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Clinical Prognostic Factors for Local Control and Survival After Irradiation of Grade II Gliomas

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Abstract. *Background/Aim: Personalized treatment for low-grade gliomas likely improves patient outcomes. This study aimed to identify predictors of local control and survival. Patients and Methods: Twenty-five patients irradiated for grade II gliomas were retrospectively analyzed. Irradiation was performed after biopsy (n=6) or incomplete resection (n=19). Nineteen patients received additional chemotherapy. Eight factors were analyzed, namely the number of glioma sites, cumulative maximum diameter, radiotherapy technique, Karnofsky performance score (KPS), gender, age, resection and chemotherapy. Results: On univariate analysis, trends for associations with local control were found for cumulative maximum diameter ≤43 mm (p=0.087) and age ≤45 years (p=0.065). In the Cox regression analysis, cumulative maximum diameter maintained significance (p=0.046). On univariate analysis, KPS 90-100 (p=0.039) and female gender (p=0.022) were significantly associated with better survival. In the Cox regression analysis, both KPS (p=0.039) and gender (p=0.016) were significant. Conclusion: Independent predictors of local control and survival were identified that can contribute to better treatment personalization.*

Gliomas account for 30-40% of primary brain tumors (1, 2). According to the classification of the World Health organization (WHO), gliomas are divided into four grades (I to IV), of which grade IV gliomas are the most aggressive and have the worst prognosis (1-3). Gliomas are also categorized as low-grade (WHO I-II) or high-grade (WHO III-IV) tumors.

Low-grade gliomas account for approximately 15% of all primary brain tumors (4, 5). This group includes grade I and grade II tumors (3). Of the histopathological criteria indicating a more aggressive tumor, namely anaplasia, cytological atypia, microvascular proliferation, mitotic activity and necrosis, none occur in grade I tumors (1, 3). Grade II tumors are characterized by cytological atypia only (1, 3). The optimal treatment for low-grade gliomas is controversial (5). Outcomes may be improved by personalization of the treatment considering the individual situation of each patient. Such personalization can be supported by the application of independent prognostic factors for the different treatment outcomes.

The present study aimed to identify independent predictors of local control of the treated glioma and survival. Since the treatment for grade I gliomas is considerably different from the management of grade II gliomas (5), the present study focused on one WHO grade, *i.e.* WHO grade II glioma.

Patients and Methods

Twenty-five patients treated with radiotherapy for a WHO grade II glioma were included in this retrospective study, which was approved by the local Ethics Committee (University of Lübeck, reference number 15-355A).

Irradiation was performed after biopsy (n=6) or macroscopically incomplete resection (n=14) or microscopically incomplete resection (corresponding to gross tumor resection, n=5) with a linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The median total dose was 54.0 Gy (range=52.2-60.0 Gy), and median dose per fraction was 1.8 Gy (range=1.7-2.0 Gy). In 19 patients (76%) radiotherapy was supplemented by chemotherapy, with 3-12 courses (median 6 courses) of temozolomide alone (n=7), 2-6 courses (median 4 courses) of procarbazine/lomustine (PC) alone (n=6), 4 courses of nimustine alone (n=1) or sequential treatment including temozolomide and PC.

In these patients, a total of eight factors were analyzed for associations with local control of the glioma and survival. These factors were the number of glioma sites (unifocal, multifocal), the

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cumulative maximum diameter of the tumor(s) (median=42.5 mm; ≤43 mm, >43 mm), radiotherapy technique (3D-conformal irradiation, volume-modulated arc therapy), Karnofsky performance score (KPS ≤80, KPS 90-100), gender (female, male), age at start of irradiation (median=45 years; ≤45 years, >45 years), resection prior to radiotherapy (no=biopsy only, yes), and additional chemotherapy (no, yes) (Table I).

Time to local progression and time to death were calculated from the last day of radiotherapy. For univariate analyses of local control and survival, we used the Kaplan–Meier method and the log-rank test. *p*-Values of less than 0.05 were considered significant, and those under 0.10 were regarded as indicating a trend. Factors with a $p<0.10$ were additionally analyzed for independence ($p<0.05$) in a multivariate Cox regression model.

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

Factor	Number of patients (%)
Number of glioma sites	
Unifocal	19 (76)
Mutifocal	4 (16)
Unknown	2 (8)
Cumulative maximum diameter	
≤43 mm	9 (36)
>43 mm	9 (36)
Unknown	7 (28)
Radiotherapy technique	
3D-conformal	9 (36)
VMAT	16 (64)
Karnofsky performance score	
≤80	6 (24)
90-100	16 (64)
Unknown	3 (12)
Gender	
Female	12 (48)
Male	13 (52)
Age at start of irradiation	
≤45 Years	13 (52)
>45 Years	12 (48)
Resection prior to irradiation	
No	6 (24)
Yes	19 (76)
Additional chemotherapy	
No	6 (24)
Yes	19 (76)

VMAT: Volume-modulated arc therapy.

Results

Data with respect to local control of the glioma were available for 20 patients. Median time to local failure was 30 months. On univariate analysis of these patients, a trend for a positive association with local control was found for cumulative maximum diameter of the glioma ≤43 mm ($p=0.087$) and age at start of radiotherapy ≤45 years ($p=0.065$) (Table II). Both factors were included in the Cox regression model, where the cumulative maximum diameter was significant ($p=0.046$) but age did not achieve significance ($p=0.19$).

Survival data were available for all 25 patients. The median survival time was 83 months. On univariate analysis, a KPS of 90-100 ($p=0.039$) and female gender ($p=0.022$) were significantly associated with better survival (Table III). In the Cox regression analysis, both KPS ($p=0.039$) and gender ($p=0.016$) maintained significance.

Discussion

Eight years ago, there were about 20,000 new glioma cases in the United States, representing 30% of all primary brain tumors in adults (1). Ongoing research is being carried out to improve the prognoses of patients with glioma (6-10). About 50% of the gliomas are low-grade tumors, *i.e.* WHO grade I or II gliomas (3-6). The present study focused on patients with WHO grade II gliomas receiving radiotherapy. A comparably novel approach aiming to improve the outcomes of patients with a malignant disease is the personalization of their treatment. For optimal personalization of a therapy protocol for a patient with glioma, the application of independent prognostic factors is helpful. In this context, survival should always be considered. Since gliomas do not metastasize, and progression of treated or new cerebral lesions that cannot be successfully treated is the main malignancy-related life-limiting factor, prognostic factors for local control of the treated glioma are also very important. Therefore, this study aimed to identify independent prognostic factors for both survival and local control.

In the corresponding multi-variate analyses, the cumulative maximum diameter of the glioma(s) was an independent predictor of local control, and KPS and gender were independent predictors of survival. In addition, younger age (≤45 years) showed a trend for a positive association with local control on univariate analysis. Some of these prognostic factors have already been reported for low-grade glioma. In 1995, Nicolato *et al.* presented a retrospective study of 76 surgically treated patients (11). KPS >70 and age ≤50 years were associated with better survival. Gross tumor resection was performed in 22% of the patients, which was similar to the 20% in the current study. However, in the study of Nicolato *et al.*, 24% of the patients did not receive immediate postoperative irradiation. In 1997, Leighton *et al.* presented the data of 167 patients who received radiotherapy, either as immediate adjuvant treatment (48%) or as delayed treatment in the case of cerebral progression (52%) (12). Residual tumor was reported to be minimal in 49% and bulky in 51% of the patients, respectively. Younger age (≤40 years) was associated with better local control and survival, and a higher KPS (≥70) with better survival. In 2002, the data of two randomized trials of the European Organization for Research and treatment of Cancer (EORTC) were re-evaluated (13). One trial (EORTC 22844) compared two postoperative radiotherapy regimens (45 Gy in 5 weeks and 59.4 Gy in 6.6

Table II. *Associations between investigated factors and local control of the glioma (n=20).*

Factor	1 Year (%)	2 Years (%)	3 Years (%)	*p*-Value
Number of glioma sites				
Unifocal (n=15)	86	73	73	0.93
Mutifocal (n=4)	100	75	n.a.	
Cumulative max. diameter				
≤43 mm (n=7)	100	100	n.a.	0.087
>43 mm (n=8)	75	50	50	
Radiotherapy technique				
3D-conformal (n=5)	80	60	30	0.31
VMAT (n=15)	93	81	n.a.	
Karnofsky performance score				
≤80 (n=5)	100	75	0	0.84
90-100 (n=12)	83	69	69	
Gender				
Female (n=10)	80	80	40	0.91
Male (n=10)	100	73	n.a.	
Age at start of irradiation				
≤45 Years (n=11)	100	89	89	0.065
>45 Years (n=9)	75	56	0	
Resection prior to irradiation				
No (n=5)	100	100	n.a.	0.23
Yes (n=15)	86	68	34	
Additional chemotherapy				
No (n=4)	100	100	0	0.86
Yes (n=16)	88	71	71	
Entire cohort (n=20)	89	75	38	

n.a.: Not available, max.: maximum, VMAT: volume-modulated arc therapy. Where the number of patients is less than 20 for a factor, data were missing for the remaining patients.

Table III. *Associations between investigated factors and survival (n=25).*

Factor	1 Year (%)	2 Years (%)	3 Years (%)	*p*-Value
Number of glioma sites				
Unifocal (n=19)	95	80	80	0.87
Mutifocal (n=4)	100	100	100	
Cumulative max. diameter				
≤43 mm (n=9)	100	83	83	0.81
>43 mm (n=9)	100	100	100	
Radiotherapy technique				
3D-conformal (n=9)	100	78	78	0.93
VMAT (n=16)	94	85	85	
Karnofsky performance score				
≤80 (n=6)	100	63	63	**0.039**
90-100 (n=16)	100	90	90	
Gender				
Female (n=12)	100	100	100	**0.022**
Male (n=13)	92	64	64	
Age at start of irradiation				
≤45 Years (n=13)	100	83	83	0.86
>45 Years (n=12)	92	79	79	
Resection prior to irradiation				
No (n=6)	100	53	n.a.	0.21
Yes (n=19)	95	87	87	
Additional chemotherapy				
No (n=6)	83	83	83	0.71
Yes (n=19)	100	79	79	
Entire cohort (n=25)	96	80	80	

n.a.: Not available, max.: maximum, VMAT: volume-modulated arc therapy. Where the number of patients is less than 25 for a factor, data were missing for the remaining patients. Statistically significant *p*-values are shown in bold.

weeks), and the other (EORTC 22845) compared postoperative radiotherapy with 54.0 Gy in 6 weeks to no immediate post-operative irradiation. Gross tumor resection was achieved in 24% (EORTC 22844) and 45% (EORTC 22845) of the patients, respectively. In the additional study presented in 2002, better survival was associated with age <40 years, maximum glioma diameter <60 mm and absence of neurological deficits, which likely would have meant a worse performance status. Similar associations were reported in 2013 for both survival and local control in another analysis of the EORTC 22844 and EORTC 22845 trials that considered only the 339 patients with a confirmed diagnosis of a grade II glioma by central pathology review (14). In 2008, the data of 281 patients with low-grade glioma were reported from the University of California (15). In that cohort, 33% of the patients underwent gross tumor resection, and only 40% of the patients received postoperative radiotherapy. However, similarly to our study, a KPS of 90-100, younger age (≤50 years) and a smaller maximum diameter of glioma (≤40 mm) were associated with improved outcomes. Despite the similarities regarding prognostic factors for treatment outcomes between our study and previous studies, the differences with respect to proportions of patients receiving immediate postoperative irradiation and those undergoing gross tumor resection should be considered. In addition to previously reported prognostic factors such as KPS, glioma diameter and age, we identified another independent predictor of survival, gender. Although the prognostic role of gender has not been defined for patients receiving radiotherapy for a low-grade glioma, female gender was associated with better treatment outcomes in studies of other primary tumor types including head-and-neck cancer, small-cell lung cancer, cancer of the urinary bladder and metastatic non-small cell lung cancer (16-21). When using the data of the present study, its limitations, including the retrospective design and the small sample size, should be kept in mind.

In summary, this study identified independent prognostic factors for local control and survival in patients irradiated for WHO grade II gliomas. These factors can contribute to better treatment personalization and may also be important stratification factors in future randomized trials.

Conflicts of Interest

The Authors state that there are 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 approved in its final form by all Authors.

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