Primary treatment and Recent survival trends in patients with Primary Diffuse Large B-Cell Lymphoma of Central Nervous System,1995-2016: a population-based SEER analysis

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Research Article

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Abstract

Purpose

This retrospective cohort study aimed to evaluate primary treatment and recent survival trends in patients with primary diffuse large B-cell lymphoma of CNS from 1995 to 2016.

Methods

Using the SEER data, patients diagnosed with non-HIV associated PCNSL-DLBCL aged ⩾18 years between 1995 and 2016 were identified. The year of diagnosis was divided into the time periods-1(1995–2002), the time periods-2(2003–2012) and the time periods-3(2013–2016). We used Chi-square tests, the Kaplan–Meier method, log-rank test and Cox regression model in the analysis.

Results

Overall, 3760 patients were included. Both the use of radiotherapy alone and the application of combined chemoradiotherapy decreased significantly, following the wider use of chemotherapy alone during 1995–2016. There was a significant improvement in PCNSL cancer-specific survival (period-1: 13 months vs period-2: 19 months vs period-3: 41 months, $P < 0.001$). Survival of patients aged above 70 years did not change from the time period-1 to the time period-2 ($P = 0.101$). However, there was an increase in CSS from the time period-2 to the time period-3 in the elderly patients (period-2: 5 months vs period-3: 9 months, $P < 0.001$). On multivariable analyses, diagnosed in the time period-3 was significantly and independently associated with better CSS (HR 0.577, 95% CI 0.506–0.659).

Conclusions

Our analysis shows the use of radiotherapy in the treatment of PCNSL has waned over the study span. There was a significant improvement in CSS during 1995–2016, which reflected developments in treatment over time. The elderly patient population also gained a significant CSS benefit in the most recent period.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is among the most aggressive variants of extranodal non-Hodgkin lymphoma that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic involvement[1]. 90%-95% of PCNSLs are pathologically diagnosed as diffuse large B-cell lymphoma (DLBCL)[1, 2]. Progress in PCNSL treatment have been gained in the past two decades[3, 4].

PCNSL tends to be highly sensitive to both radiotherapy and chemotherapy. Whole-brain radiotherapy (WBRT) was regarded as the upfront treatment for PCNSL in the early 1990s and achieved a median overall survival (OS) of approximately 1 year[5]. In the 1990s, the HDMTX-based combination chemotherapy followed by additional consolidative WBRT was regarded ‘standard’ treatment for PCNSL by many researchers. The approach resulted in high response rate of more than 90%, median OS of 12–60 months and 2-years OS of 60–85% in several prospective trials[6–9]. A non-cross-resistant conventional chemotherapy or high-dose chemotherapy with autologous stem cell transplantation showed good outcomes as options for consolidation therapy in some studies in the 2000s[10–13]. One of the consolidation regimens was chosen according to balance the benefit and risk of each regimen in clinical practice since then. Based mainly on evidence of benefit in systemic CD20-positive lymphomas, rituximab is also commonly administered along with high dose methotrexate (HDMTX)-based chemotherapy for PCNSL from the 2000s [14]. Although the response rates to induction and consolidation therapy are high, almost half of these patients will relapse generally. Salvage chemotherapy regimens containing temozolomide, pemetrexed and topotecan, either in combination with others or as a single agent, have resulted in response rates of 14%-53%[15, 16]. Since 2013, novel agents which are less toxic, lenalidomide and the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib have shown activities in several clinical trials[17–19]. The efficacy of PD-1 checkpoint inhibitor for salvage therapy of PCNSL is also being considered [20].

The clinical efficacy of these new consolidation protocols and agents has been established in a series of clinical studies. However, the results from such studies may not reflect the actual clinical practice because of the stringent eligibility criteria for clinical trials. Population-based studies which based on the general patient population may complement prospective intervention studies. Therefore, we report the outcomes of a population-based SEER retrospective cohort study on primary treatment and survival trends among adult PCNSL patients between 1995 and 2016.

2. Patients And Methods

2.1. Data source and patient selection

The current retrospective cohort study relied on the SEER database (1975–2016), which samples 28% of the United States and publishes data of cancer incidence, treatment, and survival from population-based cancer registries[21]. In the SEER database, we focused on patients with PCNSL from the SEER-18 to conduct this analysis. The SEER-18 registry includes Atlanta, Detroit, Greater California, Greater Georgia, Hawaii, Iowa, Kentucky, Los Angeles, New Mexico, New Jersey, Rural Georgia, states of Connecticut, San Francisco-Oakland, Seattle-Puget Sound, San Jose Monterey, the Alaska Native Tumor Registry, Louisiana, and Utah.

The SEER database classifies cancer histology and tomography by using the third edition of the International Classification of Disease-Oncology (ICD-O-3). PCNSL was defined by cancer diagnoses in anatomic locations of brain, spinal cord, leptomeninges, and other parts of the CNS (ICD-O-3 codes C70.0-

C72.9). PCNSL patients with diffuse large B-cell histology were identified in SEER by filtering the databases based on histology codes (9680, diffuse large B-cell lymphoma [DLBCL], NOS; 9684, malignant lymphoma, large B, diffuse, immunoblastic; 9688, T-cell histiocyte-rich large B-cell lymphoma).

For this study, we included patients with primary diffuse large B-Cell lymphoma of central nervous system aged ⩾18 years and diagnosed between 1995 and 2016. A total of 5714 patients were extracted from the SEER database. Similar to previous studies,patients with “other infectious and parasitic diseases including HIV” as cause of death and follow-up were excluded to define a non-HIV PCNSL patient population (n = 700) [22, 23]. Patients with more than one primary cancer were also excluded (n = 1026). Patients without pathological diagnosis and patients diagnosed at autopsy were excluded (n = 228).

2.2 Study variables

According to the primary treatment the patients received, information on primary treatment were divided into five classes: no anti-tumor therapy, surgery alone, radiotherapy alone(radiotherapy ± surgery), chemotherapy alone (chemotherapy ± surgery and combined chemoradiotherapy (chemoradiotherapy ± surgery). According to the progress in treatment, the year of diagnosis was divided into three time periods. The time period-1 is from 1995 to 2002. The time period-2 is from 2003 to 2012, a period expected to reflect more intense chemotherapy regimens, the availability of rituximab and the utilization of autologous stem-cell transplantation as consolidation strategy. The time period-3 is from 2013 to 2016, a period expected to reflect novel agents spring up. Covariates including age at diagnosis, sex, race, marital status and distribution by site in the CNS were introduced, to adjust the hazard ratio (HR). Data of Survival months, survival status, the cause of death were also collected.

2.3 Statistical analysis

Statistical analysis was performed using SEER stat 8.3.8 and SPSS v22.0 for Windows (SPSS Inc., Chicago, IL). Chi-square tests were used to analyze Categorical variables. Kaplan-Meier survival curves were plotted for cause-specific survival (CSS), which was defined by specifying PCNSL as the cause of death, measured from time of diagnosis of PCNSL to time of death, in months. The survival difference was compared using log-rank test. Multivariate analysis using Cox regression model was performed to identify the independent risk factors for long-term survival. Two-sided *P* values less than 0.05 were considered to be significant.

3. Results

3.1 Patient characteristics

Based on the eligibility criteria, a total of 3760 adult patients (age ⩾18 years) diagnosed with primary diffuse large B-cell lymphoma of central nervous system between 1995 and 2016 were identified in the study. Of these, 709 were diagnosed during the time period-1(1995–2002), 1989 diagnosed during the time period-2 (2003–2012) and 1062 diagnosed during the time period-3(2013–2016). Of this population, median age was 64 years (range 18–96 years). 37.1, 28.5 and 34.4% of patients were aged 18–60, 61–70 and > 70 years, respectively. Patient characteristics of the study population stratified by the period of

diagnosis are outlined and compared as shown in Table 1. Clinical features including race ($P = 0.026$), marital status($P = 0.004$) and distribution by site in the CNS ($P < 0.001$) showed significant difference over the different time periods; there was no significant difference according to age ($P = 0.079$) and sex ($P = 0.719$).

Table 1
Patient Characteristics and Comparison of the study population stratified by the period of diagnosis

		period-1	period-2	period-3	
Variable	Total	1995–2002	2003–2012	2013–2016	*P*-value
Number of patients (%)	3760	709	1989	1062	
Age (years)					0.079
Median	64	65	64	66	
18–60	1394(37.1)	260(36.7)	775(39)	359(33.8)	
60–70	1073(28.5)	199(28.1)	558(28.1)	316(29.8)	
>70	1293(34.4)	250(35.3)	656(33)	387(36.4)	
Sex (%)					0.719
Female	1874(49.1)	351(49.5)	965(48.5)	531(50)	
Male	1913(50.9)	358(50.5)	1024(51.5)	531(50)	
Race(%)					0.026*
White	3076(81.8)	602(84.9)	1634(82.2)	840(79.1)	
Black	189(5)	31(4.4)	102(5.1)	56(5.3)	
Other	495(13.2)	76(10.7)	253(12.7)	166(15.6)	
Marital status					0.004*
Married	2274(60.5)	424(59.8)	1199(60.3)	651(61.3)	
Widowed	422(11.2)	102(14.4)	228(11.5)	92(8.7)	
Other	319(30)	183(25.8)	562(28.3)	319(30)	
Distribution by site					< 0.001*
Brain parenchyma	3233(86)	588(82.9)	1738(87.4)	907(85.4)	
Leptomeninges	30(0.8)	9(1.3)	16(0.8)	5(0.5)	
Spine cord,cranial nerves	148(3.9)	41(5.8)	81(4.1)	26(2.4)	
CNS not otherwise specified	349(9.3)	71(10)	154(7.7)	124(11.7)	
*P< 0.05					

3.2 Primary treatment according to the era of diagnosis and age

As age is an important factor in deciding treatment protocols. Information on primary treatment stratified by the period of diagnosis and age is displayed in Fig. 1. The proportion of patients received no anti-tumor therapy or surgery alone has not changed appreciably over time, with most of these patients aged above 60 years. There are some consistent and notable treatment changes between different age groups. The use of radiotherapy alone decreased over time, from 28.6% in the time period-1 to 12.7% in the time period-2 and 7.8% in the time period-3. The use of radiotherapy alone all dropped substantially in different age groups, with the patients aged 18–60 years dropping most from 19.6% in the time period-1 to 8.6% in the time period-2 and 3.9% in the time period- 3. The application of combined chemoradiotherapy also decreased, following a wider range of use of chemotherapy alone over time. The application of combined chemoradiotherapy dropped and the use of chemotherapy widened consistently among patients in different age groups. The proportion of patients received combined chemoradiotherapy dropped from 36.2% in the time period-1 to 23.9% in the time period-2 and 15% in the time period-3. The proportion of patients received chemotherapy increased from 22.7% in the time period-1 to 46.6% in the time period-2 and 62.8% in the time period-3.

3.3 Survival

The median follow up time of the study patients was 17 months. Overall, there was a significant improvement in PCNSL cancer-specific survival (CSS), with the median CSS of all patients improving from 13 months in the time period-1 to 19 months in the time period-2 and 41 months in the time period-3. When analyzing changes in survival over time based on age, the survival increased most prominently for patients aged 18–60 years from the time period − 1 to the time period-2 (28 months in the period time-1 vs 71 months in the period time-2, $P = 0.01$). Survival of patients aged above 70 years did not change from the period time-1 to the period time-2 (5 months in the period time-1 vs 5 months in the period time-2, $P = 0.101$). However, there was an increase in cancer-specific survival from the time period-2 to the time period-3 in both younger patients (age < 70 years) and elder patients (age > 70 years, 5 months in the period time-2 vs 9 months in the period time-3, $P < 0.001$). Cancer specific survival curves of adult patients with PCNSL in different age groups based on the period of diagnosis were shown in Fig. 2. The median cancer-specific survival of the study population stratified by the period of diagnosis and age are outlined in Table 2.

Table 2
Median Cancer-specific Survival Based on Age, months

Time of diagnosis	all patients	18–60 years	61–70 years	> 70 years
Period-1(1995–2002)	13	28	16	5
Period-2(2003–2012)	19	71	21	5
Period-3(2013–2016)	41	Not Reached	39	9
P-value for trend	< 0.001*	< 0.001*	0.004*	< 0.001*
*$P < 0.05$				

We analyzed the influence of age, sex, race, marital status, distribution by site in the CNS and the period of diagnosis on the relative excess risk of mortality in a multivariable model.

A univariate analysis showed that age, race, marital status, distribution by site in the CNS and period of diagnosis ($P < 0.05$) were closely related to long-term cancer-specific survival. In multivariate Cox regression analysis (Table 3), diagnosed in the time period-3 was significantly and independently associated with better CSS (HR 0.577, 95% CI 0.506–0.659). This showed no difference with the results of univariate analysis. Age and distribution by site in the CNS were also independently associated with CSS (Fig. 3, Table 3).

Table 3
Multivariable analysis

Variable	Univariate analysis	Multivariate analysis		
	P-value	HR	95% CI	*P*-value
Age (years)	< 0.001**			< 0.001*
18–60		1(Ref)		
61–70		1.552	1.389 1.734	< 0.001*
>70		2.578	2.325 2.858	< 0.001*
Sex	0.362			
Female				
Male				
Race	0.007			0.123
White		1(Ref)		
Black		0.993	0.805 1.225	0.946
Other		0.874	0.767 0.994	0.041*
Marital status	0.851			
Married				
Widowed				
Other				
Period of diagnosis	< 0.001*			< 0.001*
1995–2002		1(Ref)		
2002–2012		0.827	0.748 0.916	< 0.001*
2013–2016		0.577	0.506 0.659	< 0.001*
Distribution	< 0.001*			< 0.001*
Brain parenchyma		1(Ref)		
Leptomeninges		0.305	0.152 0.612	0.001*
Spine cord,cranial nerves		0.365	0.272 0.489	< 0.001*
CNS not otherwise specified		0.783	0.672 0.913	0.002*
*P< 0.05				

4. Discussion

PCNSL is a rare and aggressive tumor and DLBCL represents 90%-95% of all primary central nervous system lymphoma[1, 2]. There are remarkable advances in the treatment of PCNSL over the last two decades[3, 4]. The present population-based study was conducted to detect the primary treatment and survival trends in patients with PCNSL diagnosed during 1995–2016. The results of our study indicates that both the use of radiotherapy alone and the application of combined chemoradiotherapy decreased, following more extensive use of chemotherapy alone as time went by. A significant improvement in survival was also demonstrated over time during 1995–2016.

The significantly increased cancer-specific survival from the time period-1 to the time period-2 is most likely bound up with the utilization of more intense chemotherapy regimens and the utilization of autologous stem-cell transplantation as consolidation strategy. As shown in our study, the use of radiotherapy alone and combined chemoradiotherapy dropped substantially with the patients aged 18–60 years dropping most and the use of chemotherapy alone increased dramatically from the time period-1 to the time period-2. Accordingly, our results showed that the survival increased most prominently for patients aged 18–60 years who may more fit to received more intense chemotherapy or high dose-ASCT for consolidation and survival of patients aged above 70 years who may have worse functional status and greater comorbidities remained unchanged from the time period-1 to the time period-2. Although wider use of chemotherapy applicated in patients aged above 70 years, a less aggressive treatment approach may performed. Although lacking of phase III randomized controlled trials to confirm the best consolidation approach, what is clear is that the application of more intense chemotherapy and the utilization of autologous stem-cell transplantation as consolidation strategy improved survival according to our population-based study. The finding that there was no improvement in survival of patients aged above 70 years the time period-1 to the time period-2 in our study falls in line with historical findings of previous studies based on population analysis[24, 25]. A cohort study carried out by Mendez JS et al. shown that survival in the elderly population (> 70) has not changed from 1973 to 2013[24]. Van der Meulen M et al. demonstrated that improved survival was found in PCNSL up to age 70 only by a population-based study in the Netherlands,1989–2015[25].

However, there was an improvement in cancer-specific survival in the most recent period in not only younger patients (< 70 years) but also the elderly patients (> 70 years). There are many causes. One of the important reasons may be that there have been no age restrictions in several clinical trials and furthermore, trials have been conducted to target the elderly patient population (Such as PRIMAIN study) in the most recent clinical trials worldwide[26]. It guide clinicians making treatment decisions in this patient population. Instead, clinical trials are only applicable to young and fit patients in the past. Another possible reason is that some new agents which are also tolerated in the elderly patients springs up in the time period-3 as we observed that elderly patients were more likely to receive chemotherapy in the time period-3. The representative agents include an antiproliferative and immunomodulatory agent lenalidomide and an oral BTK inhibitor Ibrutinib. In a prospective multicenter study reported by Ghesquieres H et. al assessing the combined chemotherapy of lenalidomide plus intravenous rituximab in relapsed/refractory PCNSL, an OR rate of 67% and an overall survival of 17.7 months were reported[18]. Recent results from the phase II 'proof-of-concept' iLOC study investigating single-agent

ibrutinib in relapse or refractory(R/R) DLBCL-PCNSL showed an OR rate of 52% and median OS of 19.2 months in 52 patients[19]. Monotherapy with lenalidomide or ibrutinib is also being explored as a potential consolidation or maintenance therapy, particularly in older DLBCL-PCNSL patients. It may become a clinical progress which may provide more effective treatment options and significantly improved outcome among the elderly patients with PCNSL in future.

The strength of this study is that analysis of a population-based registries SEER including a large number of DLBCL-PCNSL patients, demonstrates continuous improvement in survival during 1995–2016, which reflected developments in treatment over time. By contrast, both the use of radiotherapy alone and the application of combined chemoradiotherapy decreased in all aged groups over time. We can find that the application of radiotherapy in the treatment of PCNSL has waned over time in this large population-based study. In most recent years, and particularly after that a randomized German study (G-PCNSL-SG-1) did not show evidence of improved survival by adding radiation[27], the use of whole brain radiation has been questioned.

The most recent RTOG 1114 study discussing the effect of reduced-dose radiation further (R-MVP/Ara-C ± low dose WBRT) and presented orally at ASCO 2020, a better PFS was reached in the reduced-dose WBRT group compared with the chemo-alone group.
However, the analyses of toxicity, especially neurotoxicity are still ongoing, the result of which might give further insight in the use of radiation in PCNSL.

Age is one of the most major prognostic factors for PCNSL. Both of the prognostic scores of Memorial Sloan Kettering Cancer Center[28] and the International Extranodal Lymphoma Study Group[29] include age as a prognostic factor. Survival also differed greatly between age groups and the multivariable model demonstrated an adverse effect of older age in our study. This patient population has a less radical therapeutic method, poorer performance status, and greater complication which may contribute to worse overall survival. Our study also found distribution of PCNSL by site in the CNS is another prognostic factor. Median cancer-specific survival was worse in PCNSL patients occurred in the brain parenchyma in comparison to those occurred in the CNS except brain parenchyma. Prognostic models including these factors should be developed to help in deciding the optimal therapeutic schedule in future.

It's worthy to note that our study should be considered in the context of its potential limitations. First, because of the deficiency of the SEER database, we were incapable of obtaining granular data especially the specifics on treatment (chemotherapy regimens, the dose of radiation, receive ASCT or not receive, the intent of radiotherapy and the like). Second,information regarding prognostic factors (patient performance status, CSF protein, serum lactate dehydrogenase, and lesions within deep structures) and history of prior treatment is not available. Third, we were incapable of excluding every HIV-associated PCNSL.

5. Conclusions

Our analysis shows the use of radiotherapy in the treatment of PCNSL has waned over the study span. There was a significant improvement in survival during 1995–2016 in this large polulation-based study, which reflected developments in treatment over time. The elderly patient population also gained a significant cause-specific survival benefit in the most recent period.

Declarations

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Conflicts of Interest: The authors declare no conflict of interest.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions All authors contributed to the study conception and design. Cui Chen, Peng Sun and Xiaoqing Sun collected the data and drafted the manuscript. Shaoyong Chen, Yu Wang and Hang Yang performed the statistical analysis. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval Ethical approval was waived by the Ethics Committee of Sun Yat-Sen University Cancer Center because preexisting data with no personal identifiers were used.

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Figures

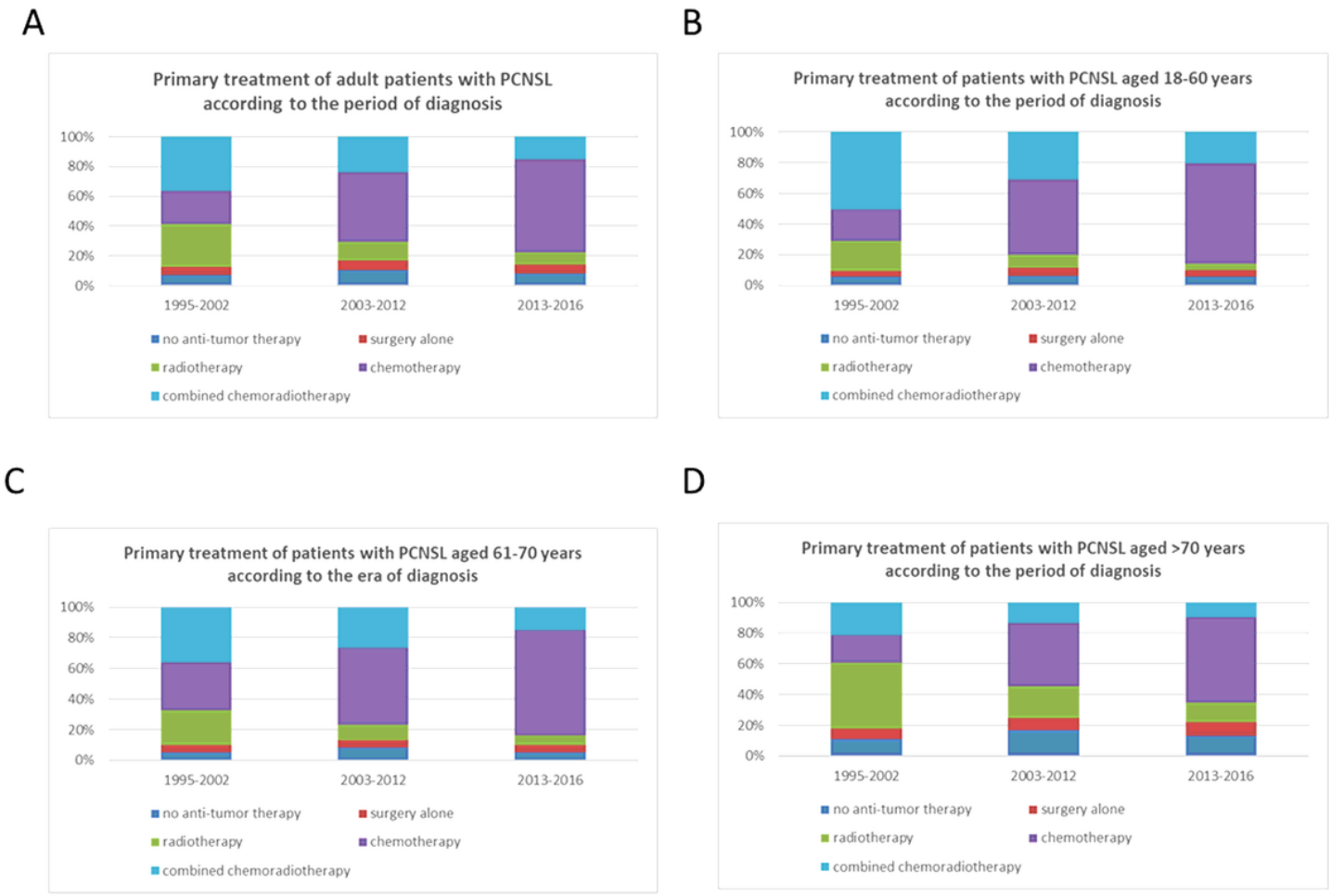

Figure 1

Primary treatment of adult patients with PCNSL according to the period of diagnosis (a) All patients (b) Patients aged 18-60 years□c□Patients aged 61-70 years (d) Patients aged >70 years

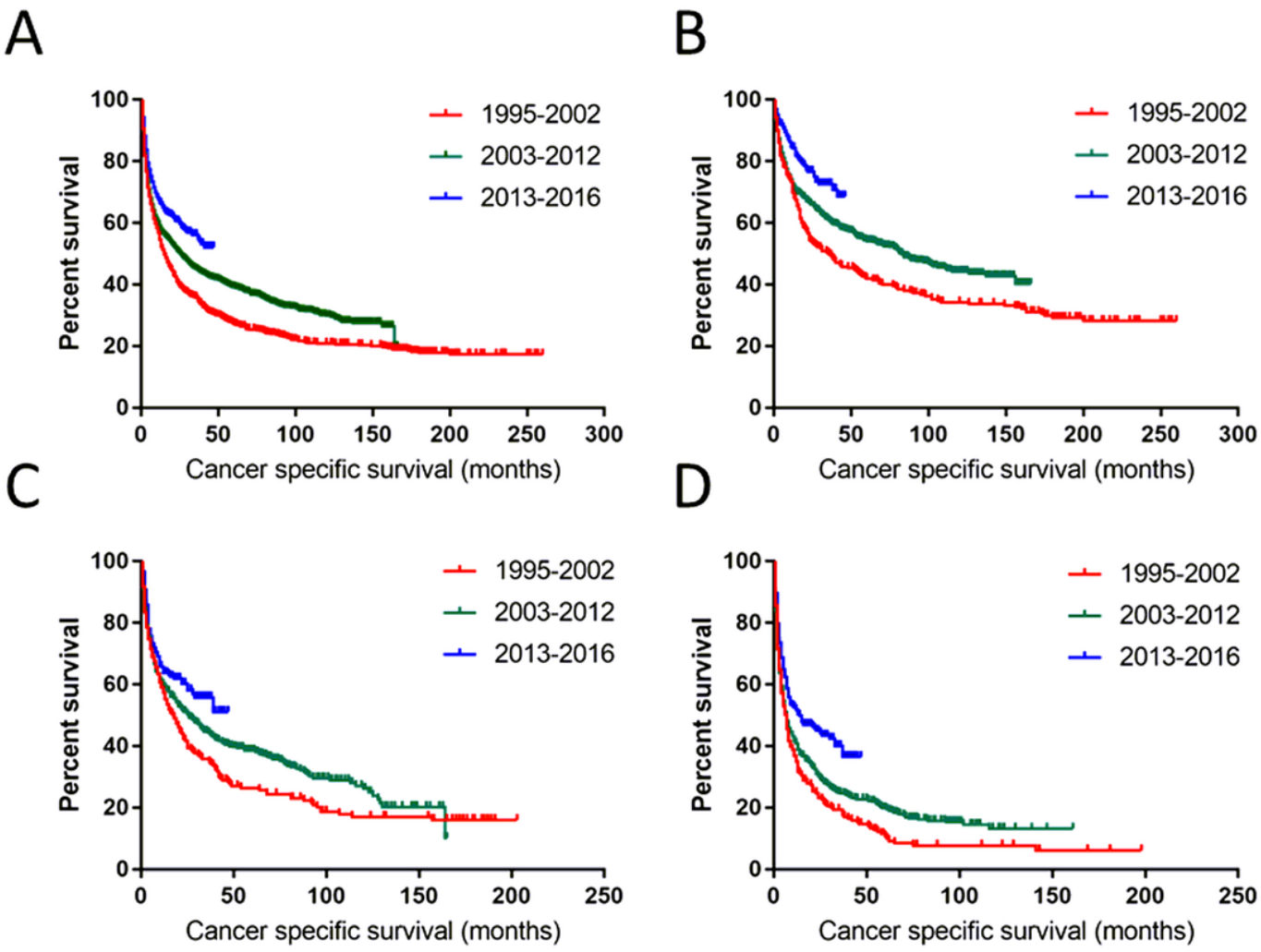

Figure 2

Cancer specific survival curves of adult patients with PCNSL based on the period of diagnosis. (a) All patients (b) Patients aged 18-60 years (c) Patients aged 61-70 years (d) Patients aged >70 years

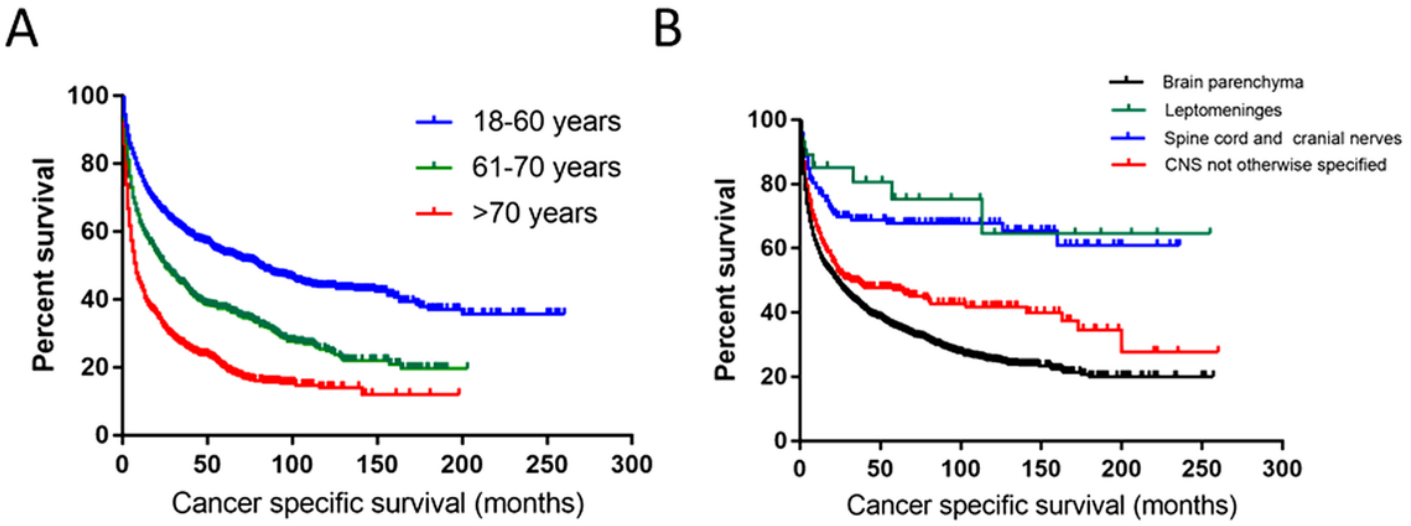

Figure 3

Cancer specific survival curves of all PCNSL patients based on (a) age and (b) distribution by site in the CNS

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Data.sav