ANTICANCER RESEARCH *40*: 7025-7030 (2020)
doi:10.21873/anticanres.14728

Prognostic Factors of Local Control and Survival in Patients Irradiated for Glioblastoma Multiforme (GBM)

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Abstract. *Background/Aim: Standard treatment of glioblastoma multiforme (GBM) includes resection, longer-course radiotherapy and chemotherapy. Some patients cannot tolerate these regimens and may benefit from personalized treatments. This study aims to contribute to treatment personalization by identifying predictors of outcomes after longer-course radiotherapy. Patients and Methods: In 91 patients, number/site/diameter of lesions, Ki-67, MGMT promoter methylation, Karnofsky performance score (KPS), symptoms, gender, age and resection were evaluated for local control and survival. Results: On univariate analyses, gross resection (p=0.029) was significantly associated with improved local control. It maintained significance in the multivariate analysis [hazard ratio (HR)=1.64, p=0.025]. MGMT-methylation (p=0.004), KPS ≥80 (p=0.022) and resection (p<0.001) were significantly associated with improved survival on univariate analyses, unifocal GBM (p=0.056) showed a trend. In the multivariate analyses, MGMT-methylation (HR=3.63, p=0.009), KPS (HR=2.01, p=0.018) and resection (HR=3.29, p<0.001) were significant. Conclusion: Predictors of local control and survival were identified that may guide physicians when tailoring treatments to patients with GBM.*

Glioblastoma multiforme (GBM) accounts for about 35% of primary brain tumors in adults (1, 2). In the United States, the overall incidence of GBM was reported to be 4.40 per 100,000 inhabitants (3). The prognoses of patients with GBM are generally poor with a 5-year survival probability of only about 5% (2, 4). Better outcomes can be achieved with a tri-modality treatment approach that is quite intensive and includes neurosurgical resection followed by longer-course radiotherapy plus concurrent and adjuvant chemotherapy (5-7). However, some patients, particularly if they are elderly or frail, may not be able to tolerate a tri-modality treatment regimen and could benefit from a personalized treatment approach (8). Personalized treatments need to consider the patient's individual situation, personal needs and preferences. Moreover, the patient's survival prognosis and the potential benefit from an intensive treatment program should be considered to avoid over- or undertreatment. Patients with favorable survival prognoses and good chances to benefit from an intensive treatment regimen in terms of improved local control and survival should receive the standard tri-modality treatment (5, 6). In contrast, patients with short survival times and little expected benefits from an intensive treatment appear better treated with less aggressive regimens (8). Such regimens may include shorter-course radiotherapy (lasting 3 instead of 6 weeks) with or without systemic treatment and omit extensive neurosurgical resection (8-10).

Tailoring a treatment regimen to a patient's individual situation can be facilitated by applying prognostic factors that allow estimating the probability of local control of the GBM and the patient's remaining survival time. This study aimed to identify predictors of both local control and survival in patients treated with longer-course radiotherapy with or without additional treatment (upfront neurosurgical resection, systemic treatment).

Patients and Methods

The data of 91 patients irradiated for histologically confirmed GBM between 2005 and 2019 were retrospectively evaluated with respect to local control and survival. The study was approved by the Ethics Committee of the University of Lübeck (15-355A).

The majority of the patients received longer-course radiotherapy with 60.0 Gy in 30 fractions of 2.0 Gy given over 6 weeks (n=54) or 59.4 Gy in 33 fractions of 1.8 Gy given over 6.5 weeks (n=19). In those 18 patients receiving less than 59.4 Gy, total doses were given as planned in 11 patients (range=54.0 to 58.0 Gy). In seven patients, the administered dose was less than initially planned; five of these patients received less than 54.0 Gy. Radiotherapy was performed as 3D-

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Key Words: Glioblastoma multiforme, longer-course radiotherapy, local control, survival, prognostic factors.

conformal radiotherapy (n=53) or as volumetric modulated arc therapy (n=38). In all but three patients, radiotherapy was supplemented by systemic treatment with temozolomide. In the entire cohort, 69 patients (81%) received upfront neurosurgical resection of the GBM, which was a gross total resection (GTR) in 18 patients (26%) and a subtotal resection (STR) in 44 patients (64%). Extent of resection was not specified in seven patients (10%).

A total of 11 characteristics were evaluated for potential associations with local control (defined as freedom from progression or recurrence of the treated GBM lesions and freedom from new GBM lesions) and survival. These characteristics included number of GBM lesions (single *vs*. multiple), main site of GBM (thalamus *vs*. temporal *vs*. frontal *vs*. parietal *vs*. occipital *vs*. parieto-occipital *vs*. fronto-parietal *vs*. temporo-frontal *vs*. temporo-parietal *vs*. other sites), maximum cumulative diameter of GBM lesions (<40 mm *vs*. ≥40 mm, median=40 mm), Ki-67/molecular immunology Borstel (MIB)1 labeling index (<25% *vs*. ≥25%, median=25%), O6-methylguanine-DNA methyl-transferase (MGMT) promoter methylation (MGMT-methylation) (no *vs*. yes), Karnofsky performance score (≤70 *vs*. ≥80, median=80), number of pre-treatment symptoms (1 *vs*. ≥2), gender (female *vs*. male), age at the start of irradiation (≤60 *vs*. ≥61 years, median=61 years), neurosurgical resection (no *vs*. yes) and extent of resection (GTR *vs*. STR). Distributions of these characteristics are shown in Table I.

Both local control of GBM and survival were referenced from the first day of radiotherapy. The methods used for the univariate analyses of local control and survival included the Kaplan-Meier method and the log-rank test. *p*-Values of <0.05 were considered significant and *p*-values of <0.06 were considered indicating a trend. Characteristics achieving significance were additionally evaluated in a multivariate analysis (Cox proportional hazards model). Characteristics that were significant in the multivariate analysis ($p<0.05$) were considered independent predictors of post-treatment outcomes. Patients were followed until death or for at least 24 months after the start of radiotherapy.

Table I. *Characteristics that were analyzed with respect to local control and survival.*

Factor	Number of patients (%) for analyses of local control	Number of patients (%) for analyses of survival
Number of GBM lesions		
Single	72 (85)	76 (84)
Multiple	13 (15)	15 (16)
Main site of GBM		
Thalamus	4 (5)	5 (6)
Temporal	23 (27)	25 (27)
Frontal	19 (22)	19 (21)
Parietal	9 (11)	10 (11)
Occipital	4 (5)	4 (4)
Parieto-occipital	7 (8)	7 (8)
Fronto-parietal	3 (4)	4 (4)
Temporo-frontal	3 (4)	3 (3)
Temporo-parietal	8 (9)	9 (10)
Other sites	5 (6)	5 (6)
Maximum cumulative diameter		
<40 mm	35 (41)	38 (42)
≥40 mm	39 (46)	42 (46)
Unknown	11 (13)	11 (12)
Ki-67/MIB 1 labeling index		
<25%	34 (40)	37 (41)
≥25%	28 (33)	31 (34)
Unknown	23 (27)	23 (25)
MGMT promoter methylation		
No	7 (8)	11 (12)
Yes	16 (19)	18 (20)
Unknown	62 (73)	62 (68)
Karnofsky performance score		
≤70	25 (29)	29 (32)
≥80	60 (71)	62 (68)
Number of pre-treatment symptoms		
1	25 (29)	29 (32)
≥2	49 (58)	51 (56)
Unknown	11 (13)	11 (12)
Gender		
Female	36 (42)	38 (42)
Male	49 (58)	53 (58)
Age at radiotherapy		
≤60 Years	41 (48)	44 (48)
≥61 Years	44 (52)	47 (52)
Neurosurgical resection		
No	16 (19)	18 (20)
Yes	69 (81)	73 (80)
Extent of resection		
GTR	18 (26)	21 (29)
STR	44 (64)	45 (62)
Not specified	7 (10)	7 (10)

GBM: Glioblastoma multiforme, MIB1: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection.

Results

Median follow-up times were 24 months (range=1-128 months) in the entire cohort and 35.5 months (range=24-128 months) in patients alive at the last contact.

Data regarding local control were available for 85 patients (93%). Of these patients, 33 (39%) experienced a local failure. In the entire cohort, the local control rates at 1 and 2 years were 91% and 70%, respectively. On univariate analyses (Table II), improved local control was significantly associated with GTR ($p=0.029$). In the subsequent multivariate analysis, extent of resection remained significant [hazard ratio (HR)=1.64, 95% confidence interval (CI)=1.06-2.75, $p=0.025$].

In 53 patients of the entire cohort (58%), death was recorded during the period of follow-up. Survival rates at 1 and 2 years were 64% and 53%, respectively. On univariate analyses (Table III), improved survival was significantly associated with MGMT promoter methylation ($p=0.004$), a KPS ≥80 ($p=0.022$) and upfront neurosurgical resection ($p<0.001$). In addition, a trend was observed for unifocal GBM ($p=0.056$). In the multivariate analyses, MGMT promoter methylation (HR=3.63, 95% CI=1.39-9.80, $p=0.009$), KPS ≥80 (HR=2.01, 95% CI=1.13-3.50, $p=0.018$) and upfront resection (HR=3.29, 95% CI=1.75-5.95, $p<0.001$) maintained significance.

Table II. *Local control rates at 1 and 2 years after the start of radiotherapy (n=85).*

Factor	1 Year (%)	2 Years (%)	*p*-Value
Number of GBM lesions			
Single	90	71	0.573
Multiple	100	60	
Main site of GBM			
Thalamus	100	100	0.761
Temporal	85	69	
Frontal	83	73	
Parietal	100	100	
Occipital	100	100	
Parieto-occipital	100	40	
Fronto-parietal	100	100	
Temporo-frontal	100	67	
Temporo-parietal	100	57	
Other sites	80	80	
Maximum cumulative diameter			
<40 mm	90	61	0.738
≥40 mm	92	78	
Ki-67/MIB 1 labeling index			
<25%	89	72	0.752
≥25%	95	81	
MGMT promoter methylation			
No	80	40	0.103
Yes	92	67	
Karnofsky performance score			
≤70	86	77	0.656
≥80	92	67	
Number of pre-treatment symptoms			
1	89	83	0.166
≥2	95	64	
Gender			
Female	92	73	0.230
Male	90	68	
Age at radiotherapy			
≤60 Years	88	75	0.886
≥61 Years	93	63	
Neurosurgical resection			
No	100	100	0.764
Yes	90	67	
Extent of resection			
GTR	94	74	**0.029**
STR	89	64	

GBM: Glioblastoma multiforme, MIB: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection. Bold *p*-values were significant.

Table III. *Survival rates at 1 and 2 years after the start of radiotherapy (n=91).*

Factor	1 Year (%)	2 Years (%)	*p*-Value
Number of GBM lesions			
Single	70	57	0.056
Multiple	33	33	
Main site of GBM			
Thalamus	20	20	0.061
Temporal	76	64	
Frontal	58	47	
Parietal	30	20	
Occipital	50	50	
Parieto-occipital	71	71	
Fronto-parietal	75	25	
Temporo-frontal	100	100	
Temporo-parietal	78	67	
Other sites	80	60	
Maximum cumulative diameter			
<40 mm	66	50	0.953
≥40 mm	52	45	
Ki-67/MIB 1 labeling index			
<25%	65	54	0.149
≥25%	52	42	
MGMT promoter methylation			
No	18	9	**0.004**
Yes	72	61	
Karnofsky performance score			
≤70	45	34	**0.022**
≥80	73	61	
Number of pre-treatment symptoms			
1	55	48	0.615
≥2	67	51	
Gender			
Female	58	47	0.490
Male	68	57	
Age at radiotherapy			
≤60 Years	70	61	0.162
≥61 Years	57	45	
Neurosurgical resection			
No	28	22	**<0.001**
Yes	73	60	
Extent of resection			
GTR	81	71	0.077
STR	69	56	

GBM: Glioblastoma multiforme, MIB: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection. Bold *p*-values were significant.

Discussion

The treatment generally considered standard for GBM includes maximum neurosurgical resection followed by concurrent radiochemotherapy (60 Gy in 30 fractions plus temozolomide) and six courses of temozolomide alone (5-7). In a randomized trial, this regimen led to a median survival time of 14.6 months and 2-year, 3-year and 5-year survival rates of 27.2%, 16.0% and 9.8%, respectively (5, 6). When looking at these low survival rates, it becomes obvious that the outcomes of patients with GBM require further improvement. Many pre-clinical and clinical studies were performed to contribute to better understanding and improved treatment of this malignant disease (11-14).

From the radiation oncologist's perspective, an important question is related to the optimal dose-fractionation schedule. Already in 1979, a pooled analysis was presented including data of patients with malignant gliomas treated with surgery plus irradiation in several studies of the Brain Tumor Study Group (15). This analysis demonstrated a dose-effect relationship. Patients receiving 60 Gy had a significantly longer median survival (42 weeks) than patients receiving 55 Gy (36 weeks), 50 Gy (28 weeks) and ≤45 Gy (13.5 weeks). Moreover, a randomized trial demonstrated that 60 Gy in 30 fractions over 6 weeks was significantly superior to 45 Gy in 20 fractions over 4 weeks (p=0.007) (16). In 2001, a phase III trial compared four treatment regimens for newly diagnosed GBM (17). Treatment regimens included accelerated-hyperfractionated radiotherapy (70.4 Gy, 2×1.6 Gy/day) with or without a radiosensitizer (difluromethylornithine=DFMO) and normofractionated radiotherapy (59.4 Gy, 1×1.8 Gy/day) with or without DFMO. The four groups were balanced for age, KPS and extent of resection. Both accelerated-hyperfractionated radiotherapy and addition of DFMO did not lead to improved overall survival and progression-free survival (17). Thus, total doses of 59.4 Gy and 60.0 Gy are considered optimal for the treatment of GBM.

However, it has been recognized that elderly patients and patients with a poor performance status have less favorable survival prognoses (4, 18). Moreover, these patients may not be able to withstand an intensive tri-modality treatment (5, 6). In 2004, a randomized trial of 100 patients with GBM aged ≥60 years compared shorter-course radiotherapy (40 Gy in 15 fractions over 3 weeks) to longer-course radiotherapy (60 Gy in 30 fractions over 6 weeks for survival (9). Median survival and survival rates at 6 months were similar (p=0.57), and shorter-course radiotherapy was considered a reasonable option for GBM patients ≥60 years of age.

Shorter-course radiotherapy may also be reasonable for patients with limited survival prognoses to avoid that they have to spend more than necessary of their remaining lifespan receiving treatment for GBM. It would be important to be able to judge a patient's survival prognosis prior to assigning a treatment regimen. Prognostic factors of survival can guide the physicians during this process. Moreover, prognostic factors of local control of the GBM are important for selecting the optimal individual treatment, particularly because GBM does not metastasize outside the brain.

In the present study, the data of 91 patients irradiated for GBM were analyzed to identify predictors of both local control and survival. The aim to facilitate the estimation of the survival of patients with GBM has been previously pursued (18). In 2004, a recursive partitioning analysis was presented, which was based on the three prognostic factors age, KPS and extent of resection. The groups with the highest risk of death included all patients >65 years of age and patients 40-65 years of age with either KPS <80 or biopsy only (18). In contrast to our present study, local control of GBM was not investigated. Moreover, since 2004 the treatment of GBM has changed considerably, particularly after publication of the randomized trial of Stupp *et al*. in 2005 (5).

In this study, improved local control of GBM was significantly associated with GTR. Thus, GTR should be aimed at whenever reasonably possible considering potential damage to important brain structures as well as the patient's performance score and comorbidity index. Worse survival was significantly associated in both univariate and multivariate analyses with absence of MGMT promoter methylation, worse KPS (≤70) and no upfront resection. In addition, multifocal GBM showed a trend for worse survival on univariate analysis. Considering the randomized trial of Roa *et al*., patients with one or more of these negative prognostic factors may be considered for shorter-course with 40 Gy in 15 fractions over 3 weeks instead of longer-course radiotherapy over 6 weeks (9). According to the randomized trial of Perry *et al*., the addition of temozolomide to shorter-course radiotherapy resulted in improved survival in elderly patients (≥65 years) and may be considered for also for patients with negative prognostic factors identified in this study who likely will tolerate the combined treatment (10). Selected patients may even be candidates for temozolomide alone (19, 20). In contrast, a retrospective study of 112 patients aged ≥60 years did not find a significant benefit for the addition of temozolomide to shorter-course radiotherapy (21). Particularly patients without MGMT promoter methylation may not significantly benefit from temozolomide (5-7, 19, 20).

MGMT promoter methylation (5-7, 10, 19, 20), a better performance score (4, 18, 22, 23), a greater extent of resection (4, 18, 22, 23) and unifocal GBM (24-26) were previously reported as predictors of improved survival of patients with GBM, consistent with the results of the present study. Therefore, these results will likely contribute to the personalization of the treatment of patients with GBM. However, when interpreting the results of this study, one should be aware of its limitations including the retrospective design, which might have led to hidden selection biases. Although patients alive at the last contact must have had a follow up of at least 24 months, some deaths might have been missed due to the retrospective nature of the data. Moreover, the patients were treated during a comparably long time period of 15 years during which treatment concepts for recurrence of GBM have changed. This likely had an impact on the patients' survival.

In summary, in patients receiving longer-course radiotherapy for GBM, better local control was associated with GTR and better survival with MGMT promoter methylation, KPS ≥80, upfront resection and unifocal GBM. These predictors of treatment outcomes may guide physicians when designing personalized treatment programs for patients with GBM.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. J.W. collected the data that were analyzed by all Authors. The draft of the article was written and finally approved by J.W., S.E.S. and D.R.

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Received October 19, 2020
Revised October 29, 2020
Accepted October 30, 2020