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Primary intramedullary spinal cord lymphoma: a population-based study

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Abstract

Background. Primary intramedullary spinal cord lymphoma (PISCL) is a rare diagnosis with poorly understood disease progression. Clarification of the factors associated with survival in PISCL patients is warranted.

Methods. We conducted a population-based cohort study utilizing prospectively collected data from the Surveillance, Epidemiology, and End Results (SEER) database. Patients with histological diagnosis of primary lymphoma in spinal cord (C72.0) from 1973 to 2012 in the SEER database were included. Multivariable survival analysis between patient, lesion characteristics, and PISCL-related death was performed to adjust for confounding factors.

Results. We included 346 PISCL patients in our study. Average age was 56.5 ± 17.8 years, with 62.7% being male. Racial distribution of these patients was white (87.6%), black (8.0%), and other (4.3%). More than half (55.8%) of patients were married. The most prevalent histology of PISCL was diffuse B-cell (46.2%), and the majority (55.2%) were low stage (Ann Arbor stage I/II). Most patients (67.9%) received radiation therapy. Average survival interval of patients with PISCL-related death (n=135, 39.0%) was 27.8 months. General cumulative survival probability at 1 year, 2 years, and 5 years was 73.8%, 67.9%, and 63.1%, respectively. Multivariable accelerated failure time (AFT) regression showed follicular lymphoma (HR:0.25, P=.008) and more recent diagnosis (HR:0.96, P<.001) was positively associated with PISCL-related survival. Conversely, nonwhite race (HR:1.69, P=.046), older age (HR:1.02, P<.001), unmarried status (HR:2.14, P<.001), and higher stage (HR:1.54, P=.022) were negatively associated with survival.

Conclusions. Age, race, marital status, tumor histology, tumor stage, and year of diagnosis were associated with survival of PISCL. While most PISCL-related deaths occur within a 1-year period, subsequent slow progression was observed after the first year of survival.

Key words

intramedullary | lymphoma | spinal cord

Primary intramedullary spinal cord lymphoma (PISCL) is a rare disease and comprises only 1% of all CNS lymphomas.[1] According to a review of PISCL by Hautzer et al. in 1983, most patients present in their fifth decade of life, the majority of lesions involve the cervical or thoracic segment of the spinal cord, and treatment is either radiotherapy or chemotherapy.[2] Approximately 30 PISCL cases have been reported, but there remains a limited understanding of the characteristics and progression of the disease.[1–19] Flanagan et al. recently reviewed an institutional series of 14 patients with PISCL

Importance of the study

Primary intramedullary spinal cord lymphoma (PISCL) is an exceptionally rare disease with unknown disease progression. This is the first study to characterize the survival of PISCL patients. We have quantified the 5-year survival of PISCL patients and demonstrated that the disease showed slow progression after the first year of follow-up. More importantly, we found that age, race, marital status, lymphoma staging, and lymphoma histological type were significantly associated with PISCL survival. Such findings may provide fundamental knowledge in the nature of this rare disease.

in which the median survival period was 16.5 months, and the estimated 2-year survival rate was 36%.[9] PISCL remains a poorly understood disease owing to its rarity and lack of long-term follow-up reports. We aim to delineate the factors influencing PISCL survival in a population-based study using a national cancer registry.

Material and Methods

Study Design and Patient Population

This study was designed as a population-based longitudinal cohort study. We utilized the Surveillance, Epidemiology, and End Results (SEER) dataset, which contains prospectively collected patient-level demographics, lesion, and survival data from state cancer registries and is actively maintained by the National Cancer Institute (NCI). For our purposes, we included patient information from the incidence-SEER 18 registries Research Data and Hurricane Katrina Impacted Louisiana Cases between years 1973 and 2012. Patients with the diagnosis of primary lymphoma as their first malignancy at spinal cord (C72.0) were included. Lesions in the spinal meninges (C70.1), the cauda equina (C72.1), or not histologically confirmed were excluded from the study. Patients with lymphomas diagnosed by autopsy were also excluded, as they had not been actively followed in the registry.

Definition of Variables

Patient demographic variables were collected including age, sex, race, and marital status. Age was defined as the age at diagnosis of PISCL, and race was categorized by SEER definition into 4 distinct categories: white, black, Asian/Pacific Islander, and American Indian/Alaska Native. Lymphoma histology staging was described in detail according to the International Classification of Disease for Oncology Version 3 (ICD-O-3) histology groupings and the 2008 World Health Organization (WHO) lymphoma classification scheme. Similarly, we recategorized histology type into 5 distinct categories to avoid overstratification of data in subsequent analyses. Diffuse B-cell lymphoma (ICD-O-3 code 9680/3), follicular lymphoma (ICD-O-3 code 9690/3, 9691/3, 9695/3, 9698/3), other B-cell lymphoma (ICD-O-3 code 9670/3, 9671/3, 9675/3, 9684/3, 9687/3, 9699/3, 9731/3), precursor cell lymphoma (ICD-O-3 code 9727/3, 9728/3), and others or not-otherwise-specified (NOS) lymphomas. Ann Arbor Staging for lymphoma was included as defined in the SEER dataset,[20] and was regrouped into low stage (stage I/II) and high stage (stage III/IV). The SEER database does not include information related to chemotherapy; therefore, we only included radiation therapy in our study. Surgical intervention is not a conventional PISCL treatment; those listed in SEER were assumed to be biopsy studies, which minimally impact patient survival. For this reason, surgery was not included as a variable in our study.

Statistical Analysis

The primary outcome was defined as PISCL-related death documented in SEER as "death (attributed to this cancer)". The definition of nontumor-related death was predefined in the SEER database as death "attributable to causes other than this cancer diagnosis." Baseline characteristics were compared between 2 groups: patients listed as alive or with death unrelated to PISCL and patients with PISCL-related death. The Student's *t*-test was used for continuous variables, and the chi-square test was used for categorical variables. For survival analysis, cases were right-censored to alive at last follow-up, death attributed to other causes, or PISCL-related death. Survival time, represented in months, was calculated as the interval between PISCL diagnosis and lymphoma-related death as reported in SEER. Certain survival analysis variables were adjusted in survival analysis to prevent overstratification of data. Race was categorized into white and nonwhite, and marital status was grouped into married, unmarried (single, separated, widowed, and divorced), and unknown. Lymphoma Ann Arbor Staging was recategorized into low stage (stage I/II), high stage (stage III/IV), and unknown. Survival of PISCL patients was described graphically using Kaplan-Meier analysis.

Preliminary diagnostic testing of Cox proportional hazards regression revealed violation of proportion assumption in several variables. Therefore, parametric univariate and multivariable accelerated failure time (AFT) regression analysis with Weibull distribution was used as an alternative. All variables considered using AFT univariate analysis were included in the multivariable AFT model to adjust for confounding effects. Coefficients for each variable generated from AFT analysis were converted into hazard ratios for convenience of interpretation. All *P* values were reported as 2-sided, with statistical significance

defined as $P<.05$. Statistical analysis was performed using R Statistical Software (Version 3.2.0, 2013, Vienna, Austria).

Results

Patient Population and Baseline Characteristics

We retrieved 403 PISCL cases from the SEER database. After applying the inclusion and exclusion criteria as illustrated in Fig. 1, our study cohort was finalized at 346 cases. According to the ICD-O-3 and WHO classification, in cases with specific classification details (n=318, 91.7%), only one case was classified as Hodgkin's lymphoma (0.3%). B-cell lymphoma was the most prevalent non-Hodgkin's lymphoma (n=263, 76.0%) and largely consisted of diffuse large B-cell lymphoma (n=160, 46.2%), followed by follicular lymphoma (n=38, 11.0%). There were only 5 (1.4%) cases of T-cell lymphoma, which was consistent with existing literature indicating rarity of primary CNS T-cell lymphoma. A detailed description of PISCL histology distributions is depicted in Table 1.

For all patients in the study cohort, the average age at diagnosis was 56.5 ± 17.8 years (Table 2), and 62.7% were male. Race distribution was as follows: white (87.6%), black (8.0%), Asian/Pacific Islander (2.9%), and American Indian/Alaska Native (1.4%). The majority of patients (55.8%) were married. At the time of last follow-up, 160 (46.2%) patients were alive; 135 (39.0%) deaths were attributable to PISCL, and an additional 51 (14.7%) patients expired due to other causes. Among the 51 patients who died from non-PISCL-related causes, only 3 (5.9%) died of cerebrovascular disease, and the majority died from cardiovascular or respiratory diseases (n=25, 49.0%). As described above, diffuse B-cell lymphoma was the most prevalent histology type in PISCL, and most tumors were classified as low stage (55.2%). Most patients received radiation therapy. Ann Arbor Staging (P=.019), lymphoma type (P<.001), and year of diagnosis (P <.001) were found to be significantly different between the 2 survival groups.

Table 1 Distribution of primary intramedullary spinal cord lymphoma histology by WHO classification

Histological Types	All Patients (N=346)
Hodgkin's lymphoma, *n (%)*	
Classic Hodgkin's lymphoma	1 (*0.3*)
Non-Hodgkin's lymphoma, *n (%)*	
Mature B cell	
Diffuse large B cell	160 (*46.2*)
Diffuse, large or immunoblastic malignant B cell	8 (*2.3*)
Follicular lymphoma, grade 1	7 (*2.0*)
Follicular lymphoma, grade 2	11 (*3.2*)
Follicular lymphoma, grade 3	6 (*1.7*)
Follicular lymphoma, NOS	14 (*4.0*)
Burkitt lymphoma	11 (*3.2*)
Small B cell, NOS	15 (*4.3*)
Mixed large and small B cell	17 (*4.9*)
Others	14 (*4.0*)
Mature T cell	
Anaplastic T cell	5 (*1.4*)
Precursor cell	
All precursor cell lymphomas	6 (*1.7*)
Others	
Malignant lymphoma, non-Hodgkin, NOS	43 (*12.4*)
Unspecified, *n (%)*	
Malignant lymphoma, NOS	28 (*8.3*)

Abbreviations: NOS, not otherwise specified.

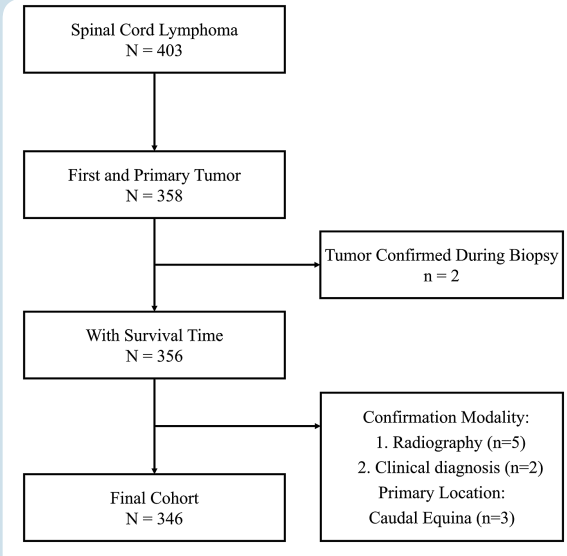

Fig. 1 Flow diagram of study cohort selection. A flow diagram of patient selection for the study cohort

Univariate and Multivariable Survival Analysis

Overall 1-year, 2-year, and 5-year survival was 73.8%, 67.9%, and 63.1%, respectively. Overall annual PISCL-related death incidence was 4.29% in a 10-year period, with the first year being 26.2%, and the death incidence rate being 26.2% in the first year and 1.9% from years 2–10. Kaplan-Meier log-rank testing suggested that unmarried patients (Fig. 2A), older age (Fig. 2B), higher lymphoma staging (Fig. 2C), nonfollicular lymphoma (Fig. 2D), and earlier diagnosis are associated with shorter survival due to PISCL-related death (Fig. 3). These findings are consistent with results of univariate AFT regression analysis. In a multivariable AFT regression model including all univariate variables, age (HR: 1.02, CI=1.01–1.03, P<.001), nonwhite race (HR: 1.69, CI=1.01–2.83, P=.046), unmarried status (HR: 2.14, CI=1.49–3.08, P<.001), high stage (HR: 1.54, CI=1.04–2.28, P=.030), follicular lymphoma (HR: 0.25, CI=0.09–0.68,

Table 2 Comparison of patient baseline characteristics between tumor-related death and alive or unrelated death

Parameters	Total *(N=346)*	Alive or Unrelated Death *(N=211)*	Tumor-related Death *(N=135)*	*P* value
Age at diagnosis, year, *mean (SD)*	56.5 (17.8)	55.3 *(17.5)*	58.2 *(18.0)*	*.149*
Sex, male, *n (%)*	217 (62.7)	132 *(62.6)*	85 *(63.0)*	*.940*
Race, *n (%)*				*.243*
White	303 (87.6)	188 *(89.1)*	115 *(85.2)*	
Black	28 (8.0)	17 *(8.1)*	11 *(8.0)*	
Asian/Pacific Islander	10 (2.9)	3 *(1.4)*	7 *(5.1)*	
American Indian/Alaska Native	5 (1.4)	3 *(1.4)*	2 *(1.4)*	
Marital status, *n (%)*				*.336*
Married	193 (55.8)	125 *(59.2)*	68 *(50.4)*	
Single (unmarried)	63 (18.1)	33 *(15.6)*	30 *(21.7)*	
Separated/divorced/widowed	79 (22.8)	47 *(22.3)*	32 *(23.7)*	
Unknown	11 (3.2)	6 *(2.8)*	5 *(3.6)*	
Ann Arbor staging, *n (%)*				*.019**
Low stage (stage I/II)	191 (55.2)	126 *(59.7)*	65 *(48.1)*	
High stage (stage III/IV)	115 (33.2)	68 *(32.2)*	47 *(34.8)*	
Unknown	40 (11.6)	17 *(8.1)*	23 *(17.0)*	
Lymphoma type, *n (%)*				*< .001**
Diffuse B cell	160 (46.2)	99 *(46.9)*	61 *(45.2)*	
Follicular	38 (11.0)	34 *(16.1)*	4 *(3.0)*	
Other B cell	65 (18.8)	34 *(16.1)*	31 *(23.0)*	
Precursor cell	6 (1.7)	5 *(2.4)*	1 *(0.7)*	
Others or NOS	77 (22.3)	39 *(18.5)*	38 *(28.1)*	
Radiation therapy, *n (%)*				*.301*
None	105 (30.3)	71 *(33.6)*	34 *(25.2)*	
Radiation	235 (67.9)	137 *(64.9)*	98 *(72.6)*	
Others or unknown	6 (1.7)	3 *(1.4)*	3 *(2.2)*	
Diagnosis years, *n (%)*				*<.001**
1973–1982	18 (5.2)	4 *(1.9)*	14 *(10.4)*	
1983–1992	49 (14.2)	21 *(10.0)*	28 *(20.7)*	
1993–2002	103 (29.8)	48 *(22.7)*	55 *(40.7)*	
2003–2012	176 (50.9)	138 *(65.4)*	38 *(28.1)*	

Abbreviation: NOS, not otherwise specified.
* Significant Variables (*P*<.050)

P=.008), and year of diagnosis (HR: 0.96, CI=0.94–0.98, *P*<.001) were associated with PISCL-related survival (Table 3).

Discussion

Our study included 346 PISCL cases extracted from the SEER database with a higher prevalence being observed in male patients. Concordant with previous reports, most patients were diagnosed in their fifth or sixth decade. Flanagan et al. presented their cohort of 14 patients with PISCL, of whom 71% were male, with an average age of 62.5 years.[9] Conversely, in an earlier study of 6 PISCL cases reported by Hautzer et al, the average age was noted to be 48 years, with the predominant presentation being in female patients.[2] Other studies focusing on PISCL were mostly case reports with the majority of patients being female but with various age distributions.[1,3–5,7,8,10,12–19] The variable demographic patterns of PISCL patients likely reflect the rarity of PISCL and therefore the limited number of studies conducted on this disease. However, when compared with literature in the context of primary CNS lymphomas, our patient demographics are consistent with existing reports.[21,22]

The histological type of PISCL in this study consisted mainly of B-cell origin lymphoma, and the most prevalent overall lymphoma is diffuse large B-cell lymphoma,

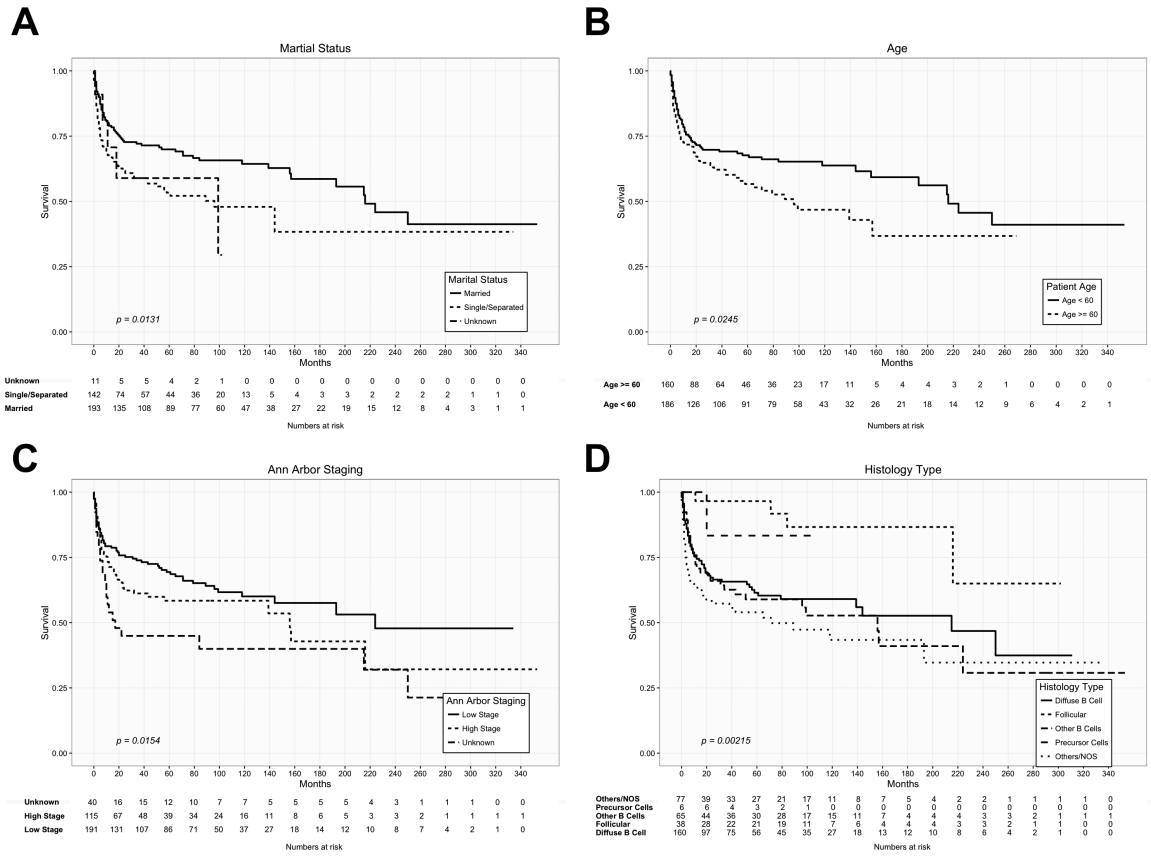

Fig. 2 **Survival analysis by risk factors. 2A**: Survival curve of marital status and patient survival in years; **2B**: Comparison of survival curve between patients 60 years and patients under 60 years; **2C**: Survival curve of higher stage versus lower stage; **2D**: Survival curve by lymphoma histologic type.

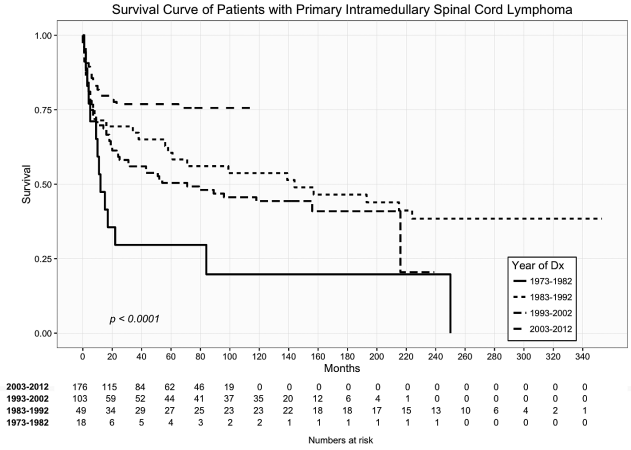

Fig. 3 **Survival Analysis by decades.** Survival of patients stratified by decades

Table 3 Univariate and multivariable accelerated failure time regression of tumor-related survival

Parameters	Univariate Analysis			Multivariable Analysis		
	HR*	95% CI	*P Value*	HR*	95% CI	*P Value*
Age, per 1 year increase	1.02	[1.01, 1.03]	*.002†*	1.02	[1.01, 1.03]	*<.001†*
Sex (male vs female)	1.00	[0.70, 1.42]	*.990*	1.21	[0.83, 1.76]	*.324*
Race (nonwhite vs white)	1.25	[0.78, 2.02]	*.347*	1.69	[1.01, 2.83]	*.046†*
Marital status						
Married	*ref*	-	-	*ref*	-	-
Single/separated/widowed/ divorced	1.67	[1.18, 2.36]	*.004†*	2.14	[1.49, 3.08]	*<.001†*
Unknown	1.70	[0.68, 4.22]	*.252*	2.53	[0.99, 6.44]	*.01*
Ann Arbor staging						
Low stage (stage I/II)	*ref*	-	-	*ref*	-	-
High stage (stage III/IV)	1.36	[0.93, 1.98]	*.111*	1.54	[1.04, 2.28]	*.030†*
Unknown	2.09	[1.30, 3.36]	*.003†*	1.62	[0.95, 2.78]	*.077*
Histology type						
Diffuse B cell	*ref*	-	-	*ref*	-	-
Follicular	0.24	[0.09, 0.65]	*.006†*	0.25	[0.09, 0.68]	*.008†*
Other B cell	1.10	[0.71, 1.69]	*.670*	0.99	[0.63, 1.56]	*.957*
Precursor cell	0.38	[0.05, 2.71]	*.333*	0.64	[0.08, 5.02]	*.675*
Others or NOS	1.43	[0.96, 2.15]	*.084*	1.29	[0.85, 1.96]	*.223*
Radiation						
None	*ref*	-	-	*ref*	-	-
Radiation	1.17	[0.79, 1.73]	*.430*	0.90	[0.59, 1.37]	*.614*
Others or unknown	1.93	[0.59, 6.30]	*.274*	3.16	[0.93, 10.69]	*.064*
Year of diagnosis, per 1 year Increase	0.96	[0.94, 0.98]	*< .001†*	0.96	[0.94, 0.98]	*< .001†*

Abbreviations: NOS, not otherwise specified
*Hazard ratio converted from coefficient in AFT model
† Statistical significance *P*< .05)

followed by follicular lymphoma. Although existing reports of the histological distribution of PISCL are limited, our finding that diffuse large B-cell lymphoma constituted approximately 40%–50% of PISCL cases was similar to that reported by Flanagan et al (35.7%)[9] and distinct from the predominance of diffuse large B-cell lymphoma observed for primary CNS lymphoma.[23] In contrast, T-cell lymphoma only accounted for 1.4% of all lymphomas in our study. As suggested by Guzzetta et al. and Giltenbeek et al., the limited number of studies on T-cell lymphoma is likely attributable to the complexity of diagnosis.[17,24] Compared with B-cell lymphomas, T-cell lymphomas are more likely to have nondefinitive immunophenotyping; thus, distinguishing T-cell lymphoma from reactive inflammatory processes is difficult. Of note, one case was found to resemble classic Hodgkin's lymphoma, which to our knowledge is the only reported case of PISCL with Hodgkin's histology.[2] The conventional definition of primary CNS lymphoma is that of non-Hodgkin's lymphoma; however, this notion has been recently challenged by Kresak et al. who reported 2 cases of primary CNS Hodgkin's lymphoma.[25] The overall survival of PISCL is poor as approximately 25% of all patients die within the first year of diagnosis. Our results suggest that the progression of disease after the 1-year period is relatively slow, with cumulative 5-year survival at 63.1%, a 10% decrease compared with the 1-year cumulative survival. Younger age, white race, married status, histology of follicular lymphoma, low Ann Arbor stage, and more recent year of diagnosis were found to have a positive impact on PISCL-related survival. The progression pattern of PISCL, its histological distribution (of which follicular lymphoma is a substantial fraction), and the influence of Ann Arbor staging on patient survival collectively suggest that the behavior of PISCL may distinguish it as more than a simple variant from other primary CNS lymphomas.

Marital status has been increasingly realized as an important factor in the survival of cancer patients. One of the landmark studies by Goodwin et al. in 1987 revealed a strong positive correlation between marriage and survival of cancer patients.[26] The authors examined 27 779 patients diagnosed with epithelial cancer and noted a relative hazard ratio of 1.23 in unmarried patients. This finding was further confirmed in a large-scale analysis by Aizer et al. that included 734 889 patients with various

types of cancer.[27] In regards to CNS tumors, Rusthoven et al. also identified marital status as a significant predictor of survival in patients with GBM or anaplastic astrocytoma.[28] Concordantly, our study suggested a 2-fold hazard ratio in unmarried PISCL patients after adjusting for other confounding variables. The underlying mechanism of prolonged survival in married patients has been largely attributed to the improved social and financial support from the family.[27] Furthermore, as suggested by previous studies, the phenomenon can be further explained by the psychological factors in cancer development itself as well as compliance or adherence to cancer-related therapy.[27,29–32] Therefore, the effect of marriage on patient survival is likely the result of interactions within a complex network of social-economic-psychological factors, and marital status maybe one of the best parameters to summarize this network.

Our study also identified follicular lymphoma as a significant factor in prolonging survival in PISCL patients, with a relative hazard of 0.25 when compared with diffuse large B-cell lymphoma; in contrast, other cell types did not demonstrate a similar association. The indolence of follicular cell lymphoma and the aggressiveness of diffuse large B-cell lymphoma have been separately highlighted in previous literature.[33,34] However, a trend of similar aggressiveness between the 2 histologic types has been observed for CNS-involving lymphomas.[35–39] Regardless, the comparative impact on patient survival between different histologic types remains obscure, and our study represents the first to provide quantification of the relative hazard of histologic types in PISCL patients. Similarly, we are also the first to describe the relationship between age, staging, and survival of PISCL patients. Our finding that diagnoses of PISCL in more recent decades are associated with prolonged survival can be reasonably inferred to be attributable to advancement of chemotherapeutic drugs, despite the SEER database not providing information regarding chemotherapy. Of note, we failed to establish an adjusted significant association between radiation therapy and survival of PISCL patients. While not proven, patients who were not radiated may have been treated with a more aggressive chemotherapy regimen.

Similar to other studies that utilize SEER as the data source, our study suffered certain limitations that require clarification for accurate interpretation of the results. A risk of misclassification of PISCL is existent as there is no explicit indicator of "intramedullary" location in the SEER database. However, rigorous adjustments were made to minimize the risk. First, we excluded spinal meninges (C70.1) from the analysis and only included the spinal cord (C72.0) location, which has been considered to be a reliable indicator of intramedullary location in previous studies.[40] Next, by eliminating nonprimary and non-first spinal cord tumors, we reduced the risk of including secondary or metastasized epidural lymphomas with invasion into the intradural space. Finally, the existence of primary intradural extramedullary spinal cord lymphoma is exceedingly rare[41] and is unlikely to impose a significant impact on the results of this study.

The lack of dosimetric information on radiotherapy has limited our ability to stratify radiotherapy by dosage, which has been proven to be of critical importance to patient survival in spinal tumors.[42] Another major limitation, as previously stated, is the lack of information on chemotherapy, and we cannot account for the effect of potential advances in chemotherapeutics. To date, the SEER database does not describe chemotherapeutic drug use for individual patients. Medicare claims may be linked to SEER to provide chemotherapy information; however, Medicare data largely describe elderly patients and would therefore not capture a substantial portion of our patient cohort with an average age of 55 years. Moreover, consistent reporting by Medicare of whether a patient received chemotherapy varies according to the primary cancer site, with overall sensitivity ranges between 7.2% and 84.4%.[43] Additionally, only intravenous or intravenous-equivalent drugs are claimed in Medicare, which would bias the data toward specific drugs. It is therefore important for future studies to further investigate the role of this important treatment modality. In addition, other factors that may impact the prognosis of lymphoma patients, especially biological and immune markers, were not included in the SEER dataset, limiting our ability to further stratify dataset based on these variables. Nevertheless, this study represents the first attempt to characterize overall survival in a large cohort of PISCL patients. Despite the exceptionally scarce occurrence of the disease, a population-based approach provides reasonable statistical utility for crude stratification of prognosis based on commonly identified factors.

Conclusions

In this exploratory study examining patients with PISCL, we adopted a population-based dataset to characterize the prognosis of an exceptionally rare disease. A rapid progression of disease was displayed in the first year after diagnosis, with 26.5% of all patients expiring. In contrast, a much slower progression was observed after the 1-year period. Younger age, marriage, lower staging, follicular histologic type, and more recent diagnosis were associated with prolonged survival of PISCL patients in a multivariable analysis.

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Conflict of interest statement. None

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