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Scientific Article

Reirradiation of High-Grade Gliomas: A Retrospective Analysis of 198 Patients Based on the Charité Data Set

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Abstract

Purpose: There is no standard of care for recurrent high-grade glioma. Treatment strategies include reresection, reirradiation, systemic agents, intratumoral thermotherapy using magnetic iron-oxide nanoparticles ("nanotherapy"), and tumor treating fields. Only a small number of patients are eligible for reresection, and because many patients receive a full course of radiation therapy, there is fear of reirradiation-induced morbidity. Modern radiation techniques have resulted in greater acceptance of reirradiation. In this work we retrospectively analyzed patients who had undergone reirradiation of high-grade glioma at Charité Universitätsmedizin Berlin.

Methods and Materials: All patients treated with reirradiation for recurrent high-grade glioma in our department from January 1997 to February 2014 were analyzed in this study. In total, 198 patients were included. The primary endpoint was overall survival after recurrence.

Results: One hundred ninety-eight patients were identified. Median time from first radiation therapy to reirradiation was 14 months. Median follow-up from the first day of reirradiation to last contact or death was 7 months. Median overall survival after relapse was 7 months for the overall cohort. For glioblastoma, median overall survival after relapse was 6 months and for grade 3 gliomas 14 months. Treatment was generally well tolerated. Common Terminology Criteria for Adverse Events grade 3 toxicity was observed in 5.1% patients and grade 4 toxicity in 2.5%. No patient developed grade 5 toxicity. The likelihood of developing severe toxicity (Common Terminology Criteria for Adverse Events grade 3 or 4) was not significantly higher in the group of patients who received reirradiation in the first 14 months after initial radiation therapy. Patients who received a higher biologically effective dose to the tumor also did not have a significantly higher rate of severe acute toxicity.

Conclusions: The prognosis of recurrent high-grade glioma remains dismal. Reirradiation is often tolerable even after early recurrence (<14 months) and with higher doses (eg, 49.4 Gy/3.8 Gy) in selected patients.

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Data in the manuscript are available by contacting the corresponding author.

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Introduction

Despite the use of multimodal approaches, treatment of high-grade glioma remains a challenge, and the prognosis is dismal.[1,2] Ultimately, almost every patient shows relapse; most sites of relapse are found within close proximity to the original tumor bed.[3] However, to date, there is no standard of care for this condition. Reresection may be considered depending on the performance status and tumor localization, but morbidity is higher than that in the initial surgery, and only a small subgroup of patients is eligible.[4] Other treatment strategies include reirradiation, unconventional temozolomide regimens and other systemic agents like bevacizumab, intratumoral thermotherapy using magnetic iron-oxide nanoparticles ("nanotherapy"), external radiofrequency approaches and tumor treating fields.[5,6] Because almost all patients with recurrent glioma receive a full course of radiation therapy, there is a legitimate fear of reirradiation-induced morbidity. Modern radiation techniques like fractionated stereotactic radiation therapy (FSRT) allow for an improved therapeutic ratio and better sparing of organs at risk (OARs) and have thus led to greater acceptance of reirradiation. However, dose constraints for normal brain tissue remain unclear. It is known from in vivo experiments that repair of irradiation-induced cell damage is dependent on fraction size, cumulative dose, and time between first and second course of irradiation.[7] Most published studies on FSRT reirradiation in high-grade glioma so far have used hypofractionated regimens ($\geq$5 Gy per fraction).[8,9] Hypofractionation does shorten treatment time in a group of patients with highly impaired life expectancy but is associated with a potentially increased late toxicity rate. An alternative could be accelerated hyperfractionation, an approach that would offer short treatment times and a lower risk of late toxicity combined with the theoretical advantage of lower tumor repopulation in treatment intervals.

In this study, we have retrospectively analyzed 198 patients with high-grade glioma treated with reirradiation at Charité Universitätsmedizin Berlin. The primary endpoint was overall survival (OS). Results were compared with the published data on patients who received reirradiation and systemic therapy.

Methods and Materials

Treatment decisions, patient selection, and dose regimens

This retrospective analysis was approved by the institutional review board. Written informed consent was acquired from all patients with respect to radiation therapy (RT) treatment and clinical data management for research purposes. All patients treated with reirradiation for recurrent glioma in our department from January 1997 to February 2014 were analyzed in this study. A total of 198 patients were included. The primary endpoint of OS was chosen because analysis of progression-free survival is prone to error in glioma cohorts owing to pseudoprogression.

Stratification, variables, and follow-up

Patients were stratified according to fractionation scheme, age, sex, Karnofsky Performance Status (KPS), extent of surgery (biopsy, partial resection, or gross total resection), O-6-methylguanine-DNA methyltransferase (MGMT) status, tumor localization (frontal, parietal, temporal, occipital, or central), chemotherapy at recurrence, whether they had received nanotherapy, histology at recurrence, and planning target volume (PTV). For patients who did not receive neurosurgical intervention when recurrence occurred, we assumed the same histology at recurrence as at initial diagnosis.

Follow-up examinations, including magnetic resonance imaging (MRI) and clinical and neurologic examinations, were performed at a 6- to 8-week interval after radiation therapy and then every 3 months.

RT treatment planning

Contrast agent–enhanced computed tomography in a thermoplastic mask and gadolinium-enhanced MRI were performed before RT planning. Target volumes were based on current MRI (not older than 4 weeks). In patients who had undergone reresection, the gross tumor volume was defined as the summation of the postoperative surgical cavity with or without residual tumor lesion(s) and tumor extension on the preoperative T1-weighted gadolinium-enhanced imaging. In patients who had not undergone reresection, the gross tumor volume was defined as tumor extension on the preoperative T1-weighted gadolinium-enhanced imaging. The size of the clinical target volume (CTV) was individually decided based on size of the initial PTV, tumor grade, time from last RT to recurrence, as well as initially received dose. CTVs varied between 0 and 2 cm. The extent of peritumoral edema was not routinely included in the CTV. For the PTV, an additional margin of 0.1 to 0.5 cm was added depending on the treatment and modality used for position verification. Intensity modulated radiation therapy was applied using a 6-MV linear accelerator with multileaf collimators or the NovalisTM therapy system (Varian; Brainlab, München, Germany).

For some patients, we provided accelerated hyperfractionation with 59.2 Gy/1.6 Gy 2 times a day when OARs, such as the optic nerves, chiasm, or brain stem would have been covered by the PTV and in cases where the patient was willing and fit enough to undergo

treatment twice daily. Hypofractionated schedules were more likely to be used in patients with lower KPS.

Intratumoral thermotherapy using magnetic iron-oxide nanoparticles

Between 2007 and 2009, a total of 32 patients received neuronavigationally controlled intratumoral instillation of an aqueous dispersion of iron-oxide (magnetite) nanoparticles and subsequent heating of the particles in an alternating magnetic field in a prospective trial for recurrent supratentorial glioblastoma (GBM) for patients between 18 and 75 years with a KPS $\geq$ 60%.[6] The thermotherapy was performed using the alternating magnetic field applicator MFH 300F with integrated thermometry unit (NanoActivator F100; MagForce Nanotechnologies, Berlin, Germany). The magnetic fluid MFL AS1 (NanoTherm AS1; MagForce Nanotechnologies), an aqueous dispersion of superparamagnetic nanoparticles with an iron concentration of 112 mg/mL, served as the energy transducer. The hyperthermia treatment generally consisted of 6 semiweekly sessions, and each thermotherapy session lasted 1 hour.

Toxicity

Retrospective analysis of long-term toxicity in recurrent GBM patients is very error prone because symptoms can either be attributed to the tumor itself or to tumor treatment in a cohort of patients with a very limited life-expectancy. Therefore, in this work only acute toxicity (90 days after treatment) was analyzed according to Common Terminology Criteria for Adverse Events (CTCAE 4.0). Toxicity data were extracted from the digital patient files.

Formulas and statistics

OS was calculated from the first day of reirradiation using Kaplan-Meier analysis and the Cox proportional hazard model. A P value of less than .05 was considered statistically significant. A P value of less than .1 was considered a trend. All variables with a P value $<$ .25 in the univariable analysis were included in multivariable analysis. All statistical analyses were performed using IBM SPSS Statistics 19 (New York). We assumed an α/β-ratio of 9.32 Gy for glioma cells when calculating the biological effective dose.[10]

Results

Patient characteristics

Patient characteristics are presented in Table 1. One hundred ninety-eight patients treated with radiation therapy for glioma were identified in our retrospective analysis. Median age at recurrence was 49 years. Median time from the first RT to reirradiation was 14 months. Median follow-up from the first day of reirradiation to last contact or death was 7 months. Median OS after relapse was 7 months for the entire cohort. For GBM (recurrent and secondary), median OS was 6 months, and for all grade 3 gliomas, OS was 14 months. Patients who received nanotherapy showed a median overall survival time of 6 months.

At last contact, 82.8% of patients had died. Of the overall cohort, 126 patients were male and 72 were female. All patients had received a neurosurgical intervention leading to the initial diagnosis. Of the total patients, 39.9% had received a surgical intervention at recurrence, 3% had received a biopsy, 8.1% partial resection, and 28.3% gross total resection; in 0.5% of the patients, the result of the surgery was unknown. About two-thirds (67.2%) of patients had been diagnosed with a recurrent GBM and 9.6% of patients with a secondary GBM. The majority of patients received FSRT (87.9%) and hypofractionated reirradiation (74.7%). The most common fractionation schemes were 41.8 Gy/3.8 Gy and 49.4 Gy/3.8 Gy. The range of single doses was 1.2 to 6.25 Gy, the range of total doses was 11.4 to 73 Gy, the range of $BED_{9.32}$ was 15.22 to 82.4 Gy.

Toxicity

Data on toxicity are presented in Table 2. Treatment was overall well tolerated. About one-third of patients (31.3%) developed minor toxicity (grade 1-2), which mainly resulted in dermal side effects and mild neurologic side effects like headache. Of the total patients, 5.1% developed grade 3 toxicity and 2.5% developed grade 4 toxicity. No patient developed acute grade 5 toxicity. The likelihood of developing severe toxicity (CTCAE grade 3/4) was not higher in the group of patients who received reirradiation in the first 14 months (median interval) after initial RT (P = .89). In addition, patients who received higher $BED_{9.32}$ ($\geq$ vs $<$ median of 58.8 Gy) did not have a significantly higher rate of severe acute toxicity (P = .06).

Overall survival and prognostic factors

Analysis of potential prognostic factors is shown in Table 3. Positive predictors of survival in univariable analysis were younger age, higher KPS, grade III tumor at recurrence instead of grade IV tumor, and higher $BED_{9.32}$ to the PTV. In multivariable analysis, only younger age and higher KPS remained significant positive predictors. Sex; MGMT status; gross total resection; application of chemotherapy, nanotherapy, or accelerated

Table 1 Characteristics of the 198 glioma patients

	Overall cohort (n = 198)	
Median age at recurrence (min/max), [y]	49	9/79
Median time from first RT to reirradiation (min/max), [m]	14	2/198
Mean PTV ± SD [ccm] at recurrence	61.9	± 63.7
Median BED provided at recurrence (a/b = 9.32)	58.8	± 12.5
	n	%
Sex		
Male	126	63.6
Female	72	36.4
Localization of recurrent tumor		
Frontal	57	28.8
Parietal	41	20.7
Temporal	45	22.7
Occipital	9	4.5
Central	7	3.5
Ventricles	1	0.5
Cerebellum	3	1.5
Brain stem	2	1.0
Other, n/a	33	16.7
MGMT-status		
Unmethylated	12	6.1
Methylated	13	6.6
n/a	173	87.4
Extent of surgery at recurrence		
No surgery	119	60.1
Biopsy	6	3.0
Partial resection	16	8.1
Gross total resection	56	28.3
Result of surgery n/a	1	0.5
KPS at recurrence		
40%	8	4.0
50%	22	11.1
60%	25	12.6
70%	58	29.3
80%	42	21.2
n/a	43	21.7
Chemotherapy at recurrence		
Temozolomide	54	27.3
CCNU	2	1.0
ACNU	2	1.0
PCV	2	1.0
Topotecan	13	6.6
Erlotinib	1	0.5
None	124	62.6
Histology at recurrence		
Recurrent glioblastoma	133	67.2
Secondary glioblastoma	19	9.6
Recurrent astrocytoma grade 3	28	14.1
Secondary astrocytoma grade 3	8	4.0
Recurrent oligoastrocytoma grade 3	3	1.5
Recurrent oligodendroglioma grade 3	1	0.5
High-grade glioma, not further characterized	2	1.0
Glioma, unclear whether low- or high-grade	4	2.0
Fractionation schema at recurrence		
Normofractionation	31	15.7
Accelerated hyperfractionation	14	7.1
Hypofractionation	148	74.7
Other, n/a	5	2.5
FSRT at recurrence		
Yes	174	87.9
No	24	12.1
Steroids during radiation therapy		
Yes	99	50
No	17	8.6
n/a	82	41.4
Nanotherapy at recurrence		
Yes	32	16.2
No	166	83.8

(*continued on next page*)

Table 1 (*continued*)

Abbreviations: FSRT = fractionated stereotactic radiation therapy; KPS = Karnofsky Performance Status; MGMT = O-6-methylguanine-DNA methyltransferase; n/a = not applicable; PTV = planning target volume; tmz = temozolomide.

hyperfractionated radiation therapy regimen; or PTV size did not affect survival.

Discussion

To our knowledge, this study included the second largest single-institution cohort of reirradiated patients after the cohort in the study published by Palmer et al in 2015.[11] In multivariable analysis, only age and KPS were significant prognostic factors. Age is a well-established factor in the literature and is used in prognostic indices for predicting outcome in recurrent glioma.[12-14] The prognostic role of KPS has been well established among other authors by Niyazi et al.[14]

Because only a minority of patients undergo surgical intervention at recurrence, the correct grading for

Table 2 Acute toxicity within the first 90 days after radiation therapy according to Common Terminology Criteria for Adverse Events version 4.0

	n	%
None	98	49.5
Grade 1 and 2	62	31.3
Grade 3	10	5.1
Grade 4	5	2.5
n/a	23	11.6

Abbreviation: n/a = not applicable.

Table 3 Univariable and multivariable analysis of potential predictive factors of overall survival after relapse

Variable	Univariable analysis			Multivariable analysis		
	P	HR	95% CI	*P*	HR	95% CI
Age (< vs ≥ median of 49 y)	< .001*	0.529	0.384-0.729	.006*	0.588	0.404-0.857
Sex (female vs male)	.298	0.842	0.610-1.163			
KPS (≥ vs < median of 70%)	< .001*	0.366	0.255-0.525	< .001*	0.366	0.246-0.543
MGMT-status (methylated vs unmethylated)	.559	0.778	0.336-1.804			
Grading (3 vs 4)	.001*	0.522	0.351-0.776	.287	0.789	0.509-1.221
Surgery (gross total resection vs no surgery/biopsy/subtotal resection)	.6	1.094	0.782-1.531			
Interval from initial RT to reirradiation (≥14 vs <14)	.269	0.835	0.606-1.15			
PTV (≥ vs < median of 46.25 ccm)	.721	1.062	0.763-1.479			
Fractionation schema (accelerated hyperfractionation vs normofractionation/hypofractionation)	.876	1.045	0.602-1.815			
BED to tumor (≥ vs < median of 58.8 Gy)	.02*	0.685	0.498-0.943	.201	0.785	0.541-1.138
Chemotherapy at recurrence (yes vs no)	.991	0.998	0.726-1.372			
Nanotherapy (yes vs no)	.256	1.324	0.816-2.148			

Abbreviations: BED = biologically effective dose; CI = confidence interval; HR = hazard ratio; KPS = Karnofsky performance status; MGMT = O-6-methylguanine-DNA methyltransferase; PTV = planning target volume.
* *P* value ≤ .05.

recurrent gliomas is not known in the majority of patients; therefore, authors tend to evaluate the prognostic role of grading at initial diagnosis.[14,15] In the present work, however, we chose to evaluate the role of histology at recurrence (in patients with no surgical intervention, the initial diagnosis was used) because we assumed that this will reflect the biologic behavior of the recurrent tumor more appropriately. However, tumor grade at recurrence was only a prognostic factor in univariable analysis but not confirmed in multivariable analysis. In an alternative analysis where grading at initial diagnosis instead of grading at recurrence was evaluated, significance was observed in univariable analysis but was also not confirmed in the multivariable model (data not shown).

Histologic grading at recurrence being a positive predictor in univariable analysis but not in multivariable analysis can probably be explained by the low number of grade 3 tumors (29.8%).

In our cohort, patients who received a higher $BED_{9.32}$ showed better OS in the univariable analysis. This was not confirmed for multivariable analysis. The effect on OS in univariable analysis is most probably due to the fact that patients with a high KPS were more likely to receive higher doses. Patients who received higher $BED_{9.32}$ did not have a significantly higher rate of severe acute toxicity (CTCAE grade 3/4), and the likelihood of developing severe toxicity was not higher in the group of patients who received reirradiation in the first 14 months (median interval) after initial RT. To this date, there is no consensus on the optimal reirradiation schema.[16] Our data suggest that careful dose escalation such as 49.4 Gy/3.8 Gy and early reirradiation are safe and tolerable in selected patients. Further work on the radiosensitivity of preirradiated tissue is necessary to better understand the limits of dose escalation, the role of new radiosensitizers as well as on concomitant targeted therapy needs to be further elucidated.

A small number of patients was treated using accelerated hyperfractionation, which is hypothesized to prevent tumor repopulation in treatment intervals and reduce late radiation injury.[17] In our population, accelerated hyperfractionation was not a prognostic factor for OS. This is in accordance with our publication in which we showed that accelerated hyperfractionation is not inferior to normofractionation in primary GBM patients in a retrospective setting.[18] One might assume that accelerated hyperfractionation is feasible in a carefully selected patient cohort with long life expectancy, good KPS, and OARs in the PTV region.

In this work we showed a median overall survival after relapse of 6 months for GBM patients who received radiation therapy. This is comparable to published data on reirradiated patients. Combs et al show a median overall survival of 8 months in an observational series (n = 59).[15]

Data on survival after GBM relapse without radiation therapy is mostly available from prospective trials evaluating alternative treatment options and often involve patients with a relatively high KPS: Friedman et al showed median overall-survival times of 9.2 and 8.7 months for patients treated with Bevacizumab alone or in combination with Irinotecan (n = 167), only patients with a KPS ≥70% were included.[19] In a phase 2 trial of Carmustine Brandes et al showed a median overall

survival time of 7.53 months (n = 40, KPS ≥60).[20] In a retrsopective series on treatment using Procarbazine, Schmidt et al show median overall-survival time of 34.3 weeks (n = 83).[21] We assume that the slightly lower survival times in our cohort can be attributed to relatively high number of patients with low KPS.

Limitations

Our study had several limitations. First, data on the MGMT status are missing in the majority of patients. Second, no analysis of chronic toxicity was performed because it is difficult to differentiate between chronic toxicity and disease progression in patients with recurrent high-grade glioma. Third, the number of patients treated with nanotherapy or accelerated hypofractionation may have been too low to identify significant differences in OS. Fourth, there is a high degree of heterogeneity in terms of CTV and PTV margins, and it is possible that smaller margins lead to a higher risk of marginal misses in the respective patients. Fifth, there is a great variability in terms of fractionation regimens, which might affect our results, even though uni- and multivariable analyses do not suggest so.

Conclusions

The prognosis of recurrent high-grade glioma remains dismal. Reirradiation is often feasible even after early recurrence (<14 months) and with higher doses ($BED_{9.32}$ > of 58.8 Gy, eg, 49.4 Gy/3.8 Gy) in carefully selected patients.

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