Primary Extranodal Diffuse Large B-Cell Lymphoma In The Rituximab Era: A Single Center, Retrospective Analysis

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Abstract

Background: A large proportion of diffuse large B-cell lymphoma originates from extranodal sites. The outcomes of Chinese patients with primary extranodal diffuse large B-cell lymphoma (PE-DLBCL) have been greatly improved.

Methods: Clinical features and outcomes of 197 patients newly diagnosed with PE-DLBCL from January 2015 to December 2020 were analyzed retrospectively.

Results: (1) Gastrointestinal tract (34%) involvement ranked first, followed by central nervous system (CNS) and intraocular (31.5%), nose/nasopharynx (7.1%), breast (5.1%), testis (3.6%) and others. (2) The 3-year overall survival (OS) rate for the entire group was 81%; The 3-year OS rate of PE-DLBCL with CNS and vitreoretinal involvement was 79%. (3) In univariate analysis of PE-DLBCL, Ann Arbor stage, evaluated LDH, IPI>2 and complete remission (CR) were significantly related to survival. The lack of CR was the only independent adverse prognostic factor in OS ($p = 0.000$; HR = 4.659). (4) Lugano stage and treatment response were independent prognostic factors for primary gastrointestinal DLBCL.

Conclusion: This is a single-center report of PE-DLBCL in China in the past 5 years with a fairly excellent outcome and a large scale. The treatment response of patients is significantly better than before, especially in patients with CNS and vitreoretinal involvement.

Introduction

The malignant lymphomas, which represented a diverse group of diseases, may arise from tissues other than lymph nodes. The definition of extranodal lymphoma is still a controversial issue, especially when both lymph nodes and extranodal sites are involved. Referring to previous studies[1-4], lymphoma is defined to be primarily extranodal if 1) dominant lesion at extranodal sites; 2) only minor or no lymph node involvement. The prevalence of primary extranodal non-Hodgkin's lymphoma (PE-NHL) varies from country to country and ranging from 8.7 to 48%[5-8]. Diffuse large B-cell lymphoma (DLBCL) was the most common pathological subtype among patients with PE-NHL with a proportion of 71-81.3%[4, 9]. Primary extranodal DLBCL(PE-DLBCL) was originated from nearly every extranodal site of body, especially most common in gastrointestinal (GI) tract, followed by nasopharynx and neck, breast, central nervous system (CNS), skin, bone, thyroid, testis and rarely in other sites[4, 10, 11].

PE-DLBCLs are well-recognized heterogeneous Entities. However, the relevant content of research on them are extremely limited. After entering the era of universal affordability of rituximab, the survival of PE-DLBCL had greatly improved. Our center had also made great efforts in standardizing treatment, intensive induction and strengthening central prevention. The main objective of this study is to analyzed the specific clinical characteristics, response to treatments, survival of patients with PE-DLBCLs in a single center of China in new era.

Patients And Methods

Patients

644 patients newly diagnosed with DLBCL between January 2015 to December 2020 at our hospital were included, and 197 patients diagnosed with PE-DLBCL were evaluated. All biopsy specimens were classified by three specialized pathologists according to the WHO classification protocol independently[12].

The baseline data, such as sex, age, Ann Arbor stage, performance status, extranodal sites, complete blood count (CBC) and biochemical routine, including liver enzymes, creatinine, serum albumin and the level of lactate dehydrogenase (LDH) were collected. Necessary imaging evaluations such as positron emission tomography/computed tomography (PET/CT) or whole body computed tomography scan (CT) were examined before and after treatment. Patients with lymphoma were staged by the Ann Arbor classification scheme[13] and evaluated according to the International Prognostic Index (IPI) score[14]. PE-DLBCL with CNS or gastrointestinal involvement were evaluated by IELSG score[15] or Lugano classification[16], respectively.

Treatment, response and follow-up

The first-line treatment for patients with PE-DLBCL, except PCNS-DLBCLs, was R-CHOP[17] (rituximab, cyclophosphamide, doxorubicin, vindesine, prednisone) or R-EPOCH regimen[18] for patients with double-protein-expression. The regimen was given every three weeks for 6-8 cycles. MTX[19] (1g/m^2 , total 4 times) was added to some patients as CNS prophylaxis in induction therapy. Local and systemic therapies were applied in patients with primary vitreoretinal DLBCL(PVR-DLBCL): intravitreal methotrexate injections for one year (400ug, total 16 injections) and R2 regimen, which contained 6 cycles of the Lenalidomide (25 mg on day 1-21) and rituximab (375mg/m^2 on day 1)[20]. Other PCNS-DLBCLs were treated by high-dose methotrexate (3.5g/m^2)-based combined chemotherapy. The regimen was given every three weeks for 6-8 cycles.

The response to treatment was assessed according to the International Working Group criteria[21]. 18 patients were lost to follow-up until the final follow-up period of December 31, 2021.

Statistical analysis

Outcomes were described by the Progression-free survival (PFS) and Overall survival (OS). PFS was defined from the time of diagnosis to the first disease progression or death for any reason. OS was calculated from the date of diagnosis to the date of last follow-up or death for any reason. The Graph Pad Prisma 9.0 was used to performed the statistical analysis. Univariate analysis and generation of survival curves were performed using Kaplan-Meier and log-rank tests. Differences were evaluated using a two-tailed test; P values < 0.05 were considered statistically significant.

Results

Clinical characteristics

Patients newly diagnosed with PE-DLBCL accounts for 30.6% (197/644) of all DLBCL patients in our study. The median age was 58 (range, 19-91) years and 90 (45.7%) patients were male. Patients with central nervous system, intraocular, bone and thyroid involvement had worse physical status than those with other areas involved. B symptom was less common in patients with CNS (7/48, 14.6%), nose/nasopharynx (1/14, 7.1%), breast (2/10, 20%) or testis (1/7, 14.3%) involvement.

No significant difference was seen in the number of patients whom were classified as clinical stages I-II (122, 61.9%) and III-IV (75, 38.1%). The major involvement sites of patients with PE-DLBCL are presented in Table 1.

The gastrointestinal tract (GIT) constituted the most common site of PE-DLBCL, accounting for 34% of cases (36 stomach, 20 duodenum/jejunum, and 11 colon). Patients with central nervous system and intraocular involvement rank second (62, 31.5%), followed by nose/nasopharynx (14, 7.1%), breast (10, 5.1%), testis (7, 3.6%), bone, skin,

thyroid gland [6 patients (3%) each], female genital system (5, 2.5%), liver (4, 2%). Figure 1 shows the site distribution of extra-nodal lymphomas. Subgroups with less than 5 patients were excluded in the subsequent survival analysis.

Figure1. Anatomic Distributions in PE-DLBCL

Table 1. Patient characteristics according to the primary involved site.

Characteristics	GI tract	CNS+Eye	Nose/nasopharynx	Breast	Testis	Bone	Skin	Thyroid gland	FGS
Total	67	62	14	10	7	6	6	6	5
Age, years									
Median	62	61	54	45	58	73	54	63	62
Range	19-75	31-74	28-70	28-65	43-52	60-83	52-83	34-91	45-67
Age>60years	35	34	6	2	3	6	2	3	3
Sex									
Male	33	29	6	0	7	3	3	2	0
Female	34	33	8	10	0	3	3	4	5
ECOG status>1	13	51	2	1	1	4	2	4	1
Elevated LDH	15	17	2	0	3	5	4	3	1
B symptoms	24	7	1	2	1	4	3	2	2
Ann Arbor stage									
I+II	53	40	10	8	4	0	0	1	0
III+IV	14	22	4	2	3	6	6	5	5
Lugano stage									
I-II	53	-	-	-	-	-	-	-	-
IV	14	-	-	-	-	-	-	-	-
IELSG score									
0-1	-	15	-	-	-	-	-	-	-
2-3	-	32	-	-	-	-	-	-	-
4-5	-	15	-	-	-	-	-	-	-
Hans classification									
GCB	35	16	8	6	4	3	5	2	4
Non-GCB	30	24	6	4	3	3	1	4	1
DE	17	12	4	5	3	2	3	1	4
IPI score									
Low	38	-	9	8	4	0	1	3	1
Low-intermediate	14	-	3	2	1	1	2	0	0
High-	9	-	2	0	0	3	1	2	3

intermediate									
High	6	-	0	0	2	2	2	1	1
Therapy									
R-CHOP	58	-	9	7	5	2	4	4	5
R-EPOCH	4	-	5	1	2	0	0	1	0
Chemotherapy only	48	44	11	4	0	3	6	2	3
Chemo+ surgery	19	18	3	6	7	2	0	4	2
CNS prophylaxis	7	-	3	7	4	1	2	0	2
Received ASCT	2	4	0	1	0	0	1	0	1

ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; ASCT, autologous hematopoietic stem cell transplantation; DE, double-protein-expression

Response to treatment and survival

9.1% patients with PE-DLBCL were lost to follow-up in this study. The median follow-up period was 31.8 (range, 0.2-80.8) months. At the last follow-up, 35.6% (69/194) patients had experienced relapse of disease and 19.6% (35/179) patients had been dead. The median PFS and OS were 23.8(range, 0.1-80.8) and 31.8 (range, 0.2-80.8) months, respectively (Figure 2). The 3-year OS rates of patients with primary GI tract, Eye+CNS, nose/ nasopharynx, breast, FGS, bone, thyroid gland, testis and skin involvement were 84%, 79%, 83%, 86%, 100%, 80%, 83%, 100%, 67%, respectively.

A total of 117(59.3%) patients achieved CR and 21(10.6%) achieved PR, leading to a total response rate (RR) of 70.1%. The RR for patients with PCNS-DLBCL and PVR-DLBCL was 67.8%, and nose/ nasopharynx, thyroid gland, testis, breast, GI tract, bone, skin, liver and FGS involvement was 92.9, 83.3, 75, 70, 68.7, 66.7, 57.1, 50 and 33.3%, respectively.

Figure 2. OS and PFS for patients with PE-DLBCL

The proportion of patients undergoing chemotherapy with surgery in PCNS-DLBCL, primary female genital system DLBCL(PFGS-DLBCL), primary breast-DLBCL(PB-DLBCL), primary thyroid gland DLBCL(PT-DLBCL) and primary GI DLBCL (PGI-DLBCL) was 37.5, 40, 60, 66.7 and 28.4%, respectively. There were no significant statistical differences between the clinical outcome in two groups of patients who had and had not undergone surgery both in PCNS-DLBCL and PGI-DLBCL (Figure 3).

Figure 3. OS (a) and PFS(b) of PCNS-DLBCL patients with or without surgery; OS (c) and PFS(d) of PGI-DLBCL patients with or without surgery. 1(9.1%) patient with primary vitreoretinal DLBCL(PVR-DLBCL) was dead during our study period. 64.3% (9/11) patients with PVR-DLBCL achieved CR after first-line therapy and 78.6% (11/14) patients experienced disease relapsed, of which 5 patients had central nervous system relapsed. Complete remission, relapse and mortality rates were 45.8% (22/48),56.2% (27/48) and 20.8% (10/48) for patients with PCNS-DLBCL,

respectively. No statistically significant differences in the clinical outcome between two groups of patients (PCNS-DLBCL versus PVR-DLBCL) were observed. (Figure 4)

Figure 4. OS(a) and PFS(b) between patients with PCNS-DLBCL and PVR-DLBCL

Prognostic factors

Univariate and multivariate analysis results of patients with PE-DLBCL are presented in table 2. According to the univariate results, Ann Arbor stage, evaluated LDH, IPI>2, not received CR and double hit were related to survival significantly. However, in multivariate analysis, failure to achieve CR after first-line therapy was independent predictor of OS and PFS in patients with PE-DLBCL.

Table 2. Risk factors for survival of PE-DLBCL

Variables	Overall survival				Progression-free survival			
	Univariate	Multivariate			Univariate	Multivariate		
	P value	HR	95%	P value	P value	HR	95%	P value
Male	0.416				0.499			
Age>60	0.127				0.115			
Evaluated LDH	0.029			NS	0.005			NS
ECOG>1	0.200				0.147			
With B symptom	0.503				0.417			
Ann Arbor stage III-IV	0.031			NS	0.019			NS
IPI>2	0.047			NS	0.152			
GCB	0.989				0.997			
DE	0.308				0.300			
DH	0.018			NS	0.000			NS
Not received CR	0.000	4.659	2.083-10.423	0.000	0.000	5.001	2.231-11.209	0.000
Primary organ	0.641				0.480			
NS: not significant; DH: double hit; DE: double-protein-expression								

The univariate and multivariate analysis results of PGI-DLBCL are presented in Table3. According to the univariate results, B symptom, evaluated LDH, IPI>2, Lugano stage, failure to achieve CR and double hit were related to survival of PGI-DLBCL significantly. The independent risk factors for PFS included not received CR and Lugano stage IV in multivariate analysis.

Table 3. Risk factors for survival of PGI-DLBCL

Variables	Overall survival				Progression-free survival			
	Univariate	Multivariate			Univariate	Multivariate		
	P value				P value			
		HR	95%	P value		HR	95%	P value
Male	0.640				0.678			
Age>60	0.068			NS	0.093			NS
Evaluated LDH	0.000			NS	0.000			NS
Anemia	0.980				0.877			
Albumin<35g/L	0.355				0.330			
ECOG>1	0.426				0.419			
With B symptom	0.042			NS	0.052			NS
Lugano stage IV	0.021			NS	0.015	3.395	1.033-11.162	0.044
IPI>2	0.043			NS	0.059			NS
GCB	0.744				0.700			
DE	0.392				0.463			
DH	0.012			NS	0.000			NS
Not received CR	0.001	2.555	1.296-5.037	0.007	0.000	2.304	1.145-4.639	0.019

NS: not significant; DH: double hit; DE: double-protein-expression

Discussion

To our knowledge, this is a cohort of extranodal lymphomas with fairly good clinical outcomes in the last 5 years. The prognosis of PE-DLBCL is getting better in the era of rituximab.

Different extranodal sites of involvement are related to distinct clinical characteristics. In contrast to previously reported studies[22–24], there are slightly more female patients with PE-DLBCL than male at our center. 38.1% patients with PE-DLBCL were in advanced staged when diagnosed, whereas primary nodal DLBCL were classified as stage III-IV more[22, 25, 26]. Possible because patients will have earlier local symptoms due to tumor mass. In addition, different definition for primary extranodal lymphoma can also lead to this difference[3, 27].

The gastrointestinal tract is the most common site of extranodal involvement, while other sites are rare[4, 28]. However, patients with central nervous system and intraocular involvement also account for a high proportion in our study, partly due to the conduct of clinical trials, which will lead to considerable differences in subsequent analysis.

The patients with PCNS-DLBCL, comparing with the largest descriptive research of China, had a better outcome in our center. Studies have shown that surgical excision for intracranial PCNS-DLBCL does not improve survival[29,

30], and our results are consistent. Systemic chemotherapy combined with intravitreal chemotherapeutic drug injection for patients with primary vitreoretinal DLBCL(PVR-DLBCL) as initial treatment may achieve a relatively better outcome[20]. Lenalidomide[31] had been demonstrated prominent effect on DLBCL, particularly non-GCB subtype. The combination of rituximab and lenalidomide (R2) can lead to good synergistic effect[32]. Recently, the R2 regimen was reported significant activity in relapsed/refractory PVRL and PCNSL patients[33]. Our center began to use R2-MTX regimen as the first choice for standard induction chemotherapy for newly diagnosed PCNS-DLBCL, with ORR of 100% (NCT 04120350). However, despite advances in initial treatment, more than 1/3 of patients relapsed[34] and no uniform treatment guidelines for relapsed and refractory PCNSL (R/R PCNSL). In this study, there was no statistically significant difference in survival between PVR-DLBCL and PCNS-DLBCL, which may be due to the higher relapsed rate of PVR-DLBCL and most of them were associated with central relapsed. In addition, bruton tyrosine kinase (BTK) inhibitors[35] and PD-1 blockade[36] therapy show good antitumor activity in R/R PCNSL. 6 patients with R/R PCNSL and treated by orelabrutinib plus sintilimab achieved PR/CR in this study and are still under follow-up. Patients do have a more promising future as new treatments and monitoring tools increase.

In rituximab era, fewer scholars still believe that surgical treatment can achieve a better prognosis than conservative treatment[37]. Most studies have shown that surgical treatment is playing an increasingly inconspicuous role in the treatment of primary gastrointestinal DLBCL(PGI-DLBCL), while mostly used for definitive diagnosis or clinical emergencies[38, 39]. The data from our study also showed no significant difference in the outcome of patients receiving chemotherapy alone compared with those treated by surgery combined with chemotherapy. The value of probably prognostic factors like gender, LDH levels, B symptoms and International Prognostic Index (IPI) remains controversial[40–42] in patients with PGI-DLBCL. We agreed with previously reported studies that Lugano stage could effectively predict prognosis of PGI-DLBCL[24, 43].

Although univariate analysis showed differences in IPI, LDH, DH, Ann Arbor stage and achieving CR following first-line treatment, achieving CR was indeed identified as factors leading to better survival in our study, which was different from our previous retrospective study[44] and research data of other centers[23]. This can be explained by the selection bias of hospitalized patients and the fact that more alternative immuno-targeted therapies have reduced the differences in outcomes associated with different baseline characteristics. The short follow-up of our study may also be a reason that cannot be ignored. In order to achieve CR in first-line treatment, we took intensive induction therapy in some patients with double-protein-expression, which also proved to have better efficacy. At the same time, it also suggests that we may need a better prognostic integral model for PE-DLBCL in the future[45–47].

Different sites of extranodal involvement are related to widely different clinical outcomes[28, 48]. Comparing the analysis of the largest comprehensive descriptive study in China[49] and SEER database[50], which is based on the anatomical distribution of DLBCL for clinical outcomes, we found that the PE-DCLBL patients in our cohort showed a better prognosis. But this result requires a longer follow-up time to confirm. In our study, primary bone DLBCL and primary thyroid gland DLBCL(PT-DLBCL), consistent with previous reports[51–53], were associated with a better prognosis. Two-thirds of patients with PT-DLBCL underwent total or subtotal thyroidectomy, which had proved to be associated with significantly improved survival[54]. Primary testis DLBCL were related to higher CNS relapsed rate and unfavorable outcome[55, 56]. 4/7 patients in our study used MTX for CNS prophylaxis, which is still controversial[57, 58], only 1/7 of them had central recurrence and all had favorable clinical outcomes.

In summary, our study demonstrated that the different sites of extranodal involvement in patients are accompanied by different clinical features and have different outcomes. The clinical outcome of PE-DLBCL in our center had been greatly improved through standardized treatment, the addition of immune-targeted drugs such as lenalidomide,

local plus systemic treatment for PVR-DLBCL in cooperation with ophthalmology, and intravenous MTX prophylaxis for central high-risk groups.

Abbreviations

DLBCL: diffuse large B-cell lymphoma

CNS: central nervous system

PE-DLBCL: primary extranodal diffuse large B-cell lymphoma

GI: gastrointestinal

IPI: International Prognostic Index

PFS: progression-free survival

OS: overall survival

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients for being included in the study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JZ analyzed and interpreted the patient data and was a major contributor in writing the manuscript. DBZ and ZW conceived and designed the work that led to the submission, acquired data and had an important role in interpreting the results. YZ, DZ, WW, JR, CW, ZW and ZZ participated in the diagnosis and treatment of patients and provided the clinical data, they also contributed significantly to acquisition and analysis of data, drafting the manuscript and

revising it critically. WZ gave final approval of the version to be published. All authors read and approved the final manuscript.

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References

1. Dawson IM, Cornes JS, Morson BC: **Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis.** Br J Surg 1961, **49**:80–89.
2. Economopoulos T, Asprou N, Stathakis N, Papageorgiou E, Dervenoulas J, Xanthaki K, Raptis S: **Primary extranodal non-Hodgkin's lymphoma in adults: clinicopathological and survival characteristics.** Leuk Lymphoma 1996, **21**(1–2):131–136.
3. d'Amore F, Christensen BE, Brincker H, Pedersen NT, Thorling K, Hastrup J, Pedersen M, Jensen MK, Johansen P, Andersen E *et al.*: **Clinicopathological features and prognostic factors in extranodal non-Hodgkin lymphomas. Danish LYFO Study Group.** Eur J Cancer 1991, **27**(10):1201–1208.
4. AlShemmari SH, Ameen RM, Sajnani KP: **Extranodal lymphoma: a comparative study.** Hematology 2008, **13**(3):163–169.
5. Zucca E, Roggero E, Bertoni F, Cavalli F: **Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas.** Ann Oncol 1997, **8**(8):727–737.
6. Zucca E, Roggero E, Bertoni F, Conconi A, Cavalli F: **Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites.** Ann Oncol 1999, **10**(9):1023–1033.
7. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM: **Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry.** Ann Oncol 2003, **14**(1):131–139.
8. Candelaria M, Oñate-Ocaña LF, Corona-Herrera J, Barrera-Carmona C, Ponce-Martínez M, Gutiérrez-Hernández O, Avilés-Salas A, Cacho-Díaz B: **CLINICAL CHARACTERISTICS OF PRIMARY EXTRANODAL VERSUS NODAL DIFFUSE LARGE B-CELL LYMPHOMA: A RETROSPECTIVE COHORT STUDY IN A CANCER CENTER.** Rev Invest Clin 2019, **71**(5):349–358.
9. Yun J, Kim SJ, Won JH, Choi CW, Eom HS, Kim JS, Kim MK, Kwak JY, Kim WS, Suh C: **Clinical features and prognostic relevance of ovarian involvement in non-Hodgkin's lymphoma: A Consortium for Improving Survival of Lymphoma (CISL) report.** Leuk Res 2010, **34**(9):1175–1179.
10. Yun J, Kim SJ, Kim JA, Kong JH, Lee SH, Kim K, Ko YH, Kim WS: **Clinical features and treatment outcomes of non-Hodgkin's lymphomas involving rare extranodal sites: a single-center experience.** Acta Haematol 2010, **123**(1):48–54.
11. Reddy S, Pelletiere E, Saxena V, Hendrickson FR: **Extranodal non-Hodgkin's lymphoma.** Cancer 1980, **46**(9):1925–1931.
12. Polyatskin IL, Artemyeva AS, Krivolapov YA: **[Revised WHO classification of tumors of hematopoietic and lymphoid tissues, 2017 (4th edition):lymphoid tumors].** Arkh Patol 2019, **81**(3):59–65.
13. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M: **Report of the Committee on Hodgkin's Disease Staging Classification.** Cancer Res 1971, **31**(11):1860–1861.
14. **A predictive model for aggressive non-Hodgkin's lymphoma.** N Engl J Med 1993, **329**(14):987–994.

15. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, Calderoni A, Rossi A, Vavassori V, Conconi A *et al*: **Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience.** J Clin Oncol 2003, **21**(2):266–272.
16. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA: **Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification.** J Clin Oncol 2014, **32**(27):3059–3068.
17. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P *et al*: **CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.** N Engl J Med 2002, **346**(4):235–242.
18. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, Steinberg SM, Little RF, Janik J, Gutierrez M *et al*: **Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy.** Blood 2002, **99**(8):2685–2693.
19. Wang W, Zhang Y, Zhang L, Yang C, Feng J, Cai H, Chen M, Cao X, Zhuang J, Zhu T *et al*: **Intravenous methotrexate at a dose of 1 g/m² incorporated into RCHOP prevented CNS relapse in high-risk DLBCL patients: A prospective, historic controlled study.** Am J Hematol 2020, **95**(4):E80-e83.
20. Zhang Y, Zhang X, Zou D, Yin J, Zhang L, Wang X, Jia C, Wang W, Zhao D, Zhou D *et al*: **Lenalidomide and Rituximab Regimen Combined With Intravitreal Methotrexate Followed by Lenalidomide Maintenance for Primary Vitreoretinal Lymphoma: A Prospective Phase II Study.** Front Oncol 2021, **11**:701507.
21. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E *et al*: **Revised response criteria for malignant lymphoma.** J Clin Oncol 2007, **25**(5):579–586.
22. Castillo JJ, Winer ES, Olszewski AJ: **Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: an analysis of the Surveillance, Epidemiology and End Results database.** Am J Hematol 2014, **89**(3):310–314.
23. Lal A, Bhurgri Y, Vaziri I, Rizvi NB, Sadaf A, Sartajuddin S, Islam M, Kumar P, Adil S, Kakepoto GN *et al*: **Extranodal non-Hodgkin's lymphomas—a retrospective review of clinico-pathologic features and outcomes in comparison with nodal non-Hodgkin's lymphomas.** Asian Pac J Cancer Prev 2008, **9**(3):453–458.
24. Huang J, Jiang W, Xu R, Huang H, Lv Y, Xia Z, Sun X, Guan Z, Lin T, Li Z: **Primary gastric non-Hodgkin's lymphoma in Chinese patients: clinical characteristics and prognostic factors.** BMC Cancer 2010, **10**:358.
25. **A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project.** Blood 1997, **89**(11):3909–3918.
26. Møller MB, Pedersen NT, Christensen BE: **Diffuse large B-cell lymphoma: clinical implications of extranodal versus nodal presentation—a population-based study of 1575 cases.** Br J Haematol 2004, **124**(2):151–159.
27. Lewin KJ, Ranchod M, Dorfman RF: **Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease.** Cancer 1978, **42**(2):693–707.
28. Lu CS, Chen JH, Huang TC, Wu YY, Chang PY, Dai MS, Chen YC, Ho CL: **Diffuse large B-cell lymphoma: sites of extranodal involvement are a stronger prognostic indicator than number of extranodal sites in the rituximab era.** Leuk Lymphoma 2015, **56**(7):2047–2055.
29. Ouyang T, Wang L, Zhang N, Zhang Z, Xiong Y, Li M, Hong T: **Clinical Characteristics, Surgical Outcomes, and Prognostic Factors of Intracranial Primary Central Nervous System Lymphoma.** World Neurosurg 2020, **139**:e508-e516.

30. Labak CM, Holdhoff M, Bettgowda C, Gallia GL, Lim M, Weingart JD, Mukherjee D: **Surgical Resection for Primary Central Nervous System Lymphoma: A Systematic Review.** *World Neurosurg* 2019, **126**:e1436-e1448.
31. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, Pileri SA, Malik F, Macon WR, Goy A, Witzig TE, Czuczman MS: **Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype.** *Cancer* 2011, **117**(22):5058–5066.
32. Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, Ottman E, Czuczman MS: **Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model.** *Clin Cancer Res* 2005, **11**(16):5984–5992.
33. Ghesquieres H, Chevrier M, Laadhari M, Chinot O, Choquet S, Moluçon-Chabrot C, Beauchesne P, Gressin R, Morschhauser F, Schmitt A *et al*: **Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†.** *Ann Oncol* 2019, **30**(4):621–628.
34. Jahnke K, Thiel E, Martus P, Herrlinger U, Weller M, Fischer L, Korfel A: **Relapse of primary central nervous system lymphoma: clinical features, outcome and prognostic factors.** *J Neurooncol* 2006, **80**(2):159–165.
35. Grommes C, Tang SS, Wolfe J, Kaley TJ, Daras M, Pentsova EI, Piotrowski AF, Stone J, Lin A, Nolan CP *et al*: **Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma.** *Blood* 2019, **133**(5):436–445.
36. Nayak L, Iwamoto FM, LaCasce A, Mukundan S, Roemer MGM, Chapuy B, Armand P, Rodig SJ, Shipp MA: **PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma.** *Blood* 2017, **129**(23):3071–3073.
37. Wang YG, Zhao LY, Liu CQ, Pan SC, Chen XL, Liu K, Zhang WH, Yang K, Chen XZ, Zhang B *et al*: **Clinical characteristics and prognostic factors of primary gastric lymphoma: A retrospective study with 165 cases.** *Medicine (Baltimore)* 2016, **95**(31):e4250.
38. Lightner AL, Shannon E, Gibbons MM, Russell MM: **Primary Gastrointestinal Non-Hodgkin's Lymphoma of the Small and Large Intestines: a Systematic Review.** *J Gastrointest Surg* 2016, **20**(4):827–839.
39. Ge Z, Liu Z, Hu X: **Anatomic distribution, clinical features, and survival data of 87 cases primary gastrointestinal lymphoma.** *World J Surg Oncol* 2016, **14**:85.
40. Ferreri AJ, Montalbán C: **Primary diffuse large B-cell lymphoma of the stomach.** *Crit Rev Oncol Hematol* 2007, **63**(1):65–71.
41. Mok TS, Steinberg J, Chan AT, Yeo WM, Hui P, Leung TW, Johnson P: **Application of the international prognostic index in a study of Chinese patients with non-Hodgkin's lymphoma and a high incidence of primary extranodal lymphoma.** *Cancer* 1998, **82**(12):2439–2448.
42. d'Amore F, Brincker H, Grønbaek K, Thorling K, Pedersen M, Jensen MK, Andersen E, Pedersen NT, Mortensen LS: **Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. Danish Lymphoma Study Group.** *J Clin Oncol* 1994, **12**(8):1673–1684.
43. Cortelazzo S, Rossi A, Roggero F, Oldani E, Zucca E, Tondini C, Ambrosetti A, Pasini F, Pinotti G, Bertini M *et al*: **Stage-modified international prognostic index effectively predicts clinical outcome of localized primary gastric diffuse large B-cell lymphoma. International Extranodal Lymphoma Study Group (IELSG).** *Ann Oncol* 1999, **10**(12):1433–1440.

44. Shen H, Wei Z, Zhou D, Zhang Y, Han X, Wang W, Zhang L, Yang C, Feng J: **Primary extra-nodal diffuse large B-cell lymphoma: A prognostic analysis of 141 patients.** *Oncol Lett* 2018, **16**(2):1602–1614.
45. Gao F, Wang ZF, Tian L, Dong F, Wang J, Jing HM, Ke XY: **A Prognostic Model of Gastrointestinal Diffuse Large B Cell Lymphoma.** *Med Sci Monit* 2021, **27**:e929898.
46. Hwang HS, Yoon DH, Suh C, Park CS, Huh J: **Intestinal diffuse large B-cell lymphoma: an evaluation of different staging systems.** *J Korean Med Sci* 2014, **29**(1):53–60.
47. Hwang HS, Yoon DH, Suh C, Huh J: **A new extranodal scoring system based on the prognostically relevant extranodal sites in diffuse large B-cell lymphoma, not otherwise specified treated with chemoimmunotherapy.** *Ann Hematol* 2016, **95**(8):1249–1258.
48. Takahashi H, Tomita N, Yokoyama M, Tsunoda S, Yano T, Murayama K, Hashimoto C, Tamura K, Sato K, Ishigatsubo Y: **Prognostic impact of extranodal involvement in diffuse large B-cell lymphoma in the rituximab era.** *Cancer* 2012, **118**(17):4166–4172.
49. Shi Y, Han Y, Yang J, Liu P, He X, Zhang C, Zhou S, Zhou L, Qin Y, Song Y *et al*: **Clinical features and outcomes of diffuse large B-cell lymphoma based on nodal or extranodal primary sites of origin: Analysis of 1,085 WHO classified cases in a single institution in China.** *Chin J Cancer Res* 2019, **31**(1):152–161.
50. Yin X, Xu A, Fan F, Huang Z, Cheng Q, Zhang L, Sun C, Hu Y: **Incidence and Mortality Trends and Risk Prediction Nomogram for Extranodal Diffuse Large B-Cell Lymphoma: An Analysis of the Surveillance, Epidemiology, and End Results Database.** *Front Oncol* 2019, **9**:1198.
51. Matikas A, Briasoulis A, Tzannou I, Oikonomopoulou D, Bakiri M, Karmiris T, Harhalakis N: **Primary bone lymphoma: a retrospective analysis of 22 patients treated in a single tertiary center.** *Acta Haematol* 2013, **130**(4):291–296.
52. Huan Y, Qi Y, Zhang W, Chu J: **Primary bone lymphoma of radius and tibia: A case report and review of literature.** *Medicine (Baltimore)* 2017, **96**(15):e6603.
53. Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, Abbondanzo SL: **Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases.** *Am J Surg Pathol* 2000, **24**(5):623–639.
54. Vardell Noble V, Ermann DA, Griffin EK, Silberstein PT: **Primary Thyroid Lymphoma: An Analysis of the National Cancer Database.** *Cureus* 2019, **11**(2):e4088.
55. Koukourakis G, Kouloulis V: **Lymphoma of the testis as primary location: tumour review.** *Clin Transl Oncol* 2010, **12**(5):321–325.
56. Xu H, Yao F: **Primary testicular lymphoma: A SEER analysis of 1,169 cases.** *Oncol Lett* 2019, **17**(3):3113–3124.
57. Vitolo U, Chiappella A, Ferreri AJ, Martelli M, Baldi I, Balzarotti M, Bottelli C, Conconi A, Gomez H, Lopez-Guillermo A *et al*: **First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial.** *J Clin Oncol* 2011, **29**(20):2766–2772.
58. Kridel R, Dietrich PY: **Prevention of CNS relapse in diffuse large B-cell lymphoma.** *Lancet Oncol* 2011, **12**(13):1258–1266.

Figures

Figure 1

Figure 2

OS and PFS for patients with PE-DLBCL

Figure 3

OS (a) and PFS(b) of PCNS-DLBCL patients with or without surgery; OS (c) and PFS(d) of PGI-DLBCL patients with or without surgery.

Figure 4

OS(a) and PFS(b) between patients with PCNS-DLBCL and PVR-DLBCL