Effect of the Extent of Resection on Survival Outcome in Glioblastoma: Propensity Score Approach

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Abstract

Objective To evaluate the effectiveness of the extent of resection (EOR) on survival outcome using propensity score-based approaches.

Materials and Methods A retrospective cohort study was performed in patients with newly diagnosed glioblastoma. Propensity score matching (PSM) and propensity score regression adjustment were used in the matched and unmatched dataset, respectively. Therefore, the Kaplan-Meier survival curve and Cox's regression analyses were performed to determine the effect of the EOR on survival outcomes.

Results One hundred and sixty-eight patients were included for analyzes. The total tumor resection in the unmatched dataset was 22.6% of all cases. Using PSM, incomplete tumor resection had an unfavorable survival outcome when compared with total tumor resection (hazard ratio (HR) 2.92, 95% confidence interval [CI] 1.72–4.94). Additionally, biopsy and partial tumor resection were significantly associated with poor prognosis when compared with total tumor resection using propensity score regression adjustment (HR of biopsy 1.89, 95%CI 1.13–3.16 and HR of partial resection 1.89, 95%CI 1.28–2.80).

Conclusions Patients with total tumor resection tend to have a more favorable prognosis than patients with partial tumor resection. The propensity score-based analysis is an alternative approach to evaluate the effect of an intervention that has limitations to perform a randomized controlled trial.

Keywords

- glioblastoma
- extension of resection
- survival analysis
- propensity score

Introduction

Glioblastoma (GBM) is a malignant primary brain tumor that has a poor prognosis. Surgery is the first treatment option for histology-confirmed diagnosis and tumor burden reduction.[1,2] From large retrospective cohort studies, extents of resection (EORs) ranging from 70 to 98% are the independent factor for significantly increased survival time.[1,3–5] Moreover, Brown et al investigated in a systematic review and meta-analysis on the EOR on survival increment in patients with GBM and reported that total resection improves overall and progression-free survival.[6] However, the lack of evidence from randomized clinical trials (RCTs) on the effect of the EOR related to survival advantages. This variable—EOR—has proven to be a limitation to the conduction of RCTs regarding ethical issues and other confounders. Owing to the infiltrative character of this type of tumor, not all GBMs are amenable to total tumor resection.[7,8] From the literature review, multiple GBMs and tumor volume $\geq$ 30 ml have been reported as limitations for complete tumor removal. In

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addition, tumors involving eloquent areas have been reported to be a limitation for total resection because neurological impairments developed after tumor resection.[9]

Because confounding factors are critical problems that need to be addressed before analysis in observational studies attempting to estimate the effect of treatments, propensity score (PS) is one of the methods used for dealing with significantly confounding factors.[10,11] From literature reviews, various techniques of the PS approach, such as matching, stratification, regression adjustment, and inverse probability of treatment weight, were effectively used in numerous studies to compare treated and controlled groups when there were limitations to perform RCT. Agrawal et al used PS-based analysis to evaluate the intracranial pressure monitoring on outcomes in severe traumatic brain injury,[12] while Cepeda et al evaluated the effect of decompressive craniectomy in the postoperative expansion of traumatic intracerebral hemorrhage using PS methods.[13]

Extent of resection is one of the variables that represents a limitation in conducting RCT. Alternatively, PS-based analysis is one of the methods that was used to evaluate the effect of EOR on survival outcomes. Therefore, the aims of the present study were to evaluate the effectiveness of EOR on survival outcomes using PS methods.

Materials and Methods

A retrospective cohort study was performed in the patients who had histologically-confirmed GBM and were newly treated between January 2000 and December 2018 in our institute. Additionally, a part of the study population was obtained from Tunthanathip et al,[9,14] whose study mentioned factors associated with the EOR and genetic factors that could influence prognosis. The exclusion criteria were as follows: 1) unavailable medical record, 2) unavailable neuroimaging for tumor volume calculation, for both the preoperative and postoperative periods, and 3) unavailable update survival status.

In the present study, the EOR was defined according to Vecht et al and Bloch et al.[15,16] Gross total resection was defined as less than 5% of residual tumor, as observed on postoperative neuroimaging. Partial resection was defined as resection of less than 95% of the tumor, as observed on postoperative neuroimaging. Biopsy was defined as an operation for tissue diagnosis only, without attempt of removing the tumor. Additionally, the percentage of resection was assessed by postoperative T1-weighted imaging with contrast.

The follow-up data were collected until June 2019 for survival outcome as update status (death or survival) or cause of death. The follow-up data were mainly collected when patients visited the outpatient clinics. Patients (or caregivers) who did not visit the hospital for appointments were interviewed by phone. Therefore, we also checked death records from the local municipality.

The present study was performed with the permission of the Ethical Committee of the Faculty of Medicine at Songklanagarind Hospital, Prince of Songkla University.

Statistical Analysis

The baseline characteristics included demographic variables, imaging , and therapeutic factors; these were obtained from studies of Tunthanathip et al that reported two variables, multiple GBMs, and tumor volume $\geq$ 30 ml, associated with the EOR.[9,14] We excluded those patients with one or more missing data before estimating the propensity score (PS).

To control selection bias, we used PS methods. We used a logit model with a binary outcome (total resection and non-total resection) to estimate the PS. Therefore, the PSs were calculated and used as a covariate to control for confounding by indication or contraindication in the final model. In detail, two PS-based methods were performed: propensity score matching (PSM) and PS regression adjustment.

Both matched and unmatched datasets as well as baseline clinical characteristics were analyzed using descriptive analysis, presented as proportions and mean $\pm$ standard deviation (SD).

In the PSM, we created a group of treated and controlled patients who were matched by the nearest neighbor matching algorithm with a ratio of 1:1. The effect of EOR on the survival of patients with GBM was analyzed by time-to-event. Survival curves were compared using the log-rank test. Cox regression analyses were performed, and the hazard ratio (HR) with 95% confidence intervals (95% CIs) was determined. In the study of Ahmadipour et al, the HR of biopsy compared with total resection was 2.33 (95%CI 1.77–3.06) for death.[17] Therefore, we calculated a sample size of 26 patients per group at 80% power and with an α level of 0.05, using the Freedman method.[18]

Propensity score regression adjustment was used to run the outcome model of the association between EOR and survival controlled by PS and posttreatment variables from the unmatched dataset. All analyses were conducted using the R version 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria) with the package MatchIt.[19]

Results

Clinical Characteristics

The 173 patients with GBM were obtained from the study by Tunthanathip et al.[9,14], but 5 patients were excluded because of missing variables. Hence, 168 patients were included for analyses, and their baseline characteristics are shown in ►**Table 1**, both unmatched and matched cohorts.

Unmatched Cohort

The unmatched cohort included 168 patients with GBM. The mean age was 51.4 years (SD 15.3), and half of the subjects were male. One-third of the GBMs commonly involved the temporal lobe, frontal lobe, and parietal lobe. Additionally, corpus callosum was found in 11.3% of the patients. The patients were divided by EOR as binary groups. Total tumor resection was observed in 38 patients (22.6%) of the unmatched cohort, whereas the remaining (77.4%) had either biopsy or partial tumor resection.

There were significant differences between total resection and non-total resection groups in several tumors and tumor

Table 1 Baseline characteristic of patients divided by the extent of resection according to full cohort and propensity score-matched cohort

Factor	Full cohort ($N = 168$)			Propensity score-matched cohort ($N = 76$)		
	Total resection n (%)	Non-total resection n (%)	*P*-value	Total resection n (%)	Non-total resection n (%)	*P*-value
Age, year			0.11			0.15
< 50	12 (31.6)	60 (46.2)		12 (31.6)	18 (47.4)	
≥ 50	26 (68.4)	70 (53.8)		26 (68.4)	20 (52.6)	
Gender			0.70			0.81
Male	20 (52.6)	73 (56.2)		20 (52.6)	19 (50.0)	
Female	18 (47.4)	57 (43.8)		18 (47.4)	19 (50.0)	
Preoperative KPS			0.11			0.10
< 80	24 (63.2)	63 (48.5)		24 (63.2)	17 (44.7)	
≥ 80	14 (36.8)	67 (51.5)		14 (36.8)	21 (55.3)	
Frontal tumor			0.33			0.81
No	25 (65.8)	96 (73.8)		25 (65.8)	24 (63.2)	
Yes	13 (34.2)	34 (26.2)		13 (34.2)	14 (36.8)	
Temporal tumor			0.54			0.80
No	26 (68.4)	82 (63.1)		26 (68.4)	27 (71.1)	
Yes	12 (31.6)	48 (36.9)		12 (31.6)	11 (28.9)	
Thalamus/Basal ganglion			0.58*			0.24*
No	38 (100)	125 (96.2)		38 (100)	35 (92.1)	
Yes	0	5 (3.8)		0	3 (7.9)	
Corpus callosum			0.07*			0.35*
No	37 (97.4)	112 (86.2)		37 (97.4)	34 (89.5)	
Yes	1 (2.6)	18 (13.8)		1 (2.6)	4 (10.5)	
Eloquent area†			0.60			0.64
No	17 (44.7)	52 (40.0)		17 (44.7)	19 (50.0)	
Yes	21 (55.3)	78 (60.0)		21 (55.3)	19 (50.0)	
Initial leptomeningeal dissemination			0.96*			1.00*
No	34 (89.5)	116 (89.2)		34 (89.5)	34 (89.5)	
Yes	4 (10.5)	14 (10.8)		4 (10.5)	4 (10.5)	
Number of tumors			0.02*			1.00*
Single	36 (94.7)	102 (78.5)		36 (94.7)	36 (94.7)	
Multiple	2 (5.3)	28 (21.5)		2 (5.3)	2 (5.3)	
Tumor volume-ml			0.003			1.00
< 30	19 (50.0)	32 (24.6)		19 (50.0)	19 (50.0)	
≥ 30	19 (50.0)	98 (75.4)		19 (50.0)	19 (50.0)	
Postoperative KPS			0.66			0.48
< 80	24 (63.2)	77 (59.2)		24 (63.2)	21 (55.3)	
≥ 80	14 (36.8)	53 (40.8)		14 (36.8)	17 (44.7)	
Adjuvant therapy			0.18			0.09
RT alone	21 (55.3)	87 (66.9)		21 (55.3)	28 (73.7)	
RT with TMZ	17 (44.7)	43 (33.1)		17 (44.7)	10 (26.3)	

(*Continued*)

Table 1 (*Continued*)

Factor	Full cohort ($N = 168$)			Propensity score-matched cohort ($N = 76$)		
	Total resection n (%)	Non-total resection n (%)	*P*-value	Total resection n (%)	Non-total resection n (%)	*P*-value
IDH1 mutation			0.83*			1.00*
Wild-type GBM	36 (94.7)	122 (93.8)		36 (94.1)	35 (92.1)	
Mutant GBM	2 (5.3)	8 (6.2)		2 (5.3)	3 (7.9))	
MGMT promoter methylation			0.14*			0.24*
Methylated GBM	0	7 (5.4)		0	3 (7.9)	
Unmethylated GBM	38 (100)	123 (94.6)		38 (100)	35 (92.1)	

Abbreviations: GBM, glioblastoma; IDH1, isocitrate dehydrogenase1; KPS, Karnofsky performance status; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiotherapy; TMZ, temozolomide.
*p-value of Fisher exact test.
†Eloquent area defined tumor involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, dentate nucleus.

volume. In detail, multiple GBMs were frequently observed in the non-total resection group ($p = 0.02$), while tumor volume < 30 ml was commonly found in the total resection group ($p = 0.003$).

Matched Cohort

Patients were equally divided into total resection and non-total resection groups, according to PS. Therefore, 38 patients were assigned to each group. After matching, differences between the two groups regarding several tumors and tumor volume were noticeably absent.

Effect of EOR on Survival Outcome

PSM

The Kaplan-Meier curves based on the EOR after PSM presented in ►**Fig. 1A-B** show overall median survival time of 11.0 months (95%CI 9.29–12.70). According to EOR subgroups, the median survival time of the total resection subgroup was 15 months (95%CI 10.1–19.8), whereas the incomplete resection subgroup had median survival time of 6 months (95%CI 2.6–9.3), as shown in ►**Table 2**. There was a significant difference in prognosis between complete and incomplete

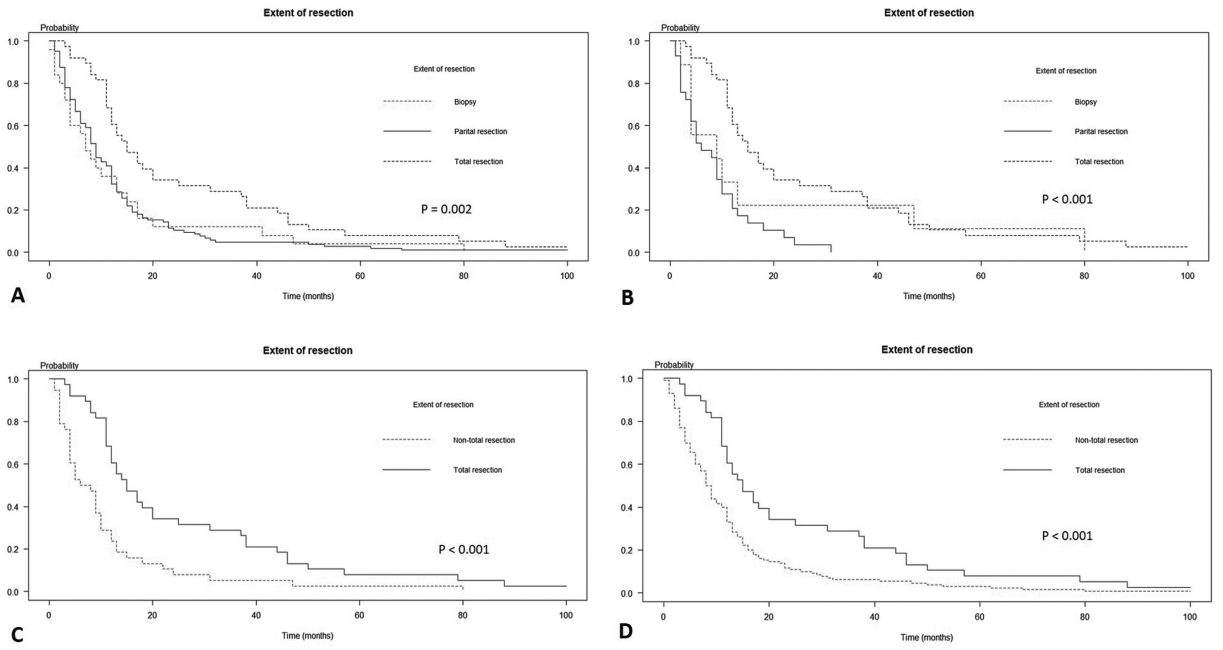

Fig. 1 The Kaplan-Meier curves of survival according to the extent of resection. (A) Bi-classifier of the extent of resection with matched data. (B) The extent of resection with matched data. (C) Bi-classifier of the extent of resection with unmatched data. (D) The extent of resection with unmatched data.

Table 2 Median survival time and survival probability of the extent of resection subgroups

Dataset	The binary outcome of the extent of resection		Extent of resection		
	Total resection (95%CI)	Non-total resection (95%CI)	Total resection (95%CI)	Partial resection (95%CI)	Biopsy (95%CI)
Unmatched dataset					
Median survival time-month	15.0 (10.1–19.8)	8.0 (6.6–9.3)	15.0 (10.1–19.8)	9.0 (7.6–10.3)	7.0 (3.7–10.2)
1-year probability of survival	60.5 (46.8–78.2)	33.0 (25.9–42.2)	60.5 (46.8–78.2)	32.3 (24.5–42.6)	36.0 (21.3–60.7)
2-year probability of survival	34.2 (22.0–53.2)	10.7 (6.5–17.6)	34.2% (22.0–53.2)	10.4 (5.9–18.3)	12.0 (4.1–34.7)
3-year probability of survival	28.9 (17.5–47.6)	6.15 (3.1–12.0)	28.9% (17.5–47.6)	4.7 (2.0–11.2)	12.0 (4.1–34.7)
Matched dataset					
Median survival time-month	15.0 (10.1–19.8)	6.0 (2.6–9.3)	15.0 (10.1–19.8)	6.0 (1.7–10.2)	9.0 (0–23.6)
1-year probability of survival	60.5% (46.8–78.2)	23.6% (13.3–41.9)	60.5% (46.8–78.2)	20.6% (10.1–42.2)	33.3% (13.2–84.0)
2-year probability of survival	34.2% (22.0–53.2)	7.8% (2.6–23.4)	34.2% (22.0–53.2)	3.4% (0.5–2.3)	22.2% (6.5–7.5)
3-year probability of survival	28.9% (17.5–47.6)	5.2% (1.3–20.3)	28.9% (17.5–47.6)	–	22.2% (6.5–7.5)

Abbreviation: 95%CI, 95% confidence interval.

Table 3 Cox regression of the extent of resection on survival outcome according to propensity score methods

Survival outcome	Hazard ratio (95%CI)	*p*-value
Death		
Propensity score matching		
Total resection	Ref	
Partial resection	1.42 (0.68–2.98)	0.34
Biopsy	2.92 (1.72–4.94)	< 0.001
Regression adjustment with the propensity score*		
Total resection	Ref	
Partial resection	1.89 (1.28–2.80)	0.001
Biopsy	1.89 (1.13–3.16)	0.01
Progressive disease		
Propensity score matching		
Total resection	Ref	
Partial resection	0.65 (0.22–1.89)	0.43
Biopsy	0.71 (0.36–1.37)	0.31
Regression adjustment with the propensity score†		
Total resection	Ref	
Partial resection	1.01 (0.62–1.65)	0.07
Biopsy	0.80 (0.41–1.57)	0.52

*Covariates of the model comprised extent of resection (hazard ratio (HR) as shown in table), postoperative Karnofsky performance status (HR 1.044; 95%CI 0.76–1.43), and propensity scores (HR 0.85; 95%CI 0.25–2.88).
†Covariates of the model comprised extent of resection (hazard ratio (HR) as shown in table), postoperative Karnofsky performance status (HR 1.02; 95%CI 0.68–1.52), and propensity scores (HR 2.06; 95%CI 0.44–9.56).

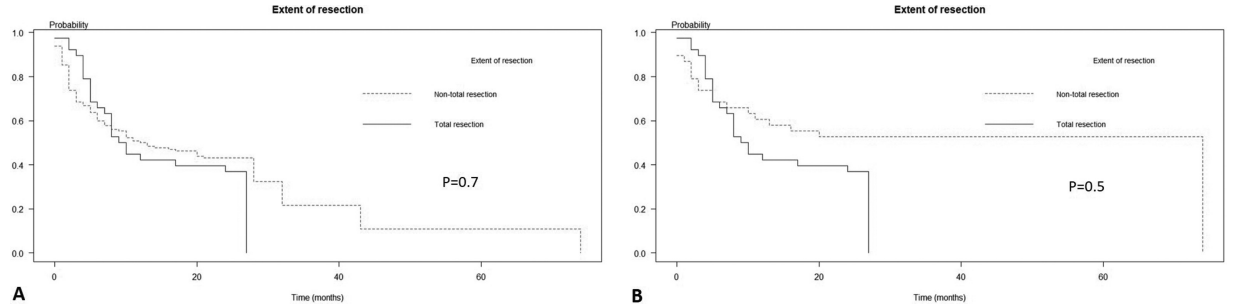

Fig. 2 The Kaplan-Meier curves of progression-free survival according to the extent of resection. (A) Matched data. (B) Unmatched data.

resection subgroups with a log-rank test < 0.001. Using Cox proportional hazard regression analysis, a biopsy had shorter survival time than total tumor resection (HR 2.92, 95%CI 1.72–4.94), and EOR is not associated with progression-free survival, as shown in ►**Table 3** and ►**Fig. 2A-B**.

PS Regression Adjustment

The overall median survival time was 11.0 months (95%CI 9.36–12.63) in the unmatched dataset. The 3-year survival probability of the total resection subgroup was 28.9%, while incomplete resection subgroup had a 3-year survival probability in 5.2%, as shown in ►**Table 2**. By PS regression adjustment, biopsy and partial tumor resection significantly associated with poor prognosis when compared with total tumor resection (HR of biopsy 1.89, 95%CI 1.13–3.16 and HR of partial resection 1.89, 95%CI 1.28–2.80). Additionally, the EOR was not associated with progression-free survival, as summarized in ►**Table 3**.

Discussion

Nowadays, lack of level I evidence exists for comparing the EOR and survival outcome in GBM.[5] Although the effects of the EOR on survival outcomes have been reported in systematic review and meta-analysis, the achievement of an RCT examining EOR in patients with GBM remains unlikely. The PS is the alternative approach to control confounder before analyses of intervention.[20] The patients were equally divided into intervention and control groups that were nearly RCT's assignment in PSM, whereas PSs was a covariate in the model in PS regression adjustment.

After adjustment with PS, total tumor resection significantly increased the survival advantages when compared with non-total resection in both PS methods. Lacroix et al. studied about the degree of resection in 416 patients with GBM and reported that 98% of tumor resection significantly increased survival time,[1] while Stummer et al reported that total tumor resection was associated with longer survival for GBM patients, according to the re-stratifying study of the aminolevulinic acid (ALA) glioma study group.[21,22]

GBM is the infiltrative tumor that has an ill-defined border during tumor resection. Therefore, total resection is not easily performed in all cases. Fluorescence-guided resections with 5-aminolevulinic acid (5-ALA) significantly enhanced rates of total resection compared with conventional microsurgical resection. However, the incremental cost with 5-ALA compared with traditional operation was € 9,021 per QALY gained in economic evaluation. Therefore, fluorescence-guided resection is not the standard treatment, notably a limited-resource setting.[24]

Although the EOR was the independent prognostic factor in the present study, treatment biases to determine the degree of tumor removal have been reported, such as young age, tumor involving eloquent area, preoperative tumor volume, and several tumors. Tunthanathip et al reported that it was hard to achieve total removal in cases of multiple GBMs. Multicentric GBM is one of the subgroups of multiple GBMs in which the centers of the tumors are clearly disconnected from each other, such as in different lobes or bilateral tumors, with no apparent route of dissemination.[25–27] Multi-stage operations need to be performed for total tumor resection in this subgroup.

To our knowledge, the present study is the first paper that demonstrated the effect of the EOR on survival outcomes by PS approaches. The limitations of the present study should be acknowledged. First, for the purpose of PSM, the patients were assigned into total resection and non-total resection groups, based on PS. Nine-two patients were removed from the dataset after matching that deleted patients cause decrease power of the study.[28,29] However, the results after PSM still demonstrate the effect of total tumor resection, which was in. Alternatively, we tried to perform the PS regression adjustment method to preserve the total number of the study population for analyzing the effect of EOR.[30] The concordance of results was observed from both PS approaches. For other limitations, fluorescence-guided resections with 5-ALA was not performed in the present study because it is unavailable in our institute.

Conclusion

Patients with total tumor resection had a statistical tendency of a more favorable prognosis than patients with non-total tumor resection. The PS-based analysis is a useful approach to evaluate the effect of the EOR on survival outcome that has limitations to conduct RCT.

Authors' Contributions

Conception and design: T. T.

Administrative support: T. T., S. M.
Provision of study materials or patients: T. T., S. M.
Collection and assembly of data: T. T., S. M.
Data analysis and interpretation: T. T.
Manuscript writing: All authors
Final approval of manuscript: All authors

Transparency Declaration

Part of the study population was obtained from the studies by Tunthanathip et al.[9,14] However, the present study focused on the effect of the EOR on prognosis.

Conflict of Interests

The authors have no conflict of interests to declare.

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