

# Clinical features, survival and prognostic factors of primary testicular diffuse large B-cell lymphoma

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**Objective:** To assess the clinical features, survival and prognostic factors of primary testicular diffuse large B-cell lymphoma (DLBCL).

**Methods:** A retrospective study of 37 patients with primary testicular DLBCL was carried out from November 2003 to May 2012. Their clinical features, survival and prognostic factors were analyzed.

**Results:** During a median follow-up period of 39.8 months (5.4-93.0 months), the median progression-free survival (PFS) was 26.2 months (95% CI: 0-65 months) and the 3-year overall survival (OS) rate was 78.4%. Within the whole cohort, the factors significantly associated with a superior PFS were limited stage (stage I/II), lactate dehydrogenase (LDH)  $\leq 245$  U/L, international prognostic index (IPI)  $\leq 1$ , primary tumor diameter  $< 7.5$  cm, and patients who had complete response (CR) and received doxorubicin-contained chemotherapy ( $P < 0.05$ ). There was a trend toward superior outcome for patients who received combined therapy (surgery/chemotherapy/radiotherapy) ( $P = 0.055$ ). Patients who had CR, primary tumor diameter  $< 7.5$  cm and IPI score  $\leq 1$  were significantly associated with longer PFS at multivariate analysis.

**Conclusions:** Primary testicular DLBCL had poorer survival. CR, primary tumor diameter and IPI were independent prognostic factors. The combined therapy of orchiectomy, doxorubicin-contained chemotherapy and contralateral testicular radiotherapy (RT) seemed to improve survival.

**Keywords:** Diffuse large B-cell lymphoma (DLBCL); testicular; survival; prognostic factor; chemotherapy; radiotherapy (RT)

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## Introduction

Primary testicular lymphoma (PTL) is an uncommon disease, and accounts for approximately 1-2% of non-Hodgkin's lymphomas and less than 5% of all testicular malignancies, among which primary testicular diffuse large B-cell lymphoma (DLBCL) is the most common type, which incidence was estimated to be 0.26/100,000 per year (1). According to the previous studies, the median overall survival (OS) of PTL is 4-5 years and a continuous risk of relapse exists after diagnosis (2,3). Distant relapse at extranodal

sites, especially the central nervous system (CNS) and the contralateral testis, remains the greatest challenge in PTL (4,5). The international extranodal lymphoma study group (IELSG) 10 trial was the first prospective study in PTL, which revealed that a trimodality treatment with RCHOP chemotherapy, contralateral testicular radiotherapy (RT) and CNS prophylaxis was associated with a good outcome in patients with PTL (6). However, the treatment for PTL is still variable and the prognostic factors remain unclear in Chinese patients.

Herein, we performed a retrospective study to assess

clinical characteristics, treatment modalities, survival and prognostic factors of 37 cases of primary testicular DLBCL. As the disease is rare and the related data in China is scarce, this paper can provide a relative deep insight into primary testicular DLBCL for Chinese patients.

## Materials and methods

### Patients

Thirty-seven cases of primary testicular DLBCL, who were admitted in Cancer Institute & Hospital, Chinese Academy of Medical Sciences (CAMS) & Peking Union Medical College (PUMC) from November 2003 to May 2012, were involved in the study. Initial staging was performed for each patient according to the Ann Arbor classification. All tumor tissue specimens were reviewed. Hans' algorithm was used to determine germinal center (GC) or non-germinal center (non-GC) classification (7). Initial responses at the end of primary treatment were recorded. The study was approved by the Ethic Committee of Cancer Institute & Hospital, CAMS & PUMC.

### Research endpoint

According to the International Workshop Criteria, initial responses include complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). When the responses could not be determined, the cases were classified as not evaluable (NE). OS was calculated from the date of diagnosis to the date of either last follow-up or deaths from any cause. Patients who were alive at last follow-up visit were referred to as censored data. Progression-free survival (PFS) was calculated from the date of the diagnosis to the date of disease progression, first relapse, deaths from any cause or last follow-up. The patients without relapse, disease progression or deaths at last follow-up visit were recognized as censored data.

### Statistical analysis

Survival rates and PFS were estimated by the Kaplan-Meier method, and the differences between the curves were analyzed using the Log-rank test. The Cox proportional hazards model was used for multivariate analysis of PFS.  $P < 0.05$  (two-sided test) was considered statistically significant. The statistical analyses were conducted using the SPSS 19.0 software package (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Thirty-seven cases were included in our study. Their characteristics are shown in *Table 1*. The median age at diagnosis was 61 years (range, 29-85 years). Thirty-one patients presented with early stage disease (stage I/II), and 6 patients with advanced stage (stage III/IV). International prognostic index (IPI) score was calculated in all patients, with 0-1 in 28 patients and  $\geq 2$  in 9 patients. Among the 33 cases examined, 29 (88%) belonged to the non-germinal center B cell (GCB) like type. Of the 25 cases evaluated, Bcl-2 expression was positive in 22 cases (88%).

Thirty-six patients underwent surgery as first therapeutic and diagnostic intervention (testicular mass resection in 6 cases; orchidectomy in 9 cases; high inguinal orchidectomy in 21 cases). Thirty-one patients received chemotherapy, including doxorubicin-contained regimen in 31 patients, etoposide-contained regimen in 7 and rituximab-contained regimen in 17. The median number of cycles was six (range, 1-8). Twenty-two patients received RT, among which 8 cases underwent RT at the contralateral testis alone and 14 cases at the contralateral testis plus abdominal lymph nodes. Twenty patients received CNS prophylaxis. Specifically, 16 patients received intrathecal methotrexate or cytarabine, and 4 patients received intravenous methotrexate (*Table 1*).

### Response

Of 32 evaluable patients, 25 patients achieved CR (78%), 6 PR (19%) and 1 SD (3%). No patients experienced PD during treatment (*Table 2*).

### Follow-up and survival

The median follow-up period of the 37 patients was 39.8 months (5.4-93.0 months). The median PFS was 26.2 months [95% confidence interval (95% CI): 0-65 months]. The 3-year OS rate was 78.4% (*Figure 1*).

Nineteen of 37 patients relapsed or progressed at the time of analysis. Sites of failure are available in *Table 3*. CNS progression and death occurred in five patients even though two of them received intrathecal prophylaxis.

### Prognostic factors

Using PFS (as defined above) as the primary endpoint, the potential prognostic factors were examined by Kaplan-

**Table 1** Pathological and clinical features of 37 primary DLBCL patients

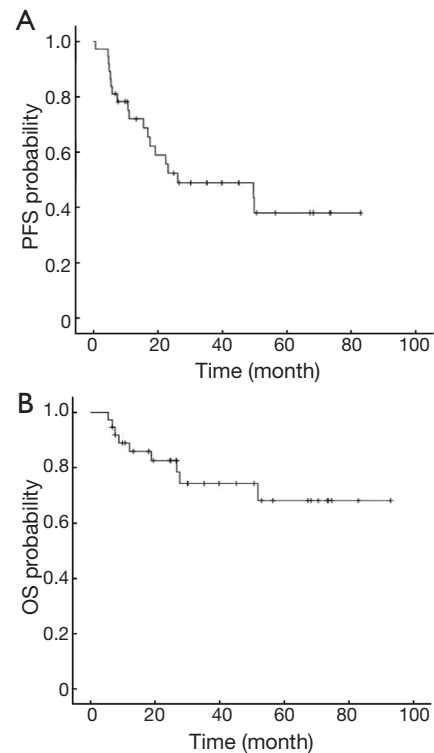
Patients	n	%
Age (year)		
<60	17	46
≥60	20	54
Laterality		
Left	10	27
Right	22	59
Bilateral	5	14
Stage		
I	22	59
II	9	24
III	1	3
IV	5	14
IPI		
0-1	28	76
≥2	9	24
Histology*		
GCB	4 [33]	12
Non-GCB	29 [33]	88
BCL-2+	22 [25]	88
Ki67		
<50%	3 [27]	11
50%<-90%	19 [27]	70
≥90%	5 [27]	19
Radiotherapy	22	59
Contralateral testis alone	8	22
Contralateral testis plus abdominal lymphnodes	14	37
Chemotherapy		
Doxorubicin-contained	31	84
Rituximab-contained	17	46
Etoposide-contained	7	19
CNS prophylaxis	20	54
Intrathecal methotrexate/cytarabine	16	43
Intravenous methotrexate	4	11
Treatment modalities		
Surgery alone	3	8
Chemotherapy alone	1	2
Surgery + radiotherapy	3	8
Surgery + chemotherapy	11	30
Surgery + chemotherapy + radiotherapy	19	52

IPI, international prognostic index; BCL-2, b-cell leukemia-2; GCB, germinal center B cell like lymphoma; non-GCB, non-germinal center B cell like lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma. \*, GCB type was evaluated in 33 patients, BCL-2 was assessed in 25 patients and Ki67 was detected in 27 patients.

**Table 2** Response evaluated at the end of primary treatment

Response	n	%
CR	25	78
PR	6	19
SD	1	3
PD	0	0
Total	32	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.



**Figure 1** PFS (A) and OS (B) in all patients. PFS, progression-free survival; OS, overall survival.

**Table 3** Recurrence sites

Site	n	%
Lymph nodes	4	11
Central nervous system	7	19
Contralateral testis	2	5
Skin	3	8
Liver	1	3
Lung	1	3
Bone	2	5
Kidney	1	3
Stomach	1	3

**Table 4** Univariate analysis of impact of various clinical variables on PFS

Variable	n	Median PFS (month)	P
<b>Tumor diameter (cm)</b>			
<7.5	26	49.7	0.046
≥7.5	11	15.5	
<b>CR status</b>			
CR	24	Not reach	0.001
Not CR	13	7.4	
<b>Stage</b>			
I/II	31	49.9	0.011
III/IV	6	7.4	
<b>LDH</b>			
≤245 U/L	25	Not reach	0.020
>245 U/L	12	11.1	
<b>IPI</b>			
0-1	27	49.9	0.004
≥2	10	7.4	
<b>Age (year)</b>			
≤60	18	26.2	0.922
>60	19	23.2	
<b>BCL-2*</b>			
0-1	10	67.3	0.456
2-3	15	26.6	
<b>Numbers of extra lymph node infiltration</b>			
1	30	49.7	0.651
≥2	7	26.2	
<b>Primary tumor</b>			
Infiltrated epididymis or spermatic cord	15	17.6	0.259
Not infiltrated	22	49.9	
<b>β2MG</b>			
Elevated	9	16.9	0.246
Normal	28	26.2	
<b>Rituximab</b>			
Contained	17	26.2	0.791
Not contained	20	23.2	
<b>Chemotherapy cycle</b>			
<6	17	23.2	0.431
≥6	20	50.0	
<b>Doxorubicin-contained regimen</b>			
Received	31	49.9	0.003
Not received	6	5.4	

**Table 4** (continued)

**Table 4** (continued)

Variable	n	Median PFS (month)	P
<b>Radiotherapy</b>			
Received	22	49.7	0.184
Not received	15	22.4	
<b>CNS prophylaxis</b>			
Received	20	50.0	0.353
Not received	17	23.2	
<b>Modality therapy (surgery/chemotherapy/radiotherapy)</b>			
Received	19	Not reach	0.055
Not received	18	22.4	

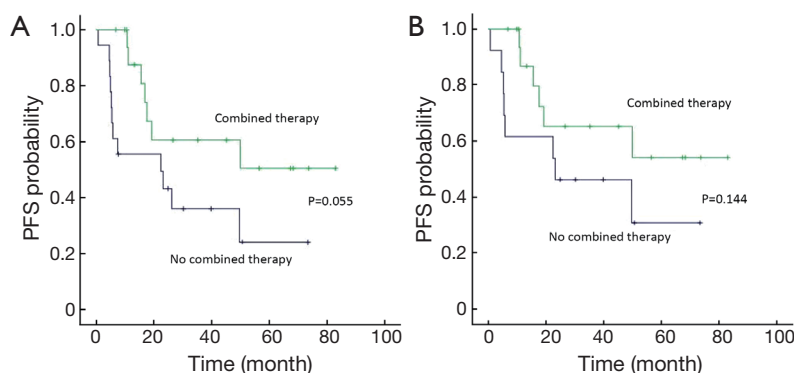
CR, complete response; LDH, lactate dehydrogenase; IPI, international prognostic index; BCL-2, b-cell leukemia-2; β2MG, β2-microglobulin; CNS, central nervous system diseases; progression-free survival; \*, BCL-2 was assessed in 25 patients.

Meier method and Log-rank test analysis (Table 4). Within the whole cohort, the factors significantly associated with a superior PFS were limited stage (stage I/II), lactate dehydrogenase (LDH) ≤245 U/L, IPI score ≤1, primary tumor diameter <7.5 cm, and patients who had CR and received doxorubicin-contained chemotherapy (P<0.05). There was a trend toward superior outcome for patients who received combined therapy (surgery/chemotherapy/radiotherapy) (P=0.055) (Figure 2). Patients who had CR, primary tumor diameter <7.5 cm and IPI score ≤1 were significantly associated with longer PFS at multivariate analysis (Table 5).

Restricting the analysis to the patients with stage I/II disease (n=31), primary tumor size <7.5 cm (P=0.030), the patients who had CR (P=0.006) and received doxorubicin-contained chemotherapy (P<0.01) were associated with significantly superior PFS at univariate analysis. There was an association between better outcomes and combined therapy (chemotherapy/radiotherapy/surgery) at univariate analysis (Figure 2).

## Discussion

PTL is a rare disease with poor prognosis, of which primary testicular DLBCL is the most common type (1). In our institute, the incidence of primary testicular DLBCL accounts for 3.9% of all DLBCL patients. In the previous IELSG retrospective study (2), the 5- and 10-year PFS rates were 48% and 33%, respectively. Similarly, a recent



**Figure 2** PFS in all patients (A) and stage I/II patients (B) treated by combined therapy or not. PFS, progression-free survival.

Table 5 Multivariate analysis of impact of various clinical variables on PFS			
Variable	n	PFS	
		HR	P
Tumor diameter (cm)		3.006	0.028
<7.5	26		
≥7.5	11		
CR status		3.844	0.030
CR	24		
Not CR	13		
IPI		4.577	0.010
0-1	27		
≥2	10		
Doxorubicin-contained chemotherapy		0.705	0.633
Received	31		
Not received	6		
Modality therapy (surgery/chemotherapy/radiotherapy)		0.652	0.479
Received	19		
Not received	18		

HR, hazard ratio; CR, complete response; IPI, international prognostic index; PFS, progression-free survival.

population-based retrospective study (3) revealed that the 5- and 10-year disease-free survival (DFS) were 62% and 50%, respectively. In our study, the median PFS was 26.2 months and the 3-year OS was 78.4%, but a longer follow-up is required for better assessment. A previous study in our institute assessed the clinical characteristics and

survival of 23 PTL patients from 1987 to 2000, indicating that the median PFS was 19 months with the 3-year PFS and OS of 42.3% and 59.8%, which were all lower than those in this study (8). The improved comprehensive therapy modality within these years in our institute might account for the difference. With a median follow-up of 39.8 months in this study, relapse was widespread with involvement of multiple extranodal sites. The most frequently affected sites were CNS, skin, bone, contralateral testis, lung, liver, kidney and stomach, consistent with the report before (5). This observation provided major implications for the optimal initial treatment. There is very strong data supporting the benefit of RT in preventing disease recurrence in the contralateral testis. According to the previous retrospective IELSG study (2), prophylactic RT at the contralateral testis appeared to prevent testicular relapses, and the recurrence rate was reduced to 8% compared with 35% among those not irradiated. Also a prospective phase II study showed that no contralateral testis relapses occurred in 47 PTL patients who received contralateral testis RT (6). Consistently, our study also revealed that contralateral testis RT was associated with longer PFS even though the difference was not statistically significant.

Based on a review of 176 cases of irradiated patients from 14 series, Shahab and Doll (9) concluded that although RT provided excellent in-field control, ultimately 70% of patients still relapsed systemically. Therefore, systemic chemotherapy is recommended. ISELG study showed that patients who received anthracyclines-based chemotherapy had longer survival. In our study, there was also an association between an improved PFS and doxorubicin-contained chemotherapy, with significant difference. Strong evidence showing the benefit of CHOP implied that a

potential benefit may also be present in PTL. Addition of rituximab to chemotherapy has been established in DLBCL, which implied that a potential benefit may also be present in PTL (10-12). Among a retrospective series of 24 patients with PTL, a similar trimodality strategy (doxorubicin-based chemotherapy, testicular RT, and intrathecal methotrexate) showed the 5-year PFS and OS were 78% and 66%, respectively (6). A comparison of these results with those of the IELSG-10 study may suggest that the addition of rituximab could be beneficial (6). However, rituximab-contained chemotherapy was not associated with superior PFS in our study. A longer follow-up period is needed to clarify the exact role of rituximab in PTL treatment. Although a randomized double-blinded controlled clinical trial was the most persuasive approach, it was impossible for PTL because of the rarity of this disease.

The CNS relapse is more common in PTL in contrast to other aggressive lymphomas. In the previous IELSG series, the 5- and 10-year risks of CNS relapse were 20% and 35%, respectively (2). The best strategy to prevent CNS relapse is still a matter to debate. The value of prophylactic intrathecal chemotherapy is controversial because CNS relapse occurs more frequently in brain parenchyma than in meninges and also prefers the patients who have received intrathecal prophylaxis (13). In our study, CNS progression and death occurred in five patients even though two of them received intrathecal prophylaxis. But in IELSG 10 study, the cumulative incidence of CNS relapse at 5 years was only 6% in patients who received CNS prophylaxis (6), and the lower incidence of CNS relapse might be ascribed to the introduction of CNS prophylaxis.

IELSG 10 was the first prospective study in PTL and showed that a trimodality treatment with RCHOP chemotherapy, contralateral testicular RT and CNS prophylaxis was associated with better outcomes and the 5-year PFS and OS rates were 74% and 85%, respectively (6). In our study, there was also a trend of better outcomes for the patients who received combined therapy ( $P=0.055$ ), but a longer follow-up is needed to compare our results with previous IELSG 10 study.

Prior studies have found a number of prognostic factors including age, performance status, stage, IPI score, elevated serum LDH, bulky disease, infiltration of adjacent tissues, the lack of systemic chemotherapy, etc. (2,14-16). In our study, only patients who have CR, IPI score  $\leq 1$  and primary tumor diameter  $< 7.5$  cm were significantly associated with longer PFS at multivariate analysis. Song *et al.* (17) reported that patients of extranodal maximum tumor diameter  $\geq 7.5$  cm

had lower PFS and OS. Hence we used the maximum tumor diameter of 7.5 cm as the critical value for survival, and demonstrated that primary tumor diameter  $\geq 7.5$  cm was an independent prognostic factor.

Limitation is also prominent in the current study. Firstly, this is a retrospective trial which covers all the shortcomings of retrospective study. Secondly, this is not a large case series due to rarity of the disease. But this paper also provided a relative deep insight into clinical characteristics, treatment modalities, survival and prognostic factors of primary testicular DLBCL in the Chinese population.

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