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ARTICLE

Impact of Postoperative Chemotherapy on Survival in Patients with Primary Central Nervous System Lymphoma: A Study Based on the SEER Database

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Abstract

Aims/Background We aimed to investigate the impact of postoperative chemotherapy (POCT) on survival in patients with primary central nervous system lymphoma (PCNSL) using data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods This study included 786 PCNSL patients, of which 605 received chemotherapy after surgery, and 181 did not. Data from the SEER registry database (2007–2020) were used to analyze PCNSL. Baseline information, including age, sex, race, marital status, primary tumour site, histological type, summary stage, surgical procedures, chemotherapy, and radiotherapy, was analyzed. Propensity Score Matching (PSM) (1:1) was employed to balance the effects of confounding variables between the two groups. Subsequently, Cox regression and bidirectional stepwise regression were used to identify independent prognostic factors. Kaplan-Meier (K-M) survival curves were constructed to assess the impact of POCT on patient prognosis. Additionally, two cases of PCNSL with typical magnetic resonance imaging appearances were presented.

Results Multivariate Cox regression results revealed that age older than 60 years (hazard ratio [HR] = 1.786; 95% confidence interval [CI]: 1.272–2.509; $p = 0.001$) and absence of POCT (HR = 2.841; 95% CI: 2.159–3.738; $p < 0.001$) were independent prognostic risk factors, while primary tumour locations in the meninges (HR = 0.136; 95% CI: 0.032–0.569; $p = 0.006$) and other nervous system regions (HR = 0.552; 95% CI: 0.326–0.936; $p = 0.027$), as well as histological morphologies such as diffuse large B-cell lymphoma (HR = 0.233; 95% CI: 0.128–0.425; $p < 0.001$) and non-Hodgkin lymphoma (HR = 0.559; 95% CI: 0.356–0.876; $p = 0.011$), were associated with favourable patient outcomes. K-M curves demonstrated that the group undergoing POCT had a significantly more favourable prognosis compared to the non-POCT group, before (HR = 0.454; 95% CI: 0.343–0.600; $p < 0.0001$) or after PSM (HR = 0.580; 95% CI: 0.431–0.780; $p < 0.0001$). For patients with PCNSL, those with tumours located in the infratentorial region (HR = 0.231; 95% CI: 0.078–0.682; $p = 0.046$), supratentorial region (HR = 0.250; 95% CI: 0.163–0.383; $p < 0.0001$), overlapping brain regions (HR = 0.201; 95% CI: 0.056–0.727; $p = 0.0058$), and those who underwent biopsy (HR = 0.740; 95% CI: 0.463–1.182; $p = 0.003$), subtotal resection (STR) (HR = 0.490; 95% CI: 0.265–0.906; $p = 0.0064$), or gross total resection (GTR) (HR = 0.613; 95% CI: 0.292–1.287; $p = 0.0003$) had better prognoses in the postoperative chemotherapy group compared to the non-chemotherapy group.

Conclusion POCT significantly improves the prognosis of PCNSL patients and identifies the characteristics of the benefiting population. This information aids clinical practitioners in designing personalized treatment plans for individuals and advancing precise treatment.

Key words: postoperative chemotherapy; overall survival; primary central nervous system lymphoma; SEER

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Introduction

Primary central nervous system lymphoma (PCNSL) represents an aggressive lymphoma that exclusively involves the brain, spinal cord, cranial nerves, meninges, and eyes, with diffuse large B-cell lymphoma (DLBCL) being its most prevalent subtype (Yuan et al, 2021). PCNSL is considered a relatively uncommon condition, constituting approximately 1–2% of all primary central nervous system tumours (Rae et al, 2019; Villano et al, 2011). Epidemiological study has shown that the general incidence rate of PCNSL stands at 0.47 per 100,000 individuals, exhibiting a higher incidence rate among males than females, and the overall incidence demonstrates an upward trend with increasing age (Villano et al, 2011). Furthermore, as the population continues to age, the incidence of PCNSL steadily rises (Shiels et al, 2016). PCNSL is linked to an unfavourable prognosis, and in the absence of treatment, the overall survival (OS) typically extends to a mere 1.5 months (Tang et al, 2022). Additionally, due to the presence of the blood-brain barrier, the efficacy of chemotherapy in treating central nervous system diseases is suboptimal. Compared to non-central nervous system lymphomas, PCNSL is characterized by a more dismal prognosis, featuring a 5-year survival rate of 33% (Han and Batchelor, 2017; Schmitz, 2015). Therefore, it is of paramount importance to investigate the optimal treatment approaches that can improve the survival rates of PCNSL patients.

Surgical resection is not the standard treatment for PCNSL due to its multifocal nature. Before 2010, surgical resection was generally discouraged as it was considered to have limited benefits for PCNSL patients (Ferreri et al, 2002; Alattar et al, 2018). However, advances in surgical techniques have challenged traditional views. Some studies have reported that surgical resection may benefit PCNSL patients, suggesting that surgery before the initiation of chemotherapy can lead to better outcomes. Research indicates that the combination of surgical resection and chemotherapy can provide more favorable prognoses compared to chemotherapy or surgery alone (Qian et al, 2017; Tang et al, 2022). Nevertheless, there is still insufficient evidence to recommend an aggressive surgical approach for PCNSL, and further investigation is needed.

High-dose methotrexate chemotherapy is currently the primary treatment for PCNSL patients (Hoang-Xuan et al, 2015; Rae et al, 2019). Methotrexate is the most effective drug against PCNSL as it can cross the blood-brain barrier and is often used in combination with other drugs such as procarbazine, vincristine, cytarabine, rituximab, and temozolomide (Bromberg et al, 2019; Chamberlain and Johnston, 2010; Song et al, 2017). Given the refractory nature of PCNSL and the presence of the blood-brain barrier, exploring effective treatment methods is crucial. Combined therapy involving surgical resection and chemotherapy is particularly important in this context, as it may help eradicate residual tumour tissue, thereby improving survival rates and quality of life for patients (Schaff and Grommes, 2022). Therefore, understanding the impact of postoperative chemotherapy on PCNSL patients can provide critical insights for improving treatment regimens, increasing survival rates, and enhancing prognosis. This is essential for optimizing clinical practice and improving patients' quality of life.

A previous study investigating the relationship between surgical resection and PCNSL survival reported that combining surgery with chemotherapy can increase survival rates, with this effect persisting even after adjusting for age (Rae et al, 2019). However, given the rarity of PCNSL, there remains a gap in knowledge regarding the long-term survival impact and the identification of suitable patient populations for the postoperative chemotherapy treatment model. Therefore, we aimed to conduct a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) database on histologically confirmed PCNSL patients to investigate the impact of postoperative chemotherapy on the survival of PCNSL patients. This study explored the factors influencing survival after surgery in PCNSL patients, addressing this critical gap in knowledge in current research and providing data support for large-scale prospective studies.

Methods

Data and Cohort Definition

The SEER program (http://seer.cancer.gov) collects comprehensive, patient-level data from diverse geographic populations representing rural, urban, and regional demographics in the United States, with the aim of conducting nationwide clinical investigations (Liang et al, 2017; Hayat et al, 2007).

For this retrospective analysis, PCNSL patient data from the SEER database were extracted from 12 centres spanning the years 2007 to 2020 (accessed on June 2, 2023). PCNSL patients were selected using SEER*Stat version 8.4.1 software (National Cancer Institute, Bethesda, MD, USA). The primary focus of this work was to ascertain whether postoperative chemotherapy (POCT) provides a survival benefit to PCNSL patients and to identify prognostic factors. PCNSL individuals were evaluated using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes (9590–9595, 9650–9699, 9702–9729), with their primary anatomical locations defined by specific ICD-O-3 codes (C70.0, C70.1, C70.9, C71.0–C72.9). Our analysis exclusively encompassed primary cancers, excluding individuals lacking histological confirmation or those diagnosed solely through autopsy, as detailed in Fig. 1. This study enrolled 786 eligible patients who received a diagnosis of PCNSL within the timeframe spanning from 2007 to 2020. Of these patients, 605 received POCT, while 181 did not. SEER data do not contain any patient identifiers and are publicly available.

Variable Definitions

Population demographic data were extracted from the SEER database, including age at diagnosis ($\leq$60 years, $>$60 years) (Deng et al, 2022), sex (male or female), race (White, Black, Asian/Pacific Islander, Indian Native/Alaska Native), and marital status (single, married, or unknown). The study also obtained tumour characteristics (histological type, tumour site, and tumour laterality), treatment information (surgery, radiation therapy, and chemotherapy), and survival data. Histological types were categorized as DLBCL, non-DLBCL, non-Hodgkin lymphoma (NHL), and not otherwise specified (NOS) lymphoma. Tumour locations were clas-

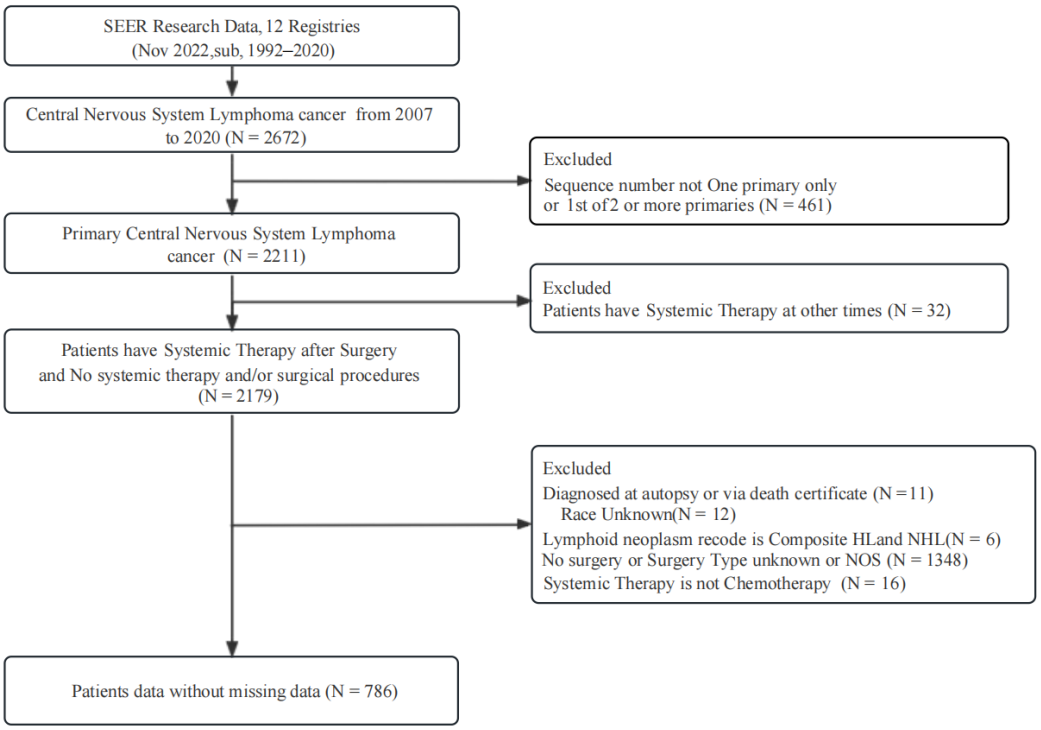

Fig. 1. Flow chart of patient selection in the Surveillance, Epidemiology, and End Results (SEER) database. HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

sified as meninges, supratentorial, infratentorial, overlap, brain NOS, and other central nervous system. The summary stage was divided into localized, distant, regional, and unknown. Surgical treatments included biopsy, subtotal resection (STR), gross total resection (GTR), partial brain lobe resection (PBLR), and gross total brain lobe resection (GBLR). Radiation therapy was categorized as postoperative beam radiation or no radiation, and chemotherapy as POCT or no chemotherapy. The clinical endpoint analyzed was overall survival (OS), defined as the period from the date of diagnosis to either the occurrence of death from any cause or the date of the last follow-up and measured in months.

Statistical Analysis

In this study, data analysis was performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Baseline data are presented as N (%). Differences in categorical variables between the postoperative chemotherapy group and the non-chemotherapy group were compared using the Chi-Square test. When the expected value (T) was $\geq$5, differences between the groups were assessed using the Pearson Chi-Square test. When the expected value (T) was between 1 and $<$5, the Likelihood Ratio Chi-Square test was used for comparison. This analysis was conducted using the 'tableone' package (https://github.com/kaz-yos/tableone). Propensity Score Matching (PSM) (1:1) with calliper matching was employed to balance confounding variables between the two groups, thereby mitigating their impact on the relationship between risk factors and outcomes. The PSM process included calculating individual propensity scores, setting a calliper, performing

matching, adjusting matches, and assessing match quality (Johara et al, 2021). After PSM, variables with a p-value < 0.05 were entered into the multivariate analysis using a univariate Cox regression model. Multivariate Cox regression used bidirectional stepwise regression to select independent prognostic factors, and hazard ratios (HRs) along with their 95% confidence intervals (CIs) were computed. Kaplan-Meier survival curves were generated to evaluate the impact of POCT on patient prognosis. Variables with a significance level of $p \leq 0.05$ were considered statistically significant.

Results

Baseline Characteristics

The demographic and clinical-pathological characteristics of both cohorts are summarized in Table 1. The data revealed notable disparities between the two groups in the light of age, race, marital status, primary site, laterality, histological type, summary stage, and the receipt of radiation therapy ($p < 0.05$). As an illustration, regarding marital status, a notably substantial difference was observed between the two groups ($p = 0.001$), with a significantly greater proportion of married patients in the POCT group (63.1%) as opposed to the non-chemotherapy group (49.2%). Additionally, the percentage of individuals who received radiation therapy was tellingly higher in the postoperative non-chemotherapy group (80.2%) compared to the POCT group (58.6%) ($p < 0.001$). Detailed characteristics are listed in Table 1.

Propensity Score Matching (PSM)

Due to the significant differences in various variables between POCT and non-chemotherapy groups as shown in Table 1, PSM was employed to balance these variables and to reduce the impact of other factors on POCT's effect on survival prognosis. The results of the PSM are presented in Table 2. After PSM, all variables showed no significant differences between the two groups ($p > 0.05$). Additionally, Fig. 2 demonstrates that there was a significant increase in the overlap between the two groups after matching, indicating a well-balanced distribution of baseline characteristics among the matched patients.

Univariate Cox Regression and Multivariate Cox Regression for Prognostic Factor Selection

In a subsequent analysis, we utilized univariate Cox regression to mine the variables influencing the OS of individuals (Table 3). We found that age >60 years (hazard ratio [HR] = 2.033; 95% confidence interval [CI]: 1.501–2.753; $p < 0.001$), Black race (HR = 0.497; 95% CI: 0.275–0.899; $p < 0.05$), primary tumour site in the meninges (HR = 0.127; 95% CI: 0.031–0.524; $p < 0.05$) or other nervous system locations (HR = 0.449; 95% CI: 0.269–0.751; $p < 0.05$), non-DLBCL histology (HR = 0.192; 95% CI: 0.109–0.338; $p < 0.001$), and NHL histology (HR = 0.601; 95% CI: 0.389–0.927; $p < 0.05$) were significant variables affecting prognosis. Additionally, Table 3 shows that the lack of POCT significantly impacted the OS (HR = 2.059; 95% CI: 1.582–2.679; $p < 0.001$).

Table 1. Baseline demographic and clinical characteristics of patients with PCNSL.

Variable	Chemotherapy (N = 605)	No chemotherapy (N = 181)	Total (N = 786)	Chi-square test	*p*-value
Age, n (%)				6.060	0.014
≤60 years	273 (45.1)	63 (34.8)	336 (42.7)		
>60 years	332 (54.9)	118 (65.2)	450 (57.3)		
Sex, n (%)				0.003	0.955
Female	286 (47.3)	86 (47.5)	372 (47.3)		
Male	319 (52.7)	95 (52.5)	414 (52.7)		
Race, n (%)				8.460	0.037
Asian or Pacific Islander	119 (19.7)	25 (13.8)	144 (18.3)		
Black	34 (5.6)	20 (11)	54 (6.9)		
Indian Native/Alaska Native	4 (0.7)	2 (1.1)	6 (0.8)		
White	448 (74)	134 (74)	582 (74)		
Marital status, n (%)				14.065	0.001
Married	382 (63.1)	89 (49.2)	471 (59.9)		
Single	208 (34.4)	81 (44.8)	289 (36.8)		
Unknown	15 (2.5)	11 (6.1)	26 (3.3)		
Primary site, n (%)				12.625	0.027
Brain, NOS	97 (16)	36 (19.9)	133 (16.9)		
Infratentorial	44 (7.3)	17 (9.4)	61 (7.8)		
Meninges	6 (1)	8 (4.4)	14 (1.8)		
Other Center Nervous System	93 (15.4)	24 (13.3)	117 (14.9)		
Overlapping in brain	37 (6.1)	14 (7.7)	51 (6.5)		
Supratentorial	328 (54.2)	82 (45.3)	410 (52.2)		
Laterality, n (%)				7.391	0.025
Not a paired site	229 (37.9)	76 (42)	305 (38.8)		
Paired site, NOS	13 (2.1)	10 (5.5)	23 (2.9)		
Unilateral tumour	363 (60)	95 (52.5)	458 (58.3)		

Table 1. Continued.

Variable	Chemotherapy (N = 605)	No chemotherapy (N = 181)	Total (N = 786)	Chi-square test	*p*-value
Histology, n (%)				25.558	<0.001
DLBCL	525 (86.8)	128 (70.7)	653 (83.1)		
Non-DLBCL	44 (7.3)	29 (16)	73 (9.3)		
Non-Hodgkin lymphoma, NOS	36 (6)	24 (13.3)	60 (7.6)		
Summary stage, n (%)				22.358	<0.001
Distant	97 (16)	22 (12.2)	119 (15.1)		
Localized	463 (76.5)	130 (71.8)	593 (75.4)		
Regional	34 (5.6)	13 (7.2)	47 (6)		
Unknown/unstaged	11 (1.8)	16 (8.8)	27 (3.4)		
Surgery type, n (%)				3.985	0.552
Biopsy	247 (40.8)	74 (40.9)	321 (40.8)		
GBLR	40 (6.6)	13 (7.2)	53 (6.7)		
GTR	115 (19)	31 (17.1)	146 (18.6)		
PBLR	36 (6)	14 (7.7)	50 (6.4)		
STR	163 (26.9)	45 (24.9)	208 (26.5)		
Surgery, NOS	4 (0.7)	4 (2.2)	8 (1)		
Radiation recode, n (%)				34.851	<0.001
Beam radiation	120 (19.8)	75 (41.4)	195 (24.8)		
No radiation	485 (80.2)	106 (58.6)	591 (75.2)		

Note: PCNSL, primary central nervous system lymphoma; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; GBLR, gross total brain lobe resection; GTR, gross total resection; PBLR, partial brain lobe resection; STR, subtotal resection.

Table 2. Baseline characteristics of the patients after PSM.

Variable	Chemotherapy (N = 181)	No chemotherapy (N = 181)	Chi-square test	*p*-value
Age, n (%)			0.198	0.656
≤60 years	59 (32.6)	63 (34.8)		
>60 years	122 (67.4)	118 (65.2)		
Sex, n (%)			0.011	0.916
Female	85 (47.0)	86 (47.5)		
Male	96 (53.0)	95 (52.5)		
Race, n (%)			0.777	0.855
Asian or Pacific Islander	30 (16.6)	25 (13.8)		
Black	19 (10.5)	20 (11.0)		
Indian Native/Alaska Native	3 (1.7)	2 (1.1)		
White	129 (71.3)	134 (74.0)		
Marital status, n (%)			1.210	0.546
Married	96 (53.0)	89 (49.2)		
Single	78 (43.1)	81 (44.8)		
Unknown	7 (3.9)	11 (6.1)		
Primary site, n (%)			2.589	0.763
Brain, NOS	34 (18.8)	36 (19.9)		
Infratentorial	14 (7.7)	17 (9.4)		
Meninges	4 (2.2)	8 (4.4)		
Other Center Nervous System	21 (11.6)	24 (13.3)		
Overlapping in brain	16 (8.8)	14 (7.7)		
Supratentorial	92 (50.8)	82 (45.3)		
Laterality, n (%)			0.430	0.806
Not a paired site	70 (38.7)	76 (42.0)		
Paired site, NOS	10 (5.5)	10 (5.5)		
Unilateral tumour	101 (55.8)	95 (52.5)		

Table 2. Continued.

Variable	Chemotherapy (N = 181)	No chemotherapy (N = 181)	Chi-square test	*p*-value
Histology, n (%)			1.061	0.588
DLBCL	135 (74.6)	128 (70.7)		
Non-DLBCL	28 (15.5)	29 (16.0)		
Non-Hodgkin lymphoma, NOS	18 (9.9)	24 (13.3)		
Summary stage, n (%)			4.235	0.237
Distant	33 (18.2)	22 (12.2)		
Localized	127 (70.2)	130 (71.8)		
Regional	12 (6.6)	13 (7.2)		
Unknown/unstaged	9 (5.0)	16 (8.8)		
Surgery type, n (%)			1.546	0.908
Biopsy	68 (37.6)	74 (40.9)		
GBLR	16 (8.8)	13 (7.2)		
GTR	29 (16.0)	31 (17.1)		
PBLR	19 (10.5)	14 (7.7)		
STR	46 (25.4)	45 (24.9)		
Surgery, NOS	3 (1.7)	4 (2.2)		
Radiation recode, n (%)			1.686	0.194
Beam radiation	63 (34.8)	75 (41.4)		
No radiation	118 (65.2)	106 (58.6)		

Note: PSM, Propensity Score Matching; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; GBLR, gross total brain lobe resection; GTR, gross total resection; PBLR, partial brain lobe resection; STR, subtotal resection.

Table 3. Cox regression univariate and multivariate screening of prognostic factors.

Variable	Level	Univariable		Multivariable	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Marital status (%)	Married	1 (Reference)			
	Single	0.982 (0.751–1.284)	0.894		
	Unknown	1.4 (0.789–2.486)	0.250		
Age (%)	≤60 years	1 (Reference)		1 (Reference)	
	>60 years	2.033 (1.501–2.753)	<0.001	1.786 (1.272–2.509)	0.001
Sex (%)	Female	1 (Reference)			
	Male	1.024 (0.789–1.328)	0.859		
Race (%)	Asian or Pacific Islander	1 (Reference)		1 (Reference)	
	Black	0.497 (0.275–0.899)	0.021	1.066 (0.556–2.047)	0.847
	Indian Native/Alaska Native	0.484 (0.116–2.016)	0.319	0.568 (0.136–2.372)	0.438
	White	0.936 (0.651–1.346)	0.721	1.1 (0.758–1.595)	0.617
Primary site (%)	Brain, NOS	1 (Reference)		1 (Reference)	
	Infratentorial	0.95 (0.559–1.613)	0.848	0.911 (0.535–1.551)	0.731
	Meninges	0.127 (0.031–0.524)	0.004	0.136 (0.032–0.569)	0.006
	Other Center Nervous System	0.449 (0.269–0.751)	0.002	0.552 (0.326–0.936)	0.027
	Overlapping in brain	0.979 (0.592–1.619)	0.934	0.905 (0.543–1.508)	0.701
	Supratentorial	0.847 (0.606–1.184)	0.332	0.829 (0.591–1.163)	0.277
Laterality (%)	Not a paired site	1 (Reference)			
	Paired site, NOS	1.015 (0.542–1.898)	0.964		
	Unilateral tumour	1.164 (0.888–1.527)	0.272		
Histology (%)	DLBCL	1 (Reference)		1 (Reference)	
	non-DLBCL	0.192 (0.109–0.338)	<0.001	0.233 (0.128–0.425)	<0.001
	Non-Hodgkin lymphoma, NOS	0.601 (0.389–0.927)	0.021	0.559 (0.356–0.876)	0.011

Table 3. Continued.

Variable	Level	Univariable		Multivariable	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Summary stage (%)	Distant	1 (Reference)			
	Localized	0.939 (0.654–1.348)	0.734		
	Regional	1.053 (0.567–1.953)	0.871		
	Unknown/unstaged	0.977 (0.542–1.763)	0.939		
Surgery type (%)	Biopsy	1 (Reference)			
	GBLR	0.718 (0.434–1.188)	0.197		
	GTR	0.862 (0.587–1.264)	0.447		
	PBLR	0.669 (0.408–1.095)	0.11		
	STR	0.843 (0.603–1.179)	0.318		
	Surgery, NOS	1.155 (0.47–2.84)	0.754		
Radiation recode (%)	Beam radiation	1 (Reference)			
	No radiation	1.299 (0.992–1.702)	0.057		
Chemotherapy record	Chemotherapy after surgery	1 (Reference)		1 (Reference)	
	No Chemotherapy therapy	2.059 (1.582–2.679)	<0.001	2.841 (2.159–3.738)	<0.001

Note: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; GBLR, gross total brain lobe resection; GTR, gross total resection; PBLR, partial brain lobe resection; STR, subtotal resection.

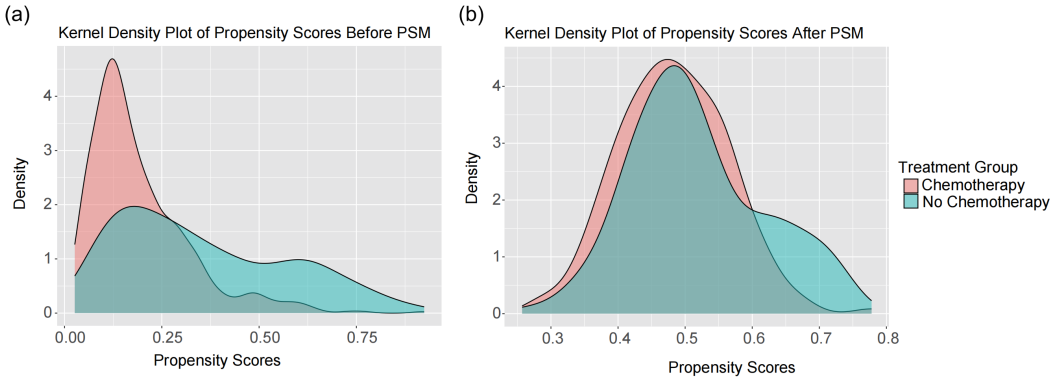

Fig. 2. Density plots showing baseline characteristics before and after Propensity Score Matching (PSM). (a) Before PSM. (b) After PSM.

Subsequently, we included the notable variables from the univariate Cox regression ($p < 0.05$) and conducted bidirectional stepwise regression using the multivariate Cox regression model. The results revealed that age older than 60 years (HR = 1.786; 95% CI: 1.272–2.509; $p = 0.001$) and not receiving POCT (HR = 2.841; 95% CI: 2.159–3.738; $p < 0.001$) were independent prognostic risk factors. Conversely, primary tumour site in the meninges (HR = 0.136; 95% CI: 0.032–0.569; $p < 0.05$) or other nervous system locations (HR = 0.552; 95% CI: 0.326–0.936; $p < 0.05$), non-DLBCL histology (HR = 0.233; 95% CI: 0.128–0.425; $p < 0.001$), and NHL histology (HR = 0.559; 95% CI: 0.356–0.876; $p < 0.05$) were favourable for patient prognosis.

Survival Curves and Subgroup Analysis

As shown in Fig. 3, both before PSM (HR = 0.454; 95% CI: 0.343–0.600; $p < 0.0001$, Fig. 3a) and after PSM (HR = 0.580; 95% CI: 0.431–0.780; $p < 0.0001$, Fig. 3b), the POCT group had significantly better prognosis than the postoperative non-chemotherapy group ($p < 0.001$). In subsequent research, we used the data after PSM to further explore the prognosis of PCNSL individuals with different primary tumour locations and surgical types, as depicted in Fig. 4a–h. When the primary tumour location was in the infratentorial region (HR = 0.231; 95% CI: 0.078–0.682; $p = 0.046$, Fig. 4a), supratentorial region (HR = 0.250; 95% CI: 0.163–0.383; $p < 0.0001$, Fig. 4b), or brain overlap region (HR = 0.201; 95% CI: 0.056–0.727; $p = 0.0058$, Fig. 4c), the survival prognosis of individuals in the POCT group was significantly better than that of the postoperative non-chemotherapy group. Subgroup analysis results for different surgical types revealed that in cases of biopsy (HR = 0.740; 95% CI: 0.463–1.182; $p = 0.003$, Fig. 4d), STR (HR = 0.490; 95% CI: 0.265–0.906; $p = 0.0064$, Fig. 4e), and GTR (HR = 0.613; 95% CI: 0.292–1.287; $p = 0.00032$, Fig. 4f), the survival prognosis for patients in the POCT group was significantly better than that of the postoperative non-chemotherapy group.

Furthermore, we conducted a comparison of the influence of various surgical procedures on the survival rates of PCNSL individuals as illustrated in Fig. 5. As shown in Fig. 5a, for long-term survival over 5 years in PCNSL individuals who did not undergo POCT, the survival rate for STR surgery was significantly higher

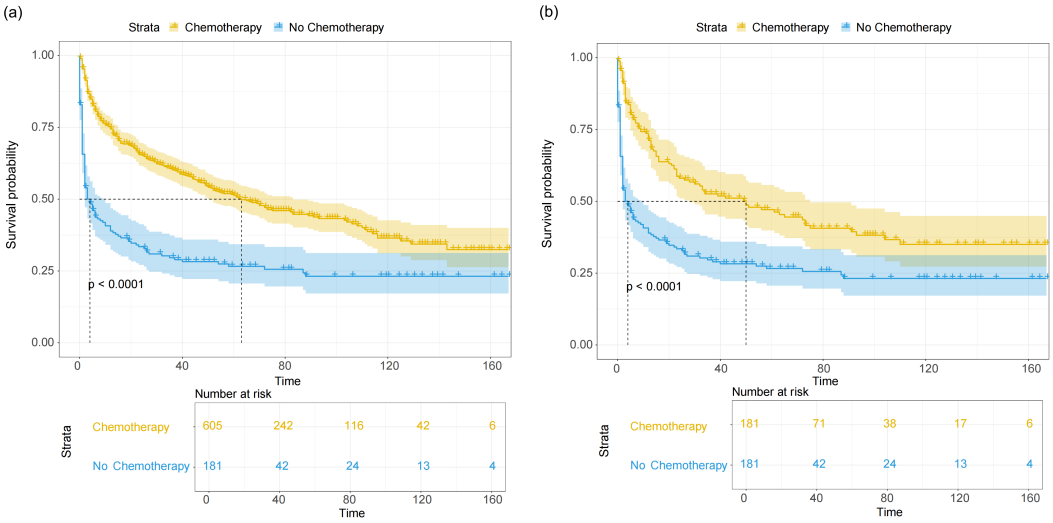

Fig. 3. Survival curves for primary central nervous system lymphoma (PCNSL) patients in the surgical chemotherapy group and surgical non-chemotherapy group. (a,b) Comparison of total survival curves for patients before PSM (a) and after PSM (b).

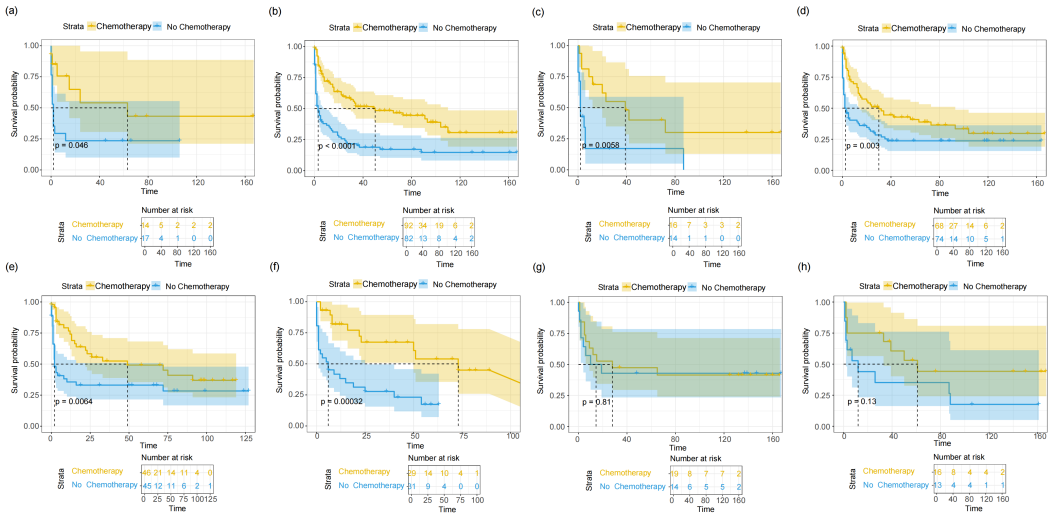

Fig. 4. Survival curve analysis of the impact of primary tumour location and surgical type on postoperative prognosis in PCNSL. (a) Survival curve for tumours located in the infratentorial area. (b) Survival curve for tumours located in the supratentorial area. (c) Survival curve for tumours located in the overlapping region. (d) Survival curve for patients with biopsy as the surgical type. (e) Survival curve for patients with STR as the surgical type. (f) Survival curve for patients with GTR as the surgical type. (g) Survival curve for patients with PBLR as the surgical type. (h) Survival curve for patients with GBLR as the surgical type.

than that for GTR and biopsy surgeries ($p < 0.05$). However, in PCNSL patients who underwent POCT, the postoperative survival rates for the various surgical types illustrated no significant disparities ($p > 0.05$) as demonstrated in Fig. 5b.

Examples of PCNSL Individuals from Our Hospital

The clinical magnetic resonance imaging (MRI) images before and after treatment for selected PCNSL patients from our hospital are shown in Figs. 6,7. Fig. 6

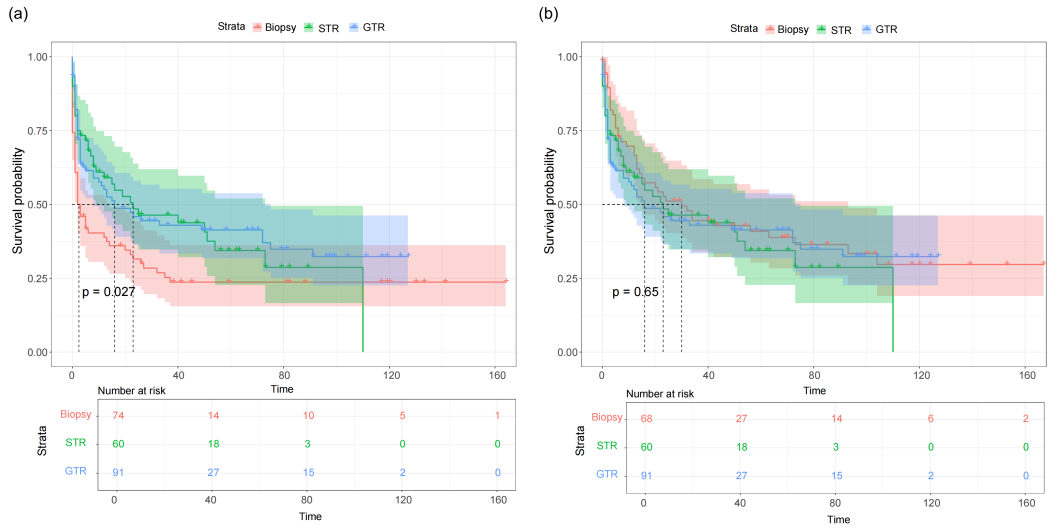

Fig. 5. Comparison of total survival curves for PCNSL patients with different surgical types in the two groups. (a,b) Total survival curve comparison for each surgical type in the surgical non-chemotherapy group (a) and surgical chemotherapy group (b).

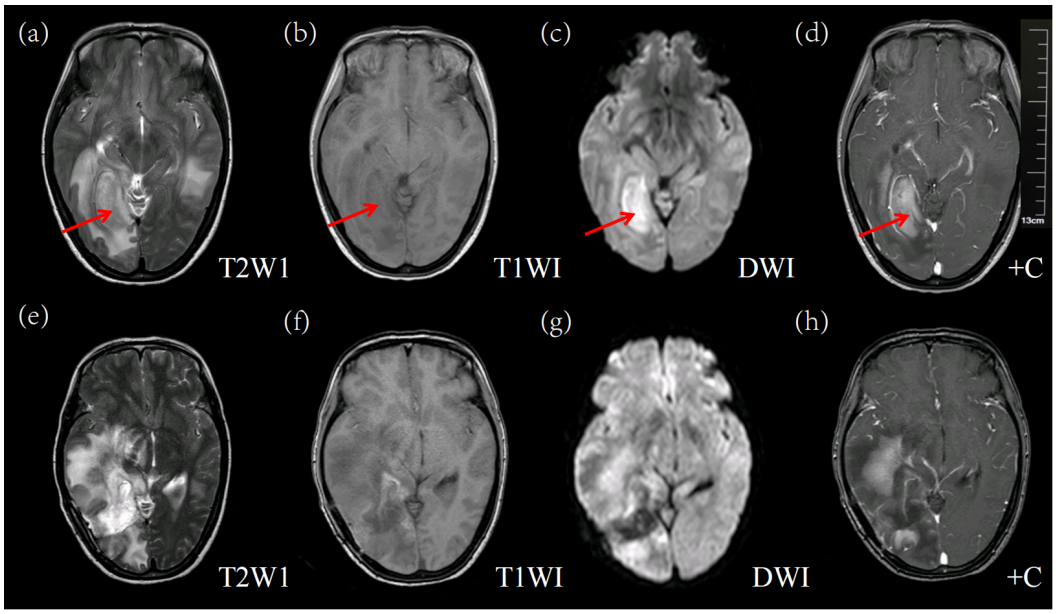

Fig. 6. Pre-and post-treatment brain magnetic resonance imaging (MRI) scans of a patient without chemotherapy after surgery. (a–d) Pre-treatment images, show a lesion in the right occipitotemporal region. Axial T2-weighted images (T2WI) (a), axial T1-weighted images (T1WI) (b), axial diffusion-weighted imaging (DWI) (c), and enhanced scan (+C) (d) show significantly uniform enhancement. (e–h) Post-surgical images after lesion resection: mixed signal shadow in the original right occipitotemporal surgical area. Axial T2WI (e), axial T1WI (f), axial diffusion-weighted imaging (DWI) (g), and enhanced scan (+C) (h) show partial enhancement around the lesion area. Red arrows indicate areas of abnormal signal intensity, suggesting lesion regions.

presents MRI images of a 49-year-old married female patient who did not undergo chemotherapy post-surgery, with clinical symptoms of unsteady gait for over 10 days. The pre-treatment MRI images (Fig. 6a–d) show a lesion in the right occipitotemporal region, with high signal intensity on T2-weighted images (T2WI), iso-

intense signals on T1-weighted images (T1WI), markedly high signals on diffusion-weighted imaging (DWI), and significant uniform enhancement on contrast-enhanced scans. Post-surgical images (Fig. 6e–h) reveal a mixed signal shadow in the original right occipitotemporal surgical area, no significant high signal on DWI, and partial enhancement around the lesion on contrast-enhanced scans.

Fig. 7 illustrates MRI images of a 64-year-old married female patient who underwent surgery followed by chemotherapy, presenting with recurrent dizziness for over half a month. The pre-treatment MRI images (Fig. 7a–c) demonstrate irregular long T2 signals with significant enhancement of the tumour shadow adjacent to the posterior horns of the bilateral ventricles. After four cycles of chemotherapy post-surgery (Fig. 7d–f), most of the lesions adjacent to the posterior horns of the bilateral ventricles disappeared.

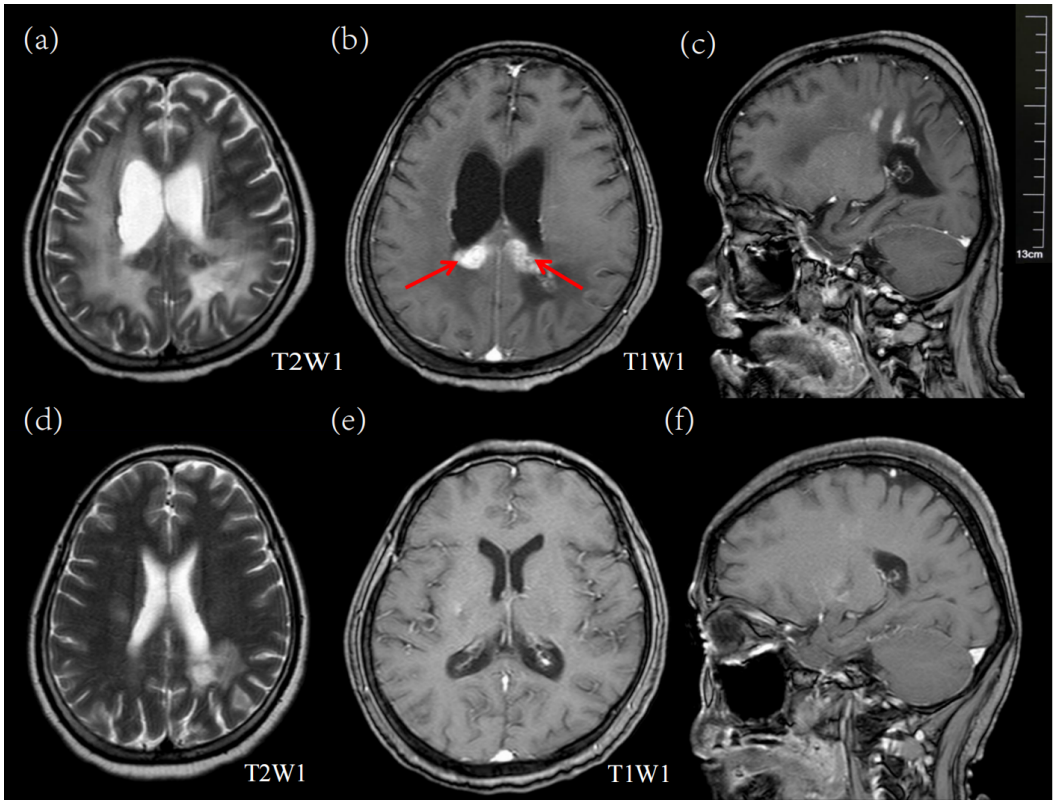

Fig. 7. Pre- and post-treatment brain MRI scans of a patient with chemotherapy after surgery. (a–c) Pre-treatment images: Axial T2WI (a) and axial/sagittal T1WI enhanced images (b,c) show irregular long T2 signals with significant enhancement of the tumour shadow adjacent to the posterior horns of the bilateral ventricles. (d–f) Post-surgical and chemotherapy images: Axial T2WI (d) and axial/sagittal T1WI enhanced images (e,f) show that most of the lesions adjacent to the posterior horns of the bilateral ventricles disappeared after four cycles of chemotherapy. Red arrows indicate areas of abnormal signal intensity, suggesting lesion regions.

Discussion

Our study conducted a retrospective cohort analysis of histologically confirmed PCNSL in patients using data from the SEER database to investigate the influence

of POCT on the survival of these patients. In our analysis, individuals in the POCT group displayed a superior median OS compared to those in the postoperative non-chemotherapy group ($p < 0.05$). Multivariable Cox regression results revealed that the tumour's primary location in the meninges and other neural systems, as well as the histological morphology of non-DLBCL, favored patient prognosis ($p < 0.05$). Additionally, with regard to the primary tumour location and surgical type, patients with PCNSL in the infratentorial region, supratentorial region, and brain overlap region, as well as those who underwent biopsy, STR, and GTR surgeries, had better postoperative survival outcomes in the POCT group compared to the non-chemotherapy group ($p < 0.05$). Furthermore, for patients who did not undergo POCT, the survival rate after STR surgery was higher than that after GTR and biopsy surgeries ($p < 0.05$). In addition, clinical MRI images of PCNSL patients at our institution demonstrated tumour improvement following tumour resection and POCT.

Characterized by frequent early and widespread dissemination and involvement of deep brain structures, PCNSL lesions typically exhibit marked enhancement and infiltrative features, and they are often situated deep within the periventricular spaces, making surgical resection challenging (Schlegel, 2009). The key to the treatment of PCNSL currently relies on high-dose methotrexate induction and whole-brain radiation therapy, with outcomes steadily improving and complete remission increasingly achievable (Gavrilovic et al, 2006; Ramadan et al, 2022). Prior research suggested that, before standardization, surgical resection results in worse outcomes compared to biopsy, discouraging surgical interventions for PCNSL (Ferreri et al, 2023; Berry and Simpson, 1981; Jellinger et al, 1975). This is mainly due to the multifocal and invasive nature of PCNSL under the microscope, which may extend beyond the visible boundary of the lesion, or the lesion is usually located deep in the periventricular region (Henry et al, 1974; Hoang-Xuan et al, 2023). Meanwhile, a historical series of studies showed that surgical resection (including complete surgical resection of GTR and partial surgical resection of STR) has no significant survival advantage, and even leads to increased mortality (Bataille et al, 2000; Bellinzona et al, 2005; Chukwueke et al, 2022; Shao et al, 2021). However, with the standardization of adjuvant chemoradiotherapy and improvements in neuroimaging and surgical techniques, there has been renewed interest in the potential role of surgical resection in the management of PCNSL. Recent studies showed that resection may bring therapeutic benefits to selected patients (Rae et al, 2019; Weller et al, 2012; Wu et al, 2021). For example, in a study involving 526 PCNSL patients, 67 of whom underwent gross total resection, the OS of the biopsy group was significantly shorter than that of the resection group, even when controlling for age and Karnofsky Performance Status (KPS) (Weller et al, 2012). In addition, a study from the SEER database showed that multimodal treatment with surgical resection and chemotherapy results in better OS and disease-specific survival than chemotherapy alone (Tang et al, 2022).

The major challenge in the treatment of patients with PCNSL lies in the radiographic assessment of the response to treatment and minimal residual disease in the brain. The standard radiological measure for response assessment is the 1990 Mac-

Donald criteria, which are based on contrast enhancement dimensions on T-1 MRI and extrapolated from studies of malignant gliomas (Macdonald et al, 1990). MRI and other imaging examinations can provide the best visualization resolution, and can noninvasively display the location, size and shape of intracranial lesions, which is helpful for the diagnosis, staging and efficacy monitoring of PCNSL (Chen et al, 2022). The partial results of MRI images of the patients from our hospital showed a beneficial effect of surgical resection on the tumour response, which was consistent with the results obtained from the SEER database, further verifying and supporting the conclusion that postoperative chemotherapy is beneficial for the survival of patients in this study. Therefore, this is an important reference for clinicians in the diagnosis and evaluation of PCNSL.

Moreover, study reported that patients who undergo GTR benefit the most, while the advantages of partial resection of brain lobes are not as pronounced, likely due to an increased rate of postoperative complications affecting patient prognosis (Yang et al, 2021). Another related study reported that PCNSL patients benefit the most from GTR and a chemotherapy regimen, even after adjusting for patient age, sex, and pathological subtypes (Kreher et al, 2015). Furthermore, in subgroup analysis, it was found that for PCNSL patients not receiving POCT, STR surgery had a higher survival rate than GTR. However, this survival advantage disappeared for PCNSL patients receiving POCT, and there was no significant difference in prognosis between the two surgical types. This suggests that the survival benefits of POCT are widespread for PCNSL patients and are not influenced by the type of surgical treatment. Therefore, for PCNSL patients who underwent surgery and had no contraindications for chemotherapy, POCT was recommended to extend their lifespan.

Age is a significant adverse prognostic factor for PCNSL (Ahn et al, 2017; Jang et al, 2016; Liu et al, 2020). Research has reported that with increasing age, the survival of patients with PCNSL significantly decreases (Tang et al, 2022), and this result is consistent with previous findings. It is also in line with the general phenomenon that many cancers are associated with lower survival rates in older individuals. Additionally, our study suggested that PCNSL patients had better survival when the primary tumour location was in the supratentorial area, infratentorial area, or overlapping brain area when they received POCT. Most PCNSL lesions were located in the supratentorial area, with a smaller percentage in the infratentorial area (Bhagavathi and Wilson, 2008). However, there is limited research on the impact of primary tumour location on POCT outcomes. It is currently believed that deep brain involvement in PCNSL leads to regional differences in vascular supply and transport, resulting in variations in patient chemotherapy outcomes (Lee et al, 2017; Meling et al, 2018). Regarding tumour histological type, our results showed that the survival of non-DLBCL patients was better than that of DLBCL patients, possibly due to the less aggressive nature of non-DLBCL (Shan and Hu, 2018).

Although our study clearly demonstrated the benefits of POCT for PCNSL patients, there are some limitations. Firstly, it is important to note that due to the inherent constraints of the SEER database, several specific factors were not examined in this study, such as lesion features, patient performance status, clinical

symptoms, comorbidities, recurrence status, and specific types of radiotherapy and chemotherapy. Secondly, as this is a retrospective study, the presence of treatment selection bias is an inherent limitation that cannot be entirely eliminated. For instance, patients with tumours situated in the supratentorial region, who were with low surgical risk or initially misdiagnosed as gliomas, were more inclined to opt for surgical intervention. Finally, while the current research supports the beneficial influence of POCT on the clinical survival outcomes of PCNSL individuals, further randomized controlled trials are necessary to validate and refine our findings, incorporating more dimensions of information.

Conclusion

This study investigated the impact of postoperative chemotherapy on the survival of patients with PCNSL. The results indicated that patients who received postoperative chemotherapy had significantly better survival rates compared to those who did not receive chemotherapy. Tumours originating in the meninges and other parts of the nervous system, as well as non-DLBCL histological types, were identified as favourable prognostic factors. Our results highlight the important role of postoperative chemotherapy in improving the prognosis of PCNSL patients regardless of the surgical treatment modality. Therefore, postoperative chemotherapy should be recommended for patients with PCNSL who receive surgical treatment and have no contraindications to chemotherapy to prolong their survival. At the same time, it is necessary to conduct further randomized controlled trials to include more dimensions of information to verify and improve our findings. In conclusion, this study provides a strong basis for clinicians to develop personalized treatment plans and promote the realization of precision medicine.

Key Points

- Patients with primary central nervous system lymphoma (PCNSL) who underwent postoperative chemotherapy exhibited a significantly improved survival prognosis than those who did not receive chemotherapy.
- Age older than 60 years and absence of postoperative chemotherapy were identified as independent prognostic risk factors for PCNSL patients. Additionally, primary tumour locations in the meninges and other nervous system regions, and histological morphologies such as non-diffuse large B-cell lymphoma and non-Hodgkin lymphoma, were associated with favorable patient outcomes.
- PCNSL patients with tumours located in the infratentorial, supratentorial, or brain overlap regions, as well as those who underwent biopsy, STR, or GTR procedures, demonstrated significantly superior postoperative survival outcomes when receiving chemotherapy.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are available in the [SEER database: https://seer.cancer.gov/] repository.

Author Contributions

YSC, SSZ and SYZ designed the research study. HL and LZW performed the research. SQC analyzed the data. YSC and SSZ wrote the first draft. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Patient informed consent has been waived by the Committee of Zhangzhou Affiliated Hospital of Fujian Medical University [2023LWB331]. The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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