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Radiotherapy of Grade III Gliomas: Identification of Clinical Prognostic Factors for Local Tumor Control and Survival

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Abstract. *Background/Aim: The prognoses of patients with grade III gliomas require improvement, which may be achieved with personalized care. We aimed to identify prognostic factors to facilitate the process of treatment personalization. Patients and Methods: Eight factors were analyzed for local tumor control and survival in 44 patients irradiated for grade III glioma. These factors included location and size of glioma, number of glioma sites, performance status, gender, age, neurosurgical intervention and chemotherapy. Results: In the Cox regression analyses, frontal location (risk ratio=4.41, p=0.048) and unifocal glioma (risk ratio=4.65, p=0.034) were associated with improved local control, and unifocal glioma with improved survival (risk ratio=6.12, p=0.033). In addition, trends for better survival were observed for frontal location (p=0.093), age ≤49 years (p=0.070), upfront resection (p=0.099) and chemotherapy (p=0.066) on univariate analyses. Conclusion: Independent predictors of local tumor control and survival were identified that can be helpful for personalizing treatment and designing clinical trials.*

The World Health Organization (WHO) classification of gliomas includes four grades (I-IV), and grade III gliomas are considered high-grade tumors (1, 2). Grade III gliomas are rare and account for about 3% of primary brain tumors and tumors of the central nervous system (3-5). Patients with grade III gliomas often have comparably poor prognoses, and the tumors can also negatively impact patients' quality of life (5). When compared to low-grade gliomas (grade I or II) and glioblastomas (grade IV), fewer studies have focused on diagnosis, treatment and prognosis of grade III gliomas (5). Moreover, most studies investigating high-grade gliomas combine grade III and IV tumors, although the progoses are quite different, and are dominated by the significantly more common grade-IV tumors (5, 6). Therefore, the present study was conducted including only patients with grade III gliomas. Its major goal is the identification of independent prognostic factors for local tumor control and survival that can lead to better personalization of individual treatment programs and likely to an improvement of the patients' prognoses.

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Key Words: Grade III glioma, neurosurgical intervention, irradiation, local tumor control, survival.

Patients and Methods

The data of 44 patients receiving radiotherapy for grade III glioma were retrospectively analyzed for local tumor control and survival. The study had received its approval from the local Ethics Committee at the University of Lübeck (reference=15-355A). Radiotherapy was performed after biopsy only (n=13, 30%) or after resection (n=31, 70%). Gross tumor resection was achieved in 7 patients, and macroscopically incomplete resection in 22 patients; the extent of resection remained unclear in 2 patients. The median total dose of radiotherapy following neurosurgical intervention was 59.4 Gy (54.0-60.0 Gy), and the median dose per fraction 1.8 Gy (1.8-2.0 Gy). Thirty-three patients (75%) received additional chemotherapy, most frequently with temozolomide (TMZ) alone (23 patients). Moreover, three patients received PC-chemotherapy including procarbazine and lomustine (CCNU) alone, six patients sequential administration of both TMZ and PC, and one patient nimustine (ACNU) alone.

Eight factors were analyzed for a potential prognostic impact with respect to local tumor control and survival, including main location of the glioma (frontal *vs.* other locations), number of glioma sites (unifocal *vs.* multifocal), cumulative maximum diameter of the glioma [<35 *vs.* ≥35 mm, according to Fang *et al.* (5)], Karnofsky performance score (KPS) (≤80 *vs.* >80%), gender, age at start of radiotherapy [≤49 *vs.* >49 years, according to Curran *et al.* (7)], upfront neurosurgical intervention (biopsy *vs.* resection), and chemotherapy in addition to radiotherapy (no *vs.* yes). Frontal location (n=22) included frontal location only (n=14), fronto-temporal location (n=5), fronto-parietal location (n=2) and frontal

plus paraventricular location (n=1). The distributions of the eight factors are shown in Table I.

Time to local tumor progression and time to death were referenced from the last day of irradiation. Univariate analyses for both endpoints were performed with the Kaplan-Meier method plus log-rank test. *p*-Values <0.10 indicated a trend, and *p*-values <0.05 demonstrated significance. The significant factors were subsequently included in a multivariate Cox regression analysis.

Table I. *Factors evaluated for local control and survival.*

Factor	Number of patients (%)
Main location of glioma	
Frontal	22 (50)
Other	22 (50)
Number of glioma sites	
Unifocal	35 (80)
Mutifocal	7 (16)
Unknown	2 (5)
Cumulative maximum diameter	
<35 mm	12 (27)
≥35 mm	18 (41)
Unknown	14 (32)
Karnofsky performance score	
≤80%	20 (45)
>80%	21 (48)
Unknown	3 (7)
Gender	
Female	22 (50)
Male	22 (50)
Age at start of radiotherapy	
≤49 Years	25 (57)
>49 Years	19 (43)
Upfront neurosurgical intervention	
Biopsy	13 (30)
Resection	31 (70)
Additional chemotherapy	
No	11 (25)
Yes	33 (75)

Results

Data for local tumor control were available for 35 patients. In these patients, the median time to local failure was 44 months, and local control rates at 1, 2 and 3 years were 73%, 68% and 57%, respectively. On univariate analysis of local tumor control, frontal location (p=0.020) and unifocal glioma (p=0.002) were significantly associated with improved outcomes (Table II). In the Cox regression analysis, both main location of the glioma (risk ratio=4.41, 95% CI=1.01-31.10, p=0.048) and number of glioma sites (risk ratio=4.65, 95% CI=1.13-17.98, p=0.034) remained significant.

In the entire cohort of 44 patients, median survival following radiotherapy was 132 months, and survival rates at 1, 2 and 3 years were 93%, 83% and 68%, respectively. On univariate analysis of survival, unifocal glioma (p=0.009) were significantly associated with improved outcomes (Table III). In addition, trends were observed for frontal location (p=0.093), age ≤49 years (p=0.070), resection prior to irradiation (p=0.099) and additional chemotherapy (p=0.066). In the Cox regression analysis, number of glioma sites (risk ratio=6.12, 95% confidence interval=1.17-28.68, p=0.033) maintained significance.

Discussion

In total, gliomas account for approximately 30% of primary brain tumors (8). Of all gliomas, only about 10% are grade III tumors (3-5). These patients were reported to have poor prognoses. Because of the rarity of grade III gliomas, very few studies have focused specifically on this subgroup of gliomas. The outcomes of patients with malignant diseases may be improved with personalized treatment programs, ideally, considering the individual prognostic factors for each patient. Survival is an important outcome that should be considered when selecting an optimal personalized treatment. In general, patients with poor estimated survival should receive short and little burdensome treatments, whereas tumor control and late sequelae require higher attention when aiming to treat long-term survivors. These strategies were particularly described for patients with metastatic cancer, but can also be important for patients with grade III gliomas (9-12).

This study was conducted to identify prognostic factors for survival and local tumor control in patients receiving radiotherapy after neurosurgical intervention for grade III glioma. In addition to survival, local tumor control is important, since local progression is often the life-limiting factor in glioma patients whose tumors do not metastasize. In the present study, frontal location and unifocal glioma showed significant associations with better local tumor control in the multivariate analysis. Improved survival was independently associated with unifocal glioma; trends were observed on univariate analyses for frontal location, age ≤49 years, upfront resection, and addition of chemotherapy.

Some of these factors were previously identified as associated with outcomes after treatment for grade III glioma, which demonstrates consistency regarding our present findings. However, when interpreting these findings, one should consider the limitations of this study including its retrospective nature and small sample size. In 2009, Park *et al*. reported a retrospective series of 133 patients with grade III gliomas, who received radiotherapy (mean dose=59.4Gy) with (50%) or without (50%) PCV-chemotherapy (procarbazine, CCNU, vincristine) (13). In the multivariate analysis, age <50 years (p=0.002), Eastern Cooperative Oncology Group performance score 0-1 representing a better performance status (p=0.003), and complete tumor resection

Table II. *Univariate analyses of local tumor control at 1, 2 and 3 years after radiotherapy (n=35).*

Factor	1 Year (%)	2 Years (%)	3 Years (%)	*p*-Value
Main location of glioma				
Frontal (n=17)	87	87	87	**0.020**
Other (n=18)	60	50	0	
Number of glioma sites				
Unifocal (n=27)	80	80	67	**0.002**
Mutifocal (n=7)	40	0	0	
Cumulative maximum diameter				
<35 mm (n=10)	64	64	64	0.58
≥35 mm (n=14)	75	75	56	
Karnofsky performance score				
≤80% (n=15)	64	43	43	0.22
>80% (n=17)	75	75	60	
Gender				
Female (n=17)	62	62	41	0.21
Male (n=18)	86	73	73	
Age at start of radiotherapy				
≤49 Years (n=18)	68	69	57	0.93
>49 Years (n=17)	79	n.a.	n.a.	
Upfront neurosurgical intervention				
Biopsy (n=10)	83	83	83	0.38
Resection (n=25)	71	65	52	
Additional chemotherapy				
No (n=8)	75	75	75	0.30
Yes (n=27)	73	67	54	

n.a.: Not available, bold *p*-values=significant. If the number of patients is less than 35 for a factor, data were not available for all patients.

Table III. *Univariate analyses of survival at 1, 2 and 3 years after radiotherapy (n=44).*

Factor	1 Year (%)	2 Years (%)	3 Years (%)	*p*-Value
Main location of glioma				
Frontal (n=22)	95	84	84	0.093
Other (n=22)	91	79	43	
Number of glioma sites				
Unifocal (n=35)	91	88	76	**0.009**
Mutifocal (n=7)	100	33	0	
Cumulative maximum diameter				
<35 mm (n=10)	100	89	89	0.87
≥35 mm (n=18)	88	88	66	
Karnofsky performance score				
≤80% (n=20)	89	73	50	0.25
>80% (n=21)	95	87	79	
Gender				
Female (n=22)	95	81	72	0.64
Male (n=22)	91	85	65	
Age at start of radiotherapy				
≤49 Years (n=25)	92	87	75	0.070
>49 Years (n=19)	95	76	0	
Upfront neurosurgical intervention				
Biopsy (n=13)	85	71	47	0.099
Resection (n=31)	97	87	74	
Additional chemotherapy				
No (n=11)	80	80	40	0.066
Yes (n=33)	97	84	78	

n.a.: Not available, bold *p*-values=significant. If the number of patients is less than 44 for a factor, data were not available for all patients.

(p=0.014) were significantly associated with improved survival. In 2015, a retrospective study of 90 patients treated with radiotherapy or chemo-radiotherapy with TMZ for grade III astrocytoma was presented from Mainz in Germany (14). In the multivariate analysis, age ≤49 years was significantly associated with progression-free survival (local tumor control, p=0.005) and overall survival (p=0.001). A significant impact was also found for complete and partial tumor resection when compared to biopsy (14). On univariate analysis of another retrospective study, which included 122 patients with a grade III glioma, extent of resection ≥53% (p=0.021) and Karnofsky performance score ≥80% (p=0.002) were significantly associated with better survival, and age <50 years (p=0.091) showed a trend (15). In that study, 97.5% of patients received radiotherapy and 95% chemotherapy (15). In an analysis of data of patients with grade III gliomas extracted from a Surveillance, Epidemiology and End Results (SEER) database, younger age and surgery were significantly associated with better survival (5). Similar to our present study, frontal location was associated with a more favorable prognosis than other locations (5).

In addition to prognostic factors identified in previous studies, the number of glioma sites was an independent prognostic factor for both local tumor control and survival in the present study. To our knowledge, this factor has not yet been evaluated specifically in patients with grade III gliomas. However, in our previous study of grade II-IV gliomas (n=222), where the majority of patients (73%) had grade IV tumors, unifocal glioma showed a significantly positive association with survival on univariate analysis (p<0.001) and a trend in the multivariate analysis (p=0.062) (16). Moreover, in another study of 139 patients with grade IV gliomas, multi-lobar glioma was associated with worse survival than uni-lobar glioma (p<0.001) (17). These data support the present finding that unifocal glioma is a significant prognostic factor for treatment outcomes in patients with grade III gliomas.

In summary, independent predictors of local tumor control and survival were identified for patients with grade III gliomas including a new factor, namely number of glioma sites. These prognostic factors that can be helpful for personalizing treatments and designing future clinical trials.

Conflict of Interest

The Authors report no conflicts of interest regarding this study.

Authors' Contributions

D.R., J.W. and S.E.S. participated in the design of the study. J.W. collected the data that were analyzed by all Authors. D.R. and S.E.S. drafted the article, which was reviewed and finally approved by all Authors.

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