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Seizures Prior to Radiotherapy of Gliomas: Prevalence, Risk Factors and Survival Prognosis

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Abstract. *Background/Aim: Seizures represent a common manifestation of gliomas. This study evaluated the prevalence of pre-radiotherapy seizures, potential risk factors and associations with survival. Patients and Methods: Eight factors were analyzed in 222 patients for associations with seizures including number, size and location of glioma, World Health Organization (WHO) grade, performance score, gender, age and upfront resection. These factors plus pre-radiotherapy symptoms and seizures were assessed for survival. Results: Prevalence of pre-radiotherapy seizures was 29.3%. A significant correlation was found for grade II (p=0.002), trends for age ≤59 years (p=0.123) and lack of upfront resection (p=0.113). Unifocal gliomas (p<0.001), grade II (p=0.045) and upfront resection (p<0.001) showed significant associations with survival (univariate analyses). A trend was found for seizures (p=0.075) and age ≤59 years (p=0.091). In the multivariate analysis, grade II (p=0.002) and upfront resection (p=0.004) maintained significance; unifocal gliomas showed a trend (p=0.062). Conclusion: Pre-radiotherapy seizures appeared to be correlated with WHO grade, age and lack of upfront resection, and with better survival.*

Gliomas represent the most common type of primary tumor in the brain (1-3). These tumors are often associated with significant symptoms including seizures (2-7). The majority of glioma-related seizures occur prior to the treatment of the glioma (8). The prevalence of pre-treatment seizures in the literature shows an extremely wide range of 9-87% (3, 9-15). For patients with glioblastomas [grade IV according to the classification of the World Health Organization (WHO)], frequencies between 9% and 45% have been reported, and for low grade gliomas (WHO grade II) frequencies between 30% and 87% (9-13). More studies are required to properly define the prevalence of pre-treatment seizures in glioma patients. Moreover, further clarification is needed with respect to potential risk factors regarding this situation (8, 9, 11, 12, 15). Risk factors may guide physicians during the phases of diagnosis and treatment, for example when considering the prophylactic use of anti-epileptic agents. Furthermore, a potential association of pre-treatment seizures in glioma patients with their survival prognoses is an important issue. The knowledge of prognostic factors for survival facilitates the development of individualized treatment protocols. This study addressed all three issues regarding pre-treatment seizures, *i.e.* prevalence, risk factors and association with survival, in a cohort of glioma patients receiving post-operative radiotherapy or radiotherapy alone.

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Key Words: Glioma, seizures, radiation therapy, prevalence, risk factors, survival.

Patients and Methods

This retrospective study included 222 patients who were irradiated for WHO grade II-IV gliomas between 2008 and 2019 (16, 17). It received approval from ethics committee at the University of Lübeck (20-120A). Radiotherapy was performed with a modern linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). Median total dose was 59.4 Gy (range=50.0-60.0 Gy), and median dose per fraction was 2.0 Gy (range=1.8-2.0 Gy). Median total doses were 54 Gy for WHO grade II gliomas, 59.4 Gy for grade III gliomas and 60.0 Gy for grade IV gliomas, respectively. Two-hundred-and-four patients (91.9%) received chemotherapy, generally with temozolomide, in addition to radiotherapy (18).

In the whole series of 222 patients, the prevalence of seizures prior to radiotherapy, potential risk factors for pre-radiotherapy seizures and a potential association between such seizures and survival were assessed. For a potential association with pre-radiotherapy seizures, eight factors were analyzed including the number of glioma sites (unifocal *vs.* multifocal), main location of the glioma (frontal *vs.* parietal *vs.* temporal *vs.* other locations), cumulative size of the glioma (<40 mm *vs.* ≥40 mm), WHO grade (II *vs.* III *vs.* IV), Karnofsky performance score (≤70 *vs.* ≥80),

Table I. *Summary of the potential prognostic factors analyzed in this study.*

Factor	Number of patients (%)
Symptoms prior to radiotherapy	
No symptoms	21 (9.5)
Seizures only	12 (5.4)
Seizures+other symptoms	44 (19.8)
Other symptoms only	145 (65.3)
Seizures prior to radiotherapy	
No	157 (70.7)
Yes	65 (29.3)
Number of glioma sites	
Unifocal	179 (80.6)
Mutifocal	32 (19.4)
Unknown	11 (5.0)
Main location of glioma	
Frontal	91 (41.0)
Parietal	62 (27.9)
Temporal	38 (17.1)
Other locations	31 (14.0)
Cumulative size of glioma	
<40 mm	90 (40.5)
≥40 mm	80 (36.0)
Unknown	52 (23.4)
WHO grade	
Grade II	18 (8.1)
Grade III	41 (18.5)
Grade IV	163 (73.4)
Karnofsky performance score	
≤70	65 (29.3)
≥80	136 (61.3)
Unknown	21 (9.5)
Gender	
Female	92 (41.4)
Male	130 (58.6)
Age	
≤59 Years	119 (53.6)
≥60 Years	103 (46.4)
Upfront resection	
No	44 (19.8)
Yes	178 (80.2)

WHO: World Health Organization.

gender, age at the time of radiotherapy (≤59 *vs.* ≥60 years, median=59 years), and upfront resection of glioma (no *vs.* yes). In addition, these eight factors plus symptoms prior to radiotherapy (no symptoms *vs.* seizures only *vs.* seizures + other symptoms *vs.* other symptoms only) and pre-radiotherapy seizures (no *vs.* yes) were assessed for correlations with survival. A summary of all ten factors is given in Table I.

For statistical analyses with respect to correlations with the occurrence of pre-radiotherapy seizures, we used the Chi-square test. *p*-Values of <0.05 were considered significant, and *p*-values of <0.13 were considered indicating a trend. The univariate analyses of survival were conducted using the Kaplan-Meier method and the Wilcoxon test. Again, *p*-values of <0.13 were considered indicating a trend. Significant ($p<0.05$) factors were also included in a multivariate Cox proportional hazard model (*p*-values of <0.05= significant *p*-values).

Table II. *Associations between patient characteristics and pre-treatment seizures.*

Factor	Patients with seizures	*p*-Value
Number of glioma sites		
Unifocal (n=179)	53 (29.6%)	0.888
Mutifocal (n=32)	10 (31.3%)	
Main location of glioma		
Frontal (n=62)	16 (25.8%)	0.715
Parietal (n=38)	12 (31.6%)	
Temporal (n=91)	25 (27.5%)	
Other locations (n=31)	12 (38.7%)	
Cumulative size of glioma		
<40 mm (n=90)	24 (26.7%)	0.856
≥40 mm (n=80)	23 (28.8%)	
WHO grade		
Grade II (n=18)	10 (55.6%)	**0.002**
Grade III (n=41)	20 (48.8%)	
Grade IV (n=163)	35 (21.5%)	
Karnofsky PS		
≤70 (n=65)	16 (24.6%)	0.407
≥80 (n=136)	42 (30.9%)	
Gender		
Female (n=92)	27 (29.3%)	0.980
Male (n=136)	38 (29.2%)	
Age		
≤59 Years (n=119)	41 (34.5%)	0.123
≥60 Years (n=103)	24 (23.3%)	
Upfront resection		
No (n=44)	18 (40.9%)	0.113
Yes (n=178)	47 (26.4%)	

RT: Radiotherapy; WHO: World Health Organization; PS: performance score; bold *p*-values were significant.

Results

Pre-radiotherapy seizures were reported for 65 of the 222 patients, *i.e.* the prevalence was 29.3%. A significant positive correlation with pre-radiotherapy seizures was found for WHO grade II gliomas when compared to grade III and grade IV tumors (55.6% *vs.* 48.8% and 21.5%, $p=0.002$). Trends for positive correlations with pre-radiotherapy seizures were observed for age ≤59 years ($p=0.123$) and lack of upfront resection ($p=0.113$). The complete analyses of potential risk factors of pre-radiotherapy seizures are shown in Table II.

Significant positive associations with survival on univariate analyses (Table III) were found for unifocal gliomas ($p<0.001$), WHO grade II tumors ($p=0.045$) and upfront resection ($p<0.001$). Trends were observed for pre-radiotherapy seizures ($p=0.075$) and age ≤59 years ($p=0.091$). In the multivariate analysis, grade II ($p=0.002$)

Table III. *Survival rates up to 3 years after radiotherapy (univariate analyses).*

Factor	1 year (%)	2 years (%)	3 years (%)	*p*-Value
Symptoms prior to RT				
No symptoms (n=12)	80	69	55	0.361
Seizures only (n=21)	90	83	69	
Seizures+others (n=44)	92	66	59	
Others only (n=145)	79	67	61	
Seizures prior to RT				
No (n=157)	79	67	60	0.075
Yes (n=65)	91	71	62	
Number of glioma sites				
Unifocal (n=179)	85	72	63	**<0.001**
Mutifocal (n=32)	65	39	39	
Main location of glioma				
Frontal (n=62)	81	64	51	0.130
Parietal (n=38)	88	74	74	
Temporal (n=91)	87	76	67	
Other locations (n=31)	70	51	51	
Cumulative size of glioma				
<40 mm (n=90)	83	62	56	0.642
≥40 mm (n=80)	84	73	63	
WHO grade				
Grade II (n=18)	100	94	94	**0.045**
Grade III (n=41)	90	73	57	
Grade IV (n=163)	78	62	57	
Karnofsky PS				
≤70 (n=65)	83	60	53	0.235
≥80 (n=136)	84	70	62	
Gender				
Female (n=92)	82	66	63	0.543
Male (n=136)	83	69	59	
Age				
≤59 Years (n=119)	87	74	65	0.091
≥60 Years (n=103)	77	60	55	
Upfront resection				
No (n=44)	65	47	39	**<0.001**
Yes (n=178)	87	72	65	

RT: Radiotherapy; WHO: World Health Organization; PS: performance score; bold *p*-values were significant.

and upfront resection (p=0.004) maintained significance; unifocal gliomas showed a trend (p=0.062) (Table IV).

Discussion

In many glioma patients, the occurrence of seizures is the first clinical manifestation of their brain tumor (8). Seizures can have a considerable negative impact on the patients' quality of life (19, 20). A better understanding of the role of seizures for glioma patients may contribute to improvement of their treatment. The current study was initiated to contribute to the knowledge of the clinical meaning of seizures for patients irradiated for WHO grade II-IV gliomas. It investigated the prevalence of pre-radiotherapy seizures, potential risk factors

Table IV. *Multivariate analysis using the Cox proportiona hazard model.*

Factor	Hazard ratio	95%-Confidence interval	*p*-Value
Number of glioma sites	1.95	0.97-3.72	0.062
WHO grade	1.96	1.26-3.30	**0.002**
Upfront resection	2.54	1.36-4.57	**0.004**

WHO: World Health Organization; bold *p*-values were significant.

and a potential association with survival. The prevalence of seizures prior to radiotherapy was 29.3%, which was well within the range of 9-87% in the literature (3, 9-15). The prevalence for glioblastoma patients was 21.5%, which also corresponded well to the previously reported rates of 9-45% (9-13). Similarly, the prevalence of pre-radiotherapy seizures (55.6%) in our patients with WHO grade II tumors was also within the range of 30-87% reported in the literature (9-12). Less data are available specifically for pre-treatment seizures in patients with WHO grade III gliomas. However, in a systematic review, seizure rates of 29-67% have been reported for patients with grade III tumors during the course of their neurological disease (3). The prevalence of 48.8% found in the present study was within this range.

According to the results of the present study, the WHO grade was significantly associated with the occurrence of pre-radiotherapy seizures. The highest prevalence of seizures was found for low-grade gliomas. These findings agree with the results of previous studies and reviews. In a retrospective study of 492 patients with primary and metastatic brain tumors including 334 glioma patients, the occurrence of pre-operative seizures was significantly associated with WHO grade I-II glioma when compared to grade III-IV glioma (odds ratio=4.0, p<0.001) (15). In another retrospective study of 190 patients with astrocytic tumors, the rates of preoperative seizures were 34%, 29% and 18%, respectively, in patients with grade II, III and IV tumors (11). The same group presented another study of 101 patients aged ≥45 years with supratentorial astrocytic tumors and reported pre-operative seizures in 35% (grade II), 11% (grade III) and 9% (grade IV) of these patients, respectively (12). In the review article of Fan *et al*., 30-87% of patients with low-grade gliomas and 21-33% of glioblastoma patients had seizures at first presentation (10). Moreover, in a larger retrospective study of 1,028 patients, the prevalence of seizures during the entire course of the disease was 85% (322 of 379 patients) for patients with low-grade gliomas, 69% (95 of 137 patients) for patients with anaplastic gliomas and 49% (251 of 512 patients) for glioblastoma patients, respectively (21).

In addition to the WHO grade, trends for correlations with pre-radiotherapy seizures were found for age ≤59 years and

lack of upfront resection. Younger age has been previously described as risk factor for pre-treatment seizures. In the study of Hwang *et al*., patients <40 years had a higher risk of pre-operative seizures than older patients (odds ratio=3.08, p=0.013) (11). In the study of Kaloshi *et al*., who compared 62 patients with supratentorial low-grade gliomas aged ≥60 years to 704 younger patients, seizures as initial symptom of glioma were found in 85% and 47% of the patients, respectively (p<0.001) (22). In the study of Skardelly *et al*., that included also patients with brain metastases, patients ≤60 years had a higher risk of pre-operative seizures than patients >60 years (odds ratio=1.66, p=0.020) (15). Lote *et al*. have reported an inverse correlation between pre-treatment seizures and age for glioblastoma patients (p<0.01) (21). However, in younger patients with low-grade glioma (<40 years), the risk of seizures increased with age (p<0.01) developing a plateau in patients ≥40 years. The association between pre-radiotherapy seizures and lack of upfront resection can be explained by the fact that resection of glioma leads to a significant reduction of seizures with post-operative rates of freedom from seizures of 43-87% (23, 24). In addition, some authors have reported tumor location as risk factor for glioma-related seizures, although the reports showed some disagreement regarding the site. In the review articles of Kerkhof & Vecht and Englot *et al*., temporal location was associated with the highest prevalence of seizures, whereas in the study of Skardelly *et al*., the highest seizure rate was found for frontal location (8, 9, 15). In the present study, a significant association between pre-radiotherapy seizures and location of the glioma was not detected, similar to several previous studies (11-13).

In the current study, pre-radiotherapy seizures showed a trend for an association with survival. A significant association has been previously reported in a large study of 1,028 glioma patients including 649 patients with high grade tumors for the entire cohort and patients with high-grade tumors but not for patients with low-grade tumors (21). However, other studies have found significant associations between seizures and improved survival for patients with low-grade gliomas (9, 25-27). Moreover, in the present study, improved survival was independently associated with lower WHO grade and upfront resection. In addition, unifocal glioma showed a trend in the multivariate analysis and age ≤59 years a trend on univariate analysis. These four factors have been previously demonstrated to be significantly associated with more favorable survival prognoses (6, 10, 27-29). This agreement with previous data revealed consistency of the findings of the current study. Despite this, the retrospective study design and the risk of a hidden selection bias should be considered during the interpretation of this study.

In summary, the prevalence of pre-radiotherapy seizures was 29.3% in the entire cohort, 55.6% in patients with low grade (WHO grade II) gliomas, 48.8% in patients with anaplastic (grade III) gliomas and 21.5% in patients with glioblastomas (grade IV). Occurrence of pre-radiotherapy seizures appeared to be correlated with lower WHO grade, younger age and lack of upfront resection, and seizures appeared to be associated with more favorable survival. The findings of this study will contribute to the knowledge regarding the meaning of pre-radiotherapy seizures in patients irradiated for WHO grade II-IV gliomas.

Conflicts of Interest

The Authors state that there are no conflicts of interest regarding this study.

Authors' Contributions

J.W., T.W.K., S.T., S.E.S. and D.R. participated in the design of the study. J.W. collected the data that were analyzed by J.W., S.E.S. and D.R. Interpretation of the data was performed by all Authors. J.W., S.E.S. and D.R. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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