Primary central nervous system lymphoma in the United States, 1975–2017

Chenglan Lv*, Jing Wang*¹, Min Zhou*, Jing-Yan Xu*, Bing Chen and Yuan Wan

Abstract

Background: Primary central nervous system lymphoma (PCNSL) has received more attention because of an inferior prognosis. Less is known about the incidence rate, histological type, and survival rate of PCNSL, especially in the 2010s.

Methods: Data of PCNSL from the Surveillance, Epidemiology, and End Results (SEER) registry database (SEER 9 registries and SEER 18 registries) were used. Incidence was estimated by age, gender, race, site, and histological type. Trends were analyzed using joinpoint regression and described as annual percent change (APC) and average annual percent change (AAPC). Five-year overall survival estimates were compared using log-rank tests.

Results: Most PCNSL occurred in the brain, followed by the spinal cord. The most frequent histological type of PCNSL was diffuse large B-cell lymphoma, followed by marginal zone lymphoma. Incidence rate increased from 0.1/100,000 to 0.5/100,000 with an AAPC of 5.3% from 1975 to 2017. Incidence rates varied greatly between the younger and older age population. The 5-year overall survival rates in SEER 9 registries and SEER 18 registries were 30.5% and 37.4%, respectively. Even though the 5-year overall survival rate significantly increased from 27.9% for the 1975–1979 time period to 44.8% for the 2010–2017 time period, survival benefit could not be expected for patients ≥ 60 years. The 5-year survival rate for elderly patients was about 30% in the 2010s.

Conclusion: With aging, the incidence of PCNSL in the elderly is increased. Over the past decade, no advances have been made in the treatment of elderly PCNSL. Prospective trials with PCNSL are warranted to improve the survival of elderly patients.

Keywords: incidence, overall survival, primary CNS lymphoma, SEER

Received: 3 June 2021; revised manuscript accepted: 19 November 2021.

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive extranodal non-Hodgkin lymphoma that emerges directly from the central nervous system (CNS), including the eye, leptomeninges, brain, and spinal cord. Like other lymphomas, it is initially sensitive to chemo- and radiation therapy. Unfortunately, the prognosis for PCNSL remains poor in comparison with systemic lymphomas outside the CNS. PCNSL is a rare disease comprising about 4% of newly diagnosed CNS tumors and only 4–6% of all extranodal lymphomas,¹ with an annual incidence rate of 0.5 per 100,000 in the United States.² The incidence of PCNSL is steadily increasing as the population ages.³ A study⁴ based on the Surveillance, Epidemiology, and End Results (SEER) database showed a peak incidence rate of PCNSL in the 1990s because of the HIV epidemic.^{5,6} Risk of PCNSL increases with age and the incidence in older people is rising over time. In the past decade, a rising incidence rate of 4.3 per 100,000 has been observed in patients aged 70–79 years.⁷ However, primary intraocular lymphoma (PIOL), a subset of PCNSL, was not included in several recent studies.^{3,7,8} Hence, we

Ther Adv Hematol

2022, Vol. 13: 1–9

DOI: 10.1177/ 20406207211066166

© The Author(s), 2022. Article reuse guidelines: sagepub.com/journalspermissions

Correspondence to: Jing Wang

Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, P.R. China

yz3466599@hotmail.com

Bing Chen Department of

Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, P.R. China

chenbing2004@126.com Yuan Wan

The Pq Laboratory of

BiomeDx/Rx, Department of Biomedical Engineering, Binghamton University State University of New York, Binghamton, NY, USA

ywan@binghamton.edu

Chenglan Lv Min Zhou

Jing-Yan Xu Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, P.R. China

*These authors have contributed equally to this work and share first authorship.

journals.sagepub.com/home/tah



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

performed a retrospective cohort study of patients with histologically confirmed PCNSL using the SEER database to update the incidence rate, trends, and survival of PCNSL, and to characterize its pathological features.

Methods

Data source

Data of PCNSL were collected from the SEER program of the National Cancer Institute (NCI). Non-Hodgkin's lymphoma (NHL) was defined using the SEER site recoding based on the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues (2008).9 PIOL was included in our study, and primary ocular adnexal lymphoma, originating from conjunctiva, lacrimal gland, orbit, eyelid, and extraocular muscle, was excluded from this study. All NHLs with topography codes C69.1–C69.4, C69.9, C70.0, C70.1, C70.9-C72.5, C72.8, and C72.9 were classified as PCNSL. We included data from two cohorts of patients: SEER 9 registries (1975-2017, Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Puget Sound) and SEER 18 registries (2000-2017, SEER 9 plus Los Angeles, San Jose-Monterey, rural Georgia, Alaska, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey). The SEER 9 registries were selected for this analysis in order to compare historical trends starting from 1970s. This study followed the guidelines of the **STROBE** (Strengthening the Reporting of Observational Studies in Epidemiology) statement.10

Statistical analyses

To maximize the representativeness of our study, we calculated the 1975–2017 incidences using SEER 9 registries, and the 2000–2017 incidences using SEER 18 registries. All incidences were age-adjusted to the 2000 US standard population and were calculated using SEER*Stat (version 8.3.8). The Joinpoint Regression Program (version 4.8.0.1) was used to compare temporal trends and to estimate the average estimated annual percent change (APC). Time from PCNSL diagnosis to death from any cause was evaluated using SEER*Stat (version 8.3.8). We provided overall survival (OS) by gender, race, age, site, time of diagnosis, and pathological type with a maximum follow-up time of 40 years using data from the SEER 9 registries. To evaluate the recent trends in survival, we also conducted survival analyses from the SEER 18 registries. OS curves were constructed using the Kaplan–Meier method and compared with the log-rank test. Univariable and multivariable Cox regression analyses were performed using GraphPad Prism (version 8.0), and only variables with $p \le 0.2$ in univariate analysis were included in multivariate analysis. Two-sided tests were used, and a p value of less than 0.05 was considered significant.

Results

Clinical character

In total, we identified 3841 cases of PCNSL in SEER 9 registries and 6647 cases in SEER 18 registries. Table 1 shows patient characteristics. The median age at diagnosis in SEER 9 registries was 63.0 years, and the median age in SEER 18 registries was 65.0 years. PCNSL in males was found to be slightly more common than in females. More than 50% of PCNSL patients were White or elderly who were >60 years of age. Most PCNSLs occurred in the brain, followed by the spinal cord. The most common histological type of PCNSL was diffuse large B-cell lymphoma (DLBCL), followed by marginal zone lymphoma (MZL) and rarely mantle-cell lymphoma (MCL) or peripheral T-cell lymphoma (PTL). The distribution of histological type of PCNSL varied greatly according to the diseased parts (Figure 1).

Incidence and trend of PCNSL

The age-adjusted incidence rate of PCNSL increased from 0.1/100,000 in 1975 to 0.5/100,000 in 2017, a fivefold increase (Figure 2). In the 2010s, the incidence rate of PCNSL ranged from 0.4 to 0.5 per 100,000 in the SEER database. The incidence rates of PCNSL varied greatly between age groups, ranging from 0.2 in patients under 60 years to around 2.0 in patients above 60 years over the last decade (Supplemental Appendix). Particularly, in 2016, an incidence rates of 3.2 per 100,000 was observed in patients aged 70–79 years (Figure 3), and incidence rates between other groups did not differ much. PCNSL incidence significantly increased with an

average annual percent change (AAPC) of 14.2% from 1975 to 1991 and significantly decreased with an AAPC of -3.3% from 1991 to 2002 (Figure 2). PCNSL APCs in SEER 18 cohort were higher than the APCs in SEER 9 cohort after 2005. Statistical significance was reached in SEER 18 cohort (Figure 2). The incidence of PCNSL had been increasing steadily after 2000. By comparison, a statistically significantly increased trend was observed in patients aged 70–79 years with an AAPC of 2.4% from 2000 to 2017 (Figure 3).

OS of PCNSL

The median follow-up time was 12 months. The 5-year OS in SEER 9 registries and SEER 18 registries was 30.5% and 37.4%, respectively. Sexrelated survival difference was observed in SEER 9 (Supplemental Appendix). No gender-related survival difference was observed on the Kaplan-Meier curve in SEER 18 (Figure 4). There was no difference in survival between White and Black race (Figure 4). Older PCNSL age (≥ 60 years old) was associated with worse OS (Figure 4). Brain parenchyma PCNSL had the worst prognosis compared with other sites (Figure 4). Also, significantly improved OS was observed in patients diagnosed in the 2010s in comparison with any other years (Figure 4). However, the prognosis of patients above 60 years remained poor, with a 5-year OS rate of about 30% (Supplemental Appendix). Multivariate analysis showed age, gender, time of diagnosis, and pathological type were independent indicators of prognosis. Race and site were not prognostic indicators. The detailed information is shown in the Supplemental Appendix.

Discussion

Our study described the incidence rate, histology type, and outcomes of PCNSL patients in the United States based on the SEER database. In our analysis, the incidence of PCNSL steadily increased from 1975 to 2017, which could be due to improvement in access to care, diagnostic methods, and awareness. The sharp spike in the early 1990s was triggered by population age and the HIV epidemic.^{5,6} Regardless of age, the incidence of PCNSL was higher in males.⁴ Incidence varied greatly by age group. In a population under age 40, incidence significantly decreased after 1996. The population people over 60 years is **Table 1.** Characteristics of PCNSL in SEER 18 registries (2000–2017) and SEER 9 registries (1975–2017).

No. ModNo. ModS mple size64473841Me lange lyears)5154.743614.73A p mu220.31310.3110 - 1641.01210.7120 - 21372.14213.2130 - 3734815.313011.0140 - 477310.115011.3150 - 57112414.915011.3160 - 671757 624.01702.03.0170 - 771758 624.01361.93197 - 1979-141.13361.93197 - 1979-221.43.14361.93197 - 1979-221.43.1431.11197 - 1979-221.43.141.21.21.31197 - 1979-221.43.141.21.21.31197 - 1979-221.43.141.21.21.31197 - 1979-221.43.141.21.21.31197 - 1979-21.14.141.21.21.31197 - 1979-21.14.141.21.21.31198 - 198 - 198322.14.811.21.21.31197 - 1979-21.14.141.21.21.31198 - 1983161.7131.61.21.31198 - 19931.61.21.3131.61.21.31199 - 19953.91.81.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21.31191 - 191120.12.1131.61.21	Characteristics	SEER 18 registries 2000–2017	SEER 9 registries 1975–2017		
<table-container>Simple size6447841R6154.74814.73R216.74814.73R210.73810.73R210.74810.71R212.71372.14R321.733010.14R7310.1750113.14R7370.1450113.14R727.71752.64R727.7474113.03R727.7474113.03R727.7474113.03R727.7474113.03R727.7474113.03R727.74741.73R741.73741.93R727.74741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.73R741.73741.74R741.73741.74R741.73741.74R741.73741.74R741.73741.74R741.73741.74R741.74741.74R741.74741.74R741.74741.74R741.74741.74R741.74741.74R741.74741.74<trr< td=""><td></td><td>No. (%)</td><td>No. (%)</td></trr<></table-container>		No. (%)	No. (%)		
HeatSole StartSole StartSole StartAAA	Sample size	6647	3841		
jerup (years)□-□22 0.313 0.3□-□64 1.028 0.7□-□137 2.128 0.7□-□34 5.340 10.4□-□73 10.153 13.1□-□124 16.950 15.3□-□1757 26.490 2 23.3□-□757 26.491 6 2.3□-□74 11.532 19.3□-□74 11.532 19.319-□94 11.532 19.3192-1979-1146 (27.3192-1979-2142 19.3192-1979-2142 19.3192-1979-2142 19.3192-1979322 (48.5)1123 19.3192-1979322 (48.5)1123 19.3193-1989340 52.1143 19.3193-1989346 152.1143 19.3193-199318 1.4318 19.3193139 181.1318 19.3193141 19.3318 19.3193141 19.3318 19.3194539 181.1318 19.3194103 19.1318 19.3194103 19.1318 19.3194103 19.1318 19.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3194104.3319.3195194.3319.31951	Median age (years), IQR	65 (54.74)	63 (48.73)		
□-P22 (0.3)13 (0.3)□-1964 (1.0)28 (0.7)□-29137 (2.1)12 (13.2)□-3964 (5.3)60 (10.4)□-49673 (10.1)503 (13.1)□-591124 (16.9)594 (15.5)□-79757 (26.4)902 (23.5)□-79764 (11.5)362 (9.5)□-79764 (11.5)362 (9.5)□197-1979-74 (1.9)362 (9.5)197-1979-74 (1.9)1046 (27.2)197-1979-74 (1.9)1046 (27.2)197-1979322 (48.5)1123 (29.3)197-1979322 (48.5)1123 (29.3)197-1979345 (51.7)1463 (43.3)197-1979346 (52.1)1463 (43.3)197-19793187 (47.9)1663 (43.3)197-19793187 (47.9)1663 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (43.3)197-19793187 (47.9)3163 (47.9)197-19793187 (47.9)3163 (47.9)197-19793187 (47.9)3163 (47.9)197-19793187 (47.9)3163 (47.9)197-19793187 (47.9)3163 (47.9)197-19793187 (47.9)3163 (47.9)197-19793197 (47.9)319 (47.9) <t< td=""><td>Age group (years)</td><td></td><td></td></t<>	Age group (years)				
10-1964 (1.0)28 (0.7)20-29137 (2.1)12 (13.2)30-3764 (5.3)40 (10.4)4-49673 (10.1)50 (13.1)50-57124 (16.9)50 (15.3)60-69757 (26.4)902 (23.5)70-79758 (26.4)916 (23.8)80-79758 (26.4)916 (23.8)19-79764 (11.5)362 (9.5)1975-1979-64 (19.1)1975-1979-404 (19.2)1970-2009322 (48.5)104 (27.2)2000-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009322 (48.5)1171 (30.5)2100-2009320 (51.5)1171 (30.5)2100-2009320 (51.1)3180 (47.9)2100-20093187 (47.9)3163 (30.8)2100-20093197 (47.9)3198 (71.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9)2100-2009321 (30.1)3198 (72.9) <tr< td=""><td>0-9</td><td>22 (0.3)</td><td>13 (0.3)</td></tr<>	0-9	22 (0.3)	13 (0.3)		
2□-2137 (2.1)121 (3.2)3□-3348 (5.3)400 (10.4)4□-4673 (10.1)503 (13.1)5□-51124 (16.9)504 (15.5)4□-4757 (26.4)902 (23.5)7□-79768 (15.6)916 (23.8)8□-4764 (11.5)362 (9.5)1975-1979-046 (15.2)362 (9.5)1975-1979-074 (1.9)1980-1989-0427 (11.1)1990-2009322 (48.5)1123 (29.3)2010-20193425 (51.5)1123 (29.3)3101-20173425 (51.5)1171 (30.5)8	10–19	64 (1.0)	28 (0.7)		
30-39348 (5.3)400 (10.4)40-49673 (10.1)503 (13.1)50-59124 (16.9)596 (15.5)60-691757 (26.4)902 (23.5)70-79758 (26.4)916 (23.8)70-79758 (26.4)916 (23.8)71-79764 (11.5)362 (9.5)19-5-1979-74 (1.9)1980-1989-427 (11.1)1990-1999322 (48.5)1046 (27.2)2010-2009322 (48.5)1123 (29.3)2010-2009322 (48.5)1123 (29.3)2010-2009346 (52.1)1171 (30.5)3010-2017346 (52.1)2178 (56.7)8	20–29	137 (2.1)	121 (3.2)		
↓□-9673 (10.1)503 (13.1)□□-501124 (16.9)506 (15.5)↓□-70757 (26.4)902 (23.5)□□-70758 (26.4)916 (23.8)□□-70758 (26.4)362 (0.5)□□-1010-74 (1.9)□□-2017-1046 (27.2)□□-2017322 (48.5)1123 (29.3)□□-20173222 (48.5)1123 (29.3)□□-20173425 (51.5)1171 (30.5)□□-2017346 (52.1)1173 (30.5)□□-2017346 (52.1)163 (43.3)□□-2017364 (52.1)163 (43.3)□□-2017361 (51.1)3120 (81.2)□□-2017363 (18.1)3120 (81.2)□□-2017363 (18.1)3120 (81.2)□□-2017363 (18.1)3120 (81.2)□□-2017303 (8.6)10.0)□□-2017303 (8.6)10.0)□□-2017321 (81.1)3120 (81.2)□□-2017323 (18.1)3120 (81.2)□□-2017331 (8.1)3120 (81.2)□□-2017321 (81.1)3120 (81.2)□□-2017321 (81.1)3120 (81.2)□□-2017321 (81.1)3120 (81.2)□□-2017321 (81.1)3120 (81.2)□□-2017321 (81.2)310 (81.2)□□-2017321 (81.2)3120 (81.2)□□-2017321 (81.2)310 (81.2)□□-2017321 (81.2)310 (81.2)□□-2017321 (81.2)310 (81.2)□□-2017321 (81.2)310 (81.2)□□-2017321 (81.2)310	30–39	348 (5.3)	400 (10.4)		
Image: Some service s	40-49	673 (10.1)	503 (13.1)		
♦-691757 (26.4)902 (23.5)P-791758 (26.4)916 (23.8)80-4764 (11.5)362 (9.5)19-5-74 (1.9)1975-1979-427 (11.1)1970-1989-1046 (27.2)200-20093222 (48.5)1123 (29.3)200-20093222 (48.5)1123 (29.3)200-20093222 (48.5)1171 (30.5)200-20093222 (48.5)1171 (30.5)200-20093220 (48.5)1171 (30.5)200-20093425 (51.5)1173 (30.5)201-20173460 (52.1)1663 (43.3)201-2017340 (52.1)3108 (43.3)201-20175391 (81.1)3120 (81.2)P-1-20175391 (81.1)3120 (81.2)101-3120 (30.1)310 (30.2)101-3320 (51.1)310 (30.2)101-3320 (52.1)10 (30.2)101-3112 (30.2)316 (30.2)101-3320 (51.2)328 (72.6)101-3112 (30.2)112 (30.2)101-3112 (30.2)310 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2)101-3112 (30.2)112 (30.2) <td>50–59</td> <td>1124 (16.9)</td> <td>596 (15.5)</td>	50–59	1124 (16.9)	596 (15.5)		
P-791758 (26.4)916 (23.8)80+54 (11.5)362 (9.5)1975-1979-74 (1.9)1975-1979-427 (11.1)1970-1989-1046 (27.2)2000-20093222 (48.5)1123 (29.3)2010-20173222 (48.5)1123 (29.3)2010-20173425 (51.5)1171 (30.5)what3460 (52.1)171 (30.5)what3187 (47.9)1663 (43.3)what5391 (81.1)3120 (81.2)what5391 (81.1)3120 (81.2)what745 (11.2)381 (9.9)0ther745 (11.2)381 (9.9)0ther320 (5)10 (0.3)what32 (0.5)10 (0.3)what32 (0.5)381 (9.2)what310 (30.2)310 (30.2)what32 (0.5)310 (8.2)what32 (0.5)310 (9.2)what32 (0.5)310 (9.2)what310 (9.2)310 (60-69	1757 (26.4)	902 (23.5)		
B0+764 (11.5)362 (9.5)IPT5-1979-74 (1.9)1975-1979-427 (11.1)1980-1989-1046 (27.2)2000-20093222 (48.5)1023 (29.3)2010-20173425 (51.5)1171 (30.5)Geruer3460 (52.1)171 (30.5)Male3460 (52.1)2178 (56.7)Male3187 (47.9)1663 (43.3)Fernale3197 (47.9)3120 (81.2)Black479 (7.2)330 (8.6)Øther745 (11.2)381 (9.9)Other32 (0.5)10 (0.3)Furlown32 (0.5)10 (0.3)B-cell non-Hodgkin lymphoma198 (78.2)2788 (72.6)Marginal zone lymphom205 (3.1)67 (1.7)	70–79	1758 (26.4)	916 (23.8)		
IPIF-1979 - 74(1.9) 1975-1979 - 427(11.1) 1970-1979 - 1046(27.2) 1970-2009 3222(48.5) 1123 (29.3) 2010-2017 3425 (51.5) 1171 (30.5) Male 3460 (52.1) 171 (30.5) Male 3460 (52.1) 2178 (56.7) Male 3187 (47.9) 1663 (43.3) Image 3187 (47.9) 1663 (43.3) Image 3197 (47.9) 3120 (81.2) Image 3197 (47.2) 3120 (81.2) Image 745 (11.2) 319 (81.2) Image 745 (11.2) 381 (9.9) Image 210.5) 10 (0.3) Image 210.5) 10 (0.3) Image 110 (9.3) 10 (9.3) Image	80+	764 (11.5)	362 (9.5)		
1975-1979 - 74 (1.9) 1980-1989 - 427 (11.1) 1990-1999 - 1046 (27.2) 2000-2009 3222 (48.5) 1123 (29.3) 2010-2017 3425 (51.5) 1171 (30.5) wale 3460 (52.1) 171 (30.5) Female 3460 (52.1) 2178 (56.7) Male 3187 (47.9) 1663 (43.3) Female 3187 (47.9) 1663 (43.3) White 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 0ther 32 (0.5) 10 (0.3) F-cell non-Hodgkin Lymphone 320 (57.2) 381 (9.2) Infifuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone Lymphone 205 (3.1) 67 (1.7)	Year of diagnosis				
1980-1989 - 427 (11.1) 1990-1999 - 1046 (27.2) 2000-2009 3222 (48.5) 1123 (29.3) 2010-2017 3425 (51.5) 1171 (30.5) whate 3426 (52.1) 1171 (30.5) Formate 3187 (47.9) 2178 (56.7) Formate 3187 (47.9) 1663 (43.3) Formate 5391 (81.1) 3120 (81.2) White 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 0thoman 32 (0.5) 10 (0.3) Pointshown 32 (0.5) 10 (0.3) piffuse large B-cell 5198 (78.2) 2788 (72.6) Infingenda 205 (3.1) 67 (1.7)	1975–1979	-	74 (1.9)		
1990-1999 - 1046 (27.2) 2000-2009 3222 (48.5) 1123 (29.3) 2010-2017 3425 (51.5) 1171 (30.5) B 3425 (51.5) 1171 (30.5) Male 3460 (52.1) 2178 (56.7) Male 3460 (52.1) 1663 (43.3) Female 3187 (47.9) 1663 (43.3) Nhite 5391 (81.1) 3120 (81.2) White 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 10 known 32 (0.5) 10 (0.3) Percelt non-Hodgkin lymphom 32 (0.5) 10 (0.3) Diffuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone lymphoma 205 (3.1) 67 (1.7)	1980–1989	-	427 (11.1)		
$2 \cup 0 - 2 \cup 0 ?$ $3222 (48.5)$ $1123 (29.3)$ $2 \cup -2 \cup 1 ?$ $3425 (51.5)$ $1171 (30.5)$ $F = 0$ $3460 (52.1)$ $2178 (56.7)$ $M = 0$ $3460 (52.1)$ $2178 (56.7)$ $P = 0$ $3187 (47.9)$ $1663 (43.3)$ $P = 0$ $3187 (47.9)$ $1663 (43.3)$ $P = 0$ $3187 (47.9)$ $1663 (43.3)$ $P = 0$ $5391 (81.1)$ $3120 (81.2)$ $P = 0$ $745 (11.2)$ $330 (8.6)$ $0 + 1 \circ 1$ $32 (0.5)$ $30 (8.6)$ $0 + 1 \circ 1$ $32 (0.5)$ $10 (0.3)$ $P = 0$ $745 (11.2)$ $381 (9.9)$ $0 + 1 \circ 1$ $32 (0.5)$ $10 (0.3)$ $P = 0$ $9 = 0 = 1 \circ 1$	1990–1999	-	1046 (27.2)		
2010-2017 3425 (51.5) 1171 (30.5) B 3460 (52.1) 2178 (56.7) Male 3460 (52.1) 1663 (43.3) Female 3187 (47.9) 1663 (43.3) R 5391 (81.1) 3120 (81.2) White 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) other 32 (0.5) 10 (0.3) P 210 (81.2) 10 (0.3) Diffuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone lymphoma 205 (3.1) 67 (1.7)	2000-2009	3222 (48.5)	1123 (29.3)		
	2010-2017	3425 (51.5)	1171 (30.5)		
Male 3460 (52.1) 2178 (56.7) F male 3187 (47.9) 1663 (43.3) Race 5391 (81.1) 3120 (81.2) Mhie 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 1mknown 32 (0.5) 10 (0.3) P=tusey 10 (0.3) 10 (0.3) Diffuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone lymphoma 205 (3.1) 67 (1.7)	Gender				
Female 3187 (47.9) 1663 (43.3) R= 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 10hrown 32 (0.5) 10 (0.3) P= 52 (0.5) 10 (0.3) P= 52 (0.5) 10 (0.3) Diffuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone lymphoma 205 (3.1) 67 (1.7)	Male	3460 (52.1)	2178 (56.7)		
Race 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) 0ther 32 (0.5) 10 (0.3) Particular Secondary	Female	3187 (47.9)	1663 (43.3)		
White 5391 (81.1) 3120 (81.2) Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) Uhknown 32 (0.5) 10 (0.3) Pathodykin Lymphoma 32 (0.5) 10 (0.3) Black 5198 (78.2) 2788 (72.6) Marginal zone Lymphoma 205 (3.1) 67 (1.7)	Race				
Black 479 (7.2) 330 (8.6) 0ther 745 (11.2) 381 (9.9) Unknown 32 (0.5) 10 (0.3) Pathology 10 (0.3) 10 (0.3) B-cell non-Hodgkin lymphoma 5198 (78.2) 2788 (72.6) Imaginal zone lymphoma 205 (3.1) 67 (1.7)	White	5391 (81.1)	3120 (81.2)		
○ther 745 (11.2) 381 (9.9) □hrown 32 (0.5) 10 (0.3) P=t+bogy 52 (0.5) 10 (0.3) B-cell non-Hodgkin lymphoma 5198 (78.2) 2788 (72.6) Diffuse large B-cell 5198 (78.2) 67 (1.7)	Black	479 (7.2)	330 (8.6)		
Unknown 32 (0.5) 10 (0.3) Patkogy B-cell non-Hodgkin lymphoma 5198 (78.2) 2788 (72.6) Diffuse large B-cell lymphoma 205 (3.1) 67 (1.7)	Other	745 (11.2)	381 (9.9)		
Pathology B-cell non-Hodgkin lymphoma Diffuse large B-cell 5198 (78.2) 2788 (72.6) Marginal zone lymphoma 205 (3.1) 67 (1.7)	Unknown	32 (0.5)	10 (0.3)		
B-cell non-Hodgkin lymphoma Diffuse large B-cell 5198 (78.2) 2788 (72.6) lymphoma Marginal zone lymphoma 205 (3.1) 67 (1.7)	Pathology				
Diffuse large B-cell 5198 (78.2) 2788 (72.6) lymphoma 205 (3.1) 67 (1.7)	B-cell non-Hodgkin lymphoma				
Marginal zone lymphoma 205 (3.1) 67 (1.7)	Diffuse large B-cell lymphoma	5198 (78.2)	2788 (72.6)		
	Marginal zone lymphoma	205 (3.1)	67 (1.7)		

Table 1. (Continued)

C	haracteristics	SEER 18 registries 2000–2017	SEER 9 registries 1975–2017	
		No. (%)	No. (%)	
	Follicular lymphoma	176 (2.6)	99 (2.6)	
	Small lymphocytic lymphoma	47 (0.7)	69 (1.8)	
	Mantle-cell lymphoma	17 (0.3)	12 (0.3)	
	T-cell non-Hodgkin lymphoma			
	Peripheral T-cell lymphoma	112 (1.7)	45 (1.2)	
Site				
	Eye	313 (4.7)	169 (4.4)	
	Meninges	73 (1.1)	55 (1.4)	
	Brain	5229 (78.7)	2964 (77.2)	
	Spinal cord	1032 (15.5)	653 (17.0)	

IQR, interquartile range; PCNSL, primary central nervous system lymphoma; SEER, Surveillance, Epidemiology, and End Results.

growing faster than any other age group, as a result of both longer life expectancy. More cases were observed in the elderly population, with the incidence being five times higher than the general population. Mendez *et al.*⁷ reported that the annual incidence of PCNSL in patients aged 70– 79 years was 4.32 per 100,000 population; however, only about 2.8 per 100,000 incidences were observed in our study and 1.90 per 100,000 incidences were observed by the patients aged \geq 75 years by Villano *et al.*¹ Incidence data of the study of Mendez *et al.* the Central Brain Tumor Registry of the United States (CBTRUS) were collected from database, which seems to be the main reason for the difference.

Miller *et al.*¹¹ reported more than 80% of PCNSL were DLBCL in Massachusetts General Hospital from 1958 to 1989. Sixty-two cases (86%) were classified as DLBCLs in the study of Camilleri-Broët *et al.*¹² Based on these studies, several reviews about PCNSL stated that approximately 90% of PCNSLs are DLBCL.^{13–17} Both data from SEER 9 registries and SEER 18 registries identified DLBCL as the most common histological type in approximately 80% of PCNSLs. The possible cause of the difference is that intraocular lymphoma was not included in this research. PIOL is a subtype of PCNSL, and 58% of PIOL carries a 50% risk of secondary involvement in the CNS beyond the eye.¹⁸ The most common PIOL by far is primary vitreoretinal lymphoma (PVRL).¹⁹ DLBCL is the most common PIOL with a prevalence estimated at 30–40%, followed by MZL. The histological type of intraocular lymphoma varies greatly according to whether the neoplasm predominantly involves the retina or the uvea. Primary retinal lymphomas are mostly aggressive, and primary choroidal lymphomas are typically low-grade lymphomas.²⁰

We investigated that age, sex, time of diagnosis, and pathological type were associated with survival in the multivariate analysis. Age is a strong negative prognostic factor in all lymphoma subtypes. Severity of physiologic dysfunction or comorbidity increasing with age can further affect the tolerability of therapy, which is associated with decreased survival.²¹ Many studies have confirmed that women have a longer cancer-specific survival than men.²²⁻²⁴ Male sex was an adverse risk factor in patients with DLBCL,25 follicular lymphoma (FL),²⁶ or MCL.²⁷ programmed cell death-1 (PD-1) Female sex was associated with decreased interferon signaling, transcription, cell cycle, and signaling,28 which might affect treatment responses. Female patients with MCL are more sensitive to lenalidomide than male patients in a UK study.29 The observation of improved survival after 2010 suggests current therapeutic approaches have improved survival.

Norden et al.³⁰ found out that despite treatment advances, the OS of PCNSL patients remains poor based on the SEER database from 1973 to 2004. In our study, the OS of PCNSL significantly improved from the 2000s, mainly because of the administration of high-dose methotrexate-based chemotherapy, immune-checkpoint inhibitors, and targeted molecules like the immunomodulatory drugs (IMiDs) or Bruton tyrosine kinase (BTK) inhibitor.³¹ OS of PCNSL in the 1990s was an exception with an OS rate of 17.8% in our analysis. Studies conducted by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) Lymphoma Study Group or the Chubu Radiation Oncology Group showed that the 5-year survival rate of PCNSL was 18.0% in the 1990s, which was consistent with our analysis.32 The French



Figure 1. Histology distribution of PCNSL by sites in SEER 18 registries.



Figure 2. Incidence of PCNSL and annual percent change (APC) trends in SEER 9 registries and SEER 18 registries (*p < 0.05).



Figure 3. Incidence of PCNSL and annual percent change (APC) trends based on patient age in SEER 18 registries (*p < 0.05).



Figure 4. Kaplan–Meier survival curves by subgroup in SEER 18 registries. (a) Gender, (b) Race, (c) Age,(d) Site, (e) Time of diagnosis, (f) Pathological type.

oculo-cerebral lymphoma network (LOC) We are unsure as to why survival declined in the 1990s. Study showed that age and sex were independent prognostic factors of PCNSL in the modern era.³³ Patients 60 years and older have an inferior prognosis even though the treatment of PCNSL has changed significantly over the past decades with superior survival. Our data underscore the urgency for clinical trials in elderly PCNSL to unearth mainstay options to evade poor prognosis.

The International Extranodal Lymphoma Study Group (IELSG) score³⁴ and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score³⁵ emphasized the crucial role of age in the evaluation of prognosis in PCNSL. Previous studies had shown that the incidence of PCNSL gradually increases with aging.^{3,7} Unlike other studies, we chose 60 years as the cutoff value for age to perform subgroup analysis. First, the incidence of PCNSL in patients aged 60-69 years was two times higher than patients who were 50-59 years in our analysis. Second, no difference in OS was observed between patients aged 40-49 years and patients aged 50-59 years. However, a significant difference in OS was observed between patients aged 50-59 years and patients aged 60-69 years. Using 50 years as the age cutoff, the study of Jahr et al.³⁶ failed to verify the age for prognostication of OS in PCNSL. Patients <60 years displayed a median OS of 53 *versus* 10 months for those ≥ 60 years (p < .05) in our study, which was consistent with the literature.³⁶

This study has some limitations to consider when discussing the current research. First, we must be aware that SEER 18 APCs are higher than SEER 9 APCs after 2005, because SEER 18 represents 28% of the US population versus 9% in SEER 9.37 However, the SEER data may not reflect true incidence due to regional variation. Second, we did not evaluate the impact of HIV on the incidence and survival of PCNSL. The HIV epidemic resulted in a sharp spike in PCNSL incidence in the early 1990s. The observation of reduced OS in the 1990s might be a reflection of increased mortality from HIV. Since 2000, remarkable progress has been made in the diagnosis and treatment of persons living with HIV. Mendez et al.7 reported that the incidence of PCNSL in patients with or without HIV was similar after 2000. Third, due to the nature of the SEER database, only six variables were selected for the Cox model. Survival analysis was unable to evaluate the value of the IELSG score³⁴ and the

MSKCC prognostic score.³⁵ The MSKCC score may be better than the IELSG score for prognostication of survival in PCNSL.³⁶ B cell receptor (BCR) Due to the lack of genetic data, we cannot evaluate the role of BTK inhibitor in PCNSL patients with mutations altering the subunit CD79B and MYD88.

In summary, the incidence of PCNSL in the elderly increased. OS of elderly PCNSL was not improved significantly over the past decade. Prospective trials in elderly patients are essential to finding a therapeutic option in clinical routine to improve the outcome.

Author contributions

Chenglan Lv: Data curation; Formal analysis; Methodology; Software; Visualization; Writing – original draft.

Jing Wang: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Min Zhou: Formal analysis; Software; Visualization; Visualization; Writing – review & editing; Writing – review & editing.

Jingyan Xu: Formal analysis; Methodology; Visualization; Writing – review & editing.

Bing Chen: Conceptualization; Supervision; Writing – review & editing.

Yuan Wan: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was partially supported by Binghamton University Faculty Startup Fund 910252-35. The work was partially supported by National Cancer Institute (1R01CA230339subawardand1R37CA255948).

ORCID iD

Jing Wang 9981-5530 https://orcid.org/0000-0001-

Supplemental material

Supplemental material for this article is available online.

References

- Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 2011; 105: 1414–1418.
- 2. O'Neill BP, Decker PA, Tieu C, *et al.* The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol* 2013; 88: 997–1000.
- Shiels MS, Pfeiffer RM, Besson C, et al. Trends in primary central nervous system lymphoma incidence and survival in the U.S. Br J Haematol 2016; 174: 417–424.
- Kadan-Lottick NS, Skluzacek MC and Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer* 2002; 95: 193–202.
- Hoffman S, Propp JM and McCarthy BJ. Temporal trends in incidence of primary brain tumors in the United States, 1985-1999. *Neuro Oncol* 2006; 8: 27–37.
- Haldorsen IS, Krossnes BK, Aarseth JH, et al. Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989-2003: time trends in a 15-year national survey. *Cancer 2007*; 110: 1803–1814.
- Mendez JS, Ostrom QT, Gittleman H, *et al.* The elderly left behind-changes in survival trends of primary central nervous system lymphoma over the past 4 decades. *Neuro Oncol* 2018; 20: 687–694.
- 8. Chihara D, Fowler NH, Oki Y, *et al.* Impact of histologic subtypes and treatment modality among patients with primary central nervous system lymphoma: a SEER database analysis. *Oncotarget* 2018; 9: 28897–28902.
- Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008.
- von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573–577.

- Miller DC, Hochberg FH, Harris NL, et al. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma: the Massachusetts General Hospital experience 1958-1989. Cancer 1994; 74: 1383–1397.
- Camilleri-Broët S, Martin A, Moreau A, et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. Groupe Ouest Est d'étude des Leucénies et Autres Maladies du Sang (GOELAMS). Am J Clin Pathol 1998; 110: 607–612.
- 13. Batchelor T and Loeffler JS. Primary CNS lymphoma. *J Clin Oncol* 2006; 24: 1281–1288.
- Grommes C and DeAngelis LM. Primary CNS Lymphoma. J Clin Oncol 2017; 35: 2410–2418.
- 15. Han CH and Batchelor TT. Diagnosis and management of primary central nervous system lymphoma. *Cancer* 2017; 123: 4314–4324.
- Grommes C, Nayak L, Tun HW, et al. Introduction of novel agents in the treatment of primary CNS lymphoma. *Neuro Oncol* 2019; 21: 306–313.
- Grommes C, Rubenstein JL, DeAngelis LM, et al. Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. *Neuro Oncol* 2019; 21: 296–305.
- Farrall AL and Smith JR. Eye involvement in primary central nervous system lymphoma. Surv Ophthalmol 2020; 65: 548–561.
- Tang LJ, Gu CL and Zhang P. Intraocular lymphoma. Int J Ophthalmol 2017; 10: 1301–1307.
- Coupland SE and Damato B. Understanding intraocular lymphomas. *Clin Exp Ophthalmol* 2008; 36: 564–578.
- 21. Pfreundschuh M. Age and sex in non-Hodgkin lymphoma therapy: it's not all created equal, or is it? *Am Soc Clin Oncol Educ Book* 2017; 37: 505–511.
- 22. Ellison LF. Differences in cancer survival in Canada by sex. *Health Rep* 2016; 27: 19–27.
- Cook MB, McGlynn KA, Devesa SS, et al. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 2011; 20: 1629–1637.
- Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009; 45: 1017–1027.
- 25. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14

with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* 2008; 9: 105–116.

- Monnereau A, Troussard X, Belot A, et al. Unbiased estimates of long-term net survival of hematological malignancy patients detailed by major subtypes in France. Int J Cancer 2013; 132: 2378–2387.
- Chandran R, Gardiner SK, Simon M, et al. Survival trends in mantle cell lymphoma in the United States over 16 years 1992-2007. Leuk Lymphoma 2012; 53: 1488–1493.
- Beheshti A, Neuberg D, McDonald JT, et al. The impact of age and sex in DLBCL: systems biology analyses identify distinct molecular changes and signaling networks. *Cancer Inform* 2015; 14: 141–148.
- 29. Eve HE, Carey S, Richardson SJ, *et al.* Singleagent lenalidomide in relapsed/refractory mantle cell lymphoma: results from a UK phase II study suggest activity and possible gender differences. *Br J Haematol* 2012; 159: 154–163.
- Norden AD, Drappatz J, Wen PY, et al. Survival among patients with primary central nervous system lymphoma, 1973-2004. *J Neurooncol* 2011; 101: 487–493.
- 31. Choi YS. Recent advances in the management of primary central nervous system lymphoma. *Blood Res* 2020; 55: S58–S62.

- Shibamoto Y, Ogino H, Hasegawa M, et al. Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s. Int J Radiat Oncol Biol Phys 2005; 62: 809–813.
- 33. Houillier C, Soussain C, Ghesquières H, et al. Management and outcome of primary CNS lymphoma in the modern era: an LOC network study. *Neurology* 2020; 94: e1027–e1039.
- Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol 2003; 21: 266–272.
- 35. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol 2006; 24: 5711–5715.
- 36. Jahr G, Broi MD, Holte H Jr, et al. Evaluation of Memorial Sloan-Kettering Cancer Center and International Extranodal Lymphoma Study Group prognostic scoring systems to predict overall survival in intracranial primary CNS lymphoma. Brain Behav 2018; 8: e00928.
- National Cancer Institute. Surveillance epidemiology and end results program, http:// www.seer.cancer.gov (accessed 15 April 2020).

Visit SAGE journals online journals.sagepub.com/ home/tah

SAGE journals