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Prognostic Factors for Progression-free Survival and Overall Survival After Recurrence of Glioblastoma

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Abstract. *Background/Aim: Many patients with glioblastoma experience an intracerebral recurrence and require a personalized treatment. This study aimed to facilitate this approach by identifying prognostic factors for progression-free survival (PFS) and overall survival (OS). Patients and Methods: In 102 patients with recurrent glioblastoma following primary treatment with resection or biopsy plus adjuvant chemoradiation, 11 characteristics were retrospectively investigated regarding PFS and OS. Results: In the multivariate analyses, Karnofsky performance score (KPS) 90-100 at the time of recurrence (p=0.032), maximum cumulative diameter of recurrent lesions ≤40 mm (p=0.002), resection of recurrent glioblastoma (p=0.025), and systemic therapy for recurrent glioblastoma (p=0.025) were significantly associated with improved PFS. In addition, KPS 90-100 (p=0.024), maximum cumulative diameter ≤40 mm (p=0.033), and systemic therapy (p=0.006) were significantly associated with better OS. Conclusion: Our study identified high Karnofsky Performance Status (KPS 90-100), maximum cumulative diameter of recurrent glioblastoma lesions ≤40 mm, and systemic therapy for recurrent glioblastoma as independent predictors of overall survival (OS) and progression-free survival (PFS). These independent prognostic factors may help select the most suitable treatment for individual patients with recurrent glioblastoma, potentially improving patient outcomes.*

Glioblastoma is the most aggressive primary brain tumor in adults (1, 2). For almost 20 years, standard primary treatment of glioblastoma includes maximum possible resection followed by chemoradiation with temozolomide (TMZ) and subsequent maintenance chemotherapy with six additional cycles of TMZ (3). More recently, selected patients are offered additional therapy with tumor treating fields (TTF) (4). Although these developments in the treatment of glioblastoma have led to improved outcomes, many patients experience an intracerebral recurrence of their disease within one year (5, 6).

Currently, the optimal treatment of recurrent glioblastoma is still under debate (2). Treatment options generally include re-resection, re-irradiation, and second-line systemic therapy (1). For selected patients, best supportive care alone plus corticosteroids may also be considered (2). Selection of the most suitable treatment for an individual patient with recurrent glioblastoma should always consider the patient's specific situation and survival prognosis. Thus, the knowledge of prognostic factors can help the corresponding selection process. Studies that investigated potential prognostic factors for overall survival (OS) in patients with recurrent glioblastoma or recurrent malignant glioma produced some conflicting results (2, 7-29). Therefore, additional investigations are required. This study evaluated 11 patient-, tumor-, or treatment-related characteristics for associations with OS or progression-free survival (PFS) in patients who developed a recurrence of glioblastoma following neurosurgical intervention and adjuvant chemoradiation.

Patients and Methods

One-hundred-and-two patients who developed a recurrence of glioblastoma between 2014 and 2024 were included in this retrospective study that received approval from the Ethics Committee at the University of Lübeck, Germany (file number 2022-509). Primary treatment included surgical intervention, which was gross total resection (GTR) in 35 patients, subtotal resection (STR) in 46 patients, and biopsy in 21 patients, followed by chemoradiation with TMZ (100 patients) or radiotherapy alone (two patients). Radiotherapy was performed with 59.4 Gy in 33 fractions of 1.8 Gy in 67 patients, 60 Gy in 30 fractions of 2.0 Gy in 28 patients, or 45 to 57.6 Gy in 25 to 33 fractions of 1.8 Gy in seven patients, respectively.

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At the time of recurrence, 34 patients received a resection of their recurrent glioblastoma lesions, which was GTR in 14 patients and STR in 20 patients. Twenty-two patients were irradiated for their recurrent glioblastoma (re-irradiation). Fifteen of these patients received hyper-fractionated or accelerated hyper-fractionated radiotherapy with two fractions of 1.1-1.5 Gy per day, with or without a simultaneous integrated boost, and total doses of 21-42 Gy. Five patients were treated with one fraction of 1.6-2.5 Gy per day up to 30.4-55.8 Gy. One patient received 15×3.0 Gy with heavy ions; in one patient treated with one fraction of 1.6 Gy per day, radiotherapy was stopped after only 4.8 Gy. Sixty-seven of the 102 patients received systemic therapy for recurrent glioblastoma. Regimens included chemotherapy with TMZ alone in 33 patients, procarbazine/lomustine (PC) in 22 patients, TMZ plus lomustine in two patients, TMZ plus PC in two patients, PC/vincristine (PCV) in two patients, lomustine alone in two patients, PC plus monoclonal antibody bevacizumab in one patient, and TMZ plus PC and bevacizumab in one patient. Moreover, two patients received bevacizumab alone.

In the entire cohort, 11 characteristics (Table I) were investigated for potential associations with PFS and OS. These characteristics included age at the time of recurrence (≤60 *vs.* ≥61 years, median age=60.5 years), sex (female *vs.* male), Karnofsky performance score (KPS) at the time of recurrence (≤80 *vs.* 90-100), interval between last day of primary irradiation and diagnosis of recurrent glioblastoma (≤5 *vs.* ≥6 months, median interval=5 months), number of recurrent glioblastoma lesions (1 *vs.* ≥2), maximum cumulative diameter of recurrent glioblastoma lesion(s) (≤40 *vs.* >40 mm), site(s) of recurrent glioblastoma lesion(s) (old *vs.* new *vs.* both), resection of recurrent glioblastoma lesions(s) (no *vs.* yes), re-irradiation of recurrent glioblastoma lesions(s) (no *vs.* yes), systemic therapy for recurrent glioblastoma lesions(s) (no *vs.* yes), and TTF for recurrent glioblastoma lesions(s) (no *vs.* yes),

PFS and OS were calculated from the day of the diagnosis of recurrent glioblastoma. Univariate analyses were performed with the Kaplan–Meier method and the log-rank test. After Bonferroni correction (11 tests), *p*-values <0.0045 were considered significant representing an alpha level of <5%. In addition, *p*-values <0.05 were considered indicating a trend for associations with PFS or OS. Factors found to be significant or indicating a trend were additionally included in a Cox proportional hazards model (multivariate analysis), where *p*-values <0.05 were considered significant indicating independence of the corresponding predictors of PFS or OS.

Results

Median follow-up times after the diagnosis of recurrent glioblastoma were 7.25 months (range=0-41.5 months) in the entire cohort and 12 months (range=3-41.5 months) in those patients alive at the last follow-up.

On univariate analyses, better PFS was significantly associated with KPS 90-100 ($p<0.001$), maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm ($p<0.001$), and systemic therapy for recurrent glioblastoma lesions(s) ($p<0.001$). In addition, a trend was found for resection of the recurrent glioblastoma lesions(s) ($p=0.017$). The complete results of the univariate analyses of PFS are shown in Table II. In the multivariate analysis of PFS (Table III), improved outcomes were significantly associated with KPS 90-100 ($p=0.032$), maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm ($p=0.002$), resection of the recurrent glioblastoma lesions(s) ($p=0.025$), and systemic therapy for recurrent glioblastoma lesions(s) ($p<0.001$).

On univariate analyses, better OS was significantly associated with KPS 90-100 ($p<0.001$), maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm ($p<0.001$), and systemic therapy for recurrent glioblastoma lesions(s) ($p<0.001$). Trends were found for single lesion of recurrent glioblastoma ($p=0.012$), recurrence of glioblastoma in old (=primary) site(s) of glioblastoma ($p=0.048$), and re-irradiation of recurrent glioblastoma ($p=0.037$). The complete results of the univariate analyses of OS are summarized in Table IV. In the multivariate analysis of OS (Table V), improved outcomes were significantly associated with KPS 90-100 ($p=0.024$), maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm ($p=0.033$), and systemic therapy for recurrent glioblastoma lesions(s) ($p=0.006$).

Discussion

Many patients with glioblastoma develop a recurrence or progression within the first year after standard treatment including resection followed by chemoradiation and maintenance chemotherapy (5, 6). The optimal treatment for recurrent glioblastoma needs further clarification. Outcomes of patients with recurrent glioblastoma may be improved by using personalized treatment regimens. Optimal treatment personalization should consider several individual factors including the patient's expected remaining OS time. Thus, significant predictors of OS can be helpful when aiming to select a personalized treatment approach for recurrent glioblastoma.

Previous studies that investigated potential prognostic factors of OS specifically for patients with recurrent glioblastoma (grade IV glioma) have produced partially conflicting results (2, 8-23). In 2012, Bloch *et al.* presented a retrospective study of 107 patients who received resection of recurrent glioblastoma (8). KPS >70, younger age, and GTR were identified as independent predictors of better OS. In the same year, Gorlia *et al.* reported data of 300 patients with recurrent glioblastoma previously included in prospective trials (9). Better performance status, maximum diameter of the largest lesion <42 mm, a single lesion, and predominant frontal location were significantly associated with better OS, whereas age was not an independent predictor of OS. In a retrospective study of 100 patients treated with bevacizumab for recurrent glioblastoma, improved OS was associated with KPS ≥70 on multivariate analysis, whereas age, tumor size, or interval between initial diagnosis and

Table I. *Characteristics analyzed for associations with progression-free survival and overall survival following the diagnosis of recurrent glioblastoma.*

Characteristic	Subgroup	Number of patients (%)
Age at the time of recurrence	≤60 Years	51 (50)
	≥61 Years	51 (50)
Sex	Female	42 (41)
	Male	60 (59)
Karnofsky performance score at the time of recurrence	≤80	60 (59)
	90-100	42 (41)
Interval between primary radiotherapy and diagnosis of recurrent glioblastoma	≤5 Months	53 (52)
	≥6 Months	49 (48)
Number of recurrent lesions	1	58 (57)
	≥2	41 (40)
	Unknown	3 (3)
Maximum cumulative diameter of recurrent lesion(s)	≤40 mm	46 (45)
	>40 mm	53 (52)
	Unknown	3 (3)
Site(s) of recurrent lesion(s)	Old site(s)	71 (70)
	New site(s)	11 (11)
	Both	17 (17)
	Unknown	3 (3)
Resection of recurrent lesion(s)	No	68 (67)
	Yes	34 (33)
Re-irradiation of recurrent lesion(s)	No	80 (79)
	Yes	22 (21)
Systemic therapy for recurrent lesion(s)	No	33 (32)
	Yes	67 (66)
	Unknown	2 (2)
Tumor treating fields for recurrent lesion(s)	No	96 (94)
	Yes	6 (6)

recurrence of glioblastoma had no significant impact (10). In the retrospective study of Franceschi *et al*. that investigated the impact of resection of recurrent glioblastoma on OS, better OS was significantly associated with younger age and MGMT (O6-methylguanine-DNA methyl-transferase) promoter methylation but not with resection of the recurrent lesions (11). In another retrospective study of patients treated with bevacizumab for recurrent glioblastoma (n=174), OS was positively associated with KPS ≥80 and addition of irinotecan but not with age, *MGMT* promoter methylation, or resection of the recurrent lesions (12). Urup *et al*. identified only multifocal disease, need for corticosteroids, and presence of neuro-cognitive deficits to be negatively associated with OS in a cohort of 219 patients receiving bevacizumab and irinotecan for recurrent glioblastoma (13). Azoulay *et al*. found in their retrospective study of 180 patients with recurrent glioblastoma that resection plus salvage chemotherapy and/or radiotherapy led to improved OS (14). Moreover, age ≤65 years at the time of recurrence and *MGMT* promoter methylation were positively associated with OS. In another retrospective study of 64 patients with recurrent glioblastoma, improved OS was significantly associated with age ≤60 years, KPS 90-100, GTR, and adjuvant treatment, particularly concurrent chemoradiation (15). *MGMT* promoter methylation and location of recurrent glioblastoma had no significant impact on OS in this study. In 2018, Audureau *et al*. developed a decision-tree based model of OS of patients with recurrent glioblastoma based on independent predictors of worse outcomes, namely increasing age at diagnosis, decreasing KPS at the time of recurrence, and improved outcomes, namely neurosurgical resection and chemotherapy (16). In 2019, Sharma *et al*. presented the data of 53 patients receiving stereotactic radiosurgery for recurrent glioblastoma (17). On both univariate and multivariate analyses, better OS was significantly associated with KPS ≥80 and cumulative tumor volume <15 cc. Seyve *et al*. found that a longer interval between initial diagnosis of glioblastoma and the time of recurrence (>11 *vs*. ≤11 months) and resection of recurrent glioblastoma were independent predictors of longer OS after recurrence (18). In contrast, age, KPS, and tumor size did not improve OS in the group of patients receiving resection of their recurrent glioblastoma. In a retrospective study of our group in 28 patients re-irradiated for recurrent glioblastoma, frontal location and higher cumulative radiation dose were independent prognostic factors of OS (19). In addition, trends were found for KPS

Table II. *Progression-free survival rates at 6 and 12 months following the diagnosis of recurrent glioblastoma (univariate analyses).*

Characteristic	Subgroup	At 6 months (%)	At 12 months (%)	*p*-Value
Age at the time of recurrence	≤60 Years	33	13	0.96
	≥61 Years	30	22	
Sex	Female	31	20	0.77
	Male	31	14	
Karnofsky performance score at the time of recurrence	≤80	18	10	**<0.001**
	90-100	49	26	
Interval between primary radiotherapy and diagnosis of recurrent glioblastoma	≤5 Months	28	17	0.44
	≥6 Months	34	16	
Number of recurrent lesions	1	36	20	0.11
	≥2	26	14	
Maximum cumulative diameter of recurrent lesion(s)	≤40 mm	51	30	**<0.001**
	>40 mm	15	7	
Site(s) of recurrent lesion(s)	Old site(s)	34	20	0.41
	New site(s)	21	0	
	Both	33	16	
Resection of recurrent lesion(s)	No	20	12	0.017
	Yes	53	25	
Re-irradiation of recurrent lesion(s)	No	29	19	0.46
	Yes	40	6	
Systemic therapy for recurrent lesion(s)	No	14	10	**<0.001**
	Yes	38	20	
Tumor treating fields for recurrent lesion(s)	No	32	18	0.25
	Yes	17	0	

After Bonferroni adjustment, *p*-values <0.0045 are considered significant and given in bold; *p*-values <0.05 indicate a trend.

Table III. *Multivariate analysis of progression-free survival following the diagnosis of recurrent glioblastoma.*

Characteristic	Hazard ratio	95% Confidence interval	*p*-Value
Karnofsky performance score (≤80 *vs.* 90-100)	0.59	0.36-0.95	**0.032**
Maximum cumulative diameter (≤40 *vs.* >40 mm)	2.18	1.33-3.58	**0.002**
Resection of recurrent lesion(s) (no *vs.* yes)	0.57	0.34-0.93	**0.025**
Systemic therapy for recurrent lesion(s) (no *vs.* yes)	0.31	0.18-0.52	**<0.001**

Significant *p*-values are given in bold.

80-100 and dose of re-irradiation on multivariate analysis, and GTR was significant on univariate analysis. Age and interval between primary radiotherapy and recurrence had no significant impact on OS. In the retrospective study of Barz *et al.* performed in 123 patients receiving resection of recurrent glioblastoma, pre-operative KPS ≥80 and GTR were significantly associated with better OS (20). In 2022, Furtak *et al.* presented the results of a prospective study of 165 patients receiving re-resection for recurrent glioblastoma (21). Younger age, absence of symptoms of increased intracranial pressure, and a longer interval between first and second surgery were independent predictors of longer OS. In the same year, Hennessy *et al.* used data from a national neuro-oncological registry to identify predictors of OS after re-resection of recurrent glioblastoma (2). Associations with improved OS were found for MGMT promoter methylation, KPS ≥70, and a longer interval between first and second resection. In addition, trends for such associations were observed for younger age and GTR. In 2023, You *et al.* investigated the option of re-irradiation plus bevacizumab for recurrent glioblastoma after treatment with bevacizumab in a retrospective series of 64 patients (22). On univariate analyses, higher KPS, smaller volume of radiotherapy, and re-resection were associated with better OS. On multivariate analysis, only the volume of radiotherapy remained significant. In 2024, Hansen *et al.* presented a retrospective study of 66 patients receiving repeat resection for recurrent glioblastoma (23). Better post-operative OS was significantly associated with younger age, tumor volume <50 cc, absence of ependymal involvement, lower Ki67 labeling index, pre-

Table IV. *Overall survival rates at 6 and 12 months following the diagnosis of recurrent glioblastoma (univariate analyses).*

Characteristic	Subgroup	At 6 months (%)	At 12 months (%)	*p*-Value
Age at the time of recurrence	≤60 Years	62	40	0.79
	≥61 Years	58	41	
Sex	Female	54	40	0.80
	Male	65	41	
Karnofsky performance score at the time of recurrence	≤80	45	24	**<0.001**
	90-100	81	64	
Interval between primary radiotherapy and diagnosis of recurrent glioblastoma	≤5 Months	57	37	0.16
	≥6 Months	64	46	
Number of recurrent lesions	1	67	47	0.012
	≥2	55	34	
Maximum cumulative diameter of recurrent lesion(s)	≤40 mm	80	60	**<0.001**
	>40 mm	46	26	
Site(s) of recurrent lesion(s)	Old site(s)	66	47	0.048
	New site(s)	52	14	
	Both	52	36	
Resection of recurrent lesion(s)	No	53	34	0.18
	Yes	74	53	
Re-irradiation of recurrent lesion(s)	No	56	36	0.037
	Yes	77	58	
Systemic therapy for recurrent lesion(s)	No	39	22	**<0.001**
	Yes	70	49	
Tumor treating fields for recurrent lesion(s)	No	62	41	0.19
	Yes	33	33	

After Bonferroni adjustment, *p*-values <0.0045 are considered significant and given in bold; *p*-values <0.05 indicate a trend.

Table V. *Multivariate analysis of overall survival following the diagnosis of recurrent glioblastoma.*

Characteristic	Hazard ratio	95% Confidence interval	*p*-Value
Karnofsky performance score (≤80 *vs*. 90-100)	0.53	0.30-0.92	**0.024**
Number of recurrent lesion(s) (1 *vs*. ≥2)	1.29	0.69-2.41	0.42
Maximum cumulative diameter (≤40 *vs*. >40 mm)	1.84	1.05-3.23	**0.033**
Site(s) of recurrent lesion(s) (old *vs*. new *vs*. both)	1.26	0.88-1.80	0.20
Re-RT of recurrent lesion(s) (no *vs*. yes)	0.73	0.36-1.51	0.40
Systemic therapy for recurrent lesion(s) (no *vs*. yes)	0.49	0.30-0.81	**0.006**

Significant *p*-values are given in bold.

operative KPS ≥70, and no decrease of KPS following re-resection, whereas *MGMT* promoter methylation had no significant impact on OS. In addition to these studies that focused on patients with recurrent glioblastoma (grade IV glioma), groups from Germany presented different survival scores based on data from patients re-irradiated for malignant glioma of different grades including grade III and lower grade gliomas (24-29). In the multivariate analyses of the corresponding studies, no factor, two factors (age, grade), two factors (age, KPS), three factors (age, grade, KPS), three factors (KPS, *MGMT* promoter methylation, radiation dose), and four factors (age, grade, KPS, interval between both radiotherapy courses), respectively, were identified as independent predictors of OS (24-29).

Considering these partially conflicting data from the available literature, it becomes obvious that additional studies aiming to identify prognostic factors of OS in patients with recurrent glioblastoma are necessary. Therefore, our present study was performed. According to its results, improved OS was independently associated with KPS 90-100, maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm, and systemic therapy for recurrent glioblastoma. Considering a Bonferroni correction for multiple tests, additional trends for associations with better OS were found on univariate analyses for single lesion of recurrent glioblastoma, recurrence of glioblastoma in old site(s), and re-irradiation of recurrent glioblastoma. Five of these prognostic factors agree with the results of several previous studies

focusing on glioblastoma that are discussed above (2, 8-10, 12-17, 20, 22, 23). Recurrence of glioblastoma in old site(s) was identified as potential prognostic factor of better OS for the first time.

In general, patients with unfavorable prognostic factors and a very poor estimated survival may be considered for best supportive care including corticosteroids instead of invasive and aggressive treatments, particularly neurosurgical resections, that may impair the patients' quality of life. Patients with poor prognoses may be considered for little burdensome palliative treatment, which may include hypo-fractionated short-course radiotherapy and moderate systemic therapy. On the other hand, patients with favorable survival prognoses can benefit from more aggressive multimodal treatment including maximum safely possible re-resection followed by adjuvant chemoradiation. However, a second course of radiotherapy may not be safely possible due to primary radiotherapy with doses of approximately 60 Gy. When aiming to perform re-irradiation, the tolerance doses of organs at risk, such as the brain stem, cochlea, optic chiasm, and optic nerves must be considered (30, 31).

When considering these recommendations, the limitations of our present study and previous studies need to be respected. Almost all of these studies were retrospective in nature and, therefore, bear the risk of hidden selection biases. An additional limitation of our study is the fact that the *MGMT* promoter methylation was not investigated, since it was available at the time of recurrence only for a few patients (18). It appeared not reasonable to use the *MGMT* promoter methylation of the primary glioblastoma, since it has been shown that the methylation status can change between primary and recurrent glioblastoma (32). Moreover, the size of the recurrent lesion was sometimes difficult to define absolute precisely because of alteration of brain tissue as a consequence of previous surgery or radiotherapy.

In addition to predictors of OS, we aimed to identify independent prognostic factors of PFS, which was done only in very few studies before (9, 15, 17). In the multivariate analysis of our study, better PFS was significantly associated with KPS 90-100, maximum cumulative diameter of recurrent glioblastoma lesion(s) ≤40 mm, resection of recurrent lesions(s), and systemic therapy for recurrent glioblastoma. In the previous three studies, higher KPS, smaller tumor volume, single lesion of glioblastoma, younger age, and/or adjuvant therapy after resection of recurrent glioblastoma were identified as independent predictors of improved PFS (9, 15, 17). Moreover, one study showed a trend for GTR with respect to better PFS (15). These prognostic factors may be used to discuss individual prognoses and expected treatment results with the patients and their relatives. This may be helpful when they have to make decisions for or against potential treatment options. However, the same limitations apply regarding the use of prognostic factors of PFS as for prognostic factors of OS. The data regarding PFS should be considered with even more caution than the data regarding OS, since the number of available studies investigating PFS is considerably lower.

In conclusion, given the limitations of this study, independent predictors of PFS and OS were identified. These factors may support physicians who aim to select the most suitable treatment for an individual patient with recurrent glioblastoma. Our results should be validated in a prospective clinical trial.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

The study was designed by all Authors. Data were collected by O.Z. and D.R.; data analyses were conducted by D.R. and N.Y.Y. The manuscript was drafted by D.R. and the final version approved by all Authors.

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References

1 Weller M, Cloughesy T, Perry JR, Wick W: Standards of care for treatment of recurrent glioblastoma – are we there yet? Neuro Oncol 15(1): 4-27, 2013. DOI: 10.1093/neuonc/nos273

2 Hennessy MA, Coyne ZL, O'Halloran PJ, Mullally W, Dablouk M, MacNally S, Morris PG: Prognostic factors influencing survival following re-resection for isocitrate dehydrogenase (IDH) -wildtype glioblastoma multiforme – Data from a national neuro-oncology registry. J Clin Neurosci 95: 142-150, 2022. DOI: 10.1016/j.jocn.2021.12.011

3 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10): 987-996, 2005. DOI: 10.1056/NEJMoa043330

4 Fabian D, Guillermo Prieto Eibl MDP, Alnahhas I, Sebastian N, Giglio P, Puduvalli V, Gonzalez J, Palmer JD: Treatment of glioblastoma (GBM) with the addition of tumor-treating fields (TTF): a review. Cancers (Basel) 11(2): 174, 2019. DOI: 10.3390/cancers11020174

5 Zemskova O, Yu NY, Trillenberg P, Bonsanto MM, Leppert J, Rades D: Identification of patients with glioblastoma who may benefit from hypofractionated radiotherapy. Anticancer Res 43(6): 2725-2732, 2023. DOI: 10.21873/anticanres.16439

6 Zemskova O, Pedachenko E, Yu NY, Rades D: Hypofractionated radiotherapy (HF-RT) *versus* conventionally fractionated radiotherapy (CF-RT) for glioblastoma. Anticancer Res 43(7): 3121-3128, 2023. DOI: 10.21873/anticanres.16484
7 Minniti G, Niyazi M, Alongi F, Navarria P, Belka C: Current status and recent advances in reirradiation of glioblastoma. Radiat Oncol 16(1): 36, 2021. DOI: 10.1186/s13014-021-01767-9
8 Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, Berger MS, Parsa AT: Impact of extent of resection for recurrent glioblastoma on overall survival. J Neurosurg 117(6): 1032-1038, 2012. DOI: 10.3171/2012.9.JNS12504
9 Gorlia T, Stupp R, Brandes AA, Rampling RR, Fumoleau P, Dittrich C, Campone MM, Twelves CC, Raymond E, Hegi ME, Lacombe D, Van Den Bent MJ: New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: A pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials. Eur J Cancer 48(8): 1176-1184, 2012. DOI: 10.1016/j.ejca.2012.02.004
10 Tabouret E, Barrie M, Thiebaut A, Matta M, Boucard C, Autran D, Loundou A, Chinot O: Limited impact of prognostic factors in patients with recurrent glioblastoma multiforme treated with a bevacizumab-based regimen. J Neurooncol 114(2): 191-198, 2013. DOI: 10.1007/s11060-013-1170-y
11 Franceschi E, Bartolotti M, Tosoni A, Bartolini S, Sturiale C, Fioravanti A, Pozzati E, Galzio R, Talacchi A, Volpin L, Morandi L, Danieli D, Ermani M, Brandes AA: The effect of re-operation on survival in patients with recurrent glioblastoma. Anticancer Res 35(3): 1743-1748, 2015.
12 Schaub C, Tichy J, Schäfer N, Franz K, Mack F, Mittelbronn M, Kebir S, Thiepold A, Waha A, Filmann N, Banat M, Fimmers R, Steinbach JP, Herrlinger U, Rieger J, Glas M, Bähr O: Prognostic factors in recurrent glioblastoma patients treated with bevacizumab. J Neurooncol 129(1): 93-100, 2016. DOI: 10.1007/s11060-016-2144-7
13 Urup T, Dahlrot RH, Grunnet K, Christensen IJ, Michaelsen SR, Toft A, Larsen VA, Broholm H, Kosteljanetz M, Hansen S, Poulsen HS, Lassen U: Development and validation of a prognostic model for recurrent glioblastoma patients treated with bevacizumab and irinotecan. Acta Oncol 55(4): 418-422, 2016. DOI: 10.3109/0284186X.2015.1114679
14 Azoulay M, Santos F, Shenouda G, Petrecca K, Oweida A, Guiot MC, Owen S, Panet-Raymond V, Souhami L, Abdulkarim BS: Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. J Neurooncol 132(3): 419-426, 2017. DOI: 10.1007/s11060-017-2383-2
15 Pessina F, Navarria P, Cozzi L, Tomatis S, Riva M, Ascolese AM, Santoro A, Simonelli M, Bello L, Scorsetti M: Role of surgical resection in recurrent glioblastoma: prognostic factors and outcome evaluation in an observational study. J Neurooncol 131(2): 377-384, 2017. DOI: 10.1007/s11060-016-2310-y
16 Audureau E, Chivet A, Ursu R, Corns R, Metellus P, Noel G, Zouaoui S, Guyotat J, Le Reste PJ, Faillot T, Litre F, Desse N, Petit A, Emery E, Lechapt-Zalcman E, Peltier J, Duntze J, Dezamis E, Voirin J, Menei P, Caire F, Dam Hieu P, Barat JL, Langlois O, Vignes JR, Fabbro-Peray P, Riondel A, Sorbets E, Zanello M, Roux A, Carpentier A, Bauchet L, Pallud J, Club de Neuro-Oncologie of the Société Française de Neurochirurgie: Prognostic factors for survival in adult patients with recurrent glioblastoma: a decision-tree-based model. J Neurooncol 136(3): 565-576, 2018. DOI: 10.1007/s11060-017-2685-4
17 Sharma M, Schroeder JL, Elson P, Meola A, Barnett GH, Vogelbaum MA, Suh JH, Chao ST, Mohammadi AM, Stevens GHJ, Murphy ES, Angelov L: Outcomes and prognostic stratification of patients with recurrent glioblastoma treated with salvage stereotactic radiosurgery. J Neurosurg 131(2): 489-499, 2019. DOI: 10.3171/2018.4.JNS172909
18 Seyve A, Lozano-Sanchez F, Thomas A, Mathon B, Tran S, Mokhtari K, Giry M, Marie Y, Capelle L, Peyre M, Carpentier A, Feuvret L, Sanson M, Hoang-Xuan K, Honnorat J, Delattre JY, Ducray F, Idbaih A: Initial surgical resection and long time to occurrence from initial diagnosis are independent prognostic factors in resected recurrent IDH wild-type glioblastoma. Clin Neurol Neurosurg 196: 106006, 2020. DOI: 10.1016/j.clineuro.2020.106006
19 Rades D, Witteler J, Leppert J, Schild SE: Re-irradiation for recurrent glioblastoma multiforme. Anticancer Res 40(12): 7077-7081, 2020. DOI: 10.21873/anticanres.14735
20 Barz M, Bette S, Janssen I, Aftahy AK, Huber T, Liesche-Starnecker F, Ryang YM, Wiestler B, Combs SE, Meyer B, Gempt J: Age-adjusted Charlson comorbidity index in recurrent glioblastoma: a new prognostic factor? BMC Neurol 22(1): 32, 2022. DOI: 10.1186/s12883-021-02532-x
21 Furtak J, Kwiatkowski A, Śledzińska P, Bebyn M, Krajewski S, Szylberg T, Birski M, Druszcz A, Krystkiewicz K, Gasiński P, Harat M: Survival after reoperation for recurrent glioblastoma multiforme: A prospective study. Surg Oncol 42: 101771, 2022. DOI: 10.1016/j.suronc.2022.101771
22 You WC, Lee HD, Pan HC, Chen HC: Re-irradiation combined with bevacizumab for recurrent glioblastoma beyond bevacizumab failure: survival outcomes and prognostic factors. Sci Rep 13(1): 9442, 2023. DOI: 10.1038/s41598-023-36290-2
23 Hansen ST, Jacobsen KS, Kofoed MS, Petersen JK, Boldt HB, Dahlrot RH, Schulz MK, Poulsen FR: Prognostic factors to predict postoperative survival in patients with recurrent glioblastoma. World Neurosurg X 23: 100308, 2024. DOI: 10.1016/j.wnsx.2024.100308
24 Niyazi M, Flieger M, Ganswindt U, Combs SE, Belka C: Validation of the prognostic Heidelberg re-irradiation score in an independent mono-institutional patient cohort. Radiat Oncol 9: 128, 2014. DOI: 10.1186/1748-717X-9-128
25 Combs SE, Edler L, Rausch R, Welzel T, Wick W, Debus J: Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. Acta Oncol 52(1): 147-152, 2013. DOI: 10.3109/0284186X.2012.692882
26 Combs SE, Niyazi M, Adeberg S, Bougatf N, Kaul D, Fleischmann DF, Gruen A, Fokas E, Rödel CM, Eckert F, Paulsen F, Oehlke O, Grosu AL, Seidlitz A, Lattermann A, Krause M, Baumann M, Guberina M, Stuschke M, Budach V, Belka C, Debus J, Kessel KA: Re-irradiation of recurrent gliomas: pooled analysis and validation of an established prognostic score-report of the Radiation Oncology Group (ROG) of the German Cancer Consortium (DKTK). Cancer Med 7(5): 1742-1749, 2018. DOI: 10.1002/cam4.1425
27 Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, Schlegel J, Meyer B, Combs SE: Modification and optimization of an established prognostic score after re-irradiation of recurrent glioma. PLoS One 12(7): e0180457, 2017. DOI: 10.1371/journal.pone.0180457
28 Niyazi M, Adeberg S, Kaul D, Boulesteix A, Bougatf N, Fleischmann DF, Grün A, Krämer A, Rödel C, Eckert F, Paulsen

F, Kessel KA, Combs SE, Oehlke O, Grosu A, Seidlitz A, Lattermann A, Krause M, Baumann M, Guberina M, Stuschke M, Budach V, Belka C, Debus J: Independent validation of a new reirradiation risk score (RRRS) for glioma patients predicting post-recurrence survival: A multicenter DKTK/ROG analysis. Radiother Oncol 127(1): 121-127, 2018. DOI: 10.1016/j.radonc.2018.01.011

29 Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, Schlegel J, Meyer B, Combs SE: Validation of an established prognostic score after re-irradiation of recurrent glioma. Acta Oncol 56(3): 422-426, 2017. DOI: 10.1080/0284186X.2016.1276621

30 Stiefel I, Schröder C, Tanadini-Lang S, Pytko I, Vu E, Klement RJ, Guckenberger M, Andratschke N: High-dose re-irradiation of intracranial lesions - Efficacy and safety including dosimetric analysis based on accumulated EQD2Gy dose EQD calculation. Clin Transl Radiat Oncol 27: 132-138, 2021. DOI: 10.1016/j.ctro.2021.01.011

31 Rades D, Simone CB 2nd, Wong HCY, Chow E, Lee SF, Johnstone PAS: Reirradiation of metastases of the central nervous system: part 1 – brain metastasis. Ann Palliat Med: apm-23-593, 2023. DOI: 10.21037/apm-23-593

32 Brandes AA, Franceschi E, Tosoni A, Bartolini S, Bacci A, Agati R, Ghimenton C, Turazzi S, Talacchi A, Skrap M, Marucci G, Volpin L, Morandi L, Pizzolitto S, Gardiman M, Andreoli A, Calbucci F, Ermani M: O(6)-methylguanine DNA-methyltransferase methylation status can change between first surgery for newly diagnosed glioblastoma and second surgery for recurrence: clinical implications. Neuro Oncol 12(3): 283-288, 2010. DOI: 10.1093/neuonc/nop050

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