# Paul Okunieff, M.D.,** Jan Buckner, M.D.,†† Lucia Zamorano, M.D.,‡‡ Minesh P. Mehta, M.D.,§§ and Walter J. Curran, Jr., M.D.§



GTV or CTV < 40mm
15-24 Gy (SRS) + 60 Gy (EBRT)

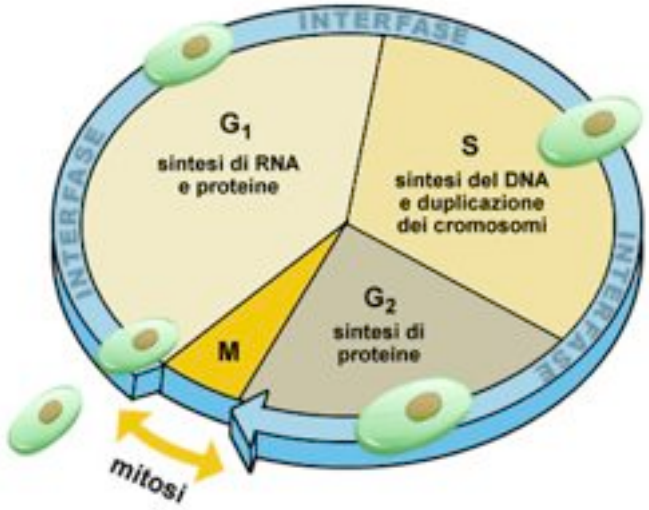
Conclusions: Stereotactic radiosurgery followed by EBRT and BCNU does not improve the outcome in patients with GBM nor does it change the general quality of life or cognitive functioning.

Hypoxia

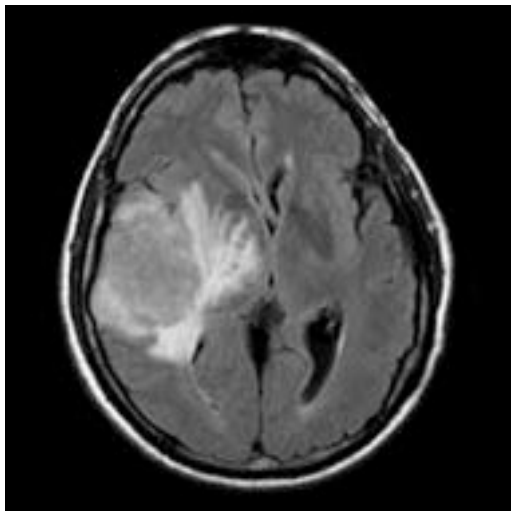


From Brown and Giaccia, Cancer Res., 58: 1408-16 (1998)

Noncycling tumor cells



Subclinical extension



FSRT + EBRT

Bullet Points

- SRS in Low Grade Gliomas
  - at the diagnosis
  - at recurrence

- High Grade Gliomas
  - at the diagnosis: SRS
    FSRT

Survival Benefit

Survival Benefit

No Survival Advantage

Retrospective

Fractionated stereotactic radiotherapy boost after post-operative radiotherapy in patients with high-grade gliomas

Brigitta G. Baumert[a,*], Johannes Lutterbach[b], René Bernays[c], J. Bernard Davis[a], Frank L. Heppner[d]

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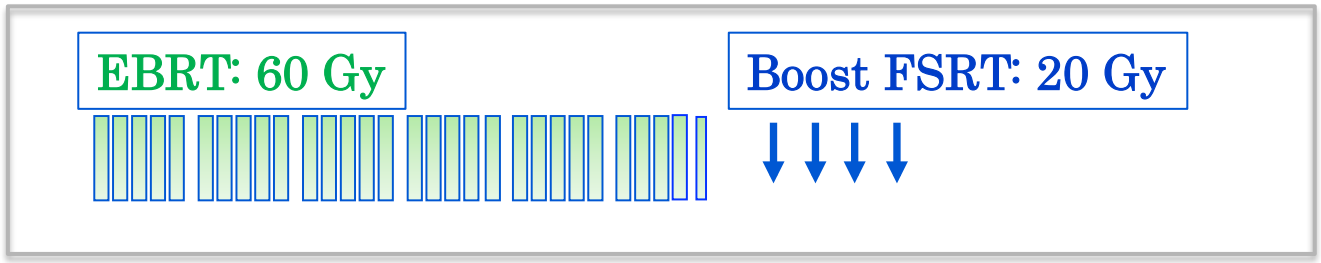
[b]Abteilung Strahlenheilkunde, Radiologische Universitaetsklinik, Freiburg, Germany
[c]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland
[d]Institute of Neuro-Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland

Received 22 2002; received in revised form 04 October 2002; accepted 01 November 2002

Radiotherapy and Oncology 67 (2003) 183–190

- At the diagnosis
- FSRT

17 pts
≤ 4 cm



PTV (if complete resection)tumor bed + 2 mm margin
PTV: pre-operative tumour + 2 mm

Fractionated stereotactic radiotherapy boost after post-operative radiotherapy in patients with high-grade gliomas

Brigitta G. Baumert[a,*], Johannes Lutterbach[b], René Bernays[c], J. Bernard Davis[a], Frank L. Heppner[d]

[a]Radiation-Oncology, University Hospital Zurich, Zurich, Switzerland
[b]Abteilung Strahlenheilkunde, Radiologische Universitaetsklinik, Freiburg, Germany
[c]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland
[d]Institute of Neuro-Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland

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Radiotherapy and Oncology 67 (2003) 183–190

- At the diagnosis
- FSRT

17pts
≤ 4 cm

Median FUP: 25 months

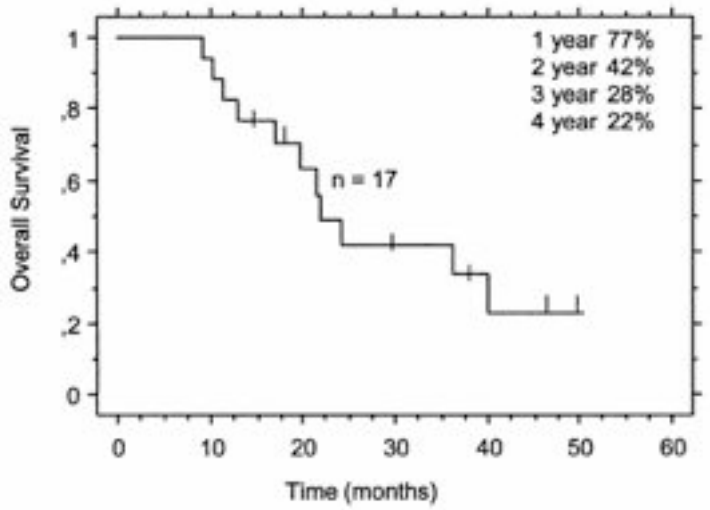


Fig. 1. Actuarial overall survival of all patients with malignant gliomas (anaplastic astrocytoma, $n = 2$ and glioblastoma multiforme, $n = 15$).

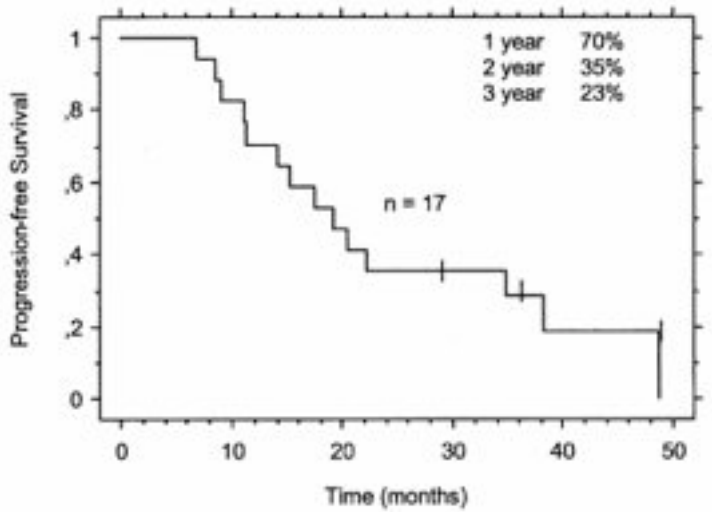


Fig. 2. Progression-free survival of all patients with malignant gliomas (anaplastic astrocytoma, $n = 2$ and glioblastoma multiforme, $n = 15$).

Fractionated stereotactic radiotherapy boost after post-operative radiotherapy in patients with high-grade gliomas

Brigitta G. Baumert[a,*], Johannes Lutterbach[b], René Bernays[c], J. Bernard Davis[a], Frank L. Heppner[d]

[a]Radiation-Oncology, University Hospital Zurich, Zurich, Switzerland
[b]Abteilung Strahlenheilkunde, Radiologische Universitaetsklinik, Freiburg, Germany
[c]Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland
[d]Institute of Neuro-Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland

Received 22 2002; received in revised form 04 October 2002; accepted 01 November 2002

Radiotherapy and Oncology 67 (2003) 183–190

- At the diagnosis
- FSRT

17pts
≤ 4 cm

Median FUP: 25 months

Conclusions: A fractionated stereotactic boost after standard external beam radiotherapy in selected patients with high-grade glioma is feasible and well tolerated with low toxicity.
Compared to historical data survival is significantly better with an additional SRT boost.
However, its effectiveness has to be proven in a randomized trial.

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 5, pp. 1422–1428, 2006 Brain

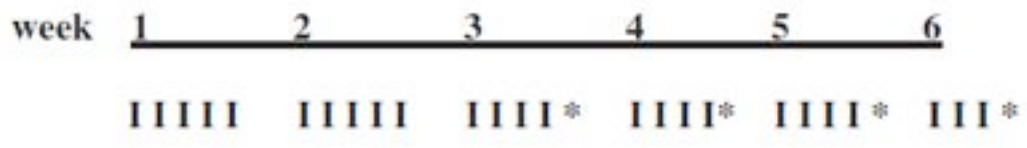
A PHASE II TRIAL OF ACCELERATED RADIOTHERAPY USING WEEKLY STEREOTACTIC CONFORMAL BOOST FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME: RTOG 0023

ROBERT CARDINALE, M.D.,* MINHEE WON, M.A.,† ALI CHOUCAIR, M.D.,‡ MICHAEL GILLIN, PH.D.,§ ARNAB CHAKRAVARTI, M.D., PH.D.,‖ CHRISTOPHER SCHULTZ, M.D.,¶ LUIS SOUHAMI, M.D.,** ALI AMIN, M.D., PH.D.,†† HUONG PHAM, M.D.,‡‡ AND MINESH MEHTA, M.D.,§§

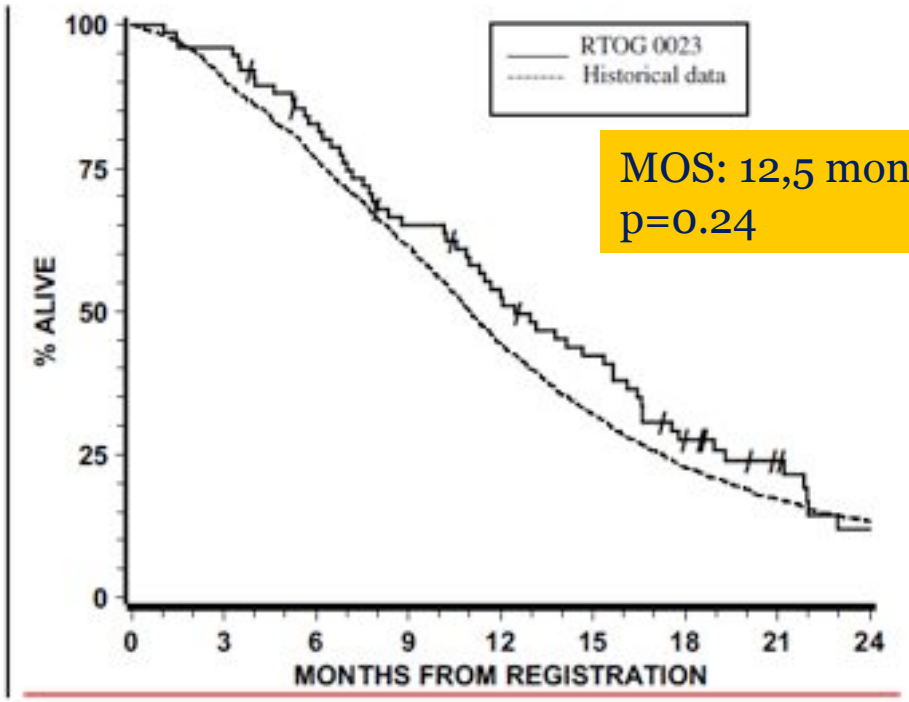
Phase II

RTOG 00-23

- At the diagnosis
- FSRT



CTV < 60mm
50 Gy (EBRT) +
20/28 Gy (FSRT) a 5/7 Gy/die



MOS: 12,5 months
p=0.24

Conclusions: This first, multi-institutional FSRT boost trial for GBM was feasible and well tolerated. There is no significant survival benefit using this dose-intense RT regimen. Subset analysis revealed a trend toward improved outcome for GTR patients suggesting that patients with minimal disease burden may benefit from this form of accelerated RT.


post

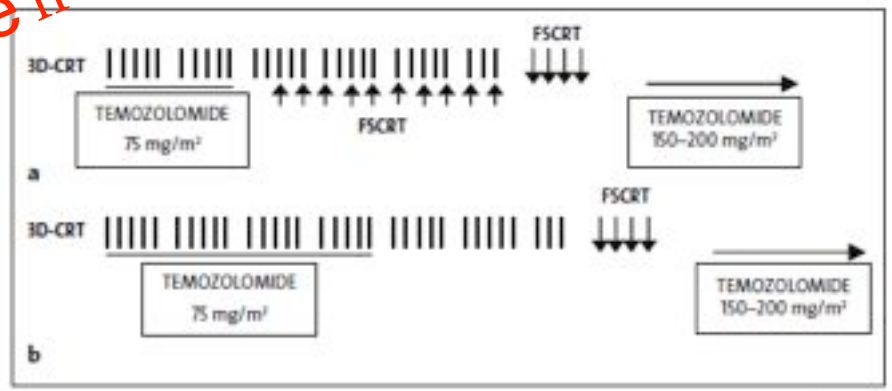
Single-Arm Phase II Study of Conformal Radiation Therapy and Temozolomide plus Fractionated Stereotactic Conformal Boost in High-Grade Gliomas

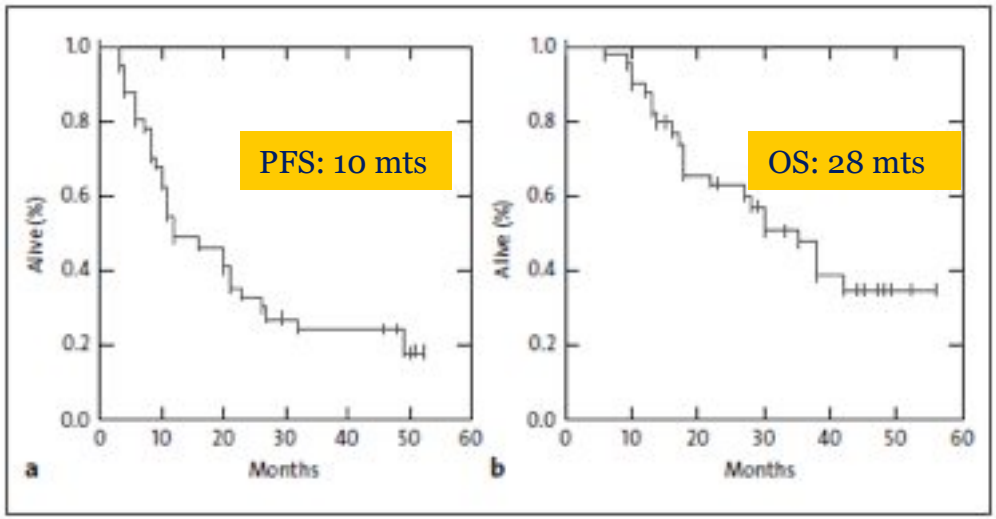
Final Report

Mario Balducci[1], Giuseppina Apicella[1,2], Stefania Manfrida[1], Annunziato Mangiola[3], Alba Fiorentino[1], Luigi Azario[4], Giuseppe Roberto D'Agostino[1], Vincenzo Frascino[1], Nicola Dinapoli[1], Giovanna Mantini[1], Alessio Albanese[3], Pasquale de Bonis[3], Silvia Chiesa[1], Vincenzo Valentini[1], Carmelo Anile[3], Numa Cellini[1]

Phase II

- At the diagnosis
- FSRT





CTV ≤ 60mm

50 Gy (EBRT) + 19 Gy (FSRT) a 90cGy/die conc + 250 cGy seq

60mm <CTV<80mm

59,4 Gy (EBRT) + 10 Gy (FSRT) a 250 cGy/die seq

Conclusions: FSCRT boost plus temozolomide is well tolerated and seems to increase survival compared to the standard treatment in patients with HGG.

CLINICAL INVESTIGATION — Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 92–97, 2010 — Brain

A PHASE I DOSE-ESCALATION STUDY (ISIDE-BT-1) OF ACCELERATED IMRT WITH TEMOZOLOMIDE IN PATIENTS WITH GLIOBLASTOMA

Alessio G. Morganti, M.D.,* Mario Balducci, M.D.,† Maurizio Salvati, M.D.,‡ Vincenzo Esposito, M.D.,‡ Pantaleo Romanelli, M.D.,‡ Marica Ferro, M.D.,* Franco Calista, M.D.,† Cinzia Digesù, M.D.,* Gabriella Macchia, M.D.,* Massimo Ianiri, M.D.,§ Francesco Deodato, M.D.,* Savino Cilla, M.D.,† Angelo Piermattei, M.P.,† Vincenzo Valentini, M.D.,‖ Numa Cellini, M.D.,‖ and Gian Paolo Cantore, M.D.‡

Departments of *Radiotherapy, †Medical Physics, and §Palliative Therapies, John Paul II Center for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy; ‖Department of Radiotherapy, Policlinico Universitario A. Gemelli, Catholic University, Rome, Italy; ‡Department of Neurosurgery, Neuromed Institute, Pozzilli, Italy; and §Department of Neurosurgery, A. Cardarelli Hospital, Campobasso, Italy

Accelerated intensity-modulated radiotherapy plus temozolomide in patients with glioblastoma: a phase I dose-escalation study (ISIDE-BT-1)

Mariangela Massaccesi · Marica Ferro · Savino Cilla · Mario Balducci · Francesco Deodato · Gabriella Macchia · Vincenzo Valentini · Alessio G. Morganti

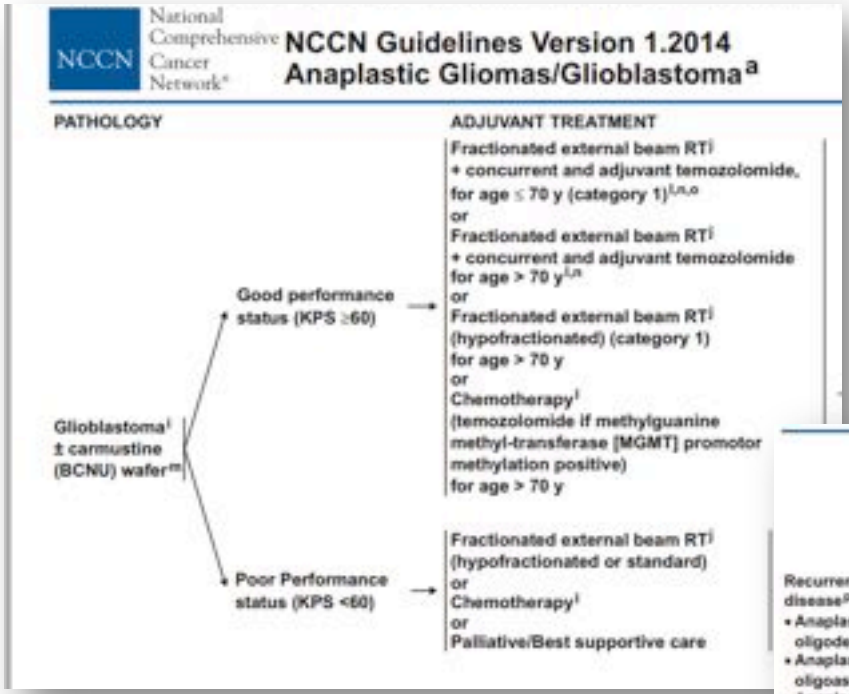
Int J Clin Oncol

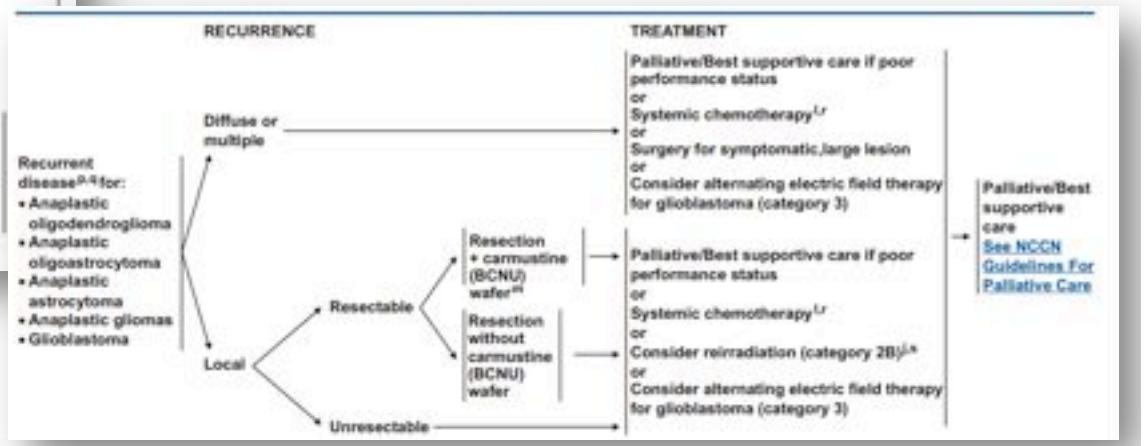
Associazione Italiana Radioterapia Oncologica
Gruppo di Lavoro Neoplasie Cerebrali

STUDI PROSPETTICI in corso

•Studio di fase II

- GBM RPA III e IV: SIB GBM, Silvia Scoccianti (67,5 a 450 cGy/die)





respectively. Another trial of 118 patients also found a benefit in median survival with radiation following surgery compared to no RT (10.8 vs. 5.2 months).[58] The typical dose is 60 Gy in 1.8 to 2.0 Gy fractions. Use of hypofractionated courses of radiation (total 40–50 Gy) has been shown to be efficacious in older patients with glioblastoma.[59-61] Studies including a radiosurgery boost or brachytherapy boost to conventional RT did not show a survival benefit.[62,63]

Summary

	Primary	Recurrent/Re-irradiation
Low Grade Glioma	SRS has not been established to have a role in the management of low grade glioma	effective treatment option with good results and few complications.
High Grade Glioma	SRS or FSRT followed by EBRT does not improve the outcome in patients nor does it change the general quality of life or cognitive functioning	

Bullet Points

- SRT in Low Grade Gliomas
  - at the diagnosis
  - at recurrence

- High Grade Gliomas
  - at the diagnosis: SRT
    FSRT
  - at recurrence

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Anaplastic Gliomas/Glioblastoma[a]

RECURRENCE[b]

There is a lack of prospective data for re-irradiating recurrent gliomas. Based on retrospective patient series, repeat RT using modern high-precision techniques such as fractionated stereotactic RT may be a palliative option for select patients with good PS and small recurrent tumors.[64,65]

Retrospective Studies

RE-IRRADIATION

RTOG 90-05

RT Dose?

CLINICAL INVESTIGATION

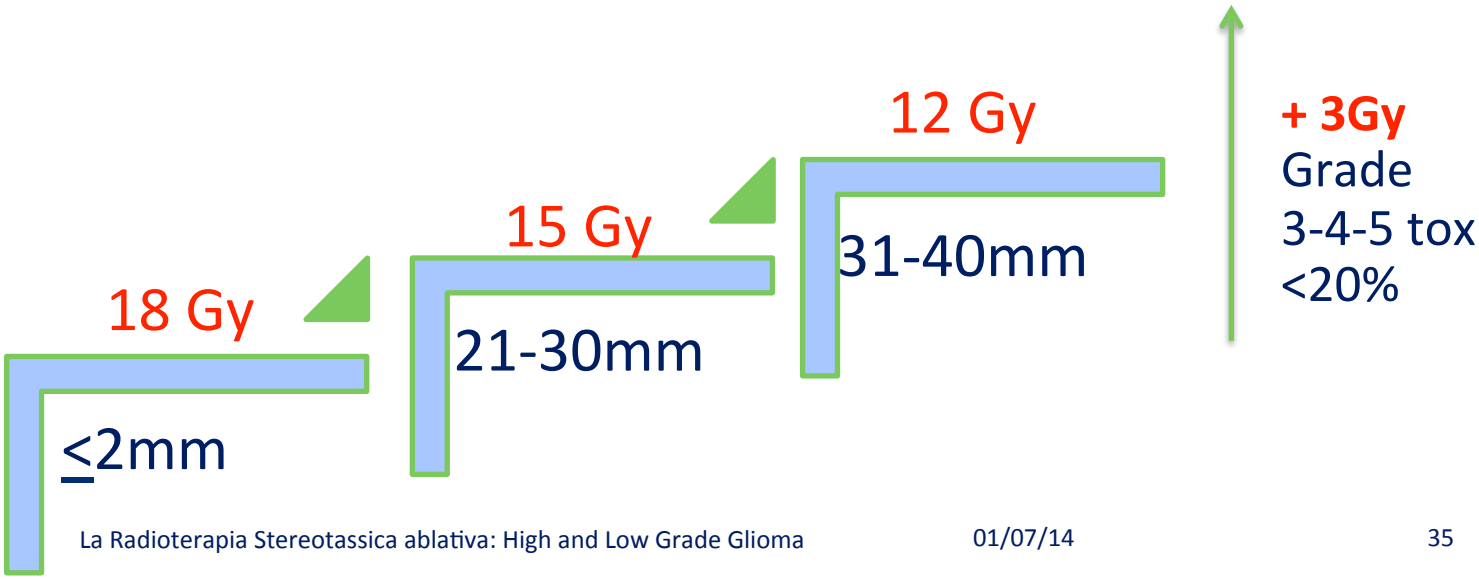
Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 2, pp. 291–298, 2000

Brain

SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05

EDWARD SHAW, M.D.,* CHARLES SCOTT, PH.D.,† LUIS SOUHAMI, M.D.,‡ ROBERT DINAPOLI, M.D.,§ ROBERT KLINE, PH.D.,‖ JAY LOEFFLER, M.D.,¶ AND NANCY FARNAN, B.S.†

*Department of Radiation Oncology, Wake Forest University School of Medicine, Winston Salem, NC; †Radiation Therapy Oncology Group, Philadelphia, PA; ‡Department of Radiation Oncology, McGill University, Montreal, Quebec, Canada; §Department of Neurology and ‖Division of Radiation Oncology, Mayo Clinic, Rochester, MN; and ¶ Joint Center for Radiation Therapy, Boston, MA



RTOG 90-05

RT Dose?

CLINICAL INVESTIGATION Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 2, pp. 291–298, 2000 Brain

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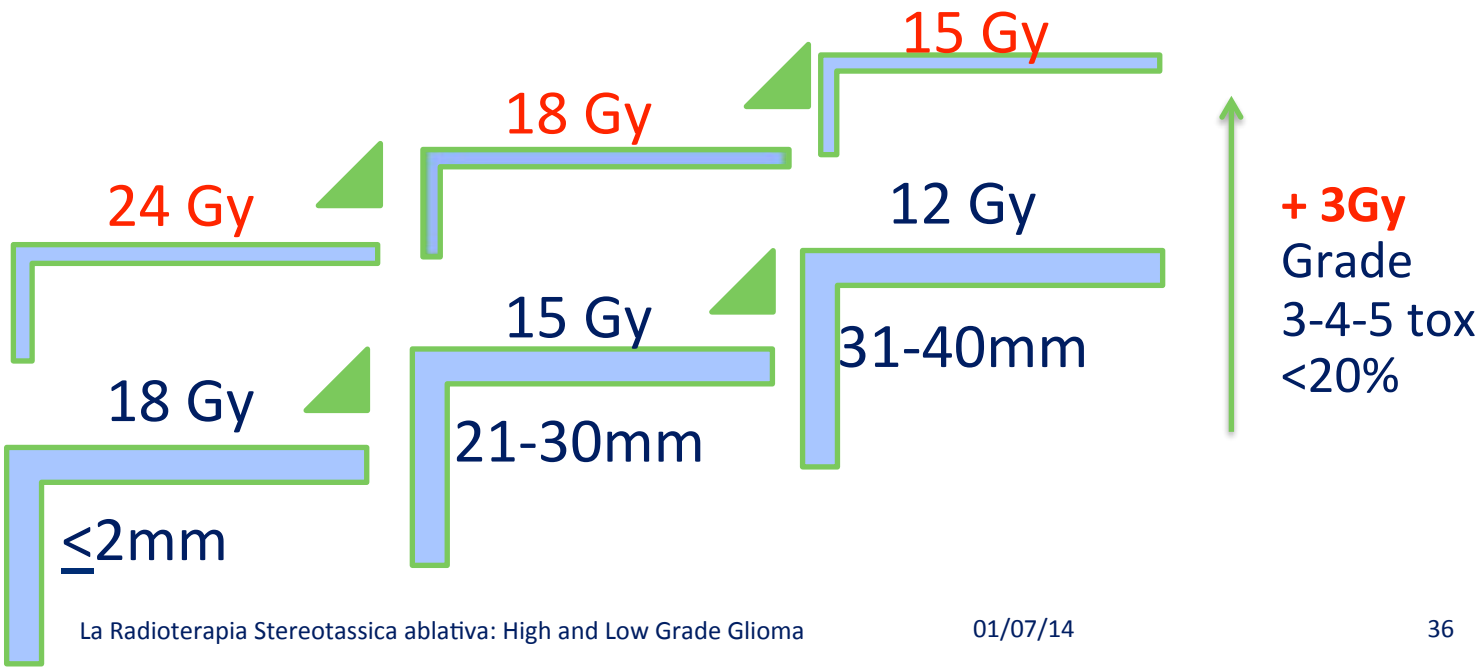

BMC Cancer

BioMed Central

Review

Open Access

Radiotherapeutic alternatives for previously irradiated recurrent gliomas

Stephanie E Combs*, Jürgen Debus and Daniela Schulz-Ertner

- At recurrence
- SRS-FSRT-H-FSRT

Table 1: Series of patients with recurrent gliomas treated with stereotactic radiosurgery (SRS).

Author	Pt. Number	Histology	Median Dose (Gy)	Tumor size (ml; median)	Median survival (months)	Rate of Severe Toxitcy/ Reoperation rate (%)
Chamberlain et al, 1994	20	5 GBM, 10 AA, 5 other	13.4	17	8	-
Cho et al., 1999	46	27 GBM/19 AA	17	10	11	22%
Combs et al., 2005	32	GBM	15	10	10	-
Hall et al., 1995	35	26 GBM, 9 AA	20	28	8	31%
Kondziolka et al., 1997	23	AA	15.6	6	31	23%
Kondziolka et al., 1997	19	GBM	15	6.5	30	19%
Shrieve et al., 1995	86	GBM	13	10.1	10.2	22%

Table 2: Series of patients with recurrent gliomas treated with fractionated stereotactic radiotherapy (FSRT).

Author	Pt. Number	Histology	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)
Cho et al., 1999	15 (10)	GBM (AA)	74	37.5	2.5	11	12%
Combs et al., 2005	71	LGG	49.3	36	2	111	-
Combs et al., 2005	42	AA		36	2	50	
Combs et al., 2005	59	GBM		36	2	21	

Table 3: Series of patients with recurrent gliomas treated with hypofractionated stereotactic radiotherapy (H-FSRT).

Author	Pt. Number	Histology	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)
Ernst-Stecken et al., 2006	15	GBM	22.4	35	7	-	0%
Hudes et al., 1999	19 (1)	GBM (AA)	12.6	30	3	10.5	0%
Laing et al., 1993	22	GBM	-	30-50 (range)	5-6 (range)	-	-
Selch et al., 2000	15 (3;3)	GBM (AA/LGG)	12	25	4-6 (range)	6.7	0%
Shepherd et al., 1997	29 (7)	GBM/AA (LGG)	24	20-50 (range)	5	11 (GBM/AA)	36%
Vordermark et al., 2005	10 (19)	II or III	15	30	5	13.5	26%
Vordermark et al., 2005	9 (19)	IV	15	30	5	7.4	

BMC Cancer

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Review

Open Access

Radiotherapeutic alternatives for previously irradiated recurrent gliomas

Stephanie E Combs*, Jürgen Debus and Daniela Schulz-Ertner

- At recurrence
- SRS

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BMC Cancer

BioMed Central

Review

Open Access

Radiotherapeutic alternatives for previously irradiated recurrent gliomas

Stephanie E Combs*, Jürgen Debus and Daniela Schulz-Ertner

- At recurrence
- FSRT-H-FSRT

Table 2: Series of patients with recurrent gliomas treated with fractionated stereotactic radiotherapy (FSRT)

Author	Pt. Number	Histology	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)
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Table 3: Series of patients with recurrent gliomas treated with hypofractionated stereotactic radiotherapy (H-FSRT).

Author	Pt. Number	Histology	Tumor size (ml; median)	Median Dose (Gy)	Median Fraction Size (Gy)	Median survival (months)	Rate of Severe Toxitcy/Reoperation rate (%)
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Laing et al., 1993	22	GBM	-	30–50 (range)	5–6 (range)	-	-
Selch et al., 2000	15 (3;3)	GBM (AA/LGG)	12	25	4–6 (range)	6.7	0%
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Vordermark et al., 2005	9 (19)	IV	15	30	5	7.4	

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

J Neurooncol (2013) 111:187–194

- At recurrence
- SRS-FSRT-H-FSRT

Table 4 Main published series on stereotactic reirradiation plus chemotherapy for recurrent malignant gliomas

Authors	Patients	Treatment	Radiation dose (Gy)	Chemotherapy	Interval	Volume (cm^3)	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)	NR	15	NR	NR	11 (HSRT + TMZ)	7 %
				HSRT alone (15 pts)					6 (HSRT alone)	
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)	21	4.5	80	5.2	11.9 (50 % at 12 months)	10 %
				SRS alone (16 pts)				2.1	3.9 (20 % at 12 months)	
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)	NR	NR	80	8	12ª (67 % at 12 months)	0 %
				FSRT alone (10 pts)				5	6ª (0 % at 12 months)	
Current study	54*	HSRT	30/5 fr	Concomitant/adjuvant TMZ	15.5	9.8	80	6	12.4 (54 % at 12 months)	7 %

HSRT hypofractionated stereotactic radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *SRS* stereotactic radiosurgery, *OS* overall survival, *PFS* progression-free survival, *KPS* Karnofsky performance status, *TMZ* temozolomide, *BVZ* bevacizumab, *NR* not reported

* Series include grade 3 and grade 4 gliomas; ** Planning treatment volume

ª Mean

SAFETY AND EFFICACY OF STEREOTACTIC RADIOSURGERYAND ADJUVANT BEVACIZUMAB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

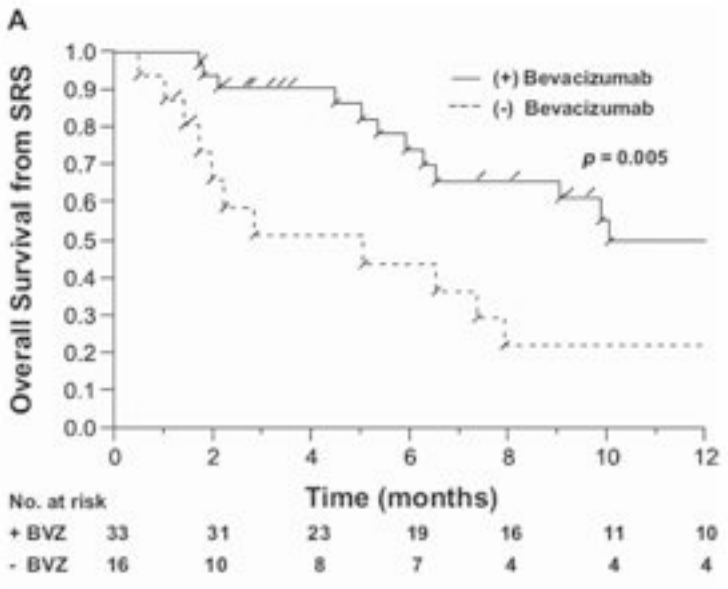
Retrospective

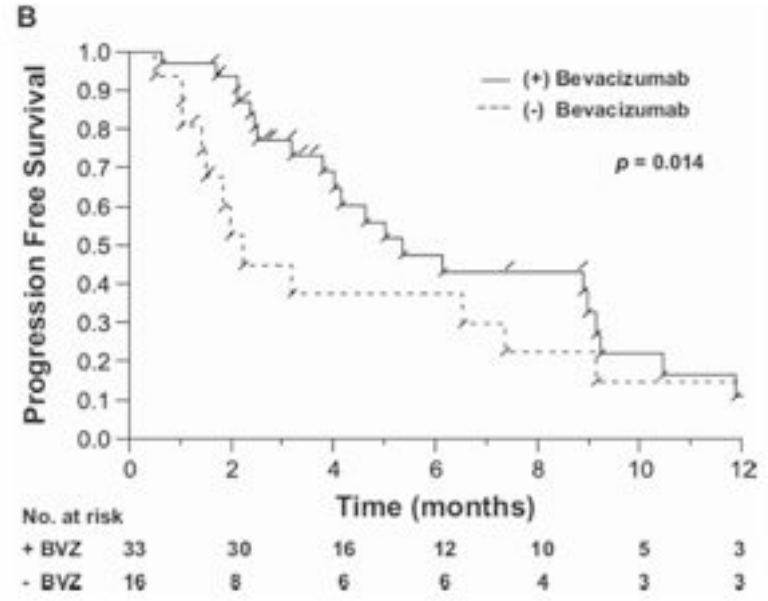
Kyle C. Cuneo, M.D.[*], James J. Vredenburgh, M.D.[†,‡], John H. Sampson, M.D., Ph.D.[†,‡], David A. Reardon, M.D.[†,‡], Annick Desjardins, M.D.[†,‡], Katherine B. Peters, M.D., Ph.D.[†,‡], Henry S. Friedman, M.D.[†,‡], Christopher G. Willett, M.D.[*], and John P. Kirkpatrick, M.D., Ph.D.[*,‡]

[*]Department of Radiation Oncology, Duke University Medical Center, Durham, NC

[†]Department of Surgery, Duke University Medical Center, Durham, NC

[‡]Department of Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC





Int J Radiat Oncol Biol Phys. 2012 April 1; 82(5): 2018–2024.

SAFETY AND EFFICACY OF STEREOTACTIC RADIOSURGERYAND ADJUVANT BEVACIZUMAB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS

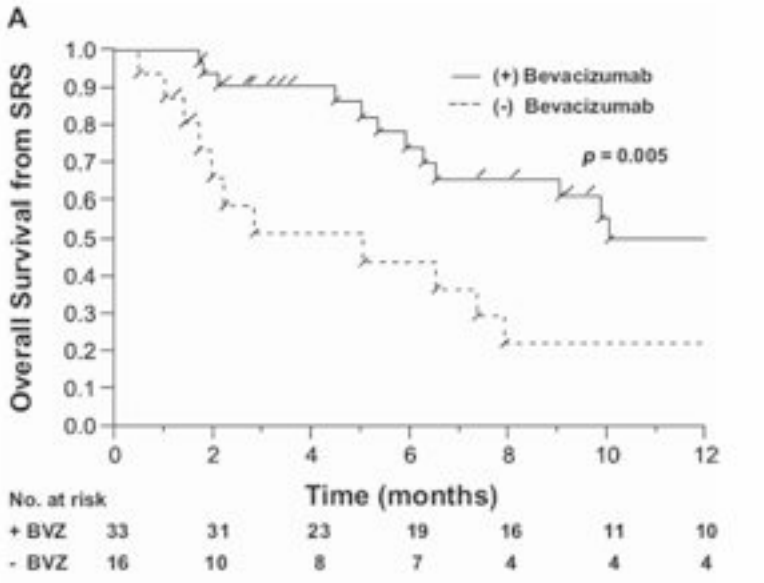
Kyle C. Cuneo, M.D.[*], James J. Vredenburgh, M.D.[†,‡], John H. Sampson, M.D., Ph.D.[†,‡], David A. Reardon, M.D.[†,‡], Annick Desjardins, M.D.[†,‡], Katherine B. Peters, M.D., Ph.D.[†,‡], Henry S. Friedman, M.D.[†,‡], Christopher G. Willett, M.D.[*], and John P. Kirkpatrick, M.D., Ph.D.[*,‡]

[*]Department of Radiation Oncology, Duke University Medical Center, Durham, NC

[†]Department of Surgery, Duke University Medical Center, Durham, NC

[‡]Department of Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC

Retrospective



Conclusions: The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas is well tolerated and seems to be associated with improved outcomes.
Prospective multiinstitutional studies are required to determine efficacy and long-term toxicity
with this approach.

Int J Radiat Oncol Biol Phys. 2012 April 1; 82(5): 2018–2024.

Concurrent Stereotactic Radiosurgery and Bevacizumab in Recurrent Malignant Gliomas: A Prospective Trial

Alvin R. Cabrera, MD,[*,1] Kyle C. Cuneo, MD,[*,||,1] Annick Desjardins, MD,[†] John H. Sampson, MD, PhD,[*,†] Frances McSherry, MA,[‡] James E. Herndon II, PhD,[‡] Katherine B. Peters, MD, PhD,[†] Karen Allen, ANP,[*] Jenny K. Hoang, MBBS,[§] Zheng Chang, PhD,[*] Oana Craciunescu, PhD,[*] James J. Vredenburgh, MD,[†] Henry S. Friedman, MD,[†] and John P. Kirkpatrick, MD, PhD[*,†]

*Departments of Radiation Oncology, †Surgery, ‡Biostatistics and Bioinformatics, and §Radiology, Duke University, Durham, North Carolina; and ||Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

Prospective

Conclusions: Treatment of recurrent MG with concurrent SRS and BVZ was not associated with excessive toxicity in this prospective trial. A randomized trial of concurrent SRS/BVZ versus conventional salvage therapy is needed to establish the efficacy of this approach

NCT01017250

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Home > Find Studies > Study Record Detail

Radiosurgery and Avastin for Recurrent Malignant Gliomas

This study has been completed.

Sponsor:
Duke University

Collaborator:
Genentech

Information provided by (Responsible Party):
Duke University

ClinicalTrials.gov Identifier:
NCT01017250

First received: November 19, 2009
Last updated: January 28, 2014
Last verified: January 2014
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Results First Received: April 11, 2012

Study Type:	Interventional
Study Design:	Endpoint Classification: Safety Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment
Condition:	Malignant Glioma
Interventions:	Radiation: Stereotactic Radiosurgery (SRS) Drug: Bevacizumab

CTV < 2.0cm: 24 Gy in 1 fraction
CTV 2.0-2.9cm: 18 Gy in 1 faction
CTV 3.0-4.9cm 25 Gy in 5Gy/fractions
Bevacizumab (Avastin) 10 mg/kg given the day before SRS and 2 weeks after SRS

The primary endpoint: proportion of patients who experience CNS toxicity,
Secondary endpoints: PFS, OS, radionecrosisi, QoL, Response, KPS

Take home message

	Primary	Recurrent/ Re-irradiation
Low Grade Glioma	SRS has not been established to have a role in the management of low grade glioma	effective treatment option with good results and few complications.
High Grade Glioma	SRS or FSRT followed by EBRT does not improve the outcome in patients nor does it change the general quality of life or cognitive functioning	Stereotactic ablative radiotherapy is feasible and safe in selected patients according to size, site and KPS