World Journal of Surgery and Surgical Research

Research Article
Published: 28 Jun, 2021

Evaluation of Efficacy in Different Treatments for Glioblastoma: A Surveillance, Epidemiology, and End Results Cohort Study

*Boya Fan[1,2], Gang Wang[1], Haolun Han[1], Baowei Li[1], Lei Wang[1], Zhezhe Sun[1], Ying Zhou[1], Yiyan Zhang[1] and Wei Wu[1]**

[1]Department of Otorhinolaryngology-Head and Neck Surgery, PLA Strategic Support Force Characteristic Medical Center, China

[2]Peking University Health Science Center, China

Abstract

Background: Clinical trials have shown that surgery, Radiotherapy (RT), and Chemotherapy (CT) are different treatment options for Glioblastoma (GBM) patients. In this study, we evaluate the efficacy of different choices of treatments on survival in GBM patients using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: A large-scale retrospective cohort study using the U.S. National Cancer Institute's SEER analysis was conducted. A total of 23,829 eligible glioblastoma patients between 2004 and 2016 were identified within SEER database. We used the Kaplan–Meier (KM) survival analysis with a log-rank test to evaluate the survival outcomes in surgery, RT, and CT choices. A multivariate stepwise Cox analyses to identify factors associated with Overall Survival (OS).

Results: Whether or not surgery was performed, survival was best with radiotherapy and chemotherapy, and chemotherapy alone was better than radiotherapy alone. If patients chose only two treatments, patients who had surgery and chemotherapy had the best survival rates. It shows that chemotherapy plays an important role in the treatment of glioblastoma. In patients who have had chemotherapy, additional surgery is better than radiotherapy. In patients who have had radiotherapy, additional surgery and chemotherapy have similar outcomes. Survival was better with chemotherapy alone than with the other two treatments alone. Patients' age and tumor size were negatively correlated with survival time, and tumor size was weakly negatively correlated with patient age. In multivariate analysis of OS, OS was significantly correlated with race, age of diagnosis, tumor size, marital status, extension, surgery, radiotherapy, and chemotherapy.

Conclusion: We constructed the first treatment evaluation of OS in patients with glioblastoma. The advantages of surgery and chemotherapy in survival are obvious. The correlation and regression results are intended for risk assessment.

Keywords: Glioblastoma; SEER database; Survival; Therapy; Prognosis

OPEN ACCESS

Correspondence:
Wei Wu, Department of Otorhinolaryngology-Head and Neck Surgery, People's Liberation Army Strategic Support Force Characteristic Medical Center, Peking University, No.9, Anxiangbeili, Chaoyang, Beijing 100101, China, Tel: 86-10-66356347; Fax: 86-10-66356347; E-mail: ent306ww@126.com

Received Date: *31 May 2021*
Accepted Date: *24 Jun 2021*
Published Date: *28 Jun 2021*

Citation:
Fan B, Wang G, Han H, Li B, Wang L, Sun Z, et al. Evaluation of Efficacy in Different Treatments for Glioblastoma: A Surveillance, Epidemiology, and End Results Cohort Study. World J Surg Surgical Res. 2021; 4: 1313.

Introduction

Glioblastoma, also known as Glioblastoma Multiforme (GBM), is the most common and highly invasive primary brain malignancy with a median age of 64 years [1]. Glioma is the most common primary malignant tumor of the central nervous system in adults. Glioblastoma (GBM) incidence rate is more than 50% of gliomas [2]. Glioblastoma is also the most invasive diffuse glioma in astrocytic lineage and is considered a grade IV glioma according to the classification of the World Health Organization (WHO) [3]. According to the report [4], the incidence rate of central nervous system tumors in 2000 was 6.7 per 100,000 people. With poor survival, the newly diagnosis patients with glioblastoma have the median survival time is approximately 1 year, and the 5-year survival rate after diagnosis is less than 5% [5-7]. At present, the standard treatment of GBM includes surgery, combined with Radiotherapy (RT) and Chemotherapy (CT) [8].

As the median age of patients with glioblastoma is 64 years, a large amount of patients who are <65 years old are suffered from this brain malignancy and they need to consider more careful for their life expectancy and the therapy. Many studies have proved that surgery, radiotherapy

and chemotherapy are effective in the treatment of GBM [9-11], and there are also effective studies of neoadjuvant radiotherapy and chemotherapy [12-14]. However, there is still no large sample retrospective study to integrate these different treatment methods for analysis of patients' survival. Therefore, it would be necessary to construct a statistical analysis and visual model which can integrate those treatments efficacy to accurately analyze and predict the survival outcomes of patients with glioblastoma in different treatments.

In addition, the association between tumor size and age has shown different results in different cancers and different clinical trials. We wanted to figure out if there was any correlation between age, survival time, and tumor size in GBM based on this large sample. In this study, we constructed some visual models to perform the survival of patients and the progress of the disease by using the Surveillance Epidemiology, and End Results (SEER) database which is one of the biggest cancer databases and is also a U.S. population-based cancer database. Most importantly, the survival analysis can be integrated to see the impact of different treatment methods on the survival time of patients. This can be helpful to the treatment choice of patients in the future.

Methods

Patient eligibility and variables

The data of patients are all from SEER database. The SEER database consists of 18 population-based cancer registries, accounting for 28% of the US population. The inclusion criteria were as follows: [1] Diagnosed with glioblastoma is the primary malignancy; [2] to collect the new data, the years of diagnosis are from 2004 to 2016 [3]. Survival months, cause of death, tumor size, marital status, race, radiotherapy record, chemotherapy record and surgery record are clear and known. The exclusion criteria were as follows: unknown uses of surgery, radiotherapy and chemotherapy; unknown records of marital status, cause of death, survival time, metastasis and marital status; outliers that are too large or too small in the data.

We selected the patients whose histologic subtype code is 9440/3 and information of the data in the SEER database include 18 regional cancer registries with information on patients' demographic information, survival months, treatment, and the cause of death.

Statistical analysis

Firstly, 35,902 patients diagnosed as glioblastoma were extracted from SEER database. After patient identification based on the inclusion and exclusion criteria, 23,829 eligible patients were retained to form the primary cohort of glioblastoma. The patients' statistical variables were sex, race, and age at diagnosis, marital status, extension, radiotherapy record, surgery record, chemotherapy record, metastasis, the vital status, and survival months. In multivariate analysis, patient age was divided into two groups, which were less than median age, 64 years old and over 64 years old. Tumor size was also divided into two groups, which were less than median size, 4.5 cm, and over 4.5 cm. The endpoint outcomes of this study are Overall Survival (OS). OS is the time from the vital status recode and it is the time from diagnosis until death. The age data of patients were also classified according to the age group of every 10 years old. Then the visualization map was constructed according to the age-groups of patients. In those continuous variables in our data, Pearson correlation analysis was carried out.

Based on clinical reasoning and importance, discontinuous variables are classified prior to modeling. Continuous variables (age and tumor size) were divided by the median values with the median of age is 64 years old and the median of tumor size is 4.5 cm which are coincident with those in other epidemiology research [1]. Continuous variables (age and tumor size) were shown as median with range, while categorical variables were presented as respective percentage of patients. As continuous variables, age, tumor size, and survival time were performed Pearson correlation analysis to figure out their associations. In order to study the effect of different treatments on the survival time of patients, the effect of each treatment factor on survival was assessed by the Kaplan-Meier method with log-rank test, as well as the survival curve. Furthermore, the patients who had surgery, who had not surgery, who had chemotherapy, who had not chemotherapy, who had radiotherapy and who had not radiotherapy were screened out respectively to analyze the survival in different treatment conditions. The Kaplan-Meier curve was carried out to visualize the survival condition of patients under different treatment conditions. Multivariate stepwise Cox proportional hazards regression was used to determine independent predictors of mortality and overall survival time. $P<0.05$ was considered statistically significant. All the above analyses were performed by SAS (University Edition). Both of them were bilateral tests, and $P<0.05$ was statistically significant with HR and 95% CI used to assess the strength of the association between each feature and the OS.

Results

Basic characteristics of patients

The basic characteristics of the patients are preliminarily classified into patients who have died (20,353 patients) and patients who are still alive (3,476 patients) at the end of the survey. The population consisted of 9,964 (41.81%) female and 13,865 (58.19%) male patients. In the race record, most of patients were white race (89.83%) and married patients 15,600 (65.47%) are the major. In the age at diagnosis and tumor size record, we divided patients by the median age so the amounts of each group were almost fifty-fifty. In surgery of primary site record, 18,431 (77.35%) patients did surgery, while 5,398 (22.65%) patients did not; 17,821 (74.79%) patients did radiotherapy, while 6,008 (25.21%) patients did not; 16,067 (67.43%) patients did chemotherapy, while 7,762 (32.57%) patients did not. In the metastasis information, most patients 23,493 (98.58%) did not have metastasis, with only a few patients having CNS metastasis or other distant metastasis. In the extension information, localized patients (80.07%) are the most, while regional patients and distant

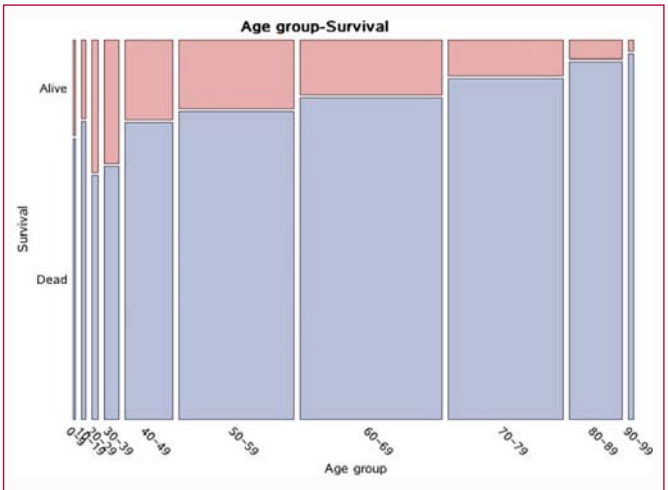

Figure 1: Mosaic diagram between living condition and age-groups.

patients decrease respectively.

We classified the patients according to their age every ten years. The relationship between patients' age-groups and their living condition was visualized by mosaic diagrams (Figure 1). The relationship between patients' age-groups and their survival time was visualized by box diagrams (Figure 2); and the relationship between patients' age-groups and their tumor size was also visualized by box diagrams (Figure 3). It is not difficult to see that the age group of 20 to 29 years old is the best in terms of survival and the number of months of survival, and then the survival of patients will gradually deteriorate with the increasing of patients' age-groups. But the relationship between patients' age-groups and their tumor size cannot be significantly shown in the figure, so we made a further correlation analysis.

Correlation analysis

Pearson correlation analysis was performed with tumor size, age and survival time as continuous variables. We screened out 20,353 patients who had died for correlation analysis. Because we need to analyze the correlation between survival time and age of patients, we excluded the censored data of patients who are still alive. Though Pearson correlation analysis, we found that the age of patients was negatively correlated with survival time (r= -0.33, p<0.0001), which means that the older the patients, the shorter the survival time. The tumor size was negatively correlated with survival time (r= -0.07, p<0.0001), which means that the larger the tumor size, the shorter the survival time. The age of patients was weakly negatively correlated with tumor size (r= -0.02, p=0.0008), which means that in our data, the older patients may be, the smaller the tumor size may be. The strange phenomenon of the correlation between tumor size and age will be described in the discussion part.

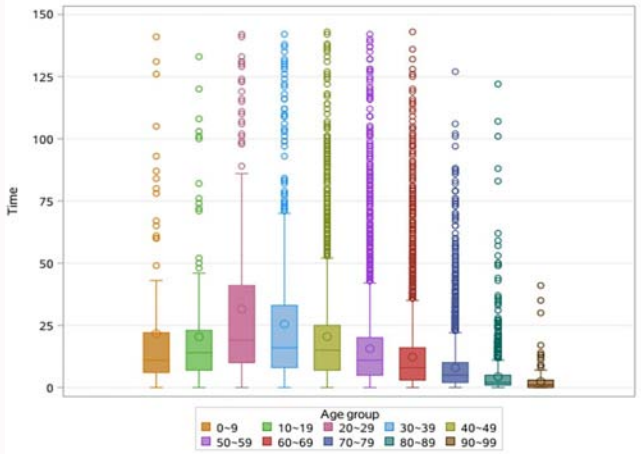

Figure 2: Box diagram between survival time and age-groups.

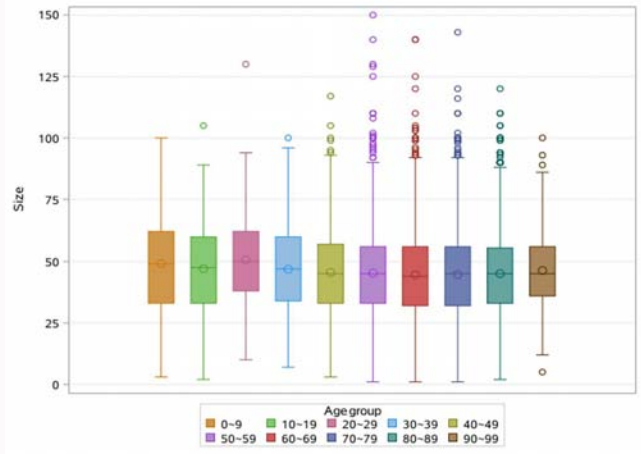

Figure 3: Box diagram between tumor size and age-groups.

Kaplan-Meier analysis

In order to evaluate the impact of different treatment methods on the survival of patients, we compared different treatment methods, screened patients into different groups, and analyzed the survival of different treatment methods. Firstly, we performed a survival analysis for all patients. As can be seen from Figure 4, the survival condition of patients with surgery, radiotherapy and chemotherapy is the best. Surprisingly, the survival condition of patients who underwent both surgery and chemotherapy was the second only to that of the three treatments mentioned above. About within 12 months after diagnosis, patients who had surgery and radiation only, surgery and chemotherapy only, and radiation and chemotherapy only, had similar survival rates. But after 12 months, patients who received surgery and chemotherapy only began to fare significantly better than those who received the other two treatments. It shows that all three treatments are best performed within one year of diagnosis. If there is only one treatment, chemotherapy alone is better than surgery or radiation alone. Survivals were similar in patients who had surgery or radiation alone. If patients just do the two, there's not a lot of difference within a year, but in the long-term survival, surgery and chemotherapy are at least what patients need to do.

We first performed a survival analysis of all patients with radiotherapy and chemotherapy. And then we screened out the patients who had surgery and the patients who had not surgery, and divided them into two groups to see whether radiotherapy or chemotherapy has any impact on the survival of patients. As can be seen from Figure 5, the survival of patients with both radiotherapy and chemotherapy is the best, but if only one treatment is done, the survival of patients with chemotherapy alone is better than that of patients with radiotherapy alone. Patients who did not receive radiotherapy or chemotherapy had the worst survival. It can also provide some suggestions for future treatment. Then we screened patients who had not undergone surgery to assess the impact of radiotherapy and

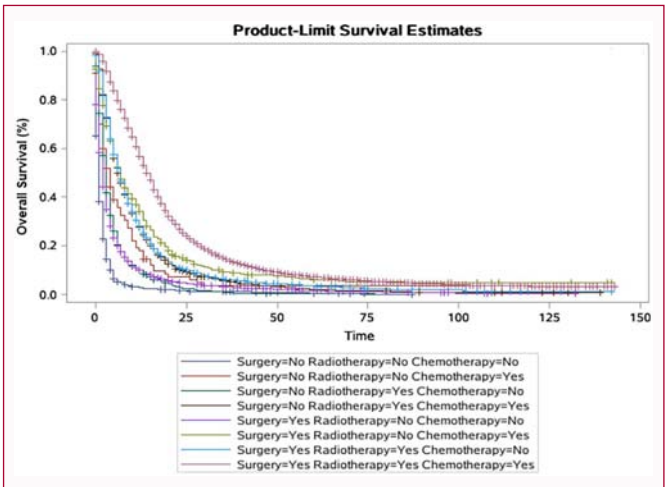

Figure 4: Overall survival of surgery, chemotherapy and radiotherapy in all patients.

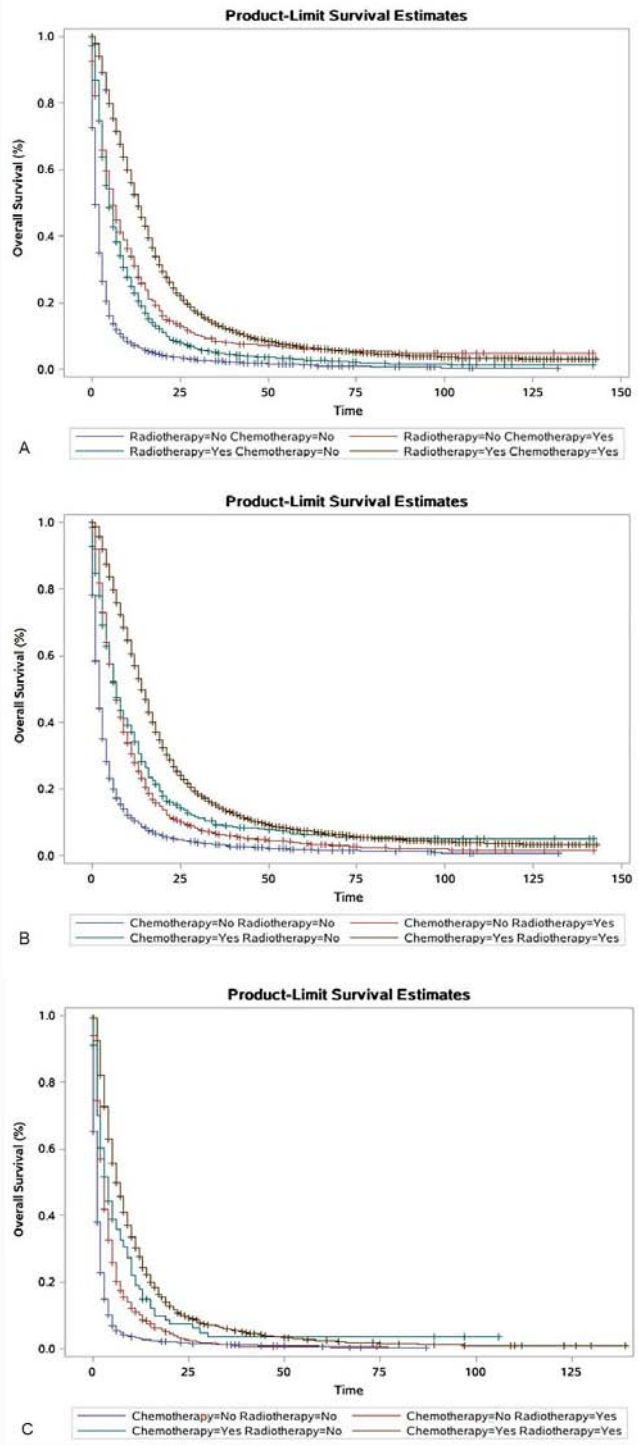

Figure 5: Overall survival of chemotherapy and radiotherapy for the all patients (A), patients who did surgery (B), and patients who did not surgery (C).

chemotherapy on their survival. Similar conclusions can be drawn from patients who have undergone surgery. Among patients who did not have surgery, it was still the combination of chemotherapy and radiation that had the best survival, followed by chemotherapy alone that did better than radiation.

According to the above conclusion, we found that patients with chemotherapy alone had better survival than patients with radiotherapy alone, regardless of whether they had surgery or not.

Table 1: Baseline. Patient demographics and clinical characteristics.

Variabless	Primary cohort (n=23829)	
	N	%
Sex		
Female	9964	41.81
Male	13865	58.19
Race		
White	21405	89.83
Black	1286	5.4
Other	1138	4.78
Age		
≤ 64	12420	52.12
>64	11409	47.88
Tumor size (mm)		
≤ 45	12467	52.32
>45	11362	47.68
Marital status		
Married	15600	65.47
Unmarried	8229	34.53
Extension		
Localized	19080	80.07
Regional	4376	18.36
Distant	373	1.57
Metastasis		
Yes	10895	98.44
No	173	1.56
Surgery		
Yes	18431	77.35
No	5398	22.65
Radiotherapy		
Yes	17821	74.79
No/unknown	6008	25.21
Chemotherapy		
Yes	16067	67.43
No/unknown	7762	32.57

Then we screened the patients who at least received chemotherapy to see the impact of surgery compared with radiotherapy on survival. As can be seen from Figure 6(A), in the case of patients with chemotherapy, the survival rate of patients with surgery and radiotherapy is still the best. The long-term survival rate of patients with surgery alone is better than that of patients with radiotherapy only. However, in the early survival, the difference between surgery alone and radiotherapy alone is not very significant. It shows that operation is good for long-term survival. And then we wanted to figure out what was the choice between surgery and chemotherapy in patients who had at least received radiation. As you can see from Figure 6(B), patients who had both surgery and chemotherapy had the best survival, but if they had either surgery or chemotherapy, they had similar survival. This suggests that surgery and chemotherapy have similar effects in the presence of radiation. The P value of log-

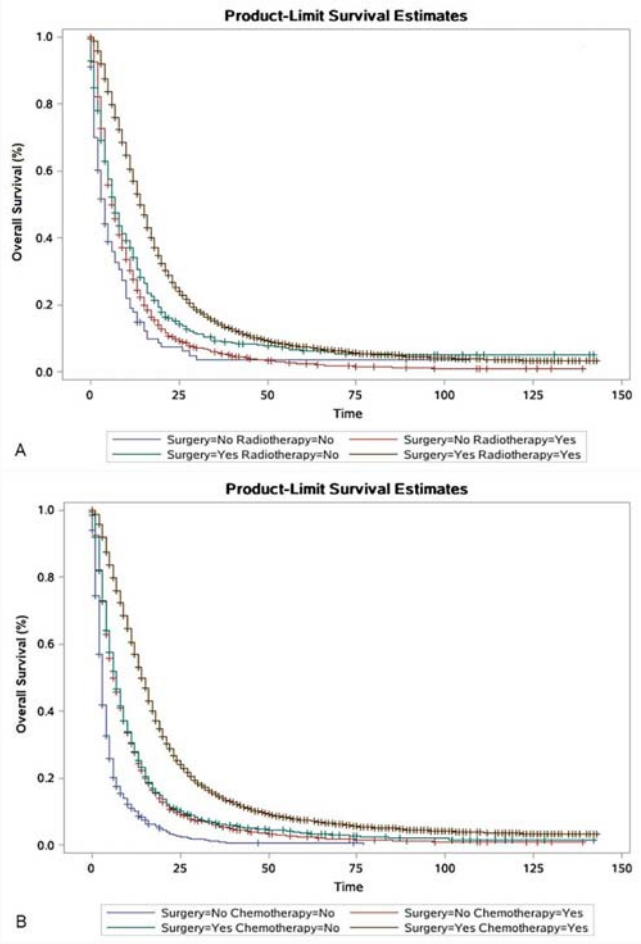

Figure 6: Overall survival of surgery and radiotherapy in patients who had received chemotherapy (A). Overall survival of surgery and chemotherapy in patients who had received radiotherapy (B).

rank tests of all survival analysis above was <0.0001.

Stepwise multivariate Cox regression

Our sample size was large enough, so we performed a stepwise multiple regression analysis and screened out statistically significant variables. Multivariate Cox proportional hazard analysis showed that the older the patient, the worse the prognosis (HR=1.776; 95% CI: 1.725-1.828; P<0.0001). The larger the tumor size, the worse the prognosis (HR=1.121; 95% CI: 1.090-1.153; P<0.0001). Female patients have a slightly better prognosis than male patients (HR=0.958; 95% CI: 0.932-0.986; P=0.003). Other Asian populations have the best prognosis, followed by black populations (HR=1.138; 95% CI: 1.042-1.244; P=0.004), while white populations have the worst prognosis (HR=1.256; 95% CI: 1.174-1.342; P<0.0001). Using localized tumor as a reference, the prognosis of patients with regional tumor was worse than that of localized tumor (HR=1.348; 95% CI: 1.300-1.398; P<0.0001), and the prognosis of distant tumor was the worst (HR=1.493; 95% CI: 1.339-1.665; P<0.0001). The prognosis of patients who underwent surgery was significantly better than that of patients who did not undergo surgery (HR: 0.574, 95% CI: 0.554-0.594; P<0.0001). The prognosis of patients who did radiotherapy was significantly better than those who did not (HR: 0.539, 95% CI: 0.517-0.563; P<0.0001). The prognosis of patients who did chemotherapy was significantly better than that of patients who did not receive chemotherapy (HR: 0.558, 95% CI: 0.536-0.581; P<0.0001). The

Table 2: Stepwise multivariate analysis of variables associated with OS.

Variables	Multivariable		
	HR	95% CI	P
Sex			
Male			
Female	0.958	(0.932, 0.986)	0.0033
Race			
White	1.256	(1.174, 1.342)	<0.0001
Black	1.138	(1.042, 1.244)	0.0041
Other			
Age at diagnosis			
≤ 64			
>64	1.776	(1.725, 1.828)	<0.0001
Tumor size			
≤ 45			
>45	1.121	(1.090, 1.153)	<0.0001
Marital status			
Married	1.078	(1.047, 1.111)	<0.0001
Unmarried			
Extension			
Distant	1.493	(1.339,1.665)	<0.0001
Regional	1.348	(1.300, 1.398)	<0.0001
Localized			
Surgery			
Yes	0.574	(0.554, 0.594)	<0.0001
No			
Radiotherapy			
Yes	0.539	(0.517, 0.563)	<0.0001
No/unknown			
Chemotherapy			
Yes	0.558	(0.536, 0.581)	<0.0001
No/unknown			

married status may have a higher risk of survival (HR: 1.078, 95% CI: 1.047-1.111; P<0.0001). The reason may be that the ages of the married patients were higher than that of unmarried patients. The results also showed that metastasis was not a statistically significant prognostic factor in multivariate regression because it was eliminated in the stepwise selection process. In multivariate analysis, we can find that age at diagnosis, race, tumor size, marital status, extension, surgery, radiotherapy, and chemotherapy are the independent significant prognostic factors.

The older the age is, the lower the degree of differentiation. Also, we did Kaplan–Meier curves analyses. The OS Kaplan-Meier curves are shown in Figure 3. In Kaplan-Meier curves, we can see that patients with old age (>64 years) had worse survival than those with young age (≤ 64 years); patients who did surgery, radiotherapy, chemotherapy had better survival, patients than those without; patients without metastasis had better survival than those with CNS or distant metastasis. The factor, age at diagnosis, had no significant relativity in the Kaplan-Meier curves.

All of the important prognostic factors in the univariate analysis

were used for multivariate Cox proportional hazard analysis.

Discussion

Glioblastoma (GBM) is the most common and invasive primary central nervous system malignancy with a median survival of 15 months [15], making up a significant proportion 48.6% of malignant primary brain and central nervous system tumors, 54% of all gliomas, and 14.5% of all primary brain and central nervous system tumors [7]. The treatment of glioblastoma is complex including surgery resection, radiation and several cycles of concurrent Temozolomide (TMZ) chemotherapy [15]. Glioblastoma is a highly malignant cancer with almost all of them being grade IV so that the 5-year survival rate is very low. With the increase of glioblastoma patients, the treatment of this highly malignant disease and how to prolong the survival time of patients have become a concern in oncologists and surgeons.

In this study, we mainly evaluated the efficacy of different treatments for glioblastoma patients based on SEER database. We also analyzed the correlation between tumor size and patient age not only as continuous variables, but also according to the median. As classified variables, they were analyzed in KM survival curve and Cox regression. In addition, we analyzed the prognosis of the disease by using univariate and stepwise multivariate Cox regression.

We have some curiosity about the relationship between the age and survival time of patients, and the relationship between the age and tumor size of patients, so we conducted a correlation study in this large sample. In the correlation analysis of patients' age and survival time, we found that the older the patients, the shorter the survival time, and it is statistically significant. This result is similar to that of other clinical trials [16,17]. There was a negative correlation between tumor size and survival time, but the correlation was not strong, indicating that the larger the tumor size was, the shorter the survival time was. Because the survival time of patients with GBM is short, the time of tumor growth is not so long, which leads to the weak correlation. We also analyzed the correlation between patients' age and tumor size. The result made us a little surprised. There was a weak negative correlation between age and tumor size. This may be that older people have slightly smaller tumors. Firstly, this proves that the age of diagnosis of GBM may not have a great relationship with the tumor size. Secondly, there is a weak negative correlation, which may be due to the high degree of malignancy and rapid growth of GBM. 70% to 80% of patients have a disease course of 3 to 6 months, and only 10% have a disease course of more than one year [18]. The patients with longer course of disease may develop from astrocytoma with lower malignancy. It indicates that the cancer progression of elderly patients will be faster, and it may be fatal when the tumor grows earlier or is diagnosed early.

As chemotherapy drugs, Temozolomide (TMZ) and Bevacizumab (BEV) were approved by FDA in 2005 and 2009 respectively and has been widely used in clinical [19-22]. Although clinical trials have proved that radiotherapy combined with chemotherapy has a great benefit for survival [23], there is still no large sample analysis to prove the treatment options of patients. Because the survival of glioblastoma is very short, a KM curve conducted to learn different treatments in survival outcomes is useful and practical for clinicians. We mainly researched the impact of different treatment choices and a very detailed study which carried out to evaluate the impact on survival among different treatment choices in patients with glioblastoma has not yet been reported yet. Obviously, the survival of patients with surgery is better than those without surgery, those with radiotherapy are better than those without radiotherapy, and those with chemotherapy are better than those without chemotherapy. It has been reported that the median survival time of patients with chemotherapy combined with radiotherapy is longer than that of patients with radiotherapy alone [24]. From the figures of Kaplan-Meier survival curve, our study can also verify this point. In addition, we can also learn from the Kaplan-Meier survival curve (Figure 5) that the survival of patients with chemotherapy alone is better than that of patients with radiotherapy alone, regardless of whether they have surgery or not. It has some reference significance for patients to choose radiotherapy or chemotherapy in the future. We also screened out patients who were confirmed to have received chemotherapy. Among these patients, those who continued to receive both surgery and radiotherapy had the best survival, and those who only received surgery had a better survival than those who only received radiotherapy. Patients who did not receive surgery or radiotherapy had the worst survival. Then we screened out the patients who had received radiotherapy. Among these patients, the patients who continued to receive both surgery and chemotherapy had the best survival, and the patients who only received surgery had similar survival with those who only received chemotherapy. Patients who did not undergo surgery or chemotherapy had the worst survival. These findings can only be found based on a large sample and it is possible to effectively avoid the bias of the patients from the research given by a single institution. Our findings are the first time to screen patients into different groups and compare the treatments. Chemotherapy alone may be more beneficial if only one of the three treatments is chosen. In the past, there have been analyses of surgical treatment [25], but the selection of the three treatment conditions has not been analyzed in detail. At least in the choice of treatment for patients, this study can provide some reference. Next, we analyzed the prognosis of GBM patients. Cancer prognosis is closely related to different aspects of demographics, tumor characteristics, and treatment conditions. The AJCC-TNM status is currently the most widely used outcome estimation system, but it is not sufficient to meet the needs of all current diseases. Using a SEER database that accounts for 28% of the US population, we were able to collect enough cases to develop the prognosis analysis. Given that the Cox model has a high degree of interpretability and comparability with previous reports, as the method in research of Valentini et al., and some other previous research methods [26-28], we also carried out a multivariate Cox regression analysis and selected the independent variables according to the stepwise method and we use the stepwise multivariate Cox proportional hazard model for overall survival analysis. As the glioblastoma is malignant tumor and the data of stage had high-proportional deficiency, we didn't analysis the stage of patients. In our multivariate Cox analysis for OS, we found that some factors were significant independent prognostic indicators such as age at diagnosis, race, marital status, tumor size, extension, surgery, radiotherapy, and chemotherapy.

Multivariate analysis also showed that patients who underwent surgery had a better prognosis than those who did not, and patients who received radiotherapy and chemotherapy had a better survival than those who did not. In addition, there was no statistically significant association between the metastasis and survival because in the stepwise selection process, the P value is so large that it is eliminated. Second, the impact of ethnic backgrounds can be multifactorial. The mortality of glioblastoma were lowest in other ethnicity (Asian populations), and there was no significant difference

in white and black mortality in glioblastoma; this is similar to previous studies [29,30]. But because the number of whites included is far more than that of blacks and others, the clinical significance of this result remains to be supported by more data. Third, tumor size is closely related to cancer prognosis and is an important independent predictor of glioblastoma prognosis. Our findings further confirm the general view that the smaller the tumor, the better the survival by using Pearson correlation analysis. Marital status also has an impact on the prognosis and deserves attention. In Kaplan-Meier analysis, unmarried patients had longer survival and this result is consistent with the results of Jun et al. [31] because the unmarried patients may be younger than the married patients and may provide compensation mechanisms to improve survival. The result in our Cox analyses were revealed that the married patients had high risk, but the Cox analyses results in our study may be different with other researches [31,32]. They found that married patients had a better prognosis than those who were unmarried because the married patients may have higher economy level and more spiritual support. But potential mechanisms still remain unclear. In this multiple regression, metastasis is excluded from the stepwise screening because it is not statistically significant. Since there were far more patients with no metastases than with metastases in our patient data, the metastases factor may not be significant in multiple regression. This may also indicate that distant metastasis of GBM is less frequent and may be fatal at an early stage of the disease. Treatment measures, such as surgery, radiotherapy, and chemotherapy can greatly improve survival rates. In some previous studies, treatment, surgery, radiotherapy and chemotherapy has also proven to be an important predictor [33-36]. And some of them may focus more on the specific treatment details which the SEER database didn't have. Limitations in our study still exist. Firstly, there is a lack of imaging, smoking history, gene mutations, tumor markers, and detailed treatments, especially detailed chemotherapy or radiotherapy regimens in the SEER database, so our treatment effect analysis can only be a little macroscopic. And the impact of these factors on the prognosis of patients with glioblastoma is not involved in our study. These factors may have effects on the treatment effect and prognosis of the patients. What's more, the tumor extension of glioblastoma was difficult to identify, those data need more precise division and analysis.

In summary, we developed KM curve to evaluate the efficacy of different choices of treatments in GBM patients. We found that surgery and chemotherapy may have more priority for treatment options. The advantages of operation combined with chemotherapy are obvious. Although those models have some limitations, they are trusted enough to provide treatment selection recommendation for patients with glioblastoma. It will help clinicians more effectively identify patients with high mortality rates and make more accurate survival and treatment assessments.

References

1. Tamimi AF, Juweid M. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma. Brisbane (AU). 2017.
2. Paolillo M, Boselli C, Schinelli S. Glioblastoma under siege: An overview of current therapeutic strategies. Brain Sci. 2018;8(1):15.
3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of tumors of the central nervous system: A summary. Acta Neuropathol. 2016;131(6):803-20.
4. Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977-2000. Cancer. 2004;101(10):2293-9.
5. Aldape KD, Okcu MF, Bondy ML, Wrensch M. Molecular epidemiology of glioblastoma. Cancer J. 2003;9(2):99-106.
6. Reuss D, von Deimling A. Hereditary tumor syndromes and gliomas. Recent Results Cancer Res. 2009;171:83-102.
7. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. Neuro Oncol. 2020;22(12 Suppl 2):iv1-iv96.
8. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, et al. NCCN Guidelines Insights: Central Nervous System Cancers, Version 1.2017. J Natl Compr Canc Netw. 2017;15(11):1331-45.
9. Sughrue ME, Sheean T, Bonney PA, Maurer AJ, Teo C. Aggressive repeat surgery for focally recurrent primary glioblastoma: Outcomes and theoretical framework. Neurosurg Focus. 2015;38(3):E11.
10. Shah JL, Li G, Shaffer JL, Azoulay MI, Gibbs IC, Nagpal S, et al. Stereotactic radiosurgery and hypofractionated radiotherapy for glioblastoma. Neurosurgery. 2018;82(1):24-34.
11. Morisse MC, Etienne-Selloum N, Bello-Roufai D, Blonski M, Taillandier L, Lorgis V, et al. Long-term survival in patients with recurrent glioblastoma treated with bevacizumab: A multicentric retrospective study. J Neurooncol. 2019;144(2):419-26.
12. Balana C, Estival A, Teruel I, Hardy-Werbin M, Sepulveda J, Pineda E, et al. Delay in starting radiotherapy due to neoadjuvant therapy does not worsen survival in unresected glioblastoma patients. Clin Transl Oncol. 2018;20(12):1529-37.
13. Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, López-Janeiro A, Porciuncula A, Idoate MA, et al. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. Nat Med. 2019;25(3):470-6.
14. Malmstrom A, Poulsen HS, Gronberg BH, Stragliotto G, Hansen S, Asklund T, et al. Postoperative neoadjuvant temozolomide before radiotherapy versus standard radiotherapy in patients 60 years or younger with anaplastic astrocytoma or glioblastoma: A randomized trial. ActaOncol. 2017;56(12):1776-85.
15. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev. 2014;23(10):1985-96.
16. Bette S, Barz M, Wiestler B, Huber T, Gerhardt J, Buchmann N, et al. Prognostic value of tumor volume in glioblastoma patients: Size also matters for patients with incomplete resection. Ann Surg Oncol. 2018;25(2):558-64.
17. Mariniello G, Peca C, De Caro Mdel B, Giamundo A, Donzelli R, Maiuri F, et al. Glioblastoma in the elderly: The impact of advanced age on treatment and survival. J NeurolSurg A Cent Eur Neurosurg. 2014;75(4):276-81.
18. Gately L, McLachlan SA, Dowling A, J Philip. Life beyond a diagnosis of glioblastoma: A systematic review of the literature. J Cancer Surviv. 2017;11(4):447-52.
19. Johnson DR, Leeper HE, Uhm JH. Glioblastoma survival in the United States improved after Food and Drug Administration approval of bevacizumab: A population-based analysis. Cancer. 2013;119(19):3489-95.
20. Reyes-Botero G, Cartalat-Carel S, Chinot OL, Barrie M, Taillandier L, Beauchesne P, et al. Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: An ANOCEF Phase II Trial (ATAG). Oncologist. 2018;23(5):524-e44.
21. Johnson DR, Omuro AMP, Ravelo A, Sommer N, Guerin A, Ionescu-Ittu R, et al. Overall survival in patients with glioblastoma before and after bevacizumab approval. Curr Med Res Opin. 2018;34(5):813-20.
22. Le Rhun E, Preusser M, Roth P, Reardon DA, van den Bent M, Wen P,

et al. Molecular targeted therapy of glioblastoma. Cancer Treat Rev. 2019;80:101896.

23. Gerstein J, Franz K, Steinbach JP, Seifert V, Fraunholz I, Weiss C, et al. Postoperative radiotherapy and concomitant temozolomide for elderly patients with glioblastoma. Radiother Oncol. 2010;97(3):382-6.

24. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.

25. Lopez-Rivera V, Dono A, Lewis CT, Chandra A, Abdelkhaleq R, Sheth SA, et al. Extent of resection and survival outcomes of geriatric patients with glioblastoma: Is there benefit from aggressive surgery? Clin Neurol Neurosurg. 2021;202:106474.

26. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J ClinOncol. 2011;29(23):3163-72.

27. Zhang ZY, Luo QF, Yin XW, Dai Z-L, Basnet S, Ge H-Y, et al. Nomograms to predict survival after colorectal cancer resection without preoperative therapy. BMC Cancer. 2016;16(1):658.

28. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, Rouzier R, Broglio KR, Hortobagyi GN, et al. Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. J Clin Oncol. 2007;25(31):4952-60.

29. Pan IW, 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):1575-81.

30. Bohn A, Braley A, Rodriguez de la Vega P, Zevallos JC, Barengo NC. The association between race and survival in glioblastoma patients in the US: A retrospective cohort study. PLoS One. 2018;13(6):e0198581.

31. Xie JC, Yang S, Liu XY, Zhao YX. Effect of marital status on survival in glioblastoma multiforme by demographics, education, economic factors, and insurance status. Cancer Med. 2018;7(8):3722-42.

32. Chang SM, Barker FG, 2nd. Marital status, treatment, and survival in patients with glioblastoma multiforme: A population based study. Cancer. 2005;104(9):1975-84.

33. Pretanvil JA, Salinas IQ, Piccioni DE. Glioblastoma in the elderly: Treatment patterns and survival. CNS Oncol. 2017;6(1):19-28.

34. Thumma SR, Fairbanks RK, Lamoreaux WT, Mackay AR, Demakas JJ, Cooke BS, et al. Effect of pretreatment clinical factors on overall survival in glioblastoma multiforme: A Surveillance Epidemiology and End Results (SEER) population analysis. World J Surg Oncol. 2012;10:75.

35. Zhu P, Du XL, Lu G, J-J Zhu. Survival benefit of glioblastoma patients after FDA approval of temozolomide concomitant with radiation and bevacizumab: A population-based study. Oncotarget. 2017;8(27):44015-31.

36. Dubrow R, Darefsky AS, Jacobs DI, Park LS, Rose MG, Laurans MSH, et al. Time trends in glioblastoma multiforme survival: The role of temozolomide. Neuro Oncol. 2013;15(12):1750-61.