Epidemiology and Survival Analysis of Patients with Brainstem Cavernous Hemangioma: A Population-Based Study Using the SEER Database

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Research Article

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Abstract

This population-based study determined the epidemiology, incidence, and outcomes of brainstem cavernous hemangioma. Data on patients with brainstem cavernous hemangioma were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Descriptive analysis assessed the distribution and tumor-related characteristics of patients with brainstem cavernous hemangioma. The Kaplan–Meier method and Cox proportional hazard model were used to analyzed the possible prognostic indicators. The age-adjusted incidence rate between 2000 and 2019 was 0.0236 cases per 100,000 person-years. A total of 283 cases of brainstem cavernous hemangioma were identified between 2000 and 2019. The median patient age was 45 years (range, 0–87 years). Most patients were diagnosed between 40–44 and 55–59 years of age. Middle-aged adults (40–59 years old) accounted for 41.34% of all patients. White patients accounted for 82.6% of all patients. All patients diagnosed with brainstem cavernous hemangioma had benign lesions. Surgery was performed in 105 (37.1%) cases, radiation therapy in 5 (1.7%) cases, and chemotherapy in 1(0.4%) case. The median survival time was 71 months (range: 0–189 months). Age at diagnosis and surgery were two strong factors affecting occurrence and prognosis. Incidence did not differ between sexes and was higher in white patients. Tumor size had little impact on early prognosis; however, for late prognosis, smaller tumors (< 3 cm) had a better prognosis. No significant differences were observed in the outcomes between surgery and conservative treatment. We suggest that more attention should be paid to the treatment of patients with brainstem cavernous hemangioma.

Introduction

Cerebral cavernous hemangioma is a type of cerebral vascular malformation disease; therefore, cerebral cavernous hemangioma is also called cerebral cavernous malformation [1]. Cerebral cavernous hemangioma is an acquired vascular anomaly associated with central nervous system hemorrhage, stroke, and epilepsy [2]. The typical histological manifestations of cerebral cavernous hemangioma are tube chamber formation and vascular leakage of cerebral capillaries, resulting in the disruption of the blood-brain barrier [3]. However, approximately 20–50% of patients with cerebral cavernous hemangioma have no symptoms, and its discovery is usually due to incidental findings during the widespread use of MRI examinations [1]. The prevalence of cerebral cavernous hemangioma is 0.5% in the general population and accounts for 5–10% of all intracranial vascular malformations. The prevalence of cerebral cavernous hemangioma in the brainstem ranges from 4% to 35% [4]. The location of cavernous hemangioma in the brainstem concerns many neurosurgeons because of the difficulty in determining their location and the risk of adverse events. At present, conservative treatment is generally adopted due to the benign nature of cerebral cavernous hemangioma and the lack of obvious clinical symptoms in most patients. However, given that cavernous hemangioma in the brainstem is more aggressive than other sites, once bleeding it is easy to lead to progressive destruction of neurological function, and surgery seems to be a more beneficial option. Nevertheless, surgery remains a controversial issue, primarily because of the high difficulty and risk of performing surgery on the brainstem [5]. Furthermore,

there are few epidemiological investigations and analyses of survival-related factors of brainstem cavernous hemangioma for the small number of patients with brainstem cavernous hemangioma currently, which leads to insufficient clinical evidence to guide the treatment of the disease.

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute represents approximately 48% of the US population (based on the 2000 census) [6]. To understand brainstem cavernous hemangioma better, we performed an epidemiological and survival analysis of 283 cases in the SEER database. This is the largest cohort study of brainstem cavernous hemangioma in the United States so far, and it may provide some reference for neurosurgeons when treating this disease.

Methods

Date Extraction and Incidence Rates

For research purposes, data from the SEER database are publicly available. Therefore, we were able to perform the analysis without ethics committee approval or informed consent. All patients were diagnosed with brainstem cavernous hemangioma. The term cavernous hemangioma was defined by the setting the variable “ICD-O-3 Hist/behav” as “‘9121/0: Cavernous hemangioma’ and ‘9121/1: Cavernous hemangioma, borderline’”. The brainstem was defined by setting the variable “Primary Site-labeled” as “C71.7-Brainstem”. The study period was from 2000 to 2019. The age-adjusted incidence rates (directly standardized to the 2000 US standard population) between 2000 and 2019 were retrieved from the SEER 17 database (November 2021 submission). Detailed patient data were obtained from the SEER Research Plus Data (November 2021 submission) [7]. All data were obtained using SEER*Stat 8.4.0 program.

Variables and Population Analysis

The demographic and clinical features included at diagnosis were: age at diagnosis (0–19 years, 20–39 years, 40–59 years and ≥ 60 years), sex (female, male), race (white, black, other, and unknown), diagnostic confirmation (positive histology, radiography without microscopic confirmation, and others), behavior code (benign, borderline malignancy, and malignant), marital status (married, others), extent of resection was coded as gross total resection (GTR), subtotal resection (STR), none and unknown from the variable “RX Summary-Surgery of Primary Site” (code ‘0’ was defined as ‘none’, code ‘20, 21, 22’ was defined as ‘STR’, code ‘30, 40, 55’ was defined as ‘GTR’, code ‘90, 99’ was defined as ‘unknown’), tumor size (< 3 cm, ≥ 3 cm, and unknown), surgery (yes, none/unknown), Age at diagnosis of patients undergoing surgery (< 50 years and ≥ 50 years). radiation therapy (yes, none/unknown), chemotherapy (yes, none/unknown), survival months, and vital status. Descriptive analysis assessed the distribution and tumor-related characteristics of the patients with brainstem cavernous hemangioma. Bar and pie charts described the distribution of patients.

Survival Analysis

We used the Kaplan–Meier method to estimate the overall survival (OS) of patients and defined survival time as the time from diagnosis to death from any cause. We also used this method to estimate OS in different groups. The differences between the curves were analyzed using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals to analyze the independent prognostic factors associated with OS in patients with brainstem cavernous hemangioma; statistical significance was defined as $p < 0.05$. All data were analyzed using the IBM SPSS Statistics 18 software (IBM Corporation, Armonk, New York, USA).

Results

Population Analysis

The age-adjusted incidence rate between 2000 and 2019 was 0.0236 cases per 100,000 person-years. A total of 283 cases of brainstem cavernous hemangioma were identified between 2000 and 2019. The demographic and clinical characteristics of patients are presented in Table 1. The median patient age was 45 years (range, 0–87 years). Most patients were diagnosed between the ages of 40–44 and 55–59, and the distribution of patient age at diagnosis is shown in a histogram (Fig. 1). Middle-aged adults (40–59 years old) accounted for 41.34% of all patients. There were 158 female (55.8%) and 125 male (44.2%) patients. White patients accounted for 82.6% of all patients (Fig. 2). Among this cohort, 118 cases were diagnosed with positive histology, and 156 were diagnosed with radiography without microscopic confirmation. According to ICD-0-3, all tumors were benign (n = 283, 100%). Married patients accounted for 54.1% of all patients, roughly equivalent to the number of unmarried patients due to other circumstances. For surgical resection of tumors, GTR accounted for 24.4% of all patients and STR for 11.7%. 62.2% of patients did not undergo surgical resection, and 1.7% of patients did not know if they had surgery or only underwent surgery at autopsy. 62.2% of the tumors were less than 3 cm in size, and 4.6% were more than or equal to 3 cm. There is no preferred treatment for patients with brainstem cavernous hemangioma, and the majority of those seeking treatment want surgery. Surgery was performed in 105 (37.1%) cases, radiation therapy in 5 (1.7%) cases, and chemotherapy in 1 case (0.4%). In term of age at diagnosis of patients undergoing surgery, there were 73 (69.5%) in ‘<50 years’ and 32 (30.5%) in ‘≥50 years’. The median survival time was 71 months (range, 0-189 months). At the time of data collection, 243 (85.9%) patients were alive and 40 (14.1%) had died.

Table 1
Demographic and clinical characteristics of patients with Brainstem Cavernous hemangioma.

VARIABLES	Number	%
Age at diagnosis	44.89 ± 19.31	
Mean ± SD	45	
Median	0–87	
Range		
0–19 years	32	11.31
20–39 years	71	25.09
40–59 years	117	41.34
≧ 60 years	63	22.26
Sex	158	55.8
Female	125	44.2
Male		
Race	234	82.6
White	11	3.8
Black	38	13.6
Others		
Diagnosis confirmation	118	41.6
Positive histology	156	55.1
Radiography without microscopic confirm	9	3.3
Others		
Behavior code	283	100
Benign		
Marital status	153	54.1
Married	130	45.9
Others		

VARIABLES	Number	%
Extent of resection	69	24.4
GTR	33	11.7
STR	176	62.2
None	5	1.7
Unknown		
Tumor Size	176	62.2
< 3 cm	13	4.6
≧ 3 cm	94	33.2
Unknown		
Surgery	105	37.1
Yes	178	62.9
None/Unknown		
Radiation	5	1.7
Yes	278	98.3
None/Unknown		
Chemotherapy	1	0.4
Yes	282	99.6
None/Unknown		
Survival months	78.29 ± 54.95	
Mean ± SD	71	
Median	0-189	
Range		
Vital status	243	85.9
Alive	40	14.1
Dead		

Survival Analysis

The OS rates 1, 3, 5, and 10 years after diagnosis were 93.4%, 90.1%, 88.0%, and 82.4%, respectively. A Kaplan–Meier curve was created to show the OS for the full cohort (Fig. 3A). The Kaplan-Meier log-rank test indicated that sex (Fig. 3B), age at diagnosis (Fig. 3C), race (Fig. 3D), surgery (Fig. 3E), marital status (Fig. 3F), extent of resection (Fig. 3G), tumor size (Fig. 3H), and age at diagnosis of patients undergoing surgery (Fig. 4B) were related to OS.

Univariate and Multivariate Cox proportional hazard regression analysis showed that sex, race, surgery, marital status, and tumor size were not independent prognostic factors. Since the variables “surgery” and the variable “extent of resection” are duplicated in some aspects, we removed the variable “extent of resection” when using Cox proportional hazard regression analysis. The number of radiotherapy and chemotherapy patients was so small that we removed the variables “radiation” and “chemotherapy” when using the Cox proportional hazard regression analysis. The results generated by the log-rank test and the univariate and multivariate Cox proportional hazards models are listed in Table 2.

Table 2
The result of log-rank test, univariate, and multivariate Cox regression analysis.

Variable	Log-Rank Test	Univariate Analysis		Multivariate Analysis	
	P value	HR(95%CI)	P value	HR(95%CI)	P value
Sex	0.180	Reference	0.184	Reference	0.086
Female		0.651 (0.346–1.226)		0.568 (0.298–1.084)	
Male					
Age at diagnosis	< 0.001	6.843 (3.290-14.234)	< 0.001	7.632 (3.445–16.898)	< 0.001
0–19		0.395 (0.051–3.082)	0.375	0.172 (0.021–1.426)	0.103
20–39		0.151 (0.019–1.169)	0.070	0.110 (0.014–0.861)	0.036
40–59		Reference		Reference	
≧ 60					
Race	0.389	0.551 (0.075–4.022)	0.123	0.440 (0.104–1.868)	0.266
White		Reference	0.557	Reference	0.690
Black		0.326 (0.078–1.357)		0.662 (0.087–5.052)	
Others					
Surgery	0.455	1.296 (0.654–2.569)	0.457	0.483 (0.220–1.061)	0.070
Yes		Reference		Reference	
None/Unknown					
Marital status	0.526	Reference	0.528	Reference	0.010
Married		0.816 (0.434–1.534)		0.403 (0.202–0.807)	
Others					
Tumor Size	0.244	Reference	0.246	Reference	0.742
< 3 CM		1.543 (0.741–3.212)	0.123	1.133 (0.538–2.386)	0.319
≧ 3 CM		2.773 (0.758–10.141)		1.986 (0.515–7.668)	
Unknown					

Discussion

Brainstem cavernous hemangioma is a relatively rare type of intracranial vascular malformation and accounts for 4–35% of cases [4]. Brainstem cavernous hemangioma can occur anywhere in the brainstem but are more common in the posterior-midbrain region [8]. However, the number of patients with brainstem cavernous hemangioma is so rare that it leads to a lack of understanding of the general features of brainstem cavernous hemangioma. The population counted in the SEER database was collected from most of the United States, representing approximately 48% of the U.S. population [6], which allowed us to investigate the general prevalence of brainstem cavernous hemangioma patients using the SEER database. In the SEER database study, we analyzed various factors that may be related to the prognosis of patients with brainstem cavernous hemangioma. Our report can explain, to some extent, the epidemiology and survival of patients with brainstem cavernous hemangioma in the United States.

First, the age-adjusted incidence rate was 0.0236 cases per 100,000 person-years between 2000 and 2019, which means that it is a very rare disease and may be the reason why there is less research related to the disease. The SEER database is a platform that allows us to analyze various variables. Among all variables considered, age was strongly associated with the occurrence and prognosis of the disease ($P < 0.001$). In Table 2 shows that age was a univariate and multivariate risk factor for disease. The best prognosis was observed in patients under 40 years of age and the worst in those over 60 ($P < 0.001$, Fig. 3C). This may be related to the time at which risk factors affecting the vasculature (e.g., hyperlipidemia, hypertension) play a role in the vascular branches supplying the brainstem. Moreover, the older the age, the longer the risk factors remain, and the greater the chance of causing brainstem cavernous hemangioma. This may also be related to the fact that people over 60 cannot tolerate surgery for treatment, have a low rate of surgical benefit, and have other brain diseases due to hypertension. However, these are only estimates, and the exact mechanism is not yet clear. In addition, brainstem cavernous hemangioma was found incidentally on MRI during the examination, and the final cause of death was brain diseases other than brainstem cavernous hemangioma [9]. Therefore, people over 60 years of age are more likely to have a poor prognosis because they are more susceptible to other brain diseases or worse physical conditions.

As in other SEER studies, there was a higher incidence in white people [10, 11]; possibly because there are more white people in the geographic area, or white people are more susceptible than others. However, the number of cases is too small to determine the correlation, which future studies can investigate.

All brainstem cavernous hemangioma were benign in nature. Therefore, we speculate that the prognosis of brainstem cavernous hemangioma is generally good, and the poor prognosis is related to the size of the tumor as benign tumors usually affect patients with symptoms of occupational compression. However, tumor size was not significantly associated with prognosis in patients with brainstem cavernous hemangioma ($P = 0.244$, Fig. 3H). Most tumors (62.2%) were < 3 cm in size. These tumors have mild compression symptoms, but hemorrhagic seizures caused by brainstem cavernous hemangioma can lead to severe symptoms such as hemiparesis, respiratory dysfunction, and disorders of consciousness due to their dangerous location [12]. In addition, the impact of brainstem cavernous hemangioma on quality of life is obvious [13]. As shown in Fig. 3H, there was no significant relationship

between the size of the tumor and the survival prognosis of the patients within four years; but after four years, the prognosis of patients with tumors less than 3 cm was significantly better than that of patients with tumors > 3 cm. It may be that the compression symptoms contributed to the poor prognosis four years later.

As brainstem cavernous hemangioma is a benign disease; many patients did not undergo surgery. Approximately 37.1% chose to undergo surgery, but the difference between those who underwent surgery and those who did not was not was not significant (P = 0.455, Table 2) according to the log-rank test, and the improvement in prognosis was not particularly significant. Nevertheless, patients who underwent GTR surgery had a better prognosis than STR and those who did not undergo surgery (P = 0.024, Fig. 3G). More interestingly, we divided patients into two groups (< 50 years, ≥ 50 years) according to the age at diagnosis (Fig. 4A), and analyzed their overall survival. As a result, patients who were diagnosed before the age of 50 and then underwent surgery had better prognosis than that of those after the age of 50 (P = 0.003, Fig. 4B). Although surgery is not effective for all patients with brainstem cavernous hemangioma, it is recommended for patients with indications for surgery and those requiring intensive care [12, 14]. Therefore, the earlier the disease is diagnosed and cleaner the tumor is resected, the better the prognosis of patients. However, surgery in the brainstem is not easy and full of risks [15].

The brainstem regulates vital activities in the body. Therefore, we suspect that diseases in this area are less suitable for surgical treatment because surgery causes greater damage compared to other treatments. However, few patients were treated with chemotherapy and radiation; therefore, we did not perform Kaplan-Meier analysis and log-rank tests for chemotherapy and radiation. Surgery remains the main treatment modality for patients with brainstem cavernous hemangioma [16]. However, for brainstem cavernous hemangioma, surgical removal comes with great risks as it is difficult to remove from the surgical site or has important nerve tissue in the adjacent area that needs to be removed. Therefore, it is challenging for neurosurgeons to choose the best surgical approach and technique for the patient prognosis [17]. According to recent studies, there is no specific recommended treatment for chemotherapy, and there are only examples of researchers using propranolol to treat brainstem cavernous hemangioma [18]. When using radiation therapy, most current studies have been performed using gamma knife radiosurgery or stereotactic radiosurgery [19–21].

This study had some limitations. First, the disease is relatively rare, with few cases. Although the SEER database provides a large data platform, there is still very little data on brainstem cavernous hemangioma, and the conclusions drawn may be biased. In addition, the understanding of brainstem cavernous hemangioma is not well developed, its etiology and risk factors are unclear, and there is no unified indicator for how it develops and the prognosis of intervention after treatment, which needs to be studied by future researchers. Furthermore, this study only epidemiologically analyzed data from more than 200 people and only found that age and treatment modality may influence their prognosis; therefore, we hope we can continue to study more in the future with more data from the SEER database. Despite these shortcomings, the limited data may help clinicians and researchers in this area of research and help them better understand this disease.

Conclusion

When treating brainstem cavernous hemangioma, age at diagnosis and surgery, tumor size, and extend of surgical resection were the main factors associated with patient outcomes. In general, patients who were diagnosed at a younger age and underwent surgery have better prognosis than older ones. Notably, tumor size had a more significant impact on late prognosis than early-stage (< 4 years) and smaller tumors (< 3 cm) led to a better prognosis for patients with advanced disease. In contrast, larger tumor size had a more negative impact on the severity of the disease and life status. Therefore, periodic brain MRI examinations is recommended for making sure that the tumor will not grow too big and patients could be diagnosed at a younger age. Although the primary treatment for brainstem cavernous hemangioma is surgery, surgery cannot significantly improve the prognosis of patients compared with conservative treatment unless GTR is performed. However, a higher extend of tumor resection in the brainstem is not a simple task. We suggest more attention should be paid to the treatment of brainstem cavernous hemangioma and hope to obtain more data from the SEER database in the future for a more comprehensive analysis.

Declarations

Author Contributions

The manuscript was written by Zhixin Zhan and Ding He. The review of literature and data collection were performed by Zedi Yang and Ziqiang Liu. The manuscript was critically reviewed and edited by Yong Chen. The project was conceptualized by Haiyan Huang. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial nor financial relationships that could be construed as a potential conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study and their parents/legally authorized representatives.

Consent for publication

All the authors agreed to publish this manu script in Neurosurgical review.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Informed consent

This is a population study that involved no identifiable information for individuals throughout the analyses. Data were obtained in accordance with SEER database policies.

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Figures

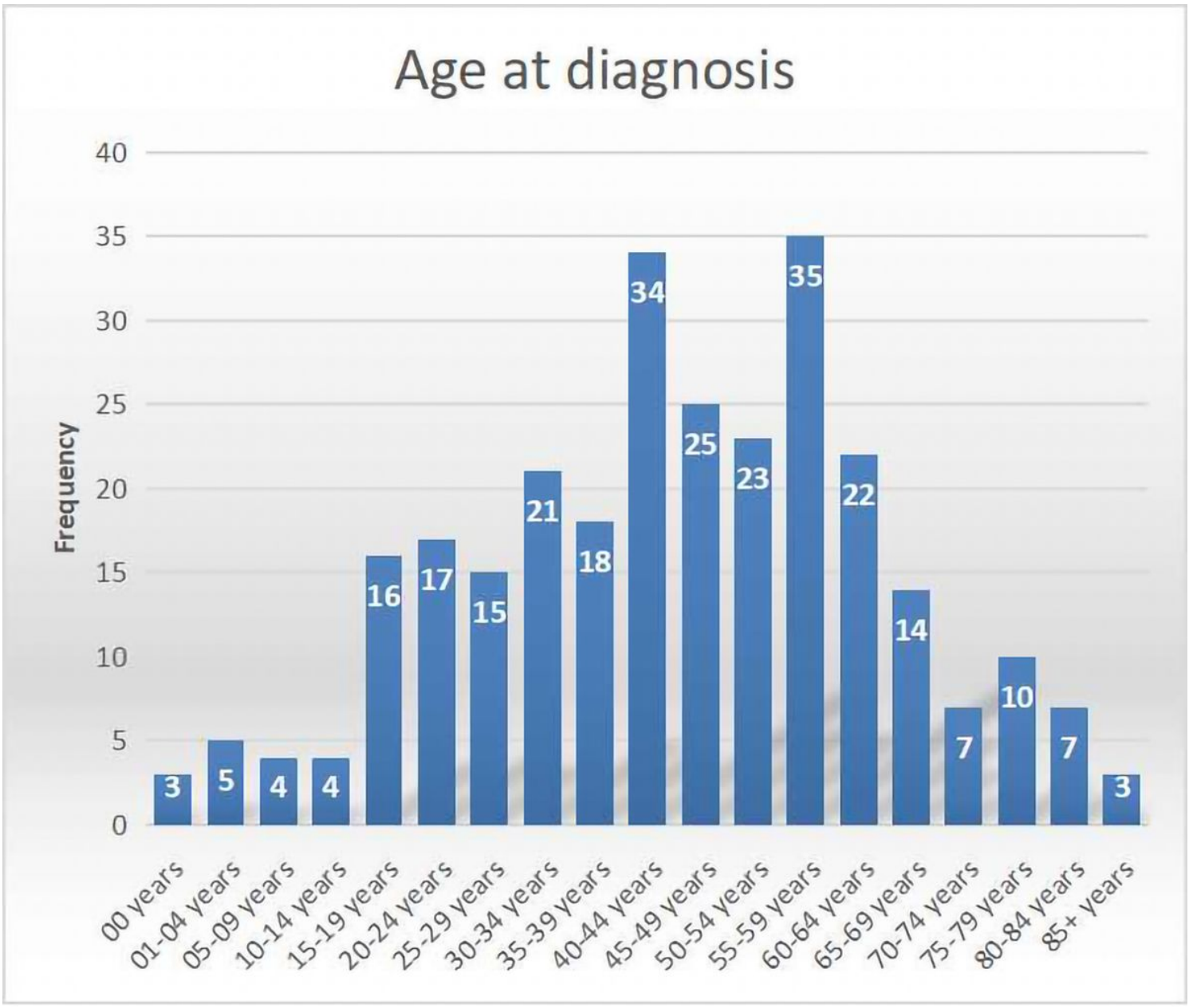

Figure 1

Age distribution of the patients at diagnosis.

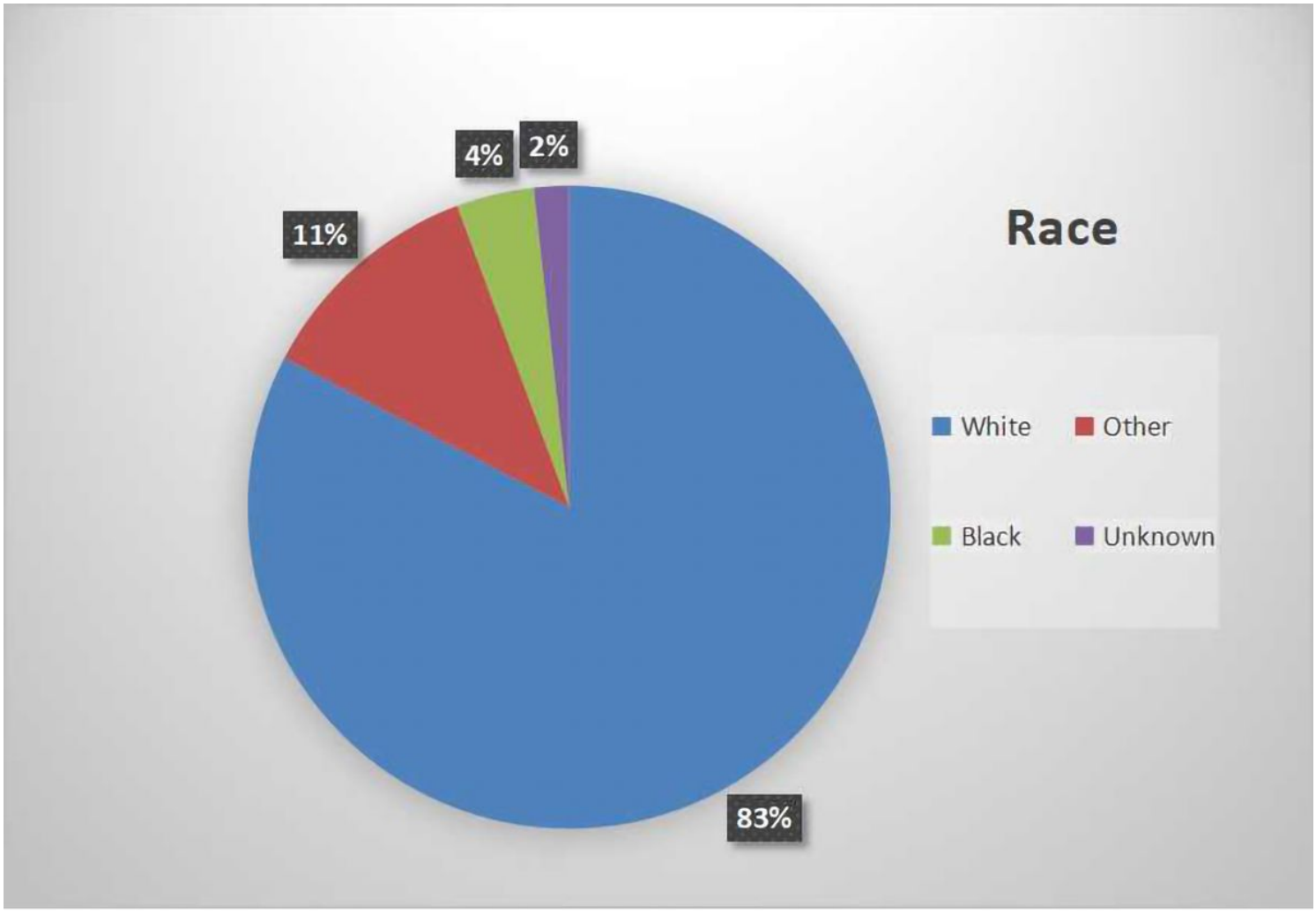

Figure 2

Racial distribution of the patients.

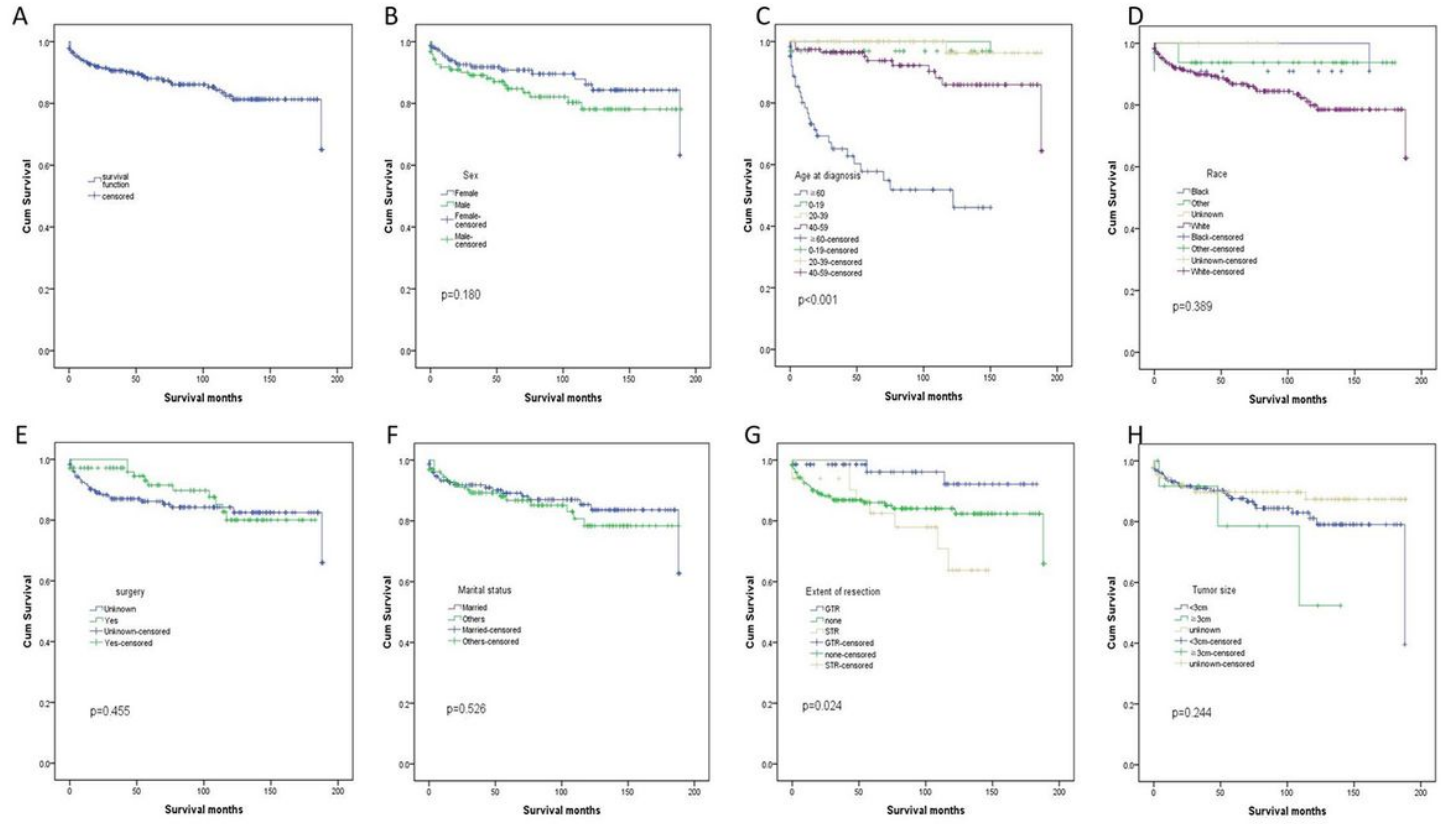

Figure 3

Kaplan-Meier survival analysis: (A) the overall survival for the whole cohort. The survival analysis of patients classified based on (B) sex, (C) age at diagnosis, (D) race, (E) surgery, (F) marital Status, (G) extent of resection, and (H) tumor size.

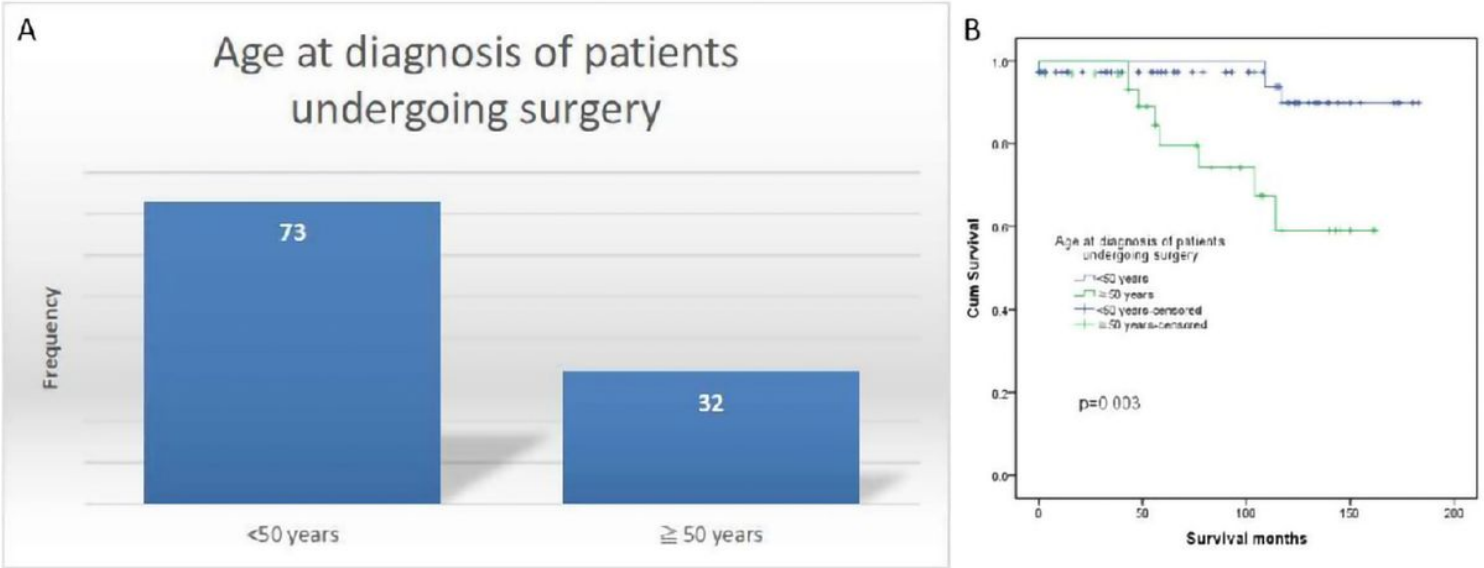

Figure 4

Age at diagnosis of patients undergoing surgery: (A) Age distribution of the patients at diagnosis and underwent surgery, (B) Kaplan-Meier survival analysis of Age at diagnosis of patients undergoing surgery.