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RESEARCH

Revisiting prognostic factors of gliomatosis cerebri in adult-type diffuse gliomas

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Abstract

Purpose There is lack of comprehensive analysis evaluating the impact of clinical, molecular, imaging, and surgical data on survival of patients with gliomatosis cerebri (GC). This study aimed to investigate prognostic factors of GC in adult-type diffuse glioma patients.

Methods Retrospective chart and imaging review was performed in 99 GC patients from adult-type diffuse glioma (among 1,211 patients; 6 oligodendroglioma, 16 IDH-mutant astrocytoma, and 77 IDH-wildtype glioblastoma) from a single institution between 2005 and 2021. Predictors of overall survival (OS) of entire patients and IDH-wildtype glioblastoma patients were determined.

Results The median OS was 16.7 months (95% confidence interval [CI] 14.2–22.2) in entire patients and 14.3 months (95% CI 12.2–61.9) in IDH-wildtype glioblastoma patients**.** In entire patients, KPS (hazard ratio [HR] = 0.98, $P = 0.004$), no 1p/19q codeletion (HR = 10.75, $P = 0.019$), MGMTp methylation (HR = 0.54, $P = 0.028$), and hemorrhage (HR = 3.45, $P = 0.001$) were independent prognostic factors on multivariable analysis. In IDH-wildtype glioblastoma patients, KPS (HR = 2.24, $P = 0.075$) was the only independent prognostic factor on multivariable analysis. In subgroup of IDH-wildtype glioblastoma with CE tumors, total resection of CE tumor did not remain as a significant prognostic factor (HR = 1.13, $P = 0.685$).

Conclusions The prognosis of GC patients is determined by its underlying molecular type and patient performance status. Compared with diffuse glioma without GC, aggressive surgery of CE tumor in GC patients does not improve survival.

Keywords Glioma · Gliomatosis cerebri · Magnetic resonance imaging · Survival · World Health Organization

Introduction

Gliomatosis cerebri (GC) is defined as a diffuse glioma that exhibits an infiltrative growth pattern affecting at least three lobes of the brain while grossly maintaining the underlying normal brain architecture [1, 2]. Initially recognized as a distinct tumor type in the 2007 World Health Organization (WHO) classification, GC was later excluded in the subsequent 2016 and 2021 WHO classifications, due to the integrated diagnostic approach incorporating molecular genetics [3, 4]. Currently, GC is considered as a growth pattern within various types of diffuse gliomas, rather than a

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distinct pathological entity. However, the incidence of GC is relatively higher than anticipated, occurring in up to 8.2% of adult-type diffuse gliomas, and individuals with GC generally exhibit poorer prognosis when compared to diffuse glioma of corresponding tumor type [5].

Despite its relatively high incidence and poor prognosis, there is a lack of comprehensive evaluation on prognostic factors of adult-type diffuse glioma patients with GC. Previous investigations on prognostic factors of GC were conducted prior to the 2021 WHO classification. Majority of these studies did not reflect molecular information of adult-type diffuse gliomas and compared different tumor types which are now biologically distinct and separate tumors [6, 7], while other population-based studies on GC lacked information of tumor types [8]. Moreover, previous studies have not adequately addressed the recent paradigm shift concerning the extent of resection (EOR) in gliomas [9]. Specifically, these studies have failed to distinguish between contrast-enhancing (CE) and non-enhancing (NE) tumors, thereby overlooking potential differences in survival outcomes associated with the resection of CE or NE tumors. Although achievement of supramaximal resection (additional removal of NE tumors along with total resection of CE borders) is not feasible in GC due to its diffusely infiltrative nature, total resection of CE tumor is sometimes feasible in GC patients. Nevertheless, the impact of total resection of CE tumor remains unclear in GC patients.

In this study, we conducted a comprehensive analysis incorporating clinical, molecular, imaging and surgical data in GC patients to investigate independent prognostic factors.

Methods

Study population and demographic data

The study was conducted retrospectively, and informed consent from the patients were waived by the institutional review board of our institution (Approval no.: 4–2023-0045). From January 2005 to December 2021, a total of 1,473 adult patients diagnosed with diffuse glioma from our institution were initially recruited for this study.

Inclusion criteria comprised: 1) grade 2 to 4 diffuse gliomas confirmed by histopathology, 2) known IDH mutation, 1p/19q codeletion, and O^6-methylguanine-DNA methyltransferase promoter (MGMTp) methylation status, and 3) aged ≥ 18 years. Exclusion criteria included: 1) not fulfilling the radiologic and/or histologic diagnostic criteria for GC (n = 1,112), 2) lack of diagnostic information necessary to assign a specific WHO diagnosis, leading to diagnosis of IDH-wildtype diffuse glioma, not otherwise specified (n = 112), 3) diagnostic work-up results not readily allowing a WHO diagnosis, despite successful performance of diagnostic testings, leading to diagnosis of IDH-wildtype diffuse glioma, not elsewhere classified (n = 21), 4) follow-up loss within 3 months (n = 93), and 5) presence of H3 K27M alteration in midline-located tumors, leading to diagnosis of diffuse midline glioma, H3 K27-altered (n = 36).

A total of 99 patients with GC were included as our study cohort. Figure 1 shows the patient flowchart.

Molecular analysis

All patients were diagnosed according to the 2021 WHO classification [4]. Both innumohistochemical (IHC) analysis and peptide nucleic acid-mediated clamping polymerase chain reaction (PCR) were performed to detect IDH1/2 mutation. In IDH1/2-negative patients on IHC analysis, IDH1/2 status was confirmed by PCR. MGMTp methylation was evaluated by methylation-specific PCR. Fluorescent in situ hybridization analysis was performed to detect 1p/19q codeletion. All patients underwent evaluation for IDH1/2 mutation, 1p/19q co-deletion, and MGMTp methylation status.

ATRX loss and p53 expression were assessed by IHC analysis. ATRX loss was defined as less than 10% expression of positive tumor cells and more than 50% of nuclei stained for p53 was considered positive expression for p53. The presence of H3 K27M mutant protein was evaluated in midline located tumors. TERTp (telomerase reverse transcriptase promoter) mutation (C228T and C250T) was determined using a pyrosequencing assay. Since 2015, targeted next-generation sequencing (NGS) was performed using Illuminal Trusight Tumor 170 panel including EGFR gene amplification and chromosome + 7/-10 [10, 11].

In 32 (32.3%) patients, IDH mutation status was determined based on IHC and PCR results without targeted NGS results. ATRX loss, p53 protein expression, TERTp mutation, EGFR amplification, chromosome + 7/-10, and TP53 information were available in 88 (88.9%), 70 (70.7%), 81 (81.8%), 71 (71.7%), 39 (39.4%) and 68 (68.7%) patients, respectively.

MRI Protocol

Preoperative and postoperative brain magnetic resonance images (MRI) including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), post-contrast 3D T1-weighted images, post-contrast FLAIR and diffusion weighted images were acquired in a 3-T unit (Achieva or Ingenia; Philips Healthcare). Detailed parameters for MRI protocols are listed in Supplementary Material S1.

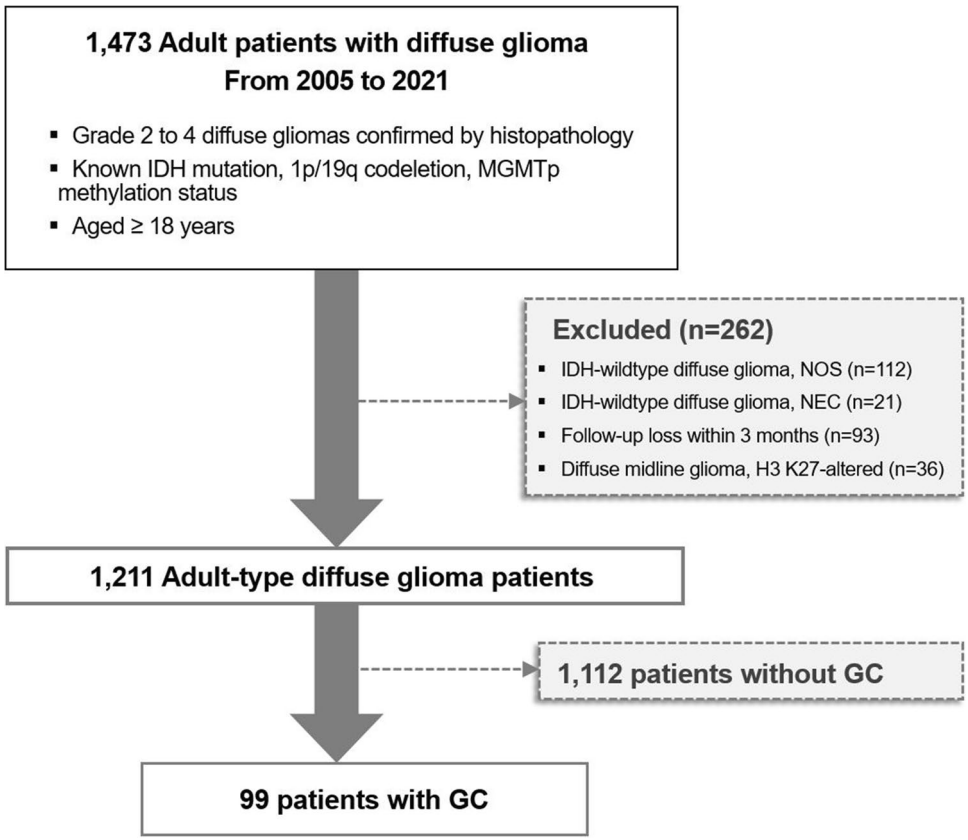

Fig. 1 Patient flowchart. GC = gliomatosis cerebri; IDH = isocitrate dehydrogenase; MGMTp = O^6-methylguanine-DNA methyltransferase promoter; NOS = not otherwise specified; NEC = not elsewhere classified

Imaging analysis

GC was defined in cases in which radiological and/or pathological findings were present: 1) T2-weighted and FLAIR images showing diffuse infiltration of tumor involving three or more consecutive lobes with relative preservation of the underlying anatomical architecture, and 2) pathological analysis confirming glial cell proliferation indicative of an infiltrative glioma [12].

Baseline preoperative MRIs were reviewed by two neuroradiologists (Y.W.P. and S.S.A., with 11 and 18 years of experience) in consensus. In preoperative MRI, the type of GC (either type 1 or type 2), location (supratentorial or infratentorial), presence of contrast enhancement, necrosis, hemorrhage, cystic change, presence of diffusion restriction, leptomeningeal metastases, and proportion of CE tumor > 5% were labeled. Type 1 GC encompassed gliomas characterized as GC without a discernable CE mass, while type 2 GC comprised of GC with formation of a discrete CE mass, according to the previous criteria [2].

Evaluation of extent of resection (EOR)

Bi-dimensional perpendicular measurement of the CE and NE tumor was performed in baseline and immediate postoperative imaging taken within 48 h. The EOR of CE and NE tumors was each labeled as either gross total removal (GTR) or non-GTR, and further categorized as GTR of both CE and NE tumors, GTR of CE tumor and non-GTR of NE tumor, non-GTR of both CE and NE tumor, and biopsy reflecting recent recommendations integrating gliomas with or without contrast enhancement [13, 14].

Clinical data analysis

Clinical data including age, sex, date of diagnosis, initial Karnofsky performance status (KPS), date of death or last follow-up were collected from the electronic medical record. All patients underwent adjuvant treatment conforming to the recommended guideline according to each tumor type [15, 16]. In case of radiotherapy, radiation fields included the extent of gliomatosis cerebri. Overall survival (OS) was defined as the duration from the initial surgery until death or last follow-up date.

Statistical analysis

Univariable and multivariable Cox proportional hazards regression modeling for OS was performed in the entire GC

patients and subgroup of GC patients with IDH-wildtype glioblastoma. Variables of interest on the univariable Cox proportional hazards regression models ($P < 0.05$) were included in the multivariable Cox proportional hazards regression modeling using backward elimination according to the likelihood ratio. Subgroup analyses was additionally performed in GC patients with CE tumor portion in IDH-wildtype glioblastoma, to determine if GTR of CE tumor improves survival. Survival rates were determined using the Kaplan–Meier method and curves which were compared using the log-rank test. For continuous variables, the cutoff point for Kaplan–Meier plots was determined using survMisc package. Statistical significance was set at $P < 0.05$. The data was analyzed using R version 4.3.2 including survMisc package [17, 18].

Results

Patient characteristics

Among 1,211 adult-type diffuse glioma patients, 99 adult-type diffuse glioma patients with GC (age range 18–89 years, 45 females and 54 males) were included. The median follow-up period was 54.0 months (95% confidence interval [CI] 33.2–121.1). Majority of the tumor types were IDH-wildtype glioblastomas (n = 77, 77.8%), followed by IDH-mutant astrocytomas (n = 16, 16.2%) and oligodendrogliomas (n = 6, 6.0%). GTR of both CE and NE tumors was not achieved in any of the patients due to the extensive infiltrative nature of GC. All patients underwent standard treatment according to the molecular type and grade [15]. The detailed patient characteristics of the study cohort are summarized in Table 1.

Table 1 Characteristics in the adult-type diffuse glioma patients with GC

Characteristics	Patients with GC (n = 99)
Clinical findings	
Age at diagnosis, years (95% CI)	57.4 (28.7–73.5)
Sex (female)	45 (45.5)
KPS (IQR)	80 (50–90)
Histopathological and Molecular findings	
WHO grade	
Grade 2	12 (12.1)
Grade 3	9 (9.1)
Grade 4	78 (78.8)
Molecular classification	
Oligodendroglioma	6 (6.0)
IDH-mutant astrocytoma	16 (16.2)
IDH-wildtype glioblastoma	77 (77.8)
Other molecular markers	
IDH mutation	22 (22.2)
1p/19q codeletion	8 (8.1)
MGMTp methylation	41 (41.4)
TERTp mutation, present/tested	68/81 (84.0)
EGFR amplification, present/tested	14/71 (19.7)
Chromosome + 7/-10, present/tested	3/39 (7.7)
TP53 mutation, present/tested	20/68 (29.4)
ATRX loss, present/tested	23/88 (26.1)
p53 protein expression, present/tested	16/70 (22.9)
MRI findings	
GC type	
GC type 1	22 (22.2)
GC type 2	75 (75.8)
Infratentorial location	3 (3.0)
Presence of contrast enhancement	83 (84.8)
Presence of necrosis	70 (70.7)
Leptomeningeal metastases	14 (14.1)
EOR	
GTR of both CE and NE tumors	0 (0)
GTR of CE and non-GTR of NE tumors	36 (36.4)
Non- GTR of both CE and NE tumors	44 (44.4)
Biopsy	19 (19.2)
Death	65 (65.7)
Median OS (95% CI)	16.7 (14.2–22.2)

CE = contrast-enhancing; CI = confidence interval; EGFR = epidermal growth factor receptor; EOR = extent of resection; GC = gliomatosis cerebri; GTR = gross total removal; IDH = isocitrate dehydrogenase; IQR = interquartile range; KPS = Karnofsky performance scale; MGMTp = O^6-methylguanine-methyltransferase promoter; NE = non-enhancing; OS = overall survival; TERTp = telomerase reverse transcriptase promoter; WHO = World Health Organization

Survival analysis in entire GC patients

The median OS was 16.7 months (95% CI 14.2–22.2) in entire patients**.** On univariable analysis, older age, sex, higher KPS, CNS WHO grade 4, IDH-wildtype, no 1p/19q codeletion, MGMTp methylation, GC type 2, presence of contrast enhancement, proportion of CE tumor > 5%, necrosis, diffusion restriction, cystic change, and hemorrhage were significant predictors of OS. On multivariable Cox analysis, higher KPS (HR = 0.98, $P = 0.004$), no 1p/19q codeletion (HR = 10.75, $P = 0.019$), MGMTp methylation (HR = 0.54, $P = 0.028$), and hemorrhage (HR = 3.45, $P = 0.001$) remained as independent prognostic factors. The univariable and multivariable Cox analysis results are show in Supplmentary Table 1. Figure 2 shows the Kaplan-Meir curves in entire GC patients according to molecular type of tumors (log-rank test, $P < 0.001$). Figure S1 shows Kaplan-Meir curves in entire GC patients according to KPS (log-rank test, $P = 0.001$), 1p/19q codeletion (log-rank test, $P = 0.001$),

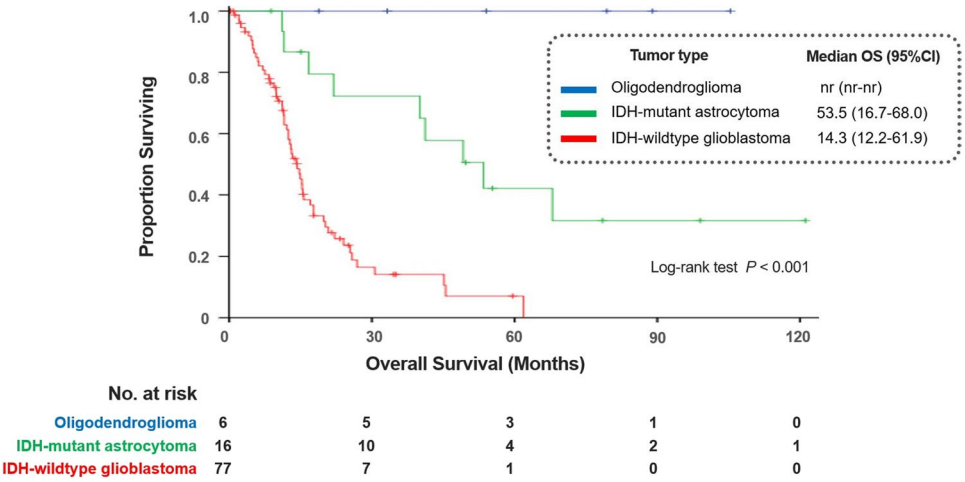

Fig. 2 Kaplan–Meier curve for overall survival of entire GC patients based on molecular type of tumor. CI = confidence interval; IDH = isocitrate dehydrogenase; OS = overall survival

MGMTp methylation (log-rank test, $P = 0.005$), and hemorrhage (log-rank test, $P < 0.001$).

Survival analysis in GC patients with IDH-wildtype Glioblastoma

The median OS was 14.3 months (95% CI 12.2–61.9) in IDH-wildtype glioblastoma patients**.** On univariable analysis in GC patients with IDH-wildtype glioblastoma (n = 77), older age, higher KPS, presence of CE tumor, proportion of CE tumor > 5%, diffusion restriction, and hemorrhage were significant predictors of OS. On multivariable analysis, high KPS (HR = 0.98, $P = 0.042$) was the only independent prognostic factor for OS. The univariable and multivariable Cox analysis results are show in Table 2. Figure 3(a) shows the Kaplan-Meir curve in GC patients with IDH-wildtype glioblastoma according to KPS (log-rank test, $P = 0.027$).

Table 2 Univariable and multivariable cox analyses of risk factors for stratifying OS in IDH-wildtype glioblastoma patients with GC

Variables	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Clinical findings				
Older age	1.04 (1.02–1.06)	0.001	1.02 (1.00–1.05)	0.092
Sex (female)	0.90 (0.68–1.18)	0.435		
Higher KPS	0.98 (0.96–0.99)	0.004	0.98 (0.97–1.00)	0.042
Molecular findings				
MGMTp methylation	1.01 (0.57–1.77)	0.986		
MRI findings				
GC type 2	2.45 (0.88–6.80)	0.086		
Infratentorial location	0.97 (0.29–3.20)	0.959		
Presence of CE tumor	4.77 (1.16–19.67)	0.031	-	-
Proportion of CE tumor > 5%	4.59 (1.40–15.03)	0.012	-	-
Necrosis	2.00 (0.94–4.27)	0.072		
Diffusion restriction	3.50 (1.09–11.26)	0.035	-	-
Cystic change	0.83 (0.11–6.05)	0.855		
Hemorrhage	3.09 (1.36–7.04)	0.007	2.24 (0.23–5.41)	0.075
Leptomeningeal metastases	1.12 (0.50–2.48)	0.786		
EOR		0.726		
GTR of CE and non-GTR of NE tumor	Reference	-		
Non-GTR of both CE and NE tumors	1.00 (0.54–1.84)	0.324		
Biopsy	1.29 (0.65–2.57)	0.382		

CE = contrast-enhancing; CI = confidence interval; EOR = extent of resection; GC = gliomatosis cerebri; GTR = gross total removal; HR = hazard ratio; KPS = Karnofsky Performance Scale; MGMTp = O^6-methyl guanine-methyltransferase promotor; NE = non-enhancing; OS = overall survival

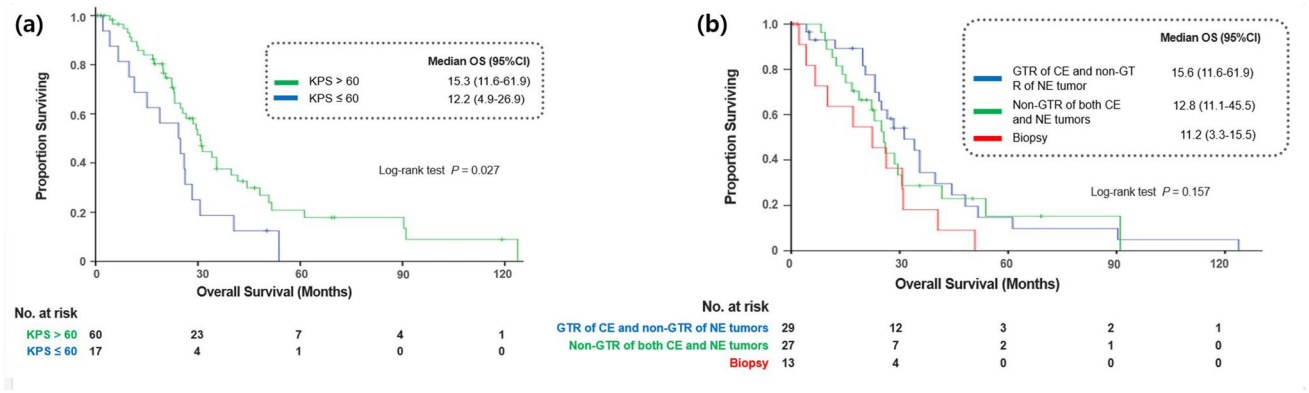

Fig. 3 **a** Kaplan–Meier curve for overall survival of GC patients with IDH-wildtype glioblastoma based on KPS. **b** Kaplan–Meier curve for overall survival of GC patients with IDH-wildtype glioblastoma and contrast enhancement based on EOR. CE = contrast-enhancing; CI = confidence interval; EOR = extent of resection; GC = gliomatosis cerebri; GTR = gross total resection; IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance status; NE = non-enhancing; OS = overall survival

Table 3 Univariable and multivariable cox analysis of risk factors for stratifying OS in subgroup of IDH-wildtype glioblastoma patients with GC and contrast enhancement

Variables	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Clinical findings				
Older age	1.03 (1.00–1.05)	0.032	1.01 (0.99–1.04)	0.066
Sex (female)	0.80 (0.46–1.39)	0.435		
Higher KPS	0.98 (0.96–1.00)	0.036	0.98 (0.96–1.00)	0.044
Molecular findings				
MGMTp methylation	0.74 (0.42–1.31)	0.306		
MRI findings				
Infratentorial location	0.77 (0.23–2.62)	0.680		
Necrosis	1.08 (0.46–2.56)	0.852		
Diffusion restriction	1.05 (0.14–7.65)	0.962		
Cystic change	0.74 (0.10–5.37)	0.761		
Hemorrhage	2.30 (0.88–6.02)	0.090		
Leptomeningeal metastases	0.97 (0.43–2.16)	0.942		
EOR		0.168		
GTR of CE and non-GTR of NE tumor	Reference	-		
Non- GTR of both CE and NE tumors	1.21 (0.66–2.22)	0.541		
Biopsy	2.03 (0.97–4.22)	0.060		

CE = contrast-enhancing; CI = confidence interval; EOR = extent of resect; GC = gliomatosis cerebri; GTR = gross total removal; HR = hazard ratio; KPS = Karnofsky Performance Scale; MGMTp = O^6-methylguanine-DNA methyltransferase promoter; NE = non-enhancing; OS = overall survival

On univariable analysis of subgroup of IDH-wildtype glioblastoma patients with CE tumor (n = 69), older age and higher KPS were significant predictors of OS. On multivariable analysis, higher KPS (HR = 0.98, *P* = 0.044) was the only independent prognostic factor for OS. Of note, EOR showed no significant association with OS (Table 3, *P* = 0.168; HR = 1.21, *P* = 0.541 for non-GTR of both CE and NE tumors, HR = 2.03, *P* = 0.060 for biopsy, reference group as GTR of CE and non-GTR of NE tumors). The median OS were 15.6 (95% CI 11.6–61.9), 12.8 (95% CI 11.1–45.5), and 11.2 (95% CI 3.3–15.5) months for GTR of CE and non-GTR of NE tumor, non-GTR of both CE and NE tumors, and biopsy, respectively (log-rank test, *P* = 0.157). Figure 3(b) shows the Kaplan–Meier curve in GC patients with IDH-wildtype glioblastoma and CE tumor according to EOR.

Discussion

Our study comprehensively analyzes the prognosis of GC patients reflecting the recent WHO classification encompassing clinical, molecular and imaging data. In the entire GC patients, higher KPS, presence of 1p/19q codeletion, presence of MGMTp methylation, and absence of hemorrhage were favorable prognostic factors. In subgroup analysis of IDH-wildtype glioblastoma patients, only higher KPS remained as an independent prognostic factor. Of note, GTR of CE tumor did not remain as an independent prognostic factor. Our findings suggest that the prognosis of GC is determined by its underlying molecular type reflecting the 2021 WHO classification. Furthermore, aggressive surgery of CE tumors may not be the preferable surgical approach in GC patients and thus the recommended surgical strategy of supramaximal safe resection in diffuse gliomas may not be applied in GC patients.

Previous studies on GC before the molecular era were restricted by the lack of integrated diagnosis comprising molecular information as well as small sample size [12, 19–21]. Previous studies lacked molecular information such as IDH mutation or 1p/19q codeletion status which are essential in diagnosing molecular types of adult-type diffuse gliomas [22], and may have analyzed misclassified tumor types based solely on histopathology. Thus, the prognostic implication of GC in line with the current 2021 WHO classification in adult-type diffuse glioma remains to be unveiled. Moreover, results from population-based studies should be interpreted with caution [8, 23]; population-based database prevents direct access to imaging, which may include inconsistently defined GC. Herein the imaging review of experienced neuroradiologists as well as clear and consistent definition of GC likely improved the reliability of our results.

Previous studies on patients with GC showed that performance status and molecular profile significantly affects prognosis [6, 7, 20, 24–26], which is also a consistent finding in glioma patients without GC. This finding is in line with our study results showing higher KPS, presence of 1p/19q codeletion, and presence of MGMTp methylation associated with longer OS in adult-type diffuse glioma patients with GC. Presence of 1p/19q codeletion indicates the diagnosis of oligodendroglioma, which is well-acknowledged for its relatively favorable prognosis [27], while MGMTp methylation is a well-known molecular marker in gliomas predicting better response to alkylating chemotherapeutic agents [28, 29]. In terms of imaging findings, presence of hemorrhage was significantly associated with poor prognosis in our study. Intratumoral hemorrhage may reflect the underlying tumor aggressiveness; it may be a result of tumor coagulopathy, or arise from dysplastic neoangiogenic vessels traversing necrotic areas or from large vessels that are invaded by the tumor [30–32].

In IDH-wildtype glioblastoma patients with GC, only preoperative KPS remained as a significant prognostic factor in our study. Of note, GTR of CE tumor did not show significant impact on survival within IDH-wildtype glioblastoma patients with CE tumor. To date, it is unclear whether extent of resection provides any survival benefit in GC. Majority of studies on GC mostly lacked results on surgical approach, owing to the fact that GC patients in these datasets predominantly underwent biopsy and analysis of the impact of surgical approach on survival was not possible [7, 20, 33–36]. Previous studies that provided results on surgical approach show discrepant results; several single-institutional studies [21, 37, 38] or population-based analysis [23] showed that extent of resection did not provide any survival benefit, while two meta-analyses showed that surgical resection was associated with improved outcomes [25, 39]. These studies were performed prior to the molecular classification, and lacks separate labeling of CE and NE tumors. Recent surgical guidelines separately label the EOR of CE and NE tumors, and recommend aggressive surgery of CE tumor when feasible [13, 40]. In patients with GC, neurosurgeons from our institution aim total resection of CE tumor when amenable. Thus, only 19.2% of GC patients from our dataset underwent biopsy while 36.4% of patients underwent GTR of CE tumor, enabling reliable prognostic analyses of extent of resection. However, this aggressive surgical approach failed to reach statistical significance on survival in GC patients. Our finding may provide solid evidence to the recommendation that IDH-wildtype patients with GC should be biopsied only [40].

This study has several limitations. First, this study is a retrospective single center study with a relatively small sample size. Despite the large number of adult-type diffuse glioma patients the sample size of patients with GC was small owing to the relatively low incidence of GC. Second, a substantial proportion (19.2%) of patients underwent limited diagnostic biopsy, which may possibly lead in undersampling of tumor. Third, we did not conduct volumetric assessment and analyses of EOR.

Conclusion

In conclusion, the prognosis of GC patients is determined by its underlying molecular type and performance. Compared with supramaximal resection recommended in IDH-wildtype glioblastoma patients without GC, aggressive surgery of CE tumor portion in GC patients may not improve survival and thus further studies should be conducted to address this issue.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-024-04656-9.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable response.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Informed consent from the patients was waived by the institutional review board of Yonsei University, College of Medicine (Approval no.: 4–2023-0045).

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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