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Comparison of Survival Outcomes Between Partial Resection and Biopsy for Primary Glioblastoma: A Propensity Score-Matched Study

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■ OBJECTIVES: **Gross total resection for glioblastoma (GBM) has been associated with better prognosis. However, it is not always feasible, and the threshold for the extent of resection required for better prognosis has been controversial. Therefore, we compared the survival and clinical outcomes of patients with GBM who had undergone partial resection (PR) or biopsy.**

■ METHODS: **Of the 110 patients, 32 and 78, who had undergone PR and biopsy, respectively, were enrolled to identify any differences in clinical outcomes. No differences were found in patient demographics between the 2 groups, except for tumor location and mean tumor volume ($P = 0.02$ and $P < 0.01$, respectively). Propensity score matching between the PR and biopsy groups was performed, in which 20 patients each in the PR and biopsy groups were matched.**

■ RESULTS: **The overall survival (OS) and progression-free survival (PFS) did not differ significantly between the PR and biopsy groups ($P = 0.84$ and $P = 0.48$, respectively). After propensity score matching, the differences in OS and PFS between the 2 groups were still not statistically significant ($P = 0.51$ and $P = 0.75$, respectively). The hazard ratios for OS and PFS for the PR group compared with biopsy were 0.98 and 0.73, respectively; however, the difference was not statistically significant ($P = 0.96$ and $P = 0.39$, respectively). The surgical complication rate was greater in the PR group (14 of 32; 43.7%) than in the biopsy group (9 of 78; 11.5%; $P < 0.01$).**

■ CONCLUSIONS: **PR failed to improve survival compared with biopsy for patients with GBM. Moreover, the surgical complication rate in the PR group was greater than that in the biopsy group.**

INTRODUCTION

As reported by Stupp et al.,[1] the consensus treatment for glioblastoma (GBM) is maximal safe resection after concurrent chemoradiation therapy (CCRT) with temozolomide (TMZ) and 6 cycles of adjuvant TMZ chemotherapy.[1] This regimen increases the overall survival (OS) and progression-free survival (PFS) of patients with GBM. However, the median survival has remained only 14 months.[2] Recent evidence has supported an association between a larger extent of resection (EOR) and a better prognosis for these patients.[3-5] This finding is considered an established theory, and efforts to achieve gross total resection (GTR) of the tumor are continuing.

In a recent meta-analysis, Brown et al.[6] reported the beneficial effect of total resection for better OS and PFS. However, debate has continued regarding the threshold level for the EOR. Chaichana et al.[7] reported that an EOR >70% was associated with better OS and PFS in patients with GBM. However, Lacroix et al.[8] reported that an EOR >98% improved the survival of patients with GBM.[8] Finally, another report advocated an "all-or-none approach" in the surgical management of GBM.[9]

However, GTR of GBM is not always feasible. In some cases, partial resection (PR) will be anticipated in the preoperative period,

Key words
- Biopsy
- Glioblastoma
- Partial resection
- Survival

Abbreviations and Acronyms
CCRT: Concurrent chemoradiation therapy
EOR: Extent of resection
GBM: Glioblastoma
GTR: Gross total resection
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
PR: Partial resection
PSM: Propensity score matching
STR: Subtotal resection
TMZ: Temozolomide

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Citation: World Neurosurg. (2019) 121:e858-e866.
https://doi.org/10.1016/j.wneu.2018.09.237

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

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and biopsy is only performed to obtain tumor tissue for histological diagnosis. When a larger portion of residual tumor is anticipated, clinicians must decide between PR and biopsy. However, research on the beneficial effects on survival from PR in GBM compared with biopsy is lacking. Therefore, we investigated the differences in clinical and survival outcomes of GBM after PR and biopsy.

METHODS

Patients

The appropriate ethics committee approved the present study (approval number, 2018-0391), which was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. For this type of study, formal patient consent was not required. Our institutional database was searched for patients aged ≥18 years who had undergone surgery and had a diagnosis of GBM from January 2007 to May 2017. Only patients with a new diagnosis were enrolled. Those who had undergone surgery at other institutions, had secondary GBM, lacked postoperative magnetic resonance imaging (MRI) data, had been lost to follow-up, or had missing information were excluded. Thus, 468 patients with primary GBM were identified. All patient clinical, radiological, and surgical records were obtained and reviewed.

Of the 468 patients with primary GBM, 241 (51.5%) had undergone GTR, 35 (7.5%) had undergone subtotal resection (STR), 39 (8.3%) had undergone PR, and 153 (32.7%) had undergone biopsy. Those patients lost to follow-up, who had undergone GTR or STR, or had missing information were excluded from the analysis. Thus, 32 patients who had undergone PR and 78 patients who had undergone biopsy were enrolled in the present study to evaluate the differences in clinical outcomes.

Imaging Findings

GBM is a diffuse infiltrating tumor; thus, the real extent of the tumor cannot be delineated. Hence, in the present study, the extent of the GBM tumors was defined according to the enhancing lesions on gadolinium-enhanced T1-weighted MRI.[10]

The EOR was defined according to the following criteria. GTR was defined as total tumor removal. STR was defined as <10% of the tumor remaining. PR was defined as >10% of the tumor remaining on the postoperative MRI study. Biopsy was defined as tissue obtained for histopathological examination.[9,11]

The volume of the tumors with spherical geometry was calculated by fitting a rotational ellipsoid defined by the maximum tumor diameters in the 3 available dimensions. The volume of the residual tumor was calculated by subtracting the volumes of the central resection defect from the space defined by the outer borders of the tumor. The volumes of residual tumors with complex shapes were segmented on individual scans, and the individual volumes were summed to determine the total volume. To decrease interobserver variability, 3 certified neurosurgeons examined the MRI scans and repeatedly measured the tumor volumes at different times.

Treatment Strategy and Follow-Up Protocol

Our institutional treatment strategy for patients with GBM remained consistent throughout the study period. At 4 or 5 weeks after surgery, all patients underwent CCRT, with a total dose of 60 Gy in 30 fractions for radiation therapy, with 6 cycles of temozolomide (TMZ; 75 mg/m^2) chemotherapy (cycle 1, 150 mg/m^2 for 5 days, followed by a 23-day pause; cycles 2–6, 200 mg/m^2 for 5 days, with a 23-day pause between each cycle). If a patient's clinical status worsened during adjuvant treatment, we delayed the treatment schedule and provided supportive care. If the clinical status appeared intolerable, we discontinued adjuvant treatment. An initial postoperative MRI scan was taken within 48 hours after surgery. Follow-up clinical examinations and MRI were performed every 3 months thereafter. The severity of postoperative surgical complication was classified using the National Institutes of Health Common Terminology Criteria for Adverse Events.

Statistical Analysis

Group comparisons were performed using Student's t tests for continuous variables and χ^2 and Fisher's exact tests for categorical variables. We also investigated the OS and PFS of the enrolled patients and evaluated the prognostic factors. OS was defined as the interval between the date of the initial diagnosis and the date of death, and PFS was defined as the interval between the date of the initial treatment and the date of tumor progression using the radiological findings read conclusively by our institutional neuroradiologist. OS and PFS were analyzed using Kaplan-Meier survival analysis, and subgroup comparisons were performed using log-rank tests. The prognostic factors for OS and PFS, including age, tumor volume, multiplicity, and EOR, were analyzed using a Cox proportional hazard model. We produced adjusted survival curves for the PR and biopsy groups using the proportional hazard model.

We also performed propensity score matching (PSM), in which we matched patients in the PR group with those in the biopsy group using the propensity scores to decrease the potential bias and make the 2 groups more comparable. The propensity score is the estimated probability of receiving 1 treatment compared with another treatment. To estimate the propensity score, a logistic regression model was used, with age, sex, tumor location, multiplicity, tumor volume, postoperative CCRT, and adjuvant TMZ therapy as covariates. PSM was performed using a 1-to-1 nearest neighbor matching with replacement and a caliper size of 0.1 standard deviation (R Library; MatchIT; R Foundation, Vienna, Austria). Balances in the distribution of baseline covariates were evaluated by calculating the absolute standardized differences of the covariates between the 2 groups after matching.

All statistical analyses, except for PSM, were conducted using PASW Statistics for Windows, version 18.0 (IBM Corp., Armonk, New York, USA). PSM was conducted using R, version 3.3.1 (available at: www.r-project.org). P values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 110 patients, 32 and 78 were in the PR and biopsy groups, respectively. Of the patients, 59.4% and 40.6% in the PR group and 62.8% and 35.9% in the biopsy group were men and women, respectively. The median age was 57 years (range, 26–73) in the PR group and 60.5 years (range, 24–83) in the biopsy group. The

Table 1. Baseline Demographic Findings of Enrolled Patients

Variable	PR Group (n = 32)	Biopsy Group (n = 78)	P Value
Sex			0.77
Male	19 (59.4)	49 (62.8)	
Female	13 (40.6)	28 (35.9)	
Age (years)			0.43
Mean	56.03	58.5	
Median	57	60.5	
Range	26–73	24–83	
Presenting symptoms			0.62
Headache	12 (37.5)	26 (33.3)	
Motor weakness	3 (9.4)	14 (17.9)	
Language dysfunction	7 (21.9)	9 (11.5)	
Seizure	4 (12.5)	7 (7.7)	
Cognitive impairment	3 (9.4)	6 (6.4)	
Memory impairment	1 (3.1)	7 (9.0)	
Visual disturbance	0 (0)	3 (3.8)	
Ataxia	0 (0)	1 (1.3)	
Dizziness	1 (3.1)	4 (5.1)	
Mental changes	1 (3.1)	0 (0)	
Incidental findings	0 (0)	1 (1.3)	
Tumor location			0.02*
Frontal	13 (40.6)	32 (41)	
Parietal	9 (28.1)	8 (10.3)	
Temporal	4 (12.5)	2 (2.6)	
Occipital	1 (3.1)	14 (17.9)	
Insula	5 (15.6)	8 (10.3)	
Deep location and other†	0 (0)	14 (17.9)	
Multiplicity			0.19
Solitary	23 (71.9)	66 (84.6)	
Multifocal	9 (28.1)	12 (15.4)	
Tumor volume (cm^3)			<0.01*
Mean	42.8	16.8	
Median	37.0	13.3	
Range	2.9–128.2	0.53–54.1	
MGMT promotor methylation			0.65
Nonmethylated	6/9 (66.7)	5/10 (50)	
Methylated	3/9 (33.3)	5/10 (50)	
Follow-up period (months)			0.25
Mean	19.7	15.8	
Range	2.5–107.2	1–107.5	

Data presented as n (%).
*Statistically significant.
†Basal ganglia, thalamus, and cerebellum.

most common presenting symptom in both the PR and biopsy groups was headache (37.5% and 33.3%, respectively). Age, sex, and presenting symptoms did not differ significantly between the PR and biopsy groups ($P = 0.77$, $P = 0.43$, and $P =$ and 0.62, respectively).

The most common tumor location in the PR and biopsy groups both was the frontal lobe (40.6% and 41%, respectively). A deep location and other location tumors (including tumors in the thalamus, hypothalamus, basal ganglia, lateral ventricle, midbrain, and cerebellum) occurred in 14 of the biopsy group (17.9%). More tumors were located in deeper areas in the biopsy group than in the PR group (14 vs. 0; $P = 0.02$). Multifocal lesions were identified in 28.1% and 15.4% of the patients in the PR and biopsy groups, respectively. However, the difference was not statistically significant between the 2 groups ($P = 0.19$). The median tumor volume was 37.0 cm^3 (range, 2.9–128.2) in the PR group and 13.3 cm^3 (range, 0.53–54.1) in the biopsy group. The difference in tumor volumes between the groups was statistically significant ($P < 0.01$).

MGMT (O^6-methylguanine-DNA methyltransferase) promoter methylation was examined in 9 samples in the PR group, of which 6 (66.7%) were unmethylated and 3 (33.3%) were methylated. Ten samples in the biopsy group were examined, of which 5 (50%) were unmethylated and 5 (50%) were methylated ($P = 0.65$).

The mean follow-up period was 19.7 months (range, 2.5–107.2) in the PR group and 14.8 months (range, 1–107.5) in the biopsy group. The baseline demographic findings of the enrolled patients are listed in Table 1.

Reasons for PR and Biopsy in Patients with GBM

In most cases, 2 or 3 reasons were given for PR or biopsy for the patients with GBM. We examined the most common reasons for patients to undergo PR or biopsy. The most common reason for PR was the presence of a deep-seated lesion ($n = 11$; 34.4%), followed by a tumor located in eloquent brain areas ($n = 8$; 25%; Figure 1C and D), midline-crossing (butterfly) lesion ($n = 6$; 18.8%; Figure 1A and B), multifocal lesion ($n = 3$; 9.4%), tumor related to the critical neurovascular structure ($n = 1$; 3.1%), and intraoperative accident ($n = 1$; 3.1%). The most common reason for performing biopsy was the presence of a deep-seated lesion ($n = 23$; 29.5%;

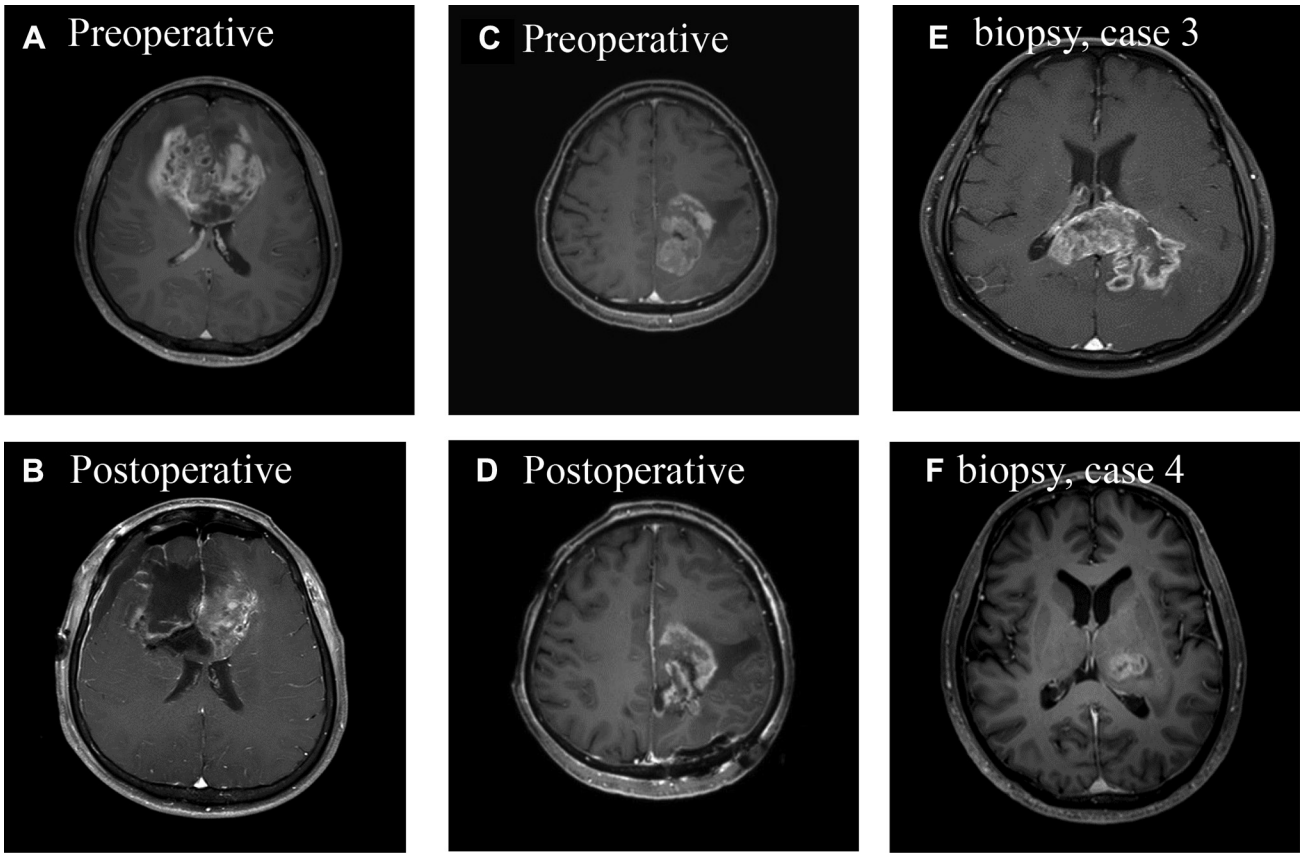


Figure 1. Representative cases of partial resection and biopsy for glioblastoma multiforme. Preoperative and postoperative gadolinium-enhancing T1-weighted magnetic resonance images of patients with glioblastoma multiforme who had undergone partial resection. Case 1: (**A**) a midline-crossing tumor involving the bilateral frontal lobes. (**B**) Residual tumor remained in the left frontal lobe after right frontal partial lobectomy and partial tumor removal. Case 2: (**C**) a tumor involving the left posterior frontal and parietal lobes. (**D**) Remaining tumor on the left posterior frontal lobe—left eloquent motor area after partial tumor removal from the left parietal lobe. (**E**) Case 3: a biopsy performed for a midline-crossing lesion in the parieto-occipital area. (**F**) Case 4: a biopsy performed for a deep-seated lesion that was expected to have a high surgical risk.

Figure 1F), followed by a tumor located in eloquent brain areas (n = 15; 19.2%), butterfly lesion (n = 13; 16.7%; Figure 1E), multifocal lesion (n = 10; 12.8%), combined leptomeningeal or ependymal seeding (n = 5; 6.4%), patient refusal of resection (n = 5; 6.4%), lesion too small (n = 4; 5.1%), and poor general condition (n = 1; 1.3%). The 3 most common reasons for performing PR and biopsy were identical. Representative cases of PR and biopsy for GBM are shown in Figure 1.

Treatment Outcomes

In the biopsy group, 67 patients (85.9%) underwent frame-assisted stereotactic biopsy, 4 (5.1%) underwent endoscopic biopsy, and 7 (9.0%) underwent open biopsy. In the PR group, the mean residual tumor volume was 43.9% (range, 10.8%–79.8%).

Surgical complications occurred in 14 of 32 patients (43.7%) in the PR group and 9 of 78 patients (11.5%) in the biopsy group ($P < 0.01$). Postoperative intracerebral hemorrhage was the most common complication in the PR and biopsy groups both (78.6% and 88.9%, respectively; $P < 0.01$). More than one half of the surgical complications in the PR group required medical or surgical treatment (Common Terminology Criteria for Adverse Events grade $\geq$II). However, only 22.2% of surgical complications in the biopsy group required intervention. One death from postoperative intracerebral hemorrhage occurred in the PR group. No patient died of surgical complications in the biopsy group.

In our institute, we administered a consistent adjuvant treatment regimen to all patients with GBM. The mean duration from surgery to the CCRT start date was 35.8 $\pm$ 14.1 days in the PR group and 25.4 $\pm$ 7 days in the biopsy group ($P < 0.01$). No difference was found in the rate of adjuvant treatment completion between the PR and biopsy groups (CCRT completion, $P = 0.50$; adjuvant TMZ completion, $P = 0.88$). Additional treatment, including salvage surgery, stereotactic radiosurgery, additional TMZ, bevacizumab therapy, and the administration of other chemotherapy agents for progressive disease, did not differ statistically between the 2 groups.

Table 2. Treatment Outcomes for Partial Resection and Biopsy Groups

Variable	PR (n = 32)	Biopsy (n = 78)	P Value
Surgical modality			NA
Stereotactic biopsy	NA	67 (85.9)	
Open biopsy	NA	7 (9)	
Endoscopic biopsy	NA	4 (5.1)	
Residual volume (%)			
Mean	43.9	NA	
Median	39.5	NA	
Range	10.8–79.8	NA	
Surgical complications			<0.01*
Total	14 (43.7)	9 (11.5)	
Brain swelling	1 (7.1)	1 (11.1)	
ICH	11 (78.63)	8 (88.9)	
EDH	1 (7.1)	0 (0)	
Cerebral infarction	1 (7.1)	0 (0)	
CTCAE grade			
I	6 (42.8)	7 (77.8)	
II	5 (35.7)	1 (11.1)	
III	2 (14.2)	1 (11.1)	
IV	0 (0)	0 (0)	
V	1 (7.1)	0 (0)	
Standard adjuvant treatment			
CCRT with TMZ			0.50
Completion	30 (93.8)	68 (87.2)	
Noncompletion	2 (6.3)	10 (12.8)	
Adjuvant 6-cycle TMZ			0.88
Completion	15 (46.9)	34 (43.6)	
Noncompletion	17 (53.1)	44 (54.4)	
Progression	29 (90.6)	54 (69.2)	
Additional treatment			
Salvage surgery	3 (9.4)	4 (5.1)	0.41
Chemotherapy			
Additional TMZ	6 (18.8)	16 (20.5)	>0.99
Bevacizumab	6 (18.8)	11 (14.1)	0.57
Other agent	8 (25)	2 (2.6)	
SRS	3 (9.4)	4 (5.1)	0.41
Surgery date to CCRT date (days)	35.8 ± 14.1	25.4 ± 7.0	<0.01*
Death	26 (81.3)	56 (71.8)	

Data presented as n (%) or mean ± standard deviation.
PR, partial resection; NA, not applicable; ICH, intracerebral hemorrhage; EDH, epidural hematoma; CTCAE, Common Terminology Criteria for Adverse Events; CCRT, concurrent chemoradiation therapy; TMZ, temozolomide; SRS, stereotactic radiosurgery.
*These results are statistically significant.

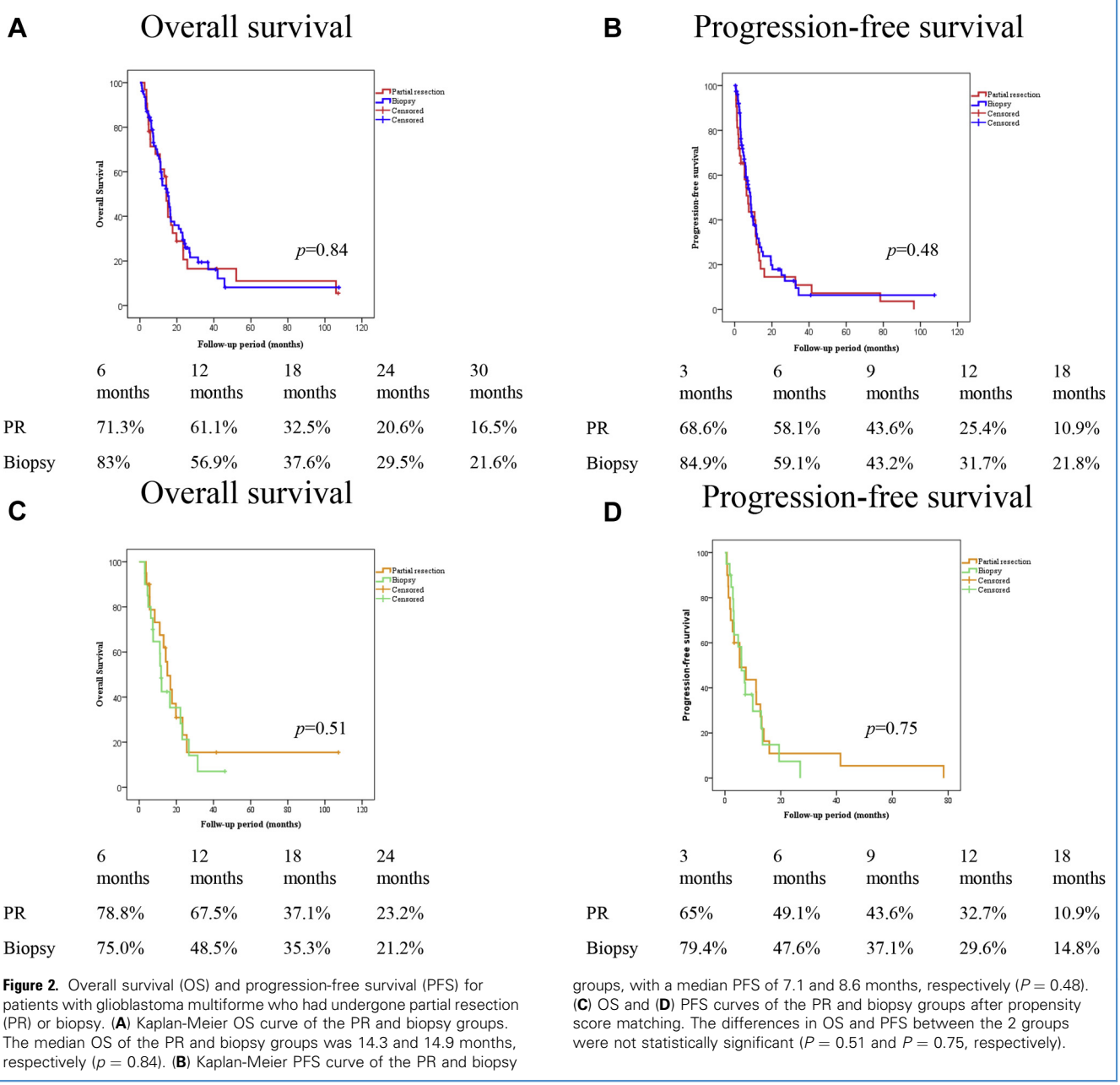
Tumor progression occurred in 29 patients (90.6%) in the PR group and 54 patients (69.2%) in the biopsy group during the follow-up period. In the PR and biopsy groups, 26 (81.3%) and 56 (71.8%) patients, respectively, died during the follow-up period. The detailed treatment outcomes of the PR and biopsy groups are listed in Table 2.

Survival Analysis

The median OS of the PR and biopsy groups was 14.3 months (range, 2.5–107.2) and 14.9 months (range, 1.1–27), respectively. The difference in OS between the PR and biopsy groups was not statistically significant ($P = 0.84$). The 6-, 12-, 18-, 24-, and 30-month OS of the PR group was 71.3%, 61.1%, 32.5%, 20.6%, and 16.5%, respectively. The corresponding results in the biopsy group were 83%, 56.9%, 37.6%, 29.5%, and 21.6%. The median PFS of the PR and biopsy groups were 7.1 months (range, 0.67–96.5) and 8.6 months (range, 0.5–20), respectively. The difference in PFS between the groups was not statistically significant ($P = 0.48$). The 3-, 6-, 9-, 12-, and 18-month PFS for the PR group was 68.6%, 58.1%, 43.6%, 25.4%, and 10.9%, respectively. The corresponding results in the biopsy group were 84.9%, 59.1%, 43.2%, 31.7%, and 21.8%, respectively. The results of Kaplan-Meier survival analysis of the enrolled patients are shown in Figure 2A and B.

Propensity Score Matching

We performed PSM between the PR and biopsy groups by matching 20 patients in the PR group with 20 patients in the biopsy group using the propensity score to decrease the potential bias and make the groups more comparable. To estimate the propensity score, a logistic regression model was used, with age, sex, tumor location, multiplicity, tumor volume, postoperative CCRT, and adjuvant TMZ therapy as covariates. The difference between the matched patients in the PR and biopsy groups was statistically insignificant, and the standardized mean difference was <0.2. After PSM, the median OS of the PR and biopsy groups was 14.3 and 11.2 months, respectively ($P = 0.51$). The PFS duration was 5.2 and 5.9 months for the PR and biopsy groups ($P = 0.75$). Compared with biopsy, the hazard ratio for OS and PFS for the PR group was 0.98 ($P = 0.96$) and 0.73 ($P = 0.39$),



	6 months	12 months	18 months	24 months	30 months
PR	71.3%	61.1%	32.5%	20.6%	16.5%
Biopsy	83%	56.9%	37.6%	29.5%	21.6%

	3 months	6 months	9 months	12 months	18 months
PR	68.6%	58.1%	43.6%	25.4%	10.9%
Biopsy	84.9%	59.1%	43.2%	31.7%	21.8%

	6 months	12 months	18 months	24 months
PR	78.8%	67.5%	37.1%	23.2%
Biopsy	75.0%	48.5%	35.3%	21.2%

	3 months	6 months	9 months	12 months	18 months
PR	65%	49.1%	43.6%	32.7%	10.9%
Biopsy	79.4%	47.6%	37.1%	29.6%	14.8%

Figure 2. Overall survival (OS) and progression-free survival (PFS) for patients with glioblastoma multiforme who had undergone partial resection (PR) or biopsy. (**A**) Kaplan-Meier OS curve of the PR and biopsy groups. The median OS of the PR and biopsy groups was 14.3 and 14.9 months, respectively ($p = 0.84$). (**B**) Kaplan-Meier PFS curve of the PR and biopsy groups, with a median PFS of 7.1 and 8.6 months, respectively ($P = 0.48$). (**C**) OS and (**D**) PFS curves of the PR and biopsy groups after propensity score matching. The differences in OS and PFS between the 2 groups were not statistically significant ($P = 0.51$ and $P = 0.75$, respectively).

respectively. After PSM, no statistically significant differences were found in OS or PFS between the 2 groups; the hazard ratios were also not significantly different. The characteristics of the matched patients and the hazard ratios for OS and PFS of PR to biopsy are listed in **Table 3**; the survival curves are shown in **Figure 2C** and **D**.

DISCUSSION

GBM is the most common primary malignant brain neoplasm,[12] comprising 15% of all intracranial neoplasms and 60%–75% of astrocytic tumors.[13] Numerous attempts have been made to improve the prognosis of patients with GBM. However, the prognosis of patients with GBM has remained poor, with a 5-year survival rate of <5%.[14]

Threshold of EOR

The effect of the EOR on survival has been a topic of interest. Most neuro-oncologists have agreed that maximal resection of a tumor provides the best chance for prolonged survival. Several reports support this finding.[4,6,15,16] GTR or near total resection of the tumor is the best surgical strategy for GBM surgery. However, the

Table 3. Propensity Score Matching Between Partial Resection and Biopsy Groups and Hazard Ratio for Overall Survival and Progression-Free Survival for Partial Resection Compared with Biopsy

Variable	PR ($n = 20$)	Biopsy ($n = 20$)	*P* Value	SMD
Covariate				
Mean age (years)	57.4	58.6	0.70	0.12*
Sex (male vs. female)	1.5	1.7	>0.99	0.103*
Multiplicity (%)	25	25	>0.99	<0.01*
Mean tumor volume (cm^3)	27.3	26.3	0.84	0.07*
Completion rate of adjuvant treatment (%)	75	80	>0.99	<0.01*
Outcome				NA
Median OS (months)	14.3	11.2	0.51	
HR	0.98		0.96	
Median PFS (months)	5.2	5.9	0.75	
HR	0.73		0.39	
Postoperative complication rate (%)	30	10	0.24	

PR, partial resection; SMD, standardized mean difference; NA, not applicable; OS, overall survival; HR, hazard ratio; PFS, progression-free survival.
*Statistically significant.

threshold of EOR for survival has not yet been established. Lacroix et al.[8] reported that an EOR >98% could improve the survival of patients with GBM, supporting the "all-or-none" surgical policy for GBM.[9] However, Sanai et al.[17] reported stepwise improvement in survival with an EOR ranging from 95% to 100% and EORs >78% showing a survival advantage.[17] In a recent report, an EOR >70% was associated with better OS and PFS in patients with GBM.[7] Therefore, the threshold of EOR has continued to be debated.

Surgical Decision Making Between PR and Biopsy

Maximal resection offers a chance for prolonged survival for patients with GBM. In clinical practice, many patients have GBM for whom GTR and near-total resection are infeasible. Sometimes, a large residual tumor is anticipated for various reasons or severe postoperative neurological deficits after tumor resection are expected. In such situations, surgical decisions are required to choose between PR and biopsy.

We investigated the reasons for performing PR versus biopsy in patients with GBM. When choosing a surgical method, several factors should be considered, including tumor size, tumor location, tumor extent, adjacent neurovascular structures, and the preoperative general health of the patient. The common reasons for performing PR and biopsy were similar, with the most frequent reason in both groups the presence of a deep-seated lesion, followed by an eloquent brain area location and the presence of butterfly lesions.

A comparison of baseline characteristics between the PR and biopsy groups revealed significant differences in tumor location and tumor volume. When the tumor was located in deep cerebral nuclei such as the thalamus, hypothalamus, or basal ganglia, clinicians preferred stereotactic frame-assisted biopsy. The mean tumor volume was larger in the PR group than in the biopsy group (42.8 cm^3 vs. 16.8 cm^3). When a large tumor shows a mass effect in the imaging study or the patient has complained of increased intracranial pressure, we should consider PR of the tumor to decrease the mass effect.

Postoperative Complications of PR and Biopsy

Aggressive surgical resection of malignant brain tumors carries an increased risk of surgical complications. The most common direct surgical complications are iatrogenic stroke and postoperative hemorrhage and/or hematoma.[18] Additionally, when residual tumor remains (in our study, the mean residual tumor volume was 43.9%), postoperative brain edema or swelling and intratumoral hemorrhage can occur, known as "wounded glioma syndrome."[19] In an early report from Ciric et al.,[20] the complication rate of PR was 40%. In contrast, when GTR or near total resection was performed for malignant astrocytoma, the complication rate was 3%.[20] In our study, the postoperative complication rate was greater in the PR group than in the biopsy group.

When the tumor volume is large or a patient presents with increased intracranial pressure symptoms; however, total resection is not feasible, and PR should be considered an alternative surgical modality. When PR is anticipated, clinicians should always be aware of the possibility of postoperative surgical complications. The postoperative complication rate in the PR group was significantly greater than that in the biopsy group in our study, and ~10% of patients received emergency surgery. Moreover, PR and its subsequent surgical complications could lead to a delay of adjuvant CCRT and TMZ chemotherapy compared with biopsy (surgery date to CCRT start date: mean, 35.8 days vs. 25.4 days; $P < 0.01$ in our study).

Prognosis of PR and Biopsy

Direct comparisons of the prognosis between PR and biopsy for GBM are lacking. Salvati et al.[21] reported better OS and PFS after PR for GBM than after biopsy (OS, 8.5 vs. 6.7 months; PFS, 7.3 vs. 5.5 months). However, that study enrolled a small number of patients and did not directly compare PR and biopsy.[21] Kreth et al.[22] reported that incomplete resection of GBM did not lead to better OS or PFS compared with biopsy, concluding that the role of incomplete resection is equivocal. However, their definition of incomplete resection as any contrast enhancement on postoperative MRI was ambiguous. An international consensus is lacking regarding the definitions of STR and PR. A recent large meta-analysis did not include the definitions for GTR, STR, and PR.[6] We followed the definitions of STR and PR used in previous well-designed studies; thus, we defined PR as an EOR of <90%.[4,21] Orringer et al.[23] reported that a 90% EOR was associated with better outcome in patients with GBM compared with an EOR of <90%, supporting our definition of PR. Not only have the survival benefits from PR or STR been ambiguous, but no clear evidence regarding the beneficial

effects of PR is available. Therefore, we designed the present retrospective study to evaluate the beneficial effect of PR in patients with GBM.

In our study, no significant differences were found in OS and PFS between the PR and biopsy groups (OS, 14.3 vs. 14.9 months; $P = 0.84$; PFS, 7.1 vs. 8.6 months; $P = 0.48$). Additionally, we performed PSM between the PR and biopsy groups to match 20 patients in the PR group with 20 patients in the biopsy group using the propensity score to decrease the potential bias and make the 2 groups more comparable. In the matched group, the OS and PFS did not differ significantly ($P = 0.51$ and $P = 0.75$, respectively). The hazard ratios for OS and PFS of PR to biopsy also failed to show any statistical significance ($P = 0.96$ and $P = 0.39$, respectively). Therefore, PR did not show an OS or PFS benefit compared with biopsy in our study. Although our results should be interpreted cautiously, PR did not show a survival benefit and did not delay progression. In addition, our results showed that the treatment had an inherently high risk of surgical complications. When the tumor volume is equivocal, the patient is neurologically stable, and a large residual tumor is anticipated, biopsy to establish the histological diagnosis after early CCRT and TMZ chemotherapy might be a good treatment option.

Study Limitations

The present retrospective study had inherent limitations. Data indicative of the quality of life and Karnofsky performance scale scores of the enrolled patients were not fully ascertainable; thus, we could not investigate these factors in the PR and biopsy groups. These are essential factors for surgical decision making. Furthermore, although 3 certified neurosurgeons repeatedly measured the tumor volumes, the present study did not use computerized volumetric analysis of the tumor, which might be a more accurate method of analyzing tumor size. We instead followed the Response Assessment in Neuro-Oncology criteria (or MacDonald criteria). Hence, the contrast-enhancing volume was used, and the T2-weighted MRI/fluid attenuation inversion recovery components of the tumor were ignored. The new Response Assessment in Neuro-Oncology criteria include these components because GBM is 1 subtype of malignant glioma with diffuse infiltrating characteristics. Thus, the contrast-enhancing tumor volume might underestimate the full extent of the tumor.[24]

The tumors assessed in the present study did not undergo routine examination of molecular markers and genotypes that affect prognosis, such as *MGMT* promoter methylation, *IDH1* (isocitrate dehydrogenase 1) mutations, and *TP53* mutations.[25] Additionally, although we used a consistent treatment strategy, not all the patients in the present study completed CCRT with TMZ and adjuvant 6-cycle TMZ chemotherapy. These patients were poor candidates for adjuvant therapy. Moreover, a small number of patients refused adjuvant therapy. Our study's findings might have been be altered if all patients had received uniform treatment.

CONCLUSION

No curative treatment is available for GBM, and efforts to improve survival of patients with GBM continue. The EOR is the most important treatment factor affecting the prognosis of patients GBM. However, in many situations, total resection is impossible. PR of GBM failed to improve survival compared with biopsy in our study. Moreover, PR resulted in a greater surgical complication rate compared with biopsy. When a tumor does not require mass decompression and a large residual lesion is anticipated, biopsy after CCRT and chemotherapy might be a better treatment option for certain patients. When PR is planned, clinicians should consider the high rate of postoperative complications. Ultimately, larger prospective studies are necessary to confirm the role of aggressive surgery in specific situations.

ACKNOWLEDGMENTS

We are indebted to Seunghee Baek, a statistician in our institute, who contributed statistical analysis and assisted in the writing of the "Methods" section of the present report.

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Received 6 June 2018; accepted 29 September 2018

Citation: World Neurosurg. (2019) 121:e858-e866.
https://doi.org/10.1016/j.wneu.2018.09.237

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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