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Re-Evaluation of Prognostic Factors for Survival After Radiotherapy of Cerebral Gliomas: A Supplementary Analysis to a Previous Study

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Abstract. *Background/Aim: Previously, we identified predictors of survival after irradiation of grade II-IV cerebral gliomas. In this supplementary analysis, survival was calculated in a more appropriate way than the original study. Patients and Methods: Ten factors were re-evaluated for survival in patients of the original study including pre-radiotherapy seizures. In the original study, survival was calculated from the end of the last radiotherapy course (primary or re-irradiation). After re-review, this approach was considered inappropriate. Survival should have always been calculated from the first radiotherapy course, as done in this supplementary analysis. Results: On multivariate analysis, WHO-grade II (p=0.006) and upfront resection (p=0.001) were associated with better survival. Unifocal glioma was significant on univariate analysis (p=0.001), where a trend could be identified for age ≤59 years (p=0.057) and seizures (p=0.060). Conclusion: The findings of this supplementary analysis regarding the identification of prognostic factors for survival agree with the results of the original study.*

Cerebral gliomas can be associated with seizures that mainly occur prior to treatment (1). Previous studies suggested that pre-treatment seizures are associated with better survival prognoses (2-5). Possible explanations include that seizures may lead to earlier diagnosis of a glioma, that slower-growing gliomas have a greater tendency to be associated with seizures, and that gliomas associated with seizures may be a special glioma subtype (3-6).

Recently, we presented a study focusing on pre-radiotherapy seizures in patients irradiated for cerebral gliomas of grade II-IV, according to the World Health Organization (WHO) classification (7). In this original study, a trend was found for a positive association between pre-radiotherapy seizures and survival (7). However, survival was calculated from the end of the last radiotherapy course (primary radiotherapy or re-irradiation). After additional review, this approach was considered inappropriate. Survival should have always been calculated from the first radiotherapy course administered for treatment of cerebral glioma. Therefore, this supplementary analysis was performed and death was calculated from the last day of the initial radiotherapy.

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Patients and Methods

This supplementary analysis was performed in the cohort of 222 patients receiving radiotherapy for grade II-IV cerebral gliomas analyzed in the previous study, which was approved by the ethics committee of the University of Lübeck (reference: 20-120A) (7). As in the previous study, ten factors were analyzed for associations with survival including symptoms prior to radiotherapy (none, seizures only, seizures plus other symptoms, other symptoms only), pre-radiotherapy seizures (no, yes), number of sites (unifocal glioma, multifocal glioma), main site(s) of glioma (frontal, parietal, temporal, other sites), cumulative diameter (<40mm, ≥40mm), WHO-grade (II, III, IV), Karnofsky performance score (≤70%, ≥80%), gender (female, male), age (≤59 years, ≥60 years) and upfront resection (no, yes) (Table I). In this new analysis, time to death was calculated in all patients from the last day of the first radiotherapy course given to treat a cerebral glioma. In the original study, survival was calculated from the end of the last radiotherapy course, which could have been the end of primary radiotherapy or the end of re-irradiation for recurrent or new gliomas (7).

In the current analysis, the Kaplan-Meier method and Wilcoxon-test were applied for univariate analyses. A p-value <0.05 indicated

Table I. *Univariate analyses of survival*.

Factor		1 year (%)	2 years (%)	3 years (%)	*p*-Value
Symptoms prior to radiotherapy	No symptoms (n=12)	82	72	72	0.30
	Seizures only (n=21)	90	84	70	
	Seizures+others (n=44)	95	68	57	
	Others only (n=145)	79	69	62	
Seizures prior to radiotherapy	No (n=157)	79	70	64	0.060
	Yes (n=65)	93	74	61	
Number of glioma sites	Unifocal (n=179)	85	74	66	**0.010**
	Mutifocal (n=32)	71	52	37	
Main location of glioma	Frontal (n=62)	81	65	52	0.11
	Parietal (n=38)	88	80	80	
	Temporal (n=91)	87	77	69	
	Other locations (n=31)	74	56	50	
Cumulative size of glioma	<40 mm (n=90)	83	68	59	0.77
	≥40 mm (n=80)	83	73	63	
WHO-grade	Grade II (n=18)	100	94	94	**0.035**
	Grade III (n=41)	93	76	58	
	Grade IV (n=163)	79	66	61	
Karnofsky performance score	≤70% (n=65)	83	64	59	0.28
	≥80% (n=136)	85	73	64	
Gender	Female (n=92)	82	69	63	0.54
	Male (n=136)	84	72	62	
Age	≤59 Years (n=119)	88	77	68	0.057
	≥60 Years (n=103)	78	62	54	
Upfront resection	No (n=44)	65	49	41	**<0.001**
	Yes (n=178)	88	75	67	

WHO: World Health Organization; bold *p*-values indicate significance. If the sum of the numbers of patients for a factor is less than 222, no data were available for the missing patients regarding this factor.

a significant association with survival. In case of a *p*-value <0.10, the situation was defined as showing a trend. Significant factors were additionally analyzed with a multivariate Cox proportional hazard model, where *p*-values <0.05 were considered significant.

Results

Median follow up was 14.5 (0-123) months in the entire cohort and 17 (3-123) months in those patients alive at the last contact. Median survival was 60 months, and survival rates at 1, 2 and 3 years were 83%, 71% and 62%, respectively. On univariate analyses (Table I), unifocal glioma (p=0.010), WHO-grade II (p=0.035) and upfront resection (p<0.001) were significantly associated with better survival. Trends were found for pre-radiotherapy seizures (p=0.060) and age ≤59 years (p=0.057). WHO-grade [hazard ratio (HR)=1.98, 95%-confidence interval (CI)=1.27–3.37, p=0.002] and resection (HR=2.67, 95%-CI=1.45–4.74, p=0.004) were significant in the multivariate analysis, where unifocal glioma was not significant (HR=1.70, 95%-CI=0.85–3.18, p=0.11). Survival rates of grade IV gliomas appeared very high. Since of the 115 surviving patients with grade IV glioma 47, 86 and 100 patients, respectively, had follow up times of <1 year, <2 years and <3 years, several deaths might have been missed in this retrospective study.

Discussion

Seizures can be the first symptom that leads to the diagnosis of a cerebral glioma (1). Pre-treatment seizures have been reported to be associated with improved survival. In the study of Lote *et al*. including both low-grade and high-grade gliomas, a significant association between seizures and survival was found in the multivariate analyses of the entire cohort (relative risk of death=0.83, 95%-confidence interval=0.70-0-98, $p<0.03$) and in patients with high-grade gliomas (relative risk of death=0.80, 95%-confidence interval=0.66-0-96, $p<0.02$) (2). In the group with low-grade tumors, a significant association was not even observed on univariate analysis ($p>0.2$). In contrast to Lote *et al*., other studies found a positive association between seizures and survival in patients with low-grade gliomas (6, 8, 9). In our original study, occurrence of pre-radiotherapy seizures showed a trend ($p=0.075$) for an association with better survival on univariate analysis (7). In our original study, WHO-grade II (HR=1.96, 95%-CI=1.26-3.30, $p=0.002$) and upfront resection (HR=2.54, 95%-CI=1.36-4.57, $p=0.004$) were identified as independent predictors of survival in the multivariate analysis. In addition, unifocal glioma was significant on univariate

analysis ($p<0.001$) and showed a trend in the multivariate analysis (HR=1.96, 95%-CI=0.97-3.72, $p=0.062$). For age ≤59 years, a trend was found on univariate analysis ($p=0.091$). Positive associations between these factors and survival of glioma patients were previously described (10-14), consistent with the results of our study (7). However, in our original study, survival was calculated from the end of the last radiotherapy course, which was re-irradiation for recurrent or new gliomas in some patients, but should have always been calculated from the end of the first radiotherapy course for cerebral glioma (7). Therefore, the survival data of the original study were re-evaluated by calculating the time to death from the last day of the initial radiotherapy course in all patients. As in the original study, WHO-grade II and upfront resection proved to be independent predictors of better survival in the current supplementary analysis (7). For occurrence of pre-radiotherapy seizures and age ≤59 years, trends for improved survival were found on univariate analysis, which agreed well with our original study. On univariate analysis, unifocal glioma was significantly associated with better survival in both the original and the current study. Unifocal glioma showed a trend for better survival in the multivariate analysis of the original study (p=0.062), which was not observed in this analysis (p=0.11). However, both results were not significant.

In conclusion, the findings of the current analysis regarding the identification of prognostic factors for survival agree with the results of the original study. The identified prognostic factors can contribute to better treatment personalization in future patients with cerebral gliomas and can be used for proper stratification in future clinical trials.

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 this additional study. Data were collected by J.W., analyzed by S.E.S. and D.R. and interpreted by all Authors. S.E.S. and D.R. drafted the manuscript that has been reviewed and finally approved by all Authors.

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