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Factors involved in maintaining Karnofsky Performance Status (≥ 50%) in glioblastoma, *IDH*-wildtype patients treated with temozolomide and radiotherapy

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Karnofsky Performance Status (KPS) is a widely used scale to assess performance status. KPS ≥ 50% implies that patients can live at home. Therefore, maintaining KPS ≥ 50% is important to improve the quality of life of patients with glioblastoma, whose median survival is less than 2 years. This study aimed to identify the factors associated with survival time with maintenance of KPS ≥ 50% (survival with KPS ≥ 50%) in patients with glioblastoma, *IDH*-wildtype. Ninety-eight patients with glioblastomas, *IDH*-wildtype, who were treated with concomitant radiotherapy (RT) and temozolomide (TMZ) followed by maintenance TMZ therapy, and whose KPS at the start of RT was ≥ 50%, were included. The median survival with KPS ≥ 50% was 13.3 months. In univariate analysis, preoperative KPS (≥ 80%), KPS at the start of RT (≥ 80%), residual tumor size (< 2 cm^3), methylated *MGMT* promotor, and implantation of BCNU wafer were associated with survival with KPS ≥ 50%. In multivariate analysis, KPS at the start of RT (≥ 80%), methylated *MGMT* promotor, and residual tumor size (< 2 cm^3) were significantly associated with increased survival with KPS ≥ 50%. A strategy of maximum possible tumor resection without compromising KPS is desirable to prolong the survival time with KPS ≥ 50%.

Keywords Glioblastoma, Karnofsky Performance Status, MGMT, Radiotherapy, Temozolomide, Tumor size

Glioblastoma is the most common malignant brain tumor[1]. The standard treatment is maximal safe resection, followed by radiotherapy (RT) and temozolomide (TMZ)[2]. Progression-free survival (PFS) and overall survival (OS) of the disease have been reported from data from clinical trials[3–5]. However, only a few studies have investigated the prognostic value of maintaining Karnofsky Performance Status (KPS) of patients with glioblastoma[6,7].

KPS is a widely used scale to assess performance status. KPS ≥ 50% indicates that patients can live at home and take care of most of their personal needs. Patients with KPS < 50% require the equivalent of institutional or hospital care[8]. Therefore, there is a significant difference in the quality of life of patients with KPS 40% and those with KPS 50%.

The revision of the classification of brain tumors has led to a change in the diagnostic criteria[9,10]. In the WHO 2021 classification of the tumors of the central nervous system, gliomas with mutations of isocitrate dehydrogenases 1 and 2 (*IDH1/2*) are no longer categorized as glioblastoma. Diffuse gliomas without *IDH*

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mutations that fulfill one of the following characteristics, i.e., microvascular proliferation, necrosis, *TERT* promoter mutation, *EGFR* gene amplification, and +7/−10 chromosome copy number alterations are now referred to as glioblastoma, *IDH*-wildtype[10].

In this study, we reviewed the data of patients with glioblastomas, *IDH*-wildtype based on WHO 2021 classification to identify the factors associated with survival time maintaining KPS ≥ 50% (survival with KPS ≥ 50%).

Materials and methods

Patients

The ethics review committee of the Fujita Health University approved this retrospective study (Approval No. HM22-434). Data of patients with glioblastoma who were first operated at the Fujita Health University Hospital between 2007 and 2021 were reviewed. All diagnoses were rereviewed according to the WHO 2021 classification of tumors of the central nervous system[10] and only cases with glioblastoma, *IDH*-wildtype who qualified all the following criteria were included in this study: (1) exclusively supratentorial cases; (2) age ≥ 18 years; (3) treated with concomitant RT and TMZ followed by maintenance TMZ therapy; (4) KPS ≥ 50% at the start of RT.

KPS score was determined from the review of medical records. Tumor size was measured from the contrast-enhanced area on MRI performed within 3 days after surgery. In many studies on glioblastoma, the extent of resection has been used to assess residual tumor[11,12]; however, the size of the residual tumor may vary depending on the preoperative size of the tumor, even if the degree of removal is the same. Therefore, for the purpose of this analysis, the residual tumor volume was categorized into large (≥ 2 cm^3) or small (< 2 cm^3) based on a previous report[13].

Histopathological and molecular assessment

DNA was isolated from frozen tissues or formalin-fixed paraffin-embedded (FFPE) samples using DNeasy Blood & Tissue Kits (QIAGEN, Hilden, Germany) or DNA FFPE Tissue Kits (QIAGEN), as previously described[14]. DNA aliquots were subjected to degenerate oligonucleotide-primed polymerase chain reaction (DOP-PCR). Comparative genomic hybridization (CGH) was used to evaluate gain of chromosome 7 and loss of chromosome 10. The detailed procedure for CGH is described elsewhere[15].

Mutational analyses of *IDH1/2* and *TERT* promoter were performed using PCR and Sanger sequencing, as previously described[14]. The following primer sequences were used: forward 5′-CGGTCTTCAGAGAAGCCAT T-3′ and reverse 5′-CACATTATTGCCAACATGAC-3′ for *IDH1* gene; forward 5′-CTCACAGAGTTCAAGCT GAAGAAG-3′ and reverse 5′- CTGTGGCCTTGTACTGCAGAG-3′ for *IDH2* gene; and forward 5′-CAGCGC TGCCTGAAACTC-3′ and reverse 5′-GTCCTGCCCCTTCACCTT-3′ for *TERT* promoter gene. The sequence analysis was performed using an ABI Prism 3100 genetic analyzer (Applied Biosystems, Foster City, CA, USA).

MGMT promoter methylation was measured by methylation-specific PCR using the EZ DNA Methylation-Direct™ Kit (Zymo Research Corp., Orange, CA) as previously described[16].

Paraffin-embedded sections were deparaffinized, placed in 10 mM citrate buffer (pH 7.0), processed five times for four minutes in a microwave oven at 600 W, and incubated overnight at 4 °C with monoclonal antibody Ki-67 (1:25 dilution) (clone MIB-1; BioGenex, Fremont, CA, USA) in PBS containing 5% bovine serum albumin and 3% horse serum. The MIB-1 index was calculated as the percentage of tumor cell nuclei immunolabeled for anti-Ki67 antibody, for a total of 1,000 tumor cell nuclei, as previously described[17].

Statistical analysis

We examined the influence of the following factors on survival time with maintenance of KPS ≥ 50%: sex, age, preoperative KPS, KPS at the start of RT, residual tumor size, treatment with bis-chloroethyl nitrosourea (BCNU) wafer, treatment with bevacizumab, the status of methylation of *MGMT* promoter, and MIB-1 index.

All analyses were performed using JMP software (version 13; SAS Institute Japan, Tokyo, Japan). PFS was defined as the time from the date of first surgery to the date of confirmation of tumor recurrence/regrowth, or patient death. Tumor recurrence was determined using the Response Assessment in Neuro-Oncology (RANO) criteria based on MRI findings. The survival time with maintenance of KPS ≥ 50 was defined as the time from the date of initial surgery to a KPS < 50%. OS was defined as the period between the date of first surgery and the date of death or last follow-up. Survival outcomes were estimated using the Kaplan–Meier method and between-group differences were assessed using the log rank test. Multivariate proportional hazards regression analysis was used to identify the factors associated with maintenance of KPS ≥ 50. P values < 0.05 were considered indicative of statistical significance.

Results

Patient characteristics

A total of 152 patients underwent surgery and were diagnosed with glioblastoma, *IDH*-wildtype during the study reference period. Of these, 98 patients qualified the inclusion/exclusion criteria and were included in this study (Fig. 1). The characteristics of the study population are summarized in Table 1. Sixty patients (61.2%) were male and 38 (38.8%) were female. The mean and median age of the patients at surgery was 62.8 ± 12.5 years and 66 years, respectively. The distribution of preoperative KPS scores in our cohort was as follows: 100% (8 patients), 90% (39 patients), 80% (30 patients), 70% (9 patients), 60% (11 patients), and 50% (1 patient); the average preoperative KPS was 82.1% ± 11.5%. The distribution of KPS scores at the start of RT was as follows: 100% (2 patients), 90% (30 patients), 80% (26 patients), 70% (18 patients), 60% (12 patients), and 50% (10 patients); the average KPS at the start of RT was 76.1% ± 13.6%. Histologically, ninety-five cases were diagnosed as glioblastoma, *IDH*-wildtype due to microvascular proliferation and/or necrosis, whereas three cases were

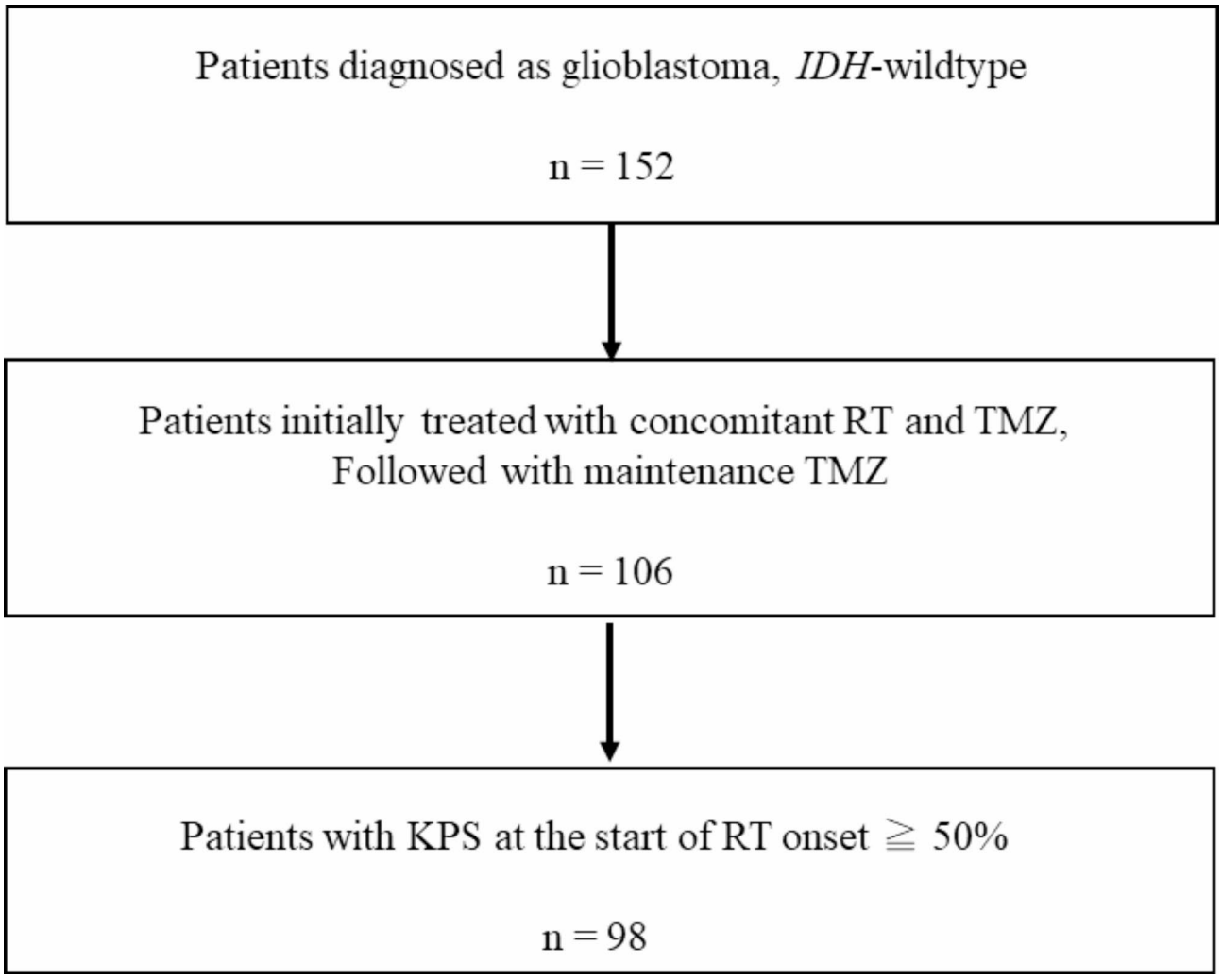

Fig. 1. Patient selection flow chart. RT, radiotherapy, TMZ, temozolomide.

Characteristics		Number of patients
Sex	Female	38
	Male	60
Age	Mean age (years) ± SD	62.8 ± 12.5
Preoperative KPS	Mean KPS ± SD	82.1 ± 11.5
	≥ 80%	77
	≤ 70%	21
Residual tumor size	< 2 cm^3	45
	≥ 2cm^3	52
KPS at the start of RT	Mean KPS ± SD	76.1 ± 13.6
	≥ 80%	58
	≤ 70%	40
BCNU wafer	With	51
	Without	47
Bevacizumab	With	51
	Without	47
MGMT promoter	Methylated	43
	Unmethylated	47
MIB-1 index	Mean index ± SD	34.7 ± 14.5

Table 1. The characteristics of the study population.

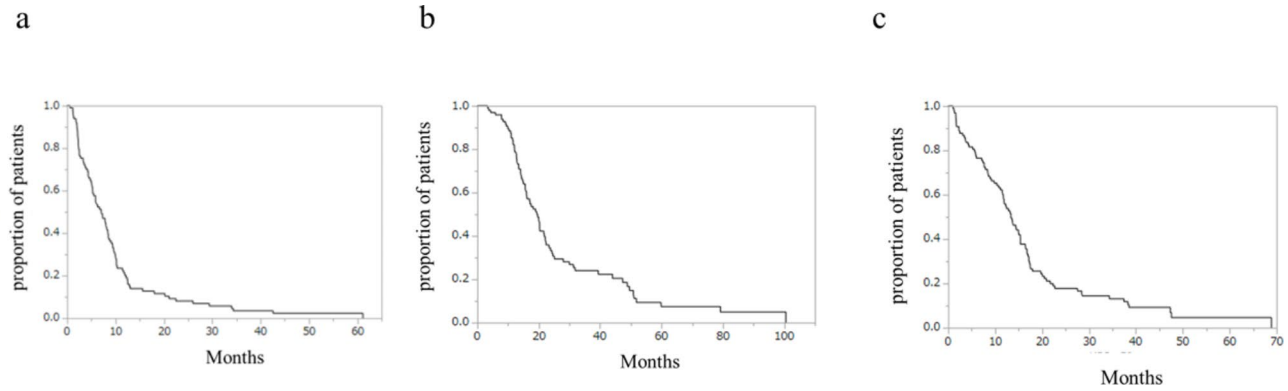

Fig. 2. (**a**) Progression-free survival, (**b**) overall survival, and (**c**) survival time with maintenance of KPS ≥ 50%.

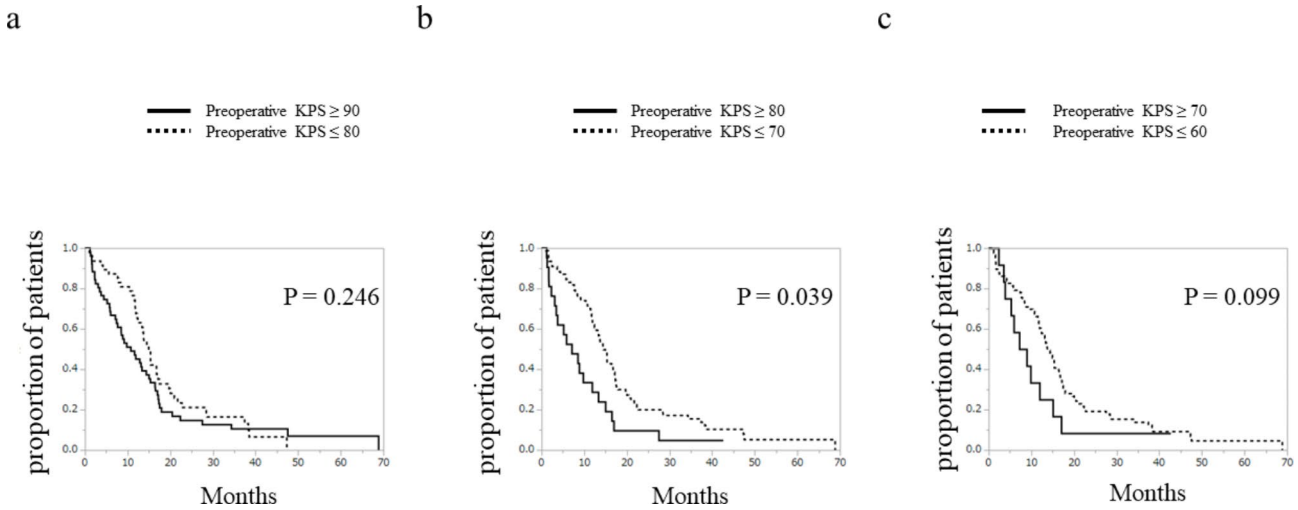

Fig. 3. Survival time with maintenance of KPS ≥ 50% using the preoperative KPS cutoff value of (**a**) 90%, (**b**) 80%, and (**c**) 70%.

histologically diagnosed as malignant astrocytoma harboring IDH-wildtype and molecularly diagnosed as glioblastoma, *IDH*-wildtype. The status of methylation of *MGMT* promoter was checked in 90 patients, and methylation of *MGMT* promoter was found in 43 cases (47.8%). MIB-1 index ranged from 6.3 to 67.3% with an average of 34.7%. BCNU wafer was implanted in 64 cases (65.3%), and 51 patients (52.0%) received bevacizumab treatment before KPS decreased below 50%.

PFS, OS, and survival with KPS ≥ 50%

The median PFS, OS, and survival with KPS ≥ 50% were 7.1 months, 19.4 months, and 13.3 months, respectively (Fig. 2). The survival time with KPS ≥ 50% was longer than PFS.

Preoperative KPS, KPS at the start of RT, and survival with KPS ≥ 50%

First, we analyzed the relationship of survival with KPS ≥ 50% with preoperative KPS or KPS at the start of RT. Compared with patients with preoperative KPS ≤ 60%, patients with preoperative KPS ≥ 70% tended to show longer survival maintaining KPS ≥ 50% ($p = 0.099$), and compared with patients with preoperative KPS ≤ 70%, patients with preoperative KP ≥ 80% showed significantly longer survival maintaining KPS ≥ 50% ($p = 0.0039$); however there was no significant difference between patients with preoperative KPS ≥ 90% and ≤ 80% ($p = 0.246$) (Fig. 3). Regarding the contribution of KPS at the start of RT, although significant differences were observed between the two groups regardless of whether the cutoff value was set at 90%, 80%, or 70%, the most significant difference was observed using 80% as the cutoff value (Fig. 4). Therefore, we used the 80% cutoff value for both preoperative KPS and KPS at the start of RT.

Univariate and multivariate analyses of factors associated with survival with KPS ≥ 50%

Several factors (sex, age, preoperative KPS, KPS at the start of RT, residual tumor size, status of *MGMT* promotor methylation, BCNU wafer implantation, treatment with bevacizumab, and MIB1-index) were analyzed to assess their potential association with survival with KPS ≥ 50%. Young age (< 65 years) group tended to show longer

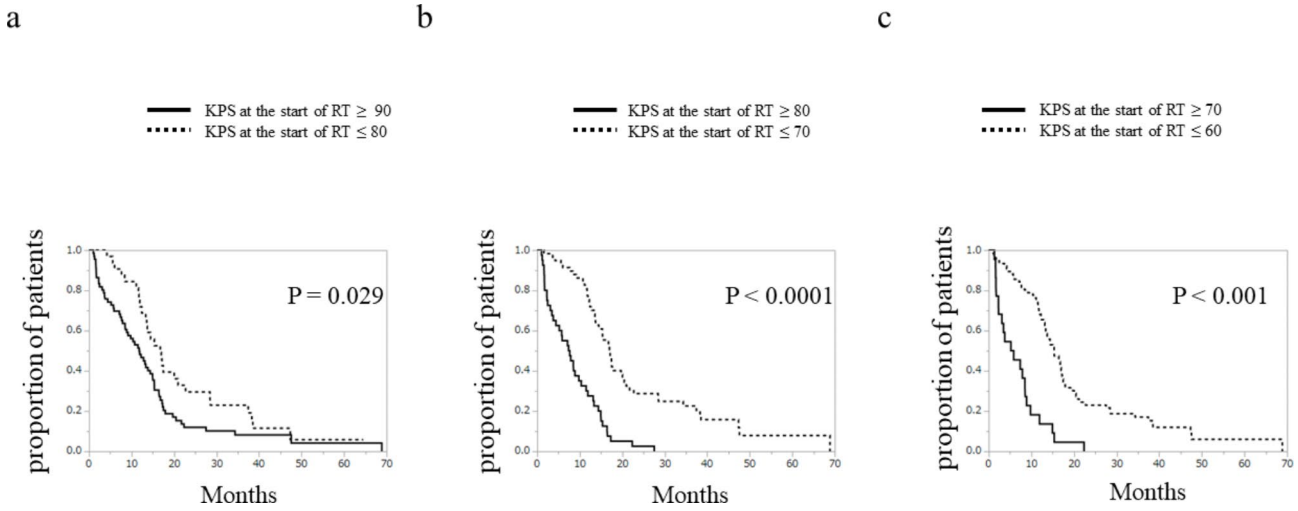

Fig. 4. Survival time with maintenance of KPS ≥ 50% using KPS cutoff value at the start of RT of (**a**) 90%, (**b**) 80%, and (**c**) 70%.

	Univariant analysis			Multivariant analysis		
		Survival time with maintaining KPS ≧ 50 (months)	P value		HR (95% CI)	P value
Sex	Female	11.69	0.344	Female vs. male	1.108 (0.690–1.765)	0.667
	Male	13.84				
Age	≤ 64 years	15.39	0.053	≤ 64 years vs. ≥ 65 years	0.641 (0.385–1.061)	0.083
	≥ 65 years	10.36				
Preoperative KPS	≥ 80%	14.41	0.004	≥ 80% vs. ≤ 70%	0.927 (0.462–1.923)	0.836
	≤ 70%	7.13				
KPS at the start of RT	≥ 80%	17.00	< 0.0001	≥ 80% vs. ≤ 70%	0.284 (0.150–0.542)	0.0002
	≤ 70%	7.53				
Residual tumor size	< 2 cm^3	16.77	0.001	< 2cm^3 vs. ≥ 2cm^3	0.540 (0.326–0.896)	0.017
	≥ 2cm^3	10.93				
BCNU wafer	With	15.03	0.012	With vs. without	1.090 (0.608–1.980)	0.775
	Without	11.20				
Bevacizumab	With	15.03	0.731	With vs. without	0.887 (0.534–1.485)	0.646
	Without	11.74				
MGMT promoter	Methylated	17.16	0.009	Methylated vs. unmethylated	0.423 (0.253–0.702)	0.0009
	Unmethylated	11.80				
MIB-1 index	≥ 35%	13.84	0.189	≥ 35% vs. < 35%	1.102 (0.654–1.861)	0.716
	< 35%	13.15				

Table 2. Multivariate analysis of factors associated with survival with KPS ≥ 50%.

survival with KPS ≥ 50% ($p = 0.053$). Preoperative KPS (≥ 80%), KPS at the start of RT (≥ 80%), residual tumor size (< 2 cm^3), methylated *MGMT* promotor, and implantation of BCNU wafer were found to be associated with survival with KPS ≥ 50% (Table 2; Fig. 5). In multivariate analysis, KPS at the start of RT (≥ 80%), methylated *MGMT* promotor, and residual tumor size (< 2 cm^3) were associated with significantly longer survival with KPS ≥ 50%. Young age (< 65 years) tended to be associated with survival with KPS ≥ 50% (Table 2). The median survival with KPS ≥ 50% in groups harboring all three favorable factors (KPS at the start of RT [≥ 80%], methylated *MGMT* promotor, and residual tumor size [< 2 cm^3]), two favorable factors, one favorable factor, and none of the favorable factors were 28.57, 15.39, 11.64, and 5.80 months, respectively (Fig. 6).

Discussion

Many studies about glioblastoma have focused on the survival time[3–5]. Because of the poor prognosis of glioblastoma, maintaining KPS is considered another goal of management. In this study of 98 cases of

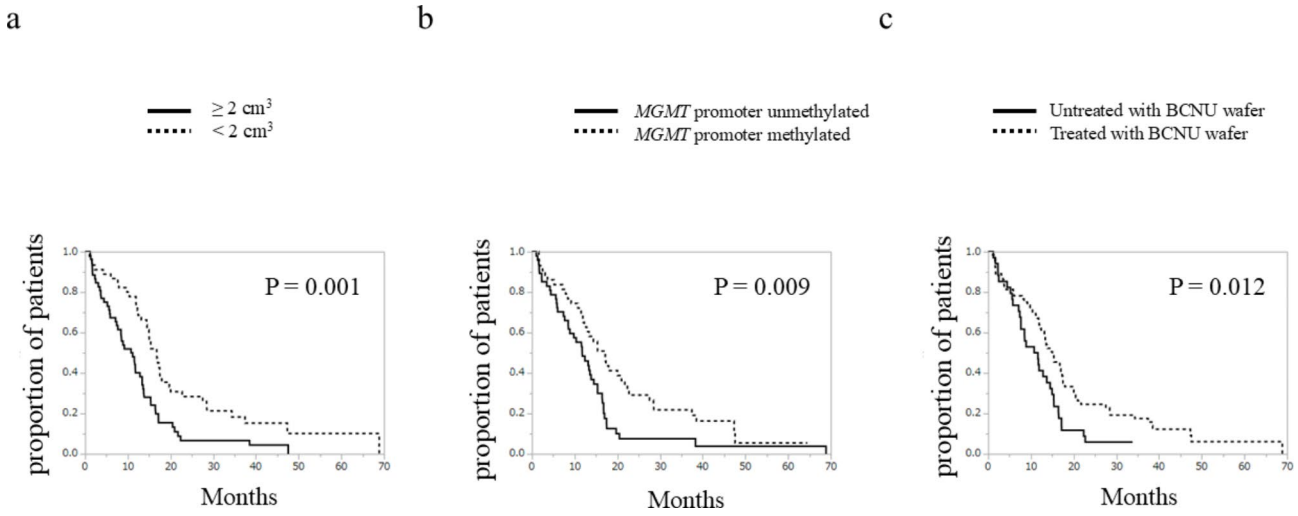

Fig. 5. (**a**) The survival time with maintenance of KPS ≥ 50% in patients with residual tumor size ≥ 2 cm^3 versus < 2 cm^3. (**b**) The survival time with maintenance of KPS ≥ 50% in patients with methylated *MGMT* promoter versus those with unmethylated *MGMT* promoter. (**c**) The survival time with maintenance of KPS ≥ 50% in patients treated with BCNU wafer versus those not treated with BCNU wafer. The median survival time with maintaining KPS ≥ 50 for each group is provided in Table 2.

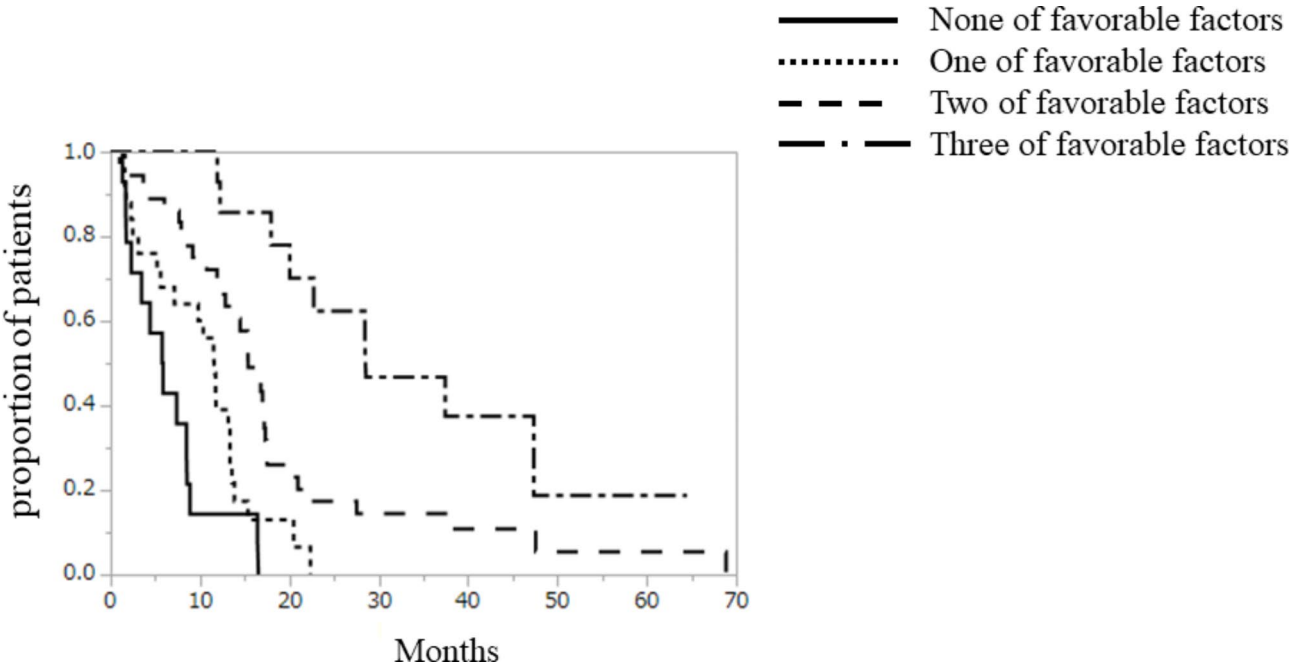

Fig. 6. The survival time with maintenance of KPS ≥ 50% in patients with none, one, two, or all three favorable factors (KPS at the start of RT ≥ 80%, methylated *MGMT* promotor, and residual tumor size < 2 cm^3).

glioblastoma, *IDH*-wildtype treated with concomitant RT and TMZ, followed by maintenance TMZ, three factors (KPS at the start of RT [≥ 80%], methylated *MGMT* promotor, and residual tumor size [< 2 cm^3]) were found to be associated with longer survival with maintenance of KPS at ≥ 50%. The results suggest that reducing the residual tumor size to less than 2 cm^3 and not allowing the KPS at the start of RT to fall below 80% can help increase the survival time with maintenance of KPS at ≥ 50%.

Previous studies have highlighted the significant impact of the extent of resection on survival outcomes in glioblastoma patients[18–20]. Our findings are consistent with these reports, showing that patients with smaller residual tumors (< 2 cm^3) were more likely to maintain a KPS ≥ 50. This underscores the importance of maximal safe resection in improving both survival and quality of life in glioblastoma patients. Furthermore, meta-analyses and recent studies confirm that gross total resection (GTR) significantly improves survival outcomes compared

to subtotal resection (STR) or biopsy alone, and that minimizing residual tumor volume provides additional benefits. These findings highlight the critical role of safe but aggressive surgical approaches in optimizing patient outcomes.

In univariate analysis, both preoperative KPS and KPS at the start of RT were related to the duration of KPS maintenance, but in multivariate analysis, only KPS at the start of RT was found to significantly influence the survival time with maintenance of KPS ≥ 50%. Thus, the KPS at the start of RT showed a stronger relationship with KPS maintenance than preoperative KPS. Similar results were reported in a previous study investigating the relationship between KPS and OS, where postoperative KPS was strongly associated with prolonged survival rather than preoperative KPS[6,21].

Although bevacizumab has been reported to prolong KPS in Avaglio trial[3], bevacizumab was not revealed to be a prognostic factor. This discrepancy may be attributed to the way bevacizumab is used. In Japan, bevacizumab is covered by insurance for use at the time of initial or recurrent disease. In our institution, bevacizumab is used in initial therapy when there is a large residual tumor and the patient's KPS is low, and at recurrence when the patient's KPS is high. Furthermore, there are 8 patients who have not yet used bevacizumab tumors and have maintained a KPS of 50 or higher. Based on the above, we believe that bevacizumab could not be extracted as a predictor of KPS maintenance.

Several previous studies have measured functional outcomes in patients with glioma, but most of these studies included several histological types of gliomas[22,23]. Only a few studies have evaluated the factors associated with maintaining KPS exclusively in patients with glioblastoma[6,7]. Chaichana et al. investigated the factors associated with functional independence (KPS ≥ 60%) following surgery in a cohort of 544 patients with primary and secondary glioblastomas. They found that preoperative KPS ≥ 90%, seizures, primary glioblastoma, gross-total resection, and TMZ were associated with improved functional outcome, whereas older age, coronary artery disease, and new postoperative motor deficit were associated with decreased functional outcome. In their study, 40% of cases had secondary glioblastoma. However, in the present study, we only included patients with *IDH*-wildtype diffuse glioma with one of the following characteristics: *TERT* promoter mutation, *EGFR* amplification, and gain of chromosome 7 and loss of chromosome 10 (the so-called molecular glioblastoma)[24], in addition to histological *IDH*-wildtype glioblastoma, based on 2021 WHO classification of central nervous system tumors[10]. For glioblastoma, the combination of radiotherapy and TMZ is the standard therapy, and most patients have received these treatments. In their study, TMZ was used in only 29% of the patients. However, our study included only those who underwent these treatments, because it is important to identify the factors associated with maintenance of KPS among patients treated with standard treatment. The status of methylation of *MGMT* promoter has been recognized as a prognostic and predictive factor in glioblastoma[25]. Patients with methylated MGMT promoter show better responses to temozolomide and longer survival, consistent with our findings. In contrast, MGMT-unmethylated glioblastomas remain a significant challenge, emphasizing the need for novel therapeutic approaches to improve outcomes in this subgroup[26,27]. Because the maintenance of KPS is associated with survival time and response to treatment, the status of *MGMT* promoter methylation should be included in the analysis.

Sacko et al. reported that surgical resection (compared to biopsy) and low steroid dosage at RT onset were associated with longer survival time with functional independence[7]. Their study was limited to 84 cases of glioblastoma initially treated with concomitant RT and TMZ. Although their study was targeted at relatively uniform tumors, the status of *IDH1/2* was not checked. Because *IDH1/2* mutation is a driver mutation of IDH-mutant glioma and is associated with prognosis, *IDH*-mutant glioma has been distinguished from glioblastoma[10,28]. Moreover, as in the study of Chaichana et al., *MGMT* was not checked in their study.

Our findings suggest that maintaining KPS at the start of RT is important to prolong survival with KPS ≥ 50%. One way to reduce surgical dysfunction is to perform awake surgery[29]. Because of the rapid progression of glioblastoma, surgery is recommended as early as possible. However, owing to the need for various preoperative preparations, awake surgery is difficult to perform for glioblastoma. However, in recent studies, OS or PFS of patients with *IDH*-wildtype glioblastoma was not significantly different between groups that underwent surgery ≤ 7 days, > 7–21 days, or > 21 days from initial imaging[30]. Thus, it may be desirable to actively perform awake surgery even for glioblastoma to maintain KPS, even if the time to surgery is somewhat longer.

Some limitations of this study should be acknowledged. First, the relatively small sample size ($n = 98$) may restrict the generalizability of our findings. Future studies with larger cohorts are warranted to confirm the observed associations and to further investigate other potential factors affecting KPS maintenance in glioblastoma patients. Additionally, this was a retrospective study and the results may not be generalizable to all patients harboring glioblastoma. Approximately 1/3 of patients were excluded from this study because our study was limited to patients whose KPS at the start of RT was ≥ 50% and were treated with radiotherapy and TMZ. Finally, this study did not assess the contribution of Tumor Treating Fields (TTFields) to the maintenance of KPS. TTFields has been reported to prolong OS and has recently been incorporated into therapy[31]. However, it was excluded from the list of variables because it was used in only 7 patients (7.1%) enrolled in this study. In addition, while most patients received the standard Stupp protocol (60 Gy in 30 fractions), hypofractionated regimens (40.5 Gy in 15 fractions or 25 Gy in 5 fractions) were used for elderly patients. Although these variations are unlikely to have significantly influenced the results, their potential impact on maintaining KPS > 50 warrants further investigation. Compared to previous reports, notable features of our study are the uniformity of diagnosis and treatment, and the fact that the status of *MGMT* promoter was investigated.

In conclusion, for patients of glioblastoma, *IDH*-wildtype treated with radiotherapy and TMZ, KPS ≥ 80% at the initiation of RT, methylated *MGMT* promotor, and residual tumor size < 2 cm^3 were associated with longer survival time with maintenance of KPS at ≥ 50%. Since the status of *MGMT* promoter is identified postoperatively, neurosurgeons should endeavor to perform maximum possible surgical resection of the tumor without compromising the KPS at the start of radio-chemotherapy to prolong the period of KPS ≥ 50%.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Shigeo Ohba, Takao Teranishi, Masanobu Kumon, Daijiro Kojima, Kiyonori Kuwahara, Eriel Sandika Pareira, and Hikaru Sasaki. The first draft of the manuscript was written by Shigeo Ohba and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fujita Health University (Approval No. HM22-434).

Additional information
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