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Original Article

Geographical distribution affects survival of patients with intracranial ependymoma in the USA: a SEER based study

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Abstract: Precision medicine, based on the relationship between personalized clinical characteristics and prognosis, leads to better patient therapeutic outcomes. Social factors directly affect patient prognosis in several cancers. However, the relationship between social factors and prognosis of patients with intracranial ependymoma (IE) remains unclear. The aim of this retrospective study was to identify the association between social factors and IE patient prognosis. Information was collected from patients histologically confirmed to have IE between 1973 and 2015, analyzing the relationship between patients and social factors using the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan-Meier and Cox's proportional hazards regression analyses were used to evaluate patient survival. Present results revealed that geographical distribution was statistically significantly associated with prognosis of IE patients, based on the SEER database. Patients from the Midwest region of the USA had a lower 5-year survival rate (64.8%) than those from the Northeast (74.8%), South (79.6%), and West (72.0%). Reducing bias, propensity score matching was further applied in analyzing relevant factors. Similarly, prognosis in the Midwest region (hazard ratio [HR] = 1) was poorer than that in the Northeast (HR = 0.62), South (HR = 0.55), and West (HR = 0.71). Therefore, geographical distribution may play an important role in the malignant progression of IE and may be beneficial for the precise treatment of patients with IE.

Keywords: Intracranial ependymoma, geographical distribution, prognosis, SEER, 5-year survival rate

Introduction

Intracranial ependymomas (IEs) are rare gliomas found in the central nervous system [1]. IEs originate from cerebral ventricular walls found inside the brain, the external ventricular system, or in ependymal cells blocked in the brain parenchyma during embryonic development [2-4]. IEs account for 1.2%-7.8% of intracranial tumors. They have a poorer overall survival, compared with spinal ependymomas [5, 6]. Incidence of IEs is greater in males than in females [7]. IEs commonly occur in children, accounting for 6%-10% of intracranial tumors [6, 8]. The 2016 World Health Organization (WHO) classification of ependymal tumors categorized sub-ependymomas and myxopapillary ependymomas as Grade I. Ependymomas, including papillary, clear cell, and tanycytic variants, are classified as Grade II. RELA fusion-positive ependymomas are classified as Grade II or III. Anaplastic ependymomas, the most malignant histological type, are classified as Grade III [9]. Epidemiological data shows that 5-year and 10-year overall survival rates are 83.4% and 79.1%, respectively [10].

Precision medicine is defined as treatment according to distinguishing characteristics of different patients with the same disease. Characteristics may be unique but not limited to one person. These include age, gender, race, histological grade, tumor size, genomics, microbiome, and social factors, such as geography, socioeconomic status, lifestyles, and environmental exposure [11-13]. Prognostic factors for IE include age, gender, histological grade, tumor location, site-specific molecular genetics,

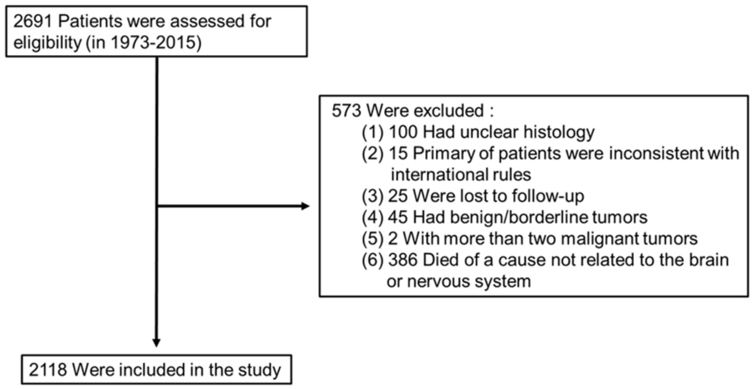

Figure 1. Inclusion and exclusion chart.

extent of resection, and adjuvant radiotherapy [14-17].

The present study reviewed clinical data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, comprising a large population of patients from the United States. The current study investigated the effect of social factors on overall survival rates of patients with IE, identifying geographical distribution as a potential prognostic indicator of IE.

Materials and methods

Database and patient population

Retrospective analysis was conducted using SEER Program (www.seer.cancer.gov) research data: Incidence-SEER 18 Registries Research Data, November 2017 Submission (1973-2015), National Cancer Institute, Division of Cancer Control and Population Sciences (DCCPS), Surveillance Research Program, Surveillance Systems Branch, released in April 2018.

The SEER database follows-up patient survival every year. It provides data, such as basic information of patients, extent of the tumors, WHO grades, metastasis at the time of diagnosis, surgery conditions, and marital status. However, the database does not contain information concerning patient physical conditions, clinical symptoms, postoperative recovery, or other adjuvant treatments.

In the present study, patients diagnosed between 1973 and 2015 were selected, aiming to improve the accuracy of survival analysis. All patients with IE were confirmed histologically and tumor behavior was identified as malignant. Primary tumors were confirmed according to international rules and originated from the brain. Cause of death was due to brain and CNS incidents. Patients that were offered active follow-ups and explicit survival results were included. Patients with benign or borderline tumors, as well as those with more than three malignant tumors, were excluded.

Variable collection

Patients with IE were included from the SEER database based on International Classification of Disease in Oncology 3rd edition (ICD-O-3) with codes 9391, 9392, 9393, and 9394. Prognostic factors were divided into three categories: (1) Personal basic factors: Age (>18 years or ≤ 18 years), gender, and race; (2) Clinical factors: Primary laterality (one site or paired site), histological grade, tumor size (>4 cm or ≤ 4 cm), tumor location (supratentorial, infratentorial, ventricle, across the velarium, and others), summary stage (unknown/unstaged was excluded from analysis), surgical resection (yes or no); and (3) Social factors: Marital status (divorced, separated, and single (never married or widowed) were combined to form the single group), insurance status (insured/no specifics were included in the insured group), rural-urban continuum conditions, and geographical distribution (Northeast included Connecticut and New Jersey, Midwest included Michigan and Iowa, South included Georgia, Kentucky, and Louisiana, and West included California, Utah, New Mexico, Washington, Hawaii, and Alaska).

Statistical analysis

Descriptive statistical methods were applied to summarize demographics and tumor characteristics of patients with IE. Kaplan-Meier survival analysis with log-rank tests were used to analyze patient 5-year survival rates and overall survival. Cox's proportional hazards regres-

Table 1. Characteristics of patients with IE

Subgroup	Number of patients	%	5-year survival rate (%)
Age (years)			
<18 yr	1023	48.3	71.5
≥18 yr	1095	51.7	73.8
Gender			
Female	987	46.6	75.3
Male	1131	53.4	70.3
Race			
White	1724	82.1	72.9
Black	223	10.6	68.0
Other	153	7.3	75.2
Laterality			
One side	2094	98.9	72.6
Paired site	24	11	74.0
Grade			
Well differentiated	83	9.6	77.6
Moderately differentiated	253	29.3	88.7
Poorly differentiated	89	10.3	43.5
Undifferentiated	438	50.8	62.3
Tumor size			
≤40 mm	639	48.6	80.2
>40 mm	676	51.4	73.8
Location			
Supratentorial	429	26.4	73.0
Infratentorial	325	17.4	76.9
Ventricle	585	31.4	79.7
Across velarium	62	3.3	60.4
Others	402	21.5	75.3
Summary stage			
Distant	65	3.7	71.7
Localized	1437	81.3	75.3
Regional	266	15.0	69.9
Surgical resection			
No	95	4.5	65.4
Yes	2000	95.5	73.3
Marital			
Single	1453	70.4	71.8
Married	610	29.6	73.5
Insurance			
Any Medical	229	25.9	75.5
Insured	626	70.9	84.6
Uninsured	28	3.2	74.2
Rural-Urban Continuum			
Metro	1889	89.2	73.0
Nonmetro	229	10.8	71.4
Geographical distribution			
Northeast	333	15.7	74.8
Midwest	277	13.1	64.8
South	342	16.1	79.6
West	1166	55.1	72.0

sion model was applied to univariate and multivariate analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Propensity score matching (PSM) analysis was performed, further adjusting potential baseline confounding factors. Two-sided *P*-values <0.05 are considered statistically significant. Statistical analysis was carried out using SPSS version 22.0 (IBM Corp, Armonk, NY) and GraphPad Prism version 6 (GraphPad Software Inc.).

Results

Study characteristics

A total of 2,691 IE patients, diagnosed between 1973 and 2015, were initially eligible. Of these, 115 patients were excluded due to unclear histology or because they were inconsistent with international rules. Another 25 patients were lost to follow-up and 45 patients had benign or borderline tumors. Two patients had more than three malignant tumors and 386 patients died of causes not related to the brain or CNS. The remaining 2,118 patients were included in the current study (**Figure 1**). Patients with incomplete IE information and individual subgroup information were excluded. Therefore, the number of patients in each subgroup displayed different statistics. Characteristics of patients with IE are summarized in **Table 1**. Most patients were white (82.1%), in which the 5-year survival rate was 72.9%. Over 90% of patients received surgical treatment. Five-year survival rates in the Northeast, Midwest, South, and West were 74.8%, 64.8%, 79.6%, and 72.0%, respectively (**Table 1**).

Survival differences

A prognostic examination of personal, clinical, and social factors was conducted, aiming to identify prognostic factors in patients with IE. Consistent with previous reports, several personal and clinical factors, including gender, race, tumor size, tumor location, histological grade, and surgical resection, were significantly correlated with IE patient survival [4, 14,

Table 2. Univariate Cox proportional hazard regression analysis of risk factors among patients with IE

Subgroup	HR	95% CI	*P* value
Age (years)			
<18	1.01	0.87-1.18	0.859
≥18	1.00	Reference	
Gender			
Female	0.81	0.69-0.95	0.008
Male	1.00	Reference	
Race			
White	1.28	0.92-1.79	0.143
Black	1.50	1.02-2.23	0.042
Other	1.00	Reference	
Laterality			
One side	1.22	0.51-2.94	0.659
Paired site	1.00	Reference	
Grade			
Well differentiated	0.53	0.34-0.82	0.005
Moderately differentiated	0.30	0.21-0.43	<0.001
Poorly differentiated	1.53	1.11-2.12	0.010
Undifferentiated	1.00	Reference	
Tumor size			
≤40 mm	0.79	0.63-0.98	0.032
>40 mm	1.00	Reference	
Location			
Supratentorial	1.07	0.84-1.37	0.589
Infratentorial	0.92	0.69-1.22	0.555
Ventricle	0.74	0.58-0.95	0.018
Across velarium	1.65	1.07-2.55	0.023
Others	1.00	Reference	
Summary stage			
Distant	0.95	0.58-1.54	0.829
Localized	0.76	0.60-0.96	0.021
Regional	1.00	Reference	
Surgical resection			
No	1.46	1.05-2.03	0.024
Yes	1.00	Reference	
Marital			
Single	1.03	0.87-1.22	0.714
Married	1.00	Reference	
Insurance			
Any Medical	1.07	0.43-2.70	0.886
Insured	0.60	0.24-1.49	0.270
Uninsured	1.00	Reference	
Rural-Urban Continuum			
Metro	0.93	0.73-1.17	0.525
Nonmetro	1.00	Reference	
Geographical distribution			
Northeast	0.87	0.69-1.11	0.258
Midwest	1.41	1.15-1.73	0.001
South	0.77	0.60-0.98	0.033
West	1.00	Reference	

15, 17, 18], according to univariate analysis. Furthermore, two social factors were found to play potential prognostic roles. Regional stage patients showed poorer progress, compared with patients with other stages. Patients from the Midwest region showed a poorer prognosis, compared with those from other regions (**Table 2**). The effects of geographical distribution on IE patient survival were confirmed using Kaplan-Meier survival analysis and log-rank tests. As shown in **Figure 2A**, patients from the Midwest region showed a significant risk for poor survival, compared with those from the Northeast (HR = 0.62, 95% CI = 0.47-0.82), South (HR = 0.55, 95% CI = 0.41-0.72), and West (HR = 0.71, 95% CI = 0.58-0.87).

Identifying independent risk factors for survival of patients with IE, multivariate Cox regression was conducted with significant factors ($P < 0.05$) from univariate analysis. Race, histological grade, and geographical distribution were found to be significant risk factors affecting survival of patients (**Table 3**). Aiming to reduce selection bias, PSM was applied for gender, race, and surgical resection. According to survival analysis, patients from the Midwest region had a shorter survival, compared with those from the Northeast (HR = 0.62, P = 0.001), South (HR = 0.55, P<0.0001), and West (HR = 0.71, P = 0.001). Similarly, after conducting PSM for gender, race, and surgery status, patients from the Midwest had worse survival rates, compared with those from the Northeast (HR = 0.50, P<0.0001), South (HR = 0.54, P<0.0001), and West (HR = 0.52, P = 0.0001) (**Figure 2B-D**). Although race and histological grade have been reported to be independent prognostic factors for IE [18, 19], the current study identified geographical distribution as a novel social independent prognostic factor for IE.

Discussion

Most current cancer research has focused on personal and clinical factors. The association between social factors and prognosis of cancer patients is often overlooked. The present study analyzed personal, clinical, and social characteristics of patients with IE selected from the SEER database. The current study also confirmed current IE prognostic factors, including race and histological grade. Present results

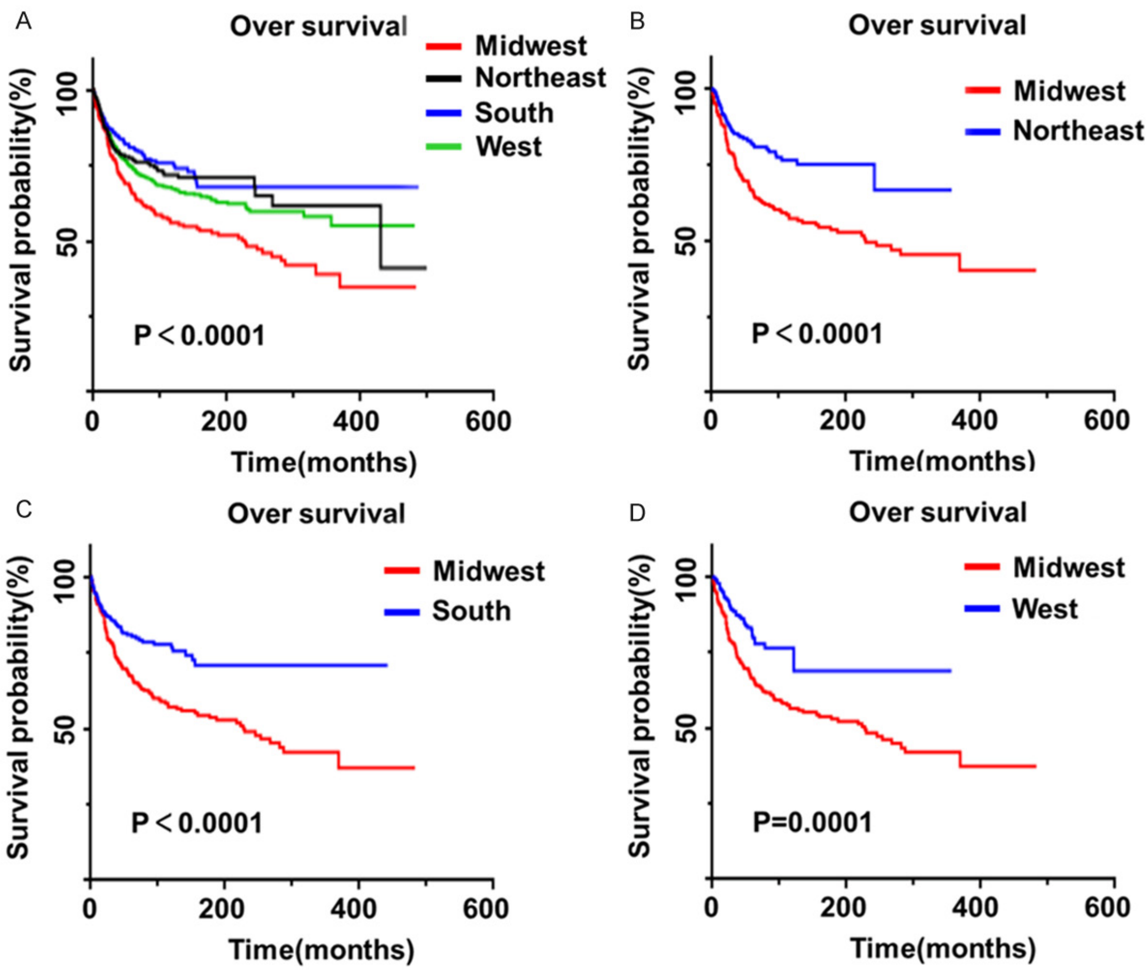

Figure 2. Kaplan Meier curves of patients stratified by all different geographical regions (A) and survival probability of patients for matched age, gender, race, and surgical resection matched between the Midwest and Northeast (B), South (C), and West (D), respectively.

suggest geographical distribution as a new independent prognostic factor.

Gastric cancer is a typical regional high-risk cancer in East Asia, including South Korea, China, and Japan [20, 21]. However, incidence of gastric cancer has sharply decreased in Japanese immigrants in Hawaii, indicating that different lifestyles and modifiable factors affect the incidence frequency of gastric cancer [22]. Substantial evidence from cohort studies has strongly suggested that salt intake and *Helicobacter pylori* infections play synergistic roles in the occurrence and development of gastric cancer [21]. Environmental exposure has also been associated with geological characteristics of high mortality clusters, including environmental exposure to naturally occurring heavy metals [23, 24]. Moreover, lifestyle factors, such as alcohol consumption, smoking, and low fruit intake, have been reported as other potential risk factors for gastric cancer [22, 25].

Similarly, there is an obvious geographical aggregation in the morbidity and mortality of esophageal cancer [26]. Incidence and mortality rates of esophageal cancer are especially high in Henan and Hebei Provinces of North China [27]. The types and quality of the drinking water, as well as dietary habits, are related to the high morbidity and mortality rates of esophageal cancer in these areas. Use of tobacco and the consumption of alcohol, hot food, hard and rough food, and fast food have been associated with an increased likelihood of developing esophageal cancer [28, 29]. Moreover, *N*-nitroso compounds, found in pickled vegeta-

Table 3. Multivariate Cox proportional hazard regression analysis of risk factors among patients with IE

Subgroup	HR	95% CI	*P* value
Gender			
Female	0.74	0.53-1.03	0.076
Male	1.00	Reference	
Race			
White	1.89	0.98-3.66	0.058
Black	2.56	1.20-5.46	0.015
Other	1.00	Reference	
Grade			
Well differentiated	0.51	0.24-1.05	0.067
Moderately differentiated	0.25	0.15-0.42	<0.001
Poorly differentiated	1.43	0.88-2.32	0.152
Undifferentiated	1.00	Reference	
Tumor size			
≤40 mm	0.99	0.70-1.40	0.944
>40 mm	1.00	Reference	
Location			
Supratentorial	1.32	0.59-2.99	0.502
Infratentorial	1.51	0.66-3.44	0.327
Ventricle	1.76	0.77-4.02	0.182
Across velarium	1.66	0.66-4.17	0.282
Others	1.00	Reference	
Summary stage			
Distant	1.15	0.48-2.78	0.758
Localized	0.67	0.28-1.59	0.362
Regional	1.00	Reference	
Surgical resection			
No	1.77	0.74-4.26	0.203
Yes	1.00	Reference	
Geographical distribution			
Northeast	0.41	0.19-0.88	0.023
Midwest	1.88	0.51-1.54	0.657
South	0.82	0.53-1.27	0.373
West	1.00	Reference	

bles and barbecued food, have also been shown to play an important role in the induction of esophageal cancer [30].

Nasopharyngeal carcinoma is a rare cancer. However, it occurs frequently in South China. It exhibits a unique morbidity and mortality in Guangdong and Guangxi Provinces [31]. It is believed to be related to geological environment properties and traditional lifestyles [32]. In these areas, patients with the disease are frequently infected with the Epstein-Barr virus. Moreover, the nickel-rich soil directly influences morbidity and mortality rates of nasopharyngeal carcinoma [33, 34]. Commonly eaten foods, such as salted fish, often contain a high quantity of carcinogens (e.g., nitrosamines) that increase incidence rates of nasopharyngeal carcinoma in South China [35].

Differences in geographical distribution could also be reflected in climate conditions. Many studies have demonstrated the effects of climate on human health [36]. Specific climate conditions, such as heat waves, sunshine, and cold exposure, could increase mortality [36, 37]. The weakened physiology of cancer patients makes them more susceptible to weather conditions, which may lead to death in patients with advanced cancers [38].

Precision medicine represents an important focus of disease management. Individualized treatment protocols have been developed, based on specific factors, and the roles of social factors may have been underestimated [13]. However, the database used in the present study lacked social information, including lifestyles, dietary habits, family history, microbiome, and environmental exposure. Therefore, further data collection and research are required.

The current study had many limitations. First, PSM analysis was not applied to all influential factors. This was due to a low number of patients with ependymomas. Therefore, selection bias could not be minimized. Second, characteristic information was not available for some IE patients in the SEER database. In addition, information may have been lacking for other factors that cause diversity in survival, such as family history, genetic profiles, and disease presentation. Third, there was no information concerning radiotherapy. This may be a significant prognostic factor in patients with IE. Fourth, factors such as climate, lifestyle, and environmental exposure may have confounded present results.

In summary, present results suggest that race, histological grade, and geographical distribution were significant prognostic factors for patients with IE. Patients in Midwest USA showed poorer survival, compared with those in the Northeast, South, and West. This is the first report showing the effects of geographical distribution for IE. Present findings may be beneficial for precise treatment for patients with IE.

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Disclosure of conflict of interest

None.

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