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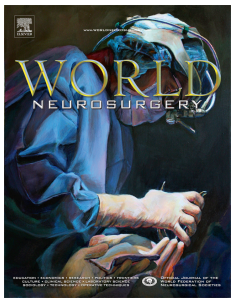

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Impact of timing of surgery and adjuvant treatment on survival of adult IDH-wildtype glioblastoma: a single-center study of 392 patients

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ABSTRACT

Background: The purpose of our study was to analyze the impact of time interval from referral to surgery and from surgery to adjuvant treatment on survival of adult IDH-wildtype glioblastomas.

Methods: Data on 392 IDH-wildtype glioblastomas diagnosed at the Tampere University Hospital in 2004–2016 were obtained from the electronic patient record system. Piecewise Cox regression was used to calculate hazard ratios for different time intervals between referral and surgery, as well as between surgery and adjuvant treatments.

Results: The median survival time from primary surgery was 9.5 months (interquartile range: 3.8–16.0). Survival among patients with an interval exceeding four weeks from referral to surgery was no worse compared to <2 weeks (hazard ratio: 0.78; 95% confidence interval: 0.54–1.14). We found indications of poorer outcome when the interval from surgery to radiotherapy exceeded 30 days (hazard ratio: 1.42; 95% confidence interval: 0.91–2.21 for 31–44 days and 1.59; 0.94–2.67 for over 45 days).

Conclusions: Interval from referral to surgery in the range of 4–10 weeks was not associated with decreased survivals in IDH-wildtype glioblastomas. In contrast, delay exceeding 30 days from surgery to adjuvant treatment may decrease long-term survival.

INTRODUCTION

Gliomas are the most common primary malignant central nervous system (CNS) tumors in adults, and astrocytomas are the largest histological subtype.[1] Despite substantial progress in treatment, the prognosis of adult glioma is still poor, especially in glioblastomas.[2] Isocitrate dehydrogenase (IDH) mutation is important in diagnostics of astrocytomas. It is present in most grade 2–3 astrocytomas, while most grade 4 astrocytomas are IDH-wildtype.[2,3]

Besides treatment modality (with surgery as the primary approach), time interval to adjuvant treatment (treatment delay) is considered a potentially important determinant of glioblastoma outcome.[4–11] However, some studies have suggested that very early initiation of adjuvant treatment could be associated with decreased survival.[6,12–16] Hence, optimal timing or longest acceptable interval from surgery to adjuvant treatment in terms of patient outcome is not well established. Furthermore, most previous studies have ignored the detailed IDH mutation status despite its prognostic importance.

We analyzed the impact of the time interval from referral to surgery and from surgery to adjuvant therapy on long-term survival of patients with IDH-wildtype glioblastoma.

MATERIALS AND METHODS

Data sources

The study protocol was reviewed by the ethical committee of Tampere University Hospital (TAUH) and the National Authority for Medicolegal Affairs in Finland. We obtained data from the TAUH Brain Tumor Database on all primary malignant astrocytomas (grade 4; WHO 2016 classification codes 9440–9442 and 9445) diagnosed at TAUH in 2004–2016. The data included sex, age at surgery, date of surgery (resection or biopsy), tumor histological type and grade according to the 2016 WHO classification of CNS tumors,[17] IDH mutation status, tumor location, post-operative treatments, time from referral to surgery and from surgery to adjuvant radiotherapy (RT) or chemoradiotherapy (CRT).

IDH mutation status was determined using immunohistochemistry for mutant R132H IDH1 protein.[18] Time between referral and surgery was calculated from the date when a referral was accepted to the neurosurgery unit or from the date when a neurosurgeon was consulted. If the time interval from surgery to adjuvant treatment exceeded two months, we confirmed from the patient records that the indication for adjuvant treatment was the primary tumor. We followed the patients from surgery for at least two years for death from any case through the Finnish Cancer Registry. The follow-up was complete (no patients lost to follow-up).

Classification and exclusion criteria

We focused on adult primary IDH-wildtype glioblastomas. We excluded IDH-mutant grade 4 astrocytomas according to the 2016 WHO classification of CNS tumors.[17] Patients younger than 20 years were also excluded, because pediatric astrocytomas are biologically distinct from those in adults.[1,19] Of the tumors excluded because of young age, 90% were brainstem gliomas (most of which would likely be currently classified as “diffuse midline glioma H3 K27M altered”). Patients with brain tumor diagnosis based only on imaging, and those who

did not undergo surgery, were excluded. These patients generally had either poor performance status or refused operation. Operated patients represent the TAUH catchment population, as no patients were referred to other hospitals for CNS tumor surgery. In Finland, neurosurgical treatments are centralized in five university hospitals, TAUH covering the population base of approximately a million people.

Statistical analysis

We used piecewise proportional hazards regression for survival analyses and estimated hazard ratios (HR) with 95% confidence intervals (CI) for the evaluated prognostic factors. The survival time was calculated from the date of surgery, and the outcome was death from any cause. Survival analyses by time interval from referral to surgery and from surgery to RT or CRT were adjusted for age, sex, and tumor location. Adjusting for the year of surgery did not affect the results, so it was not used in the final analyses. As the proportionality assumption was violated with full follow-up, with dissimilar effects of radiotherapy over time, survival analyses by time interval from surgery to adjuvant treatment were performed incorporating separate time-dependent effects for follow-up time under 6 months and beyond six months. Using this model, we conducted likelihood ratio tests for an overall and a time-period specific (beyond six months) difference between the groups. In addition, we used Kaplan-Meier curves to illustrate the effect of different variables on survival time. We also calculated the median survival times (MST) with interquartile ranges (IQR) and assessed statistical significance using log-rank tests. Statistical analyses were performed using Stata (version 15.1), IBM SPSS Statistics (version 27) and Microsoft Excel (version 16.0).

RESULTS

In 2004–2016, 392 grade 4 IDH-wildtype glioblastomas were diagnosed at TAUH (Table 1). IDH-wildtype glioblastomas were more common in men, with 241 male cases (61.5%) and 151 female cases (38.5%). The median age at diagnosis was 64 years (IQR: 57–70 years), and the largest age group was 60–69 years (159 cases, 40.6%). The MST of IDH-wildtype glioblastomas was 9.5 months (IQR: 3.8–16.0).

Most patients underwent resection (350 cases, 89.3%), while only biopsy was performed on 42 patients (10.7%) (Table 1). The median age for patients treated with resection was 63 years (IQR: 57–70 years) and 67 years for those operated with biopsy (IQR: 63–72 years). The MST of patients treated with resection was 9.9 months (IQR: 4.5–16.9) while MST of patients operated with biopsy was 4.4 months (IQR: 1.7–10.0) (log rank p=0.001). Of the patients treated with resection, 42 (12.0%) did not receive any adjuvant treatment, while 9 (21.4%) patients with biopsy only did not receive any further treatment.

Most of the tumors were treated with post-operative CRT (187 cases, 65.2% of the cases with full adjuvant treatment details). Data on CRT was unavailable for 26.8% of the cases. Post-operative RT alone was given to 45 patients (11.5%). RT data was unavailable for one case. Post-operative chemotherapy alone was given to five patients, while data was unavailable for four cases.

Time interval from referral to surgery

Time interval from referral to surgery could be defined for 388 patients (99.0%) with IDH-wildtype glioblastoma. The median time interval (MTI) from referral to surgery was 17 days (IQR: 12–23 days). Time interval was less than two weeks for 129 patients (33.3%), 2–4 weeks for 206 patients (53.1%) and exceeded four weeks for 53 patients (13.7%). The MTI was 44 days (IQR: 35–66 days) for the group with delay times exceeding four weeks.

Patients operated with biopsy and those undergoing resection were analyzed separately. Most patients were treated with resection (n=346, 89.2%). Of them, 121 (35.0%) were operated within less than two weeks, 185 patients (53.5%) 2–4 weeks and 40 (11.5%) over four weeks (Table 2). Longer time interval from referral to resection was not associated with decreased survival (Figure 1A). Patients with an interval of 2–4 weeks had an HR of 0.85 (95% CI: 0.67–1.08) and over four weeks HR of 0.78 (95% CI: 0.54–1.14) relative to <2 weeks.

Similarly, no clear survival differences were observed for patients operated with biopsy (n=42, 10.8%) (Figure 1B). Of them, 8 (19.0%) were operated in less than two weeks, 21 patients (50.0%) 2–4 weeks and 13 (31.0%) over four weeks. A time interval of 2–4 weeks was associated with an HR of 1.16 (95% CI: 0.43–3.12) and over four weeks HR of 0.62 (95% CI: 0.22–1.76) compared to an operation within two weeks.

Time interval from surgery to adjuvant therapy

Overall, a time interval from resection surgery to adjuvant therapy (RT alone or CRT) could be defined for 185 patients (88.9%) with IDH-wildtype glioblastoma. Patients with biopsy (17 cases) were excluded from these analyses. The MTI from surgery to initiation of radiotherapy was 36 days, IQR being 29–46 days. Adjuvant treatment was commenced within 30 days for 50 patients (27.0%), in 31–44 days for 85 patients (46.0%) and 45 days or more for 50 patients (27.0%). The MTI was 52 days (IQR: 47–58 days) for the group with the longest times to adjuvant treatment. We analyzed separately the follow-up period up to 6 months and more than 6 months after surgery.

Interval from surgery to adjuvant therapy (RT alone or CRT) did not affect the prognosis of IDH-wildtype glioblastomas during the first six months after surgery (Table 3). After six months from surgery, a time interval of 31–44 days or 45 days or longer to adjuvant treatment was associated with a slightly, though non-significantly, decreased survival

compared with treatment within 30 days, HR being 1.42 (95% CI: 0.91–2.21) and 1.59 (95% CI: 0.94–2.67), (p=0.16). Kaplan-Meier curves suggested a slightly decreased survival during the first six months for patients with adjuvant treatment started within 30 days than those with a longer interval (Figure 2). However, the difference disappeared and seemed to reverse in longer follow-up.

We also analyzed separately patients with RT alone and those receiving CRT as adjuvant treatment. Time interval from resection to radiotherapy could be determined for 145 patients (84.3%) treated with CRT. Of them, 41 (28.3%) commenced radiotherapy within 30 days, 70 patients (48.3%) in 31–44 days and 34 (23.5%) 45 days or more. During the first six months of follow-up, an interval of 31–44 days was related to an HR of 0.61 (95% CI: 0.18–2.02), while start of radiotherapy exceeding 45 days showed an HR of 1.75 (95% CI: 0.53–5.78) compared with 30 days or less. After six months of follow-up, a longer interval from surgery to CRT showed some indications towards decreased survival, but the results were not statistically significant (p=0.61). A time interval of 31–44 days gave an HR of 1.22 (95% CI: 0.75–1.97) and 45 days or longer HR of 1.31 (95% CI: 0.74–2.33) relative to 30 days or less.

Time interval from resection to radiotherapy could be determined for 35 patients (97.2%) treated with RT alone. Of them, nine (25.7%) received radiotherapy within 30 days and 14 patients (40.0%) in 31–44 days (Table 3). The interval exceeded 45 days in 12 cases (34.3%). During the first six months of follow-up, patients commencing radiotherapy in 31–44 days had an HR of 0.68 (95% CI: 0.21–2.19), while an interval exceeding 45 days was related to an HR of 0.65 (95% CI: 0.20–2.18) compared with 30 days or less. After six months of follow-up, a time interval of 31–44 days showed a decreased survival with an HR of 5.60 (95% CI: 1.08–29.13). Patients with an interval exceeding 45 days had some indication of decreased survival, though with an imprecise result (HR: 2.39; 95% CI: 0.44–12.90).

DISCUSSION

Here, we present a large population-based series of IDH-wildtype glioblastoma patients that represent real-world data on how duration from referral to surgery and from surgery to adjuvant treatment affect long-term survival in the era of chemoradiotherapy. In our series of 392 IDH-wildtype glioblastomas, time interval from referral to surgery exceeding four weeks was not associated with poorer survival. This suggests that operation within 4–5 weeks from referral does not affect treatment outcomes compared with shorter waiting time. In cases with severe tumor edema, it might be even beneficial to operate the patient after some delay since steroids reduce swelling and can improve patient's clinical condition before craniotomy.

On the other hand, postponing adjuvant treatment (radiotherapy or chemoradiotherapy) more than 30 days after surgery showed some indications of poorer survival. Considering these findings and the fact that radiotherapy or chemoradiotherapy impairs wound healing, it seems appropriate to postpone the adjuvant therapy for 2–3 weeks after surgery to allow the craniotomy wound to heal, but no longer than 4–6 weeks.

Our results are comparable to previous studies reporting indications towards decreased long-term survival for patients with prolonged delay from surgery to adjuvant therapy.[4–11] Sun et al.[10] found that >42 days' interval was associated with HR of 1.84 (95% CI: 1.10–3.05) and three months shorter MST compared with treatment within 42 days. Also, Amsbaugh et al.[4] reported decreased survival for prolonged delay from surgery to initiation of adjuvant treatment. An interval of >62 days had an HR of 1.16 (95% CI: 1.05–1.27) compared with ≤42 days. Spratt et al.[9] found even greater increase in the risk of death when delaying post-operative RT. Over six weeks interval was associated with an HR of 3.76 (95% CI: 1.01–14.57) compared with 1–2 weeks. A major issue in these studies was that they did not take into account the IDH mutation status leading to more heterogenous patient population. In

addition, two studies included also grade 3 astrocytomas. Besides our study, we found only one previous report focusing specifically on IDH-wildtype glioblastomas.[8] They also reported poorer survival associated with prolonged time interval from surgery to adjuvant treatment. An interval exceeding 48 days was associated with an MST of 11 months (95% CI: 7.4–14.7) while patients treated within 28–33 days had an MST of 18 months (95% CI: 13.8–22.2).

Interestingly, several studies did not report any association of time interval from surgery to adjuvant therapy with survival.[20,21,30,22–29] Some studies have reported lower survival with early initiation of adjuvant treatment after surgery,[6,12–16] but this was not confirmed in our study population. Previous studies have not analyzed how the time from referral to surgery affects the survival of glioblastoma patients. Our study focused on this issue, and we found no clear association between an interval up to 4–5 weeks before surgery in IDH-wildtype glioblastomas and patient outcome.

A strength of our study is the large patient cohort of IDH-wildtype glioblastomas. Excluding grade 4 IDH-mutant astrocytomas made our patient population more homogenous and thus increasing the validity of our results. In addition, we were able to account for the major prognostic factors including patient age, sex, and tumor location. Also, being a single-center study ensured both homogenous treatment protocols and patient population.

Surgical delay can be calculated in many ways. One option is to start counting the delay from the first symptoms and the first clinical neurological evaluation. This was not feasible for us, as we did not have access to patient records from primary health care. Also, some first symptoms, for example epileptic seizures, make patients seek medical help sooner than less conspicuous symptoms – and mode of first presentation can associate with tumor aggressiveness. Another possibility would have been to calculate the time interval from diagnostic imaging to surgery. The date of the imaging was not comprehensively available, as

for some patients imaging was performed outside TAUH and we did not have access to the patient records in other hospitals. Hence, we counted the time interval to surgical treatment from the date of referral. The rationale was that this aspect can be more readily influenced by the neurosurgeons, while the time from the actual radiological diagnosis to the referral reflects the processes outside the neurosurgical department.

Our study has also some limitations. Although the vast majority of the patients included in the study were operated on with tumor resection, approximately 10% of the patients received only a tumor biopsy, based on the neurosurgeon´s clinical evaluation. In our clinical practice, most patients receiving a biopsy are generally older and with more comorbidities. In addition, none of the patients in our study were operated with awake craniotomy, which has been proposed to give some prognostic benefit for IDH-wildtype glioblastoma patients.[31,32]

Due to the observational nature of the analysis, comparability of patient groups is a major concern. Clinical decisions regarding timing of treatment may be influenced by patient characteristics, as well as clinical resources and availability. However, this is unavoidable, as an intervention study assigning patients to longer versus shorter time to treatment would not be ethically feasible. We were not able to account for two well-known prognostic factors, preoperative Karnofsky Performance Scale (KPS) score and the O6-methylguanine DNA methyltransferase (MGMT) methylation status. The latter is not routinely analysed at TAUH due to its high cost and most patients receive adjuvant CRT regardless of the MGMT methylation status. The KPS scores were not readily available as they were rarely reported in our retrospective data.

Furthermore, from our retrospective database, some other factors affecting the patient prognosis, e.g. tumor volumes, extent of the neurosurgical resection, neurological deficits, surgical complications, and comorbidities, could not be assessed. We could not take into

account the effect of possible re-operations after initial surgery. Also, possible oncological therapies given for the residual or metastatic tumors may have affected the results. In addition, data on post-operative treatments was not available for a quarter of the cases. Those patients underwent surgery at TAUH but received subsequent treatments in other hospitals. These shortcomings raise a need for future prospective studies with rigorous data collection protocols.

In this retrospective study, we used the older WHO 2016 version of the classification of central nervous system tumors. In addition, we used only IDH1^{R132H} mutation specific immunohistochemistry to define IDH-mutant and -wildtype astrocytomas. This is because IDH1^{R132H} mutation is by far the most predominant IDH1/2 mutation in gliomas (>90%).[33] According to the recent WHO 2021 classification, "glioblastoma, IDH-wildtype, is a diffuse, astrocytic glioma that is IDH-wildtype and histone H3-wildtype and has one or more of the following histological or genetic features: microvascular proliferation, necrosis, TERT promoter mutation, EGFR gene amplification, +7/−10 chromosome copy-number changes".[34] Although some novel genetic features are now included in the classification, we applied the negative R132H-mutant immunohistochemistry in the diagnosis alone, because this analysis still finds by far the most cases of the category of IDH-mutant astrocytomas.

Although our patient population was strictly defined, some heterogeneity among IDH-wildtype glioblastomas is unavoidable. Large tumors with greater mass effect and primarily worse prognosis are often operated more urgently compared with smaller tumors. It is therefore possible that tumors with worse prognosis are operated in a faster schedule, which could reduce comparability between patients with shorter versus longer delay and affect our findings. Due to small numbers of events, we were not able to exclude even major differences within the first six months from surgery. However, as the survival curves crossed several

times and the results were consistent with those in extended follow-up, substantial survival differences did not appear credible.

It seems, once again, that an interval of a month or two from diagnosis to operation and from surgery to oncological therapies has only minor impact on survival. Patients' overall well-being and management in daily activities seem much more important. Therefore, future studies analyzing the effect of treatment delays and adjuvant therapies on quality of life would be very meaningful for malignant astrocytoma patients with short life expectancy.

In the future, it would be interesting to also analyze the effect of a time interval from first symptoms to a referral to the neurosurgery unit on survival of glioblastoma, as well as IDH-mutated glioma patients. We could not include that in our study, as time from the first symptoms to referral was not comprehensively available in our retrospective data. Prospective studies are needed to assess this in the future.

In conclusion, times in the range of 4–10 weeks from referral to surgery were not associated with longer survival in IDH-wildtype glioblastomas. In contrast, waiting time from surgery to adjuvant treatment exceeding one month may decrease long-term survival.

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Declaration of interest

Declarations of interest: none.

Data statement

The datasets generated and/or analysed during the current study are not publicly available due to the GDPR and Finnish legislation concerning sharing personal data. As most of the patients in this study have died, we did not have their informed consent for sharing the data publicly. However, data are available from the corresponding author on reasonable request.

Figure Captions

Fig. 1 Kaplan-Meier survival estimates of IDH-wildtype glioblastomas operated with (A) resection and (B) biopsy by time interval from referral to surgery

Fig. 2 Kaplan-Meier survival estimates of IDH-wildtype glioblastomas by time interval from resection surgery to adjuvant therapy

Table 1. IDH-wildtype glioblastomas diagnosed at TAUH, 2004 – 2016

	Frequency	
	n	%
Total	392	100.0
Sex		
Male	241	61.5
Female	151	38.5
Age		
20–29	3	0.8
30–39	5	1.3
40–49	29	7.4
50–59	89	22.7
60–69	159	40.6
70–79	100	25.5
>80	7	1.8
Tumor location		
Frontal lobe	68	17.4
Temporal lobe	104	26.5
Other lobes	51	13.0
Tumors in two different locations	116	29.6
Multiple + brainstem	53	13.5
Treatment		
Surgery		
Resection	350	89.3
Biopsy	42	10.7
Post-operative radiation therapy		
Yes	45	11.5
No	346	88.3
Unknown	1	0.3
Post-operative chemotherapy		
Yes	5	1.3
No	383	97.7
Unknown	4	1.0
Post-operative chemoradiotherapy		
Yes	187	47.7
No	100	25.5
Unknown	105	26.8
Drugs used in chemotherapy / chemoradiotherapy		
Temozolomide	172	83.1
Temozolomide + other	24	11.6
Other	3	1.4
Unknown drug	8	3.9

Table 2. The effect of surgical timing on the prognosis of IDH-wildtype glioblastomas

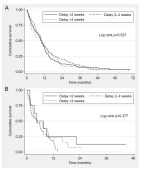
	Frequency		Median survival time (months)		Adjusted hazard ratio*	
	n	%	MST	IQR	HR	95% CI
Resection						
Interval (weeks)						
<2	121	35.0	9.6	3.8–14.8	1.00	ref.
2–4	185	53.5	10.2	5.2–19.4	0.85	0.67–1.08
>4	40	11.5	9.5	2.5–17.5	0.78	0.54–1.14
Biopsy only						
Interval (weeks)						
<2	8	19.0	4.4	1.6–8.8	1.00	ref.
2–4	21	50.0	4.4	1.7–9.6	1.16	0.43–3.12
>4	13	31.0	4.8	2.4–10.0	0.62	0.22–1.76

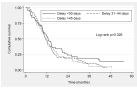
Note: * adjusted for age, sex and tumor location
IQR: interquartile range

Table 3. The effect of adjuvant treatment timing after resection on the prognosis of IDH-wildtype glioblastomas

	n (%)	Median survival time in months (IQR)	HR (95% CI)	p
RT or CRT				
FT: <6 months				
Interval (days)				
<30	50 (27.0)	12.6 (7.0–23.5)	1.00 (ref.)	
31–44	85 (46.0)	11.3 (7.8–16.6)	0.67 (0.29–1.54)	
>45	50 (27.0)	11.4 (5.9–18.0)	1.33 (0.58–3.06)	
FT: >6 months				
Interval (days)				
<30	40 (26.9)	14.5 (10.1–29.1)	1.00 (ref.)	
31–44	72 (48.3)	12.5 (9.6–17.5)	1.42 (0.91–2.21)	
>45	37 (24.8)	15.1 (10.5–21.9)	1.59 (0.94–2.67)	
Likelihood ratio test*				0.156
Likelihood ratio test†				0.163
RT only				
FT: <6 months				
Interval (days)				
<30	9 (25.7)	3.5 (2.2–16.9)	1.00 (ref.)	
31–44	14 (40.0)	5.5 (3.3–9.9)	0.68 (0.21–2.19)	
>45	12 (34.3)	5.5 (2.9–9.1)	0.65 (0.20–2.18)	
FT: >6 months				
Interval (days)				
<30	4 (25.0)	16.9 (14.4–20.6)	1.00 (ref.)	
31–44	7 (43.8)	9.9 (7.0–13.4)	5.60 (1.08–29.13)	
>45	5 (31.3)	10.5 (9.1–12.4)	2.39 (0.44–12.90)	
Likelihood ratio test*				0.266
Likelihood ratio test†				0.091
CRT				
FT: <6 months				
Interval (days)				
<30	41 (28.3)	12.7 (9.3–26.1)	1.00 (ref.)	
31–44	70 (48.3)	12.3 (9.2–17.4)	0.61 (0.18–2.02)	
>45	34 (23.5)	15.1 (9.5–26.3)	1.75 (0.53–5.78)	
FT: >6 months				
Interval (days)				
<30	36 (28.1)	14.3 (9.7–29.1)	1.00 (ref.)	
31–44	64 (50.0)	13.0 (9.9–17.5)	1.22 (0.75–1.97)	
>45	28 (21.9)	16.2 (11.9–26.6)	1.31 (0.74–2.33)	
Likelihood ratio test*				0.388
Likelihood ratio test†				0.611

Note: * Test for any difference between groups across the entire follow-up period
† Test for a difference between groups beyond six months of follow up
CI: confidence interval; CRT: chemoradiotherapy; FT: follow-up time; HR: hazard ratio adjusted for age, sex and tumor location; IQR: interquartile range; p: likelihood-ratio test; RT: radiation therapy





Abbreviation List

CI - confidence interval

CNS - central nervous system

CRT - chemoradiotherapy

EGFR - epidermal growth factor receptor

FT - follow-up time

GBM - glioblastoma

HR - hazard ratio

IDH - isocitrate dehydrogenase

IQR - interquartile range

KPS - Karnofsky Performance Scale

MTI - median time interval

MGMT - O6-methylguanine DNA methyltransferase

MST - median survival time

RT - radiotherapy

TAUH - Tampere University Hospital

TERT - telomerase reverse transcriptase

WHO - World Health Organization

Declaration of interest

Declarations of interest: none.

CRediT author statement

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