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ORIGINAL REPORT

Efficacy of Fractionated Stereotactic Reirradiation in Recurrent Gliomas: Long-Term Results in 172 Patients Treated in a Single Institution

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ABSTRACT

Purpose
To evaluate the efficacy of fractionated stereotactic radiotherapy (FSRT) performed as reirradiation in 172 patients with recurrent low- and high-grade gliomas.

Patients and Methods
Between 1990 and 2004, 172 patients with recurrent gliomas were treated with FSRT as reirradiation in a single institution. Seventy-one patients suffered from WHO grade 2 gliomas. WHO grade 3 gliomas were diagnosed in 42 patients, and 59 patients were diagnosed with glioblastoma multiforme (GBM). The median time between primary radiotherapy and reirradiation was 10 months for GBM, 32 months for WHO grade 3 tumors, and 48 months for grade 2 astrocytomas. FSRT was performed with a median dose of 36 Gy in a median fractionation of 5 × 2 Gy/wk.

Results
Median overall survival after primary diagnosis was 21 months for patients with GBM, 50 months for patients with WHO grade 3 gliomas, and 111 months for patients with WHO grade 2 gliomas. Histologic grading was the strongest predictor for overall survival, together with the extent of neurosurgical resection and age at primary diagnosis. Median survival after reirradiation was 8 months for patients with GBM, 16 months for patients with grade 3 tumors, and 22 months for patients with low-grade gliomas. Only time to progression and histology were significant in influencing survival after reirradiation. Progression-free survival after FSRT was 5 months for GBM, 8 months for WHO grade 3 tumors, and 12 months for low-grade gliomas.

Conclusion
FSRT is well tolerated and may be effective in patients with recurrent gliomas. Prospective studies are warranted for further evaluation.

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INTRODUCTION

The treatment of primary CNS tumors still remains one of the most challenging tasks in neuro-oncology. Despite numerous therapeutic approaches, including neurosurgery, radiotherapy, and chemotherapy, overall survival remains poor, especially for WHO grade 3 and 4 gliomas, with few long-term surviving patients.[1] The vast majority of gliomas recurs within or adjacent to the original tumor bed.[2-4] The inability to achieve local tumor control is strongly correlated with marked neurologic deficits, leading to eventual death in most patients with recurrent gliomas.

Treatment options for recurrent astrocytomas are commonly limited because most therapeutic alternatives have already been performed, including neurosurgery and a full course of radiotherapy and/or chemotherapy.

Optimal surgical resection might be possible in a subgroup of patients; however,

it is accompanied by a high risk of morbidity because of the infiltrative nature of the tumor.[5,6] Radiotherapeutic alternatives are often limited with respect to dose prescription because radiotherapy is a component of first-line therapy in most patients.[3] Systemic chemotherapy might offer modest benefit for a subgroup of patients.[7-9]

Stereotactic radiosurgery (SRS) is appealing because of its ability to precisely deliver high doses of irradiation to a defined target volume in a single fraction with less treatment-associated morbidity compared with surgery.[10,11] However, SRS is limited to smaller lesions, as the risk of radiation-induced side effects increases with treatment volume. Fractionated stereotactic radiotherapy (FSRT) enables the precise application of radiotherapy to a defined target volume, while exploiting the radiobiologic advantage of fractionation and minimizing the risk for severe radiation-induced side effects.[3,12] The present study updates our results on FSRT in recurrent tumors[2,3] and evaluates the efficacy and long-term outcome of FSRT performed as reirradiation in 172 patients with recurrent low-grade, anaplastic, and high-grade gliomas treated at the University of Heidelberg.

PATIENTS AND METHODS

The study population consisted of 172 patients with recurrent gliomas treated with FSRT as reirradiation from January 1990 to December 2004. All patients were treated in a single institution. Patient characteristics are listed in Table 1.

The median age at primary diagnosis of the tumor was 41 years (range, 5 to 76 years) for all patients. Seventy-nine patients were female, and 93 patients were male.

All patients had undergone at least one neurosurgical intervention. At primary diagnosis, a total resection was performed in 54 patients (31.4%), a subtotal resection was performed in 78 patients (45.3%), and a biopsy was conducted in 40 patients (23.3%). Seventy-one patients suffered from WHO grade 2 gliomas (41.3%), WHO grade 3 gliomas were diagnosed in 42 patients (24.4%), and 59 patients (34.3%) were diagnosed with glioblastoma multiforme (GBM) at primary diagnosis[13] (Fig 1). Of all

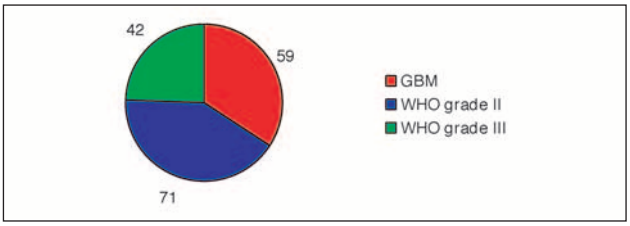


Fig 1. Histology at primary diagnosis of the tumor. GBM, glioblastoma multiforme.

patients with WHO grade 2 tumors, pure astrocytomas could be diagnosed in 57 patients, and oligoastrocytoma and pure oligodendroglioma could be diagnosed in seven patients each. The group of WHO grade 3 gliomas consisted of 24 pure astrocytomas, 10 pure oligodendrogliomas, and eight oligoastrocytomas.

All patients received a full course of radiotherapy after primary diagnosis with a median dose of 60 Gy in conventional fractionation. Nine of the patients with low-grade gliomas had received I^{125}-Seeds for radiotherapy at primary diagnosis. Before FSRT as reirradiation, 56 patients had experienced treatment failure with at least one chemotherapeutic regimen including temozolomide; carmustine; procarbazine, cyclophosphamide, and vincristine (PCV), or nimustine/teniposid (ACNU/VM26).

Tumor progression was diagnosed on magnetic resonance imaging (MRI) scans performed during follow-up after primary treatment in all 172 patients. MRI scans were performed as regular follow-up examinations or when clinical worsening developed. MRI spectroscopy or positron emission tomography and single-photon emission computed tomography examinations were scheduled as needed to differentiate between radiation-induced changes or tumor progression.

The majority of the recurrences were localized within the former high-dose radiotherapy (RT) field (Fig 2). For the treatment of tumor progression, a neurosurgical procedure could be conducted in 60 of 172 patients; a total resection was performed in four patients (7%), a subtotal resection was performed in 47 (78%), and a biopsy was performed in only nine patients (15%).

The median time between primary RT and reirradiation was 10 months (range, 3 to 71 months) for GBM, 32 months (range, 3 to 126 months) for WHO grade 3 tumors, and 48 months (range,

Table 1. Patient Characteristics

	WHO Grade					
	2		3		4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age at primary diagnosis, years						
Median	35		39		54	
Range	13-64		21-74		18-76	
Age at recurrence, years						
Median	42		43		55	
Range	16-66		24-75		19-77	
Presence of neurologic symptoms at recurrence	55	77	32	76	37	63
KPS ≥ 80 at recurrence	65	92	39	93	37	63

Abbreviation: KPS, Karnofsky performance score.

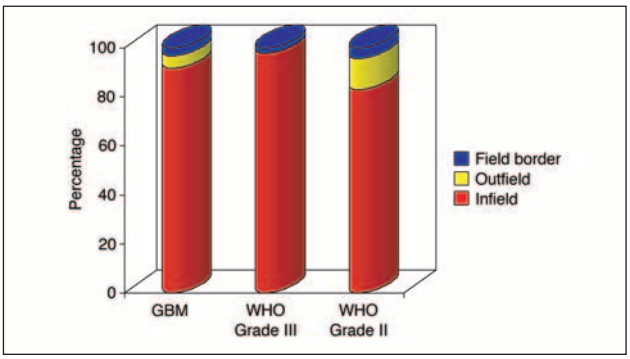


Fig 2. Location of tumor recurrence after primary radiotherapy. GBM, glioblastoma multiforme.

5 to 204 months) for grade 2 astrocytomas. Median age at tumor recurrence was 46.5 months (range, 5 to 77 months).

All patients were treated with FSRT for reirradiation. To allow for accurate treatment planning and daily repositioning for FSRT, an individually manufactured mask fixation made of Scotch Cast (3M, St Paul, MN) was made for each patient. This fixation system has been described previously and allows for an overall repositioning accuracy of 1 to 2 mm.[3,12,14] Treatment planning was performed three dimensionally based on contrast-enhanced computed tomography (CT) and MRI. Both CT and MRI scans were performed with a stereotactic localization system attached to a stereotactic base frame.[15] After stereotactic image fusion of CT and MRI images, the target volume was defined on each slice of the three-dimensional data cube. The slice thickness was 3 mm. The gross target volume (gross tumor volume) was defined as the area of contrast enhancement on T1-weighted MRI sequences; the planning target volume included the gross tumor volume, adding a 0.5- to 1-cm safety margin. The median size of the defined PTV was 49.3 mL (range, 2.5 to 636 mL).

Treatment planning was performed using the three-dimensional treatment planning system Voxelplan (dkfz Heidelberg, Germany) using the beam's eye view technique for field optimization. We applied three to five noncoplanar isocentric fields that were irregularly shaped using a midsize multileaf collimator with a leaf thickness of 5 mm at isocenter. The target doses were prescribed to the isocenter at a median of 36 Gy (range, 15 to 62 Gy), delivered in a median fractionation of 5 × 2 Gy/wk. The defined target volume was encompassed by the 90% isodose. All patients were treated at a linear accelerator with energies of 6 or 15 MV (Fa. Siemens, Erlangen, Germany). The median RT dose for reirradiation was prescribed with respect to prior RT portals and prescribed total dose, as well as size and location of the lesion, especially with respect to organs at risk, such as the optic chiasm, brainstem, and the optic nerves. No concomitant chemotherapy was applied.

Patients were seen for follow-up visits 6 weeks after completion of FSRT, then in 3 months' intervals or as needed clinically. All follow-up visits included a thorough neurologic assessment as well as contrast-enhanced MRI scans. Additional diagnostic procedures, including positron-emission tomography and single-photon emission computed tomography imaging as well as MRI spectroscopy, were scheduled as required.

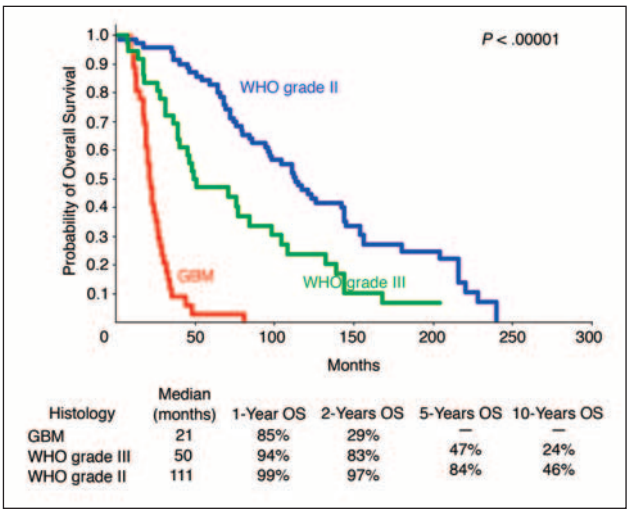
Primary end point of the analysis was survival. Overall survival was calculated from primary diagnosis of the tumor, and survival from reirradiation was calculated from initiation of FSRT. Progression-free survival after FSRT was calculated from the initiation of radiotherapy for recurrence until tumor progression or death (by any cause), whichever happened first.[16] Influence of prognostic factors on outcome was evaluated using the univariate and multivariate Cox proportional regression model.[17] We performed bi-variate Cox regression for each potential prognostic factor together with histologic grading. Histology and those factors statistically significant together with histology were finally included into a multivariate analysis when exhibiting a *P* value of .01 or less. All calculations were performed using the SAS System (SAS Institute, Cary, NC) and the survival analysis programs of the system ADAM of the Biostatistics Unit of the German Cancer Research Center, Heidelberg, Germany.

RESULTS

FSRT was well tolerated by all patients, and the intended treatment could be completed without interruptions. The median follow-up time after FSRT was 7 months (range, 1 to 105 months) for GBM, 13 months (range, 1 to 99 months) for recurrent WHO grade 3 astrocytomas, and 23 months (range, 2 to 104 months) for grade 2 astrocytomas.

Minor temporary side effects of FSRT included alopecia, headaches, nausea/vomiting, and skin erythema. We observed radiographically diagnosed and histologically confirmed radiation-induced necrosis after reirradiation in one patient only. No other severe early or late side effects more than National Cancer Institute common toxicity criteria grade 2 could be documented.

Twenty-two patients were alive at the time point of analysis; 150 patients died of tumor progression during follow-up. Median overall survival for patients with GBM was 21 months (range, 7 to 180 months; Fig 3). Median overall survival for patients with WHO grade 3 astrocytomas was 50 months (range, 7 to 204 months). For low-grade



Histology	Median (months)	1-Year OS	2-Years OS	5-Years OS	10-Years OS
GBM	21	85%	29%	—	—
WHO grade III	50	94%	83%	47%	24%
WHO grade II	111	99%	97%	84%	46%

Fig 3. Overall survival (OS) calculated from primary diagnosis of 172 patients treated with fractionated stereotactic radiotherapy for reirradiation. GBM, glioblastoma multiforme.

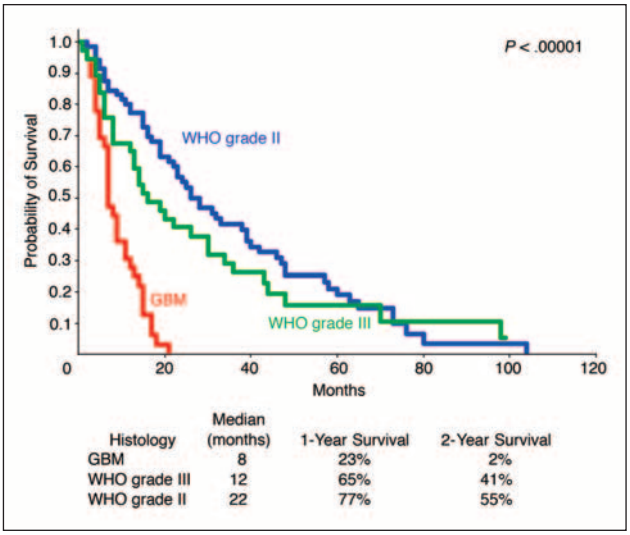


Fig 4. Survival after reirradiation of 172 patients treated with fractionated stereotactic radiotherapy. GBM, glioblastoma multiforme.

gliomas (WHO grade 2), median overall survival was 111 months (range, 13 to 240 months). Histology was the strongest predictor for overall survival ($P < .00001$). Extent of neurosurgical resection also significantly influenced overall survival ($P = .0004$). In bivariate analysis, the influence of histology ($P < .00001$) was significant in combination with the extent of neurosurgical resection ($P < .0001$) and age at primary diagnosis (< 50 *v* ≥ 50 years of age; $P = .0008$; Table 2).

In multivariate analysis, histology ($P < .00001$), extent of neurosurgical resection ($P = .00001$), and age at primary diagnosis ($P = .01$) remained significant factors influencing overall survival (Table 2).

Median survival after FSRT was 8 months for patients with GBM (range, 1 to 105 months; 23% at 1 year). For patients with grade 3 astrocytomas, median survival after FSRT was 16 months (range, 1 to 99 months). Median progression-free survival after FSRT for patients with low-grade gliomas was 22 months (range, 2 to 104 months). Histologic grading at primary diagnosis remained the strongest influencing factor on survival ($P < .00001$). Time to progression ($P = .046$) in combination with histology ($P < .00001$) was significant in influencing survival (Table 3).

Progression-free survival after FSRT was 5 months (range, 1 to 21 months) for GBM, 8 months (range, 1 to 99 months) for WHO grade 3 tumors, and 12 months (range, 1 to 69 months) for low-grade gliomas (Fig 5). Histology at primary diagnosis ($P < .00001$) was a strong prognostic factor for progression-free survival after FSRT.

To analyze the impact of histologic subtypes on survival times, the groups consisting of patients with WHO grade 2 and 3 gliomas were subdivided into the categories oligodendroglioma, oligoastrocytoma, and pure astrocytoma. Statistical analysis revealed that the oligo-component did not have a significant impact on overall survival, survival after FSRT, and progression-free survival after FSRT in this patient collective (Fig 6).

At tumor progression after FSRT, chemotherapy was performed in 36 patients, including the administration of temozolomide, carmustine, PCV, or ACNU/VM26, taking into consideration prior systemic treatments.

Table 2. Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival

Variable 1	Variable 2	*P* (univariate)
Histology	—	< .00001
—	Extent of neurosurgical resection	.0004
Histology	Extent of neurosurgical resection	> .00001
Histology	Age at primary diagnosis	.0008
Histology	Sex	.404
Histology	Karnofsky performance score	.889
Histology	Presence of neurological symptoms	.06

Variable	*P* (multivariate)
Histology	< .00001
Extent of neurosurgical resection	.00001
Age at primary diagnosis	.01

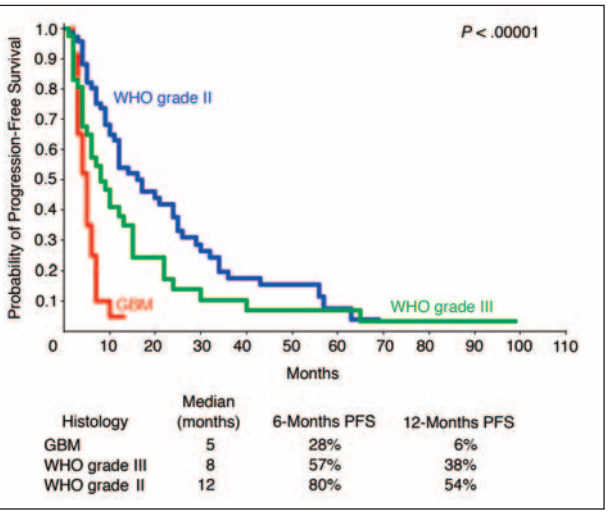
DISCUSSION

The achievement of local tumor control is the main goal in the treatment of astrocytomas. Over the years, combined treatment with neurosurgical resection and postoperative radiotherapy has been shown to be an effective treatment as compared with surgery or radiotherapy alone. Recently, novel radio-chemotherapeutic approaches have been evaluated and could extend overall and progression-free survival time significantly as compared to radiotherapy alone.[18,19] However, most patients eventually develop recurrences within or in close vicinity of the primary tumor site,[20] requiring effective and tolerable salvage treatment. However, therapeutic alternatives for tumor progression

Table 3. Univariate Analysis of Prognostic Factors for Survival After Fractionated Stereotactic Radiotherapy

Variable 1	Variable 2	*P* (univariate)
Histology	Extent of neurosurgical resection	.95
Histology	Age at recurrence	.8
Histology	Sex	.56
Histology	Karnofsky performance score	.96
Histology	Presence of neurologic symptoms	.38
Histology	Size of the PTV	.497
Histology	Time to progression	.046

Abbreviation: PTV, planning target volume.



Histology	Median (months)	6-Months PFS	12-Months PFS
GBM	5	28%	6%
WHO grade III	8	57%	38%
WHO grade II	12	80%	54%

Fig 5. Progression-free survival after reirradiation of 172 patients treated with fractionated stereotactic radiotherapy. GBM, glioblastoma multiforme.

are often limited because of previously performed aggressive multimodality treatment.

Neurosurgical resection is possible in a subgroup of patients, but may be associated with high morbidity and mortality; also, an optimal extent of resection may be difficult to achieve in most cases because of the infiltrative nature of gliomas.[5,6] However, the decision to perform a neurosurgical resection has to be made individually for each patient depending on a number of factors, including overall performance status, size, and location of the tumor, as well as on previously performed therapies. Chemotherapy is probably the most frequent salvage treatment used for recurrent low- and high-grade gliomas. Despite numerous studies performed, only modest benefit has been shown in the past.[7-9,21-24]

A number of radiotherapeutic approaches have been proposed for recurrent astrocytomas (Table 4). However, reirradiation with conventional external-beam RT was often associated with only modest benefit for the patients, whereas toxicity outweighed the benefits.[25]

Several groups have performed brachytherapy for recurrent disease,[26-28] implementing different technical approaches. For high-activity I-125 interstitial implants, median survival times in highly selected patients with recurrent astrocytoma or GBM were between 54 and 81 weeks.[27] Glia-Site brachytherapy, using an inflatable balloon catheter implanted into the surgical resection cavity for delivery of homogeneous low-dose rate radiation, has shown promising results in patients with recurrent gliomas.[29] Similarly, implementation of Gliadel (carmustine wafers) after surgical resection has shown to increase survival in patients with recurrent gliomas as compared with surgery alone.[8,30] In a subgroup of patients, the effect of brachytherapy might be comparable to the outcome achievable with single-dose irradiation (SRS), as reported by Shrieve et al.[26]

	WHO Grade II *P*	WHO Grade III *P*
Overall survival	.18	.06
Survival after FSRT	.98	.26
Progression-free survival after FSRT	.54	.58

WHO Grade II		WHO Grade III	
• Astrocytoma	n = 57	• Astrocytoma	n = 24
• Oligoastrocytoma	n = 7	• Oligoastrocytoma	n = 8
• Oligodendroglioma	n = 7	• Oligodendroglioma	n = 10

Fig 6. Influence of histologic subtypes of WHO grade 2 and 3 astrocytomas on overall survival, survival after fractionated stereotactic radiotherapy (FSRT), and progression-free survival after FSRT.

The main advantage of SRS over brachytherapy is the noninvasive approach, enabling the local application of radiation without surgical intervention. Patients will most likely benefit from the noninvasive application. Therefore, SRS is often performed as salvage treatment for recurrent gliomas, and survival times between 8 and 12 months have been reported.[11,26,31-34]

SRS is appealing because of its ability to precisely deliver high doses of irradiation to a defined target volume in a single fraction with a steep dose-gradient around the target. Because of the potential toxicity associated with the single-fraction treatment, SRS is limited to a subgroup of patients with smaller lesions, because the risk for side effects becomes a concern with larger tumor volumes. This is mainly due to the fact that with SRS, no attempt is made to spare normal cells within or around the irradiated volume by dividing the total tumor dose into a number of fractions.[10,35] With precise positioning devices allowing for exact daily repositioning, it is possible to exploit the radiobiologic advantages of fractionation with improvement of the therapeutic ratio compared with single-fraction treatments, especially for somewhat larger treatment volumes or tumors not treatable with SRS. Therefore, FSRT plays a central role in the treatment of recurrent gliomas.

Our preliminary results could show survival times after reirradiation of 23 and 8 months achieved by stereotactically guided reirradiation in patients with recurrent low-grade gliomas and GBM, respectively.[2,3] Cho et al[10] treated 25 patients with recurrent gliomas with FSRT and observed median survival times of 14.7 months after FSRT for anaplastic astrocytoma and 7.1 months for recurrent GBM. Factors significantly influencing survival were histologic grading and reoperation before FSRT, younger age, and smaller tumor volumes. Hudes et al[36] reported median survival times of 10.5 months in patients with WHO grade 3 and 4 astrocytomas treated with FSRT for tumor progression, with total doses of 30 Gy delivered in 3-Gy single fractions. For this analysis, only patients with smaller tumor volumes (median, 12.7 mL) were included.

The main disadvantage of most reports on fractionated reirradiation is the inclusion of smaller groups of several

Table 4. Reirradiation of Recurrent Gliomas: A Literature Overview Including Different Radiation Modalities

Author	Technique	No. of Patients	Tumor Size (mL)		Median Dose (Gy)	Median Survival (months)
			Median	Range		
Leibel, 1989[27]	I-125	45		N/A	70	12.5
Leibel, 1989[27]	I-125	50		N/A	70	18.7
Sneed, 1991[24A]	I-125 + HT	28		N/A	51	12.7
Shibamoto, 1994[24C]	IORT	19		N/A	25	12
Baumann, 1996[24B]	EBRT	34		N/A	NR	8.3
Arcicasa, 1999[24D]	EBRT	31		N/A	34.5	13.7
Kim, 1999[24H]	EBRT	20		N/A	36	9
Veninga, 2001[38]	EBRT	42		N/A	46	10.9
Shrieve, 1995[26]	SRS	86	10.1	2.2-83	13	10.2
Chamberlain, 1994[32]	SRS	20	17	3.0-53.5	13.4	8
Sanghavi, 1999[24G]	SRS	30	7.2	0.42-35.1	12	8
Hall, 1995[11]	SRS	35	28	2.4-98	20	8
Park, 2000[24J]	SRS	23	9.9	0.9-37.9	15	10.3
Cho, 1999[10]	SRS	46	10	1-54	17	11
Combs, 2005[34]	SRS	32	10	1.2-59.2	15	10
Selch, 2000[24F]	FSRT	21	12	4.5-33.7	25	6.7
Shepherd, 1997[37]	FSRT	29	24	3-93	35	10.7
Vyonov, 2002[24I]	FSRT	10	34.7	4.3-75.2	30	10.1
Combs, 2005[2]	FSRT	59 (GBM)	47.7	7.5-636	36	8
Combs, 2005[24E]	FSRT	42 (WHO Gr.3)	56.2	2.5-296	36	16
Combs, 2005[3]	FSRT	71 (WHO Gr.2)	42.3	5.5-636	36	23

Abbreviations: I-125, I125-Seeds; HT, hyperthermia; IORT, intraoperative radiotherapy; EBRT, external-beam radiotherapy; SRS, single-dose irradiation; FSRT, fractionated stereotactic radiotherapy; GBM, glioblastoma multiforme; Gr., grade; N/A, not available.

histologic subtypes, leading to survival times higher than expected for a chosen histology.

The present analysis represents the largest group of patients treated with FSRT for reirradiation. The large patient group, consisting of 172 patients, enables the performance of detailed statistical analysis, providing outcome data strongly representative for each histologic subgroup. It is known that histology is the main prognostic factor influencing outcome in patients with astrocytomas, which is supported by the present analysis ($P < .00001$). High-grade tumors are commonly associated with shorter survival times as compared with low-grade tumors.[10,33,37] This is reflected by the survival times reported in the present analysis, with an overall survival of 21 months for GBM and 50 months and 111 months for WHO grade 3 astrocytomas and low-grade gliomas, respectively. In accordance with other groups, the extent of neurosurgical resection and younger age together with histology significantly influenced overall survival.[10,33]

Survival times after FSRT were 8 months for GBM and 16 and 22 months for grade 3 and 2 astrocytomas, respectively; in this analysis, histology and time to tumor progression were the strongest predictors for survival, as reported also by other groups.[10,33,38]

Only minor side effects, such as alopecia, skin erythema, headaches, and nausea/vomiting, could be observed. Only one patient developed brain necrosis. No large number of severe short- and long-term side effects could be documented. Only one patient developed brain necrosis. This leads to the conclusion that FSRT is not only an effective means to achieve local control of recurrent gliomas for a subgroup of patients, but is also well tolerable and safe with regard to therapy-related side effects. However, the present results are not obtained from a prospective randomized study. A number of limitations must be considered, including patient selection criteria and difficulty in assessing treatment toxicity. As FSRT in a precision head mask is a physical strain on patients, an overall acceptable clinical performance status is required for reirradiation, possibly resulting in a favorable outcome.

Other modern radiotherapeutic treatment alternatives, such as high-precision RT applied as intensity modulated radiotherapy (IMRT), might also achieve comparable treatment outcomes when applied appropriately.

Considering the extensive research on the implementation of radiochemotherapeutic regimens as primary therapy of gliomas, including the implementation of temozolomide, ACNU/VM26 or PCV,[18,19,39] further improvement of outcome might be possible if chemotherapy is added concomitantly to FSRT for recurrent tumors. Therefore, prospective trials are required to further consolidate the results obtained in the present analysis and to reach the ambitious goal we have set for this highly devastating tumor entity.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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