Association Between the Extent of Resection and Prognosis in Adult Patients With WHO Grade III Gliomas: a Population-based Study

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Abstract

Purpose

The role of surgical resection in the treatment of anaplastic glioma is poorly understood. The aim of the present retrospective study was to clarify the survival of patients with anaplastic gliomas.

Methods

We utilized the SEER database to assess the association between prognostic and demographic data, tumor characteristics, and treatment factors in adult patients with anaplastic glioma. Overall survival and cause-specific survival were analyzed using multivariable Cox regression and competing risk regression, respectively.

Results

A total of 3979 patients with anaplastic glioma who had undergone surgical intervention were included in the analysis. Patients who underwent gross total resection (GTR) had significantly better 5-year and 10-year overall survival (OS) (59.9% vs. 44.0%, 45.0% vs. 29.4%, $p < 0.001$) than those who did not. The 5-year and 10-year cumulative incidence rates of cancer-specific death in the GTR group were lower than those in the corresponding N-GTR group (36.6% vs. 51.9%, 49.9% vs. 65.5%, $p < 0.001$). Multivariable analysis identified GTR as an independent significant predictor for prolonged OS (HR:0.72; 95% confidence interval [CI] 0.65-0.79, $P < 0.05$) and cause-specific survival (CSS) (HR:0.72, 95% CI 0.65-0.80, $P < 0.05$). Further subgroup analysis revealed a stable association between the extent of resection and OS (P values for interaction > 0.05), except for tumor location and histologic type groups.

Conclusions

While the survival of patients with anaplastic glioma remains poor, GTR is associated with increased OS and CSS compared to N-GTR.

Introduction

Anaplastic gliomas account for 11%-20% of malignant brain and other central nervous system [1–3] and have poor prognosis despite active treatment. The 2016 World Health Organization (WHO) currently uses histological criteria to stratify anaplastic astrocytoma, oligodendroglioma, and oligoastrocytoma [4]. Most studies have reported the overall survival (OS) and predictors of survival in the anaplastic glioma population, of which several have revealed that surgery is associated with improved survival in WHO grade III gliomas [5–8]. The extent of resection for anaplastic gliomas has not been associated with survival [9, 10]. Therefore, the impact of the extent of resection (EOR) on improving survival in patients with this tumor type is currently unclear.

Few large-sample studies on surgery to facilitate long-term survival of WHO grade III gliomas have been conducted to date. Even if studies reported survival in this population, the follow-up time was short or the impact of other causes of death in this population was not considered [7, 11, 12]. Therefore, exploring trends in patients' survival of these tumors is necessary, including OS and cause-specific survival (CSS) [13, 14].

To facilitate evidence-based clinical decisions regarding the use of surgery in anaplastic gliomas, we aimed to explore whether patients who underwent gross total resection (GTR) can gain survival benefits compared with N-GTR using data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Study population

The clinical information and treatment data of patients with anaplastic glioma diagnosed between 2006 and 2018 released in August 2021 were extracted from the SEER database (2000–2018). The data release time was August 20, 2021. First, we focused on adult (aged ≥ 20 years old) patients with the following ICD-O-3 histology codes: 9382/3 (anaplastic oligoastrocytoma), 9401/3 (anaplastic astrocytoma), 9451/3 (anaplastic oligodendroglioma); and positive histology. Second, patients with a pathological glioma diagnosis and those with tumors located in the central nervous system (code C70.0-72.9) were selected. Third, patients without important information, including radiation after surgery, chemotherapy after surgery, OS status, and CSS status were excluded. Lastly, patients treated with no surgical primary tumor and surgical data were excluded. The final study population included patients treated with N-GTR (code 20, code 21) and GTR (codes 30, 40, and 55) [15] (Supplement.1). Our study findings were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. This was a retrospective study; therefore, the requirement for ethical approval and informed consent was waived for the present study.

Seer Coding And Covariates Included

The following demographic data were obtained for analysis: age at diagnosis (patients were divided into groups of 20-49 and 50+ years of age), gender, race (white, black, other, and unknown), marital status (single, married, other, and unknown), year of diagnosis (2006-2010, 2011-2015, and 2016-2018), and tumor location (supratentorial, infratentorial, brain overlap, and unknown). Regarding treatment options, the extent of surgery (N-GTR [biopsy and subtotal resection], GTR), and therapies after surgery (radiation [RT], chemotherapy [CT], no, and yes) were included. In the current study, OS was defined as the time from surgery to death from any cause, and CSS was defined as the time from surgery to death from anaplastic glioma.

Statistical analysis

Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate. The Kaplan–Meier curve (K-M) and log-rank test were utilized to provide univariable OS visualization, and multivariable Cox regression analysis of OS and subgroup analysis was also performed for each variable. Nelson-Aalen curve and Gray's test were utilized to provide univariable visualization of cause-specific death (CSD) when considering competing events, and Fine and Gray's competing risk regression was used to assess cause-specific survival.

All statistical analyses were performed using Free Statistics software version 1.3 (R Foundation for Statistical Computing, Version 3.3.2)[16]. Differences were considered statistically significant at $p < 0.05$.

Results

Baseline demographic and clinical information

A total of 3979 patients with anaplastic gliomas were included in the present analysis. Supplement.1 presents a flow chart of the participants. Among them, 2064 (51.87%) and 1915 (48.13%) underwent N-GTR and GTR, respectively. The proportion of patients under 50 years of age (54.71%) was higher than that over 50 years of age (45.29%). Factors associated with the extent of resection included age at diagnosis, sex, race, marital status, year of diagnosis, location, histologic type, radiation, and chemotherapy (Table 1). Most patients were white and married. The most common tumor location and histologic type was supratentorial (85.47%) and anaplastic astrocytoma (54.96%), respectively. Most postoperative patients received RT (76.28%) and CT (70.95%) in both arms.

Table 1

Distribution of histology, demographics and tumor characteristics of adult WHO Grade III gliomas

Parameters	Total (n = 3979)	N-GTR ^b (n = 2064)	GTR ^b (n = 1915)	Pvalue
Age at diagnosis n (%)				< 0.001 ^a
<50	2177 (54.71)	999 (48.40)	1178 (61.51)	
≥50	1802 (45.29)	1065 (51.60)	737 (38.49)	
Gender n (%)				0.617
Male	2285 (57.43)	1177 (57.03)	1108 (57.86)	
Female	1694 (42.57)	887 (42.97)	807 (42.14)	
Race n (%)				0.523
White	3428 (86.15)	1773 (85.9)	1655 (86.42)	
Black	237 (5.96)	123 (5.96)	114 (5.95)	
Other	285 (7.16)	156 (7.56)	129 (6.74)	
Unknown	29 (0.73)	12 (0.58)	17 (0.89)	
Marital status n (%)				0.120
Single	980 (24.63)	489 (23.69)	491 (25.64)	
Married	2387 (59.99)	1236 (59.88)	1151 (60.10)	
Other	455 (11.44)	246 (11.92)	209 (10.91)	
Unknown	157 (3.95)	93 (4.51)	64 (3.34)	
Year of diagnosis n (%)				< 0.001 ^a
2006-2010	1310 (32.92)	543 (26.31)	767 (40.05)	
2011-2015	1753 (44.06)	993 (48.11)	760 (39.69)	
2016-2018	916 (23.02)	528 (25.58)	388 (20.26)	
Location n (%)				< 0.001 ^a
Supratentorial	3401 (85.47)	1687 (81.73)	1714 (89.50)	
Infratentorial	93 (2.34)	63 (3.05)	30 (1.57)	

^a Statistical significance (p < 0.05)^b Abbreviation: N-GTR, Non-Gross total resection; GTR, Gross total resection.

Parameters	Total (n = 3979)	N-GTR ^b (n = 2064)	GTR ^b (n = 1915)	Pvalue
Brain overlap	351 (8.82)	223 (10.8)	128 (6.68)	
Unknown	134 (3.37)	91 (4.41)	43 (2.25)	
Histologic type n (%)				< 0.001 ^a
Anaplastic oligodendroglioma	844 (21.21)	386 (18.70)	458 (23.92)	
Anaplastic astrocytoma	2187 (54.96)	1249 (60.51)	938 (48.98)	
Anaplastic oligoastrocytoma	948 (23.83)	429 (20.78)	519 (27.10)	
Radiation n (%)				0.775
No	944 (23.72)	494 (23.93)	450 (23.50)	
Yes	3035 (76.28)	1570 (76.07)	1465 (76.50)	
Chemotherapy n (%)				0.897
No	1156 (29.05)	602 (29.17)	554 (28.93)	
Yes	2823 (70.95)	1462 (70.83)	1361 (71.07)	
^a Statistical significance (p < 0.05)				
^b Abbreviation: N-GTR, Non-Gross total resection; GTR, Gross total resection.				

Overall Survival and cause specific death of patients

The impact of patient OS was graphically presented in the K-M survival curves. The median survival was 45 and 101 months for the N-GTR and GTR patients, respectively. The 5-year and 10-year OS in the GTR group were 59.9% and 45.0%, respectively, which were higher than the corresponding values of 44.0% and 29.4% in the N-GTR group, respectively (Supplement.2). The five-year and ten-year OS of those who underwent N-GTR and those who underwent GTR differed significantly ($P < 0.001$) (Fig. 1). The cumulative incidence curve of the GTR group is illustrated in Fig. 2, accounting for causes of death as a competing risk. The 5-year and 10-year cumulative incidence rates of cancer-specific death in the N-GTR group were 51.9% and 65.5%, respectively, which were higher than the corresponding values of 36.6% and 49.9% in the GTR group, respectively (Supplement.3). The cumulative incidence function (CIF) was lower in patients who underwent GTR for cause-specific death ($P < 0.001$), and did not differ significantly between the N-GTR and GTR groups for other causes of death ($P = 0.689$).

Multivariable analysis for OS and CSS among patients with grade III gliomas

We employed multivariate Cox regression to adjust for confounding bias caused by unbalanced baseline variables and examine the prognostic effect of patients for OS and used competing risk regression to examine the prognostic effects of factors affecting CSS in our study (Table 2). We adjusted for known confounding variables between the two groups, including age, sex, race, marital status, year of diagnosis, location, histologic type, RT, and CT. Multivariate Cox regression analysis showed that these variables were independent influencing factors for OS. We found extent of resection was associated with an improved OS (HR: 0.72, 95% CI: 0.65-0.79, $P < 0.001$). Similar results were observed for CSS. Multivariate competing risk regression analysis revealed that age, gender, marital status, year of diagnosis, location, histologic type, extent of resection, RT, and CT influenced CSS independently. We also found extent of resection was associated with an improved CSS (HR: 0.72, 95% CI: 0.65-0.80, $P < 0.001$).

Table 2
Multivariable analysis for overall survival and cause-specific survival

Parameters	Overall survival		<i>p</i> value	Cause-specific survival		
	HR	95%CI		HR	95%CI	<i>p</i> value
Age(versus < 50 years)						
≥50	3.65	(3.30,4.04)	< 0.001 ^a	3.24	(2.91,3.60)	< 0.001 ^a
Gender(versus Male)						
Female	0.85	(0.78,0.94)	< 0.001 ^a	0.85	(0.76,0.94)	0.005 ^a
Race(versus White)						
Black	1.23	(1.02,1.48)	0.029 ^a	1.13	(0.93,1.38)	0.210
Other	0.84	(0.69,1.02)	0.085	0.82	(0.66,1.02)	0.077
Unkown	0.71	(0.32,1.59)	0.411	0.78	(0.35,1.76)	0.550
Marital status(versus Single)						
Married	1.06	(0.93,1.20)	0.385	1.06	(0.93,1.22)	0.360
Other	1.65	(1.40,1.94)	< 0.001 ^a	1.46	(1.22,1.76)	< 0.001 ^a
Unkown	1.09	(0.84,1.40)	0.513	1.02	(0.76,1.37)	0.910
Year of diagnosis(versus 2006-2010)						
2011-2015	0.90	(0.81,0.99)	0.040 ^a	0.89	(0.80,0.99)	0.031 ^a
2016-2018	0.74	(0.62,0.87)	< 0.001 ^a	0.68	(0.57,0.81)	< 0.001 ^a
Location(versus Supratentorial)						
Infratentorial	1.65	(1.28,2.13)	< 0.001 ^a	1.44	(1.05,1.99)	0.031 ^a
Brain overlap	1.34	(1.15,1.55)	< 0.001 ^a	1.37	(1.16,1.62)	< 0.001 ^a

^a Statistical significance (p < 0.05)

^b Multivariable model selected all parameters was forced into the model

Parameters	Overall survival		<i>p</i> value	Cause-specific survival		
	HR	95%CI		HR	95%CI	<i>p</i> value
Unkown	1.89	(1.51,2.36)	< 0.001 ^a	1.73	(1.29,2.31)	< 0.001 ^a
Histologic type(versus Oligodendroglioma, anaplastic)						
Astrocytoma, anaplastic	2.30	(2.01,2.62)	< 0.001 ^a	2.19	(1.89,2.53)	< 0.001 ^a
Aligoastrocytoma,anaplastic	1.03	(0.89,1.20)	0.677	1.06	(0.89,1.26)	0.510
Extent of resection (versus N-GTR)						
GTR	0.72	(0.65,0.79)	< 0.001 ^a	0.72	(0.65,0.80)	< 0.001 ^a
Radiation (versus No)						
Yes	0.79	(0.70,0.90)	< 0.001 ^a	0.80	(0.69,0.93)	0.003 ^a
Chemotherapy(versus No)						
Yes	0.65	(0.58,0.73)	< 0.001 ^a	0.81	(0.71,0.93)	0.002 ^a
^a Statistical significance (p < 0.05)						
^b Multivariable model selected all parameters was forced into the model						

Results of multivariate Cox analysis for overall survival in different subgroups

In the full cohort, GTR was associated with improved OS (HR: 0.72; 95% CI, 0.65-0.79; P<0.001) (Fig. 1, Fig. 3). Considering that age, tumor location, histologic type, radiation, and CT may influence the extent of resection in patients, we divided the cohort into five subgroups to perform subgroup analysis (Fig. 3). Data showed that tumor location and histologic type played an interactive role in the association between the extent of resection and OS (both P for interaction< 0.001). Patients with an infratentorial phenotype exhibited lower OS, but the differences were not statistically significant (HR: 1.32, 95% CI, 0.75-2.32, P =0.332). However, subgroup analysis was performed according to the confounders including age,

radiation, and chemotherapy, we did not find any significant interaction in these subgroups (P for interaction > 0.05 for all).

Discussion

With the power of the SEER database, data from 3979 patients with anaplastic glioma were included, including 2064 who underwent either biopsy or partial excision and 1915 who underwent GTR, which enabled us to perform multivariable OS and CSS analyses. In the present study, we found a significant association between GTR and prolonged survival. We employed multivariate Cox regression and competing risk models to reduce confounding bias, and our findings remained valid in these multivariate models.

The prognosis for anaplastic glioma remains poor despite combination treatment with surgery, RT, and CT [6]. In our cohort, 48.13% of patients with anaplastic glioma underwent complete resection, and our findings were consistent with those of previous studies, in which the percentage ranged from 30-60% in different reported cohorts [5, 17, 18]. Randomized controlled trials (RCTs) have shown that patients with anaplastic glioma are more likely to benefit from postoperative adjuvant treatment [19, 20]. We also found that anaplastic astrocytomas accounted for approximately 54.96% of cases, making them the highest proportion among all patients with anaplastic glioma. Most postoperative patients included in our study had received radiation (76.28%) and CT (70.95%) in both arms. A possible explanation is that AA has a relatively high proportion, while adjuvant RT can improve survival [3], and CT prolongs survival for cases of AO or AOA [21, 22].

Although improved survival has been correlated with greater extent of resection in anaplastic glioma [12, 18, 23, 24], the longer survival benefit has not yet been determined. Other clinical studies have also suggested that patients with anaplastic glioma might not benefit from surgical resection [9, 10]. Two measures of survival were calculated for each resection group, namely OS and CSS, as each of these measures has unique strengths [25]. Some studies analyzed 5-year OS instead of 10-year OS, and did not assess specific survival. We found that the 5-year and 10-year OS rates of the GTR group (59.9% and 45.0%, respectively) were higher than those of the N-GTR group (44.0% and 29.4%, respectively) ($p < 0.001$). This is consistent with the results of several other studies in which those who underwent GTR exhibited improved survival rates [5, 18]. However, OS analyses after tumor diagnosis may be heavily influenced by competing causes of death; therefore, the CSD rate was analyzed in the present study, taking deaths unrelated to anaplastic glioma and confounding bias into consideration. The 5-year and 10-year CSD rates of the GTR group were lower than those of the N-GTR group in our cohort ($p < 0.001$), whereas the difference in death from other causes between the two groups was similar ($p = 0.689$). After controlling for competitive risk [26], the extent of resection was not found to be associated with a decreased risk of CSD in patients with metastatic tumor. However, we found that the risk of CSD was higher in the N-GTR group than in the GTR group. We speculated that this might be related to the relatively long survival time of the patients in the present study. The results of our study demonstrated that GTR was associated with increased survival in these patients.

Several studies have analyzed the risk factors associated with survival among patients diagnosed with grade III gliomas, including age, sex, tumor location, histologic type, extent of resection, and postoperative adjuvant therapy [27] [28] [20, 29, 30]. However, few studies have reported the relationship between CSS and the extent of surgical resection in patients with anaplastic glioma. The GTR group was significantly associated with improved OS (HR: 0.72, 95% CI, 0.65-0.79, < 0.001) and CSS (HR: 0.72, 95% CI, 0.65-0.80, < 0.001) compared with the N-GTR group in the present study.

Interestingly, the association between OS and the extent of resection was stable for other clinical subgroups with respect to age, radiation, and CT. This showed that the extent of resection was positively associated with better OS in younger (HR: 0.65, 95% CI, [0.56-0.76] in N-GTR) or older individuals (HR: 0.78, 95% CI, [0.70-0.88] in GTR), in those who did not undergo radiation (HR: 0.82, 95% CI, [0.68-0.99] in N-GTR) or in those who did (HR: 0.70, 95% CI, [0.63-0.78] in GTR), and in no-CT groups (HR: 0.76, 95% CI, [0.65-0.90] in N-GTR) or in CT groups (HR: 0.70, 95% CI, [0.62-0.78] in GTR). However, the associations in GTR were not observed in the infratentorial site and histologic type compared with N-GTR (both p for interaction < 0.001). A possible explanation is that the aim of the surgical approach should be limited to infratentorial tumors due to the high incidence of surgery-related neurological impairment [31]. The benefit of maximal surgery may be attenuated in patients in AO or AOA-relevant subgroups because of the chemosensitivity of the histologic type [32]. GTR had OS benefits on cases of supratentorial tumors and AA subgroups [28]. The effect of surgical resection in patients with anaplastic glioma should be explored further.

This study had several limitations. First, information on tumor molecular data or patient functional performance, which are factors that affect survival, were missing from the SEER database. Second, the detailed CT regimen and RT dosage were not recorded in the SEER database. Third, EOR threshold values are important for anaplastic gliomas [33]. Fourth, the SEER database does not provide information on disease recurrence or subsequent treatment data.

Conclusion

In summary, the current study suggested that GTR could provide an OS and CSS advantage in cases of grade III glioma, particularly in patients with supratentorial tumors or anaplastic astrocytomas. This study provides valuable data for further clinical studies and highlights the need for more clinical studies on histologically diagnosed grade III gliomas.

Statements And Declarations

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Competing Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and no relevant financial or non-financial interests.

Author contributions

Dongjie He and Siying Zhu analyzed the data and drafted the paper. QiMing Wang, Gaiyan Li and Bing Zhang collected the data, QiMing Wang and YuHong Qi analyzed the data. QiuJu Shao and Hao Chang conceived and designed the idea to this paper. All authors drafted the work/revised, provided final approval of the version, and agree to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study.

Data Availability

The data were abstracted from an open database, the Surveillance, Epidemiology, and End Results (SEER) 18 Registries Data (<https://seer.cancer.gov/>). Researchers should use the link to request access to study data.

Ethics approval

This was a retrospective study. Therefore, the requirement for ethical approval and informed consent was waived for the present study.

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Figures

Figure 1

Kaplan–Meier survival curve of anaplastic glioma by extent of resection.

Figure 2

Cumulative incidence estimates of death of anaplastic glioma by extent of resection (red line and blue line: cancer-specific death; pink and black line: other cause of death).

Figure 3

Subgroup analyses of the association OS and extent of resection.

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