Original Article

Factors associated with the extent of resection of glioblastoma

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Background: The extent of resection (EOR) has been reported to be the leading factor associated with the prognosis of patients with glioblastoma (GBM). The purpose of this study was to identify the factors related to EOR and to determine the confounding effects of EOR for survival in patients with GBM.

Methods: The study was a retrospective cohort review of the electronic medical records of newly diagnosed patients with GBM. Binary logistic regression analyzed the factors associated with total resection. Furthermore, stratification and multivariable analysis were used to fit the prognostic models according to the anatomical factors to control confounding effects.

Results: One hundred and seventy-three patients were newly diagnosed with GBM. The EOR in this study was composed of total resection (22.0%), partial resection (63.0%), and biopsy (15.0%). The EOR was dichotomized into total resection and non-total resection subgroups. In univariate analysis, the factors associated with complete resection were single GBM [odds ratio (OR), 4.71; 95% CI, 1.06–20.76] and tumor volume <30 mL (OR, 3.06; 95% CI, 1.44–6.48). Therefore, the factors associated with complete resection were single GBM (OR, 6.81; 95% CI, 1.47–31.38) and tumor volume <30 mL (OR, 3.79; 95% CI, 1.72–8.34) in the multivariable analysis.

Conclusions: Not all GBMs are amenable to complete surgical resection, and multiple lesions and tumor volume of ≥30 mL are the potential limiting factors. Before evaluating the association between the EOR and survival time, the EOR should be controlled from confounders by stratification, multivariable analysis, or propensity scores.

Keywords: Glioblastoma (GBM); extension of resection; multiple glioblastomas; butterfly glioma; tumor volume; confounder

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Introduction

Glioblastoma (GBM) has an invasive and aggressive behavior and is the most common malignant primary brain tumor in adults. The multidisciplinary treatment, composed of surgical resection, radiation, and chemotherapy, has provided an improvement in survival time. The extent of resection (EOR) has been reported to be the leading prognostic factor for enhanced survival in patients when the EORs range 70–98% (1-5).

However, eloquent areas of the brain are distinctive structures concerning resection because potential impairments in the quality of life often limit the goal of total resection (6,7). However, several factors affect total resection in infiltrative tumors. Considering anatomical limitations, "butterfly" GBM, multiple lesions, and leptomeningeal dissemination are challenging conditions for total resection in clinical practice (8-10). Awad *et al.* reported a significant interaction between EOR and preoperative tumor volume.

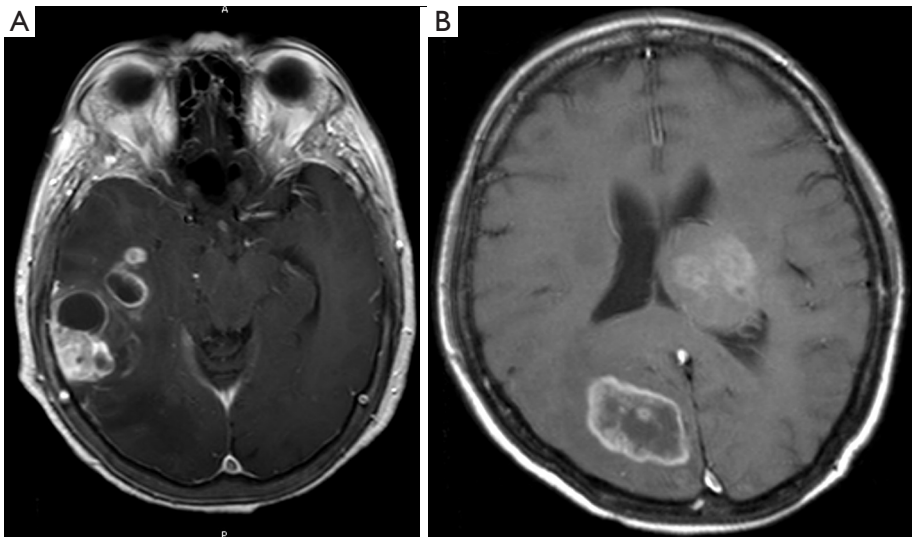

Figure 1 Types of multiple glioblastomas. (A) Multifocal glioblastoma has the centers of tumors located a short distance apart; (B) multicentric glioblastoma has the centers of tumors that belong to different lobes or bilateral brains with no apparent route of dissemination.

The EOR alone did not correlate with survival after adjusting for other factors. Therefore, the interaction between the EOR and preoperative volume was an essential predictor for improved survival (11). In the literature, there is a lack of evidence on the factors that correlate with EOR. The purpose of this study was to identify which factors are associated with EOR. Therefore, the confounders should be controlled before time-to-event analysis will be conducted in GBM patients.

Methods

The study was a retrospective cohort review of electronic medical records from our hospital information system. We enrolled consecutive patients who were newly diagnosed with GBM. The inclusion criteria for the study were patients who had histologically-confirmed GBM, which was consistent with the World Health Organization classification (12) by a pathologist at Songklanagarind Hospital between January 2000 and December 2018. The data collected for analysis comprised of the demographics, neuroimaging, treatment, and outcome.

Magnetic resonance images (MRI) of the brain were reviewed prospectively to demonstrate tumor location, the extent of tumor invasion, and tumor size. Adapted from Lacroix *et al.* (1), the degree of tumor necrosis, mass effect, and enhancement were determined. Tumor volume was quantified from preoperative MRI and postoperative MRI or contrast-enhanced computerized tomography (CT) or both of the brain.

The EOR was defined from the studies of Vecht *et al.* and Bloch *et al.* (13,14). Gross total resection was defined as less than 5% of residual tumor was observed on postoperative neuroimaging. Partial resection was defined as resection less than 95% of residual tumor that was visible on postoperative neuroimaging. The biopsy was defined as an operation for tissue diagnosis only, and no attempt was made to remove the tumor. Additionally, percent of resection was assessed by postoperative T1W with contrast imaging.

The eloquent areas for tumor removal involved the motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, and dentate nucleus (1). Multiple GBMs were defined as at least two separated foci of enhancing tumors. This group included two types: multifocal and multicentric GBMs. A multifocal GBM was defined where the centers of the tumor had a short distance apart between each other that tumor cells migrate elsewhere and develop into a new tumor center, as shown in *Figure 1A*. Multicentric GBM was defined as the centers of tumor clearly separated from each other, for example, different lobes or bilateral brains, with no apparent route of dissemination, as shown in *Figure 1B* (15,16). Furthermore, the hypervascular sign was defined as visualizing vascular structures inside or around a tumor (flow void sign) in neuroimaging (8).

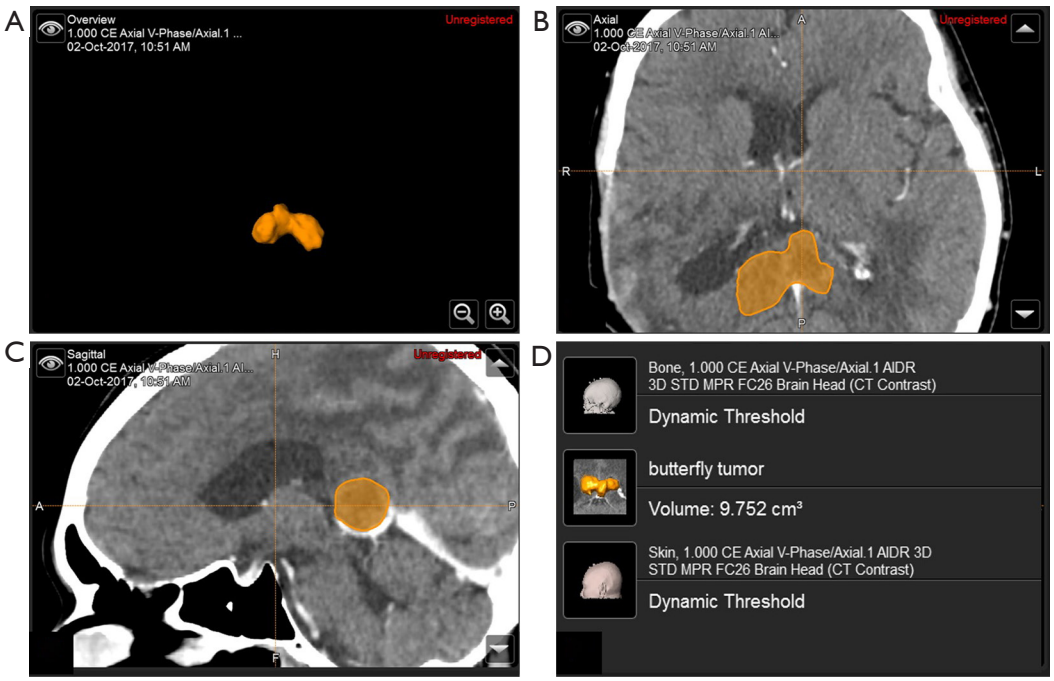

Figure 2 Tumor volume estimation. (A) 3D-tumor morphology was created from the selected areas in multiple-plains of neuroimaging; (B,C) axial and sagittal plains of CT of the brain show a selected tumor area using the Smart Brush tool; (D) display window shows the tumor volume.

Tumor volume estimations were performed using the Smart Brush tool of BrainLAB® software (Feldkirchen, Germany) by outlining the pathologies across neuroimaging modalities, as shown in *Figure 2*. The study was performed with the permission of the Ethical Committee of the Faculty of Medicine, Songklanagarind Hospital, Prince of Songkla University (REC 61-293-10-1).

Statistical analysis

The patient characteristics, imaging factors, and therapeutic factors were analyzed using descriptive analysis presented as proportions and mean ± standard deviation (SD). The extension of resection was dichotomized into total resection and non-total resection groups. Therefore, the association between several factors and the extension of resection were analyzed by binary logistic regression. The candidate risk factors with P<0.10 from the univariate regression analysis were entered into the multivariable regression model. The Hosmer-Lemeshow goodness-of-fit test and concordance statistics were used to fit the model. Furthermore, multicollinearity between variables in the model was checked by the variance inflation factor (VIF) and tolerance methods. Moreover, the sample size was calculated using the level of significance 0.05 and power 0.8. Statistical analysis was performed with the R program version 3.4.1 (R Foundation, Vienna, Austria).

Results

Clinical characteristics

The clinical manifestations of the 173 patients with GBM are shown in *Table 1*. GBM was predominant in males and common in adults. The mean ± SD age was 51.2±15.3 years (range, 8–87 years). The patients usually presented with hemiparesis and progressive headache. One-quarter of the cases had a seizure at presentation. The common GBM location involved the frontotemporal lobe.

Using 3D tumor volume software, the mean ± SD tumor volume was 54.9± 40.6 mL, and 82.7% of the GBM were solitary tumors, while 17.3% were multiple tumors.

In this study, the total resection rate was 22.0%, while the rates of partial resection and biopsy were 63.0% and 15.0%, respectively. Half of the patients (64.7%) underwent radiotherapy alone after resection, while patients who

Table 1 Baseline characteristics (N=173)

Factor	N (%)
Sex	
Male	97 (56.1)
Female	76 (43.9)
Age	
<60	123 (71.1)
≥60	50 (28.9)
Age, years, mean ± SD	51.2 (15.3)
Signs and symptoms	
Hemiparesis	87 (50.3)
Headache	85 (49.1)
Seizure	43 (24.9)
Cranial nerve palsy	33 (19.1)
Behavior change	22 (12.7)
Alteration of consciousness	23 (13.3)
Aphasia	14 (8.1)
Preoperative Karnofsky performance status	
<80	90 (52.0)
≥80	83 (48.0)
Number of the tumor at the first time of presentation	
Single tumor	143 (82.7)
Multiple tumor	30 (17.3)
Multifocal type	27 (15.6)
Multicentric type	3 (1.7)
Tumor involvement	
Temporal	60 (34.7)
Frontal	51 (29.5)
Parietal	32 (18.5)
Corpus callosum	19 (11.0)
Periventricular	7 (4.0)
Occipital	7 (4.0)
Thalamic/Basal ganglion	5 (2.9)
Brainstem	3 (1.7)
Pineal	1 (0.6)
Cerebellum	1 (0.6)
Suprasellar	1 (0.6)
Eloquent area*	99 (57.2)
Midline shift	
<0.5	75 (43.4)
≥0.5	98 (56.6)
Hypervascular signs	
No	114 (65.9)
Yes	59 (34.1)
Leptomeningeal dissemination at first time of presentation*	18 (10.4)
Maximum diameter of the tumor, cm, mean ± SD	5.3 (1.75)
Tumor volume, mL, mean ± SD	54.9 (40.6)
IDH1 profile	
Wild-type	162 (93.6)
Mutation	11 (6.4)
MGMT promoter methylation (N=84)	
Unmethylation	3 (3.6)
Methylation	81 (96.4)
Surgery	
Total resection	38 (22.0)
Partial resection	109 (63.0)
Biopsy	26 (15.0)
Radiotherapy alone	112 (64.7)
Temozolomide with radiotherapy	61 (35.3)
Postoperative Karnofsky performance status	
<80	105 (60.7)
≥80	68 (39.3)

*, eloquent areas defined as tumor that involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem or dentate nucleus.

received adjuvant chemotherapy were 35.3% of all patients. In detail, Temozolomide was used in one-third of the patients because the cost of temozolomide is not reimbursed by all medical insurance programs in Thailand.

The EOR was dichotomized into total resection and non-total resection subgroups. The non-total resection group had a greater number of corpus callosum tumors, multiple tumors, and greater tumor volume than the total

resection group, as shown in *Table 2*. Multiple GBMs were found in 30 (17.3%) patients, and 2 (5.3%) patients of the multiple tumors were total resection. Additionally, all of those was the multifocal type of multiple GBM. In tumor volume (N=168), the success rate of total resection in the group with a tumor volume ≥30 mL group was 16.2% (19/117) of all patients, while the group with a tumor volume <30 mL was totally resected in 37.3% (19/51) of all patients. Other clinical characteristics were not different between the two groups.

Table 2 Clinical characteristics divided by the extent of resection

Factor	Total resection, N (%)	Non-total resection, N (%)	P value
Sex			0.62
Male	20 (52.6)	77 (57.0)	
Female	18 (47.4)	58 (43.0)	
Age, year			0.10
<60	23 (60.5)	100 (74.1)	
≥60	15 (39.5)	35 (25.9)	
Preoperative Karnofsky performance status			0.12
<80	24 (63.2)	66 (48.9)	
≥80	14 (36.8)	69 (51.1)	
Frontal tumor involvement			0.46
No	25 (65.8)	97 (71.9)	
Yes	13 (34.2)	38 (28.1)	
Temporal tumor involvement			0.64
No	26 (68.4)	87 (64.4)	
Yes	12 (31.6	48 (35.6)	
Parietal tumor involvement			0.35
No	29 (76.3)	112 (83.0)	
Yes	9 (23.7)	23 (17.0)	
Occipital tumor involvement			0.17
No	35 (92.1)	131 (97.0)	
Yes	3 (7.9)	4 (3.0)	
Tumor of corpus callosum			0.07*
No	37 (97.4)	117 (86.7)	
Yes	1 (2.6)	18 (13.3)	
Periventricular tumor			0.61
No	37 (97.4)	129 (95.6)	
Yes	1 (2.6)	6 (4.4)	
Thalamic/basal ganglion tumor			0.58*
No	38 (100.0)	130 (96.3)	
Yes	0 (0.0)	5 (3.7)	

Table 2 (continued)

Table 2 (continued)

Factor	Total resection, N (%)	Non-total resection, N (%)	P value
Brainstem tumor			0.52*
No	37 (97.4)	133 (98.5)	
Yes	1 (2.6)	2 (1.5)	
Cerebellar tumor			0.22*
No	37 (97.4)	135 (100.0)	
Yes	1 (2.6)	0 (0.0)	
Pineal tumor			1.0*
No	38 (100)	134 (99.3)	
Yes	0 (0.0)	1 (0.7)	
Suprasellar tumor			1.0*
No	38 (100)	134 (99.3)	
Yes	0	1 (0.7)	
Eloquent area involvement†			0.78
No	17 (44.7)	57 (42.2)	
Yes	21 (55.3)	78 (57.8)	
Leptomeningeal dissemination at first time of presentation			0.97
No	34 (89.5)	121 (89.6)	
Yes	4 (10.5)	14 (10.4)	
Hypervascular signs			0.43
Negative	27 (71.1)	87 (64.4)	
Positive	11 (28.9)	48 (35.6)	
Midline shift, cm			0.57
<0.5	18 (47.4)	57 (42.2)	
≥0.5	20 (52.6)	78 (57.8)	
Number of the tumor at the first time of presentation			0.02*
Single tumor	36 (94.7)	107 (79.3)	
Multiple tumor	2 (5.3)	28 (20.7)	
Tumor volume, mL (N=168)			0.003
<30	19 (50.0)	32 (24.6)	
≥30	19 (50.0)	98 (75.4)	
IDH1 profile			1.0*
Wild-type	36 (94.7)	126 (93.3)	
Mutation	2 (5.3)	9 (6.7)	
MGMT promoter methylation			1.0*
Methylation	20 (100.0)	61 (95.3)	
Unmethylation	0 (0.0)	3 (4.7)	

†, eloquent areas defined as tumor that involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, dentate nucleus; *, P value of Fisher's exact test.

Factors associated with total resection

Binary logistic regression was used to analyze factors predicting total resection as shown in *Table 3*. In univariate analysis, the significant factors were single GBM [odds ratio (OR), 4.71; 95% CI, 1.06–20.76] and tumor volume <30 mL (OR, 3.06; 95% CI, 1.44–6.48). Therefore, the candidate factors, which had a P-value <0.10 from univariate analysis, were entered into the multivariable regression model. The factors associated with complete resection were single GBM (OR, 6.81; 95% CI, 1.47–31.38) and tumor volume <30 mL (OR, 3.79; 95% CI, 1.72–8.34) in the multivariable analysis with the backward elimination method. Moreover, we repeated the multivariable analysis with a forward selection procedure and obtained identical results.

Discussion

GBM is the most common primary malignant tumor in

Table 3 Univariate and multivariable for total resection

Factor	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Gender				
Male	Ref			
Female	1.19 (0.58–2.46)	0.62		
Age-year				
<60	Ref			
>60	1.86 (0.87–3.96)	0.10		
Signs and symptoms				
Motor weakness*	1.37 (0.65–2.85)	0.39		
Seizure*	0.51 (0.19–1.32)	0.16		
Aphasia*	0.99 (0.26–3.76)	0.99		
Preoperative Karnofsky performance status				
<80	Ref			
>80	0.55 (0.26–1.17)	0.12		
Tumor involvement				
Frontal lobe*	1.32 (0.61–2.86)	0.47		
Temporal lobe*	0.83 (0.38–1.80)	0.64		
Parietal lobe*	1.51 (0.63–3.61)	0.35		
Occipital lobe*	2.80 (0.60–13.1)	0.19		
Periventricular*	0.58 (0.06–4.98)	0.62		
Corpus callosum*	0.17 (0.02–1.36)	0.09		
Brainstem*	1.79 (0.15–20.3)	0.63		
Eloquent area*†	0.90 (0.43–1.86)	0.78		
Leptomeningeal dissemination at first time of presentation				
No	Ref			
Yes	1.01 (0.31–3.29)	0.97		

Table 3 (continued)

Table 3 (continued)

Factor	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Midline shift-cm				
<0.5	Ref			
>0.5	0.81 (0.39–1.67)	0.57		
Number of the tumor at the first time of presentation				
Multiple	Ref		Ref	
Single	4.71 (1.06–20.76)	0.04	6.81 (1.47–31.38)	0.01
Tumor volume, mL				
≥30	Ref		Ref	
<30	3.06 (1.44–6.48)	0.003	3.79 (1.72–8.34)	0.001
IDH1 profile				
Wild-type	Ref			
Mutation	0.77 (0.16–3.76)	0.75		

*, data show only "yes group" while reference groups (no group) are hidden; †, eloquent area defined tumor involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, dentate nucleus.

adults and has aggressive behavior.

The EOR has been shown to be an important prognostic factor for survival (1-5). Because GBM is an infiltrative tumor, the rates of total tumor resection were reported in the range of 17.6–40% (5,17). In clinical experience, the EOR depends on several factors, but no evidence has been reported in the literature.

A GBM rising bilaterally at the corpus callosum usually builds a "butterfly" pattern on the axial view. The biopsy is the common EOR of the butterfly GBM in 64.1–69% of the patients (18,19). In the present study, total resection was performed in 0.6% (1/173) of all patients because surgical resection of a corpus callosum tumor is a challenge to balance between maximum resection for prolonged survival time and a permanent neurological deficit (19). Consequently, tumor infiltration at corpus callosum was not significantly with total resection.

The incidence of multifocal tumors ranged from 11.7% to 12.8%, and patients with multifocal tumors experienced a significantly shorter survival compared with the solitary GBM group (20-22). The success rate of total resection in multiple GBM was 1.2% (2/173) of all patients in the present study, and Patil *et al.* reported that 87.2% of multiple GBM underwent either a biopsy or partial resection. Therefore, residual tumors from non-total resection rapidly progress and were correlated with a poor prognosis (22).

Additionally, tumor volume <30 mL in GBM was the prognostic factor that was significantly associated with total resection. The surgical approach in smaller tumors is more comfortable to manipulate than the larger tumors (11,23). In this study, a large GBM was significantly associated with the degree of brain edema and midline shift that directly interfered with the degree of tumor resection.

According to our knowledge, the present study is the first paper to mention the factors associated with the EOR, which were reported only as potential prognostic factors in GBM. Therefore, a survival analysis of the patients with GBM should be stratified by these factors because EOR may be the confounder. Awad *et al.* reported that EOR alone did not correlate with survival after adjusting for other factors because EOR and preoperative tumor volume significantly interact with each other (11). The stratification, according to the number of tumors or tumor volume and multivariable analysis, is methods to control the confounding effect, which should be the approach in a future survival study of GBM (24,25).

Alternatively, propensity scores are an increasingly

popular method to adjust for confounding in observational studies that cannot conduct the randomized control trial. Before evaluating the association of the EOR and survival of GBM patients, the pretreatment variables associated with the EOR should be adjusted by propensity scores (26,27).

Conclusions

Not all GBMs are amenable to complete surgical resection. Multiple lesions and tumor volume ≥30 mL are the potentially limiting factors. Therefore, the EOR should be controlled from confounding factors by stratification, multivariable analysis, or propensity scores before performing a survival analysis.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm.2020.01.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was performed with the permission of the Ethical Committee of the Faculty of Medicine, Songklanagarind Hospital, Prince of Songkla University (REC 61-293-10-1). Because of the retrospective nature of the research, the informed consent was waived.

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