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Survival Outcome and Prognostic Factors of Primary Spinal Cord Lymphoma

Ding QIANJIN, Cheng ZHENGUO, Wang YANG, Du BAOSHUN, Sun LAIGUANG

Xinxiang Center Hospital, Department of Neurosurgery, Xinxiang City, Henan Province, China

Corresponding author: Sun LAIGUANG ✉ slg18603736708@163.com

ABSTRACT

AIM: To identify the predictive factors associated with the survival of patients with a diagnosis of primary spinal cord lymphoma (PSCL).

MATERIAL and METHODS: The Surveillance, Epidemiology, and End Results (SEER) database was used in this study, which involved 254 patients with PSCL. Data on the patients' age, sex, race, pathology, Ann Arbor stage, adjuvant therapy, and year of diagnosis were collected. Univariate and multivariate Cox regression models were conducted to detect the predictive variables.

RESULTS: Of the 254 patients, 67 (26.4%) die from lymphoma at the time of data collection. Cancer-specific survival at 1, 3, and 5 years was 81.0%, 74.6%, and 74.1%, respectively. Diffuse large B-cell lymphoma (DLBL) was the highest prevalent histotype (n=140, 55.1%). The multivariate Cox regression models revealed that chemotherapy (hazard ratio (HR): 0.47; 95% confidence interval (CI), 0.16–0.82; p=0.040) and radiochemotherapy (HR: 0.43; 95% CI, 0.10–0.57; p=0.045) were independent predictors of favorable cancer-specific survival, whereas age ≥ 80 years (HR: 6.51; 95% CI, 1.65–25.64; p=0.003) and DLBL (HR:1.71; 95% CI, 1.02–2.88; p=0.030) were independently associated with poor cancer-specific survival.

CONCLUSION: The survival outcome of PSCL is favorable in the current treatment strategy. Chemotherapy and radiochemotherapy were predictors of favorable outcomes, whereas older age and DLBL were associated with poor prognosis.

KEYWORDS: Lymphoma, Spinal cord, Intramedullary, Prognostic factors, Survival

ABBREVIATIONS: CNS: Central nervous system, **DLBL:** Diffuse large B-cell lymphoma, **IQR:** Interquartile range, **PSCL:** Primary spinal cord lymphoma, **SD:** Standard deviation, **SEER:** Surveillance, Epidemiology, and End Results database

INTRODUCTION

Primary spinal cord lymphoma (PSCL) is an infrequent disorder and constitutes only 0.4% of all primary intradural spinal tumors (19). Due to its rarity, few studies focused on this disease, and the characteristics of PSCL are not well understood. Using a large population database, a survival study was conducted to delineate survival outcomes and prognostic factors for PSCL.

MATERIAL and METHODS

Data Retrieval

This is a retrospective study, and data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database (source database: Incidence-SEER Research Plus Data, 18 Registries, Nov 2019 Sub (2000-2017)). Only individuals diagnosed with lymphoma and those with lesions located in the spinal cord (ICD-O-3 code: C72.0) or cauda

Ding QIANJIN : 0000-0002-8446-9724
Cheng ZHENGUO : 0000-0001-6031-1052
Wang YANG : 0000-0002-5834-9104
Du BAOSHUN : 0000-0002-0858-5459
Sun LAIGUANG : 0000-0001-5193-2252

equina (ICD-O-3 code: C72.1) were recruited. The following cases were excluded: individuals with metastasis, those with PSCL not confirmed by tissue pathology, cases whose data on radiotherapy or chemotherapy are unknown, and those whose survival time was unknown. Of note, metastasis could be recognized by a sequence number, which describes the number and sequence of primary tumors that occur over the lifetime of a patient; a sequence number of "one primary only" or "1st of 2 or more primaries" denotes the primary lesion. The detailed screening flow is shown in Figure 1.

Definitions of Variables

The patients were divided into age groups, as follows: ≤30, 31–59, 60–79, and ≥80 years. The races were classified as white, black, and others. Based on the ICD-O-3 code recorded in the SEER database (Table I), the detailed pathological diagnosis of each case could be defined and was regrouped into diffuse large B-cell (DLBL) and non-DLBL. Lymphomas were categorized using the Ann Arbor staging classification, as follows: stage I/II, stage III/IV, and unknown. The year of diagnosis was classified into four categories, separated by 3-year intervals.

The survival outcome was divided into two categories: alive/unrelated death and cancer-specific death.

Statistical Analysis

Categorical variables are presented as frequencies (percentages), whereas continuous variables are presented as means ± standard deviations or medians and interquartile ranges (IQRs), as appropriate. To assess variations, a two-tailed t-test or nonparametric test was used for continuous data, whereas the chi-square test or Fisher's test was used for categorical variables. The Kaplan–Meier survival curves were developed and contrasted using a logrank test. Univariate Cox proportional hazards regression was employed to examine and determine the predictive variables of PSCL, and multivariate Cox regressions (enter-model) were used to determine independent risk factors for survival among variables with p-values < 0.25 in the univariate analysis. P-values of less than 0.05 were considered statistically significant. R language package (vs. 3.6.1, R Foundation for Statistical Computing) was used to conduct all statistical analyses.

Ethics approval

This is a retrospective study, and data were gained from an open-access database. The Xinxiang Center Hospital Ethics Committee has proven that ethical approval is not needed.

RESULTS

Baseline Characteristics of Patients

Overall, 254 patients with PSCL were included. The median age at diagnosis was 58.5 years (IQR: 23.4 years), and 157 (61.8%) were male. DLBL (n=140, 55.1%) was the most prevalent pathological type. Only one (0.4%) and five (2.0%) patients had Hodgkin lymphoma and T-cell lymphoma, respectively (Figure 2). Most lesions (59.1%) were Ann Arbor stage I/II. Of all patients included in this study, 33 (13.0%), 90 (35.4%), and 117 (46.1) received radiotherapy alone, chemotherapy alone, and radiochemotherapy, respectively; the remaining patients did not receive adjuvant therapy. When comparing subgroups classified according to the survival status, no variable presented significant differences (Table II).

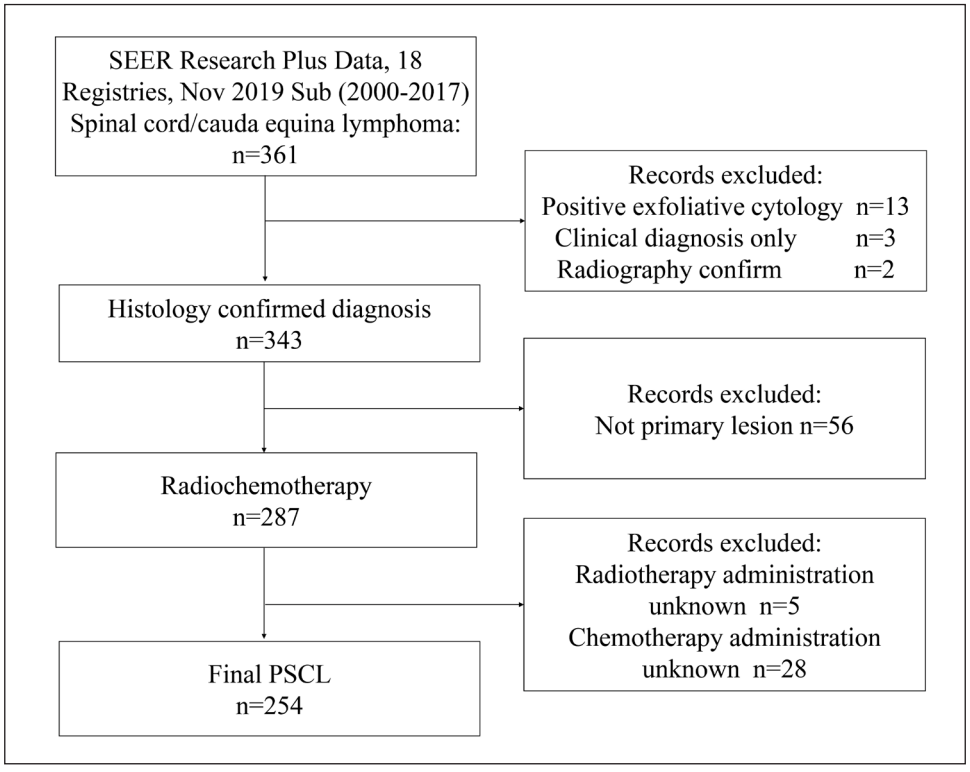

Figure 1: Flow diagram of patient selection.

Table I: ICD-O-3 Code for Lymphoma

Pathology	ICD-O-3 code
Malignant lymphoma, NOS	9590
Malignant lymphoma, non-Hodgkin	9591
Composite Hodgkin and non-Hodgkin lymphoma	9596
Hodgkin lymphoma, nodular sclerosis, NOS	9663
Small B lymphocytic, NOS	9670
Mixed small and large cell, diffuse	9675
Large B-cell, diffuse	9680
Large B-cell, diffuse, immunoblastic, NOS	9684
Burkitt lymphoma, NOS	9687
Follicular lymphoma, NOS	9690
Follicular lymphoma, grade 2	9691
Follicular lymphoma, grade 1	9695
Follicular lymphoma, grade 3	9698
Marginal zone B-cell lymphoma, NOS	9699
Mature T-cell lymphoma, NOS	9702
Anaplastic large cell lymphoma, T-cell and Null cell type	9714
Precursor cell lymphoblastic lymphoma, NOS	9727
Precursor B-cell lymphoblastic lymphoma	9728
Plasmablastic lymphoma	9735
B lymphoblastic leukemia/lymphoma, NOS	9811
Chronic lymphocytic leukemia/small lymphocytic lymphoma	9823

Table II: Demographic and Treatment Characteristics of Patients with Primary Spinal Cord/Cauda Equina Lymphoma

	Total		**Alive or unrelated death**		**Cancer-specific death**		
	(n=254)		**(n=187)**		**(n=67)**		**p-value**
Age, median (IQR)	58.5	(23.4)	54.8	(24.0)	59.9	(27.5)	0.085
Age groups, n (%)							0.117
≤30	25	(9.8)	22	(11.8)	3	(4.5)	
31-59	107	(42.1)	77	(41.2)	30	(44.8)	
60-79	101	(39.8)	76	(40.6)	25	(37.3)	
≥80	21	(8.3)	12	(6.4)	9	(13.4)	
Sex, n (%)							0.642
Male	157	(61.8)	114	(61.0)	43	(64.2)	
Female	97	(38.2)	73	(39.0)	24	(35.8)	
Race, n (%)							0.593
White	214	(84.2)	156	(83.4)	58	(86.6)	
Black	27	(10.6)	22	(11.7)	5	(7.5)	
Others	13	(5.1)	9	(4.8)	4	(6.0)	

Table II: Cont.

	Total		Alive or unrelated death		Cancer-specific death		
	(n=254)		(n=187)		(n=67)		p-value
Pathology, n (%)							0.553
Large B-cell, diffuse	140	(55.1)	101	(54.0)	39	(58.2)	
Non-DLBL	114	(44.9)	86	(46.0)	28	(41.8)	
Ann Arbor Stage, n (%)							0.270
Stage I/II	150	(59.1)	116	(62.0)	34	(50.7)	
Stage III/IV	89	(35.0)	61	(32.6)	28	(41.8)	
Unknown	15	(5.9)	10	(5.3)	5	(7.5)	
Adjuvant therapy, n (%)							0.330
None adjuvant therapy	14	(5.5)	10	(5.3)	4	(6.0)	
Radiotherapy only	33	(13.0)	20	(10.7)	13	(19.4)	
Chemotherapy only	90	(35.4)	68	(36.4)	22	(32.8)	
Radiochemotherapy	117	(46.1)	89	(47.6)	28	(41.8)	
Year of diagnosis, n (%)							0.371
2000-2003	35	(13.8)	23	(12.2)	12	(17.9)	
2004-2007	67	(26.4)	47	(25.1)	20	(29.9)	
2008-2011	64	(25.2)	47	(25.1)	17	(25.4)	
2012-2017	88	(34.6)	70	(37.4)	18	(26.9)	

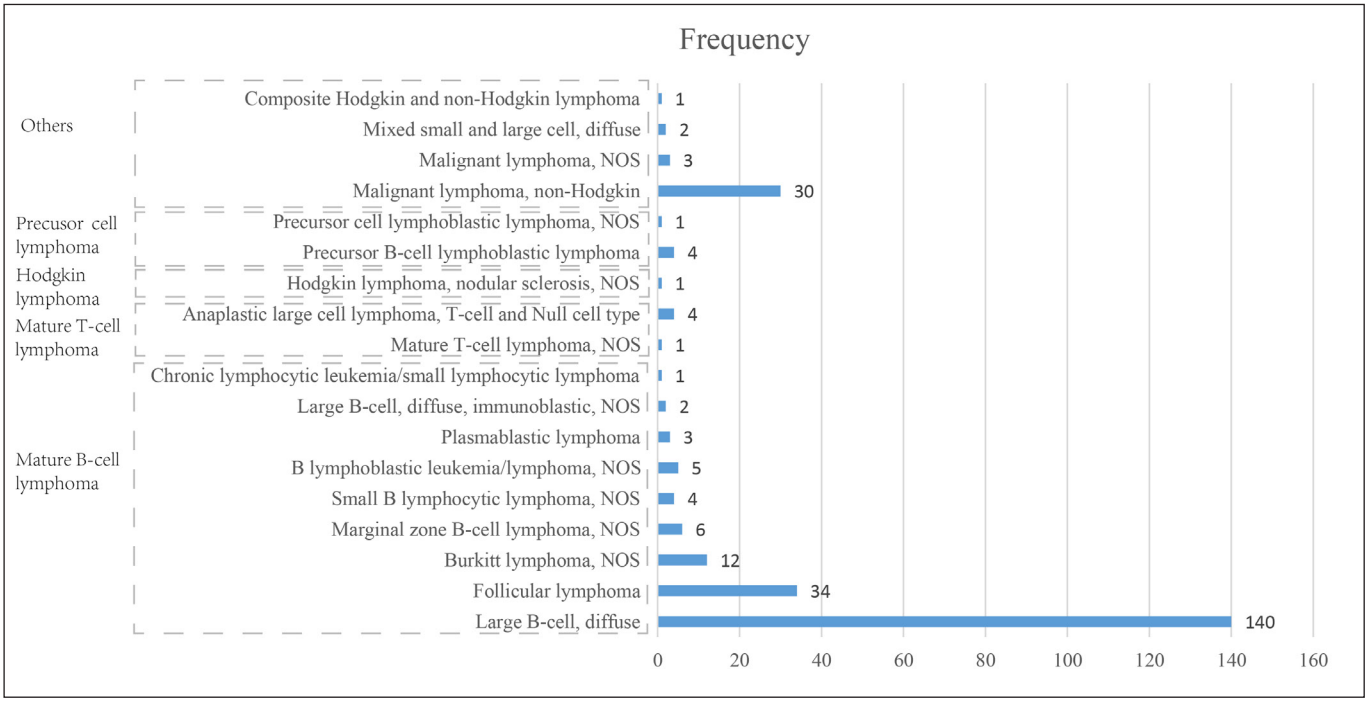

Figure 2. Histotype distribution of 254 patients with PSCL.

Variables Related to Survival

Generally, cancer-specific survival at 1, 3, and 5 years was 81.0%, 74.6%, and 74.1%, respectively (Figure 3A). The Kaplan–Meier survival curves demonstrated that adjuvant therapy and Ann Arbor stage were associated with survival (logrank test p=0.002 and 0.03, respectively) (Figure 3B–H). The univariate Cox regression analysis demonstrated that chemotherapy alone (hazard ratio (HR): 0.46; 95% confidence interval (CI), 0.16–0.78; p=0.017) and radiochemotherapy (HR: 0.42; 95% CI, 0.14–0.89; p=0.010) were related to favorable survival, whereas age ≥ 80 years was associated with poor survival. After correcting for the confounding impact of each covariate using the multivariate Cox regression model, the results demonstrated that chemotherapy (HR: 0.47; 95% CI, 0.16–0.82; p=0.040) and radiochemotherapy (HR: 0.43; 95% CI, 0.10–0.57; p=0.045) were independent predictors of favorable cancer-specific survival, whereas age ≥ 80 years (HR: 6.51; 95% CI, 1.65–25.64; p=0.003) and DLBL (HR:1.71; 95% CI, 1.02–2.88; p=0.030) were independently associated with poor cancer-specific survival (Table III).

DISCUSSION

PSCL is a rare extranodal lymphoma. Most studies focusing on PSCL were case reports (1,2,17,21). Here, we leveraged data retrieved from the SEER database to describe the survival outcomes of PSCL. The highest frequent histotype was DLBL in our cohort (55.1% of PSCL cases were DLBL), whereas Hodgkin lymphoma and T-cell lymphoma were rare histological subtypes. In contrast, the proportion of DLBL in primary brain lymphoma could reach approximately 90% (3,11,13). Regarding the overall outcome, PSCL had a favorable prognosis with a 5-year overall survival (OS) of

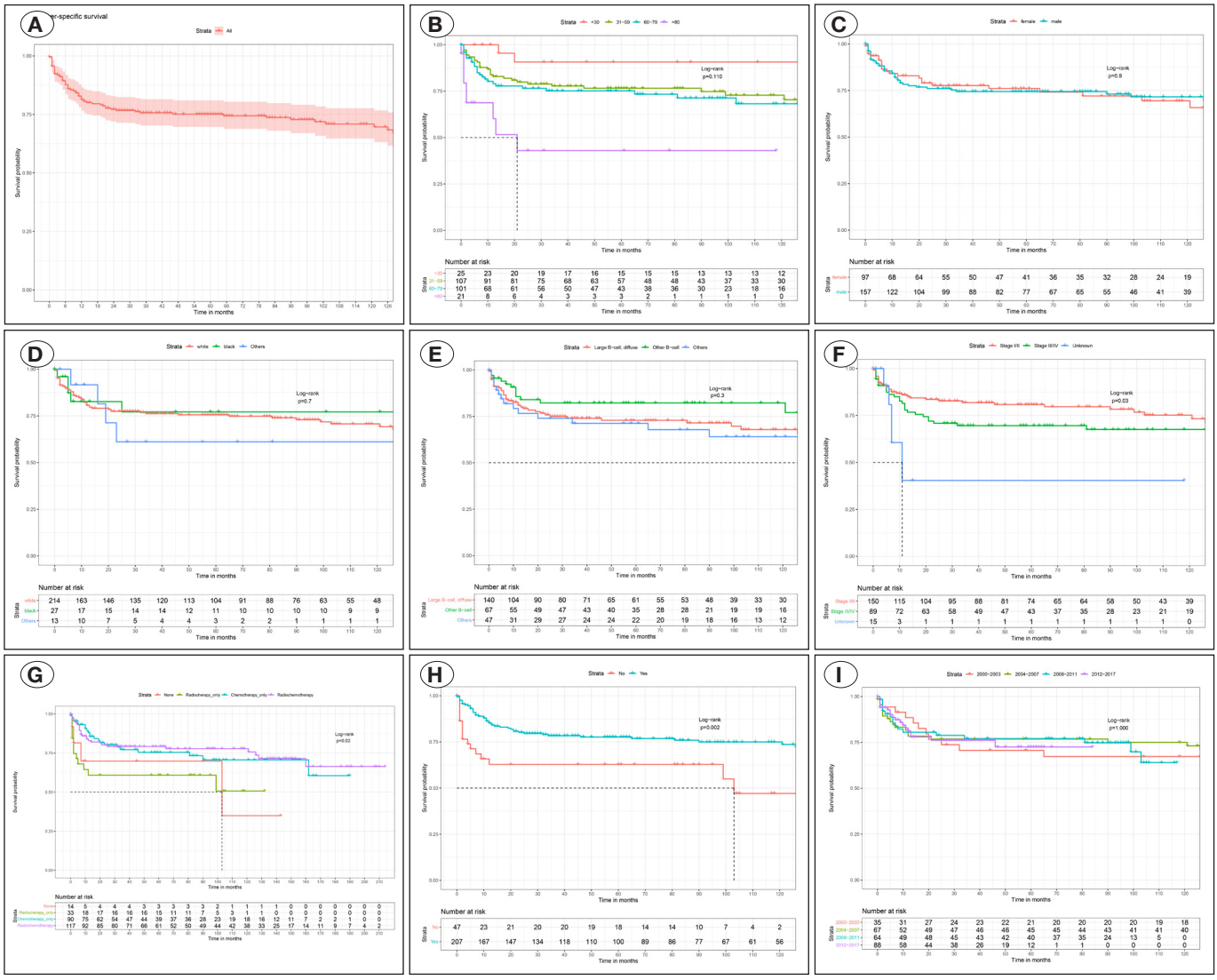

Figure 3: A) Kaplan–Meier survival curves of cancer-specific survival for all 254 patients demonstrated that OS outcome was favorable in the current treatment strategy; **(B–I)** Kaplan-Meier survival curves by variables revealed that adjuvant therapy and Ann Arbor stage were related to survival.

Table III: Univariate and Multivariate Cox Analysis of Cancer-Specific Survival

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age groups			**0.002**			**0.040***
≤30	Ref.			Ref.		
31-59	2.76	0.84-9.05	0.094	2.72	0.81-10.70	0.102
60-79	2.94	0.88-9.78	0.078	2.62	0.78-8.83	0.121
≥80	9.62	2.57-36.06	**0.001***	6.51	1.65-25.64	**0.007***
Sex (female as Ref.)	1.04	0.63-1.72	0.866			
Race			0.700			
White	Ref.					
Black	0.74	0.30-1.85	0.519			
Others	1.28	0.46-3.53	0.636			
Pathology						
Non-DLBL	Ref.			Ref.		
Large B-cell, diffuse	1.16	0.72-1.89	0.541	1.71	1.02-2.88	**0.030***
Ann Arbor Stage			0.003			0.271
Stage I/II	Ref.			Ref.		
Stage III/IV	1.41	0.86-2.22	0.177	1.44	0.85-2.45	0.177
Unknown	3.18	1.22-8.27	0.201	2.07	0.76-5.66	0.156
Adjuvant therapy			0.020			**0.033***
None adjuvant therapy	Ref.			Ref.		
Radiotherapy only	1.04	0.34-3.22	0.933	0.81	0.26-2.56	0.719
Chemotherapy only	0.46	0.16-0.78	**0.017**	0.47	0.16-0.82	**0.040***
Radiochemotherapy	0.42	0.14-0.89	**0.010**	0.43	0.10-0.57	**0.045***
Year at diagnosis			1.000			
2000-2003	Ref.					
2004-2007	1.01	0.49-2.10	0.975			
2008-2011	1.08	0.50-2.33	0.845			
2012-2017	1.09	0.50-2.35	0.835			

74.1%, whereas the 5-year OS of intracranial lymphoma was only approximately 30.1% (12,20). Conversely, Flanagan et al. revealed that the 2-year survival was 36% and that 50% of patients were wheelchair-dependent at 10 months in a cohort of 14 patients with PSCL; of note, all patients in that study were treated between 1996 and 2009, whereas 53.1% (not shown) of the patients in our cohort were treated after 2009. Advancements in chemotherapeutic drugs in recent decades have possibly contributed to the prolonged survival (9).

In our study, age ≥ 80 years was associated with poor prognosis. Consistently, the study by Ferreri et al. demonstrated that age > 60 years was one of the five adverse prognostic factors. Similarly, elderly age was also found to be a poor prognostic factor for non-Hodgkin lymphoma primarily occurring in the lymphatic system (8,15).

Other B-cell lymphomas (non-DLBL), which mostly comprised follicular lymphoma and Burkitt lymphoma, were found to have favorable impact on survival compared with DLBL. Speculatively, the improved treatment outcomes of follicular

lymphoma in the rituximab era (10-year OS: ~ 80%) and Burkitt lymphoma (5-year OS: ~85%), both of which are classified as non-DLBL, have possibly contributed to this finding (4,6). The 5-year survival rates of DLBL is approximately 64% in the rituximab era, which is shorter than that of follicular lymphoma and Burkitt lymphoma (7). Additionally, a study revealed that patients with histologic transformation from follicular lymphoma to DLBL had poorer OS than those without histologic transformation (18). However, limited to the small sample size of non-DLBL lymphoma in our cohort, a comparison of the survival outcomes among each histological subtype could not be performed. Definitely, histotype was associated with survival outcomes, and DLBL was not the histotype that has the most favorable survival outcome.

Chemotherapy alone and radiochemotherapy showed significant associations with cancer-specific survival, whereas radiotherapy alone did not show a beneficial effect on cancer-specific survival. High-dose methotrexate-based combination chemotherapy is the recommended intervention for newly diagnosed primary CNS lymphoma (10). However, the benefit of radiotherapy on primary CNS lymphoma is controversial. For patients who cannot tolerate systemic chemotherapy, radiotherapy could be administered by combining methotrexate with temozolomide, not radiotherapy alone (10,14,22). In brief, in line with previous study results, chemotherapy was proven to be beneficial to PSCL. Of note, radiochemotherapy was also found to be associated with favorable survival outcomes; we presumed that the benefit of radiochemotherapy on survival outcomes might have predominately resulted from chemotherapeutic agents. Regarding radiotherapy, further study should be conducted to identify potential subgroup patients that could benefit from radiotherapy.

Ann Arbor stage has not shown association with survival. This staging system was primarily developed for lymphomas arising from the lymphatic system, and the principle of staging is mainly based on the extent of lymphatic dissemination (5). Nevertheless, cerebrospinal fluid dissemination, rather than lymphatic dissemination, is inferred to be closely associated with OS of primary CNS lymphoma (16). Hence, the Ann Arbor staging system is possibly inappropriate for primary CNS lymphomas.

This study has some drawbacks. First, detailed treatment strategies, particularly chemotherapy and radiotherapy strategies, were unreported in the SEER database. Second, radiological information, which was possibly associated with survival, was unknown. Although the survival outcomes of PSCL were favorable owing to the current treatment strategy, neurological function should be investigated in the future. Finally, the lifetime of the database was approximately 17 years, during which the chemoradiotherapy technique has changed.

CONCLUSION

DLBL was the most prevalent histotype of PSCL and was not the subtype that has the most favorable survival outcome. Elderly age was associated with poor prognosis of PSCL, whereas chemotherapy alone and radiochemotherapy were independent predictors of favorable survival.

AUTHORSHIP CONTRIBUTION

Study conception and design: SL
Data collection: DQ, CZ, WY, DB
Analysis and interpretation of results: SL
Draft manuscript preparation: DQ
Critical revision of the article: SL
All authors (DQ, CZ, WY, DB, SL) reviewed the results and approved the final version of the manuscript.

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