Characteristics and prognostic factors of age-stratified high-grade intracranial glioma patients: A population-based analysis

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ABSTRACT

We evaluated characteristics and different prognostic factors for survival in age-stratified high-grade glioma in a U.S. cohort. Eligible patients were identified in the Surveillance, Epidemiology, and End Results (SEER) registries and stratified into 3 age groups: 20–39 years old (1,043 patients), 40–59 years old (4,503 patients), and >60 years old (5,045 patients). Overall and cancer-related survival data were obtained. Cox models were built to analyze the outcomes and risk factors. It showed that race was a prognostic factor for survival in patients 40 to 59 years old and in patients ≥60 years old. Partial resection was associated with lower overall survival and cause-specific survival in all age groups (overall survival: 20–39 yr: HR = 6.41; 40–59 yr: HR = 4.84; >60 yr: HR = 5.06; cause-specific survival: 20–39 yr: HR = 5.87; 40–59 yr: HR = 4.01; >60 yr: HR = 3.36). The study highlights that, while some prognostic factors are universal, others are age-dependent. The effectiveness of treatment approaches differs for patients in different age groups. Results of this study may help to develop personalized treatment protocols for glioma patients of different ages.

KEY WORDS: Age; intracranial glioma; prognosis; surveillance; Epidemiology and End Results (SEER) Program

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INTRODUCTION

Malignant glioma is one of the most common brain tumors, with an incidence of approximately 5 cases per 100,000 people, and accounting for about 30% of all intrinsic neoplasms of the central nervous system. Glioblastoma is the most common type of glioma, accounting for approximately 60% to 70% of all glioma cases. It is diagnosed at a median age of 64 years [1,2]. The updated World Health Organization (WHO) classification [3,4] divides glioma into four grades (I to IV) based on the histological features, as follows: Grade I (pilocytic astrocytoma), Grade II (diffuse astrocytoma), Grade III (anaplastic astrocytoma), and Grade IV (glioblastoma). Grade III and IV tumors are considered malignant or high-grade gliomas, which are often rapidly progressive brain tumors that include anaplastic astrocytoma, anaplastic oligodendroglioma, and glioblastoma on the basis of their histopathological features [3,4].

Currently, safe optimal surgical resection followed by adjuvant radiotherapy and chemotherapy is considered the standard treatment approach for glioblastoma patients. However, despite recent advances, the prognosis remains poor [5]. Curative resection is almost impossible due to the diffuse invasive nature of glioblastoma, and high recurrence rates are inevitable. Research on the pathogenesis and molecular mechanisms underlying glioma growth and progression is necessary to enhance early detection and develop new effective treatment modalities. Currently, increasing efforts are being made to identify biomarkers and genetic mutations that may provide guidance for choosing optimal personalized therapy plans and additional prognostic information [1,2]. Meanwhile, the most established prognostic factors in patients with malignant gliomas include advanced age, incomplete surgical resection, glioblastoma diagnosis, and poor Karnofsky Performance Status [1,2].

Patient age at diagnosis may reflect the underlying cause of the disease. Numerous reports have shown substantial differences in the molecular features underlying pediatric

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and adult high-grade gliomas, which may lead to different treatment responses [6]. For example, even though long-term survival is noted among pediatric cases, results observed in adults treated with combined radiation and chemotherapy still show a dismal prognosis, with a median survival of about 14 months [5]. It is also reasonable to hypothesize that the processes responsible for malignant transformation of brain tissue may differ between adults from different age groups. In such case, age-related survival prognostic factors may suggest underlying mechanisms of tumor development and aid in treatment selection. Thus, the aim of this study was to examine the factors influencing the outcome of high-grade intracranial gliomas among adults from different age groups using the United States (U.S.) Surveillance, Epidemiology, and End Results (SEER) database.

MATERIALS AND METHODS

Data source

This study involved a retrospective evaluation of cancer registry records from the SEER Program (www.seer.cancer.gov) Research Data (1973–2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch. SEER is a population-based registry sponsored by the National Cancer Institute, which collects data on cancer incidence and survival from 18 geographic areas in the U.S., including approximately 30% of the U.S. population [7]. SEER contains de-identified data, and analysis of the data does not require an Institutional Review Board (IRB) approval or informed consent from patients. We were granted permission by the National Cancer Institute, U.S. (reference number 15310-Nov2017) to access the research data files in the SEER program.

Study population

Patients with surgical therapy for intracranial glioma (the third edition of the International Classification of Diseases for Oncology [ICD-O-3] of C71.0 to C71.9) who received radiation after surgery were included. A surgical procedure that removes and/or destroys the tissue of the primary site was performed as part of the initial work-up or first course of therapy and was referred to by SEER as SEEReras part of the init(SS_SURG or SURGPRIF =10~80, 90). Histological types were limited to high-grade (GRADE=3 and 4) gliomas (ICD-O-3: including, glioblastoma, not otherwise specified [NOS], 9440/3; astrocytoma, anaplastic, 9401/3; gliosarcoma, 9442/3; oligodendroglioma, anaplastic 9451/3; ependymoma, anaplastic 9392/3; giant cell glioblastoma, 9441/3; and astroblastoma, 9430/3), as previously described [8]. Categorical age at diagnosis was: 20–39 years, 40–59 years, and ≥60 years as previously described [9]. Patients who did not undergo surgery or underwent unknown surgical procedures (SS_SURG or SURGPRIF=00, 98, 99) were excluded.

Study variables

The outcomes of the present study were overall survival and cause-specific survival. It was calculated from the day of diagnosis to the date of death, which was indicated as "Vital Status" in the SEER database. The variables obtained for each case included patient demographics (age at diagnosis, sex, and race), disease characteristics (grade of glioma and histology), and treatment modalities, including extent of performed surgery and radiotherapy.

Statistical analysis

Basic demographics and clinical characteristics of patients with high-grade glioma were presented as numbers and percentages for each age group. For each age group, univariate time-dependent Cox regression models (after testing for assumptions of a Cox proportional hazards model) were used to evaluate associations between overall survival, cause-specific survival, and potential prognostic factors. To avoid excluding important covariates, variables having $p < 0.2$ in univariate analyses were included in and evaluated by multivariate analyses. All p values were two-sided and $p < 0.05$ was considered statistically significant; hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated. All analyses were carried out using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of study subjects

We identified 10,591 eligible patients with primary high-grade glioma in the SEER database from 2005 to 2013 (Figure 1). The patients were stratified into 3 age groups: 20–39 years old (1043 patients), 40–59 years old (4503 patients), and ≥60 years old [5045 patients] (Table 1).

Clinical characteristics varied across age groups. The majority of patients were male (20–39 years: 60.1%; 40–59 years: 60.5%; >60 years: 57.2%), White (20–39 years: 84.7%; 40–59 years: 87.9%; >60 years: 90.6%), and with Grade 4 glioma (20–39 years: 53.5%; 40–59 years: 85.2%; >60 years: 92.9%), glioblastoma (20–39 years: 48.4%; 40–59 years: 81.9%; >60 years: 89.6%), frontal lobe tumor (20–39 years: 45.9%; 40–59 years: 33.1%; >60 years: 27.2%), beam radiation (20–39 years: 98.3%; 40–59 years: 98.6%; >60 years: 98.6%), and partial resection [20–39 years: 76.5%; 40–59 years: 76.8%; >60 years: 79.6%] (Table 1).

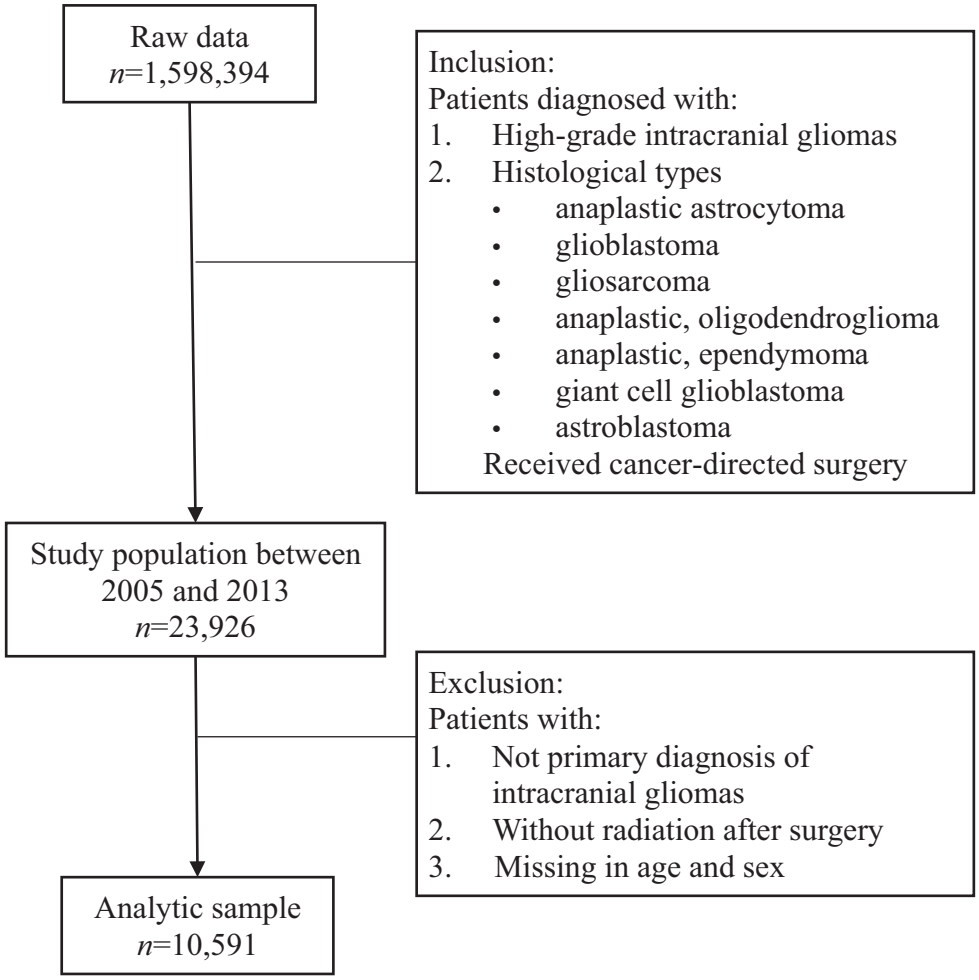

FIGURE 1. Flow diagram of the study population.

Risk of overall survival across different age groups

The univariate analysis of variables for patients 20–39 years old identified that partial resection (HR = 6.41; 95% CI = 4.08, 10.07) was associated with lower overall survival (Table 2).

In 40–59-year-old patients, the results showed that Black race (HR =1.36; 95% CI = 1.10, 1.67) and partial resection (HR = 4.87; 95% CI = 3.81, 6.23) were associated with lower overall survival (Table 2). The results remained significant in multivariate analysis after adjusting for gender and type of radiation (Table 3).

The results of patients ≥60 years old were similar to those of patients 20–39 years old, except that "other races" (HR =1.70; 95% CI = 1.28, 2.26) was associated with lower overall survival (Table 2). The results remained significant in multivariate analysis after adjusting for the type of radiation and extent of surgery (Table 3).

Risk of cause-specific survival across different age groups

For patients in 20–39 years old group, partial resection (HR = 5.95; 95% CI = 3.85, 9.20) was associated with lower cause-specific survival (Table 4). The results remained significant in multivariate analysis after adjusting for race (Table 5). In 40–59-year-old patients, the results showed that Black race (HR =1.35; 95% CI = 1.11, 1.65) and partial resection (HR = 4.05; 95% CI = 3.25, 5.06) were associated with lower cause-specific survival (Table 4). The results remained significant in multivariate analysis after adjusting for gender and type of radiation (Table 5).

For patients over 60 years old, Black race (HR = 1.31; 95% CI = 1.01, 1.68), other races (HR = 1.57; 95% CI = 1.20, 2.05), and partial resection (HR = 3.49; 95% CI = 2.76, 4.42) were associated with lower cause-specific survival (Table 4). The results remained significant in multivariate analysis after adjusting for type of radiation (Table 5).

DISCUSSION

To the best of our knowledge, the present study is one of the largest studies examining the factors influencing outcomes in different age groups in patients with high-grade intracranial glioma. We specifically aimed to determine prognostic factors for survival in high-grade intracranial glioma patients of different ages. We found that while some poor prognostic factors, such as glioblastoma, tumor site other than the cerebrum, and

TABLE 1. Basic demographics and clinical characteristics of patients with high-grade glioma from 2005 to 2013, stratified by age

Characteristics	20–39 years (*n*=1043)	40–59 years (*n*=4503)	≥60 years (*n*=5045)
	n (%)	*n* (%)	*n* (%)
Gender			
Male	627 (60.12)	2722 (60.45)	2884 (57.17)
Female	416 (39.88)	1781 (39.55)	2161 (42.83)
Race			
White	883 (84.66)	3957 (87.87)	4571 (90.60)
Black	59 (5.66)	299 (6.64)	238 (4.72)
Others	101 (9.68)	247 (5.49)	236 (4.68)
Grade of glioma			
Grade 3	485 (46.50)	666 (14.79)	356 (7.06)
Grade 4	558 (53.50)	3837 (85.21)	4689 (92.94)
Histologic type			
Glioblastoma	505 (48.42)	3687 (81.88)	4521 (89.61)
Astrocytoma, anaplastic	371 (35.57)	422 (9.37)	244 (4.84)
Gliosarcoma	13 (1.25)	111 (2.47)	140 (2.78)
Oligodendroglioma, anaplastic	100 (9.59)	208 (4.62)	93 (1.84)
Ependymoma, anaplastic	33 (3.16)	29 (0.64)	7 (0.14)
Giant cell glioblastoma	19 (1.82)	43 (0.95)	39 (0.77)
Astroblastoma	2 (0.19)	3 (0.07)	1 (0.02)
Location of tumor			
Cerebrum	37 (3.55)	97 (2.15)	81 (1.61)
Frontal lobe	479 (45.93)	1490 (33.09)	1372 (27.20)
Temporal lobe	216 (20.71)	11217 (27.03)	1511 (29.95)
Parietal lobe	120 (11.51)	707 (15.70)	915 (18.14)
Occipital lobe	26 (2.49)	206 (4.57)	268 (5.31)
Ventricle	10 (0.96)	21 (0.47)	16 (0.32)
Cerebellum	13 (1.25)	28 (0.62)	34 (0.67)
Brainstem	14 (1.34)	17 (0.38)	3 (0.06)
Overlapping lesion of brain	95 (9.11)	561 (12.46)	626 (12.41)
Brain	33 (3.16)	159 (3.53)	219 (4.34)
Type of radiation			
Beam radiation	1025 (98.27)	4441 (98.62)	4974 (98.59)
Radioactive implants	1 (0.10)	4 (0.09)	3 (0.06)
Radioisotopes	1 (0.10)	2 (0.04)	3 (0.06)
Combination of beam radiation with radioactive implants or radioisotopes	1 (0.10)	7 (0.16)	8 (0.16)
Radiation not specified	14 (1.34)	49 (1.09)	57 (1.1)
Extent of surgery			
Total resection	239 (22.91)	1013 (22.50)	994 (19.70)
Partial resection	798 (76.51)	3459 (76.82)	4016 (79.60)
Not specified	6 (0.58)	31 (0.69)	35 (0.69)
Survival status			
Alive	640 (61.36)	1573 (34.93)	1126 (22.32)
Dead	403 (38.64)	2930 (65.07)	3919 (77.68)
Cause-specific status			
Alive	657 (62.99)	1707 (37.91)	1356 (26.88)
Dead	386 (37.01)	2796 (62.09)	3689 (73.12)

partial resection were universal for patients in all age groups, others were age-dependent. For example, non-White races were poor prognostic factors of overall survival for patients older than 40 years old. Furthermore, mortality was associated with the histological type of glioblastoma in patients older than 60 years. On the other hand, non-cerebral site of tumor and glioblastoma diagnosis were significantly associated with mortality in the youngest group of adults. Importantly, the effectiveness of some treatment approaches differed among patients of different ages. For example, non-beam radiation was found to be associated with improved survival among older adult patients. In contrast, total resection was equally associated with improved survival in all age groups, and the effects of adjuvant radiation and surgery on the prognosis were independent of age. In addition, we found that patients who did not receive radiation treatment had even poorer survival outcomes.

Multivariate analysis revealed that black patients 40–59 years old had significantly higher risks of overall and cause-specific mortality compared with white patients.

TABLE 2. Univariate Cox regression analysis of overall survival in patients with high-grade glioma according to various clinicopathological variables, stratified by age[a]

Variables	20–39 years		40–59 years		≥60 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender						
Male	Ref		Ref		Ref	
Female	1.05 (0.82,1.34)	0.72	1.15 (1,1.32)	0.06	0.97 (0.83,1.13)	0.68
Race						
White	Ref		Ref		Ref	
Black	1.15 (0.78,1.69)	0.47	1.36 (1.10,1.67)*	0.004*	1.25 (0.94,1.66)	0.13
Others	1.41 (0.96,2.06)	0.08	1.20 (0.92,1.58)	0.19	1.70 (1.28,2.26)*	0.0003*
Grade of glioma						
Grade 3	Ref		Ref		Ref	
Grade 4	1.10 (0.86,1.41)	0.45	1.02 (0.86,1.23)	0.79	1.01 (0.77,1.32)	0.96
Histological type[b]						
Glioblastoma	Ref		Ref		Ref	
Non-glioblastoma	1.02 (0.79,1.3)	0.89	1.00 (0.84,1.18)	0.97	0.91 (0.72,1.16)	0.45
Type of radiation[c]						
Beam radiation	Ref		Ref		Ref	
Non-beam radiation	1.29 (0.53,3.14)	0.57	0.49 (0.21,1.13)	0.09	0.47 (0.2,1.12)	0.09
Extent of surgery						
Total resection	Ref		Ref		Ref	
Partial resection	6.41 (4.08,10.07)*	<0.0001*	4.87 (3.81,6.23)*	<0.0001*	5.30 (3.94,7.13)*	<0.0001*
Not specified	6.88 (2.06,22.93)*	0.002*	2.78 (1.23,6.27)*	0.01*	3.69 (1.54,8.89)*	0.004*

HR: Hazard ratio; CI: Confidence interval. [a]The covariates with $p<0.2$ in univariate models are included in multivariate models. [b]Because of the small numbers of patients who had intracranial glioma other than glioblastoma, all patients were divided into two histological types: Glioblastoma and non-glioblastoma. [c]Due to the small numbers of patients who underwent radiation therapy other than "beam radiation," patients were classified as the "beam radiation" group and the "non-beam radiation" group. *Statistically significant at $p<0.05$

TABLE 3. Multivariate Cox regression analysis of overall survival in patients with high-grade glioma according to various clinicopathological variables, stratified by age

Variables	20–39 years		40–59 years		≥60 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender						
Male	-		Ref		-	
Female			1.13 (0.98,1.30)	0.09		
Race						
White	-		Ref		Ref	
Black			1.28 (1.04,1.57)	0.02	1.29 (0.97,1.72)	0.08
Others			1.17 (0.89,1.54)	0.26	1.67 (1.25,2.23)	0.001
Grade of glioma						
Grade 3	-		-		-	
Grade 4						
Histological type[a]						
Glioblastoma	-		-		-	
Non-glioblastoma						
Type of radiation[b]						
Beam radiation	-		Ref		Ref	
Non-beam radiation			0.49 (0.21,1.12)	0.09	0.48 (0.2,1.16)	0.10
Extent of surgery						
Total resection	Ref		Ref		Ref	
Partial resection	6.41 (4.08,10.07)	<0.0001	4.84 (3.78,6.18)	<0.0001	5.06 (3.75,6.81)	<0.0001*
Not specified	6.88 (2.06,22.93)	0.002	2.77 (1.22,6.28)	0.02	3.42 (1.42,8.26)	0.01*

aHR: Adjusted hazard ratio; CI: Confidence interval. [a]Because of the small numbers of patients who had intracranial glioma other than glioblastoma, all patients were divided into two histological types: Glioblastoma and non-glioblastoma. [b]Due to the small numbers of patients who underwent radiation therapy other than "beam radiation," patients were classified as the "beam radiation" group and the "non-beam radiation" group. "-" indicates that corresponding variables were not included in the multivariate Cox regression analysis because they were not significant in the univariate Cox regression analysis. *Statistically significant at $p<0.05$

It is still not well established if and how racial differences contribute to glioma survival. Pan et al. [10] analyzed outcomes of glioblastoma in a population-based study, showing that Asian and Hispanic patients had a significantly lower risk of mortality compared to non-Hispanic Caucasian patients. In another study, Asian patients also had a lower risk of death

TABLE 4. Univariate Cox regression analysis of cause-specific survival in patients with high-grade glioma according to various clinicopathological variables, stratified by age[a]

Variables	20–39 years		40–59 years		≥60 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender						
Male	Ref		Ref		Ref	
Female	1.05 (0.82,1.34)	0.69	1.1 (0.96,1.26)	0.16	0.93 (0.8,1.07)	0.31
Race						
White	Ref		Ref		Ref	
Black	1.12 (0.77,1.65)	0.55	1.35 (1.11,1.65)*	0.003*	1.31 (1.01,1.68)*	0.04*
Others	1.42 (0.97,2.07)	0.07	1.16 (0.89,1.51)	0.28	1.57 (1.20,2.05)*	0.001*
Grade of glioma						
Grade 3	Ref		Ref		Ref	
Grade 4	1.11 (0.87,1.42)	0.41	1.1 (0.92,1.31)	0.29	1.06 (0.82,1.35)	0.67
Histological type [b]						
Glioblastoma	Ref		Ref		Ref	
Non-glioblastoma	1.03 (0.81,1.31)	0.81	0.91 (0.77,1.08)	0.28	0.90 (0.72,1.11)	0.32
Type of radiation[c]						
Beam radiation	Ref		Ref		Ref	
Non-beam radiation	1.24 (0.51,3.01)	0.64	0.44 (0.19,1.02)	0.06	0.46 (0.21,0.99)	0.05
Extent of surgery						
Total resection	Ref		Ref		Ref	
Partial resection	5.95 (3.85,9.20)*	<0.0001*	4.05 (3.25,5.06)*	<0.0001*	3.49 (2.76,4.42)*	<0.0001*
Not specified	6.06 (1.84,19.98)*	0.003*	2.05 (0.92,4.58)	0.08	4.21 (2.27,7.8)*	<0.0001*

HR: Hazard ratio; CI: Confidence interval. [a]The covariates with $p<0.2$ in univariate models are included in multivariate models. [b]Because of the small numbers of patients who had intracranial glioma other than glioblastoma, all patients were divided into two histological types: Glioblastoma and non-glioblastoma. [c]Due to the small numbers of patients who underwent radiation therapy other than "beam radiation," patients were classified as the "beam radiation" group and the "non-beam radiation" group. *Statistically significant at $p<0.05$

TABLE 5. Multivariate Cox regression analysis of cause-specific survival in patients with high-grade glioma according to various clinicopathological variables, stratified by age

Variables	20–39 years		40–59 years		≥60 years	
	aHR (95% CI)	*p*	aHR (95% CI)	*p*	aHR (95% CI)	*p*
Gender						
Male	-		Ref		-	
Female			1.09 (0.95,1.25)	0.23		
Race						
White	Ref		Ref		Ref	
Black	1.05 (0.71,1.55)	0.81	1.27 (1.04,1.55)*	0.02*	1.33 (1.03,1.72)*	0.03*
Others	1.28 (0.88,1.87)	0.20	1.13 (0.87,1.47)	0.37	1.56 (1.19,2.04)*	0.001*
Grade of glioma						
Grade 3	-		-		-	
Grade 4						
Histological type[a]						
Glioblastoma	-		-		-	
Non-glioblastoma						
Type of radiation[b]						
Beam radiation	-		Ref		Ref	
Non-beam radiation			0.44 (0.19,1.02)	0.06	0.46 (0.21,1.01)	0.05
Extent of surgery						
Total resection	Ref		Ref		Ref	
Partial resection	5.87 (3.79,9.08)*	<0.0001*	4.01 (3.22,5.01)*	<0.0001*	3.36 (2.65,4.25)*	<0.0001*
Not specified	5.63 (1.7,18.71)*	0.005*	2.05 (0.91,4.61)	0.08	3.89 (2.09,7.24)*	<0.0001*

aHR: Adjusted hazard ratio; CI: Confidence interval. [a]Because of the small numbers of patients who had intracranial glioma other than glioblastoma, all patients were divided into two histological types: Glioblastoma and non-glioblastoma. [b]Due to the small numbers of patients who underwent radiation therapy other than "beam radiation," patients were classified as the "beam radiation" group and the "non-beam radiation" group. "-" indicates that corresponding variables were not included in the multivariate Cox regression analysis because they were not significant in the univariate Cox regression analysis. *Statistically significant at $p<0.05$

and improved survival compared to Caucasian patients [11]. It is possible that genetic differences may contribute to the observed variations; however, more studies are required to address this question of race/ethnicity.

The impact of gender on the survival from glioma remains to be resolved. Some authors claim that female gender is a predictor of long-term survival [12], while others did not observe correlations between female gender and survival [13]. In the present study, although not significantly, female gender was found to be associated with poor overall and cause-specific survival in adults aged 40–59. Understanding the underlying causes of these gender differences may point to new targeted treatments for these aggressive tumors.

Postoperative adjuvant radiotherapy is a crucial element in the treatment plan of patients with glioma [5]. External beam radiotherapy is usually recommended to start within 2–4 weeks following surgical resection or biopsy. A number of studies showed that radiotherapy is a significant prognostic factor in the outcome of glioma patients and improves survival [11,14-16]. Dey et al. [17], however, reported that radiation treatment was not associated with a statistically significant benefit in survival in adult patients with high-grade brainstem astrocytoma. The results of the present study highlight that postoperative radiation therapy is associated with survival in patients aged 40–59 years and >60 years. Furthermore, the estimated HR for not receiving radiation treatment is the highest compared with other variables in patients aged >60, suggesting that postoperative radiation therapy should be strongly considered as part of the treatment plan for older adults. This result, combined with the finding that patients who did not receive radiation treatment in recent years (2005–2013) had even poorer survival outcomes, further highlights the importance of this treatment modality.

The relationship between the extent of glioma resection and patient outcome is still not clear. Complete curative resection is considered to be impossible due to the invasive behavior of the tumor and lack of clear tumor borders. Despite that, a number of studies have demonstrated the critical role of surgical resection in glioblastoma management [10,18-22]. Lacroix et al. [18] showed that a significant survival advantage was associated with a resection of 98% or more of the tumor volume (median survival 13 months), compared with resections of less than 98% (median survival 8.8 months). McGirt et al. [20] found that the median survival after maximal resection, near total resection, and subtotal resection was 13, 11, and 8 months, respectively. In a study by Sanai et al. [21], a significant survival advantage was seen with the resection of as little as 78% of tumor, and a stepwise improvement in survival was observed with an increased percentage of tumor resection. Pan et al. [10] also observed that gross total resection was associated with a survival advantage for patients compared to biopsy or partial resection. In addition, a recent meta-analysis by Brown et al. [22] reports that total resection substantially improves overall and progression-free survival of glioblastoma patients. Those authors suggested that total resection increases the likelihood of 1-year and-2-year survival by about 61% and 19%, respectively compared with partial resection. Moreover, the 1-year risk for mortality for partial resection was lower compared with biopsy, and the risk for mortality was reduced for any resection compared with biopsy at years 1 and 2. Our data are in agreement with the published literature and confirm the beneficial role of gross tumor resection in the survival of glioma patients of all age groups, confirming also the higher risk of mortality in those receiving partial tumor resection.

The feasibility and extent of surgical resection depend on tumor size and location in the brain. Supratentorial and cerebellar tumors are more accessible to surgical resection compared to tumors in the brainstem or diencephalon [23]. The results of the present study confirm that patients with tumors in the cerebrum have a better prognosis.

We should also mention the prognostic importance of molecular factors, including isocitrate dehydrogenase (IDH) mutations, telomerase reverse transcriptase (TERT) promoter mutation, and O^6-methylguanine-DNA-methyltransferase (MGMT) methylation status, among others. In particular, the powerful prognostic capability of TERT promoter mutations has been shown to predict a poorer disease course in individuals with glioblastoma, which is also associated with age at diagnosis [24]. IDH mutation and MGMT promoter methylation in combination with TERTp have been reported to be reliable prognostic biomarkers in Grades II to IV diffuse gliomas [25]. Although these biological factors are not available in SEER data, they will surely be important in future investigations of population-based outcomes in patients with high-grade glioma.

The strengths and limitations of this study arise from using the SEER database as a data source. This database is large and comprehensive and includes information on various tumor characteristics, follow-ups for vital status, and causes of death. Data are collected primarily from an institutional source, and findings are applicable to the general population with limited selection bias. In addition, a quality control program is conducted each year by the National Cancer Institute to evaluate the quality and completeness of the SEER data. Nevertheless, caveat remains as to generalize racial dominance of a disease from population-unadjusted cohort studies to the U.S. general population, of which White alone accounts for over 75% yet Black alone for less than 15%. This issue was illustrated in this study by the overwhelming predominance of white over black patients with high-grade gliomas (15:1), whereas the typical incidence rate of glioblastoma for the white population was roughly two times higher than that for the Black in the U.S. [26]. The information and details of chemotherapy and radiotherapy are under-reported in the SEER database. Positive effects of chemotherapy treatment in the management of glioma

patients were reported in several recent studies [27,28], and the lack of this information limits our analysis and may have potentially confounded our results. Similarly, information on previous brain lesions was not available to suggest secondary glioblastoma, which accounts for approximately 10% of all glioblastoma and that have a more indolent course of disease and better prognosis than primary glioblastoma. Finally, the SEER database lacks randomization, information on the preoperative neurological function, and other potential comorbidities.

CONCLUSION

The results of multivariate analysis in this study highlight that the effectiveness of treatment approaches differs in patients from different age groups. Specifically, beam radiation is effective in all age groups but is particularly important for older adult patients. In contrast, total resection is associated with improved survival in all age groups, and the effect of the sequence of radiation and surgery is independent of age. Furthermore, patients who did not receive radiation treatment had even poorer survival outcomes. The major findings of this study also appear to highlight the importance of gender in some age groups and race in other age groups. The results of this study may help in the development of personalized treatment protocols for glioma patients of different ages.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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