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Incidence and Survival of Patients With Malignant Primary Spinal Cord Tumors: A Population-Based Analysis

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Objective: Epidemiological studies on spinal cord tumors are rare, and studies on primary intramedullary tumors are even rarer. The incidence and survival of patients with primary intramedullary spinal cord tumors have not been well documented. We aimed to study the incidence and survival of patients with primary spinal cord malignant and borderline malignant tumors based on data from the Surveillance, Epidemiology, and End Results (SEER) database and provide information for revealing the epidemiology and exploring the prognosis of patients with primary intramedullary tumors.

Methods: Patients in the SEER database with microscopically diagnosed malignant and borderline malignant primary spinal cord tumors from 2000 and 2019 were included in this study. We analyzed the distribution of patients according to the demographic and clinical characteristics. Then, we extracted the incidence rate and 5-year relative survival for the whole cohort and different subgroups of the cohort. Finally, multivariate Cox proportional hazards models were used to analyze the independent prognostic factors associated with overall survival.

Results: A total of 5,211 patients with malignant and borderline malignant primary spinal cord tumors were included in this cohort study. Ependymoma, astrocytoma (including oligodendrogliomas and glioblastoma), lymphoma and hemangioblastoma were the most common pathological types. The age-adjusted incidence rates of primary spinal cord ependymoma was 0.18 per 100,000. The incidence rate for females was significantly lower than that for males. The incidence rate was highest in Caucasian. The incidence rate of ependymoma was significantly higher than that of other pathological types. The incidence of astrocytoma was highest among people aged 0–19 years, the incidence of ependymoma was highest among people aged 40–59 years, and the incidence of lymphoma was highest among people aged 60 years or older. The 5-year observed survival and relative survival rates for the whole cohort were 82.80% and 86.00%, respectively. Patients diagnosed with ependymoma had significantly better survival than their counterparts. We also found the impact of surgery and chemotherapy on the prognosis of patients with different tumors varies a lot.

Conclusion: We conducted a population-based analysis of malignant and borderline malignant primary spinal cord tumors with the aim of revealing the epidemiology and survival of patients with primary intramedullary spinal cord tumors. Despite some shortcomings, this study provides valuable information to help us better understand the epidemiological characteristics of primary intramedullary spinal cord tumors.

Keywords: Intramedullary tumor, Ependymoma, Epidemiology, Survival, SEER Program

INTRODUCTION

The spinal cord is one of the 2 components of the central nervous system (CNS). According to the recent CBTRUS (Central Brain Tumor Registry of the United States) report on primary CNS tumors,[1-3] tumors of the cranial nerves and the spinal cord/cauda equina accounted for approximately 10% of all CNS tumors. We searched PubMed with the medical subject heading

(MeSH) terms for spinal cord tumors, which yielded less than 7% of the results obtained for a search on brain tumors. We obtained even fewer results when searching PubMed with the MeSH terms for spinal cord tumors and epidemiology. We believe that the incidence and survival of patients with primary intramedullary spinal cord tumors have not been well documented. The Surveillance, Epidemiology, and End Results (SEER) Program provides information on cancer incidence and survival in an effort to reduce the cancer burden among the U.S. population; it is one of the largest databases of clinical information worldwide. The SEER database includes approximately 48.0% of the U.S. population, including 42.0% of Caucasian, 44.7% of African American people, 66.3% of Hispanic people, 59.9% of American Indian and Alaska Native people, 70.7% of Asian people, and 70.3% of Hawaiian/Pacific Islanders.[4] The number of SEER-based studies targeting spinal canal tumors has been increasing in recent years. For example, Cao et al.[5] reported the epidemiology and survival of patients with spinal meningiomas. Primary spinal ependymomas,[6] lymphomas[7] and hemangioblastomas[8] have also been reported. However, to our knowledge, no studies of primary intramedullary tumors have been conducted. Although it is difficult to isolate cases of intramedullary tumors with the variables in the SEER database, we found that if we included malignant and borderline malignant primary spinal cord tumors, the data would cover almost 99% of intramedullary tumors. Therefore, we conducted this analysis of data in the SEER database that described the incidence and survival of patients with malignant and borderline malignant primary spinal cord tumors, with the aim of helping clinicians better understand the epidemiology of patients with primary intramedullary tumors.

MATERIALS AND METHODS

Since the data from the SEER registry were de-identified and publicly available, no institutional review board approval was necessary and no informed consent was signed for this study. This study was exempt from Institutional Review Board approval because the original data were from a public database.

The latest version of the SEER database, SEER Research Plus Data 17 Registries, was adopted.[9] The patients who were diagnosed between 2000 and 2019 were considered for inclusion in the study. The patients with microscopically diagnosed malignant and borderline malignant primary spinal cord tumors were indexed. Then, we selected patients with primary sites of C72.0, in the spinal cord, and C72.1, in the cauda equina. The exclusion criteria were as follows: (1) patients with unknown age, (2) surviving patients with unknown survival time, and (3) patients diagnosed by death certificate only or autopsy only. The primary site of the tumor and tumor behavior were confirmed according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).

The detailed demographic and clinical data were extracted by the case listing session. We analyzed the characteristics of the patients according to the demographic and clinical variables, including age, sex, race, pathology type and treatments. The SEER adolescents and young adults (AYA) site recode 2020 revision[10] was adopted as the classification scheme to analyze the distribution of pathology types among the patients. Then, we divided the patients into different groups according to their demographic data and extracted the incidence rates of the whole cohort and different subgroups. We aimed to find the most common tumors in different demographic groups. Incidence rates are expressed as number of patients affect per 100,000 and age-adjusted to the 2000 United States Standard Population (19 age groups-Census P25-1130) standard; 95% confidence intervals (Tiwari mod[11]) were calculated for rates and ratios. The rate ratio was got by comparing the rate for each subsequent grouping the reference grouping's rate.[12] Statistical significance for the rate ratio was defined as $p < 0.05$. We extracted the 5-year observed survival (overall survival with all causes of death), relative survival (survival in the absence of other causes of death) data based on the survival session using the Kaplan-Meier method, and the Ederer II method was adopted as the cumulative expected method (which is necessary to calculate the relative survival).[13,14] The incidence and survival were calculated and extracted by SEER*Stat version 8.4.0 software.

Finally, multivariate Cox proportional hazards models were used to analyze the independent prognostic factors associated with overall survival for the whole cohort and patients with different tumors separately. The patients were stratified based on demographic and clinical data and treatments. The overall survival was defined as the number of months from the diagnosis of tumor to death due to any cause; statistical significance was defined as $p < 0.05$. The hazard ratios and 95% confidence intervals were calculated by IBM SPSS Statistics 25.0 software (IBM Corporation, Armonk, NY, USA).

RESULTS

We indexed 8,412 patients with benign primary spinal cord

tumors. A total of 91.8% of them were diagnosed with meningiomas, neurilemmoma and neurofibroma, with only 62 cases of glioma. Ultimately, 5,211 patients with malignant and borderline malignant primary spinal cord tumors were indexed and included in this study. The demographic and clinical data and treatments of the patients are shown in Table 1. We found that female patients accounted for 45.5% of the whole cohort.

Table 1. Demographic and clinical data and treatments of patients with primary spinal cord malignant tumors

Variable	Value
Sex	
Female	2,372 (45.5)
Male	2,839 (54.5)
Age at diagnosis (yr)	
Mean ± SD	42.92 ± 20.376
Median (range)	45 (0–95)
0–19	791 (15.2)
20–39	1,381 (26.5)
40–59	1,889 (36.3)
≥ 60	1,150 (22.1)
Race	
White	4,360 (83.7)
Black	399 (7.7)
Asian or Pacific Islander	333 (6.4)
American Indian/Alaska Native	41 (0.8)
Unknown	78 (1.5)
Surgery	
Yes	4,653 (89.3)
None	542 (10.4)
Unknown	16 (0.3)
Radiation	
Yes	1,355 (26)
None/unknown	3,856 (74)
Chemotherapy	
Yes	697 (13.4)
None/unknown	4,514 (86.6)
Survival months	
Mean ± SD	87.28 ± 66.062
Median (range)	79 (0–239)
Vital status	
Alive	4,051 (77.7)
Dead	1,160 (22.3)

Values are presented as number (%) unless otherwise indicated.
SD, standard deviation.

The median age at diagnosis was 45 years old. Most of the patients, 36.3% of the whole cohort, were diagnosed at 40–59 years old. Most of the patients were white (n = 4,360, 83.7%). Currently, surgery is the first-line treatment in clinical use, and 89.3% of the patients chose surgery (n = 4,653). The median survival time of the patients was 79 months. The distribution of pathological types, classified according to the SEER AYA site record 2020 revision scheme, in the cohort is shown in Table 2. We found that ependymoma, astrocytoma (including oligodendrogliomas and glioblastoma), lymphoma and hemangioblastoma were the 4 most common pathology types.

The age-adjusted incidence rates of malignant (including borderline malignant) primary spinal cord and ependymoma

Table 2. Pathology type of the tumors classified according to the SEER AYA site recode 2020 revision

Pathology type	No. (%)
1. Leukemias and related disorders	7 (0.13)
2. Lymphomas	388 (7.45)
3. CNS and other intracranial and intraspinal neoplasms	4,235 (81.27)
3.1 Astroglial and related neoplasms	3,844 (73.77)
3.1.1 Oligodendrogliomas	36 (0.69)
3.1.2 Glioblastoma	118 (2.26)
3.1.3 Ependymoma	3,012 (57.8)
3.1.4 Other astrocytoma/astroglial neoplasms	678 (13.01)
3.1.4.1 Pilocytic astrocytoma	265 (5.09)
Others	413 (7.93)
3.2 Medulloblastoma and other invasive embryonal CNS tumors	91 (1.75)
3.3 Neuroblastomas/ganglioneuromas	51 (0.98)
3.4 Neuronal and mixed neuronal-glial neoplasms	185 (3.55)
3.5 Meningiomas	4 (0.08)
3.6 Choroid plexus neoplasms	1 (0.02)
3.10 Other and unspecified CNS neoplasms	59 (1.13)
4. Sarcomas	95 (1.82)
4.13 Chordoma	69 (1.32)
Others	26 (0.5)
5. Blood and lymphatic vessel tumors	328 (6.29)
5.1.1 Hemangioblastoma and tufted hemangioma	276 (5.3)
Others	52 (1)
6. Nerve sheath tumors	130 (2.49)
7. Gonadal and related tumors	19 (0.36)
8. Melanoma-malignant	9 (0.17)

SEER, Surveillance, Epidemiology, and End Results; AYA, adolescents and young adults; CNS, central nervous system.

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Table 3. The incidence rate of malignant primary spinal cord tumors

Variable	Count	Rate	Rate ratio (95% CI)	p-value
All	5,211	0.32		
Sex				
Male	2,839	0.35	Reference	
Female	2,372	0.28	0.799 (0.756–0.844)	<0.001*
Age at diagnosis (yr)				
0–19	791	0.18	Reference	
20–39	1,381	0.30	1.722 (1.576–1.881)	<0.001*
40–59	1,889	0.43	2.427 (2.232–2.641)	<0.001*
≥60	1,150	0.40	2.261 (2.063–2.480)	<0.001*
Race				
White	4,360	0.35		
Black	399	0.21	0.595 (0.535–0.660)	<0.001*
American Indian/Alaska Native	41	0.16	0.464 (0.330–0.638)	<0.001*
Asian or Pacific Islander	333	0.19	0.557 (0.496–0.623)	<0.001*
Pathology type				
Ependymoma	3,012	0.18	Reference	
Astrocytoma	832	0.05	0.231 (0.212–0.251)	<0.001*
Lymphoma	388	0.02	0.128 (0.114–0.142)	<0.001*
Hemangioblastoma	276	0.02	0.091 (0.080–0.103)	<0.001*

CI, confidence interval.
*The rate ratio indicates that the rate is significantly different than the rate for reference ($p < 0.05$).

Table 4. The incidence rates of primary spinal cord ependymoma, astrocytoma, lymphoma and hemangioblastoma in different populations

Variable	Ependymoma		Astrocytoma		Lymphoma		Hemangioblastoma	
	Rate	Rate ratio (95% CI)	Rate	Rate ratio (95% CI)	Rate	Rate ratio (95% CI)	Rate	Rate ratio (95% CI)
Sex								
Male	0.20	Reference	0.06	Reference	0.03	Reference	0.02	Reference
Female	0.17*	0.861 (0.801–0.926)	0.04*	0.749 (0.651–0.862)	0.02*	0.496 (0.399–0.614)	0.02	0.965 (0.755–1.234)
Age at diagnosis (yr)								
0–19	0.05	Reference	0.07	Reference	0.01	Reference	0.01	Reference
20–39	0.21*	4.007 (3.467–4.647)	0.04*	0.609 (0.505–0.732)	0.01	1.501 (0.796–2.894)	0.02*	3.608 (2.250–6.000)
40–59	0.29*	5.561 (4.830–16.430)	0.05*	0.671 (0.558–0.805)	0.03*	6.770 (4.105–11.813)	0.02*	4.422 (2.784–7.298)
≥60	0.19*	3.777 (3.236–4.420)	0.05*	0.690 (0.558–0.850)	0.08*	19.831 (12.252–34.098)	0.02*	4.712 (2.897–7.929)
Race								
White	0.21	Reference	0.05	Reference	0.02	Reference	0.02	Reference
Black	0.09*	0.458 (0.391–0.534)	0.05	0.876 (0.696–1.093)	0.02	0.790 (0.538–1.128)	0.02	0.996 (0.664–1.454)
American Indian/Alaska Native	0.09*	0.424 (0.259–0.660)	0.02*	0.390 (0.140–0.923)	0.02	0.884 (0.315–2.082)	0.02	0.985 (0.261–2.685)
Asian or Pacific Islander	0.09*	0.459 (0.390–0.538)	0.04	0.824 (0.635–1.053)	0.01*	0.450 (0.261–0.726)	0.01*	0.505 (0.283–0.847)

CI, confidence interval.
*The rate ratio indicates that the rate is significantly different than the rate for reference ($p < 0.05$).

tumors were 0.32 and 0.18 per 100,000 population, respectively. The incidence rate for females was significantly lower than that for males. The incidence rate was highest among Caucasian, and lowest among American Indian/Alaska Native people. Regarding age, the incidence rate was highest among people aged 40–59 years. The incidence rate of ependymoma was significantly higher than that of other pathology types. The incidence rate results are shown in Table 3. The incidence rates of primary spinal cord ependymoma, astrocytoma, lymphoma and hemangioblastoma in different populations are shown in Table 4. We found that females had significantly lower incidences of ependymoma, lymphoma and astrocytoma than males. Children between the ages of 0 and 19 years old had a significantly lower incidence of ependymoma but a significantly higher incidence of astrocytoma than the adult population. The highest incidence rate of ependymoma was observed in people aged 40–59 years old, while the highest incidence rate of lymphoma was observed in the ≥60-year-old population. We also found the incidence of ependymoma was significantly higher in Caucasian than in people of other races.

The 5-year observed survival and relative survival for the whole cohort were 82.80% and 86.00%, respectively. Female patients, white patients, patients diagnosed between 40–59 years old and patients diagnosed with ependymoma had better five-year relative survival than their counterparts (Table 5). The results of the Cox proportional hazards models are shown in Tables 6 and 7. These results reaffirmed that patients diagnosed with ependymoma had significantly better survival than their counterparts. We also found that for the patients with ependymoma and astrocytoma surgery of the primary tumor can significantly improve the survival, while chemotherapy can significantly improve the survival for the patients with lymphoma.

Table 5. Five-year observed survival and relative survival for different populations

Variable	Observed survival	Expected survival	Relative survival
All	82.80%	96.30%	86.00%
Sex			
Male	81.00%	95.90%	84.50%
Female	84.90%	96.90%	87.70%
Age at diagnosis (yr)			
0–19	81.70%	99.80%	81.80%
20–39	88.50%	99.30%	89.10%
40–59	88.10%	97.50%	90.30%
≥60	68.20%	87.50%	77.90%
Race			
White	83.50%	96.10%	86.80%
Black	78.30%	96.80%	80.80%
American Indian/Alaska Native	79.10%	95.70%	82.40%
Asian or Pacific Islander	78.20%	98.50%	79.40%
Pathology type			
Ependymoma	93.60%	96.70%	96.70%
Astrocytoma	60.40%	97.70%	61.80%
Lymphoma	61.90%	91.10%	67.70%
Hemangioblastoma	91.10%	95.80%	94.40%

DISCUSSION

Spine tumors were classified into 3 main groups: extradural, intradural extramedullary and intramedullary.[15] Extradural tumors are primarily systemic cancer metastases.[16] Primary spinal

Table 6. The hazard ratios (HR), 95% confidence intervals (CI), and p-values were calculated using multivariable Cox regression

Variable	HR (95% CI)	p-value
Sex		
Male	Reference	
Female	0.831 (0.739–0.935)	0.002
Age at diagnosis (yr)		
0–19	0.727 (0.596–0.888)	0.002
20–39	0.886 (0.741–1.059)	0.182
40–59	Reference	
≥60	2.647 (2.292–3.056)	<0.001
Race		
White	Reference	
Others	1.243 (1.064–1.450)	0.006
Pathology type		
Ependymoma	0.369 (0.319–0.426)	<0.001
Others	Reference	
Surgery		
Yes	0.854 (0.734–0.994)	0.042
None/unknown	Reference	
Radiation		
Yes	2.000 (1.762–2.270)	<0.001
None/unknown	Reference	
Chemotherapy		
Yes	1.521 (1.313–1.762)	<0.001
None/unknown	Reference	

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Table 7. The results of hazard ratio (HR), 95% confidence interval (CI), and p-value calculated through multivariable Cox regression for patients with different tumors

Variable	Ependymoma		Astrocytoma		Lymphoma	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex						
Male	Reference		Reference		Reference	
Female	0.745 (0.601–0.923)	0.007	0.928 (0.753–1.145)	0.488	0.999 (0.740–1.348)	0.994
Age at diagnosis (yr)						
0–19	0.684 (0.397–1.177)	0.170	0.562 (0.414–0.763)	<0.001	0.166 (0.023–1.219)	0.078
20–39	0.812 (0.591–1.115)	0.198	0.843 (0.633–1.124)	0.245	0.985 (0.456–2.125)	0.969
40–59	Reference		Reference		Reference	
≥60	5.024 (3.919–6.441)	<0.001	2.266 (1.706–3.009)	<0.001	2.991 (2.069–4.323)	<0.001
Race						
White	Reference		Reference		Reference	
Others	1.272 (0.931–1.739)	0.130	0.950 (0.740–1.219)	0.685	1.172 (0.763–1.800)	0.470
Surgery						
Yes	0.468 (0.318–0.690)	<0.001	0.748 (0.583–0.959)	0.022	0.882 (0.660–1.178)	0.394
None/unknown	Reference		Reference		Reference	
Radiation						
Yes	1.891 (1.473–2.428)	<0.001	2.013 (1.557–2.602)	<0.001	0.793 (0.577–1.090)	0.153
None/unknown	Reference		Reference		Reference	
Chemotherapy						
Yes	5.366 (2.686–10.719)	<0.001	2.425 (1.924–3.057)	<0.001	0.562 (0.415–0.762)	<0.001
None/unknown	Reference		Reference		Reference	

cord tumors are anatomically separable into 2 broad categories: intradural intramedullary and intradural extramedullary.[17] At first, we aimed to choose intramedullary spinal tumors as the study objective. However, we could not define intramedullary tumors by their primary site according to ICD-O-3. At the same time, we found that the most common primary intradural extramedullary tumors are meningioma, neurofibroma, and schwannoma, and most of them are benign tumors.[18] Gliomas (astrocytoma and ependymoma) account for 80% of all intramedullary tumors,[19] and most gliomas are considered to be malignant or borderline malignant according to ICD-O-3 classification. Subsequently, we chose spinal cord malignant tumors as the topic of research and included borderline malignant tumors to cover almost 99% of spinal cord gliomas in the SEER database. Among the benign tumors in the database, classified according to ICD-O-3 guidelines, only 62 cases were gliomas. We believe this study design can elucidate the epidemiology and survival of intramedullary tumors. At the same time, we acknowledge that this cohort included 130 cases of nerve sheath tumors, 4 cases of meningiomas and 1 case of choroid plexus neoplasms etc., accounting for 2.6% of the whole cohort. We had not excluded these cases in this study due to the difficulty of defining the query syntax. This inclusion might lead the reported incidence rate to be slightly higher than the true incidence rate of primary intramedullary tumors.

Park et al.[20] reported that the frequent pathologies of primary intramedullary spinal cord tumors were spinal ependymoma (45.1%), hemangioblastoma (20.0%), and astrocytic tumors (17.4%). Spinal cord hemangioblastomas are reported to account for 2% to 15% of primary intramedullary spinal cord tumors.[21] Most of our results were consistent with the previous report. Because benign tumors were not included in our analysis, the resulting incidence of primary spinal cord hemangioblastoma should be lower than the actual incidence. It was reported that the most common primary intramedullary tumor pathology in pediatric patients is astrocytoma; however, as age increases, the most common pathology becomes ependymoma.[22,23] In our cohort study, we clearly demonstrate this by comparing the incidence of different tumors in different age groups. Primary intramedullary spinal cord lymphoma has been re-

ported as a rare diagnosis with poorly understood disease progression.[7,24] However, we found that the incidence of primary spinal cord lymphoma was only exceeded by the incidences of ependymoma and astrocytoma and was significantly higher in populations older than 60 years than in other age groups. Therefore, when treating elderly patients, lymphoma should be considered in addition to gliomas.

Because intramedullary spinal cord tumors comprise diverse tumor types, distinct management strategies are chosen based on histopathology; nonetheless, advances in microsurgical techniques and technological adjuncts have improved the extent of resection and outcomes.[23] Persson et al.[25] performed a retrospective cohort study of 95 patients who underwent surgery for intra- or juxtamedullary tumors and found that long-term progression-free survival could be achieved by gross-total resection without additional adjuvant treatment. Matthew et al. reviewed the treatment strategies for intramedullary spinal cord tumors and concluded that most evidence-based treatments involve resection. Patients who cannot undergo gross-total resection or have subtotal resection only have radiotherapy and chemotherapy as treatment options. However, these treatments are associated with the potential for significant adverse side effects and still leave patients with a poor prognosis.[26] In this study, we also found the impact of surgery and chemotherapy on the prognosis of patients with different tumors varies a lot. We believe that more efforts should be made to design specific treatment plans for individual patients.

One limitation of our analysis was that use of the registry-based approach precluded access to some specific clinical data. For example, we could not confirm the specific location (cervical, thoracic, or lumbar spinal cord) of the tumor. We also could not confirm the pathology according to the 2021 edition of World Health Organization classification, because of lack of genetic and molecular data. There was also a lack information about specific therapeutic methods used as well as imaging manifestations of the tumors. As a registry-based population analysis, we must also acknowledge the possibility that there may be inaccurate data collection. Nevertheless, to the best of our knowledge, this study represents the first attempt to characterize the incidence and survival of patients with primary intramedullary spinal cord tumors based on a nationwide registry. Our results provide information that may be useful for further investigating the epidemiology and exploring the prognosis of patients with primary intramedullary tumors.

CONCLUSION

We conducted a population-based analysis of malignant and borderline malignant primary spinal cord tumors to reveal the epidemiology and survival of patients with primary intramedullary spinal cord tumors. Despite some shortcomings, this study still provides valuable information to help us better understand the epidemiological characteristics of primary intramedullary spinal cord tumors.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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