Hypofractionated Stereotactic Reirradiation of Recurrent Glioblastomas

A Beneficial Treatment Option after High-Dose Radiotherapy?

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Background and Purpose: Recurrent malignant gliomas have a very poor prognosis. This trial aimed to evaluate the benefits of reirradiation in case of recurrent glioblastoma multiforme (GBM) using hypofractionated stereotactic radiotherapy (hFSRT) after primary high-dose percutaneous irradiation.
Patients and Methods: Between 1998 and 2008, 53 patients with recurrent GBM were treated by hFSRT based on CT and MR imaging. At the time of recurrence, a median total dose of 30 Gy (20–60 Gy) was delivered in median fractions of 3 Gy/day (2–5 Gy).
Results: The reirradiation was well tolerated (no acute or late toxicity > grade 2), despite the relatively large median tumor volume (35.01 ml). Karnofsky Performance Score was the strongest predictor for survival after reirradiation (p = 0.0159). Tumor volume (p = 0.4690), patient age (p = 0.4301), second operation (p = 0.6930), and chemotherapy (p = 0.1466) at the time of reirradiation did not affect survival. After hFSRT, the median survival was 9 months, and the 1-year progression-free survival (PFS) amounted to 22%.The median overall survival from initial diagnosis was 27 months. 1-year survival from first diagnosis was 83%, 2-year survival 45%. The median time to progression from the end of initial irradiation to recurrence was 12 months. 1-year PFS before reirradiation was 40%.
Conclusion: hFSRT as a secondary treatment of recurrent GBM is a feasible and effective treatment option. Only minor side effects were observed with prolonged life expectancy of 9 months.

Key Words: Recurrent glioblastoma · Stereotactic radiotherapy · Reirradiation · Survival

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Ist die hypofraktionierte stereotaktische Reradiatio eine sinnvolle Behandlungsoption rezidivierter Glioblastome nach vorheriger hochdosierter Bestrahlung?

Hintergrund und Ziel: Die Prognose im Rezidivfall eines malignen Glioms ist schlecht. Diese Studie hatte zum Ziel, den Stellenwert einer hypofraktionierten stereotaktischen Rebestrahlung (hFSRT) bei rezidiviertem Glioblastom (GBM) nach perkutaner hochkonformaler Radiotherapie zu evaluieren.
Patienten und Methodik: Zwischen 1998 und 2008 wurden 53 Patienten mit einem rezidivierten GBM stereotaktisch rebestrahlt. Die mediane Gesamtherddosis betrug 30 Gy (20–60 Gy), die mediane Einzelherddosis 3 Gy/Tag (2–5 Gy).
Ergebnisse: Trotz großer Tumorvolumen von median 35,01 ml wurde nach hFSRT keine Akut- oder Spättoxizität > Grad 2 beobachtet. Der Karnofsky-Perfomance-Score war der einzige determinante Faktor hinsichtlich des Gesamtüberlebens nach hFSRT (p = 0,0159). Hingegen beeinflussten Tumorvolumen (p = 0,4690), Patientenalter (p = 0,4301), Zweitoperationen (p = 0,6930) oder Chemotherapie (p = 0,1466) das Gesamtüberleben nach hFSRT nicht. Das mediane Gesamtüberleben nach hFSRT betrug 9 Monate, das progressionsfreie 1-Jahres-Überleben (PFS) 22%. Das mediane Gesamtüberleben nach initialer Diagnosestellung eines GBM lag bei 27 Monaten, das 1- bzw. 2-Jahres-Gesamtüberleben bei 83% bzw. 45%. Der mediane Zeitpunkt bis zum ersten Rezidiv nach initialer Bestrahlung betrug 12 Monate, das 1-Jahres-PFS nach initialer Bestrahlung bis zum ersten Rezidiv 40%.
Schlussfolgerung: Die hFSRT ist eine geeignete und effektive Behandlungsoption für rezidivierte GBM. Das mediane Gesamtüberleben nach hFSRT konnte bei geringer Nebenwirkungsrate um 9 Monate verlängert werden.

Schlüsselwörter: Rezidiviertes Glioblastom · Stereotaktische Bestrahlung · Reradiatio · Überleben

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Introduction

High-grade malignant gliomas, especially glioblastoma multiforme (GBM), are usually refractory to aggressive combined-modality treatment and show a dismal prognosis. Despite the progress in neurosurgery, radiotherapy and oncology, recurrences develop in virtually all patients, resulting in poor survival [10, 12, 22, 28, 32]. The standard of care for patients with recurrent GBM has not yet been clearly defined.

Repeated irradiation of the same tumor site in conventional manner is considered to be critical, regarding acute and late side effects. Physicians are often reluctant to offer a second course of radiation to the brain due to lack of experience and concern about potential toxicity. Hypofractionated stereotactic radiotherapy (hFSRT) as a salvage therapy is a noninvasive approach to deliver a precisely localized high radiation dose into a small volume. This method is characterized by a steep dose fall-off to the periphery and may be a gentle option for recurrent treatment after high-dose percutaneous radiotherapy by means of limiting the dose to the surrounding critical structures [5–7, 13].

A combination with chemotherapy, especially temozolomide (TMZ), is probably the most frequent salvage treatment employed for recurrent GBM which leads to an elongated overall survival (OS) especially in younger patients [27–29]. Reoperation can only be performed in selected patients of younger age and in good condition. Indeed, the infiltrative nature of the disease does not always allow a total resection without compromising neurologic functions [27].

Our retrospective analysis therefore focused on the benefit of hFSRT for recurrent GBM concerning efficacy and toxicity.

Patients and Methods

Patient Characteristics

Between 1998 and 2008, 53 patients, 35 male and 18 female, with recurrent GBM were treated with hFSRT at our department. The initial diagnosis of all patients was proven histologically and radiologically. Median age at first diagnosis was 53 years (22–71 years), and minimum Karnofsky Performance Score (KPS) 70%. In 13 cases, the tumor was subtotally resected after initial diagnosis, 39 patients underwent complete resection, and only one biopsy was performed. All patients received fractionated external-beam radiotherapy to a median dose of 54 Gy (38.5–64 Gy), depending on tumor size and localization. The median daily dose was 2 Gy over 5 days per week. 41 patients received chemotherapy during and/or after initial radiotherapy. 28 patients were treated with TMZ, nine patients with ACNU/VM-26 (nimustine/teniposide), two patients with PCV (procarbazine, lomustine and vincristine) and two patients with topotecan.

Different regimens of chemotherapy were applied in 25 patients during and/after completion of the reirradiation. Eight patients were treated with TMZ, nine patients received ACNU/VM-26 as second-line chemotherapy, and five patients were treated with PCV. 3 patients were sequentially treated with TMZ and nitrosoureas. After recurrence, 23 patients also obtained a reresection before reirradiation.

Reirradiation

All patients were presented to our institute's interdisciplinary neurooncology tumor conference. The main indication for reirradiation was tumor recurrence and the main purpose was to increase local tumor control. Patients were fixed by an individually formed helmet mask system attached to a relocatable stereotactic frame [13, 20]. Reposition accuracy represented < 2 mm as previously reported [11]. Localizing contrast-enhanced CT and MRI scans with 3 mm thickness were transferred to the planning system. After image fusion, the target volume was defined by the contrast-enhanced tumor edges with a safety margin of 3 mm. Treatment planning was performed by Voxelplan™ [13]. Irradiation dose was prescribed in respect to the organs at risk. The latter included the optic nerves, the eyes, the optic chiasm as well as the brainstem.

hFSRT was delivered with an energy of 6-MV photons from a linear accelerator with a micro multileaf collimator. Leaf thickness was 1 mm resulting in a resolution of 1.5 mm at the isocenter. The latter was defined as reference point and the irradiation dose was applied by three to five noncoplanar, individually collimated static beams. The planning target volume was encompassed by 90–95% of the prescribed dose at the isocenter [3].

The tumor recurrences were localized as follows: 21 tumors in the temporal, seven in the temporoparietal, three in the temporooccipital, eight in the frontal, six in the parietooccipital, and three in the occipital lobe, and five in various localizations. For reirradiation, 37 patients received a median dose of 3 Gy (26 patients, total dose: 30 Gy; eleven patients, total dose: 36 Gy), nine patients a fraction dose of 3.5 Gy, five patients received 2 Gy, one patient 4 Gy, and one patient 5 Gy. The median cumulative doses were 30–36, 35, 60, 20, and 25 Gy, respectively. At the time of recurrence 34 patients had a KPS < 70% and 19 patients showed a KPS ≥ 70%. The median planning tumor volume measured 35.01 ml (3–204 ml).

Follow-Up

Patients were followed up regularly by clinical examinations after 6 weeks. Clinical examination and the first MRI were performed every 3 months after reirradiation or in the event of unexpected neurologic worsening. Otherwise, neurologic or radiologic examinations were performed adapted to the clinical symptoms. The median follow-up was 8 months (2–31 months).

Clinical response was defined as neurologic improvement, supported by stable or improved MRI scans. Stable disease was defined as at least unchanged tumor volume at the time of radiologic follow-up, including patients with partial regression of tumor size. A progression was defined by increased radio-

logic tumor volume with or without the incidence of neurologic symptoms. CTC and LENT-SOMA scales were used for clinical evaluation of the acute and late toxicity, respectively [7, 8, 21, 22].

Statistical Analysis

OS, survival after reirradiation, progression-free survival (PFS), and survival curves were computed using the Kaplan-Meier method and compared by the Cox-Mantel log-rank test. Samples were divided into high and low subgroup by cutting at the median value to get an equal size each and most accuracy of the test. P-values of < 0.05 were considered significant. All statistical analyses were performed using the SPSS 15.0.0 software.

Results

After reirradiation, the median survival was 9 months. The 1-year PFS amounted to 22%, the 2-year PFS to 5%. KPS at the time of recurrence (< 70%: 34 patients; ≥ 70%: 19 patients) was the strongest predictor for survival (p = 0.0159; Figure 1). No statistical differences were observed according to tumor volume at the time of reirradiation (< 30 ml: 26 patients vs. ≥ 30 ml: 27 patients; p = 0.4690; Figure 2), age (< 56 vs. ≥ 56 years of age; 9 months each; p = 0.4301; Figure 3), and chemotherapy (yes: 11 vs. no: 8 months; p = 0.1466; Figure 4). Similarly, second operation after recurrence displayed no significant benefit regarding median survival upon reirradiation (9 months each; p = 0.693).

hFSRT was well tolerated and all patients completed reirradiation without difficulties or breaks. No acute or late toxicities > grade 2 were observed, even in patients receiving high daily doses (≥ 3 Gy) and to large tumor volume. The most common side effects were alopecia and fatigue. Steroids were not given prophylactically, except in one patient with raised intracranial pressure. Neuroradiologic investigation did not reveal any radionecrosis in the complete collective.

Median OS after first diagnosis was 27 months (Figure 5), 1-year and 2-year OS were 83% and 45%, respectively. PFS after the initial treatment was 12 months (Figure 5) with a

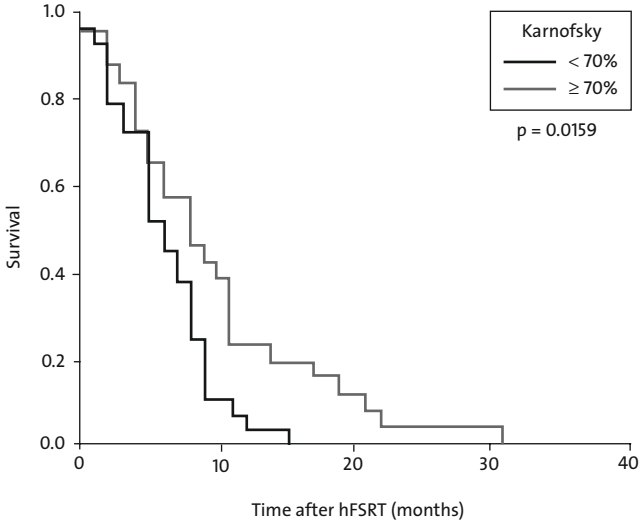

Figure 1. Survival after hFSRT of recurrent GBM depending on KPS.

Abbildung 1. Überleben nach hFSRT bei rezidiviertem GBM in Abhängigkeit vom Karnofsky-Index.

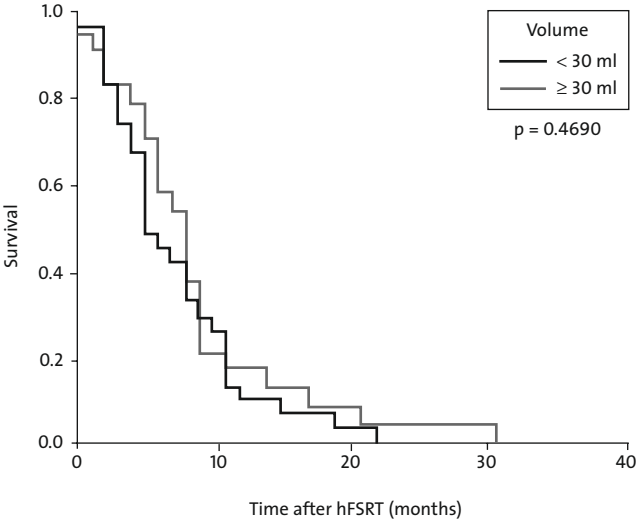

Figure 2. Survival after hFSRT of recurrent GBM depending on tumor volume.

Abbildung 2. Überleben nach hFSRT bei rezidiviertem GBM in Abhängigkeit vom Tumorvolumen.

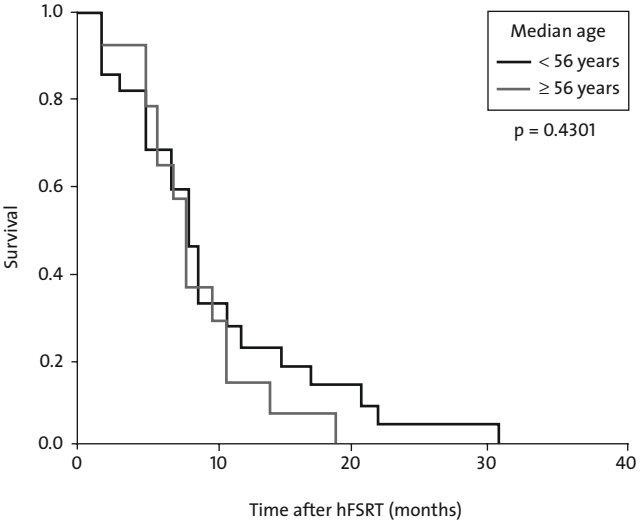

Figure 3. Survival after hFSRT of recurrent GBM depending on age.

Abbildung 3. Überleben nach hFSRT bei rezidiviertem GBM in Abhängigkeit vom Patientenalter.

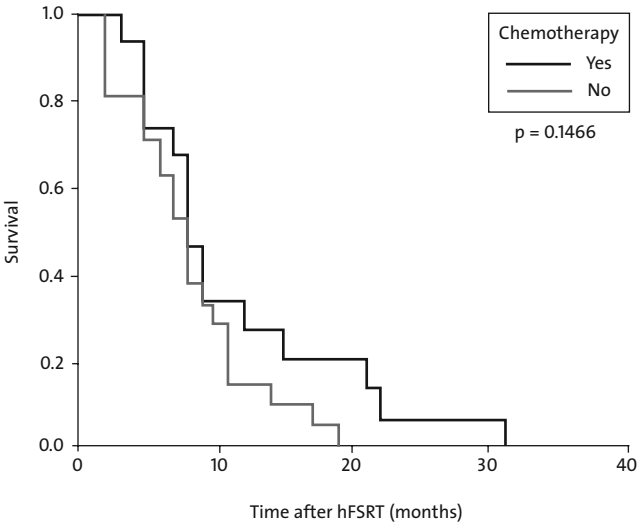

Figure 4. Survival after hFSRT of recurrent GBM depending on the application of chemotherapy.

Abbildung 4. Überleben nach hFSRT bei rezidiviertem GBM in Abhängigkeit von der Applikation einer Chemotherapie.

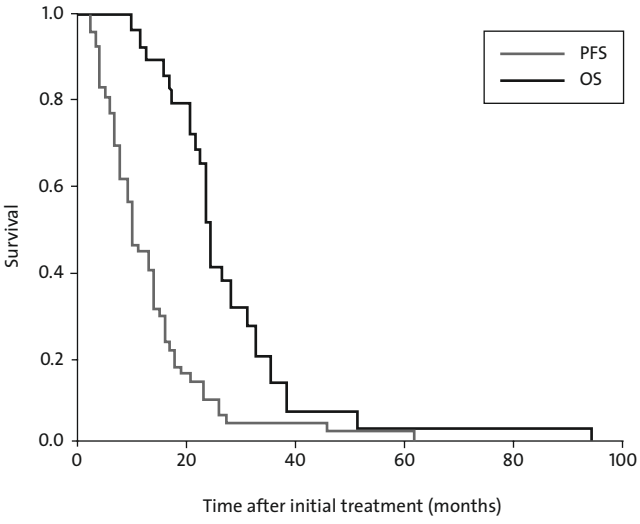

Figure 5. Overall survival and progression-free survival after initial treatment.

Abbildung 5. Gesamtüberleben und progressionsfreies Überleben nach Ersttherapie.

1-year PFS of 40% and a 2-year PFS of 10%. There was a significant difference of the PFS after initial therapy in regard to age (< 56 years: 16 months; ≥ 56 years: 8 months; p = 0.005) and chemotherapy (yes: 14 vs. no: 9 months; p = 0.031). No significant difference in the OS was found depending on the age (< 56 years: 30 months; ≥ 56 years: 23 months; p = 0.1878) or the application of chemotherapy during the whole treatment (yes: 29 vs. no: 19 months; p = 0.1116), despite a trend observed for better OS on the patients that received chemotherapy.

Discussion

GBM is the most common malignant primary brain tumor in adults. Surgery and radiotherapy constitute the cornerstones for the therapeutic management of GBM. Different regimens of chemotherapy, either as first-line or second-line therapy in combination with irradiation, are applied, such as TMZ or nitrosoureas [15, 26, 27, 29, 30]. The latter has improved PFS and OS, but long-time survival is extremely rare. Despite the use of conventional therapeutic modalities such as surgery, chemotherapy, and ionizing radiation treatment, the prognosis remains poor due to the high incidence of local recurrence. Up to 90% of all glioblastomas relapse in close proximity to the resection cavity or the target volume of postoperative radiotherapy [27]. Radiologic evidence of primary and recurrent GBM should be confirmed by MRI investigation while lately, new promising diagnostic methods such as SPECT have been suggested [1].

During the last decade, there has been an increased interest in fractionated stereotactic reirradiation as a palliative measure for patients with recurrent GBM, in combination with chemotherapy and reresection, if possible [9, 16, 21, 22]. In this study, we found a median OS of 27 months estimated from the first diagnosis. In addition, the median PFS of 12 months after the initial radiotherapy and the survival of 9 months after reirradiation are comparable with the literature [6, 23, 32]. Combs et al. reported a median OS after reirradiation of 8 months by applying normofractionated stereotactic radiotherapy (single doses of 2 Gy) [6]. The median OS after first diagnosis was 21 months. Vordermark et al. [32] presented a median OS after hFSRT of 7.9 months by administering a median dose of 5 Gy/day in a collective of 19 patients. The median irradiated volume in this study was 15 ml. A trial from Grosu et al. [12] showed a median OS after hFSRT of 8 months (for a collective with astrocytomas *and* gliomas) by applying a median single dose of 5 Gy/day at a median irradiated volume of 15 ml.

An important finding of the present study regards the median tumor volume irradiated using hFSRT. In our study, the median tumor volume irradiated was 35.01 ml, which is double the average irradiated tumor volume that was reported in previous studies [12, 17, 23]. Interestingly, this did not lead to a higher toxicity, despite the raised doses per fraction. Thus, our results consolidate previous reports concerning the survival after hFSRT and show that the risk of side effects is lower than expected. Importantly, even for larger tumor sizes, daily doses up to 3.5 Gy and cumulative doses > 30 Gy were well tolerated.

In our study, KPS ≥ 70% was associated with longer patient survival, as previously described for recurrent GBM [22]. In addition, tumor volume did not influence survival of patients after hFSRT. Similarly to our study, previous work has reported no difference on survival, based on tumor vol-

Table 1. Survey of median OS after stereotactic irradiation: FSRT, radiosurgery, or brachytherapy of recurrent GBM (reirradiation). FSRT: fractionated stereotactic radiotherapy; GBM: glioblastoma multiforme; hFSRT: hypofractionated stereotactic radiotherapy; OS: overall survival; SRS: stereotactic radiosurgery.

Tabelle 1. Medianes OS nach stereotaktischer Bestrahlung: FSRT, Radiochirurgie oder Brachytherapie bei rezidiviertem GBM (Reradiatio). FSRT: fraktionierte stereotaktische Radiotherapie; GBM: Glioblastoma multiforme; hFSRT: hypofraktionierte stereotaktische Radiotherapie; OS: Gesamtüberleben; SRS: stereotaktische Radiochirurgie.

Authors	Patients (n)	Therapy	Volume (ml)	Median dose (Gy)	Median OS
Simon et al., 2002 [25]	42	Iridium brachytherapy	23	50	12.5 months
Chan et al., 2005 [2]	24	Brachytherapy	No data	53	9.1 months
Larson et al., 2002 [18]	14	SRS + marimastat	8–9		9.5 months
Combs et al., 2005 [6]	32	SRS	No data	15	10 months
Shrieve et al., 1995 [24]	86	SRS	10.1	13	10.2 months
Shrieve et al., 1995 [24]	32	Brachytherapy	29	50	11.5 months
Grosu et al., 2005 [12]	33	FSRT	15	30	8 months (calculated for astrocytomas and gliomas)
Kohshi et al., 2007 [16]	25	FSRT	8.7	22	19 months for astrocytomas and 11 months for GBM
Own data	53	hFSRT	35.01	30	9 months

ume [22]. Mixed findings regarding the influence of tumor volume on survival have been reported and are probably due to the different radiation doses, schedules and multimodal therapy used, and more studies are needed to draw firm conclusions. Lederman et al. showed that patients with tumor volumes < 30 ml who received fractionated stereotactic radiosurgery (SRS) and paclitaxel survived longer [19]. In another study, tumor volumes < 20 ml were associated with better response [14].

Other therapy options include brachytherapy (BT) or SRS but they are strictly limited to smaller tumor volumes in patients in good general condition. In addition, BT and SRS show a higher risk of toxicities (e.g., radionecrosis) than hFSRT and, thus, higher rates of reoperation. Besides, the results in terms of survival do not differ substantially from the results of hFSRT (SRS: 9.5–10.2 months, BT: 9.1–12.5 months) [2, 24] (Table 1).

Because of the high total dose applied during the initial irradiation, the reirradiation is contradictorily debated regarding the risk of acute or late toxicity. In line with previous reports [8, 22, 32], all patients in the present study tolerated reirradiation well and only acute and late toxicities up to grade 2 were observed, even in patients who received doses > 3.5 Gy per fraction. Moreover, late toxicities such as cognitive deficiencies were not observed. The latter could be attributed to the short survival after reirradiation.

In our study, chemotherapy applied during or after reirradiation resulted in a higher but statistically not significant median patient survival, as compared with the patients that were treated only with hSFRT. Nevertheless, concomitant chemoradiotherapy followed by monotherapy with TMZ has become the standard of care for patients with GBM [27]. Chemotherapy with TMZ should be considered after recurrence to prolong patient survival [15, 27, 30]. In most of our cases, the chemotherapy administered either during and/or after initial radiotherapy and reirradiation was well tolerated. Nevertheless, all of our long-time survivors received different regimens of chemotherapy.

We acknowledge that different factors could potentially have influenced this study: previously applied treatments in combination with the initial radiotherapy, primary applied radiation dose, neurosurgical interventions, and factors such as patients' age and gender. This study is a retrospective trial and we tried to build a homogeneous collection, but our patients represent a small number of people in good condition with recurrent GBM.

Conclusion

hFSRT is a palliative modality and should be considered a valuable therapeutic option for recurrent GBM. hFSRT has demonstrated beneficial results in patient survival, whether it is combined with chemotherapy or not. The reirradiation is well tolerated by the patients with low acute or late toxicity, despite high single (up to 3.5 Gy) and cumulative doses (up to 35 Gy) and large tumor size. A cumulative dose of 30 Gy is recommended. Prospective quality-of-life studies and greater patient collectives are needed to better define the sequelae of reirradiation.

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