THE OUTCOMES OF GLIOBLASTOMA MULTIFORME: THE UNIVERSITY MALAYA MEDICAL CENTRE EXPERIENCE 2008-2018

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Abstract

Glioblastoma multiforme (GBM) is the most common and biologically aggressive adult primary brain tumour. The standard of care treatment is maximal safe resection (MSR) followed by post-operative concurrent chemoradiotherapy (CCRT) and adjuvant temozolomide (TMZ). This retrospective single-centre study was carried out at a tertiary academic hospital, University Malaya Medical Centre, between 2008–2018. This study aims to analyse the overall survival (OS) and progression free survival (PFS) and identify the prognostic factors affecting survival in our cohort of patients. Data including patient demographics, clinicopathologic characteristics and treatment characteristics were collected and correlated with survival. Survival analysis was performed with the Kaplan–Meier method. The multivariate analysis using Cox proportional hazard regression was performed to evaluate the prognostic clinicopathological for survival. A total of 100 patients were analysed. The median OS and PFS for the whole sample population was seven months (95% CI = 4-10 months) and four months (95% CI = 3.2-4.8 months) respectively. The factors associated with worse median OS were no adjuvant treatment (HR = 6.03; 95% CI = 2.40-15.16; p = 0.00), age older than 65 years old (HR = 2.22; 95% CI = 0.10-4.96; p = 0.05), post-operative ECOG PS >2 (HR = 6.13; 95% CI = 1.70-22.11; p = 0.01), and the temporal-lobe-located tumour (HR = 3.89; 95% CI = 1.51-10.01; p = 0.01). The fundamental points that could be deduced from the observed difference in survival outcome from our study to the literature are (1) age and PS were the two crucial pre-treatment factors that influenced the outcome, and (2) radiotherapy (RT) was demonstrated as the essential treatment in GBM and that the dose fractionation played an essential role on the outcome.

Keywords: Glioblastoma Multiforme, Concurrent Chemo-radiotherapy, Temozolomide

Introduction

Primary central nervous tumours are among the ten most common causes of death worldwide, with an estimated mortality of 18020 in 2020 (1). Glioblastoma multiforme (GBM) usually presents in the sixth or seventh decade of life and is more common in men than women (2). The standard treatment is maximal safe resection (MSR), followed by post-operative concurrent chemoradiotherapy (CCRT) and adjuvant temozolomide (TMZ) (3). The median survival is six months following surgical resection alone (4, 5), and about 12.1 months in patients who undergo surgery followed by radiotherapy (RT) (3). The addition of TMZ prolongs the median survival to 14.6 months (3).

The interpretation of the outcome in the literature to the Malaysian cohort is challenging due to the difference in the patient cohort selection, geographic distribution, heterogeneity of treatments received, various outcome endpoints and methodology variability. This study aims to retrospectively analyse the outcome of the standard treatment as suggested by Stupp et al. (3) and the effect of various treatment schedules in our cohort of patients. Furthermore, the influence of prognostic factors on the outcome is also analysed.

Materials and Methods

Sample collection

This retrospective single-centre study was performed at a tertiary academic hospital. Samples included all adult patients (>18 years old) with a histological diagnosis of GBM treated between 2008 and 2018. The sampling frame was identified from Clinical Oncology and Pathology Departments. Ethical approval was obtained from The Hospital Medical Research Ethics Committee.

The patients were grouped into groups 1 to 4 based on their treatment (Figure 1). Data including patient demographics, clinicopathologic and treatment characteristics were collected from electronic medical records. The survival data were obtained from the National Registration Department. The follow-up was performed until 30th June 2021, with an additional telephone follow-up for sketchy details.

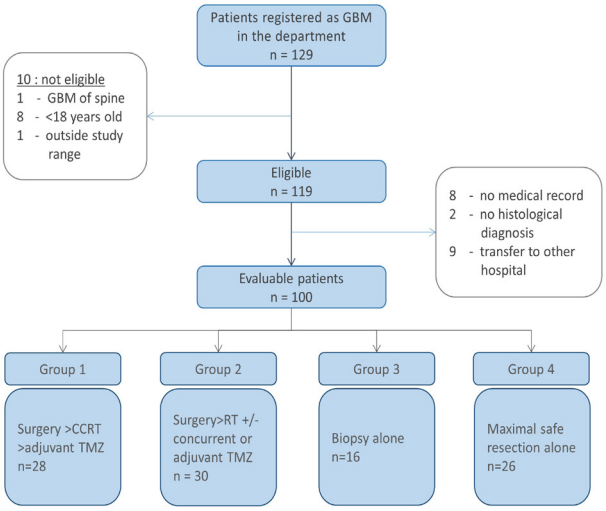

Figure 1: Consort diagram showing patients selection and the treatment grouping.

GBM = glioblastoma multiforme
n = sample size
CCRT = concurrent chemotherapy-radiotherapy
TMZ = temozolomide
RT = radiotherapy

RT dose was the prescribed dose to the tumour. The extent of resection was determined either from surgical resection documented by the surgeon or from the post-operative scans done within 72 hours. Overall survival (OS) was the duration from diagnosis to death or the last follow-up for surviving patients. Progression free survival (PFS) was determined either via radiological imaging or suggestive clinical signs and symptoms.

Data analysis

Kaplan Meier curves were used to calculate the probability of survival. The multivariate analysis using Cox proportional hazard regression was performed to evaluate the independent variables for survival. A p-value less than 0.05 was considered statistically significant. All analyses were performed using Statistical Package for Social Sciences for Windows version 23 (SPSS Inc; Chicago, IL, USA) software package.

Results

Between 2008-2018, 129 patients were registered as GBM. Hundred evaluable patients were included in the final analysis. The patient flow diagram and the treatment groups are shown in Figure 1. There were four treatment groups, and treatment combinations in each group are heterogeneous, as shown in (Table 1). The median follow-up time was seven months (range: 1-84 months).

Table 1: The groups with details of the treatment received.

Group	Treatment Received	n	Total
Group 1	Bx > CCRT > TMZ	4	
	GTR > CCRT > TMZ	16	n = 28
	STR > CCRT > TMZ	8	
Group 2	Bx > CCRT	2	
	GTR > CCRT	5	n = 8
	STR > CCRT	1	
	Bx > RT	8	
	GTR > RT	8	n = 19
	STR > RT	3	
	Sx > RT > TMZ	3	n = 3
Group 3	Biopsy alone		n = 16
Group 4	MSR alone		n = 26

n = sample size
Bx = biopsy
CCRT = concurrent chemotherapy-radiotherapy
TMZ = temozolomide
GTR = gross total resection
STR = subtotal resection
RT = radiotherapy
MSR = maximal safe resection.

The pre-treatment characteristics are described in (Table 2). Most patients were men 58 (58%) while women patients were 42 (42%). The Chinese ethnicity constituted the majority of the patients (51%), followed by Indian (29%) and Malay (20%). The median age of patients was 59.5 years. Compared to other treatment groups, group 1 patients were observed to have favourable pre-treatment characteristics (Table 2). It was noted that 57% were younger than 45 years old, and only 3.6% were above 65 years old. Most group 1 patient also had no significant medical comorbidities and had good ECOG ≤ 2 (86%).

Table 2: Pre-treatment characteristics.

Pre-treatment characteristics		All samples		Group 1		Group 2		Group 3		Group 4	
		n = 100	(%)	n = 28	(%)	n = 30	(%)	n = 16	(%)	n = 26	(%)
Age	≤ 45	25	25	16	57	2	6.7	1	6.3	6	23
	46-65	45	45	11	39	15	50	8	50	11	42
	> 65	30	30	1	3.6	13	43	7	44	9	35
Gender	Male	58	58	17	61	15	50	13	81	13	50
	Female	42	42	11	39	15	50	3	19	13	50
Ethnic	Chinese	51	51	16	57	15	50	8	50	12	46
	Malay	20	20	6	21	6	20	1	6.2	7	27
	India	29	29	6	21	9	30	7	44	7	27
Comorbidities	HPT	41	41	6	21	14	47	7	44	14	54
	DLP	15	15	1	3.6	5	17	5	31	4	15
	Diabetes	20	20	2	7.1	8	27	3	19	7	27
	Nil	42	42	17	61	11	37	6	38	8	31
ECOG pre-op	≤ 2	68	68	24	86	18	60	8	50	18	69
	> 2	30	30	2	7.1	12	40	8	50	8	31
	Unknown	2	2	2	7.1	0	0	0	0	0	0
ECOG post-op	≤ 2	67	67	24	86	19	63	7	44	17	65
	> 2	31	31	2	7.1	11	37	9	56	9	35
	Unknown	2	2	2	7.1	0	0	0	0	0	0
Site	Frontal	23	23	6	21	3	10	6	37	8	31
	Temporal	10	10	2	7.2	4	13	1	6.3	3	12
	Parietal	26	26	7	25	11	37	2	13	6	23
	Occipital	5	5	1	3.6	3	10	1	6.3	0	0
	Other	17	17	6	21	4	13	4	25	3	12
	Junctional*	19	19	6	21	5	17	2	13	6	23

n = sample size
HPT = hypertension
DLP = dyslipidaemia
ECOG = Eastern Cooperative Oncology Group performance score
*Temporoparietal, frontoparietal, frontotemporal, parietooccipital

Gross total resection (GTR) was commonly achieved (57.1-73.1%), whereas subtotal resection (STR) was less (13.4-28.6%) (Table 3). More than 80% of the evaluation of resections was from surgeons' impressions. iMRI was used mainly in group 1 (46.4%), while minimally used in other groups (7.7-13.3%). The rate of completion of RT was high (80-100%), and the most common dose fractionation was 60 Gy / 30F (43.3-67.8%). Most RT was delivered via 3DCRT (57.1-83.3%). The rate of completion of six cycles of adjuvant TMZ was low in both group 1 (n = 11, 39.3%) and group 2 (n = 0, 0%). Some patients received more than six cycles of adjuvant TMZ (n = 5, 17.9%).

At the time of analysis, 95 of the 100 patients had died. The median OS for the whole sample population was seven months (95% CI = 4-10 months) (Figure 2). The one- and two-year OS rates were 30% and 12%. Group 1 had the most prolonged median OS of 22 months (95% CI = 18.2-25.8 months).

Disease progression occurred in 96% (n = 96) of the patients, and the majority did not receive any treatment at progression 80.2% (n = 77). The median PFS was four months for the whole sample population (95% CI = 3.2-4.8 months) (Figure 3). Group 1 had the longest median PFS of 14 months (95% CI = 10.9-17.1).

Table 3: Treatment characteristics for groups 1, 2 and 4.

Treatment characteristics		Group 1		Group 2		Group 4	
		n = 28	(%)	n = 30	(%)	n = 26	(%)
Surgery	GTR	16	57.1	16	53.3	19	73.1
	STR	8	28.6	4	13.4	7	26.9
	Biopsy	4	14.3	10	33.3	0	0
Evaluation of resection	Surgeons' impression	23	82.1	25	83.3	21	80.8
	Post-operative scan	5	17.9	5	16.7	5	19.2
Intra-operative MRI	Yes	13	46.4	4	13.3	2	7.7
	No	15	53.6	26	86.7	24	92.3
Radiotherapy	**Complete**						
	Yes	28	100	24	80	N/A	
	No	0	0	6	20		
	Dose fractionation						
	60 Gy / 30F	19	67.8	13	43.3	N/A	
	40 Gy / 15F	1	3.6	6	20		
	60 Gy / 25F	1	3.6	0	0		
	54 Gy / 30F	3	10.7	1	3.3		
	30 Gy / 6F	0	0	7	23.4		
	Other	4*	14.3	3¥	10		
	CCRT						
	Yes	28	100	8	26.7	N/A	
	No	0	0	22	73.3		
	RT Techniques						
	3DCRT	16	57.1	25	83.3	N/A	
	IMRT	8	28.6	3	10		
	2DCRT	1	3.6	2	6.7		
	Cyberknife	3	10.7	0	0		
Adjuvant TMZ	Yes	28	100	3	10	N/A	
	No	0	0	27	90		
	No. of cycles adjuvant TMZ					N/A	
	≤ 5	12	42.8	3	100		
	6	11	39.3	0	0		
	> 6	5	17.9	0	0		

n = sample size
GTR = gross total resection
STR = subtotal resection
3DCRT = three-dimensional conformal RT
iMRT, intensity modulated RT
2DCRT = two-dimensional conformal RT
* 25 Gy / 5F cyberknife + EBRT 45 Gy / 20F or 66 Gy / 30F IMRT
¥ 35 Gy / 10F, 36 Gy / 12F or 20 Gy / 4F

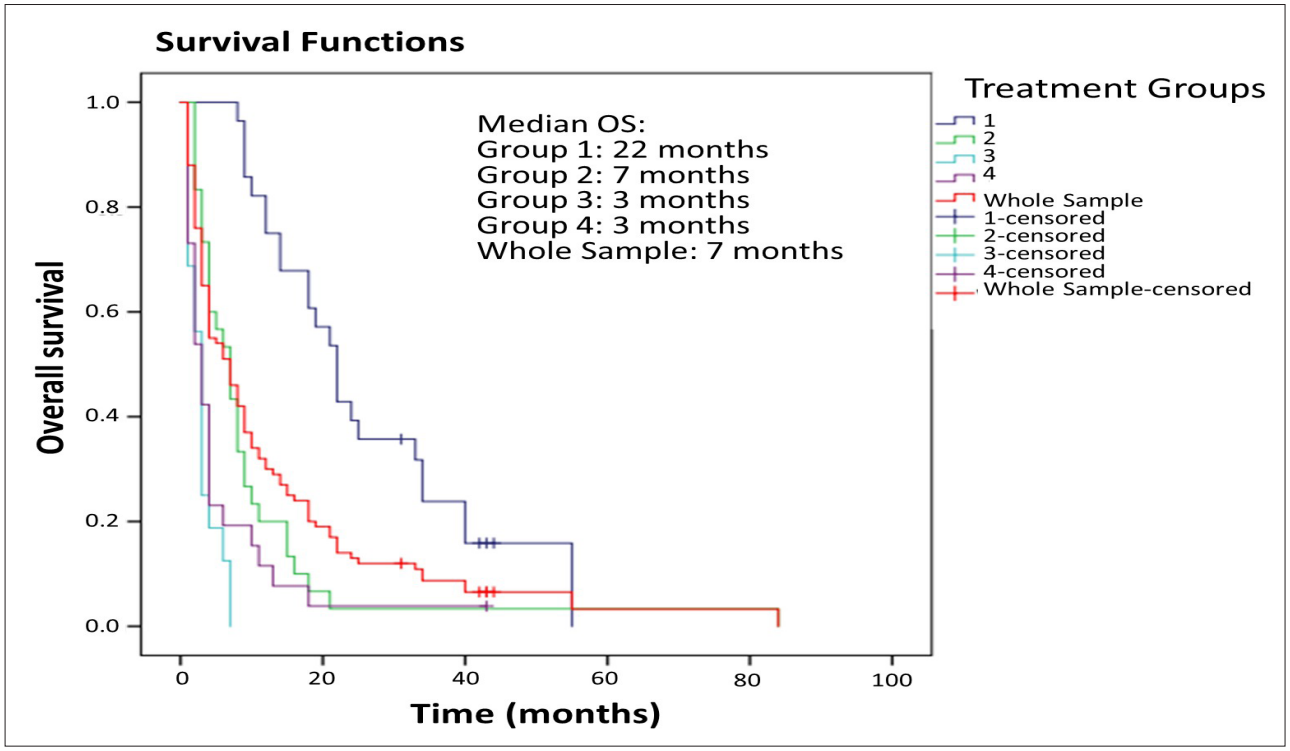

Figure 2: Kaplan-Meier estimates for OS for the whole sample population and groups 1-4.

OS=overall survival

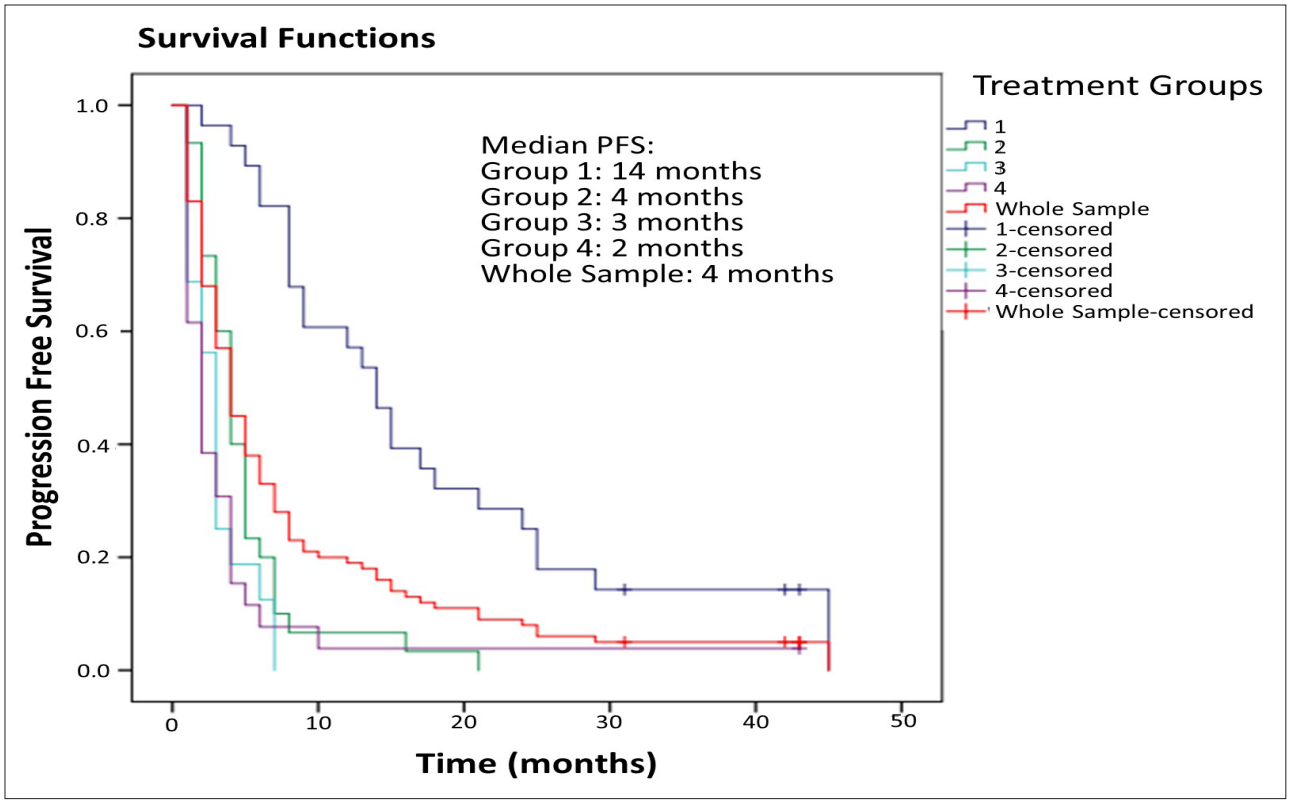

Figure 3: Kaplan-Meier estimates for PFS for the whole sample population and groups 1-4.

PFS=progression free survival

The results of the univariate analysis combining all cases are shown in Table 4. At the multivariate analysis, only age, post-operative ECOG, tumour site, and treatment groups were significant predictors for OS and PFS at $p < 0.05$ (Table 5). Statistically, treatment group 1 showed the best outcome in terms of OS and PFS. Patients older than 65 years, poor post-operative ECOG PS > 2, and temporal located tumour showed poor OS and PFS.

Table 4: Univariate analysis for PFS and OS.

Characteristics		PFS p-value	OS p-value
Pre-treatment			
Age	≤ 45 46-65 > 65	0.00	0.00
Gender		0.20	0.08
Ethnic		0.79	0.66
Comorbidities	HPT DLP Diabetes	0.00 0.00 0.00	0.00 0.00 0.00
ECOG pre-operative		0.00	0.00
ECOG post-operative		0.00	0.00
Tumour site	Parietal Frontal Temporal Occipital Junctional* Other	0.07	0.13
Treatment			
Treatment groups		0.00	0.00

PFS = progression free survival
OS = overall survival
HPT = hypertension
DLP = Dyslipidaemia
ECOG = Eastern Cooperative Oncology Group performance score
*Temporoparietal, frontoparietal, frontotemporal, parietooccipital

Discussion

The median age of GBM patients was approximately 60-year-old, which is similar in the literature (2, 6-7). The finding of a higher men's incidence of GBM (58%) is also consistent with previous studies (2, 8). GBM is frequently located at the frontal lobe, multiple lobes (junctional tumours), followed by temporal and parietal lobes (9). Our finding was relatively similar, where most tumours were located at the parietal (26%), followed by the frontal lobe (23%) and junctional tumours at multiple lobes (19%).

The best survival rate was in group 1 that received multimodality treatment (median OS 22 months; 95% CI = 18.2-25.8 months). The observed better OS than the Stupp et al. (3) trial (median OS 14.6 months; 95% CI = 13.2-16.8 months) was likely due to age distribution differences. Group 1 patients were primarily <50 years (60.7%) compared to the multimodality arm in the Stupp et al. (3) trial, where the majority were aged ≥50 years old (69%).

The treatment combinations received by individual patients in group 2 were heterogeneous, reflecting the real-world clinical practice. Nonetheless, all the patients received the treatment of surgery followed by RT. The median OS in group 2 was seven months (95% CI = 4.3-9.7 months) compared to 12.1 months (95% CI = 11.2-13.0 months) in the arm receiving surgery followed by RT alone in Stupp et al. (3). The difference was perhaps due to the difference in RT fractionation received.

Group 3 patients who had biopsy alone showed a median OS of three months (95% CI = 2.3-3.7 months), consistent with the literature finding (10-13). Previous studies had shown median survival of six months following surgical resection alone (4, 5). However, in this study, Group 4 patients showed a median OS of three months (95% CI = 1.8-4.2 months), which was as poor as those who had biopsy alone (group 3). The shorter survival observed could be due to the less objective determination of surgical extension through the surgeon's impression rather than post-operative scans. Not only that, but the shorter survival observed could be due to other competing factors leading to death. 73.3% died due to either post-operative complications from either resection of GBM (n = 2) or another synchronous tumour (n = 1); one patient died due to substantial residual post-operative tumour; seven patients had poor post-operative PS. Thus, the demonstrated survival for group 4 in this study did not correctly reflect the actual duration of survival expected from the intended surgical intervention.

The longest median PFS was 14 months (95% CI = 10.9-17.1) in group 1, which is better than the experimental arm in the Stupp et al. (3) trial (median PFS 6.9 months, 95% CI = 5.8-8.2). The apparent longer PFS could be due to the difference in the protocol for monitoring progression. A regular scan was not mandatory in the present study compared to the more stringent protocol in the Stupp et al. (3) trial.

Age, post-operative PS, tumour site, and treatment groups were significant prognostic factors in the present study. Age and PS have been shown in literature as independent prognostic factors of patient survival (14-20). Temporal lobe tumour was associated with poorer OS and a trend to poor PFS in the present study, similar to the retrospective review of the three ROTG trials. It showed worse survival for tumours at the temporal than the frontal lobe (9.1 months vs. 11.4 months) (21). Treatment grouping was a significant predictor for outcome in the present study, and we know that multimodality treatment offered the best survival rate (3, 22-23).

The present study had several limitations. Firstly, it was retrospective with a small sample size. Secondly, no data on IDH mutation or MGMT methylation status was presented due to lack of testing; thus, the possibility remains that this unmeasured confounder may influence our findings.

Table 5: Multivariate analysis for OS and PFS.

Covariates		OS			PFS		
		HR	CI	p-value	HR	CI	p-value
Age	≤ 45	1			1		
	46-65	1.17	0.58-2.36	0.66	1.93	0.93-4.03	0.08
	> 65	2.22	0.10-4.96	0.05	2.877	1.23-6.68	0.02
Gender	Male	1			1		
	Female	0.61	0.35-1.07	0.08	0.85	0.50-1.45	0.56
Comorbidities	HPT	1.25	0.70-2.23	0.46	1.18	0.67-2.08	0.57
	DLP	1.41	0.65-3.08	0.37	1.50	0.72-3.16	0.28
	Diabetes	1.33	0.72-2.46	0.37	1.38	0.75-2.54	0.31
ECOG pre-operative	≤ 2	1			1		
	> 2	2.00	0.62-6.44	0.24	1.94	0.69-5.45	0.21
ECOG post-operative	≤ 2	1			1		
	> 2	6.13	1.70-22.11	0.01	3.55	1.19-10.55	0.02
Tumour site	Frontal	1			1		
	Temporal	3.89	1.51-10.01	0.01	2.44	0.96-6.19	0.06
	Parietal	0.77	0.37-1.62	0.50	0.67	0.32-1.40	0.289
	Occipital	0.93	0.32-2.69	0.90	0.91	0.31-2.72	0.87
	Other	1.51	0.66-3.43	0.33	2.46	1.06-5.69	0.04
	Junctional*	1.09	0.52-2.30	0.82	0.80	0.37-1.70	0.56
Treatment groups	1	1			1		
	2	3.07	1.40-6.73	0.01	2.98	1.32-6.69	0.01
	3	6.03	2.40-15.16	0.00	3.14	1.24-7.92	0.02
	4	6.60	3.12-13.97	0.00	5.77	2.81-11.86	0.00

OS = overall survival
PFS = progression free survival
HR = hazard ratio
CI = confidence interval
HPT = hypertension
DLP = dyslipidaemia
ECOG = Eastern Cooperative Oncology Group performance score

*Temporoparietal, frontoparietal, frontotemporal, parietooccipital

Thirdly, there were slight differences in the treatment parameters among patients in the same treatment groups (e.g., RT dose fractionation, number of TMZ cycles, receipt of TMZ as concurrent or adjuvant alone). Nonetheless, the grouping was the best to reflect the intention of treatment in our setting, i.e., either the standard of care with multimodality treatment vs. the non–standard of care treatment and debulking surgery alone vs. biopsy alone group.

In future trials, a larger scale audit involving multiple oncology centres would be helpful to better reflect the findings in our country. Incorporating IDH mutation and MGMT methylation status as stratification status is valuable in line with the current interest in molecular subtyping in GBM.

Conclusion

In conclusion, the fundamental points observed are (1) age and PS were the two crucial pre-treatment factors that influenced the outcome, and (2) RT was the essential treatment in GBM and that the dose fractionation played an essential role in the outcome.

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Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

All the study conducts complied with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. The UMMC Medical Research Ethics Committee approved the study on the 7th of January 2019 (MREC Id No: 2018112-6844).

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1):7-30.
2. Tamimi AF, Juweid M. Epidemiology and outcome of glioblastoma. In Glioblastoma. S De Vleeschouwer, eds. Brisbane (AU): Codon Publications. 2017. Accessed 19 March 2023.
3. Stupp R, Mason WP, Bent M, Weller M, Fisher B, Taphoorn MJB, *et al*. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med. 2005; 352(10):987-96.
4. Pichlmeier U, Bink A, Schackert G, Stummer W. Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. Neuro Oncol. 2008; 10(6):1025-34.
5. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, *et al*. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006; 7(5):392-401.
6. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, *et al*. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol. 2013; 15(suppl 2):ii1-56.
7. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol. 2002; 4(4):278-99.
8. Darefsky AS, King JT, Dubrow R. Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of surveillance, epidemiology, and end results registries. Cancer. 2012; 118(8):2163-72.
9. Chakrabarti I, Cockburn M, Cozen W, Wang YP, Preston-Martin S. A population-based description of glioblastoma multiforme in Los Angeles County, 1974-1999. Cancer. 2005; 104(12):2798-806.
10. Balana C, Vaz MA, Sepulveda JM, Mesia C, Barco SD, Pineda E, *et al*. A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GEINO 14-01). Neuro Oncol. 2020; 22(12):1851-61.
11. Dobbs J, Barrett A, Morris S, Roques T. Practical Radiotherapy Planning Fourth Edition. Abingdon, Oxon: Taylor & Francis. 2009.
12. Fazeny-Dörner B, Wenzel C, Veitl M, Piribauer M, Rössler K, Dieckmann K, *et al.* Survival and prognostic factors of patients with unresectable glioblastoma multiforme. Anticancer Drugs. 2003; 14(4):308-9.
13. Malmström A, Grønberg BJ, Marosi C, Stupp R, Frappaz D, Schultz H, *et al.* Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol. 2012; 13(9):916-26.
14. Bauchet L, Mathieu- Daudè H, Fabbro-Peray P, Rigau V, Fabbro M, Chinot O, *et al.* Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. Neuro Oncol. 2010; 12(7):725-35.
15. Filippini G, Falcone C, Boiardi A, Broggi G, Bruzzone MG, Caldiroli D, *et al.* Prognostic factors for survival in 676 consecutive patients with newly diagnosed primary glioblastoma. Neuro Oncol. 2008; 10(1):79-87.
16. Helseth R, Helseth E, Johannesen TB, Langberg CW, Lote K, Rønning P, *et al.* Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand. 2010; 122(3):159-67.
17. Jeremic B, Milicic B, Grujicic D, Dagovic A, Aleksandrovic J. Multivariate analysis of clinical prognostic factors in patients with glioblastoma multiforme treated with a combined modality approach. J Cancer Res Clin Oncol. 2003; 129(8):477-84.
18. Li SW, Qiu XG, Chen BS, Zhang W, Ren H, Wang ZC, *et al.* Prognostic factors influencing clinical outcomes of glioblastoma multiforme. Chin Med J. 2009; 122(11):1247-8.
19. Ma X, Lv Y, Liu J, Wang D, Huang Q, Wang X, *et al*. Survival analysis of 205 patients with glioblastoma multiforme: clinical characteristics, treatment and prognosis in China. J Clin Neurosci. 2009; 16(12):1595-8.
20. Tugcu B, Postalci LS, Gunaldi O, Tanriverdi O, Akdemir H. Efficacy of clinical prognostic factors on survival in patients with glioblastoma. Turk Neurosurg. 2010; 20(2):117-25.
21. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, *et al.* Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive radiation therapy oncology group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993; 26(2):239-44.
22. Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, MisailidouD, *et al.* Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol. 2005; 23(10):2372-7.
23. Szczepanek D, Marchel A, Moskala M, Krupa M, Kunert P, Trojanowski T. Efficacy of concomitant and adjuvant temozolomide in glioblastoma treatment. A multicentre randomized study. Neurol Neurochir Pol. 2013; 47(2):101-8.