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Prognosis of Patients With Brainstem Glioblastoma Based on "age, surgery and radiotherapy": A SEER Database Analysis

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Abstract

Introduction: Primary brainstem glioma is a rare tumor with a dismal prognosis that poses significant treatment challenges. The purpose of the current study is to identify and determine prognostic factors associated with survival in high-grade brainstem glioma patients. **Methods:** We gathered the data from the SEER database for the duration of years from 1973 to 2016 to examine the survival of patients particularly reported with the high-grade brainstem glioma and subsequently ascertained the potential impact of demographic features, tumor, and clinical characteristics on the overall survival of these patients. The survival patterns were assessed using Kaplan-Meier curves and Cox proportional hazards models. Propensity score matching (PSM) analysis was performed between patients with or without radiation therapy based on age and surgical resection to investigate the effect of radiotherapy on overall survival (OS). **Results:** A total 232 patient's data were obtained from the SEER database and included in this study. The median overall survival was 8 months. Kaplan-Meier survival analysis delineated that the patients who were in younger age ($P = .001$) and underwent surgery ($P = .001$) exhibited typically a better prognosis. Among 232 patients, a total of 204 patients were categorized as radiotherapy group (RG) received radiation therapy whereas 28 patients were considered as nonradiotherapy group (NRG), who were not receiving radiotherapy. Radiotherapy was associated with an improvement in the overall survival without statistical significance ($P = .104$). PSM was performed between RG and NRG based on age and surgical resection. After the PSM, 56 patients were included. Overall Survival was significantly different between both groups ($P = .038$). **Conclusion:** Furthermore, the patients with high-grade brain glioma who received "both radiotherapy and chemotherapy" exhibited significantly longer survival compared to the patients who received chemotherapy alone. Multivariate analysis showed that treatment with surgery and radiotherapy were considered as the independent prognostic factors ($P < .05$).

Keywords

brainstem neoplasms, high-grade brainstem glioma, age, surgery, radiotherapy, chemotherapy, prognosis, SEER program

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Abbreviations

SEER, surveillance, epidemiology, and end results; PSM, propensity score matching; RG, radiotherapy group; NRG, nonradiotherapy group; CNS, central nervous system; OS, overall survival.

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Introduction

High-grade brainstem glioma is the most frequent and aggressive primary central nervous system (CNS) tumor, with an annual incidence rate of 3.19 per 100 000 individuals in the United States.[1] Several therapeutic strategies such as "maximal safe resection, radiotherapy with concurrent temozolomide chemotherapy, subsequent adjuvant temozolomide chemotherapy, bevacizumab" have been reported for the treatment of high-grade glioma. Despite the advancement in both diagnosis and treatment, the median survival of patients with high-grade glioma is only 14.6 months.[2] Primary high-grade brainstem glioma is a rare tumor and accounts for 10% to 20% among the other pediatric CNS tumors,[3] and less than 2% of adult CNS cases.[4,5] Due to the special characteristics of the brainstem, the clinical manifestations occurred in the incidence of brainstem glioma are eventually deteriorating, and resulting in a worse prognosis. Previous studies pertinent to supratentorial glioblastoma reported a significant correlation of variables such as the younger age, higher Karnofsky Performance Status (KPS), adjuvant chemotherapy, brachytherapy, and surgical resection with a better prognosis[6–8]; however, these variables were not well characterized for brainstem glioma, especially in high-grade brainstem glioma because of their rarity. The majority of the published studies on high-grade brainstem glioma are retrospective studies with relatively small cohorts.[9–11] SEER database is one of the largest population-based studies and delineates the specific correlation of variables such as surgery and radiotherapy with a better prognosis for several cancers including glioblastoma.[12–14] Thus, the purpose of the current study is to identify and determine prognostic factors associated with the survival in high-grade brainstem glioma based on the surgery, chemotherapy, radiotherapy, year of diagnosis in the patients using the data from the SEER database.

Materials and Methods

Data Source

Data collection was performed from the SEER database; the data acquired from this database was approved by the local ethical committee of the First affiliated hospital of Zhengzhou University for further analysis. Hence, our study does not require any ethical approval statement. The SEER database collects population-based cancer information from 18 registration centers in the United States, covering approximately 28% of the population. We obtained the patient data from the SEER Program between the years 1973 and 2016 who were diagnosed and histologically confirmed glioblastoma (ICD-O-3: 9440/3, N = 49 104) in the brainstem (primary site code C71.7). Among them, 269 patients with high-grade brain stem glioma were selected, subsequently, the patients without survival data or whose tumors were not their first or only primary lesion were excluded. Nineteen patients exhibited an overall survival (OS) time of 0 months. Hence, we removed these cases from the study to avoid bias occurring due to the therapeutic strategies and finally, a cohort of 232 patients was selected for the study (Figure 1).

SEER Coding and Variable Definition

Age at the time of diagnosis, gender, race, and marital status were considered demographic variables. The patient's age was assessed and divided into 0 to 18, 19 to 59, and ≥ 60 years old, respectively. The race was categorized into White, Black, Asian/Pacific Islander, American Indian/Alaska Native, and unknown. The marital status was registered as married, single, or divorced/widowed/separated for the adults who were > 18 years old. We measured the largest linear tumor size (in millimeters) and categorized it as < or ≥30 mm. Treatment variables used in this research include the extent of surgical resection, radiotherapy, chemotherapy, and the year of diagnosis. The extent of resections such as gross total resection, subtotal resection, unspecified, biopsy, or no resection based on previously described schemes were included for this study.[15] Patients who underwent the biopsy were categorized as nonresection group. Known receipt of chemotherapy and radiotherapy were coded as binary variables (yes vs no or unknown). The Year of diagnosis was dichotomized into a two-decade span: 1973 to 2002, 2003 to 2016.

Statistical Analyses for Survival and Prognosis

Descriptive analyses were used to describe the patient demographic and clinical characteristics. A total number of cases and percentages were shown in the study. The Kaplan-Meier survival curves with log-rank tests were used to compare OS among groups. PSM analysis was performed between the patients with or without radiation therapy based on the age and surgical resection in order to investigate the effect of radiotherapy on the OS. Cox proportional hazards and regression analyses were performed to assess potential prognostic factors associated with the patient's OS. All P values were two-sided and $P < 0.05$ were considered statistically significant. Statistical analyses were performed using the statistical software package SPSS version 26 (IBM, Armonk, NY).

Results

Patient Characteristics

A total of 232 patients were included in the study (Table 1) with an age range between 1 and 84 years, and with a median age of 35 years. The age distribution was as follows: 1 to 18 years (n = 87, 37.5%), 19 to 59 years (n = 104, 44.83%), and ≥ 60 years (n = 41, 17.67%). Comparatively the males were higher

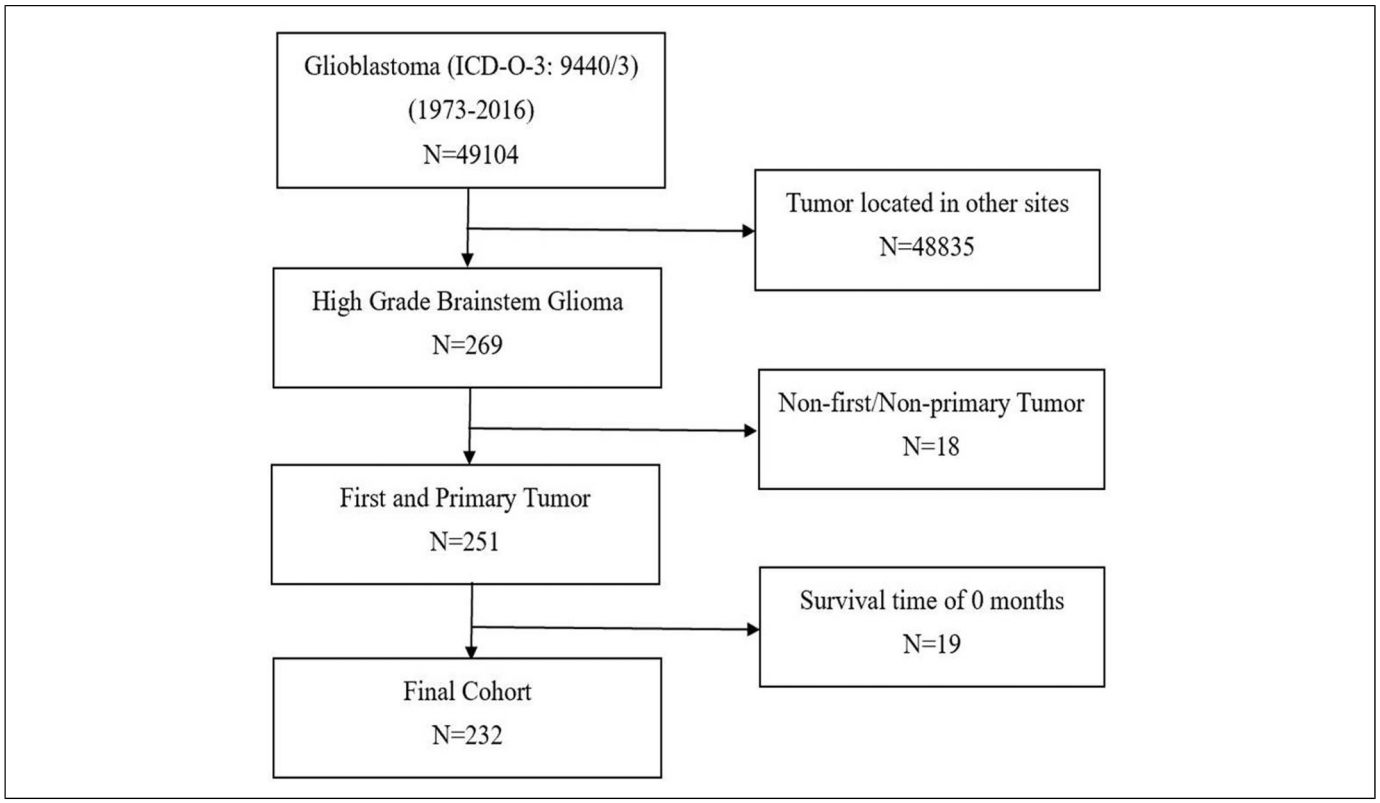

Figure 1. SEER database and patient selection flow diagram.

(n = 130, 56.03%) than the females. Most patients were White (n = 180, 77.59%), followed by Black (n = 29, 12.5%), Asian/Pacific Islander (n = 20, 8.62%), American Indian/Alaska Native (n = 2, <1%), and unknown (n = 1, <1%).

Among 232 patients, 62 patients (26.72%) were associated with tumors greater than or equal to the median tumor size of 30 mm, whereas 61 patients (26.29%) exhibited tumors smaller than the median size. Total of 109 patients (46.98%) were reported with tumors of unknown sizes. Furthermore, 80 patients (34.48%) were registered and underwent surgical resection, whereas 14 patients (6.03%) underwent a gross total resection, 58 patients (25.0%) underwent a partial resection, and 8 patients (3.45%) were unspecified for any kind of surgical intervention.

Overall, 152 (65.51%) patients underwent the nonsurgical resection, including 48 patients (20.68%) to whom the biopsy was performed. Moreover, the majority of patients received radiotherapy (n = 204, 87.93%). Total 134 (57.76%) patients have received chemotherapy.

The median OS of the patients was 8 months (95% CI [6.89-9.11 months]); For 6-month, 9-month, 1-year, 2-year, and 3-year duration, the survival rates were observed as 59.6%, 42.2%, 31.8%, 11.5%, and 6.5%, respectively (Figure 2).

Univariable and Multivariable Analysis

The impact of demographics variables, tumor size, and treatment factors on OS were compared using Kaplan-Meier survival curves. Among these parameters, the younger age ($P = .001$) and surgery ($P = .001$) were reported with a better prognosis (Figures 3 and 4). In addition, the majority of the patients (n = 204, 87.93%) received radiotherapy (radiotherapy group: RG), whereas 28 patients did not receive radiotherapy (nonradiotherapy group: NRG) for the entire study population. Radiotherapy resulted in a significant improvement in the OS without statistical significance ($P = .104$) (Figure 5a). Total 130 patients received both radiotherapy and chemotherapy (56.03%), whereas 74 patients (31.9%) received radiotherapy alone, 4 patients (1.72%) received chemotherapy alone, and 24 patients (10.34%) did not receive either.

OS was significantly longer in the radiotherapy and chemotherapy cohort (median: 9 months, 95% CI [7.7-10.3 months]) when compared to those with chemotherapy alone (median: 4 months, 95% CI [1.5-6.5 months], $P = .001$). There was no significant difference observed between other groups as depicted in Figure 5b. To explore the clinical efficacy of radiotherapy efficiently, a 1:1 nearest-neighbor PSM with a caliper width of 0.02 was performed between the RG and NRG based on the age and surgical resection. After PSM, a total of 56 patients were included (n = 28 each) of similar age, who underwent surgery. OS was significantly different between both of these groups (RG vs NRG: 9.0 vs 4.0 months, $P = .038$) (Figure 5c).

Total 152 cases registered after the year 2002 and further, they were included in the analysis. Most of the patients received chemotherapy (n = 105, 69%) and there was no difference observed with the chemotherapy intervention (yes vs no: 9.0 vs 5.0 months, $P = .082$) (Figure 6a). Patients who received radiation therapy lived

Table 1. Distribution of Demographics, Tumor, and Treatment Characteristics of High-Grade Brainstem Glioma.

Parameters	Total ($N = 232$)
Age, median (range)	35 (1-84)
Age, categorized	
1-18 years, *n* (%)	87 (37.5)
19-59 years, *n* (%)	104 (44.83)
≥ 60 years, *n* (%)	41 (17.67)
Gender	
Male, *n* (%)	130 (56.03)
Female, *n* (%)	102 (43.97)
Race	
White, *n* (%)	180 (77.59)
Black, *n* (%)	29 (12.5)
Asian/Pacific Islander, *n* (%)	20 (8.62)
American Indian/Alaska Native, *n* (%)	2 (<1%)
Unknown, *n* (%)	1 (<1%)
Marital status	
>18 years, *n* (%)	145 (62.5)
Married, *n* (%)	59 (25.43)
Single, *n* (%)	69 (29.74)
Divorced/widowed/separated, *n* (%)	17 (7.33)
Tumor size	
≥30 mm, *n* (%)	62 (26.72)
<30 mm, *n* (%)	61 (26.29)
Unknown, *n* (%)	109 (46.98)
Surgery	
No, *n* (%)	152 (65.51)
Yes, *n* (%)	80 (34.48)
Gross total resection	14 (6.03)
Partial resection	58 (25.0)
Unspecified	8 (3.45)
Radiotherapy	
Yes, *n* (%)	204 (87.93)
No, *n* (%)	28 (12.07)
Chemotherapy	
Yes, *n* (%)	134 (57.76)
No, *n* (%)	98 (42.24)
Radiotherapy + Chemotherapy (RC), *n* (%)	130 (56.03)
Year of diagnosis	
1973–2002, *n* (%)	80 (34.48)
2003–2016, *n* (%)	152 (65.52)

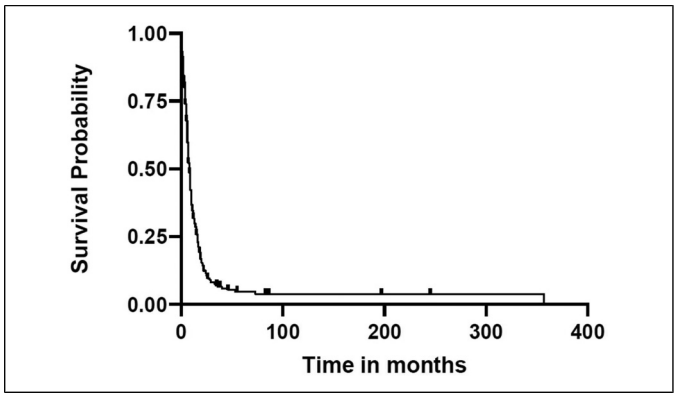

Figure 2. Kaplan-Meier overall survival curves for the entire patient cohort of 232 SEER high-grade brainstem glioma patients.

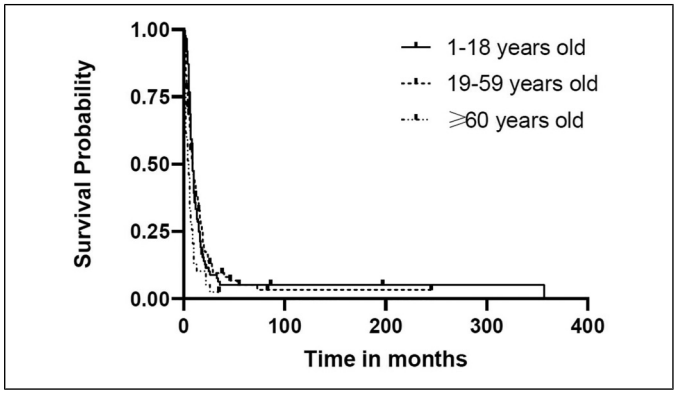

Figure 3. Kaplan-Meier survival curves for the patient cohorts of different age groups.

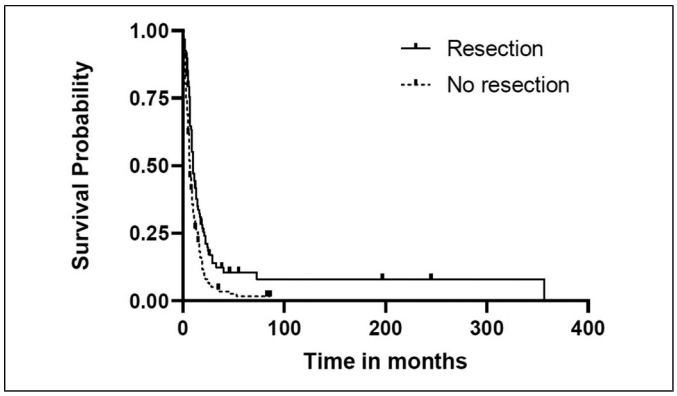

Figure 4. Kaplan-Meier survival curves for the entire cohort of patients with or without resection.

significantly longer period (n = 132, 86.8%, median: 9 months, 95% CI, 7.28-10.72 months) when compared to the patients who were not received radiotherapy (n = 20, 13.2%, median: 3 months, 95% CI 1.25-4.74 months, $P = .001$) (Figure 6b). Among these, most of the patients received both "radiotherapy and chemotherapy" (n = 102, 67.11%), whereas 30 patients (19.74%) received radiotherapy alone, and 3 patients (1.97%) were treated with chemotherapy alone. Finally, 17 patients (11.18%) did not receive either. Patients who received a regimen of "radiotherapy and chemotherapy" lived significantly longer period (median: 9 months) when compared to the patients who received chemotherapy alone (median: 4 months, $P = .001$) and the patient cohort without any treatment regimen (median: 3 months, $P = .001$) (Figure 6c).

The multivariable model cannot be included in this study due to the limited number of patients; the selected variables mainly included for this study were age, surgery, and radiotherapy. In the multivariate Cox proportional hazard regression analysis, surgery (HR = 0.582, [0.431, 0.787], $P = .001$) and radiotherapy (HR = 0.609, [0.399, 0.928], $P = .029$) were independently associated with a better OS of the patients.

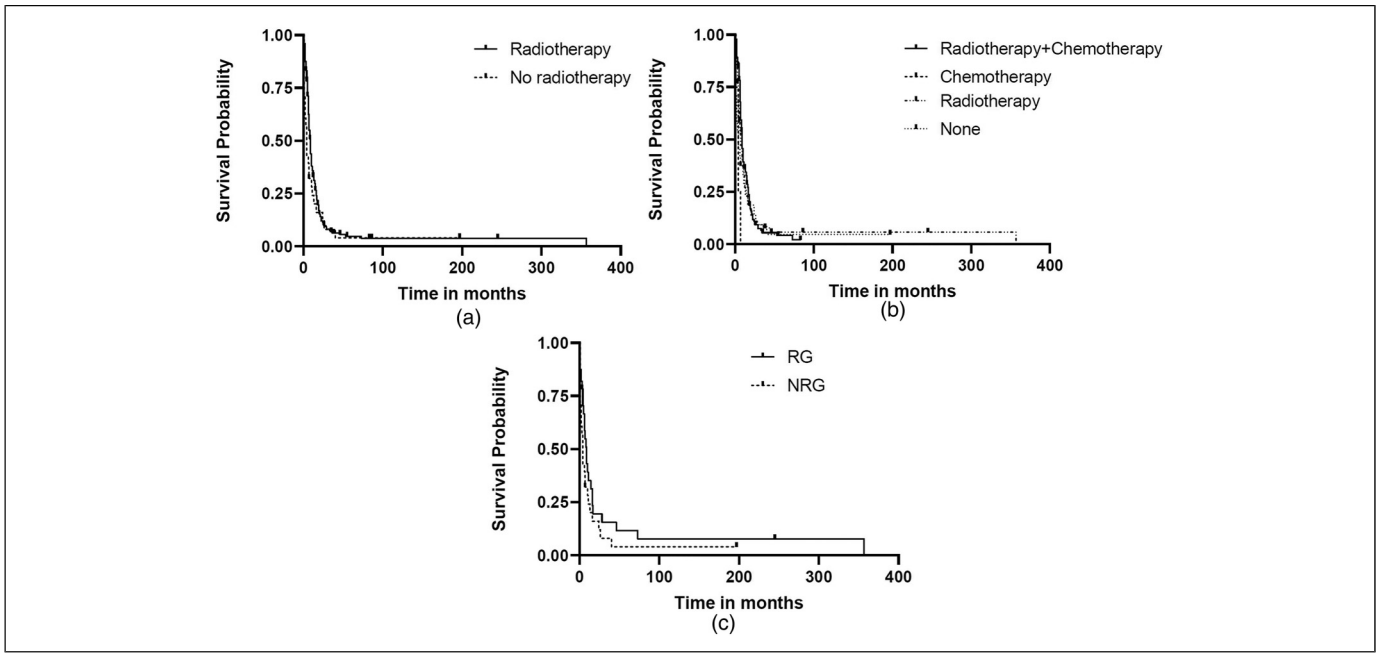

Figure 5. (a) Kaplan-Meier survival curves for the entire cohort of patients with or without radiotherapy. (b) Kaplan-Meier survival curves for the patients who received both radiotherapy and chemotherapy, chemotherapy alone, radiotherapy alone, and none. (c) Kaplan-Meier survival curves for the 56 patients with or without radiotherapy, (RG vs NRG: 9.0 vs 4.0 months, $P = .038$) were performed after PSM analysis based on the age and surgical resection.

Discussion

This study is one of the largest population-based cohorts, which benefits oncologists, clinicians to examine the effects of demographic variables, tumor size, and treatment factors on the overall patient's survival during high-grade brainstem glioma.

Surgical intervention in the brainstem region during the treatment of brainstem glioma was previously considered controversial due to the poor prognosis, and various other safety concerns. Advancement in microsurgical techniques, electrophysiological monitoring, efficient neuroimaging, and neurointensive care support, has facilitated the surgical intervention for brainstem lesions as an alternative option to enhance the OS by choosing a suitable therapeutic regimen.[16–18] Doyle et al[19] reported a group of 103 brainstem high-grade glioma adult patients who underwent surgical intervention. In this study, the median survival for the patients receiving gross total resection, subtotal resection, and biopsy were 16, 11, and 8 months, respectively. A higher OS was observed in "gross total resection" (HR = 0.24, $P < .001$) and subtotal resection group (HR = 0.32, $P = .006$) when compared to the patients who underwent biopsy. A similar conclusion was obtained in pediatric patients with glioblastoma. Khalid et al[20] described that partial resection (HR = 0.11, $P < .001$) and gross-total resection (HR = 0.03, $P < .001$) were associated with a prolonged OS. Our findings also indicated that the surgery has yielded considerably a favorable outcome, concluding that the patients who have been receiving surgical resection survived for longer days than the patients who have not received surgical resection. It is crucial to preserve the nerve function and quality-of-life after the surgery in glioblastoma.[21] In addition, the resection should be performed by experienced surgeons in highly selected patients.

In the case of adult glioblastoma, radiotherapy is considered the standard treatment and reported as a good clinical response rate by mitigating tumor progression.[22,23] However, only a few studies focused on the prognosis of patients with high-grade brainstem patients; and the adult high-grade brainstem glioma patients received typically minimal benefit during the radiotherapy.[15] The variable median survival was reported between the patients who received radiotherapy (1 month) and those who were not received (9 months), without a statistical difference. Moreover, the survival analysis was not performed in the patients of different histopathological grading. In a previous study of pediatric patients with high-grade brainstem glioma, radiotherapy significantly improved the OS at 6 and 9 months but not beyond these periods.[22,23] Patients with glioblastoma who received radiotherapy were reported with a rise in the OS rate when compared to the patients who have not received radiotherapy (9.0 vs 3.0 months; $P < .001$). However, radiotherapy has not delivered statistically significant improvement in the OS of patients with anaplastic astrocytoma.[24] In this present study, most of the patients (n = 204, 87.93%) received radiotherapy, only 28 patients have not received radiotherapy. Radiotherapy was associated with an improvement in the OS without any statistical significance. OS was significantly higher in the patient group received both radiotherapy and chemotherapy (median: 9 months,

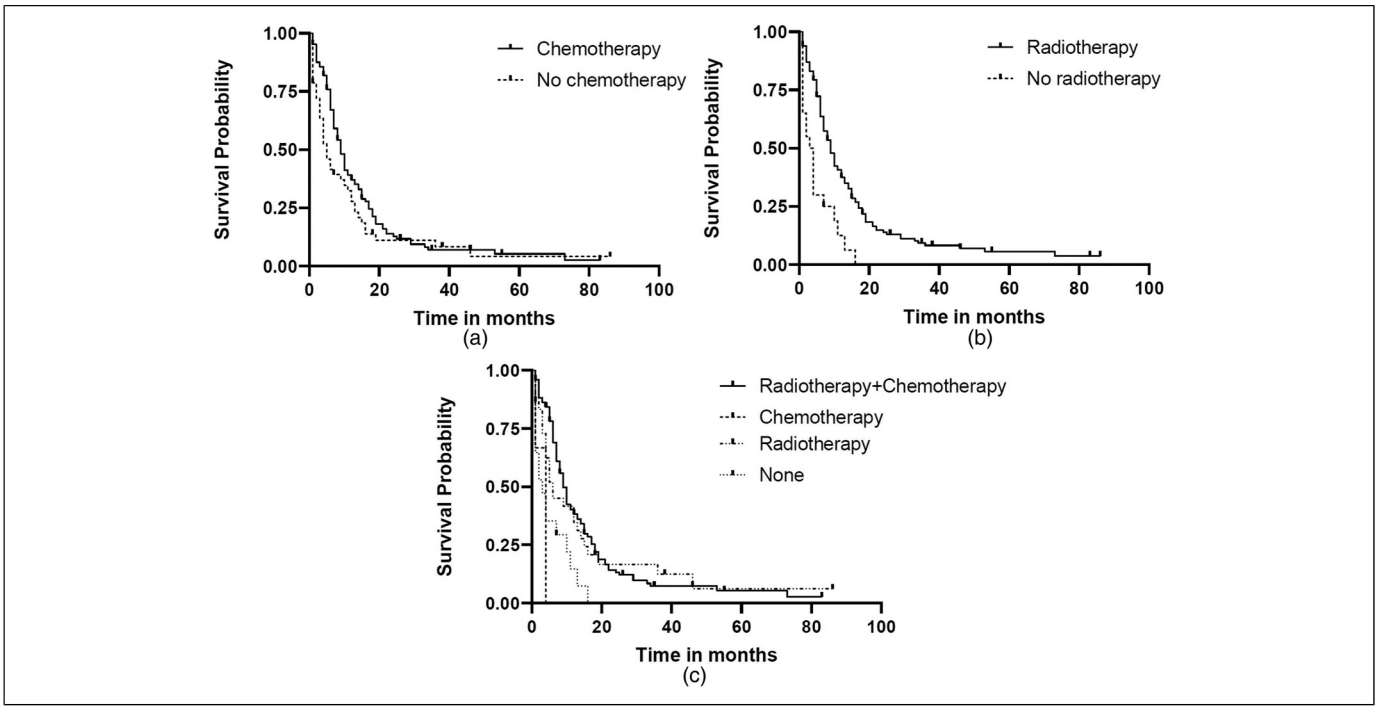

Figure 6. Kaplan-Meier survival curves for the patients diagnosed after 2002. (a) With or without chemotherapy. (b) With or without radiotherapy. (c) With or without radiotherapy and chemotherapy.

95% CI [7.7-10.3 months]) than the patient cohort received chemotherapy alone (median: 4 months, 95% CI [1.5-6.5 months]), $P = .001$]. During PSM analysis with the patient's age and surgical resection, the OS was significantly different between both groups (RG vs NRG: 9.0 vs 4.0 months, $P = .038$). These results delineated the importance of radiotherapy in high-grade brainstem glioma, however, due to its small sample size and retrospective study design, the conclusions of this study should be further confirmed using large patient size cohorts.

Overall clinical outcomes produced by the therapeutic regimen of adjuvant temozolomide with radiotherapy have been reported as significant in the adult patients, who were newly diagnosed with glioblastoma,[25] but not significant in the pediatric patients with glioblastoma.[25,26] The results of our study suggested that neither children nor adults could benefit from chemotherapy even after 2002, which was possible because of the poor prognosis of brainstem glioma itself and inappropriate chemotherapy regimens.

There are some limitations to this study. The quality of our study is limited to the quality of data available from the SEER database. SEER database contains minimal information about the location and focality of lesions, the extent of surgical resection, radiation dose or type, and chemotherapy regimens. There was no information of molecular markers such as isocitrate dehydrogenase (IDH) and H3 status, and we could not define whether the tumor originated from the midbrain, medulla, or pons, and we also could not define whether the tumor was focal or diffuse based on the data available in the SEER database. High-grade astrocytic neoplasms have been significantly modified in recent years, although only glioblastoma (ICD-O-3: 9440/3) were included in our study, other types of gliomas such as IDH-mutant, diffuse midline glioma, H3 K27-altered, diffuse hemispheric glioma, H3 G34-mutant, diffuse high-grade pediatric-type, H3-wild type, and IDH-wild type might be included in the meantime. Thus, we present this study specifically for the better prognosis of patients with high-grade brainstem glioma.

Conclusion

Our study concluded that high-grade brainstem glioma, surgery, and radiotherapy are associated with a better prognosis. Patients predominantly who received "both radiotherapy and chemotherapy" exhibited longer periods of survival and this study significantly delineates the clinical benefits to choose specific personalized oncomedicine for the treatment of high-grade brainstem glioma.

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Ethics Approval and Consent to Participate

Not applicable: Data collection was performed from the SEER database; the data acquired from this database was complete with authorized approval of the committee of the First affiliated hospital of Zhengzhou University for further analysis. Hence, our study does not require any ethical approval statement.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Availability of Data and Materials

Supplemental material was attached as a separate file.

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References

1. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro Oncol.* 2016;18(suppl5): v1-v75.
2. Stupp R, Mason WP, Van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
3. Jallo GI, Biser-Rohrbaugh A, Freed D. Brainstem gliomas. *Child's Nerv Syst.* 2004;20:143-153 (2004).
4. Guillamo J-S, Monjour A, Taillandier L, et al. Brainstem gliomas in adults: prognostic factors and classification. *Brain*. 2001;124(Pt12):2528-2539.
5. Salmaggi A, Fariselli L, Milanesi I, et al. Natural history and management of brainstem gliomas in adults. *J Neurol.* 2008;255(2):171-177.
6. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol.* 2004;6(3):227-235.
7. Pan I-W, Ferguson SD, Lam S. Patient and treatment factors associated with survival among adult glioblastoma patients: a USA population-based study from 2000–2010. *J Clin Neurosci.* 2015;22(10):1575-1581.
8. Lam S, Lin Y, Zinn P, Su J, Pan I-W. Patient and treatment factors associated with survival among pediatric glioblastoma patients: a surveillance, epidemiology, and end results study. *J Clin Neurosci.* 2018;47:285-293.
9. Yoshida K, Sulaiman NS, Miyawaki D, et al. Radiotherapy for brainstem gliomas in children and adults: a single-institution experience and literature review. *Asia-Pacific Journal of Clinical Oncology*. 2017;13:e153-e160.
10. Hundsberger T, Tonder M, Hottinger A, et al. Clinical management and outcome of histologically verified adult brainstem gliomas in Switzerland: a retrospective analysis of 21 patients. *J Neuro-Oncol.* 2014;118:321-328.
11. Kesari S, Kim RS, Markos V, Drappatz J, Wen PY, Pruitt AA. Prognostic factors in adult brainstem gliomas: a multicenter, retrospective analysis of 101 cases. *J Neuro-Oncol.* 2008;88 (2): 175-183.
12. Liu H, Qin X, Zhao L, Zhao G, Wang Y. Epidemiology and survival of patients with brainstem gliomas: a population-based study using the SEER database. *Front Oncol.* 2021;11(692097):2254.
13. Yang Y, Yao M, Long S, et al. Prognostic nomograms for primary high-grade glioma patients in adult: a retrospective study based on the SEER database. *BioMed Res Int.* 2020;2020. 1-19
14. Tian M, Ma W, Chen Y, et al. Impact of gender on the survival of patients with glioblastoma. *Biosci Rep.* 2018;38(6): BSR20180752.
15. Dey M, Lin Y, Melkonian S, Lam S. Prognostic factors and survival in primary adult high grade brainstem astrocytoma: a population based study from 1973–2008. *J Clin Neurosci.* 2014;21(8):1298-1303.
16. Mukherjee D, Antar V, Soylemez B, et al. High-resolution diffusion tensor magnetic resonance imaging of the brainstem safe entry zones. *Neurosurg Rev.* 2020;43(1):153-167.
17. Cavalheiro S, Yagmurlu K, da Costa MDS, et al. Surgical approaches for brainstem tumors in pediatric patients. *Child's Nerv Syst.* 2015;31(10):1815-1840.
18. Lesniak MS, Klem JM, Weingart J, Carson Sr BS. Surgical outcome following resection of contrast-enhanced pediatric brainstem gliomas. *Pediatr Neurosurg.* 2003;39(6):314-322.
19. Doyle J, Khalafallah AM, Yang W, Sun Y, Bettegowda C, Mukherjee D. Association between extent of resection on survival in adult brainstem high-grade glioma patients. *J Neuro-Oncol.* 2019;145:479-486.
20. Khalid SI, Kelly R, Adogwa O, et al. Pediatric brainstem gliomas: a retrospective study of 180 patients from the SEER database. *Pediatr Neurosurg.* 2019;54(3):151-164.
21. Bricolo A. Surgical management of intrinsic brain stem gliomas. *Operative techniques in neurosurgery*. 2000;3(2):137-154.
22. Theeler BJ, Gilbert MR. Advances in the treatment of newly diagnosed glioblastoma. *BMC Med.* 2015;13(293):1-11.
23. Eisele SC, Reardon DA. Adult brainstem gliomas. *Cancer*. 2016;122(18):2799-2809.
24. Maxwell R, Luksik AS, Garzon-Muvdi T, et al. Population-based study determining predictors of cancer-specific mortality and survival in pediatric high-grade brainstem glioma. *World Neurosurg.* 2018;119:e1006-e1015.
25. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10(5):459-466.
26. Cohen K.J., Heideman R.L., Zhou T.; et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the children's oncology group. *Neuro Oncol.* 2011, 13(4), 410-416.