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Clinical study

The survival impact of significant delays between surgery and radiochemotherapy in glioblastoma patients: A retrospective analysis from a large tertiary center

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ABSTRACT

The optimal timing of adjuvant radiochemotherapy (RCT) in glioblastoma (GBM) patients remains unknown and the paradigm of 'the sooner, the better' has been challenged by many recent publications. In this study, we present unique data on the outcomes of patients with significant treatment delays. The study group consisted of 346 GBM patients (median age 56.8 years) who received surgical treatment (total or subtotal resection) and then underwent adjuvant concurrent RCT at one institution. The main endpoint was overall survival (OS). The Univariate and multivariate Cox Proportional-Hazard Model, log-rank test, and Kaplan-Meier method were used for the analysis. The median OS was 18.7 months and the 5-year overall survival was 8.5%. The median time interval from surgery to RCT was 9.8 weeks. The Cox regression showed that the time interval had no statistically significant impact on OS both in uni- and multivariate analysis. The explorative analysis suggested a positive trend for improved survival for patients in the 1st quartile of the time interval, especially for patients with residual disease or local recurrence prior to RCT, However, considering the 6.9 weeks median interval in the 1st quartile, this subgroup should still be regarded as 'moderate delay' compared with other literature data. The results indicate that the time interval is not a clear prognostic factor in the treatment of GBM. Prospective trials are highly warranted, as data suggest that moderate delays in the initiation of adjuvant treatment might be associated with survival benefit.

1. Introduction

Glioblastoma is the most common malignant brain tumour, accounting for one-fifth of primary central nervous system tumours in adults. The treatment is truly comprehensive, including surgery, radiotherapy (RT), and chemotherapy (CT), yet the prognosis remains dreadful with a median survival of 15 months and no notable improvement in population statistics over the last three decades [1]. The dire everyday reality, however, can hardly be attributed to scientific neglect. The current millennium brought us two practice-changing discoveries. Regarded as one of the most important studies on the subject of glioblastoma, the study by Roger Stupp published in 2005 showed that the addition of temozolomide-based concurrent and adjuvant CT to RT improves the overall survival of patients [2]. Ten years later, the same author published the results of another randomized clinical trial on the subject of Tumor Treating Fields as an addition to temozolomide-based adjuvant treatment, which showed a statistically significant and clinically meaningful survival benefit [3]. Nevertheless, the median survival did not exceed 14.6 and 20.5 months in the respective study groups.

There is a paradigm in post-operative radiotherapy suggesting that "the sooner the better". However, to our best knowledge, there is no strong evidence to support such claims in the treatment of GBM patients. Due to a heavily overburdened public healthcare system and the lack of in-house neurosurgical ward, the average time interval between surgery and adjuvant radiochemotherapy in our study group was significantly longer compared to other data available in the literature. In this article, we tested the hypothesis

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that these prolonged time intervals have a negative effect on survival in GBM patients.

To our best knowledge, up to this date this is the first analysis that provides data regarding patients with > 12 weeks' time interval between surgery and TMZ-based RCT in glioblastoma patients. We believe that the analysis, however challenged by a few limitations adherent to retrospective studies, provides a new insight on a clinically important subject of RCT timing in glioblastoma treatment.

2. Materials and methods

The study group consists of 346 patients treated with postoperative radical radiochemotherapy up to 60 Gy in 30 fx (or equivalent), with concurrent and adjuvant temozolomide for glioblastoma multiforme in accordance with Stupp protocol [2], at one institution between 2009 and 2017. The initial database consisted of 465 cases, 119 of which had to be removed due to age (<18 years), different RCT schemes, no prior tumor resection (biopsy only) or RCT outside of our institution.

The study included only patients with histopathologically proven glioblastoma multiforme, as described by the 2007 WHO Classification of Tumours of the Central Nervous System [4]. The classification includes two distinct subtypes - giant cell glioblastoma and gliosarcoma and two specific patterns: small cell glioblastoma and glioblastoma with an oligodendroglioma component, which were included in the analysis as co-factors.

The extent of the resection was assessed based on the operation report provided by the neurosurgeon, as the majority of the patients had no MRI performed immediately after operation. The pre-RT MRI (including contrast-enhanced multiparametric MRI) and preoperative MRI were examined by a certified radiologist to determine any interval recurrence or post-operational residual disease.

Patients that have had received a lower doses of RT or CT than planned (for example, due to treatment toxicity or general state deterioration) have not been excluded from the database in accordance to 'intention -to-treat' approach.

The information regarding patients' characteristic was based on institutional database. In case of patients that were lost to follow-up, their current status and date of death in applicable cases was checked in National Cancer Registry. The missing data (11.5%) was recorded as censored observations using the date of the last control visit during follow-up. The primary endpoint of Overall Survival (OS) was calculated from the day of primary neurosurgical operation to the day of death.

The computation was performed using StatSoft Statistica software (v.13). The primary analysis employed the univariate and multivariate Cox Proportional-Hazard Models. Covariates at a level of significance $p < 0.1$ were selected for the multivariate model. A complete list of covariates used in the analysis can be found in Tables 2 and 3. The log-rank testing and Kaplan-Meier method were used for data visualisation and explorative analysis. Additionally, comparative analysis of patients representing subsequent time interval quartiles were performed using t-Student and Mann-Whitney U tests for independent samples.

3. Results

The median overall survival was 18.7 months, the 5-year overall survival was 8.5%, and 6% of the patients were alive at the time of study completion. The median age of the patients was 56.8 years (mean 54.9, 19.9–80.2), and the male to female ratio in the study group was 1.26.

The detailed description of the study group is presented in Table 1. Between the groups based on the length of the time interval, there was a statistically significant difference in prevalence of GBMO diagnosis ($p = 0.029$), in favour of higher GBMO occurrence in longer time interval group, and a significant difference in number of received adjuvant cycles of Temozolomide ($p = 0.01$).

The univariate Cox Proportional-Hazard Model presented in Table 2 showed that the time interval between operation and radiotherapy did not significantly impact the risk of death (HR = 1.01; 0.98–1.05; $p = 0.41$). The covarietes significantly associated with mortality were age, gliosarcoma histopathology, GTR operation, no gross disease on pre-RT MRI, incomplete concurrent chemotherapy, radiotherapy dose, number of concurrent and adjuvant Temozolomide cycles, any salvage treatment, salvage: chemotherapy, stereotactic radiosurgery, reoperation and reirradiation. In the multivariate analysis, presented in Table 3, age, sex, gliosarcoma histopathology, no gross disease on pre-RT MRI, radiotherapy dose, number of adjuvant Temozolomide cycles, salvage chemotherapy and salvage reoperation were found to be independent prognostic factors for the risk of death.

As the time interval did not reach the $p < 0.1$ level of significance, it was not included in the multivariate analysis. Considering the purpose of the article, we performed a second multivariate analysis including the time interval as a covariate, which remained insignificant with HR of 1 (CI 95% 0.96–1.03) and $p = 0.87$. The addition of time interval to the model did not significantly affect other covariates and hence is not presented in a separate table.

We have further analysed the impact of time interval on OS through log-rank testing, using quartiles of time interval as cut-off values for the groups. The median OS were 21.8, 18.6, 15.6, and 17.5 months, while the 2-year survival rates were 43.5%, 35.8%, 30.3% and 29.7% for the 1st, 2nd, 3rd, and 4th quartile, respectively (Fig. 1). The the p-value of log-rank test was insignificant ($p = 0.105$).

In order to account for Type II Error, we have performed an explorative analysis comparing the patients with the shortest time interval (<7.7 weeks) and the longest median survival (21.8 months) with the rest of the group. The median survival was longer for patients with shorter time interval, with a closely significant p-value of 0.038 (Fig. 2).

The difference between the patients within the 1st quartile of time interval and the rest of the study group was highly significant for patients that have had residual disease or recurrence based on radiological assessment of MRI prior to RT (Fig. 3A), but there was no significant difference for patients with no sign of disease (Fig. 3B).

After excluding patients diagnosed with GBMO, due to its higher prevalence in the long time interval subgroup, the difference between the groups presented in Fig. 1 was significant ($p = 0.047$) in favour of the short time interval group. The median OS were 21.8, 18.8, 15.6, and 15.9 months, while the 2-year survival rates were 43.1%, 37.8%, 28% and 25% for the 1st, 2nd, 3rd, and 4th quartile, respectively (Fig. 1). However, the time interval remained an insignificant prognostic factor for survival in the Cox analysis (HR = 1.02; 0.99–1.06; $p = 0.2$).

4. Discussion

The analysis presented in this article was initiated because of a concern that due to the overburdened healthcare in Poland and suboptimal administrative solutions, we are in a necessity for a change in order to provide better care for our glioblastoma patients. However, contrary to our expectations, we did not find a clear detrimental effect of delays in RCT on patients' survival. Despite the median time interval of 9.8 weeks, the overall median

Table 1
Description of the study group.

Parameter	Whole group n = 346	Subgroups separated on the basis of quartiles of the time interval				P-value
		Q1 <7.7w n = 89	Q2 7.7–9.8w n = 84	Q3 9.8-12w n = 87	Q4 >12w n = 86	
Treatment interval (median, weeks)	9.8	6.9	8.8	10.7	13.9	**<0.001**
Age (median)	56.8	54.2	58.6	57.6	57.3	0.117
Sex (% female)	43.6%	37%	47.6%	41.4%	48.8%	0.4
Primary side (% left lobe)	48.3%	56.2%	46.4%	41.4%	48.8%	0.25
Localisation:						
Frontal	38.4%	37%	40.5%	36.8%	39.5%	0.871
Parietal	39.6%	40.4%	31%	40.2%	46.5%	0.254
Temporal	44.5%	42.7%	46.4%	56.3%	32.6%	0.821
Occipital	13.6%	21.3%	9.5%	10.3%	12.8%	0.122
GBM subtypes:[a]						
Giant cell glioblastoma	4.9%	3.4%	3.6%	5.7%	7%	0.656
Gliosarcoma	2.9%	2.2%	3.6%	4.6%	1.2%	0.447
GBMO[b]	7.5%	1.1%	7.1%	9.2%	12.8%	**0.029**
Small cell glioblastoma	3.2%	4.5%	2.4%	5.7%	0%	0.107
Operation type (% GTR)[c]	82.9%	80.9%	83.3%	87.4%	80.2%	0.628
No gross disease preRT[d]	27.8%	32.5%	28.9%	27.1%	22.9%	0.575
Zubrod:						
0–1	93.9%	94.4%	94%	93.1%	94.2%	
2	6.1%	5.6%	6%	6.9%	5.8%	0.986
RT interruption	12.1%	14.6%	13.1%	6.9%	14%	0.38
CT interruption	20.8%	19.1%	27.4%	13.8%	23.3%	0.203
RT dose < 60 Gy	8.4%	7.9%	3.1%	2.3%	10.5%	0.068
Concurrent CT <40 cycles	17.1%	10.3%	24.7%	14%	20%	0.067
Adjuvant CT (# of cycles):						
>4	49.8%	63%	51.3%	46.3%	59.3%	
1–4	29.5%	22.2%	25%	35.4%	34.5%	
0	20.7%	14.8%	23.7%	18.3%	26.2%	**0.01**
Clinical trial participation	6.5%	21.3%	4.8%	0%	0%	
Salvage treatment:	63.9%	82.7%	68.4%	58.5%	46.3%	**<0.001**
Chemotherapy	20.2%	34.6%	21.1%	14.6%	11%	**0.001**
Stereotactic radiotherapy	39.6%	58%	42.1%	34.1%	24.4%	**<0.001**
Reoperation	23.4%	28.4%	19.7%	24.4%	20.7%	0.56
Reirradiation	6.6%	7.4%	5.3%	6.1%	7.4%	0.56

[a] As defined in WHO 2007 classification [b]Glioblastoma with oligodendroglioma pattern [c]based on the operation report by neurosurgeon [d]based on the pre-RT MRI, assessed by a certified radiologist.

survival was 18.7 months with a 5-year overall survival of 8.5%. Compared to the median OS of 14.6% presented in the article by Stupp et al. [2] or the average 5-year OS of 6.8% based on The Central Brain Tumor Registry of the United States report [5], the results were at least satisfactory, which might be partially attributed to the selection criteria, as our study excluded patients treated with palliative intent or biopsy as only surgical treatment. Such patients tend to have shorter intervals, but worse survival, which should be taken into consideration when comparing our results with other literature findings.

The results are not sufficient to conclude that the time interval has no effect on the survival of the patients. An explorative analysis performed after obtaining the primary results suggests that despite no statistically significant adverse effect of time interval on the risk of death in Cox regression, the subgroup of patients with the shortest time interval had statistically significantly longer survival. Similarly, we have performed an analysis excluding patients with GBMO due to the fact that its prevalence was significantly different between groups, and obtained a significant p-value in favour of shorter time interval. Such analysis is challenged by the arbitrary choice of the group and preselection bias of a retrospective study. For example, patients with better performance status and lower extent of operation tend to recover faster, and therefore could be more prevalent in the subgroup of patients with short time interval. On the other hand, some of the patients with aggressively growing tumours could have deteriorated prior to RCT initiation, which is more likely in patients with > 12 weeks' time interval compared to < 8 weeks. Such patients could then be then qualified for alternative treatment schemes (i.e., palliative, RT-alone or hypofractionated), thus leading to positive selection in the long interval subgroup. It is also important to note that the 'short' interval group in our study would be considered 'normal' or 'long' by majority of the authors. Our study in fact compares long intervals with even longer intervals, therefore the subgroup which presented improved survival in log-rank testing should be regarded as 'moderate delay'.

Patients that have had biopsy-only were excluded from the analysis. Such patients accounted for only 4.1% of the initial study group, had worse performance status (including ZUBROD 3 patients), shorter OS (median – 10.8 months), and shorter median time interval by almost 3 weeks. The difference in time interval was most likely a sequelae of the lesser extent of the surgical procedure, as there were no significant differences in the length of time interval between STR and GTR patients. Therefore, the inclusion of biopsy-only patients could decrease the accuracy of the analysis and falsely lower the OS in the short interval subgroup. For the same reason, we did not include patients treated with pallative intent in the analysis. Due to to that, the median age of the study groups differs from the median age of diagnosis in population (64 years [6]), but is consistent with other studies including patients treatet with radical intent (i.e. median age of 56 years reported by Stupp et al. [2], 57.5 years reported by Louvell et al. [7] or 58 years reported by Sun et al. [8]).

Interestingly enough, our analysis suggests that for patients with residual disease or relapse, the time interval is a more important factor than for those with no sign of macroscopic disease at

Table 2
Univariate Cox Proportional-Hazard Model for OS.

Covariates		HR	HR (CI 95%)	P-value
Treatment interval (weeks)		1.01	0.98–1.05	0.41
RT duration (days)		0.98	0.94–1.02	0.235
Age		1.02	1.01–1.03	**<0.001**
Sex (female)		0.81	0.64–1.03	0.079
Primary side (left lobe)		1.12	0.89–1.42	0.33
Localisation:				
	Frontal	0.98	0.77–1.24	0.841
	Parietal	0.94	0.74–1.19	0.593
	Temporal	1.08	0.93–1.26	0.324
	Occipital	1.22	0.88–1.70	0.241
GBM subtypes:[a]				
	Giant cell glioblastoma	0.56	0.31–1.01	0.055
	Gliosarcoma	2.94	1.52–5.66	**0.001**
	GBMO[b]	0.87	0.56–1.34	0.518
	Small cell glioblastoma	0.79	0.41–1.5	0.466
Operation type (GTR)[c]		0.62	0.46–0.83	**0.002**
No gross disease preRT[d]		0.49	0.37–0.64	**<0.001**
Zubrod		1	0.82–1.23	0.972
Incomplete RT		1.18	0.83–1.68	0.363
Incomplete concurrent CT		1.38	1.04–1.84	**0.027**
RT dose (Gy)		0.94	0.92–0.96	**<0.001**
# concurrent TMZ		0.98	0.96–0.99	**0.013**
# adjuvant TMZ		0.81	0.77–0.85	**<0.001**
Clinical trial participation		0.76	0.49–1.17	0.211
Concurrent Cilentigide		0.73	0.43–1.25	0.253
Salvage treatment:		0.57	0.44–0.74	**<0.001**
Chemotherapy		0.56	0.41–0.76	**<0.001**
Stereotactic radiotherapy		0.66	0.52–0.85	**0.001**
Reoperation		0.60	0.45–0.80	**<0.001**
Reirradiation		0.55	0.33–0.90	**0.016**

[a] As defined in WHO 2007 classification [b]Glioblastoma with oligodendroglioma pattern [c]based on the operation report by neurosurgeon [d]based on the pre-RT MRI, assessed by a certified radiologist.

Table 3
Multivariate cox proportional-hazard model for OS.

Covariates	HR	HR (CI 95%)	P-value
Age	1.02	1.01–1.03	**<0.001**
Sex (female)	0.69	0.54–0.9	**0.006**
Giant cell glioblastoma	0.79	0.42–1.48	0.46
Gliosarcoma	3.65	1.83–7.3	**<0.001**
Operation type (GTR)[a]	0.81	0.58–1.12	0.2
No gross disease preRT[b]	0.50	0.37–0.67	**<0.001**
CT interruption	0.96	0.66–1.4	0.84
RT dose (Gy)	0.95	0.92–0.99	**0.013**
# concurrent TMZ	1	0.97–1.04	0.95
# adjuvant TMZ	0.82	0.78–0.87	**<0.001**
Salvage treatment:	0.82	0.57–1.18	0.28
Chemotherapy	0.66	0.47–0.93	**0.02**
Stereotactic radiotherapy	0.91	0.66–1.26	0.58
Reoperation	0.65	0.47–0.89	**0.007**
Reirradiation	1.05	0.59–1.86	0.88

[a] based on the operation report by neurosurgeon [b]based on the pre-RT MRI, assessed by a certified radiologist.

the onset of radiotherapy. The relation between residual disease and the impact of time interval has been previously observed by some of the authors [9–11], but each of them formed different conclusions. Based on our data, we speculate that in patients with residual disease, radiochemotherapy should be regarded as a salvage treatment and therefore initiated earlier. However, the value of this analysis is significantly limited by the fact that the assessment occurred prior to RT, and post-operational MR was not routinely performed in those patients. Although not statistically significant, the fraction of patients with no radiographic signs of active disease prior to RCT decreased in each consecutive time-interval group (32.5%, 28.9%, 27.1% and 22.9% respectively).

The phenomenon of little adverse effect of delay in RCT could be associated with the biological and clinical characteristics of GBM. For example, the assumption of 'the sooner, the better' is primarily based on the Gompertz sigmoid curve-like growth of the tumour, which suggests that the dynamic of cell cycles decreases over time and thus decreases the radio-sensitivity [12]. However, on a case-to-case basis, the degree of tumour growth does not seem to correlate well with the time interval in GBM patients, which diminishes the value of early initiation of RCT [13]. Besides, the oedema imminent to brain tumours and post-operative tumour bed subsides over time, which might increase radiosensitivity [14] and decrease the volume of irradiation, increasing its precision and lowering the probability of adverse effects [15]. This effect, however, most likely reaches its peak within a few weeks after surgery, and further delay would not be associated with profit for the patient, but only increase the probability of interval relapse or progression.

In order to compare our findings with other studies, we have conducted literature research through PubMed and Google Scholar for studies that investigated the impact of radiochemotherapy timing in the treatment of glioblastoma. After removing duplicates, we had found 26 articles published in the last 10 years. We further excluded 6 studies performed mainly prior to TMZ-based regimens, due to the major inclusion of WHO III and/or RT-alone patients, small sample size, and clinically significant differences in study groups. A brief description of the studies is presented in Table 4, and the data regarding median overall survival in groups is visually presented in Fig. 4, with the further exclusion of 2 studies which did not provide sufficient data. In the absence of a precise description of median time to radiotherapy in groups, the upper and lower thresholds were multiplied by 1.25 and 0.8, respectively, to produce a graphic representation of the results.

The majority of studies available in the literature support the notion that the time interval might not impact OS in TMZ-based

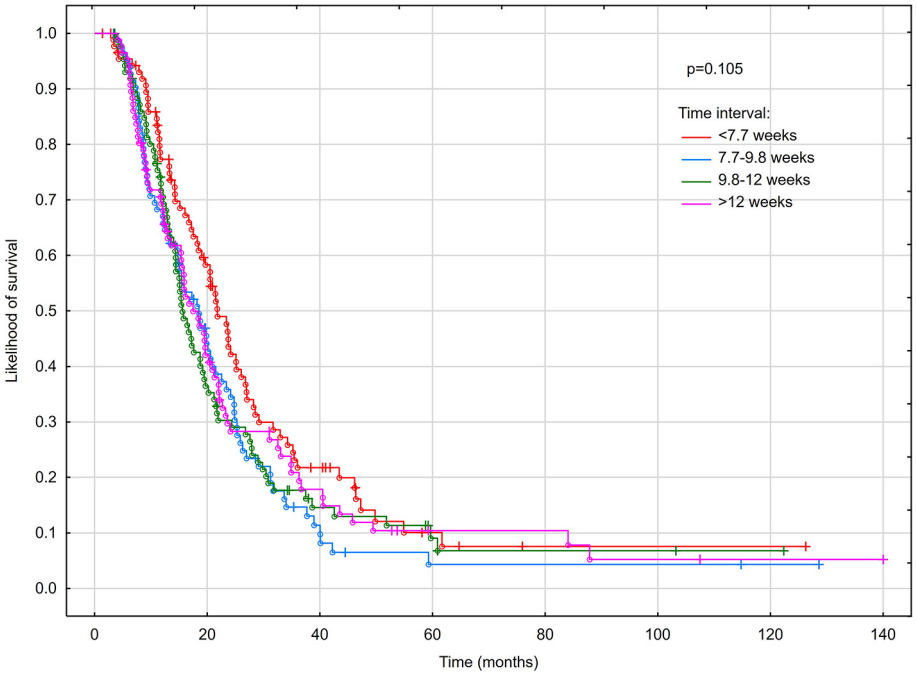

Fig. 1. The overall survival in groups based on the quartiles of time interval from surgery to radiochemotherapy.

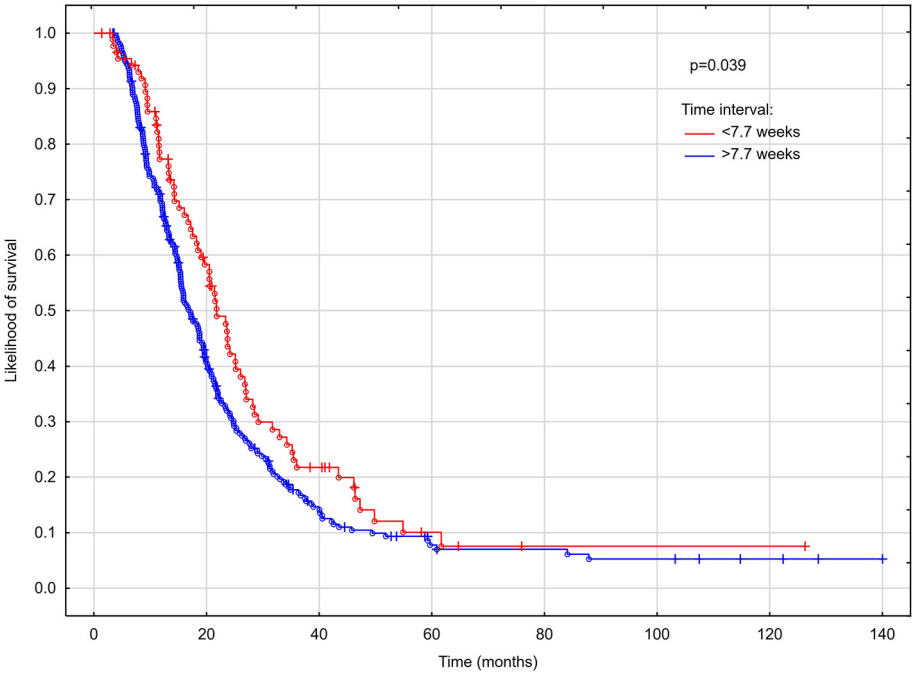

Fig. 2. The overall survival in patients with the shortest time interval compared to the rest of the group.

adjuvant RCT. To our best knowledge, Noel et al. [16] published the first retrospective analysis, based on an EORTC-NCIC clinical trial, which showed no statistically significant differences in OS between patients irrespective of the delay. It was followed by many other retrospective studies presenting similar results, including an analysis by Seidlitz et al. [17], Loureiro et al. [18], Graus et al. [19], Sun et al. [8], Randolph et al. [10], Blumenthal et al. [20], Osborn et al. [21], Ahn et al. [9], and Katsigiannis et al. [22], Louvel et al. [7], and are consistent with our findings.

Moreover, a series of retrospective studies suggest that in contrary to the popular belief, short time interval could be detrimental for the patients. For example, a study by Adberg et al. [23] found that an interval of < 24 days was associated with both significantly decreased OS and PFS. Similar results were found by Wang et al. [24], an interval of < 21 days was associated with significantly reduced OS in univariate analysis. This trend has been also observed in a study by Han et al. [25], where an interval of 30–34 days was predictive of prolonged OS compared to < 30 days.

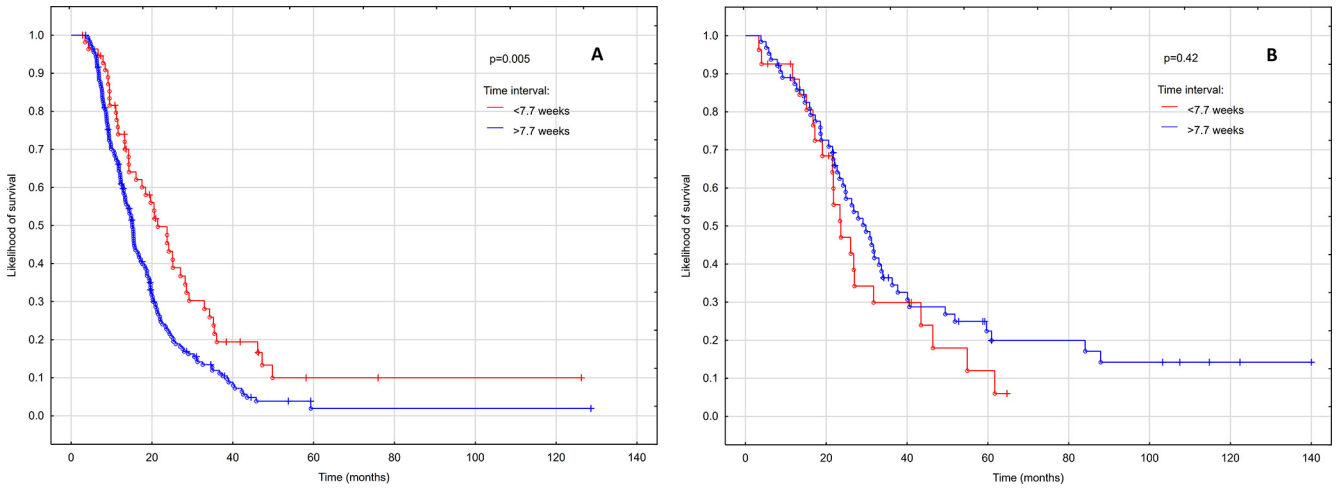

Fig. 3. The overall survival in patients within the 1st quartile of time from surgery to radiotherapy compared to the rest of the group, for patients that had residual disease or relapse (A), or no sign of disease (B) based on radiological assessment of MR prior to RT.

In another study by Zur et al. [26], the authors found that a time interval of > 6 weeks is associated with significantly higher survival compared to 4–6 and < 4 weeks (p = 0.0092), and HR of 0.498 (0.319–0.777, p = 0.002) in multivariate analysis of overall survival.

Similar findings were provided by three high-volume retrospective analysis based on national cancer databases. Yusuf et al. [27] found that a time interval of 22–42 days from surgery compared to patients that started RCT earlier was associated with a significantly reduced risk of death. Finally, a recent study by Buszek et al. [11] showed that < 4 weeks' time interval negatively impacted the survival of the patients.

A study by Spratt et al. [28], on the contrary, showed that the time interval of > 6 weeks was associated with an increased risk of death in multivariate analysis. The study, however, included highly nonhomogeneous subsets of patients, which has been pointed out by the authors. Another study by Amsbaugh et al. [29] demonstrated a decrease in survival in patients with time interval > 61 days, which suggested a detrimental effect of prolonged interval on OS. However, the size of the investigated groups differed by 31-fold (15824 vs 511), which might suggest that the difference in OS could be due to clinical differences (i.e., patients that have had RCT delayed due to general state deterioration). Finally, a retrospective analysis by Potharaju et al. [30] compared very short intervals and found a significant difference in OS between $\leq$ 10, 11–20, and > 20 days. However, the authors provide limited data on the statistical analysis including comparison of clinical factors between groups. Moreover, even though the authors excluded patients that had received <4 cycles of adjuvant chemotherapy from the analysis, the median OS was only 14.7 months.

The most important limitation of this study is the lack of molecular markers such as MGMT methylation and IDH mutation, which were not routinely performed at our institution until the last year included in the analysis (the IDH/MGMT status was available in 0.9% of the cases), and due to ethical as well as financial concerns, it was not possible to assess them retrospectively. The study was based on the 2007 WHO Classification of Tumours of the Central Nervous System which included glioblastoma, giant cell glioblastoma, and gliosarcoma. Besides, we included two relatively common patterns: small cell glioblastoma and glioblastoma with an oligodendroglioma component [4]. The 2016 WHO Classification of Tumors of the Central Nervous System introduced IDH-mutant glioblastoma diagnosis, which accounts for about 10% of GBM patients and is associated with a significantly improved prognosis [31]. Moreover, MGMT methylation is a known positive prognostic factor associated with improved survival [32]. As we had no information regarding this two prognostic factors, we could not account for the differences between groups which could have affected survival. Besides, our analysis is subject to the bias of a retrospective study. Therefore, we believe that the results should be verified in a prospective manner and include information regarding IDH mutation and MGMT methylation as co-varieties, which we will try to do in the future.

5. Conclusions

The time interval between surgery and radiochemotherapy did not prove to be a statistically significant prognostic factor for the overall survival in GBM patients. The study group had OS comparable to other literature data despite significant delays between surgery and radiochemotherapy, substantially longer than those considered a standard of care.

The explorative analysis suggested a marginally significant improvement in survival for patients with < 7.7 weeks time interval, especially for patients with residual disease or local recurrence prior to RCT, and after excluding GBMO from the analysis, which should be verified in the setting of IDH/MGMT-based histopathologicall GBM classification. However, such time interval should still be regarded as 'moderate delay' in comparison with literature data.

Despite the fact that the majority of the analysis available in the literature found no clear association between delays in RCT and OS, many studies suggest that short time intervals might have an adverse effect on the survival of the patients. Considering the available literature data and relatively high OS in our study group despite the median time interval of 9.8 weeks, we believe that moderate delays in the initiation of adjuvant RCT might be associated with improved survival compared to early initation of RCT. Prospective clinical trials regarding timing in GMB treatment are highly warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 4
Literature review of survival impact of radiochemotherapy timing in treatment of glioblastoma.

Study	n	Type of surgery	CT	Time interval subgroups (days)					Median OS in subgroups (months)			p-value	Conclusion
Graus (2013)	396	GTR / STR	TMZ +/- BCNU wafer	≤42		>42			19.8		17	0.08	• time interval has no impact on OS
Spratt (2013)	345	GTR, STR or biopsy	TMZ	7–14	21–35	≥42			10.2[a]	13.3[a]	14.7[a]	0.11	• survival detriment in MVA for time interval of ≥ 42 days
Adeberg (2015)	177	GTR / STR	TMZ	35 (18–49)		28 (5–98)			16.2		18.2	0.64	• survival improvement in UVA for time interval of ≥ 24 days
Han (2015)	198	GTR, STR or biopsy	Erlotinib + TMZ / Enzastaurin + TMZ / Erlotinib + Bev + TMZ	<30	30–34	>34			16.2	24.6	18.8	**0.004**	• time interval of 30–34 days may be associated with prolonged OS
Loureiro (2015)	115	GTR, STR or biopsy	TMZ or none	≤42		>42			13.5	14.2	0.470		• time interval has no impact on OS
Wang (2015)	447	GTR, STR or biopsy	TMZ or none	<21	21–32	>32			12.5	15.5	15.9	**0.004**	• interval of < 21 days is associated with reduced OS
Seidlitz (2015)	369	GTR, STR or biopsy	TMZ or none	≤27		>27			15.1		16	0.207	• time interval has no impact on OS
Sun (2015)	218	GTR / STR	TMZ	≤27		>27			15.9		14.9	0.180	• time interval has no impact on OS
Louvel (2016)	692	GTR / STR	TMZ +/- BCNU wafer	<45		>45			18.2		20.4	–	• time interval has no impact on OS
Randolph (2016)	161	GTR, STR or biopsy	TMZ or none	≤28		>28			12.2		12.2	0.16	• time interval has no impact on OS • time interval of > 28 days improves OS for STR or biopsy patients
Blumenthal (2018)	1395	GTR, STR or biopsy	TMZ	≤28		>28			16		15.9	0.52	• time interval has no impact on OS
Osborn (2018)	11,652	GTR / STR	TMZ	<24	25–30	31–37	>37	15	16.3	16.6	15.9	**0.04**	• time interval has no impact on OS
Ahn (2019)	138	GTR, STR or biopsy	TMZ	≤28		>28			15.5		14.5	0.707	• time interval has no impact on OS • time interval of > 28 days may have detrimental effect for STR or biopsy patients
Katsigiannis (2019)	151	GTR	TMZ	<28	28–33	>33	15		17.4		18.2	0.902	• time interval has no impact on OS
Potharaju (2019)	425	GTR, STR or biopsy	TMZ	<10	11–20	>20	18.3		13.3		15	**<0.001**	• time interval of > 10 days may be detrimental for OS
Amsbaugh (2019)	16,335	GTR / STR	TMZ	22–61		≥62			14.1		12	**0.0035**	• time interval of ≥ 62 days was associated with worse OS
Buszek (2020)	45,942	GTR, STR or biopsy	TMZ or none	<28	28–42	43–56	>56	13.9	15.2	14.4	14.6	**<0.0001**	• time interval of 28–42 days improves OS
Zur (2020)	204	GTR, STR or biopsy	TMZ	<28	28–42	>42	11.7			15.8	19.4	**0.0092**	• time interval of > 42 days is associated with improved OS
This study	346	GTR / STR	TMZ	<54	54–69	70–84	>84	21.8	18.6	15.6	17.5	0.105	• time interval has no impact on OS

[a] calculated from the last day of radiation therapy.

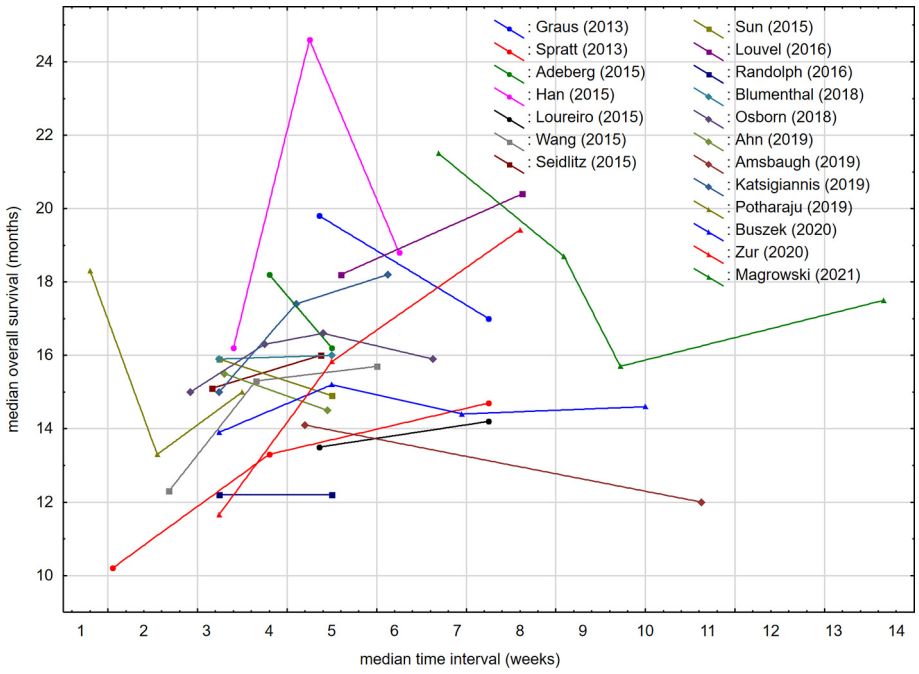

Fig. 4. The median survival and respective approximate median time interval in groups, as presented in different studies regarding the impact of time interval on outcomes of GBM patients' treatment with postoperative TMZ-based RCT.

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