Prognosis of patients with brainstem glioblastoma based on ‘age, surgery and radiotherapy’: a SEER database analysis

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Abstract

Primary brainstem glioblastoma is a rare tumor with dismal prognosis that poses significant treatment challenges. The purpose of the current study is to identify and determine prognostic factors associated with the survival in the brainstem glioblastoma patients. We gathered the data from SEER database (1973–2016) to examine the survival of patients with brainstem glioblastoma and potential impact of demographic, tumor and clinical characteristics on the overall survival of the patient. 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 the overall survival. Total 232 patients were included from the SEER database. The median overall survival was 8 months. Kaplan–Meier survival analysis delineated that thepatients with younger age ($P = 0.001$) and surgery ($P = 0.001$) exhibited better prognosis. Among 232 patients, 204 patients received radiotherapy (radiotherapy group, RG), and only 28 patients did not receive radiotherapy (non-radiotherapy group, NRG). Radiotherapy was associated with an improvement of overall survival without statistical significance ($P = 0.104$). PSM was performed between the RG and NRG based on age and surgical resection. After the PSM, 56 patients were included. Overall Survival was significantly different between both groups ($P = 0.038$, $p < 0.05$). Multivariate analysis showed that treatment with surgery and radiotherapy were considered as the independent prognostic factors ($P < 0.05$).

Key Points

Most published studies on brainstem glioblastoma to date are retrospective studies with relatively small cohorts; the prognosis factors were not well characterized in brainstem glioblastoma because of their rarity.

This article provides a prognostic strategy to diagnostic strategy to identify and analyze factors associated with survival among brainstem glioblastoma patients using data from the SEER database.

This one of the largest population-based study indicates that in brainstem glioblastoma, surgery and radiotherapy are associated with a better prognosis subsequently benefits clinicians to prefer personalized oncomedicine in the brainstem glioblastoma patients

Introduction

Glioblastoma is the most frequent and aggressive primary central nervous system (CNS) tumor, with an annual incidence of 3.19 per 100,000[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 glioblastoma. Despite the advancement in both diagnosis and treatment, the median survival of patients with glioblastoma is only 14.6 months[2]. Primary brainstem glioblastoma is a rare tumor and accounts for 10–20% all pediatric

CNS tumors[3], and less than 2% of adult CNS cases[4, 5]. Due to the special characteristics of the brainstem, the clinical feature of brainstem glioblastoma is eventually deteriorating, and resulting in the worse prognosis. Previous studies in supratentorial glioblastoma reported that the younger age, higher KPS, adjuvant chemotherapy, brachytherapy, and surgical resection were significantly correlated with better prognosis[6–8]; however, these variables were not well characterized for brainstem gliomas, especially in brainstem glioblastoma because of their rarity. Till date, majority of the published studies on brainstem glioblastoma are retrospective studies with relatively small cohorts[9–11]. SEER database is one of the largest population-based study and delineates that the brainstem glioblastoma, surgery, and radiotherapy are associated with a better prognosis [12–14].Thus, the purpose of the current study is to identify and determine prognostic factors associated with the survival in brainstem glioblastoma based on the surgery, chemotherapy, radiotherapy, year of diagnosis in the patients using 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 for analysis. Hence, our study has not required 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 patient data from the SEER Program between1973 and 2016who were diagnosed and histologically confirmed glioblastoma (ICD-O-3: 9440/3) located within the brainstem (primary site code C71.7)were included. We excluded patients without survival data or whose tumors were not their first or only primary lesion. Nineteen patients exhibited survival time of 0 months. We removed these cases from the study to avoid bias occurring due to therapeutic options (**Figure 1**).

SEER coding and variable definition

Age at the time of diagnosis, gender (male or female), race, and marital status are considered as demographic variables. Patient's age was divided into 0-18, 19–59, and ≥60 years old. Race was categorized into White, Black, Asian/Pacific Islander, American Indian/Alaska Native and unknown. For adults (>18 years old), the marital status was registered as married, single or divorced/widowed/separated. We measured the largest linear tumor size (in millimeters) and categorized it as < or ≥30mm.Treatment variables used in this research include the extent of surgical resection, radiotherapy, chemotherapy, and the year of diagnosis. Extent of resection 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 non-surgical group. Known receipt of chemotherapy and radiotherapy were coded as binary variables (yes vs. no or unknown). Year of diagnosis was crudely dichotomized into a two-decade-span: 1973–2002, 2003–2016.

Statistical Analyses for survival & prognosis

Descriptive analyses were used to describe the patient demographic and clinical characteristics. Number of cases and percentages were shown in the study. The Kaplan-Meier survival curves with log-rank tests were used to compare overall survival (OS) among groups. PSM analysis was performed between patients with or without radiation therapy based on the age and surgical resection to investigate the effect of radiotherapy on the overall survival. Cox proportional hazards regression analyses were performed to assess potential prognostic factors associated with the patient's overall survival. 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 brainstem glioblastoma patients were included in the study (Table 1) of patient's age in the range of 1 to 84, 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%), ≥ 60 years (n = 41, 17.67%). Comparatively males were higher (n = 130, 56.03%)t han the females. Brainstem glioblastoma was mostly diagnosed among 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%). Out of 232 patients,62 patients (26.72%) were associated with tumors greater than or equal to the median tumor size of 30mm, whereas 61 patients (26.29%) exhibited tumors smaller than the median size. Total 109 patients (46.98%) were reported with tumor with unknown size. Furthermore, 80 patients (34.48%) were registered and underwent surgical resection, whereas 14patients (6.03%) underwent a gross total resection, 58patients (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 non-surgical resection, including 48 patients (20.68%) with biopsy performed. Moreover, the great majority of brainstem glioblastoma patients received radiotherapy (n = 204, 87.93%). There were 134(57.76%) patients receiving chemotherapy.

Table 1
Distribution of demographics, tumor and treatment characteristics of brainstem glioblastoma

Parameters	Total (*N* = 232)
Age, median (range)	35(1–84)
Age, categorized	87(37.5)
1 to 18 years, *n* (%)	104(44.83)
19 to 59 years, *n* (%)	41(17.67)
≥ 60 years, *n* (%)	
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	145(62.5)
> 18 years, *n* (%)	
Married, *n* (%)	59(25.43)
Single, *n* (%)	69(29.74)
Divorced/widowed/separated, *n* (%)	17(7.33)
Tumor size	62(26.72)
≥ 30mm	61(26.29)
< 30mm	109(46.98)
Unknown	

Parameters	Total (*N* = 232)
Surgery	152(65.51)
No, *n* (%)	80(34.48)
Yes, *n* (%)	14(6.03)
Gross total resection	58(25.0)
Partial resection	8(3.45)
Unspecified	204(87.93)
Radiotherapy	28(12.07)
Yes, *n* (%)	134(57.76%)
No, *n* (%)	98(42.24)
Chemotherapy	80(34.48)
Yes, *n* (%)	
No, *n* (%)	
Year of diagnosis	
1973–2002, *n* (%)	
2003–2016, *n* (%)	152(65.52)

The median OS of patients was 8 months [95%CI(6.89–9.11 months)], with 6-month, 9-month, 1-year, 2-year, and 3-year survival rates of 59.6%, 42.2%, 31.8%, 11.5% and 6.5%, respectively (Fig. 2).

Univariable And Multivariable Analysis

Impact of demographics variables, tumor size, and treatment factors on survival were compared in Kaplan–Meier survival curves. Among these parameters, younger age ($P = 0.001$) and surgery ($P = 0.001$) indicated better prognosis (Fig. 3,4).

For the entire study population, most of the patients (n = 204, 87.93%) received radiotherapy (radiotherapy group, RG), only 28 patients did not receive radiotherapy (non-radiotherapy group, NRG). Radiotherapy was associated with significant improvement in the overall survival without statistical significance ($P = 0.104$) (Fig. 5a). In order 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 underwentsurgery. Overall survival was significantly different between both groups (RG vs NRG: 9.0 vs 4.0months, $P = 0.038$, $p < 0.05$) (Fig. 5b).

The multivariable model cannot be included in this study due to the limited number of patients; the selected variables mainly included for this study are age, surgery, and radiotherapy. In the multivariate Cox proportional hazard regression analysis, surgery (HR = 0.582, [0.431, 0.787], $P = 0.001$) and radiotherapy (HR = 0.609, [0.399, 0.928], $P = 0.029$) were independently associated with a better overall survival of the patients.

Discussion

This 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 brainstem glioblastoma.

Surgical intervention in the brainstem region in the treatment of brainstem glioma was previously considered controversial due to the poor prognosis, and various other safety concerns. Advancement in the microsurgical techniques, electrophysiological monitoring, efficient neuroimaging and neurointensive care support, has facilitated the surgical intervention for brainstem lesions as an alternative option for those carefully selected patients with survival benefit[16–18]. Doyle et al reported a group of 103 brainstem highgrade glioma adult patients who underwent surgical intervention. In this study, the median survival for patients receiving gross total resection, subtotal resection and biopsy were 16, 11 and 8 months, respectively. Compared to the patients with biopsy only, the survival benefits were observed in 'gross total resection' (HR = 0.24, $P < 0.001$) and subtotal resection group (HR = 0.32, $P = 0.006$)[19]. The similar conclusion was obtained in the pediatric patients with glioblastoma. Khalid et al described thatthe 'partial resection' (HR = 0.11, $P < 0.001$) and 'gross-total resection' (HR = 0.03, $P < 0.001$) were associated with a prolonged overall survival[20]. Our findings also indicated that, even among the more malignant and aggressive glioblastoma patients, the surgery yielded considerably a favorable outcome, deducing that the patients who are receiving surgical resection have been surviving longer than those who have not received surgical resection. It is important to pay attention to the nerve function preservation and quality-of-life after the surgery in glioblastoma[21]. Therefore, the resection should be performed by experienced surgeons in highly selected patients.

In case of adult glioblastoma, the radiotherapy is considered as the standard treatment and has exhibited a good clinical response rate by mitigating tumor progression[22, 23]. However, only a few studies focused on the prognosis in brainstem patients and the adult high-grade brainstem glioma patients received typically minimal benefit during the radiotherapy[15]. The median survival appears to be variable between the patients who received radiotherapy (1 month) and those who were not received (9 months), without a statistical difference between the two groups. It has been observed that there were only 36 and 201 patients in the radiation group and non-radiation group respectively; Moreover, the survival analysis wasn't performed in the patients of different histopathological grading. In a previous study of pediatric patients with high-grade brainstem gliomas, the radiotherapy significantly improved the overall survival at 6 and 9 months but not beyond these periods. Patients with glioblastoma who received radiotherapy were reported with a significant rise in the overall survival rate compared with those who have not received

radiotherapy(9.0 vs. 3.0months; $P < 0.001$).However, the radiotherapy has not delivered statistically significant improvement in the overall survival of patients with anaplastic astrocytoma[24]. In our study, most patients (n = 204, 87.93%) received radiotherapy, only 28 patients have not received radiotherapy. Radiotherapy was associated with an improvement in the overall survival without any statistical significance. During PSM analysis based on the patient's age and surgical resection, the overall survival was significantly different between both groups (RG vs NRG: 9.0 vs 4.0months, $P = 0.038$, $p < 0.05$). These results delineated the importance of radiotherapy in brainstem glioblastoma, however, due to its small sample size and retrospective study design, the conclusion should be further confirmed.

Benefits of adjuvant temozolomide with radiotherapy has been significant reported in the adult patients, who were newly diagnosed with glioblastoma[25], but not in pediatric patients[25, 26]. The results of our study suggested that neither children nor adults could benefit from chemotherapy, which was possibly because of the poor prognosis of brainstem glioblastoma itself and the unclear 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 contains minimal information about the location and focality of lesions, extent of surgical resection, radiation dose or type, chemotherapy regimens, tumor molecular data.

Our study concluded that the brainstem glioblastoma, surgery, and radiotherapy are associated with a better prognosis.

Abbreviations

SEER: Surveillance, Epidemiology, and End Results; PSM: Propensity score matching; RG: Radiotherapy group; NRG: Non-radiotherapy group; CNS: Central nervous system; OS: Overall survival;

Declarations

Conflict of Interests

The authors declare no conflict of interest.

Author Contributions

Yitong Li (YL), Narasimha M. Beeraka (NMB), Wenchang Guo (WG), Yuying Lei (YL), Qilu Hu (QH), Litao Guo (LG), Ruitai Fan (RF), Junqi Liu (JL), Aixia Sui (AS) conceptualized and designed the study. NMB, YL, WG, RF, JL, AS, and QH performed the literature analysis, and wrote the original manuscript draft. NMB, JL, RF revised, edited, and extended the final draft. All authors have reviewed and approved the manuscript before submission.

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Availability of data and materials

Supplementary material was attached as a separate file.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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References

1. Ostrom, Q.T.; Gittleman, H.; Xu, J.; Kromer, C.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro-oncology* **2016**, *18*, v1-v75.

2. Stupp, R.; Mason, W.P.; Van Den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M.J.; Belanger, K.; Brandes, A.A.; Marosi, C.; Bogdahn, U. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England journal of medicine* **2005**, *352*, 987-996.

3. Jallo, G.I.; Biser-Rohrbaugh, A.; Freed, D. Brainstem gliomas. *Child's Nervous System* **2004**, *20*, 143-153.

4. Guillamo, J.-S.; Monjour, A.; Taillandier, L.; Devaux, B.; Varlet, P.; Haie-Meder, C.; Defer, G.-L.; Maison, P.; Mazeron, J.-J.; Cornu, P. Brainstem gliomas in adults: prognostic factors and classification. *Brain* **2001**, *124*, 2528-2539.

5. Salmaggi, A.; Fariselli, L.; Milanesi, I.; Lamperti, E.; Silvani, A.; Bizzi, A.; Maccagnano, E.; Trevisan, E.; Laguzzi, E.; Rudà, R. Natural history and management of brainstem gliomas in adults. *Journal of neurology* **2008**, *255*, 171-177.

6. Lamborn, K.R.; Chang, S.M.; Prados, M.D. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro-oncology* **2004**, *6*, 227-235.

7. Pan, I.-W.; Ferguson, S.D.; Lam, S. Patient and treatment factors associated with survival among adult glioblastoma patients: a USA population-based study from 2000–2010. *Journal of clinical neuroscience* **2015**, *22*, 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. *Journal of Clinical Neuroscience* **2018**, *47*, 285-293.

9. Yoshida, K.; Sulaiman, N.S.; Miyawaki, D.; Ejima, Y.; Nishimura, H.; Ishihara, T.; Matsuo, Y.; Nishikawa, R.; Sasayama, T.; Hayakawa, A. 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.; Brügge, D.; Roelcke, U.; Putora, P.M.; Stupp, R.; Weller, M. Clinical management and outcome of histologically verified adult brainstem gliomas in Switzerland: a retrospective analysis of 21 patients. *Journal of neuro-oncology* **2014**, *118*, 321-328.

11. Kesari, S.; Kim, R.S.; Markos, V.; Drappatz, J.; Wen, P.Y.; Pruitt, A.A. Prognostic factors in adult brainstem gliomas: a multicenter, retrospective analysis of 101 cases. *Journal of neuro-oncology* **2008**, *88*, 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. *Frontiers in Oncology* **2021**, *11*, 2254.

13. Yang, Y.; Yao, M.; Long, S.; Xu, C.; Li, L.; Li, Y.; Li, G. Prognostic nomograms for primary high-grade glioma patients in adult: a retrospective study based on the SEER database. *BioMed research international* **2020**, *2020*.

14. Tian, M.; Ma, W.; Chen, Y.; Yu, Y.; Zhu, D.; Shi, J.; Zhang, Y. Impact of gender on the survival of patients with glioblastoma. *Bioscience reports* **2018**, *38*.

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. *Journal of Clinical Neuroscience* **2014**, *21*, 1298-1303.

16. Mukherjee, D.; Antar, V.; Soylemez, B.; Cikla, U.; Gürer, B.; Ekici, M.A.; Field, A.S.; Salamat, M.S.; Başkaya, M.K. High-resolution diffusion tensor magnetic resonance imaging of the brainstem safe entry zones. *Neurosurgical review* **2020**, *43*, 153-167.

17. Cavalheiro, S.; Yagmurlu, K.; da Costa, M.D.S.; Nicácio, J.M.; Rodrigues, T.P.; Chaddad-Neto, F.; Rhoton, A.L. Surgical approaches for brainstem tumors in pediatric patients. *Child's Nervous System* **2015**, *31*, 1815-1840.

18. Lesniak, M.S.; Klem, J.M.; Weingart, J.; Carson Sr, B.S. Surgical outcome following resection of contrast-enhanced pediatric brainstem gliomas. *Pediatric neurosurgery* **2003**, *39*, 314-322.

19. Doyle, J.; Khalafallah, A.M.; Yang, W.; Sun, Y.; Bettegowda, C.; Mukherjee, D. Association between extent of resection on survival in adult brainstem high-grade glioma patients. *Journal of neuro-*

oncology **2019**, *145*, 479-486.

20. Khalid, S.I.; Kelly, R.; Adogwa, O.; Carlton, A.; Tam, E.; Naqvi, S.; Kushkuley, J.; Ahmad, S.; Woodward, J.; Khanna, R. Pediatric Brainstem gliomas: a retrospective study of 180 patients from the SEER database. *Pediatric neurosurgery* **2019**, *54*, 151-164.

21. Bricolo, A. Surgical management of intrinsic brain stem gliomas. *Operative techniques in neurosurgery* **2000**, *2*, 137-154.

22. Theeler, B.J.; Gilbert, M.R. Advances in the treatment of newly diagnosed glioblastoma. *BMC medicine* **2015**, *13*, 1-11.

23. Eisele, S.C.; Reardon, D.A. Adult brainstem gliomas. *Cancer* **2016**, *122*, 2799-2809.

24. Maxwell, R.; Luksik, A.S.; Garzon-Muvdi, T.; Yang, W.; Huang, J.; Bettegowda, C.; Jallo, G.I.; Terezakis, S.A.; Groves, M.L. Population-based study determining predictors of cancer-specific mortality and survival in pediatric high-grade brainstem glioma. *World neurosurgery* **2018**, *119*, e1006-e1015.

25. Stupp, R.; Hegi, M.E.; Mason, W.P.; Van Den Bent, M.J.; Taphoorn, M.J.; Janzer, R.C.; Ludwin, S.K.; Allgeier, A.; Fisher, B.; Belanger, K. 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. *The lancet oncology* **2009**, *10*, 459-466.

26. Cohen, K.J.; Heideman, R.L.; Zhou, T.; Holmes, E.J.; Lavey, R.S.; Bouffet, E.; Pollack, I.F. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. *Neuro-oncology* **2011**, *13*, 410-416.

Figures

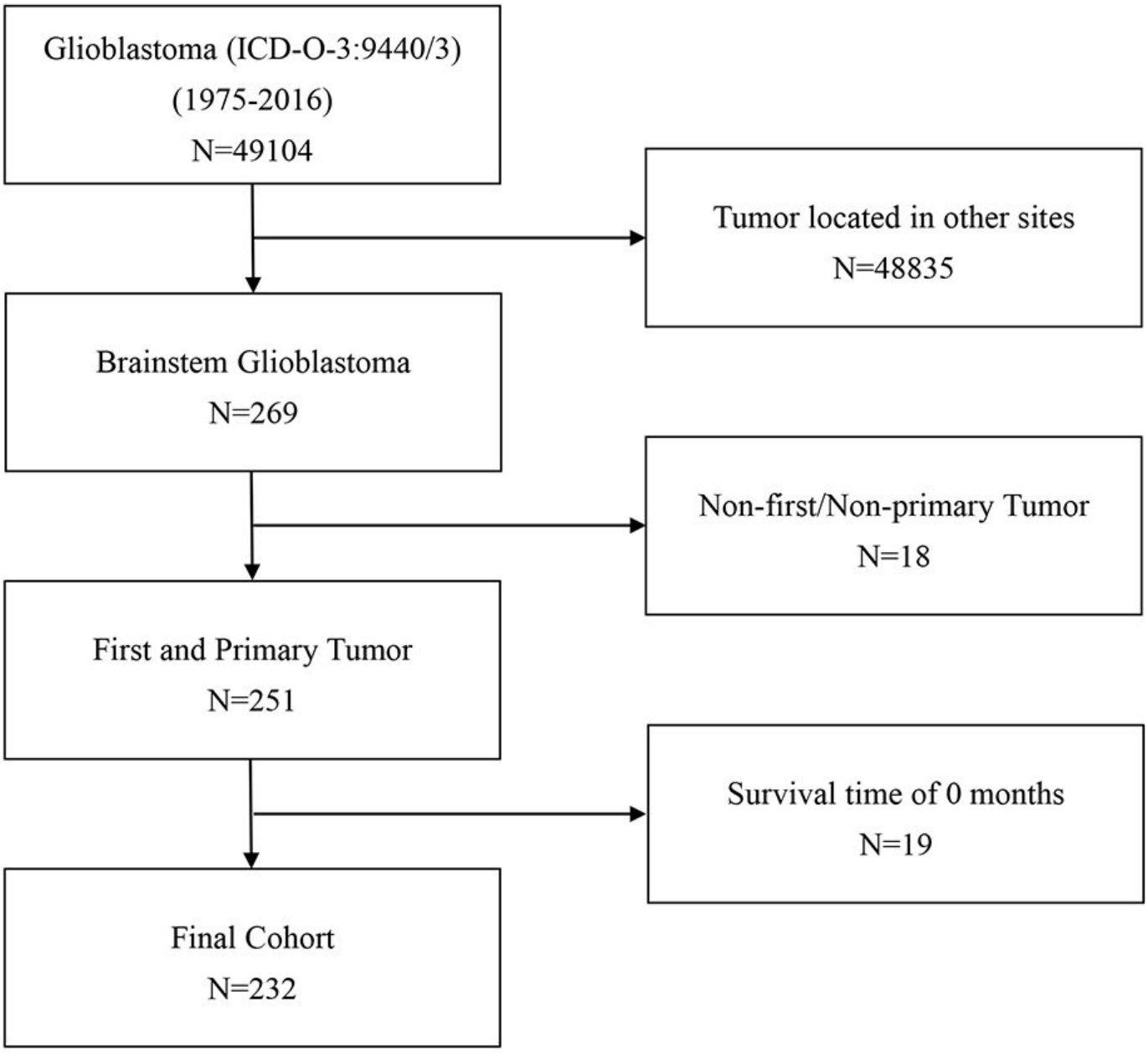

Figure 1

SEER Database and patient selection flow diagram.

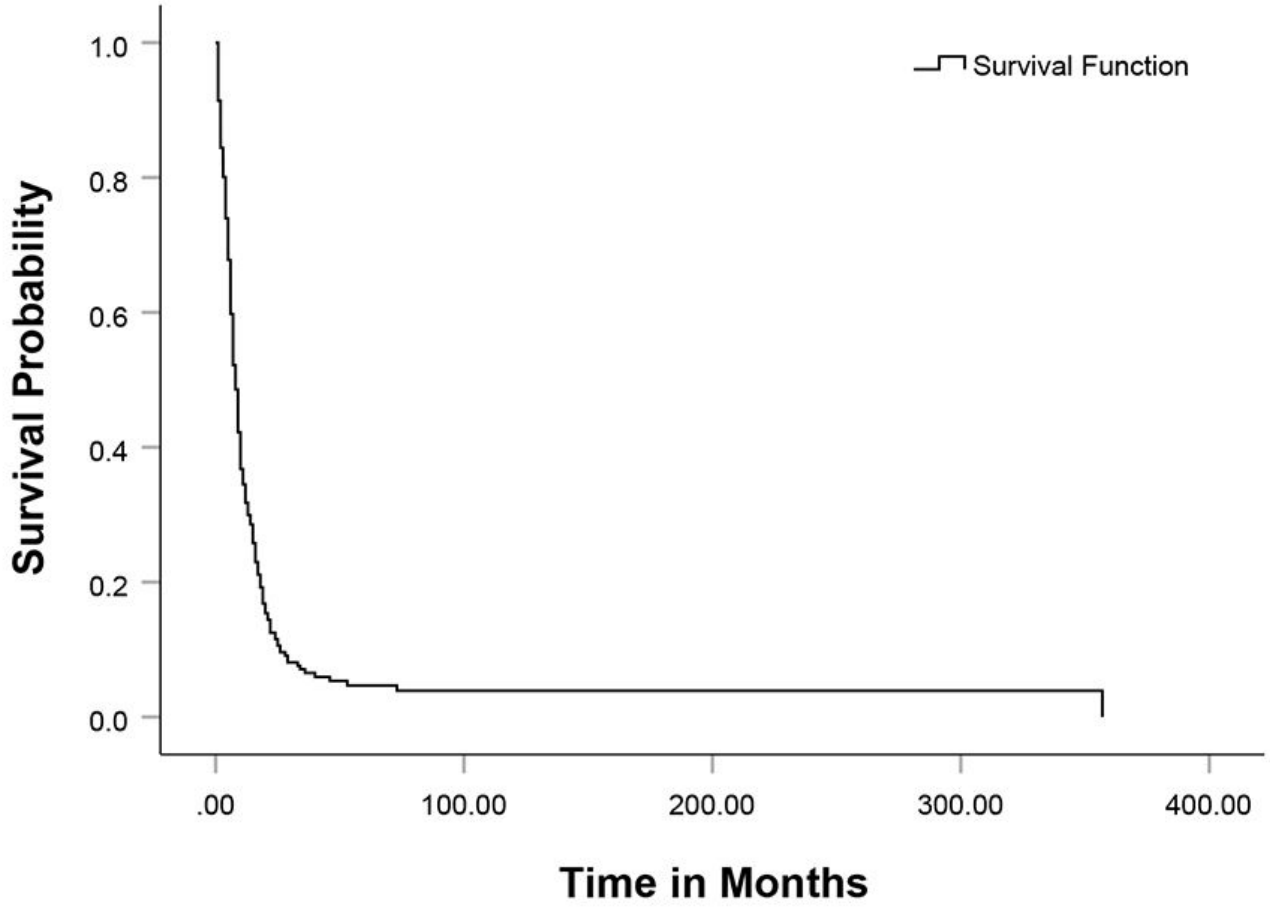

Figure 2

Kaplan-Meier overall survival curves for the entire cohort of 232 SEER brainstem glioblastoma patients.

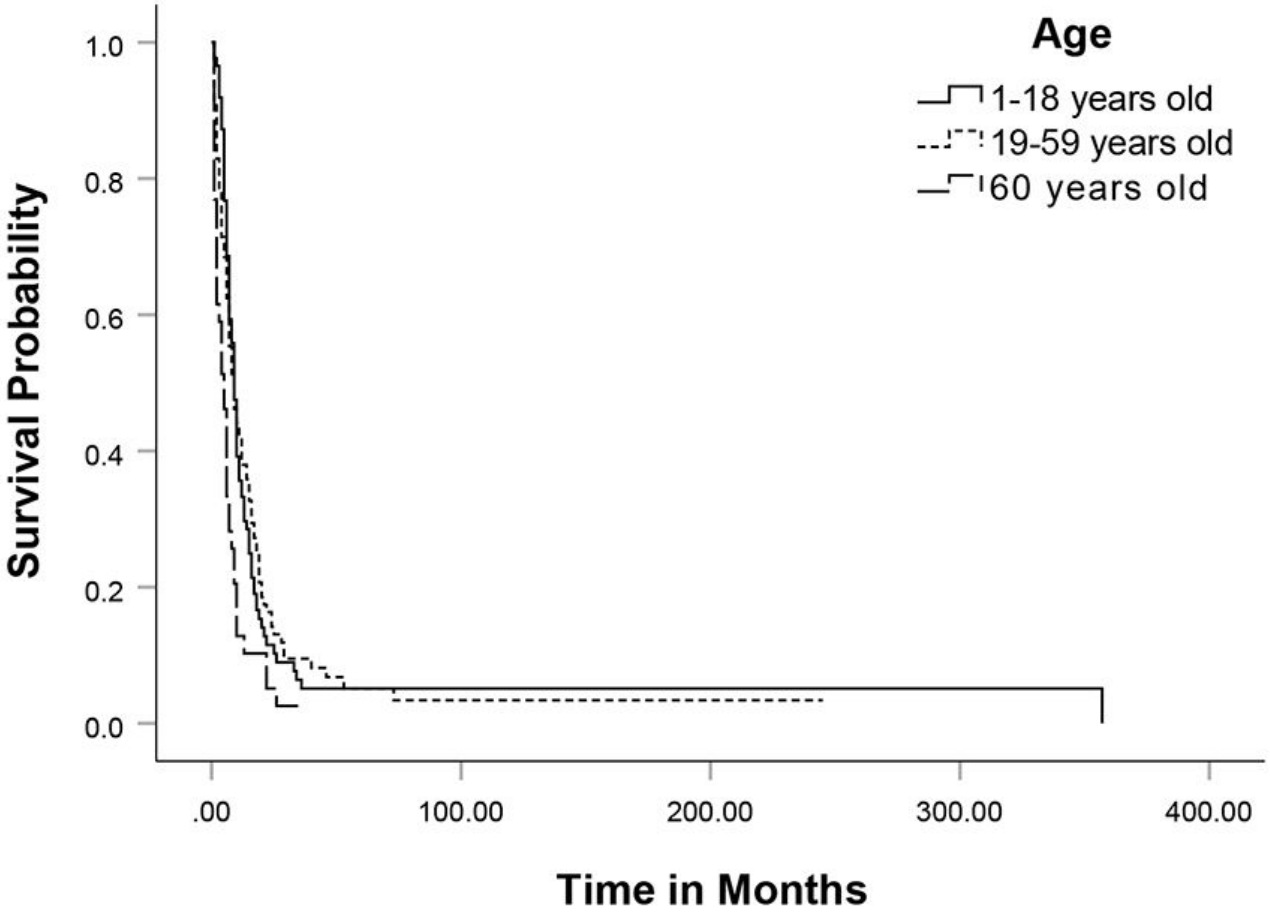

Figure 3

Kaplan-Meier survival curves for the patients of different age groups.

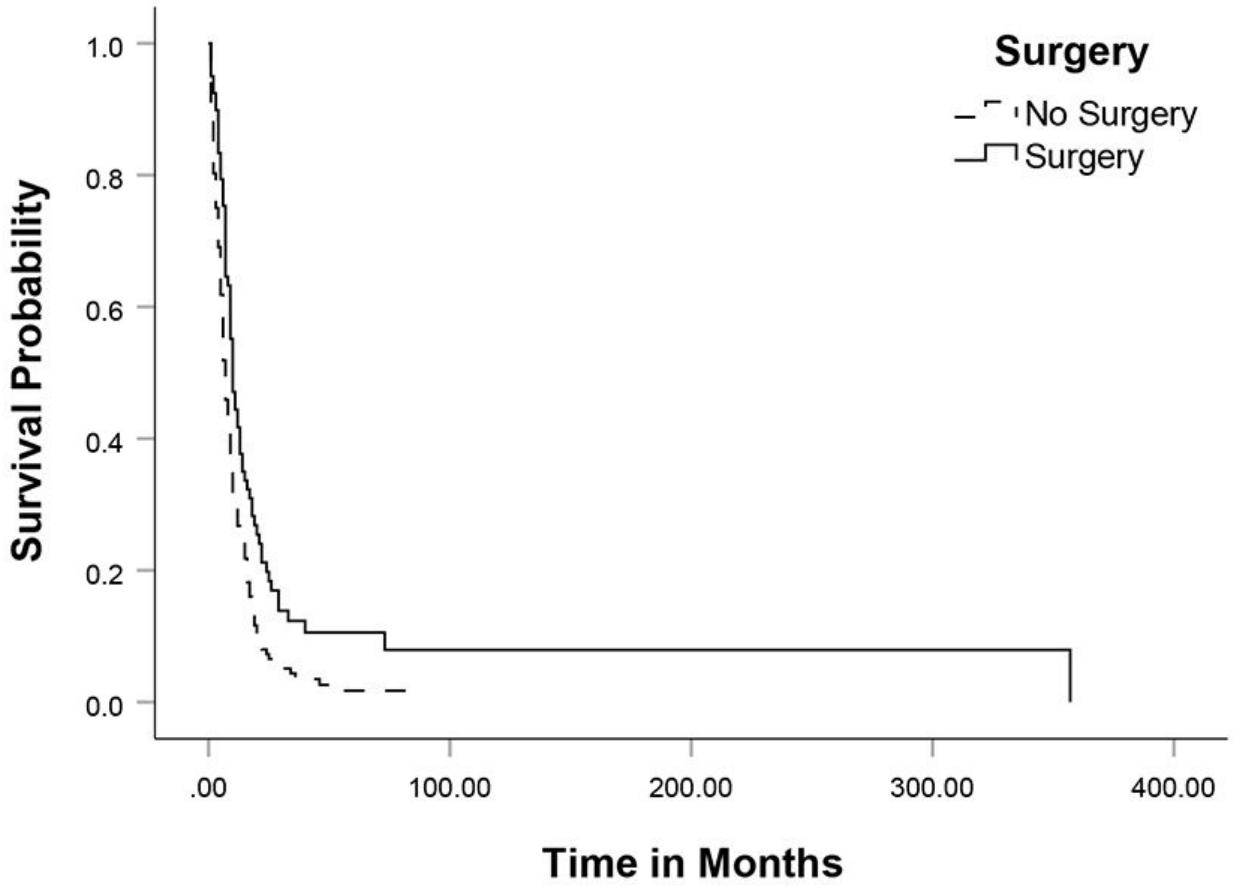

Figure 4

Kaplan-Meier survival curves for the entire cohort of patients with or without surgery.

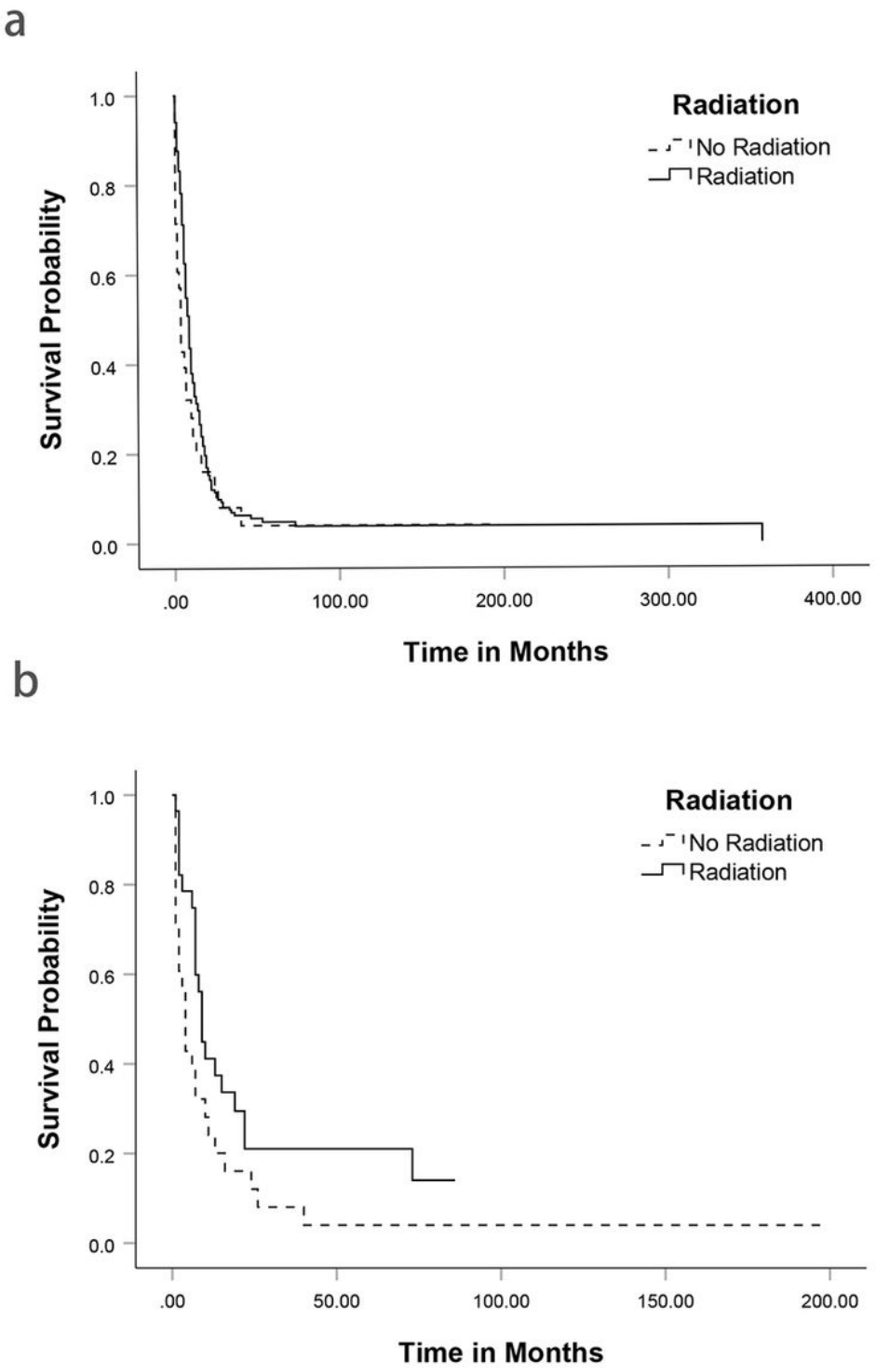

Figure 5

(a). Kaplan-Meier survival curves for the entire cohort of patients with or without radiation. (b).Kaplan-Meier survival curves for the 56 patients with or without radiation, (RG vs NRG: 9.0 vs 4.0months, P=0.038, $p < 0.05$) was performed after PSM analysis based on the age and surgical resection.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplimentarybrainstemGBM.xlsx