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Therapy Intensity Outweighs the Prognostic Importance of the Timing of Chemoradiotherapy in Newly Diagnosed Glioblastoma Patients

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Abstract. *Background/Aim: To investigate the significance of the timing of chemoradiotherapy together with clinical and laboratory features in newly diagnosed glioblastoma. Patients and Methods: Clinical and laboratory parameters of 209 patients with glioblastoma potentially influencing overall (OS) and progression-free (PFS) survival were analyzed in univariable and multivariable models. Results: On univariable analyses, Karnofsky performance status (p<0.001), recursive partitioning analysis (RPA) class (p<0.001), O^6-methylguanine-DNA methyltransferase (MGMT)-status (p<0.001), extent of resection (p<0.001), radiotherapy dose (p=0.01), and the number of adjuvant temozolomide (TMZ) cycles (p<0.001) were significantly associated with OS. Additionally, MGMT-status (p<0.001), extent of resection (p=0.03), surgical site infections (p=0.02), and the number of adjuvant TMZ cycles (p<0.001) were significantly associated with PFS. Multivariable analysis identified radiotherapy dose as the only independent predictor (p=0.049) of OS. MGMT-status (p=0.02) and the number of adjuvant TMZ cycles (p<0.001) were independent predictors of PFS. Conclusion: The timing of chemoradiotherapy did not play a prognostic role. For OS, the radiotherapy dose, and for PFS, MGMT-status and the number of adjuvant TMZ cycles were identified as independent prognostic factors.*

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With an incidence of 5.26 cases per 100,000 people and 17,000 annual first-time diagnoses (1), glioblastoma (GBM) constitutes the most common primary brain tumor in adults. The gold standard of therapy involves maximal safe surgical resection, followed by a temozolomide (TMZ)-based chemoradiotherapy (CRT) and adjuvant TMZ maintenance thereafter (2). Since the publication of this treatment regimen by Stupp *et al*. in 2005, hardly any changes have been made to this strategy (2). Although various research efforts have been undertaken in the meantime to improve the poor prognosis of GBM, the median survival time still ranges from 10.1 to 20.9 months (despite a multimodal treatment approach) (3, 4).

The available literature indicates that patient age (5-10), functional status (5, 7, 10), tumor localization and extent (bilateral, multifocal) (6, 7, 9-11) as well as the extent of surgical resection (7-11), O^6-methylguanine-DNA methyltransferase

(*MGMT*) status (2), and oncological therapy (6-12) are important predictors of survival. Recently, several studies investigated the time-to-surgery (TTS) after the diagnostic magnetic resonance imaging (MRI) scan as a further influencing factor of survival: In a multicenter study by Müller *et al*. the majority of patients with GBM (*n*=889, 86%) underwent surgery within one month after radiological diagnosis without affecting overall survival (OS) compared to patients who received early surgery within three days (n=235, 23%) (13). This observation is supported by the results of the retrospective cohort study by Young *et al*. (14). In this study, 145 patients underwent surgery for GBM within 7, 7 to 21, and more than 21 days from initial imaging with no impact on clinical outcomes. The results of these studies suggest that longer TTS do not appear to impact OS or progression-free survival (PFS) despite interim tumor growth.

For patients with newly diagnosed GBM, the optimal time interval between definitive surgery and initiation of CRT is still uncertain and under debate. In highly aggressive tumors with rapid growth such as GBM, a delay in CRT initiation might have adverse effects on patients' tumor recurrence and survival rates. The available literature on this issue is stilly sparse and provides inconsistent results. Buszek *et al*. recommended an optimal interval between 4 to 8 weeks from resection to CRT, whereas this interval should be shortened to ≤4 weeks in case of subtotal resection (15). A comparable time interval is also recommended by Katsigiannis *et al*. They reported that OS worsened in patients who started CRT after more than 48 days (16).

Nevertheless, data on the "correct" time interval from surgery in patients with GBM remain very limited and thus controversial. In addition, prognostic scores and laboratory markers have not yet been included in the available studies. The aim of this study was to evaluate the impact of the time interval between surgery and the initiation of CRT on PFS and OS in patients with newly diagnosed GBM, considering clinical prognostic factors as well as prognostic scores and laboratory features/scores. To our knowledge, the latter has not yet been investigated in a patient population as large as the one presented here.

Patients and Methods

Patient population. We retrospectively analyzed adult patients (≥18 years of age) with newly diagnosed and histologically confirmed GBM. All patients underwent and/or concurrent CRT according to Stupp *et al*. at the University Medical Center Schleswig-Holstein (Lübeck Campus) in Germany during the last 10 years (*i.e.,* between January 2013 and December 2023). Patients with mutations in isocitrate dehydrogenase (*IDH*) enzyme isoform 1 and 2 (secondary high grade glioma) were excluded from the analysis (2). The ethics committee of the University of Lübeck (Germany) approved the present analysis (file 2024-409). Written informed consent was not required due to the retrospective nature of this analysis.

Selection of factors influencing survival. In addition to time interval between surgery and the start of CRT, we selected patient age (5-10), functional status (5, 7, 10), tumor localization and extension (multifocality) (6, 7, 9-11), extent of resection (7-11), *MGMT* status (2) and the oncological therapy performed (6-12) as potential factors influencing patients' survival. Moreover, we included the tumor volume, the GPS (Glasgow prognostic score) (17), the LabBM score (18) as well as the laboratory biomarkers (ratios) neutrophil-to-lymphocyte ratio (NLR) (19), platelet-to-lymphocyte ratio (PLR) (20), and monocyte-to-lymphocyte ratio (MLR) (21), and as further

Table I. *Baseline patient characteristics*.

Characteristics	n=209	*p*-Value
Median age (range)	62 (23-86) years	–
Sex		0.072[1]
Male	118 (56.5%)	
Female	91 (43.5%)	
Median Karnofsky performance score (range)	90 (40-100)	–
Median tumor volume (range)	25.3 (0.1-120.4) cm^3	–
Multifocal GBM	56 (26.8%)	**<0.001**[1]
Prognostic scores		
Median RPA class (range)	5 (3-6)	–
Median GPS (range)	0 (0-2)	–
Median LabBM score (range)	0.5 (0-3)	–
MGMT-status		0.29[1]
Positive	109 (52.2%)	
Negative	93 (44.5%)	
Not available	7 (3.3%)	
Laboratory biomarkers (ratios)		
Median NLR (range)	4.5 (1-48)	–
Median PLR (range)	210 (30-1854)	–
Median MLR (range)	0.5 (0-8)	–
Time interval from surgery till initiation of RT (days)	32 (2-161)	**<0.001**[2]
<1 week	1 (0.5%)	
1-2 weeks	13 (6.2%)	
3-4 weeks	89 (42.6%)	
5-6 weeks	86 (41.1%)	
>6 weeks	20 (9.6%)	
Extent of resection		0.51[2]
Biopsy	50 (23.9%)	
Partial resection	54 (25.8%)	
Subtotal resection	45 (21.5%)	
Complete resection	60 (28.7%)	
Fluorescein-guided surgery	107 (51.2%)	0.48[1]
Surgical site infections	17 (8.1%)	**<0.001**[1]
Median total dose of RT (range)	59.4 (5-60)	–
Median number of adjuvant TMZ cycles (range)	2 (0-12)	–

[1]Test for binomial distribution. [2]Chi-square test. RT: Radiotherapy; KPS: Karnofsky performance status; GBM: gioblastoma multiforme; GPS: Glasgow prognostic score; LabBM: prognostic score based on laboratory parameters (hemoglobin, white blood cell count, platelet count, serum albumin, creatinine, lactate dehydrogenase, and C-reactive protein) validated for patients with brain metastases (BM); n/a: not available; MGMT: O-6-methylguanine-DNA methyltransferase; TMZ: temozolomide; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; RPA: recursive partitioning analysis. Statistically significant values are shown in bold.

parameters. Since stratification according to recursive partitioning analysis (RPA) may predict outcome in newly diagnosed GBM, RPA was also tested (22).

Retrospective volumetry of GBM tumors was performed using the Brainlab software (version 032, Munich, Germany). Following Woo *et al*. (23), partial resection was defined as removal of less than 85% and subtotal resection of at least 85% of the tumor. Complete resection was specified as the absence of residual tumor.

Statistical analysis. For descriptive statistics, medians were given with the corresponding range (minimum to maximum). The binomial distribution test was chosen to examine the distribution of dichotomic features. The chi-square test was used to determine the distribution of frequencies in nominally scaled samples.

Cut-off values for our patient characteristics (Table I and Table II) were defined by calculating the Youden-index from the receiver-operating characteristics (ROC) method.

In a first step (univariable survival analysis), the Kaplan-Meier-method with log-rank-test was applied to all clinical and laboratory factors/variables. In a second step, all variables $p<0.05$ (log-rank-test), were then entered into a multivariable regression model to test their independency. The calculations were performed separately for both OS and PFS, so that accordingly, two different multivariable models were built (backward selection method).

For descriptive statistics as well as for the univariable analysis (Kaplan-Meier method) and multivariable regression models, SPSS (version 29, IBM Corp., Armonk, NY, USA) was used. MedCalc (version 19.6, MedCalc Software Ltd, Ostend, Belgium) was applied for the ROC-analysis with Youden-index estimation to define cut-off values. *p*-Values <0.05 at the 2-sided significance level were considered statistically significant. Since this is an exploratory analysis, we did not adjust for multiple testing.

Results

Between January 1, 2013, and December 31, 2023, 448 patients were identified who presented with a glioma. After a further patient selection, 209 patients met the inclusion criteria and were included into this analysis. Our inclusion and exclusion criteria are highlighted in the Consolidated Standards for Reporting Trials (Consort) diagram (Figure 1). Our patients were predominantly men (n=118, 56.5%) presenting with a median age of 62 (23-86) years and a median Karnofsky performance status (KPS) of 90% (40-100%). Patient characteristics are summarized in Table I.

Univariable (survival) analysis. For OS, KPS ($p<0.001$), RPA ($p<0.001$), *MGMT*-status ($p<0.001$), extent of surgery ($p<0.001$), RT dose ($p=0.01$) and the number of adjuvant TMZ cycles ($p<0.001$) were influencing parameters (log-rank test). A KPS >90%, a lower RPA class, a positive *MGMT*-status, a complete resection of the contrast-enhancing tumor as well as a radiation dose of more than 58 Gy and the implementation of an adjuvant TMZ chemotherapy were associated with a longer median OS in the univariable survival analysis.

Regarding PFS, *MGMT*-status ($p<0.001$), extent of surgery ($p=0.03$), surgical site infections ($p=0.02$) as well as the application of adjuvant TMZ chemotherapy ($p<0.001$) were influencing factors (log-rank test). The time interval between surgery and radiotherapy showed a *p*-value <0.05 ($p=0.004$). Here, the pairwise comparison between the individual subgroups displayed that this difference existed between the subgroup "<1 week" and all other groups. However, as there was only one patient in the "<1 week" subgroup, we did not consider this result to be valid but rather a random finding. Therefore, this parameter was not included in further multivariable analysis. The results of the univariable survival analysis for OS and PFS are shown in Table II.

Timing of chemoradiotherapy after surgical resection. Regarding the time interval between surgical resection and the start of CRT, various cut-off values (>4 *vs*. ≤4 weeks; >6 *vs*. ≤6 weeks; >8 *vs*. ≤8 weeks; 1-14, 15-28, 29-42, >42 days) were tested for both oncological endpoints (OS and PFS). None of the time intervals mentioned appeared to be statistically associated with a survival advantage or disadvantage. Table II presents 2-week time intervals. The corresponding *p*-value of 0.004 for PFS was not considered statistically reliable (see above).

Multivariable analysis. All significant parameters ($p<0.05$) were then entered into two different multivariable regression models depending on the endpoint to be tested (OS *versus* PFS). For OS, only the applied RT dose was predictive (coefficient=0.008, 95%CI=0-0.01, $p=0.049$), while *MGMT*-status (coefficient=0.15, 95%CI=0.03-0.27, $p=0.02$) and the number of adjuvant TMZ cycles (coefficient=–0.05, 95%CI=1.3-1.5, $p<0.001$) were identified as independent predictors for PFS. Results from both multivariable regression models are shown in Table III.

Discussion

This retrospective single-center study aimed to investigate the potential impact of the time interval between surgery and the start of CRT on survival outcome, considering potentially confounding clinical and laboratory features/scores in one of the largest patient cohorts published to date. To our knowledge, prognostic scores have mainly not been considered in most previous studies. Previously published data showed that the time interval between the initiation of CRT after initial surgery may have an impact on survival (15, 24), although this effect could not be confirmed in our patient population.

Although our results show that the median estimates of the OS (in months) decrease with an increasing time interval between resection and initiation of CRT, these survival differences did not reach statistical significance (Table II). Our findings suggest that the time interval may play a subordinate prognostic role compared to other investigated factors. Especially in regions with an undersupply of radiation units (scarcity of resources), this may facilitate the therapeutic

Table II. *Univariable analyses of overall survival (OS) and progression-free survival (PFS).*

Characteristic	Overall survival		Progression-free survival	
	Median estimate (months) (95% CI)	*p*-Value	Median estimate (months) (95% CI)	*p*-Value
Age[1]		0.12		0.18
<54 Years	21 (17.3-24.7)		8 (4.9-11.1)	
≥54 Years	14 (11.8-16.2)		9 (7.3-10.7)	
Sex	0.23		0.65	
Male	15 (12.6-17.4)		9 (7-11)	
Female	16 (13.1-19)		9 (7.4-10.6)	
Karnofsky performance score[1]		**<0.001**		0.3
≤90	13 (11.1-14.9)		9 (7.2-10.8)	
>90	22 (16.4-27.6)		9 (7.6-10.5)	
Tumor volume[1]		0.06		0.96
≤32.2 cm^3	15 (12.3-17.7)		9 (7.3-10.7)	
>32.2 cm^3	14 (10.9-17.1)		9 (6.7-11.3)	
Multifocal GBM		0.47		0.18
Yes	14 (10.1-17.9)		7 (5.4-8.6)	
No	16 (13.4-18.6)		10 (8.4-11.6)	
Prognostic scores				
RPA class		**<0.001**		0.33
3	21 (15.7-26.3)		6 (3.3-8.7)	
4	19 (14.7-23.3)		9 (6.8-11.1)	
5	13 (10.2-15.8)		10 (8-12)	
6	7 (4-10)		7 (3.2-10.8)	
GPS		0.72		0.16
0 Points	15 (11.2-18.8)		9 (5.5-12.5)	
1 Point	14 (12.4-15.6)		12 (7.5-16.5)	
2 Points	17 (4.5-29.5)		12 (0-26)	
LabBM		0.9		0.8
≤1.5 Points	14 (12.3-15.7)		9 (6.9-11.1)	
>1.5 Points	(5.9-24.1)		9 (4.4-13.6)	
MGMT-status		**<0.001**		**<0.001**
Positive	18 (14.5-21.5)		12 (9.6-14.4)	
Negative	13 (11.2-15)		7 (5.1-8.9)	
Laboratory biomarkers[1]				
NLR		0.77		0.4
≤6	15 (12.8-17.2)		9 (6.4-11.6)	
>6	14 (9.3-18.7)		11 (3.6-18.4)	
PLR		0.72		0.62
≤246	14 (12.5-15.5)		9 (6.3-11.7)	
>246	16 (11-21)		11 (8.8-13.2)	
MLR		0.37		0.51
≤0.4	15 (11.7-18.3)		10 (7.3-12.7)	
>0.4	14 (11-17)		10 (6.1-13.9)	
Time interval from surgery till initiation of RT		0.5		**0.004**
<1 week[2]	9 (-)		3 (-)	
1-2 weeks	22 (6.9-37.1)		8 (4.9-11.1)	
3-4 weeks	16 (12.8-19.2)		10 (7.6-10.4)	
5-6 weeks	15 (11.9-18.1)		9 (7.6-10.4)	
>6 weeks	15 (9.9-20.1)		10 (8.5-11.5)	
Time from initial diagnostic imaging till surgery[1]		0.11		0.65
<7 days	13 (6.6-19.4)		9 (2.7-15.3)	
≥7 days	15 (12.9-17.1)		9 (7.6-10.4)	
Extent of resection		**<0.001**		**0.03**
Biopsy	9 (7.7-10.3)		8 (6.3-9.7)	

Table II. *Continued*

Table II. *Univariable analyses of overall survival (OS) and progression-free survival (PFS).*

Characteristic	Overall survival		Progression-free survival	
	Median estimate (months) (95% CI)	*p*-Value	Median estimate (months) (95% CI)	*p*-Value
Partial resection	19 (143-23.8)		9 (6.2-11.8)	
Subtotal resection	14 (11.3-16.7)		9 (5.5-12.5)	
Complete resection	22 (20.1-23.9)		11 (9-13)	
Fluorescein-guided surgery		0.24		0.25
Yes	16 (13.4-18.6)		10 (7.9-12.1)	
No	14 (10.4-17.1)		9 (7.6-10.4)	
Surgical site infections		0.87		**0.02**
Yes	17 (8.1-25.9)		6 (5-7)	
No	15 (13-17)		9 (7.4-10.6)	
Total dose of RT[1]		**0.01**		0.24
≤58 Gy	9 (6.6-11.4)		11 (7.1-14.9)	
>58 Gy	17 (14.9-19.1)		9 (7.6-10.4)	
Number of adjuvant TMZ cycles		**<0.001**		**<0.001**
0	6 (4.6-7.4)		13 (6.7-19.3)	
1-3	13 (11-15)		5 (4.5-5.5)	
4-6	23 (19.1-26.9)		12 (10.5-13.5.)	
7-9	20 (16.9-23.1)		13 (10-16)	
≥10	22 (19.7-24.3)		15 (11.4-18.6)	

[1]Cut-off value defined by means of the Youden-index from receiver-operating characteristics (ROC). [2]n=1. RPA: Recursive partitioning analysis; GPS: Glasgow prognostic score; LabBM: prognostic score based on laboratory parameters (hemoglobin, white blood cell count, platelet count, serum albumin, creatinine, lactate dehydrogenase, and C-reactive protein) validated for patients with brain metastases (BM); MGMT: O-6-methylguanine-DNA methyltransferase; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; TMZ: temozolomide; RT: radiotherapy. Statistically significant values are shown in bold.

procedure. However, it should be emphasized that other authors have gained contrary findings based on larger patient collectives: There are several working groups that attribute prognostic value to the time interval between surgery and the onset of CRT. Buszek *et al*. reported that delays of more than eight weeks in patients with a gross total resection and delays <4 weeks in patients with a subtotal resection or biopsy led to worse survival (15). Between 2014 and 2019, Zhang *et al*. retrospectively reviewed 66 patients with GBM regarding the impact of postoperative time between surgery and adjuvant treatment on OS and PFS (24). Although these authors, in agreement with our analysis, performed both univariable and multivariable statistical testing of certain possible influencing factors (age, KPS, maximum diameter of primary tumor, extent of resection, *IDH*-mutation status and *MGMT*-status), they concluded that delaying the start of RT beyond six weeks leads to a worsening of OS and PFS. The Taiwanese working group of Lee *et al*. analyzed data from the Taiwanese Taiwan National Health Insurance Database on 228 patients with GBM who received TMZ-based CRT. They compared patient survival based on the timing of concurrent CRT (≤2 weeks *vs*. 2-4 weeks *vs*. 4-6 weeks *vs*. 6-8 weeks) and the location of the primary tumor (frontal lobe *vs*. other localizations). Within eight weeks after surgical resection, the timing of CRT initiation showed no effect on patients' survival. At the same time, these authors concluded that the shortening of the time interval between surgery and RT should not necessarily be enforced (25). Although the authors' results are only available in the form of a congress abstract and do not appear to have been published elsewhere as a complete manuscript to date, their findings support the results of our analysis. Nevertheless (referring to the published abstract), our multivariable analysis seems to have taken significantly more influencing variables into account.

In general, our univariable analysis revealed that patients who were in better general condition (as indicated by KPS and RPA), having tumors with favorable genetic profiles (*MGMT*-positivity), and with more aggressive treatment (complete tumor resection, higher radiotherapy (RT) doses, and more cycles of adjuvant chemotherapy) presented with better survival outcomes. Interestingly, after performing the multivariable analysis, only RT dose remained a predictive factor for OS. This underlines the crucial role of adequate RT in improving survival by achieving an adequately high irradiation dose (of at least 58 Gy), even when other prognostic factors are considered. By analyzing data from 84 patients with newly diagnosed GBM in Taiwan between 2005 and 2016, Shieh *et al*. were even able to prove that a dose escalation >60 Gy led to an improvement in OS. However, it should be noted that only 15 patients received the dose-escalated RT regimen and were younger than the

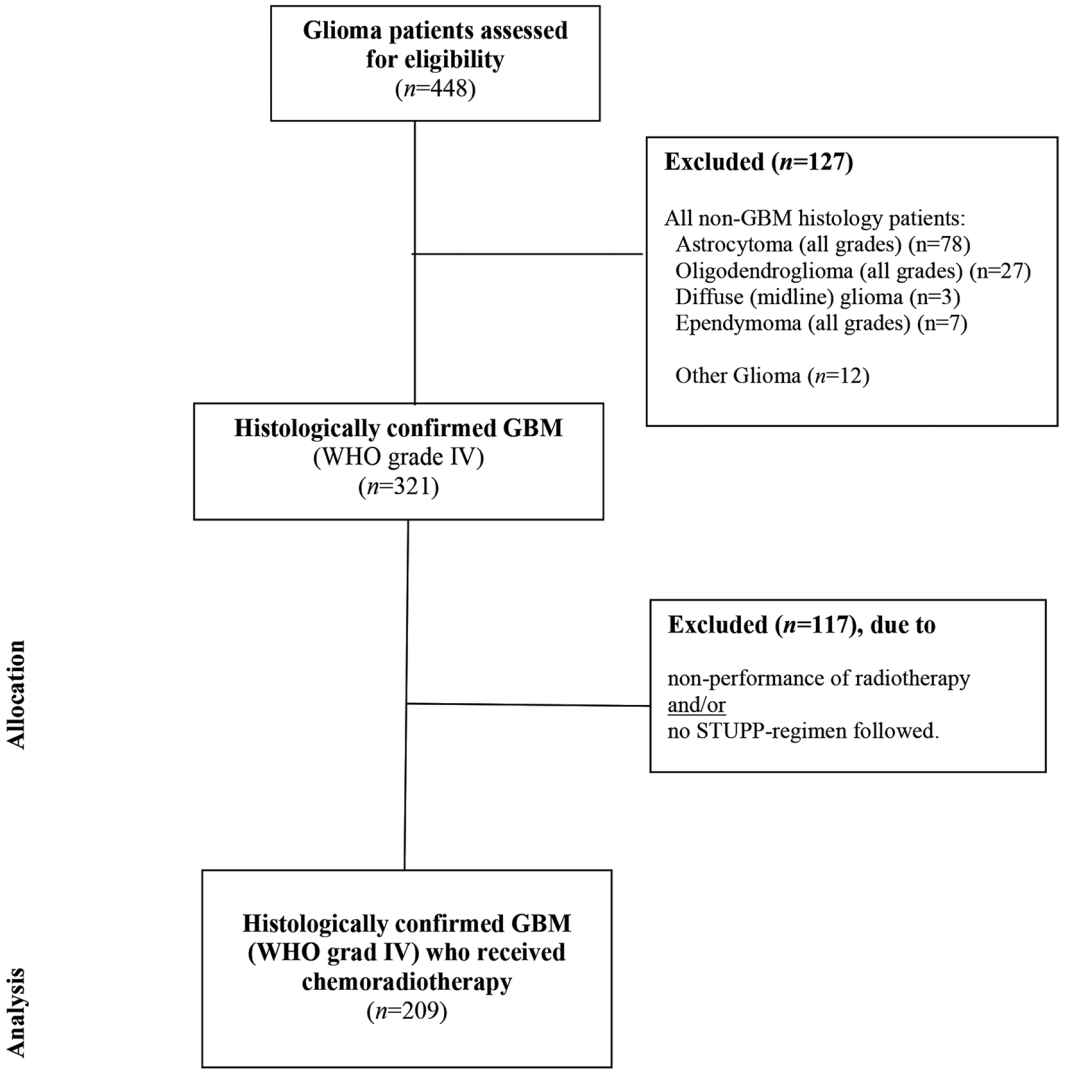

Figure 1. *CONSORT diagram (period: January 1, 2013 – December 31, 2023).*

remaining 69 patients (26). In contrast, Madan *et al*. reported preliminary data of RT dose escalation using 68Ga-Pentixafor PET scan derived from 30 patients suffering from grade IV glioma or GBM. Irradiation was carried out in two different phases with simultaneous integrated boost (SIB) (total dose to PTV PET=67 Gy/30 fractions). While no statistical correlation was seen between the escalated dose and survival, the extent of resection and KPS were found to influence OS. At the same time, it must be emphasized that this is a very small patient number (*n*=30) and that the 68Ga-pentixafor PET scan is not yet a standard method in clinical routine (27). In comparison, the KPS and the extent of surgical resection did also show a $p<0.05$ in the univariable analysis and were therefore included (together with other variables) in the multivariable model.

For PFS, the time interval between surgery and CRT also showed a significant *p*-value in the univariable analysis, particularly between the subgroup "<1 week" and others. However, due to the small sample size in the "<1 week" group, this result was not considered reliable and was excluded from further analysis. The lack of statistical association between different time intervals (*e.g.*, >4 *vs.* ≤4 weeks) and survival outcomes suggests that within the tested time frames, the timing of initiating radiotherapy post-surgery does not have a decisive impact on PFS. This finding could be incorporated into clinical practice, as it allows flexible planning of CRT without compromising treatment efficacy. In the multivariable analysis, *MGMT*-status and the number of adjuvant TMZ cycles remained significant predictors for PFS. The positive *MGMT*-status and increased

Table III. *Results from multivariable regression analyses for overall survival (OS) and progression-free survival (PFS).*

Overall survival				
Independent variables	Coefficient β	Std. error	*p*-Value	95%CI
Constant	0.04	0.47	0.22	–0.36-1.5
RT dose	**0.008**	**0.004**	**0.049**	**0-0.01**
RPA-class	0.05	0.04	0.3	–0.04-0.13
MGMT	–0.07	0.05	0.18	–0.18-0.03
KPS	–0.003	0.003	0.25	–0.01-0.002
Extent of resection	–0.03	0.03	0.33	–0.07-0.03
Number of adjuvant TMZ cycles	–0.01	0.01	0.19	–0.03-0.01
Progression-free survival				
Independent variables	Coefficient β	Std. error	*p*-Value	95%CI
Constant	**1.4**	**0.07**	**<0.001**	**1.3-1.5**
MGMT	**0.15**	**0.06**	**0.02**	**0.03-0.27**
Extent of resection	–0.002	0.03	0.94	–0.06-0.05
Surgical site infections	–0.16	0.1	0.14	–0.38-0.05
Number of adjuvant TMZ cycles	**–0.05**	**0.01**	**<0.001**	**1.3-1.5**

Only parameters with $p<0.05$ from univariable Kaplan-Meier analysis were entered. For OS and PFS, the corresponding multivariable model's *p*-value equaled 0.02 and <0.001, respectively. RT: Radiotherapy; RPA recursive partitioning analysis; KPS: Karnofsky Performance Score; MGMT: O-6-methylguanine-DNA methyltransferase; TMZ: temozolamide; CI: confidence interval. Statistically significant values are shown in bold.

chemotherapy cycles were independently associated with longer PFS, emphasizing the value of molecular profiling and the cumulative effect of chemotherapy in preventing disease progression.

In 2020, Zur *et al*. published their retrospective analysis of 204 patients with GBM who were treated with CRT between 2005 and 2014. Interestingly, the authors even recommended a time-gap of six weeks (median of 8 weeks) between surgery and CRT (28). Compared to other published studies, this is a longer time interval, which in this case was associated with both a better OS and PFS. Certainly, this cannot be equated with an automatic recommendation to specifically delay the start of CRT. At the same time, however, it supports the result of our study, namely that the time-gap plays a subordinate role and that a delay does not result in a worsening of prognosis. However, the opposite conclusion was reached by Amsbaugh *et al*. (29), who analyzed 16,335 patients with GBM from the National Cancer Database. Patients who started CRT after more than 61 days were prone to a higher risk of death and an inferior survival.

In 2020, Press *et al*. published their results of 30,414 patients with GBM (30). Considering RPA classes III, IV the authors stated that short delays of CRT initiation (of more than five weeks) did not negatively affect survival, while starting CRT less than three weeks after initial resection may even be detrimental. The latter may be explained by certain negative prognostic factors that have encouraged a faster procedure (30, 31).

Prognostic scores and laboratory values play a crucial role in assessing the prognosis of patients with GBM. In 1993, the RPA score was introduced for the first time to stratify patients with GBM by Curran *et al*. (32). In 2017, this score was further modified, and the new molecular-based RPA classification system (NRG-GBM-RPA; including c-MET and *MGMT*-status) was developed (33). In the RTOG 0525 cohort, a phase III cohort comparing different dosing regimens of adjuvant TMZ in newly diagnosed GBM (34), the revised NRG-GBM-RPA achieved a better prognostic outcome stratification than the clinically based RPA score (33). In 2024, Zemskova *et al*. investigated different Glasgow prognostic scores (GPS) (original GPS, modified GPS, high-sensitivity mGPS, and high-sensitivity oGPS) as well as the LabBM score in newly diagnosed GBM treated with CRT. It was concluded that the oGPS was an independent predictor of OS, while the LabBM score may predict PFS (35). Besides prognostic scores hematologic parameters may also have a prognostic impact. Although there is insufficient data to define clear cut-off values, an elevated neutrophil-to-lymphocyte ratio (NLR) was reported to be associated with worse prognosis (36, 37). According to Gomes dos Santos *et al*. it is an effective prognostic factor associated with tumor grading and OS in glioma patients (38). Like NLR, higher PLR may also be linked to poorer outcomes, while lower lymphocyte-to-monocyte ratios (LMR) may be associated with worse prognosis, indicating an immunosuppressive environment that favors tumor

growth (36, 39). In our analysis, the RPA had an influence on the OS in the univariable analysis. However, RPA could not be confirmed as an independent predictor in the multivariable model.

The present study is limited by its retrospective nature since selection bias cannot be ruled out. Moreover, the accuracy and completeness of patients' medical data may be limited. Missing data or inaccuracies in medical records can distort the results and lead to false conclusions. The small sample size in some subgroups, such as the "<1 week" subgroup for the time interval between surgery and CRT, poses another limitation. The small number of patients in this group reduces the statistical power of the analysis and can lead to unreliable findings, which is reflected in the exclusion of this parameter from further analysis. Moreover, the study population and treatment protocols may not be generalizable to all clinical settings. Being a single-center analysis, it must be noted that all findings are specific to the patient cohort involved in this study. Differences in treatment approaches, patient demographics, and healthcare systems can limit the applicability of the results to other settings.

In conclusion, the time interval between surgery and CRT seems to play a subordinate role in the treatment of patients with GBM. This finding provides more flexibility in scheduling RT without compromising the efficacy of treatment.

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 J.L., C.D., and M.V.V. Data were analyzed by M.G., C.Z., and A.L. The manuscript was drafted by A.L., and reviewed, revised, and finally approved by all Authors.

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