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ORIGINAL ARTICLE

Optimal extent of resection for glioblastoma according to site, extension, and size: a population-based study in the temozolomide era

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Abstract
The effect of the extent of resection (EOR) on prognosis in glioblastoma may differ depending on various conditions. We evaluated the prognostic impact of the EOR for glioblastoma according to the tumor site, extension, and size. Data from glioblastoma patients who underwent gross total resection (GTR), subtotal resection (STR), or open biopsy between 2005 and 2014 were retrieved from the Surveillance, Epidemiology, and End Results database. Univariate and multivariate analyses for overall survival (OS) were performed. Between 2005–2009 and 2010–2014, the proportion of GTR and STR performed increased from 41.4 to 42.3% and 33.0 to 37.1%, respectively. EOR only affected OS in the 3 years after diagnosis. Median survival in the GTR ($n = 4155$), STR ($n = 3498$), and open biopsy ($n = 2258$) groups was 17, 13, and 13 months, respectively ($p < .001$). STR showed no significant difference in OS from open biopsy ($p = .33$). GTR increased OS for midline-crossing tumors. Although STR was more frequently performed than GTR for tumors ≥ 6 cm in size, GTR significantly increased the OS rate relative to STR for tumors 6–8 cm in size ($p = .001$). For tumors ≥ 8 cm, STR was comparable to GTR ($p = .61$) and superior to open biopsy ($p = .05$). GTR needs to be performed more frequently for glioblastoma measuring ≥ 6 cm or that have crossed the midline to increase OS. STR was marginally superior to open biopsy when the tumor was ≥ 8 cm.

Keywords Open biopsy · Extent of resection · Glioblastoma · Gross total resection · SEER database · Subtotal resection

Introduction

Glioblastoma is the most common primary malignant tumor with a median survival of approximately 14 months [1]. The current standard of care is a maximal safe resection followed by a combination of radiotherapy and temozolomide [1–3]. Although radiotherapy is performed as a local treatment, surgical resection is an important step because the prognosis for radiotherapy alone is inferior to that of surgery and radiotherapy [4, 5].

Even though many studies have shown that the extent of resection (EOR) is a significant prognostic factor, gross total resection (GTR) is not always possible due to extensive tumor infiltration, and tumor involvement in eloquent or critical areas [6–10]. Therefore, a significant number of glioblastoma patients have to undergo subtotal resection (STR) or open biopsy [11, 12]. However, the precise grounds for performing STR remain obscure [13].

Until now, quantitative analyses of the rate and survival impact of the EOR have rarely been conducted in population-based studies. One study using the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that elderly patients may have a survival benefit from GTR

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although the proportion of GTRs performed decreases in old age [14]. Other such studies may encourage the performance of GTRs for tumors in specific situations for which GTR has a significant survival benefit. These analyses would also be helpful in estimating a more accurate survival rate in each situation according to the surgery type.

To increase the rationality of decision making regarding the surgical treatment of glioblastoma, we analyzed the characteristics of patients who underwent surgical treatment (GTR, STR, or open biopsy) and their survival rates in variable subgroups using the modern SEER database from 2005 to 2014.

Materials and methods

Study population

This study is a population-based retrospective cohort study using the SEER 18 registry. SEER database is an authoritative source of information on cancer incidence and survival in the USA supported by National Cancer Institute (NIH). According to NIH, all 50 states in the USA have laws requiring newly diagnosed cancers to be reported to a central registry. Currently, SEER covers approximately 34.6% of the US population. Cancer patient data generated by physicians or surgeons are collected from hospitals, laboratories, clinics, and death certificates. Highly qualified cancer registrars of SEER program collect and consolidate data on cancers diagnosed and treated within hospitals.

Data of patients with pathologically confirmed newly diagnosed glioblastoma (ICDO-3, 9440/3, glioblastoma, NOS) during the period when temozolomide was used (from 2005 to 2014) were retrieved. Among them, patients who were aged ≥ 20 years old at the time of diagnosis; who did not have any other primary tumor; underwent GTR (surgery code of 30 and 55), STR (surgery code of 21 and 40), or open biopsy (surgery code of 20); underwent postoperative external-beam radiotherapy and chemotherapy; and had information available concerning tumor size were included in this study. Patients who did not have information regarding follow-up time were excluded from the study. Since the SEER data consists of anonymized data, this study was exempt from review by an institutional review board. For this type of study, formal consent was not required.

Classification of open biopsy and STR in the surgery data field of the SEER data was registered by the SEER registrars based on information available at each hospital, and no information was available on the proportion of tumor remaining after open biopsy or STR in the SEER database. Since the distinction between open biopsy and STR was not based on quantitative evaluation criteria, the surgical classification may be ambiguous in some cases. GTR was defined as a resection that does not have any enhancing lesions remaining on the postoperative magnetic resonance imaging (MRI) [14].

According to correspondence with the SEER Data Quality Team, the cancer registrar recorded the tumor size and site, and classified the extension using the information available for each case, and the SEER data do not record the source of the information, such as T1-weighted or T2-weighted magnetic resonance images.

Statistical analysis

The patient characteristics in the treatment groups were compared using Pearson's chi-square test for categorical variables and one-way analysis of variance (ANOVA) with post-hoc Tukey Honestly Significant Difference (HSD) for continuous variables.

Overall survival (OS) rates according to surgery type were calculated using the Kaplan–Meier method, and pairwise comparison using a log-rank test adjusted using the Benjamini–Hochberg (BH) method was performed.

Univariate analyses of OS were performed by using a two-sided log-rank test. Variables which were potentially prognostic with a p value less than 0.2 in the univariate analysis, or variables which were significantly different between the surgery groups (open biopsy vs STR or STR vs GTR) with a p value less than 0.2 were incorporated in a Cox regression multivariate analysis. A sensitivity analysis was performed on the hazard ratio of the surgery types by calculating the E value [15, 16]. A large E value implies that the evidence for causality between the corresponding factor and the outcome is reasonably strong, because substantial unmeasured confounds would need to be incorporated to the analysis to reduce the observed association to null. Statistical analyses were carried out using the R software (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria) with R packages, "survival" and "survminer."

Results

Extent of resection and tumor size

The total number of patients was 9911. The number of patients who underwent GTR, STR, and open biopsy was 4155 (41.9%), 3498 (35.3%), and 2258 (22.8%), respectively (Fig. 1). A total of 7623 (76.9%) patients died during follow-up. The median follow-up was 12 months.

A comparison of patient characteristics between the surgery types is summarized in Table 1. The proportion of open biopsy decreased from 25.6% (1106/4317) to 20.6% (1152/5594) between the two diagnostic periods of 2005–2009 and 2010–2014. In contrast, GTR and STR increased from 41.4% (1788/4317) to 42.3%

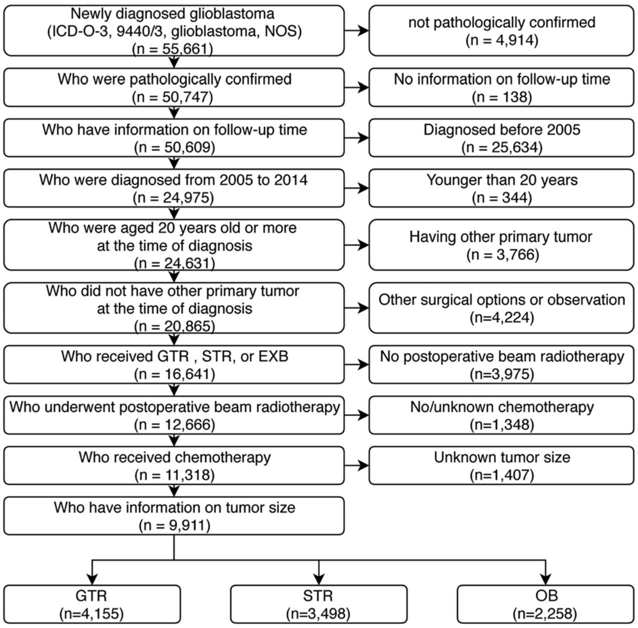


Fig. 1 Flow diagram of patients entered into the study. GTR, gross total resection; STR, subtotal resection; OB, open biopsy

(2367/5594) and from 33.0% (1423/4317) to 37.1% (2075/5594), respectively, indicating that more active surgical resections were attempted over time with recent advancements in surgical techniques.

Tumor size and the proportion of STR to GTR or open biopsy showed a positive correlation ($p < .001$ for GTR vs STR and $p < .001$ for STR vs open biopsy) (Fig. 2). When the tumor size exceeded 6 cm, the STR rate was higher than that of GTR. Although the difference in tumor size was statistically significant between the surgery types, the mean differences between the surgery groups were less than 1 cm (4.5, 4.9, and 4.5 cm in the GTR, STR, and open biopsy groups, respectively), suggesting that tumor size was a considerable but not only factor in determining the type of surgery. Other factors such as tumor extension or tumor location might have affected the resection feasibility.

In a subgroup analysis according to the tumor extension, a statistically significant difference in tumor size between the surgery groups was only observed in tumors confined to a single cerebral hemisphere (one-way ANOVA with Tukey HSD test, $p < .001$ for GTR vs STR, $p < .001$ for STR vs open biopsy, and $p = 0.96$ for STR vs open biopsy). In the case of tumors confined to a cerebral hemisphere, STR was performed more often than GTR for a tumor size of ≥ 7 cm, whereas STR was always performed more frequently than GTR for tumors that crossed the midline or for supratentorial tumors that extended infratentorially and vice versa regardless of tumor size (Table 1).

Impact on overall survival by surgery type

Figure 3a shows that the effect of the EOR on survival is observed within the 3 years after diagnosis, implying that the long-term survivors of glioblastoma are a unique group of patients unaffected by the treatment modality. When open biopsy or STR was performed, the greatest proportion of deaths occurred at 4 months after diagnosis and then decreased gradually. In the GTR group, the highest proportion of deaths occurred at 11 months after diagnosis. The rates of deaths during the first 6 months after GTR, STR, and open biopsy were 13.3% (554/4155), 22.3% (779/3498), and 24.3% (548/2258), respectively (Fig. 3a). The median survival in the GTR, STR, and open biopsy groups was 17, 13, and 13 months, respectively (log-rank test, $p < .001$) (Fig. 3b).

The 2-year OS rates according to the surgery type and other variables are listed in Table 2. Excisional biopsy and STR showed no significant difference in OS across all subgroups. However, GTR generally increased the 2-year OS rate relative to open biopsy and STR except for several situations.

Although not statistically significant, in patients younger than 50 years, the survival rate of the open biopsy group was higher than that of the STR group. In subgroup analysis for patients aged of < 50 years and having tumors that cross the midline, 89, 122, and 71 patients underwent GTR, STR, and open biopsy and the median survival rates were 22, 15, and 20 months, respectively. It suggests that the severity of the disease in the STR group might be worse than the open biopsy group. Median survival of GTR, STR, and open biopsy was 11, 10, and 8 months, respectively, in patients aged 50 years or older with tumor crossing the midline.

To investigate the effect of tumor size on the prognostic difference according to surgery type, the 2-year OS of the surgery groups were obtained from each subgroup stratified by tumor size (per cm) (Table 3). GTR showed significantly favorable OS in tumors < 8 cm in size. The survival benefit of GTR, however, was not sustained when tumor was ≥ 8 cm in size.

Determinants of the surgery type and survival

The 1-year OS rate was summarized by surgery type, tumor size, and site (Fig. 4). The 2-year and 3-year OS rates are available in supplementary Figures S1 and S2. For tumors less than 8 cm in size and located in the frontal, temporal, and parietal lobes, GTR showed the best survival rate among surgery types. The survival benefit of GTR for the occipital lobe tumors was not clear compared to other lobe tumors. GTR showed a good survival rate even for tumors overlapping multiple lesions.

The 1-year OS rate by surgery type, tumor size, and extension is shown in Fig. 5. The 2-year and 3-year OS

Table 1 Patient characteristics

Characteristics	No. of patients	Gross total resection		Subtotal resection		Open biopsy		*p* value*
		no.	%	no.	%	no.	%	
Total	9911	4155	(100.0)	3498	(100.0)	2258	(100.0)	
Age								
< 50	1897	813	(19.6)	657	(18.8)	427	(18.9)	
50–59	2906	1234	(29.7)	1023	(29.2)	649	(28.7)	.35
60–69	3131	1294	(31.1)	1141	(32.6)	696	(30.8)	
≤ 70	1977	814	(19.6)	677	(19.4)	486	(21.5)	
Race								
White	8883	3746	(90.2)	3135	(89.6)	2002	(88.7)	
Black	538	209	(5.0)	180	(5.1)	149	(6.6)	.08
Others	474	192	(4.6)	180	(5.1)	102	(4.5)	
Unknown	16	8	(0.2)	3	(0.1)	5	(0.2)	
Sex								
Male	5914	2451	(59.0)	2134	(61.0)	1329	(58.9)	
Female	3997	1704	(41.0)	1364	(39.0)	929	(41.1)	.13
Year of diagnosis								
2005–2009	4317	1788	(43.0)	1423	(40.7)	1106	(49.0)	
2010–2014	5594	2367	(57.0)	2075	(59.3)	1152	(51.0)	< .001
Size								
< 2 cm	536	233	(5.6)	167	(4.8)	136	(6.0)	
≥ 2 cm and < 6 cm	7346	3175	(76.4)	2461	(70.4)	1710	(75.7)	< .001
≥ 6 cm and < 8 cm	1795	671	(16.1)	755	(21.6)	369	(16.3)	
≥ 8 cm	234	76	(1.8)	115	(3.3)	43	(1.9)	
Size as continuous variables								
(Mean, cm)	9911	Mean	(4.5)	Mean	(4.9)	Mean	(4.5)	
(Quartile, Q, cm)	9911	Q1	(3.2)	Q1	(3.5)	Q1	(3.2)	G vs S; < .001†
		Q2	(4.3)	Q2	(4.8)	Q2	(4.3)	G vs O; .79†
		Q3	(5.5)	Q3	(5.9)	Q3	(5.5)	S vs O; < .001†
Site and extension								
Confined to cerebral hemisphere	7514	3456	(83.2)	2472	(70.7)	1586	(70.2)	
-Frontal lobe	2094	957	(23.0)	660	(18.9)	477	(21.1)	< .001
-Temporal lobe	2389	1161	(27.9)	786	(22.5)	442	(19.6)	
-Parietal lobe	1413	678	(16.3)	450	(12.9)	285	(12.6)	
-Occipital lobe	407	191	(4.6)	122	(3.5)	94	(4.2)	
-Hemisphere, NOS	1211	469	(11.3)	454	(13.0)	288	(12.8)	
Confined to cerebellum	57	13	(0.3)	26	(0.7)	18	(0.8)	
Confined to brain stem	63	8	(0.2)	15	(0.4)	40	(1.8)	
Both cerebellum and brain stem	8	0	(0.0)	4	(0.1)	4	(0.2)	
Confined to ventricles	390	132	(3.2)	154	(4.4)	104	(4.6)	
Tumor crossing the midline	1195	328	(7.9)	534	(15.3)	333	(14.7)	
Supratentorial tumor extended infratentorially or vice versa	125	29	(0.7)	73	(2.1)	23	(1.0)	
Tumor invades skull, major blood vessel, meninges, nerves, or spinal cord	104	41	(1.0)	45	(1.3)	18	(0.8)	

Table 1 (continued)

Characteristics	No. of patients	Gross total resection		Subtotal resection		Open biopsy		p value*
		no.	%	no.	%	no.	%	
Others or unknown	455	148	(3.6)	175	(5.0)	132	(5.8)	
Insurance								< .001
Uninsured	274	101	(2.4)	111	(3.2)	62	(2.7)	
Insured	7231	2936	(70.7)	2508	(71.7)	1787	(79.1)	
Medicaid	757	256	(6.2)	313	(8.9)	188	(8.3)	
Unknown	1649	862	(20.7)	566	(16.2)	221	(9.8)	
Marriage								.01
Married	6804	2900	(69.8)	2416	(69.1)	1488	(65.9)	
Others	2818	1135	(27.3)	994	(28.4)	689	(30.5)	
Unknown	289	120	(2.9)	88	(2.5)	81	(3.6)	

S subtotal resection, *G* gross total resection, *O* open biopsy

*Pearson's chi-square test

†One-way ANOVA test followed by post-hoc Tukey Honestly Significant Difference (HSD) test

rates are in supplementary Figures S3 and S4. According to the results of the analysis, the GTR had a significantly beneficial effect on OS in cases where the tumor was confined to one cerebral hemisphere with a size of less than 6 cm, and the tumor that crossed the midline with the size of 4–8 cm. For small-sized tumors that crossed the midline, GTR failed to increase OS compared to other surgery types. In the multivariate analysis incorporating all variables for tumors crossing the midline with a size of less than 4 cm, the GTR was still not superior to STR (hazard ratio [HR] of GTR compared to STR, 0.831; 95% confidence interval [CI], 0.576–1.199; $p = .32$). In tumors ≥ 8 cm in size, GTR was not superior to STR in terms of survival, irrespective of the type of tumor extension.

STR did not significantly improve OS when compared to open biopsy in any situation. For tumors confined to the ventricle, GTR and STR did not significantly increase OS compared to open biopsy. All other variables were not comparable between the surgery groups.

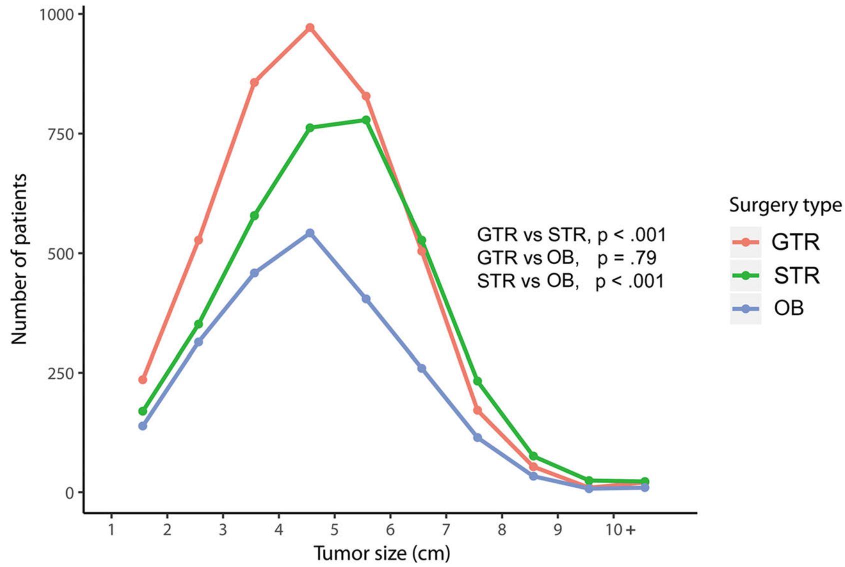
Univariate and multivariate analyses for overall survival

The univariate analysis of OS using all the available clinical values found that the prognosis was worse in patients who were older, white, male, who had tumors involving the midline or supratentorial tumors that extended infratentorially or vice versa, and who underwent open biopsy or STR. OS differences according to initial tumor size were not significant ($p = .58$) (Table 4). Even in the Cox univariate analysis including the continuous variable of tumor size, tumor size did not predict OS ($p = .53$).

All variables met the aforementioned conditions to be included in the multivariate analysis. On multivariate analysis, old age, male sex, a tumor involving the brain stem, a tumor confined to the ventricles, and a tumor crossing the midline or supratentorial tumors that extended infratentorially or vice versa were still poor prognostic factors. GTR showed a significantly favorable OS rate relative to STR (HR of GTR compared to STR, 0.791; 95% CI, 0.751–0.834; $p < .001$; $E = 1.52$), whereas STR did not show a significant benefit over open biopsy (HR of open biopsy compared to STR, 0.971; 95% CI, 0.914–1.031; $p = .33$). Tumor size did not affect the prognosis (Table 4).

Multivariate analysis was performed in each subgroup classified by tumor size after incorporating all variables. In the subgroup of tumors with a size ≥ 6 cm and < 8 cm, multivariate analysis showed a significant survival benefit from GTR (HR of GTR compared to STR, 0.819; 95% CI, 0.725–0.924; $p = .001$; $E = 1.56$; HR of open biopsy compared to STR, 0.979; 95% CI, 0.848–1.130; $p = .77$). Multivariate analysis of the subgroup of tumors

Fig. 2 Number of glioblastoma patients who underwent gross total resection (GTR), subtotal resection (STR), or open biopsy (OB) in each surgery group according to tumor size. The *p*-values: one-way ANOVA test followed by post-hoc Tukey Honestly Significant Difference (HSD) test. GTR gross total resection, STR subtotal resection, OB open biopsy



≥ 8 cm in size found that GTR did not significantly increase survival relative to STR (HR of GTR compared to STR, 1.106; 95% CI, 0.749–1.631; $p = .61$), while STR had a marginally favorable OS rate relative to open biopsy (HR of open biopsy compared to STR, 1.523; 95% CI, 0.997–2.325; $p = .05$; $E = 2.01$). The E values of the sensitivity analyses implied that the strength of causality is moderate [15].

Therefore, although STR was more frequently performed than GTR when the tumor size was ≥ 6 cm, GTR significantly increased OS compared to STR for tumors with a size of 6–8 cm. The survival rate of STR was similar to that of GTR and marginally higher than that of open biopsy only when the tumor size was ≥ 8 cm.

Cause of death by surgery type

The cause of death was compared according to the surgery type. The incidence of non-glioblastoma death among all deaths was approximately 5% irrespective of surgery type. The causes of death that might be related to surgical complications such as accidents/adverse effects, cerebrovascular diseases, pneumonia, septicemia, and infection in the GTR, STR, and open biopsy groups were 2.2%, 1.2%, and 1.9% within 6 months after diagnosis and 0.6%, 1.1%, and 0.7% after 6 months from the time of diagnosis, respectively, suggesting a higher incidence of complication-related mortality within 6 months from the diagnosis (Pearson's chi-square test, $p = .003$). However, there was no significant difference in the distribution of these causes of death among the surgery groups regardless of the time of death (supplementary Tables S1, S2, and S3).

Discussion

Key results

In this population-based study using a contemporary data set, tumor size, extension, and location of the tumor affected the rate of GTR. GTR had a survival benefit even when tumors were ≥ 6 cm in size or when tumors crossed the midline in which GTR was performed passively. Therefore, GTR needs to be performed more actively with advanced surgical techniques even with the latest radiotherapy techniques and chemotherapy regimens.

Extent of resection in glioblastoma

There are several arguments for re-evaluating the EOR. The first is that as there is no significant difference in survival between STR and open biopsy; STR beyond the range of open biopsy might not be necessary in situations where GTR cannot be safely performed [17]. On the other hand, STR can significantly improve the survival rate as long as the EOR exceeds a certain threshold (e.g., 78%) [18]. Others have suggested that there is a continuous, non-linear relationship between survival and EOR, suggesting that any degree of resection provides a survival advantage without a threshold [19]. Of these, the second and third points should be based on volumetric analyses of the EOR.

In this study, we did not stratify open biopsy and STR according to a numeric value for the EOR. However, it seems evident that treatments considered to be STR in clinical practice did not show a significant survival difference over open biopsy in this population-based study. As more effective and accessible chemoradiotherapy has become widespread, the

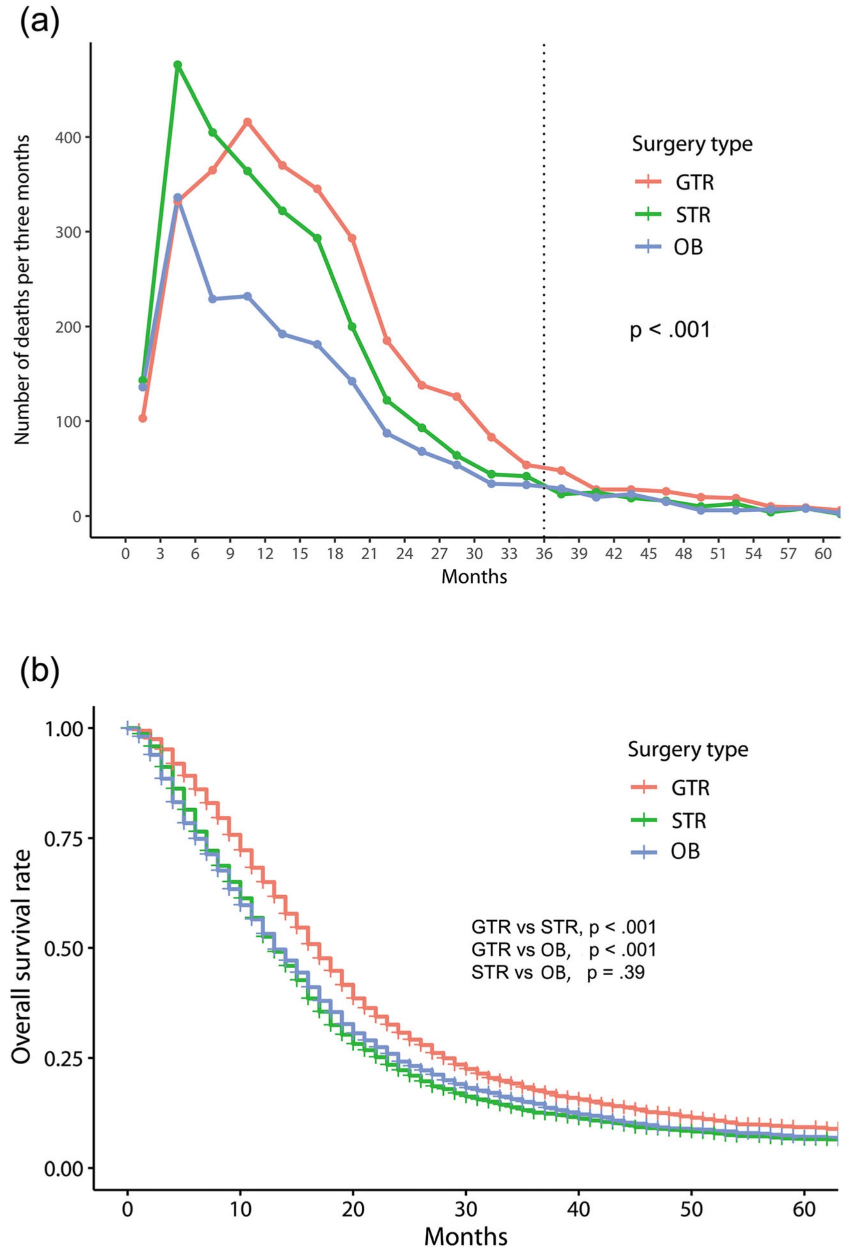


Fig. 3 **a** Number of deaths per 3 months for each surgery group over time. The *p* values: Pearson's chi-square test (death in each surgery group × month). **b** Kaplan–Meier survival estimate according to surgery type. The *p* values: pairwise comparison using a log-rank test adjusted using the Benjamini–Hochberg (BH) method. GTR gross total resection, STR subtotal resection, OB open biopsy

survival difference between open biopsy and STR may have reduced. This current analysis only enrolled patients who underwent both chemotherapy and radiotherapy. Furthermore, as GTR has always had a better survival rate than STR in all of the aforementioned studies regarding the EOR, efforts to achieve GTR appears to be justified.

Extent of resection of gross total resection considering tumor size

There is also controversy about the ideal EOR when performing GTR. One study showed that the removal of the region appearing abnormal on FLAIR imaging in addition to the 100% contrast-enhancing resection may improve survival [9]. However, this surgery is not only impossible in many cases but can also fail to achieve the desired results when considering the results of extremely extensive resections in the past. Cerebral hemispherectomy for glioblastoma from the 1920s to the 1970s showed an unfavorable prognosis—patients died from postsurgical complication or recurrence even after hemispherectomy [20]. Rahman et al. demonstrated that developing a new neurological deficit after resection of glioblastoma decreased OS [21].

In this current study, there was no difference in survival between GTR and STR when the tumor size was 8 cm or greater. The average size of the brains is 14–15 cm in biparietal diameter and 19–20 cm in occipitofrontal

Table 2 Two-year overall survival according to surgery type and clinical variables in glioblastoma

Characteristics	Gross total resection		Subtotal resection		Open biopsy		*p* value* (G vs S)	*p* value* (G vs O)	*p* value* (S vs O)
	2-year OS	95% CI	2-year OS	95% CI	2-year OS	95% CI			
Total	30.8	(29.2–32.3)	22.2	(20.7–23.8)	24.2	(22.3–26.1)	< .001	< .001	.39
Age									
< 50	44.9	(41.1–48.6)	37.7	(33.6–41.8)	43.9	(38.8–48.9)	< .001	< .001	.29
50–59	33.8	(30.9–36.8)	25.6	(22.6–28.6)	26.9	(23.3–30.6)	< .001	< .001	.35
60–69	26.3	(23.7–29.0)	17.6	(15.4–20.4)	19.6	(16.5–22.8)	< .001	< .001	.65
70 ≤	18.5	(15.6–21.6)	9.3	(7.0–11.9)	10.0	(7.4–13.1)	< .001	< .001	.50
Race									
White	30.3	(28.6–31.9)	21.0	(19.4–22.6)	23.4	(21.4–25.4)	< .001	< .001	.30
Black	34.1	(27.1–41.3)	28.7	(21.9–35.9)	26.2	(18.8–34.1)	.20	.20	.80
Others	37.2	(29.7–44.7)	36.8	(28.9–44.7)	36.6	(26.6–46.6)	.60	.60	.60
Unknown	35.0	(4.9–69.3)	0.0	NA	50.0	(0.6–91.0)	1.00	1.00	1.00
Sex									
Male	28.8	(26.8–30.8)	21.9	(20.0–23.9)	23.5	(21.1–25.9)	< .001	< .001	.75
Female	33.5	(31.1–36.0)	22.7	(20.2–25.2)	25.3	(22.3–28.3)	< .001	< .001	.33
Year of diagnosis									
2005–2009	30.1	(27.9–32.2)	21.2	(19.1–23.4)	24.5	(22.0–27.0)	< .001	< .001	.04
2010–2014	31.2	(28.9–33.6)	23.1	(21.0–25.4)	24.1	(21.3–27.0)	< .001	< .001	.33
Size									
< 2 cm	31.1	(25.1–38.7)	22.0	(15.9–30.3)	25.9	(19.0–35.3)	.004	.004	.95
≥ 2 cm and < 6 cm	30.9	(29.2–32.8)	21.6	(19.9–23.5)	23.9	(21.8–26.2)	< .001	< .001	.21
≥ 6 cm and < 8 cm	30.3	(26.7–34.4)	23.8	(20.6–27.4)	24.2	(20.0–29.4)	.005	.05	.77
≥ 8 cm	28.7	(19.4–42.4)	26.1	(18.6–36.7)	28.6	(17.7–46.1)	.88	.34	.34
Site and extension									
Confined to cerebral hemisphere	31.6	(29.9–33.3)	23.8	(21.9–25.7)	24.9	(22.7–27.2)	< .001	< .001	.34
-Frontal lobe	33.3	(30.2–36.8)	27.2	(23.7–31.3)	28.0	(24.0–32.7)	.02	.03	.97
-Temporal lobe	33.0	(30.1–36.1)	24.8	(21.7–28.4)	25.9	(21.8–30.7)	< .001	.004	.62
-Parietal lobe	30.5	(26.8–34.7)	23.1	(19.2–27.8)	21.6	(17.1–27.4)	< .001	< .001	.96
-Occipital lobe	28.8	(22.5–36.8)	28.6	(20.9–39.1)	14.9	(0.09–24.2)	.29	0.02	.26
-Hemisphere, NOS	27.3	(23.1–32.3)	16.5	(13.1–20.8)	25.5	(20.6–31.5)	< .001	.30	.04
Confined to cerebellum	30.8	(9.5–55.4)	33.7	(16.2–52.3)	30.4	(10.4–53.4)	.49	.49	.96
Confined to brain stem	25.0	(3.7–55.8)	27.6	(6.9–53.7)	23.9	(11.3–39.1)	.47	.44	.44
Both cerebellum and brain stem	NA	NA	33.3	(0.9–77.4)	50.0	(5.8–84.5)	NA	NA	.31
Confined to ventricles	28.4	(20.1–37.2)	20.7	(14.0–28.4)	21.0	(13.4–29.7)	.45	.40	.45
Tumor crossing the midline	25.6	(20.6–30.8)	14.3	(11.1–17.8)	18.3	(14.1–22.9)	< .001	< .001	.38
Supratentorial tumor extended infratentorially or vice versa	26.1	(9.7–46.0)	17.1	(8.6–28.2)	15.2	(3.8–33.6)	.74	.74	.74
Tumor invades skull, major blood vessel, meninges, nerves, or spinal cord	31.8	(17.9–46.6)	20.0	(9.1–34.0)	50.0	(25.9–70.1)	.55	.22	.22
Unknown	26.9	(19.3–35.1)	24.8	(18.1–32.1)	29.6	(21.2–38.3)	.41	.88	.41
Insurance									
Uninsured	30.7	(20.6–41.3)	30.6	(21.6–40.2)	28.5	(17.4–40.6)	.66	.66	.67
Insured	31.2	(29.2–33.1)	21.4	(19.5–23.2)	24.2	(22.1–26.3)	< .001	< .001	.33
Medicaid	32.9	(26.4–39.5)	26.0	(20.7–31.5)	22.5	(16.3–29.4)	.03	.008	.33
Unknown	29.0	(26.0–32.1)	21.6	(18.3–25.1)	24.4	(18.9–30.4)	< .001	.17	.30
Marriage									
Married	31.4	(29.6–33.3)	21.9	(20.0–23.7)	23.5	(21.2–25.9)	< .001	< .001	.60
Others	28.8	(25.9–31.8)	22.6	(19.7–25.5)	25.0	(21.7–28.5)	< .001	< .001	.52
Unknown	33.3	(23.6–43.4)	28.7	(18.8–39.3)	29.8	(19.4–40.9)	.11	.11	.81

OS overall survival, *CI* confidence interval, *G* gross total resection, *S* subtotal resection, *O* open biopsy, *NA* not applicable

*Pairwise comparison using a log-rank test, adjusted by the Benjamini–Hochberg (BH) method

diameter [22]. Thus, tumors larger than 8 cm may cross the midline or occupy nearly half of the hemisphere. For these tumors, STR was not only superior to open biopsy but also not inferior to GTR. This suggests that as the tumor size increases, the difference in the tumor burden between open biopsy and STR may increase, while the prognostic gap between STR and GTR might be reduced owing to the increased possibility of surgery-induced morbidity from GTR. Even though an 8-cm tumor size may not be an absolute criterion, GTR for huge tumors may need to consider the possibility of surgery-induced morbidity.

Table 3 Two-year overall survival according to surgery type and tumor size in glioblastoma

Tumor size	Gross total resection			Subtotal resection			Open biopsy			*p* value* (G vs S)	*p* value* (G vs O)	*p* value* (S vs O)
	No.	2-year OS (%)	95% CI	No.	2-year OS (%)	95% CI	No.	2-year OS (%)	95% CI			
All	415 5	30.8	(29.2–32.3)	3498	22.2	(20.7–23.8)	2258	24.2	(22.3–26.1)	< .001	< .001	.39
≥ 2 cm	3922	30.8	(29.1–32.4)	3331	22.2	(20.7–23.8)	2122	24.1	(22.2–26.1)	< .001	< .001	.35
≥ 3 cm	3397	29.8	(28.1–31.5)	2982	22.0	(20.4–23.7)	1810	23.3	(21.2–25.4)	< .001	< .001	.48
≥ 4 cm	2542	29.8	(27.8–31.7)	2406	22.2	(20.3–24.0)	1354	23.7	(21.3–26.1)	< .001	< .001	.53
≥ 5 cm	1573	30.2	(27.7–32.7)	1646	22.9	(20.6–25.2)	814	23.1	(20.1–26.2)	< .001	< .001	.88
≥ 6 cm	747	30.1	(26.5–33.8)	870	24.1	(21.0–27.3)	412	24.8	(20.5–29.3)	.02	.03	.78
≥ 7 cm	245	33.1	(26.5–39.7)	345	22.7	(17.9–27.7)	155	28.6	(21.3–36.3)	.09	.09	.81
≥ 8 cm	76	28.7	(18.1–40.1)	115	26.4	(17.9–35.6)	43	28.6	(16.0–42.6)	.88	.34	.34
≥ 9 cm	25	24.6	(9.0–44.2)	42	28.7	(14.9–44.1)	12	27.3	(6.5–53.9)	.96	.74	.74
≥ 10 cm	18	27.9	(8.8–51.2)	20	31.5	(11.4–54.1)	7	33.3	(4.6–67.6)	.93	.93	.93
< 2 cm	233	31.1	(24.6–37.9)	167	22.0	(15.3–29.4)	136	26.1	(18.4–34.4)	.004	.004	.95
≥ 2 cm and < 3 cm	525	36.9	(32.4–41.5)	349	23.8	(18.9–29.0)	312	29.0	(23.8–34.5)	< .001	.01	.63
≥ 3 cm and < 4 cm	855	29.8	(26.4–33.3)	576	21.7	(18.1–25.5)	456	21.9	(17.9–26.2)	< .001	< .001	.83
≥ 4 cm and < 5 cm	969	29.1	(26.0–32.3)	760	20.7	(17.6–24.0)	540	24.6	(20.8–28.5)	< .001	< .001	.22
≥ 5 cm and < 6 cm	826	30.2	(26.8–33.8)	776	21.5	(18.4–24.9)	402	21.2	(17.1–25.7)	< .001	< .001	.96
≥ 6 cm and < 7 cm	502	28.8	(24.5–33.2)	525	25.0	(21.0–29.2)	257	22.8	(17.7–28.4)	.14	.17	.92
≥ 7 cm and < 8 cm	169	35.4	(27.3–43.5)	230	20.9	(15.3–27.0)	112	28.1	(19.5–37.4)	.01	.18	.46
≥ 8 cm and < 9 cm	51	30.8	(17.8–44.9)	73	25.0	(14.8–36.5)	31	29.0	(14.5–45.3)	.69	.52	.52
≥ 9 cm and < 10 cm	7	17.1	(0.8–52.6)	22	26.7	(9.7–47.2)	5	20.0	(0.8–58.2)	.91	.51	.51
≥ 10 cm	18	27.9	(8.8–51.2)	20	31.5	(11.4–54.1)	7	33.3	(4.6–67.6)	.93	.93	.93

OS overall survival, *CI* confidence interval, *G* gross total resection, *S* subtotal resection, *O* open biopsy

*Pairwise comparison using a log-rank test, adjusted by the Benjamini–Hochberg (BH) method

Extent of resection for large tumors

On the other hand, it is noticeable that STR was more frequently performed than GTR when the size of the tumor was ≥ 6 cm, although the survival benefit of performing GTR was observed even in this large-sized tumor group. Given that most of the STRs (70.7%) were performed for tumors confined to a cerebral hemisphere, it is possible that despite the absence of critical organ invasion, passive resections might have been performed for relatively large tumors. More drastic GTR for tumors larger than 6 cm may be helpful to improve prognosis relative to STR.

Extent of resection for tumors crossing the midline

For small-sized (< 4 cm) tumors that crossed the midline, GTR did not significantly increase OS compared to other surgery types. This might be because the surgery was performed too early in the course of the disease, and supramaximal resection is presumed to be necessary in this case. In tumors with a size of ≥ 4 cm that crossed the midline, GTR showed a better OS rate than STR. That is, a tumor crossing the midline may not be an absolute contraindication to GTR, and GTR needs to be actively performed on these tumors by increasing surgical accessibility.

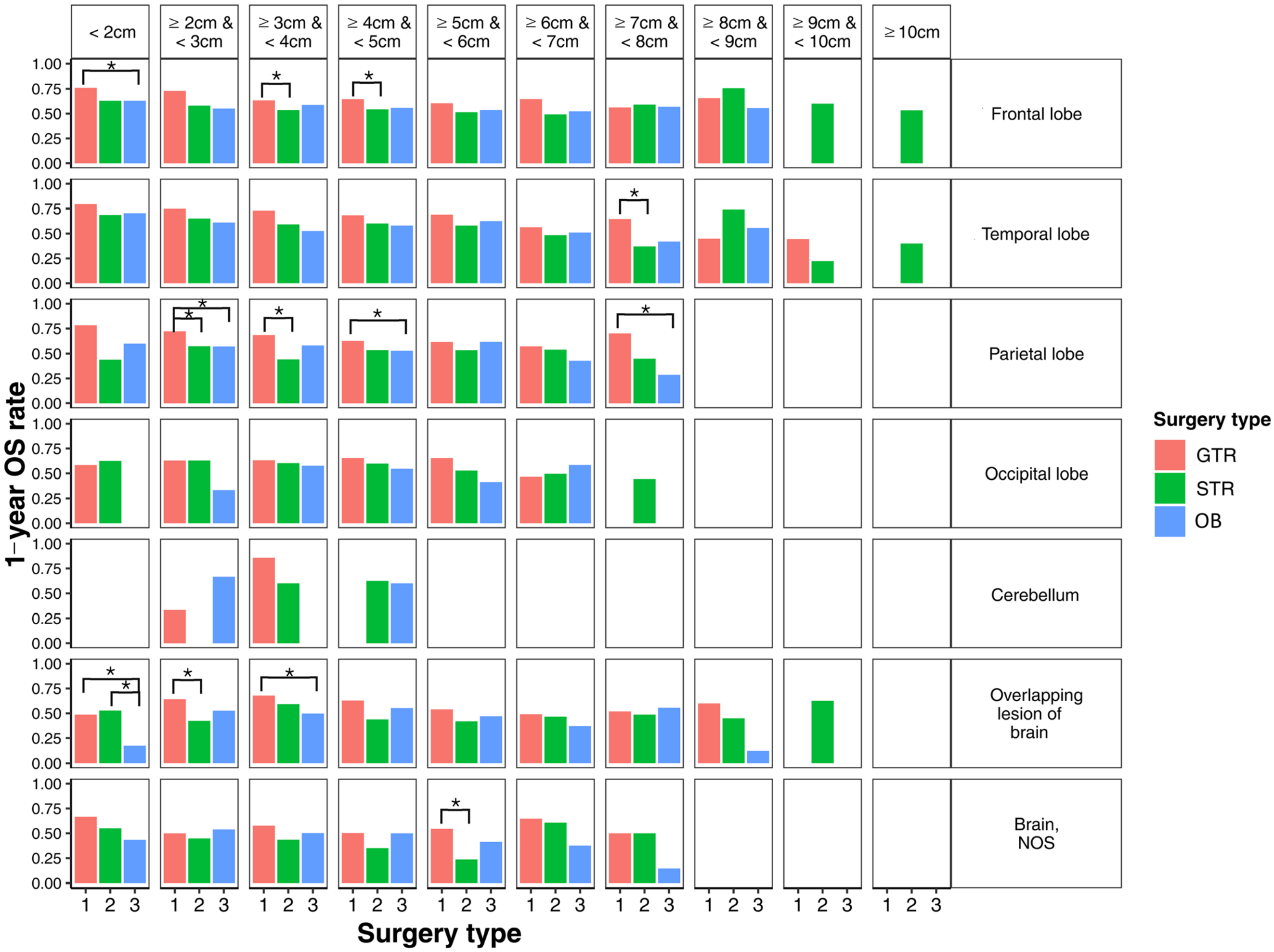


Fig. 4 One-year overall survival (OS) rate according to the surgery type, tumor size, and site. GTR gross total resection, STR subtotal resection, OB open biopsy. *Pairwise comparison using a log-rank test adjusted using the Benjamini–Hochberg (BH) method with $p < .05$

Extent of resection according to the tumor location

However, GTR was not necessarily more effective than STR for tumors involving the occipital lobe, brain stem, cerebellum, or tumors that invade surrounding structures. STR might be considered for tumors located where GTR is difficult to perform without significant sacrifice of the patient's survival and/or quality of life. A retrospective study from the Rare Cancer Network demonstrated that any resection (complete or partial) for cerebellar glioblastoma significantly improved survival compared to excision for biopsy. In this study, among 43 patients with cerebellar glioblastoma, only nine (20.9%) patients underwent complete resection, suggesting that GTR for cerebellar glioblastoma is difficult to achieve [23].

Chemotherapy and radiotherapy according to EOR

Radiotherapy and chemotherapy following surgery for glioblastoma patients might not be significantly affected by EOR at the time of surgery. This is because the chemotherapy and radiotherapy regimens are usually determined not by EOR but by patients' age, performance status, and methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter [24].

Even though the regimens of radiotherapy and chemotherapy differ between the GTR group and the non-GTR group, the non-GTR group may have been treated more aggressively. For example, a higher radiation dose might have been added to the remnant tumor area, or chemotherapy may have been performed longer than the basic protocol. Therefore, it is unlikely that the survival rate of the non-GTR group would be worse because of differences in radiotherapy or chemotherapy.

Limitations

The main limitation of this study arises from its retrospective nature. However, as a randomized controlled trial to compare GTR, STR, and open biopsy for glioblastoma is not feasible, a population-based retrospective study may be one of the

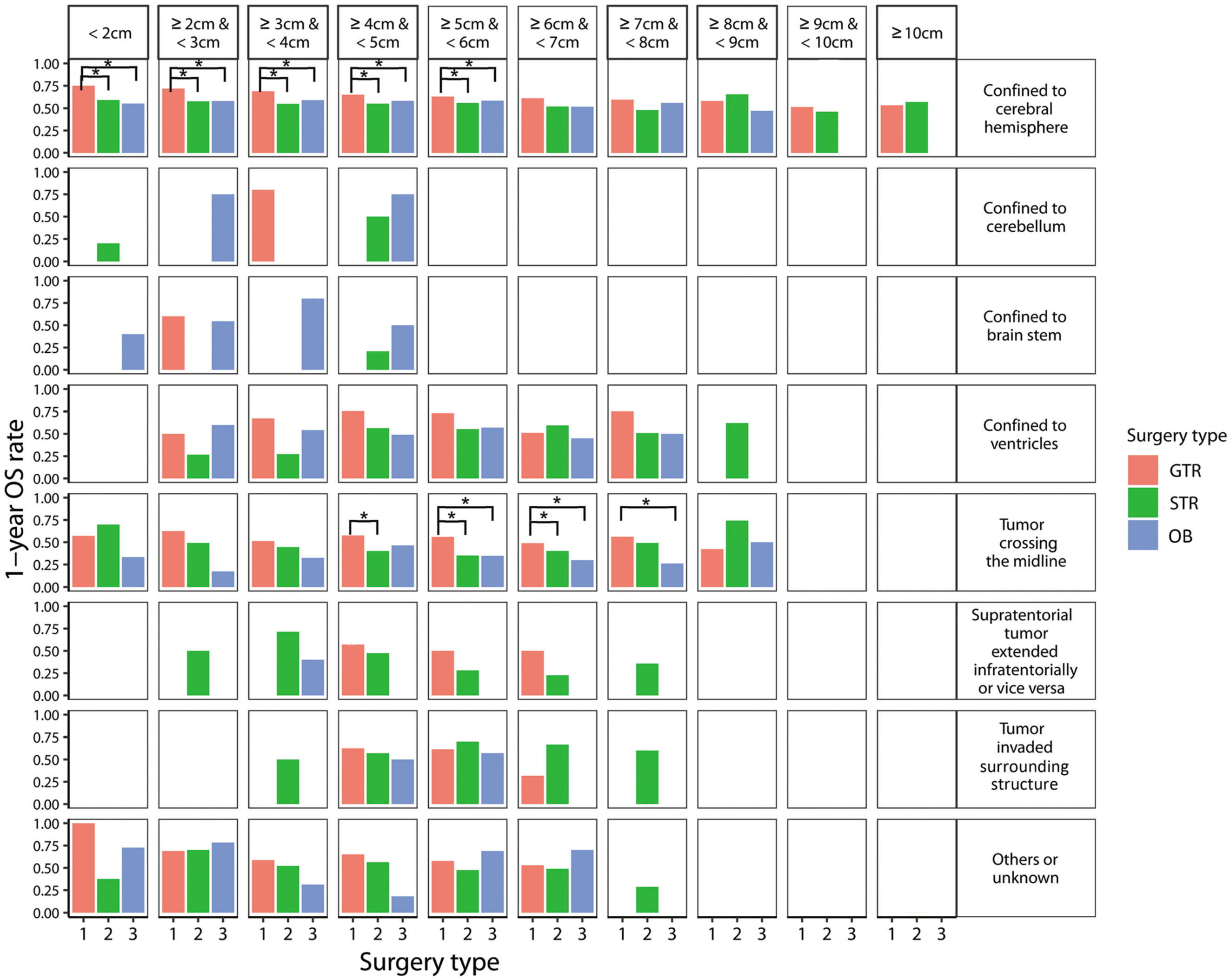


Fig. 5 One-year overall survival (OS) rate according to the surgery type, tumor size, and extension. GTR gross total resection, STR subtotal resection, OB open biopsy. *Pairwise comparison using a log-rank test adjusted using the Benjamini–Hochberg (BH) method with $p < .05$

optimal strategies. It is not known in how many patients STR was intentionally performed. In order to know this, it is necessary to compare the preoperative and postoperative surgery names, but only the definite surgery name was known.

As the information of EOR is based on the database entries, tumor image review or volumetric calculation was impossible. Tumor volumetric information rather than linear size may more clearly reflect the preoperative and postoperative residual tumor burden. More accurate conclusions can be reached if population-based studies with volumetric information are followed. Even with this limitation, no clear survival difference between the open biopsy and STR was observed unless the tumor was ≥ 8 cm in our study. Therefore, performing GTR might be more effective in improving survival than satisfying an ideal specific EOR threshold for STR.

If the extents of crossing the midline were also quantifiable (from "the tip of the iceberg" to "the tumor that involves both sides equally"), we could make clearer conclusions about the relationship between the surgery type and survival in tumors that crossed the midline.

Because of the large data size, some registration errors might be possible. In this study, the number of patients in several overlapped categories between the tumor site and tumor extension was slightly unmatched. Thus, we have integrated these two variables in the way that the tumor with an extension confined to hemisphere was classified by several lobes based on the tumor site information. We performed multivariate analyses incorporating the site and extension variables in various ways, and the results were similar (data not shown).

Although the SEER database is a well-organized population based cohort, it does not provide details such as disease-free survival, patients' performance status, and post-operative persisting neurological deficit. Also, the SEER database does not provide information of specific treatment regimens (radiation total dose and dose per fraction, chemotherapy regimen

Table 4 Univariate and multivariate analyses for overall survival in glioblastoma

Characteristics	Univariate analysis				Multivariate analysis		
	No. of patients	2-year OS (%)	95% CI	*p* value*	HR	95% CI	*p* value†
Total	9911	26.3	(25.3–27.2)				
Age							
< 50	1897	42.2	(39.8–44.7)		Reference		
50–59	2906	29.4	(27.6–31.2)	< .001	1.489	(1.388–1.597)	< .001
60–69	3131	21.7	(20.2–23.4)		1.948	(1.818–2.088)	< .001
≤ 70	1977	13.2	(11.6–14.9)		2.972	(2.755–3.207)	< .001
Race							
White	8883	25.5	(24.5–26.5)		Reference		
Black	538	30.1	(25.8–34.3)	< .001	0.931	(0.841–1.031)	.17
Others	474	36.9	(32.1–41.7)		0.746	(0.667–0.833)	< .001
Unknown	16	37.8			0.652	(0.310–1.368)	.26
Sex							
Male	5914	25.1	(23.9–26.4)		Reference		
Female	3997	27.9	(26.4–29.5)	.02	0.897	(0.856–0.940)	< .001
Year of diagnosis							
2005–2009	4317	25.7	(24.4–27.0)		Reference		
2010–2014	5594	26.8	(25.4–28.2)	.13	0.956	(0.908–1.007)	.09
Size							
< 2 cm	536	27.0	(23.1–31.5)		Reference		
≥ 2 cm and < 6 cm	7346	26.2	(25.1–27.3)	.58	0.980	(0.886–1.085)	.70
≥ 6 cm and < 8 cm	1795	26.3	(24.2–28.6)		1.012	(0.904–1.133)	.84
≥ 8 cm	234	27.6	(22.0–34.6)		0.937	(0.784–1.121)	.48
Site and extension							
Confined to cerebral hemisphere	7514	27.6	(26.5–28.7)				
-Frontal lobe	2094	30.2	(28.1–32.4)	< .001	Reference		
-Temporal lobe	2389	29.0	(27.0–31.1)		0.968	(0.904–1.036)	.34
-Parietal lobe	1413	26.2	(23.8–28.9)		1.040	(0.962–1.124)	.33
-Occipital lobe	407	24.9	(20.8–29.9)		1.041	(0.924–1.173)	.51
-Hemisphere, NOS	1211	22.8	(20.3–25.6)		1.137	(1.048–1.233)	< .002
Confined to cerebellum	57	32.0	(21.6–47.6)		0.929	(0.692–1.245)	.93
Confined to brain stem	63	24.9	(15.6–39.7)		1.582	(1.194–2.095)	< .001
Both cerebellum and brain stem	8	42.9	(18.2–100.0)		1.387	(0.621–3.099)	.43
Confined to ventricles	390	23.4	(19.2–28.6)		1.169	(1.033–1.323)	.01
Tumor crossing the midline	1195	18.7	(16.4–21.2)		1.518	(1.400–1.646)	< .001
Supratentorial tumor extended infratentorially or vice versa	125	17.8	(11.4–27.8)		1.497	(1.214–1.845)	< .001
Tumor invades skull, major blood vessel, meninges, nerves, or spinal cord	104	30.5	(22.5–41.4)		1.056	(0.851–1.309)	.62
Unknown	455	26.8	(22.7–31.8)		1.057	(0.940–1.188)	.36
Surgery							
Gross total resection	4155	30.8	(29.2–32.3)		0.791	(0.751–0.834)	< .001
Subtotal resection	3498	22.2	(20.7–23.8)	< .001	Reference		
Open biopsy	2258	24.2	(22.3–26.1)		0.971	(0.914v1.031)	.33

Table 4 (continued)

Characteristics	Univariate analysis				Multivariate analysis		
	No. of patients	2-year OS (%)	95% CI	*p* value*	HR	95% CI	*p* value†
Insurance							
Uninsured	274	30.4	(24.5–36.5)		Reference		
Insured	7231	26.0	(24.9–27.2)	.37	0.937	(0.813–1.079)	.37
Medicaid	757	27.4	(23.8–31.0)		1.035	(0.880–1.216)	.68
Unknown	1649	25.9	(23.8–28.0)		1.017	(0.875–1.182)	.82
Marriage							
Married	6804	26.3	(25.2–27.5)		Reference		
Others	2818	25.7	(24.0–27.5)	.21	1.093	(1.038–1.150)	< .001
Unknown	289	31.0	(25.0–37.1)		0.966	(0.839–1.111)	.97

OS overall survival, *CI* confidence interval, *HR* hazard ratio

*Kaplan–Meier survival estimate compared by a two sided log-rank test

†Cox's regression model

and cycles, and the use of tumor treating fields). Elderly patients may have been treated with less aggressive treatment regimens such as the NORDIC trial regimen [25]. Since our study only included patients diagnosed by 2014, the Perry scheme would not have been applied to these patients yet [26].

Genetic information such as MGMT, isocitrate dehydrogenase (IDH), and telomerase reverse transcriptase (TERT) genes was not obtained in this study. Therefore, the updated World Health Organization (WHO) classification according to IDH-mutant was not available [27]. It is well known that MGMT promoter methylation and IDH mutation in glioblastoma are significantly favorable factors [28, 29], whereas TERT promoter mutation is a poor prognostic factor [30]. If this information is added to our study, it would be more helpful to determine how EOR affects survival rate based on genetic subtype.

Conclusions

Although GTR remains the gold standard treatment for glioblastoma, STR/open biopsy was performed more frequently in clinical practice. As GTR is beneficial to OS, even for tumors that cross the midline and tumors ≥ 6 cm in size, GTR should be more actively performed than STR or open biopsy.

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Data availability The datasets generated during and/or analyzed during the current study are available in the SEER repository, https://seer.cancer.gov/seertrack/data/request/.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent was not required.

References

1. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996

2. Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62:753–766
3. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen H-J, Group A-GS (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7: 392–401
4. Simpson J, Horton J, Scott C, Curran W, Rubin P, Fischbach J, Isaacson S, Rotman M, Asbell S, Nelson J (1993) 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 26:239–244
5. Kreth FW, Warnke PC, Scheremet R, Ostertag CB (1993) Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. J Neurosurg 78:762–766
6. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190–198
7. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, Patel AS, Rizk EB, Suki D, Sawaya R (2016) Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol 2:1460–1469
8. Chaichana KL, Halthore AN, Parker SL, Olivi A, Weingart JD, Brem H, Quinones-Hinojosa A (2011) Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. J Neurosurg 114:604–612
9. Li YM, Suki D, Hess K, Sawaya R (2016) The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg 124:977–988
10. Reyes-Botero G, Mokhtari K, Martin-Duverneuil N, Delattre J-Y, Laigle-Donadey F (2012) Adult brainstem gliomas. Oncologist 17: 388–397
11. Eljamel S (2015) 5-ALA fluorescence image guided resection of glioblastoma multiforme: a meta-analysis of the literature. Int J Mol Sci 16:10443–10456
12. Almeida JP, Chaichana KL, Rincon-Torroella J, Quinones-Hinojosa A (2015) The value of extent of resection of glioblastomas: clinical evidence and current approach. Curr Neurol Neurosci Rep 15:517
13. Coburger J, Renovanz M, Ganslandt O, Ringel F, Wirtz CR, von Riehm JS (2017) Evaluation of surgical decision making and resulting outcome in patients with highly eloquent glioblastoma: results of a multicenter assessment. Clin Neurol Neurosurg 162: 29–35
14. Noorbakhsh A, Tang JA, Marcus LP, McCutcheon B, Gonda DD, Schallhorn CS, Talamini MA, Chang DC, Carter BS, Chen CC (2014) Gross-total resection outcomes in an elderly population with glioblastoma: a SEER-based analysis. J Neurosurg 120:31–39
15. VanderWeele TJ, Ding P (2017) Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 167:268–274
16. Mathur MB, Ding P, Riddell CA, VanderWeele TJ (2018) Web site and R package for computing E-values. Epidemiology 29:e45–e47
17. Kreth F-W, Thon N, Simon M, Westphal M, Schackert G, Nikkhah G, Hentschel B, Reifenberger G, Pietsch T, Weller M (2013) Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol 24:3117–3123
18. Sanai N, Polley M-Y, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115:3–8
19. Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE (2014) Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. J Clin Oncol 32:774
20. Han SJ, Sughrue ME (2012) The rise and fall of “biopsy and radiate”: a history of surgical nihilism in glioma treatment. Neurosurg Clin N Am 23:207–214
21. Rahman M, Abbatematteo J, De Leo EK, Kubilis PS, Vaziri S, Bova F, Sayour E, Mitchell D, Quinones-Hinojosa A (2016) The effects of new or worsened postoperative neurological deficits on survival of patients with glioblastoma. J Neurosurg 127:123–131
22. Aukland SM, Odberg MD, Gunny R, Eide GE, Rosendahl K (2008) Assessing ventricular size: is subjective evaluation accurate enough? New MRI-based normative standards for 19-year-olds. Neuroradiology 50:1005
23. Weber DC, Miller RC, Villà S, Hanssens P, Baumert BG, Castadot P, Varlet P, Abacioglu U, Igdem S, Szutowicz E (2006) Outcome and prognostic factors in cerebellar glioblastoma multiforme in adults: a retrospective study from the Rare Cancer Network. Int J Radiat Oncol Biol Phys 66:179–186
24. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, Fenstermaker RA, Forsyth P, Hattangadi-Gluth J, Holdhoff M (2017) NCCN guidelines insights: central nervous system cancers, version 1.2017. J Natl Compr Cancer Netw 15: 1331–1345
25. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, Abacioglu U, Tavelin B, Lhermitte B, Hegi ME (2012) 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 13:916–926
26. Perry JR, Laperriere N, O’callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, Nishikawa R, Cairncross JG, Roa W (2017) Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 376:1027–1037
27. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820
28. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, De Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997–1003
29. Parsons DW, Jones S, Zhang X, Lin JC-H, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu I-M, Gallia GL (2008) An integrated genomic analysis of human glioblastoma multiforme. Science 321:1807–12
30. Nonoguchi N, Ohta T, Oh J-E, Kim Y-H, Kleihues P, Ohgaki H (2013) TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol 126:931–937