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ORIGINAL ARTICLE

Clinical characteristics and outcomes of primary adrenal diffuse large B cell lymphoma in a large contemporary cohort: a SEER-based analysis

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Abstract

Primary adrenal lymphoma (PAL) is an extremely rare lymphoma, and the most common histologic type is diffuse large B cell lymphoma (DLBCL). Primary adrenal DLBCL has a quite poor prognosis, but the prognostic determinants are rarely reported. With the Surveillance, Epidemiology, and End Results (SEER) program, we collected the demographic, clinical, therapeutic information of patients with primary adrenal DLBCL from 1983 to 2015. The Kaplan-Meier method was used to obtain overall survival (OS) and cause-specific survival (CSS) curves. The prognostic values of OS and CSS were assessed using Cox proportional hazards regression model with univariate and multivariate analyses. A total of 136 patients were included in our cohort. Adrenal DLBCL predominantly affected male and the aged, and there was a high rate of unilateral adrenal origin. The patients were more likely to present advanced stage disease. The OS rates of the entire cohort of patients with adrenal DLBCL at 5 and 10 years were respectively 19.17% and 3.33%, and the similar results were shown in 5-year and 10-year CSS rates. Age more than 70 years old and bilateral were identified as independent prognostic factors that were correlated with both adverse OS and CSS, and patients with chemotherapy had a superior OS and CSS to the patients without any treatment.

Keywords Primary adrenal lymphoma · Diffuse large B cell lymphoma · SEER · Survival · Prognosis

Introduction

Primary extranodal non-Hodgkin's lymphoma (NHL) is defined as lymphoma confined wholly or mainly to an anatomic site other than lymph nodes [1, 2]. Among the extranodal sites, adrenal gland is an extremely rare one, accounting for less than 1% of all NHL and 3% of primary extranodal lymphomas [3–6]. Primary adrenal lymphoma (PAL) predominantly affects male and the elderly [4, 7–10]. The most common histologic subtype of PAL is diffuse large B cell lymphoma (DLBCL), with a non-germinal center B cell (non-GCB) phenotype [11–14]. Because of its rarity, the clinical and pathologic features and therapeutic options of PAL have not been defined in detail [4]. Whereas PAL is known to have poor prognosis, how it compares with primary nodal and other extranodal lymphoma of similar histology is still unknown, and few studies focus on the prognostic factors.

To date, fewer than 200 publications on PAL appear in the literature; most of the papers are case reports and literature reviews based on small single-institution case series [13]. Conclusions drawn from clinical data, treatment outcomes, and combined analysis with other lymphoma histologies of

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these reviews cannot accurately reflect the nature of primary adrenal NHL. Consequently, further studies with a larger number of patients are needed.

The Surveillance, Epidemiology, and End Results (SEER), which has been founded by the National Cancer Institute since 1973, is a valued source of high-quality information for cancer incidence and survival in the USA and covers approximately 28% of the US population [15, 16]. Based on the SEER database, we conducted a retrospective study to evaluate the clinical characteristics and treatment outcome, and to identify relevant prognostic factors for PAL.

Methods

Data source and cohort selection

The cohort consisted of patients diagnosed with DLBCL of the adrenal from 1983 to 2015. Patient data were obtained using the case-listing function in the SEER*Stat Version 8.3.4 (www.seer.cancer.gov), which was updated in November 2017. This study was performed in accordance with standard guidelines and was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine.

To obtain the cohort of interest, we used the third edition of the International Classification of Diseases for Oncology [ICD-O-3] histology codes 9680/3, 9675/3, and 9684/3 to identify DLBCL cases. Determination of the primary site of DLBCL came from the treating physicians. Primary DLBCL that originated from the adrenal gland was identified using the lesion number C74.0 (cortex), C74.1 (medulla), and C74.9 (adrenal gland, not otherwise specified [NOS]). All patients were diagnosed by histologic confirmation, and cases diagnosed from only clinical presentation, radiography, and/or reported from death certificate or autopsy only were excluded. A similar screening process was performed to obtain the comparative cohorts of extranodal DLBCL (excluding adrenal bland) and nodal DLBCL. Data extracted from the SEER database included patient demographics, laterality of adrenal involvement, stage at diagnosis, cause of death, year of diagnosis, treatment, and length of survival.

Outcomes and statistical methods

Patient characteristics were summarized using descriptive statistics, and differences between nodal/extra-nodal and adrenal groups were assessed using the χ^2 test for categoric or t test for continuous variables.

We analyzed survival data according to both overall survival (OS) and cause-specific survival (CSS) using the Kaplan-Meier method. OS was measured from the first date of diagnosis until death from any cause, with surviving patients censored at the last follow-up date. CSS was defined from the first date of diagnosis until death due to lymphoma or treatment related. We evaluated the prognostic effect of the various clinical variables using univariate and multivariate Cox proportional hazards models. The hazard ratios (HRs) with corresponding 95% CIs were used to predict the impact of factors on both OS and CSS. Log-rank test was used to compare survival distributions. All calculations and graphs were obtained using SPSS 16.0 Statistical Package. p value < 0.05 was considered statistically significant in all analyses.

Result

Incidence of PAL

We identified 185 cases of primary NHL of the adrenal, including 136 (73.5%) cases of DLBCL between 1983 and 2015. The other top 3 histologies were non-Hodgkin, B cell, NOS ($n = 13$, 7.03%), lymphoid neoplasm, NOS ($n = 12$, 6.49%), and follicular lymphoma ($n = 8$, 4.32%). The 136 adrenal DLBCL cases accounted for 0.14% of all primary DLBCL ($n = 93{,}995$) and 0.43% of all primary extranodal DLBCL ($n = 31{,}374$) over the same period. In addition, 4.32% of all primary cancers of the adrenal ($n = 4758$) belonged to NHL, covering 3.1% of DLBCL (data not shown).

Clinical features and treatment

Demographic, clinical characteristics, and treatment received of patients with DLBCL of the adrenals, other extranodal (non-adrenal), and nodal are summarized in Table 1. Adrenal DLBCL was generally a disease of the elderly, with a median age at diagnosis of 71 years. Only 2.94% of patients with adrenal DLBCL aged less than 40 years, and the proportion was much lower than that of extranodal and nodal DLBCL. Adrenal DLBCL was more likely to affect men with a male to female ratio of 2:1, whereas in other DLBCL, men and women were equally likely to develop the disease. The majority of patients (83.84%) diagnosed with adrenal DLBCL were white, which was consistent with other DLBCL. Among those with complete staging workup, early stages (stages I and II) predominated (61.08%). Arising from unilateral adrenal gland (61.76%), particularly the left side (36.76%), was more frequently than that from the bilateral adrenal glands (38.24%) in adrenal DLBCL. For treatment, the minority (16.17%) of patients underwent cancer-directed surgery (CDS) after diagnosis, and less that 10% patients received prophylactic radiation, which was consistent with treatment trends for other extranodal DLBCL. With very few exceptions, chemotherapy was the most common choice for treating patients with primary adrenal DLBCL.

Table 1 Demographic and clinical characteristics of patients with DLBCL of adrenal gland, other extranodal sites, and nodal sites diagnosed in SEER database (1983–2015)

Characteristic	Adrenal DLBCL ($n = 136$)		Extranodal DLBCL ($n = 31,374$)		Nodal DLBCL ($n = 62,485$)		*P* value
	No. of patients	Percent	No. of patients	Percent	No. of patients	Percent	
Median age (range)	71 (32–85+)		66 (0–85+)		65 (0–85+)		
Age							0.000***
< 40	4	2.94	3556	11.33	7315	11.71	
40–49	7	5.15	3409	10.87	6867	10.99	
50–59	24	17.65	4723	15.05	10,271	16.44	
60–69	28	20.59	6376	20.32	13,090	20.95	
70–79	42	30.88	7417	23.64	14,196	22.72	
≥ 80	31	22.79	5893	18.78	10,746	17.20	
Year of diagnosis							0.001**
1983–1999	21	15.44	8160	26.01	17,006	27.22	
2000–2009	68	50.00	13,941	44.43	26,914	43.07	
2010–2015	47	34.56	9273	29.56	18,565	29.71	
Sex							0.002**
Female	49	36.03	14,124	45.02	28,754	46.02	
Male	87	63.97	17,250	54.98	33,731	53.98	
Race							0.420
White	114	83.84	25,910	82.58	52,433	83.91	
Black	3	2.21	2228	7.10	4910	7.86	
API	18	13.24	2879	9.18	4452	7.12	
AI/AN	1	0.74	147	0.47	310	0.50	
Unknown	0	0.00	210	0.67	380	0.61	
Ann Arbor stage							0.018*
I–II	77	61.08	20,614	65.70	23,059	36.90	
III–IV	54	39.71	8885	28.32	35,902	57.46	
Unknown	3	2.21	1877	5.98	3524	5.64	
Laterality							NA
Right	34	25.00					
Left	50	36.76					
Bilateral	52	38.24					
Radiation							0.319
Yes	11	8.09	9830	31.33	11,459	28.34	
No	125	91.91	21,544	68.67	51,026	81.66	
Surgery							0.291
Yes	22	16.17	11,361	36.21	15,460	24.74	
No	113	83.09	19,983	63.69	46,210	73.95	
Unknown	1	0.74	30	0.10	815	1.30	
Chemotherapy							0.247
Yes	97	71.32	21,284	67.84	48,089	76.96	
No	39	28.68	10,090	32.16	14,396	23.04	

DLBCL diffuse large B cell lymphoma, *API* Asian or Pacific Islander, *AI/AN* American Indian/Alaska Native, *NA* not available

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Survival

OS and CSS for the entire cohort of adrenal DLBCL patients are presented in Fig. 1 and compared with extra-nodal/nodal DLBCL. The OS rates of the entire cohort of patients with adrenal DLBCL at 5 and 10 years were respectively 19.17% and 3.33%, and the results were similar in 5-year and 10-year CSS rates. Although our cases presented with an early-staged disease, the prognosis of the entire group was much worse as compared with that of their nodal counterparts or that of DLBCL at other extranodal sites (Supplemental Table 1). Thereafter, a plateau was observed on the OS and CSS curves with few additional events after the third year, indicating that fatal late recurrences were rare. The median OS improved overtime, with a median OS time of 10 months for patients diagnosed in 1983 to 1990 compared with 17 months for patients diagnosed in 1991 to 2000, respectively. For patients diagnosed in 2001 to 2015, the median OS was 20 months (data not shown).

Univariate/multivariate analysis for predicting independent prognostic factors

Univariate survival analysis indicated that age was an important prognostic factor for OS (HR = 2.597, 95% CI 1.675–4.028, $p < 0.001$; Table 2, Fig. 2a) and CSS (HR = 2.828, 95% CI 1.730–4.625, $p < 0.001$; Table 3, Fig. 3a). Similarly, there was a significant difference in both OS and CSS based on the laterality of disease in the adrenals (OS: unilateral vs. bilateral, HR = 2.217, 95% CI 1.433–3.431, $p = 0.000$; CSS: bilateral vs. unilateral, HR = 2.221, 95% CI 1.279–3.857, $p = 0.005$; Tables 2 and 3; Figs. 2b and 3b). In terms of treatment, patients with chemotherapy had better OS (HR = 0.322, 95% CI 0.198–0.975, $p < 0.001$) and CSS (HR = 0.198, 95% CI 0.088–0.444, $p < 0.001$) than those without it. However, there was no significant difference between survival and risk factors, such as gender, race, years of diagnosis, and stage (Tables 2 and 3; Supplemental Figs. 1 and 2).

On multivariate analysis, age and the laterality were independent predictors of OS (HR = 2.093 95% CI 1.327–3.301, $p = 0.001$ and HR = 2.105, 95% CI 1.319–3.356, respectively; Table 2) and CSS (Table 3). Receipt of chemotherapy was an independent factor for indicating better OS (HR = 0.338, 95% CI 0.206–0.555, $p = 0.000$), but not CSS (HR = 0.720, 95% CI 0.404–1.284, $p = 0.266$; Tables 2 and 3).

Discussion

PAL is a rare form of primary adrenal neoplasia, accounting for less than 1% of all NHL cases [9]. Due to the aggressive performance and the failure to persistently control the disease by chemotherapy, PAL confers a poor prognosis [11]. In some cases, the diagnosis was not even established until autopsy [3]. Previously, the clinical presentation, radiographic features, experimental treatment choice, and outcomes of PAL were reported. However, the prognostic results of those patients are scarce. Moreover, most of these studies are single-case reports and literature reviews based on small single-institution case series. Schmitz et al. reported 146 patients with involvement of the kidney and/or adrenal glands, accounting for 4% of the aggressive B cell lymphomas retrieved from two large datasets; however, most of them were likely nodal DLBCLs rather than extranodal lymphomas solely affecting adrenal glands [17]. Rashidi et al. systematically reviewed a total of 187 PAL patients by searching several databases [18], but the results need to be interpreted with caution. First, these PAL cases diagnosed by the clinical symptoms, imaging, and laboratory tests were included in the study, as well as autopsy cases. Though the definition of primary extranodal NHL is still controversial [19], the accepted prerequisite is that PAL must be confirmed histologically [14]. Second, adrenal DLBCL cases were analyzed together with other subtypes of lymphoma. Either of the two problems above are known to lead a bias in the conclusions.

To our best knowledge, the current study is the first population-based study, which exactly reflects the

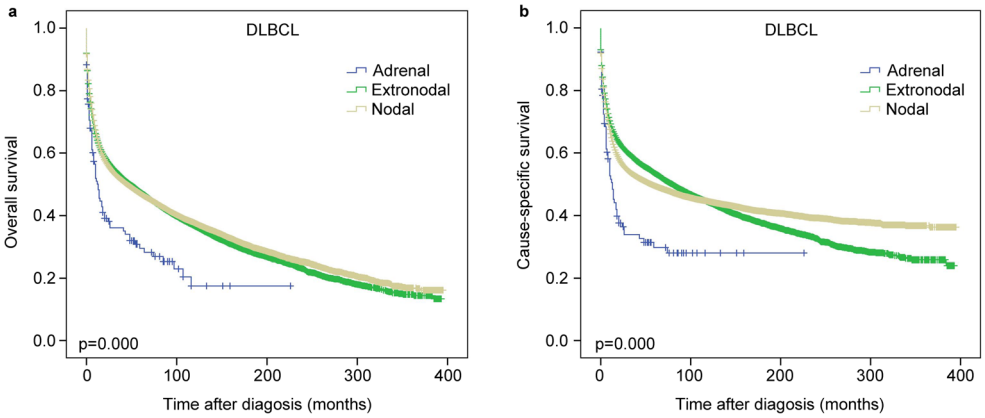

Fig. 1 The Kaplan-Meier survival curve of OS (**a**) and CSS (**b**) of patients with DLBCL by primary sites: adrenal ($n = 136$), other extranodal sites ($n = 31{,}374$), and nodal site ($n = 62{,}485$)

Table 2 Univariate and multivariate analyses of factors associated with risk of OS for patients with primary adrenal DLBCL identifed in the SEER program database from 1983 to 2015

	Univariate analysis			
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
< 70	1		1	
≥ 70	2.597 (1.675–4.028)	0.000***	2.093 (1.327–3.301)	0.001**
Gender				
Female	1			
Male	1.382 (0.880–2.171)	0.160		
Race				
White	1			
API	1.145 (0.643–2.041)	0.646		
Year of diagnosis				
1983–1999	1			
2000–2009	0.641 (0.310–1.324)	0.229		
2010–2015	1.026 (0.485–2.170)	0.946		
Laterality				
Unilateral	1		1	
Bilateral	2.217 (1.433–3.431)	0.000***	2.105 (1.319–3.356)	0.002**
Ann Arbor stage				
I–II	1			
III–IV	1.479 (0.958–2.282)	0.077		
Chemotherapy				
No	1		1	
Yes	0.322 (0.198–0.975)	0.000***	0.338 (0.206–0.555)	0.000***

OS overall survival, *DLBCL* diffuse large B cell lymphoma, *SEER* Surveillance, Epidemiology, and End Results, *HR* hazard ratio, *CI* confidence interval, *API* Asian or Pacific Islander

**$p < 0.01$, ***$p < 0.001$

demographic and clinical characters of patients with adrenal DLBCL and is to improve understanding of adrenal DLBCL by comparing this with other extranodal DLBCL (excluding the adrenal) and nodal DLBCL. Furthermore, we also identify the prognostic factors that affect the survival of patients with primary adrenal DLBCL using multivariate regression analysis. We identified 136 cases of primary adrenal DLBCL according to the SEER database from 1983 to 2015. Our study confirmed that DLBCL was the most common histology for patients diagnosed with PAL. Adrenal DLBCL had been indicated a strong male predominance (6:1) by Kasaliwal [20], but our series demonstrated only a slight male to female predominance (2:1). As the year at diagnosis increased, the number of patients in the series also increased. Moreover, the age of patients in the cohort ranged widely from 32 to 85+ years old, with a median age of 71 years. Therefore, it is important to suspect adrenal DLBCL in the elderly patients, while the possibility of this disease in young patients could not be ignored to avoid delayed diagnosis.

Most of the cases reported that adrenal DLBCL showed bilateral adrenal gland involvement [4, 14, 21] and advanced stage predilection, whereas our statistics revealed that adrenal DLBCL cases that arose from unilateral adrenal were more frequent. This might be due to the development of modern diagnostic modalities for early diagnose of the entity [5, 22, 23], the variation in the definition of primary extranodal involvement, or differences in staging criteria [24], approximately 2/3 of patients with adrenal DLBCL in the SEER database presented in early stage. Considering the poor prognosis, it indirectly proved that adrenal DLBCL or PAL was highly aggressive. The reasons for the aggressive behavior are unknown and prior studies speculated that it might be attributable to bulky tumor size at presentation, non-germinal center B cell phenotype, and BCL-6 gene rearrangement in the DLBCL cases [13].

Though patients with adrenal DLBCL always present early-stage disease, adrenal DLBCL has a much worse prognosis than other DLBCL, and the median survival time was only 14 months, which is consistent with previous reports [14]. The reasons for such findings are confusing, it might be associated with the rapid progress of the disease, and most cases had adrenal insufficiency, B symptoms, and elevated lactate dehydrogenase, which were identified as adverse prognostic factors [18]. Moreover, Ann Arbor stage system might

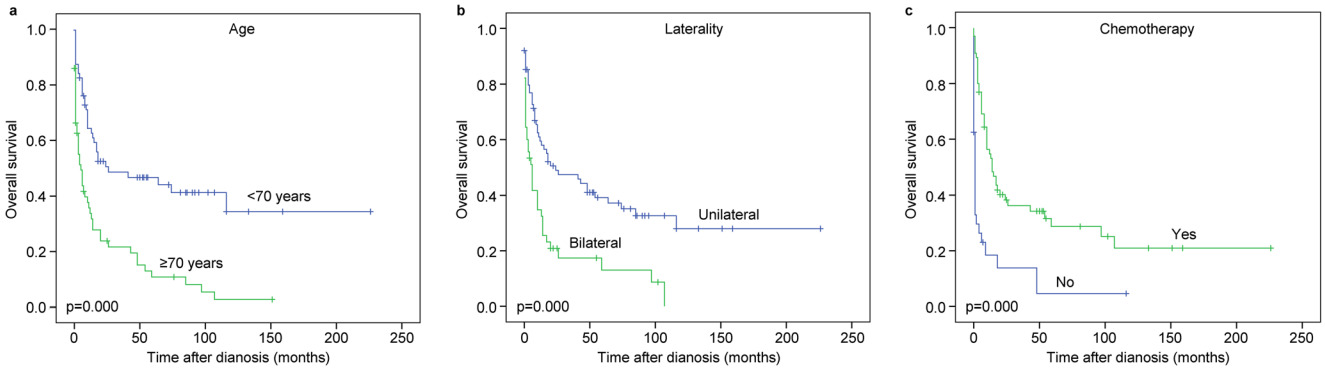

Fig. 2 The Kaplan-Meier survival analyses illustrating OS in patients with primary adrenal DLBCL stratifed by **a** age, **b** laterality, and **c** treatment

not enforceable in special lymphoma like PAL. The estimated 5- and 10-year OS rates were scarcely reported because of the rarity of adrenal DLBCL. Our series demonstrated the OS rates for the entire cohort of patients with adrenal DLBCL at 5 and 10 years were 19.17% and 3.33%, respectively. Moreover, complete or partial remissions with a long mean duration of survival were also reported in some cases [4, 25]. Therefore, the existence of significant differences in patient survival suggested that it was truly worthy to study the prognostic factors of adrenal glands for guiding personalized treatment and predicting outcome.

In terms of prognostic determinants, we performed univariate and multivariate analyses. The results of univariate analysis showed that a significant decrease in

Table 3 Univariate and multivariate analyses of factors associated with risk of CSS for patients with primary adrenal DLBCL identifed in the SEER program database from 1983 to 2015

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
< 70	1		1	
≥ 70	2.828 (1.730–4.625)	0.000***	2.538 (1.541–4.184)	0.000***
Gender				
Female	1			
Male	1.354 (0.816–2.246)	0.240		
Race				
White	1			
API	1.296 (0.679–2.475)	0.432		
Year of diagnosis				
1983–1999	1			
2000–2009	0.644 (0.282–1.469)	0.296		
2010–2015	0.986 (0.430–2.258)	0.973		
Laterality				
Unilateral	1		1	
Bilateral	2.165 (1.333–3.509)	0.002**	2.221 (1.279–3.857)	0.005**
Ann Arbor stage				
I–II	1			
III–IV	1.503 (0.926–2.441)	0.099		
Chemotherapy				
No	1		1	
Yes	0.312 (0.181–0.540)	0.000***	0.720 (0.404–1.284)	0.266

CSS cancer-specific survival, *DLBCL* diffuse large B cell lymphoma, *SEER* Surveillance, Epidemiology, and End Results, *HR* hazard ratio, *CI* confidence interval, *API* Asian or Pacific Islander

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

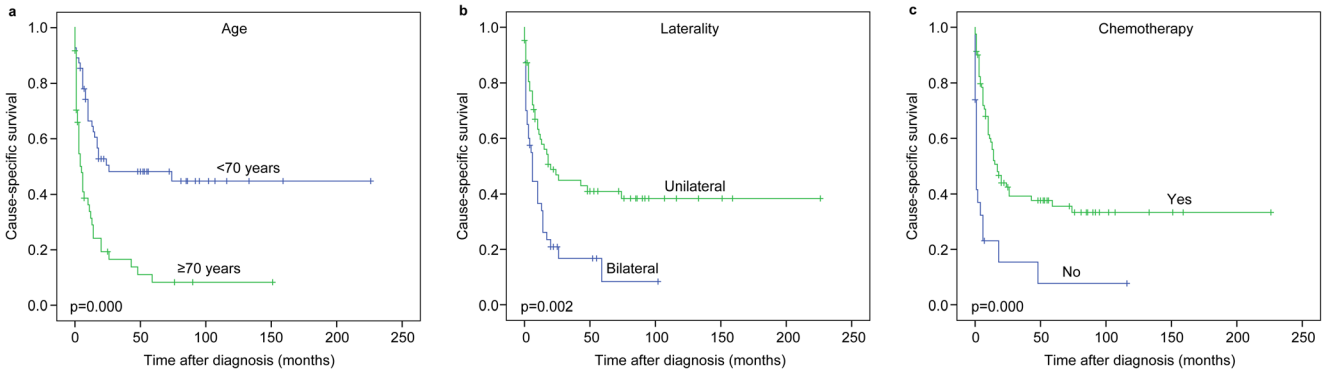

Fig. 3 The Kaplan-Meier curves estimated CSS in primary adrenal DLBCL patients based on **a** age, **b** laterality, and **c** treatment

both OS and CSS was noted for patients with the features of age ≥ 70 years, bilateral involvement, and without chemotherapy. On multivariate analysis, advanced age was an independent prognostic factor of decreased OS and CSS in adrenal DLBCL, while DLBCL located in the left adrenal and with chemotherapy were independent factors indicating prolonged OS and CSS. DLBCL with kidney or adrenal gland involvement was significantly associated with central nervous system (CNS) relapse or progression [17]; similarly, Shen et al. and Ichikawa et al. found that increased risk of CNS relapse would lead to poor OS in patients with PAL; however, the proportion of CNS relapse in this PAL cohort was unclear.

Treatment of PAL is similar to treatment of other types of lymphoma. The therapeutic modalities include surgery, combination chemotherapy, and surgery followed by chemotherapy and/or radiation therapy, in addition to corticosteroid replacement [26, 27]. Compared to patients with no treatment, people underwent chemotherapy were positive prognostic factors for predicting OS and CSS. This is consistent with what has been shown for other extranodal NHL including primary lymphomas of the bone [28], breast [29], and mediastinum [30]. As reported in the previous studies, the most common combinational chemotherapy regimens were CHOP or R-CHOP. Zhang et al., who tracked the outcomes of 14 patients with primary adrenal DLBCL in their series, encouraged the regimen of R-CHOP and reported that achieving CR after R-CHOP was predictive of survival [31]. Likewise, Yu et al. suggested that R-CHOP combination chemotherapy was an effective first-line regimen for primary adrenal DLBCL [11]. In addition, the rituximab-containing chemotherapy will prevent or reduce CNS relapse in patients with primary adrenal DLBCL [23, 32]. Despite the advent of rituximab-containing chemotherapeutic regimens, the long-term prognosis of primary adrenal lymphoma remains poor [30].

Conclusion

In conclusion, PAL is a rarity of extranodal NHLs, and the most common histological subtype is DLBCL. The features of primary adrenal DLBCL include single adrenal origin, staging early, effecting predominantly male, white, and the aged. Age more than 70 years old and bilateral were identified as independent prognostic factors that were correlated with both adverse OS and CSS, and patients with chemotherapy had a superior OS and CSS to the patients without any treatment.

Limitations

Though the SEER program database provided important insights into rare cancers such as adrenal DLBCL, some potential limitations that might interfere with the results could not be ignored.

First of all, the most common treatment for adrenal DLBCL is experiential chemotherapy as previous studies reported, but SEER database does not record adequately the administration of chemotherapy and the patient's performance status which the administration of treatment is biased based on. Therefore, it is impossible to evaluate different chemotherapy regimens to find the optimal personal treatment and make any confirm chemotherapy-related conclusions.

Next, it's better to differentiate subgroups within DLBCL, which correspond to different stages of B cell differentiation or cell-of-origin: germinal center B cell-like and activated B cell-like [13]. Usually, the former is associated with a better outcome. Regretfully, we were unable to conduct further study due to limited availability of materials.

Another limitation of this study is that the SEER database does not allow for analysis of other risk factors such as serum level of lactate dehydrogenase [33], tissue level of BCL-2 [34], tumor volume, or IPI [25] score for patients with primary adrenal DLBCL. It was unclear if the survival differences in our series are due to factors discussed above or due to other confounding factors that we could not account for. Further research was still needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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