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ORIGINAL ARTICLE

Role of prophylactic radiotherapy in Chinese patients with primary testicular diffuse large B-cell lymphoma: a single retrospective study

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Summary

Purpose: *To retrospectively evaluate the role of prophylactic radiotherapy (RT) and clinical prognostic factors for primary testicular diffuse large B-cell lymphomas (PT-DLBCL) patients in our cohort.*

Methods: *Thirty patients diagnosed with PT-DLBCL between January 2007 and June 2017 were included in our study. Data came from electronic records and a histopathology electronic database. R and SPSS 23.00 were used for statistical analysis based on actual needs.*

Results: *Median age at diagnosis of PT-DLBCL was 60 years (28-82). At the time of analysis, 6 patients (20.0%) suffered disease progression. The estimated 5-year risk of recurrence after treatment was 24.7%. In multivariate analysis, international prognostic index (IPI) was identified as the only independent prognostic factor for overall survival (OS) (p=0.025, HR 1.675, 95%CI: 1.065-2.634) and progression-free survival (PFS) (p=0.037, HR 1.669, 95%CI: 1.032-2.700). No correlation was established between prophylactic RT and superior OS or PFS, respectively (p=0.745, p=0.194). No significant correlation was established in either group between RT and OS (Low-risk: p=0.848; High-risk group: p=0.433) or PFS (Low-risk: p=0.170; High-risk: Fig 4H, p=0.871).*

Conclusions: *Chinese PT-DLBCL patients had an earlier age of onset and the number of advanced stage patients occupied a larger proportion. Also, the effect of prophylactic RT was not as good as expected.*

Key words: *diffuse large B-cell lymphoma (DLBCL), testicular, prognosis, radiotherapy, treatment*

Introduction

Primary testicular lymphoma (PTL) accounts for less than 2% of all types of non-Hodgkin lymphomas (NHL), while at the same time it is the most common testicular malignancy in elderly men over 60 years old [1]. The major type of PTL (>80%) is histologically diffuse large B-cell lymphoma (DLBCL) [2,3], which can be abbreviated as PT-DLBCL. The typical clinical manifestation is a firm and painless testicular mass. About 40% of all cases may develop associated hydrocele and less than 10% may suffer bilateral involvement. According to previous data, the median overall survival (OS) of PT-DLBCL patients is 4 to 5 years [4]. In the rituximab era, the survival of pure DLBCL patients improved significantly [5,6], yet, the therapeutic advantage does not apply to PT-DLBCL patients, or it remains unclear [7].

PT-DLBCL is an uncommon but aggressive extranodal lymphoma, which often relapses in the CNS as well as the contralateral testis despite the initially complete remission (CR). A retrospective analysis in the pre-rituximab era of 381 PT-DLBCL patients conducted by the International Extranodal Lymphoma Study Group (IELSG) established that these patients had ongoing risk of late CNS relapses [4]. Moreover, the skin, lungs, bone mar-

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row, soft tissues, and pleura were also potential sites of extranodal recurrence [8]. Guidelines have recommended the use of scrotal radiotherapy (RT) (25-30 Gy) in PT-DLBCL patients (stage I-IV) to better prevent recurrence. According to previous studies, patients who refused prophylactic RT had relapse rates in the contralateral testis of 15% and 42% at 3 and 5 years, respectively [9].

Despite these results, according to Gundrum et al. [7], the proportion of patients who received RT remained only 30-40%, without apparent improvement over time. In our center, various uncontrollable factors prevent all patients from receiving prophylactic RT. Therefore, the purpose of our study was to retrospectively evaluate the role of prophylactic RT and clinical prognostic factors for PT-DLBCL patients in our cohort. As the disease is rare, this study may provide some insights for clinical choices, especially in Chinese patients.

Methods

Patients

Thirty patients with a testicular mass and newly histologically diagnosed PT-DLBCL by needle biopsy or orchiectomy in our hospital between January 2007 and June 2017 were enrolled in the study. Data were collected from electronic records and a histopathology electronic database at our hospital. The study was approved by the ethics committee of Zhongshan Hospital,

Table 1. Baseline characteristics of 30 PT-DLBCL patients

Characteristics	*n (%)*	*Received RT n (%)*	*No RT n (%)*	*p value*
Age (yrs, median, range)	60, 28-82	12 (41.4)	17 (58.6)	0.025
<60	15 (50.0)	9 (64.3)	5 (35.7)	
≥60	15 (50.0)	3 (20.0)	12 (80.0)	
Involvement site				0.438
Right	18 (60.0)	6 (33.3)	12 (66.7)	
Left	12 (40.0)	6 (54.5)	5 (45.5)	
Bilateral	0 (0.0)			
Pathological type				0.717
GCB	12 (40.0)	4 (36.4)	7 (63.6)	
Non-GCB	18 (60.0)	8 (44.4)	10 (55.6)	
Ann Arbor stage				0.774
I + II	12 + 4 (40.0 +13.3)	7 (43.8)	9 (56.2)	
III + IV	2 + 12 (6.7 + 40.0)	5 (38.5)	8 (61.5)	
B symptoms				1.000
Yes	7 (23.3)	3 (42.9)	4 (57.1)	
No	23 (76.7)	9 (40.9)	13 (59.1)	
BM involvement				1.000
Yes	5 (17.2)	2 (40.0)	3 (60.0)	
No	24 (82.8)	10 (43.5)	13 (56.5)	
Missing data	1			
CNS involvement				1.000
Yes	4 (13.3)	2 (50.0)	2 (50.0)	
No	26 (86.7)	10 (38.5)	16 (61.5)	
IPI				0.251
Low + Low intermediate	16 + 2 (53.3 + 6.7)	9 (52.9)	8 (47.1)	
High intermediate + High	2 + 10 (6.7 + 33.3)	3 (25.0)	9 (75.0)	
CMV IgG (U/mL)				0.363
<1	2 (12.5)	0 (0.0)	2 (100.0)	
≥1, ≤500	11 (68.8)	4 (40.0)	6 (60.0)	
>500	3 (18.8)	0 (0.0)	3 (100.0)	
Missing data	14			

PT-DLBCL: primary testicular diffuse large B-cell lymphomas; RT: radiotherapy; GCB: germinal center B-cell; BM: bone marrow; CNS: central nervous system; IPI: international prognostic index; CMV: cytomegalovirus

Fudan University and was conducted according to the Declaration of Helsinki. All patients signed an informed consent form.

Clinical data

Each patient with newly diagnosed with PT-DLBCL underwent the following investigations: blood counts, urine and stool, liver and kidney function, serum albumin and immunoglobulin, C-reactive protein (CRP), protein electrophoresis, serum lipid level, LDH, and β2 microglobulin (β2 MG), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV) and hepatitis B virus (HBV), systematic computed tomography (CT) or positron emission tomography (PET) scan, bone marrow (BM) cytology analysis and biopsy. General status, Ann Arbor stages and IPI were also evaluated.

Treatment

The 30 PT-DLBCL patients received formal therapy. In addition to the severe infection of HBV or patient refusal, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was prescribed as the frontline regimen for therapy in PT-DLBCL patients. The remaining patients were administered appropriate regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), ICE (ifosfamide, carboplatin and etoposide), or GDP (gemcitabine, cisplatin and dexamethasone) according to individual conditions. During chemotherapy, some patients received CNS prophylaxis with intrathecal methotrexate (MTX) and cytarabine. After completion of chemotherapy, some patients received prophylactic scrotal RT.

Table 2. Treatment and response of PT-DLBCL patients

Treatment/Responses	*n (%)*
Radical orchiectomy	
Yes	27 (90.0)
No	3 (10.0)
Induction therapy	
R-CHOP based	22 (73.3)
Chemotherapy without R	8 (26.7)
Prophylactic scrotal RT after the initial treatment	
Yes	11 (37.9)
No	18 (62.1)
Missing data, n	1
Prophylactic CNS RT	
Yes	20 (74.1)
No	7 (25.9)
Response to initial treatment	
CR	17 (56.7)
PR	9 (30.0)
OR	26 (86.7)
SD	2 (6.7)
PD	0 (0.0)
Early death	2 (6.7)

For abbreviations see text

Endpoint assessment

Overall survival (OS) refers to the time interval from the initial diagnosis to the last follow-up or death. Progression-free survival (PFS) refers to the period between the initial diagnosis and the disease progression. Complete remission (CR) refers to the complete absence of all radiologic manifestations of lymphoma lesions, which were normally evaluated through PET scan or CT. Partial remission (PR) refers to cases when at least 50% of measurable disease exhibited regression without appearance of new lesions. Overall response rate (ORR) was defined as the rate of CR plus PR.

Statistics

Survival analysis was performed using the Kaplan-Meier method (log-rank test) coupled with stepwise Cox regression analysis. One-way ANOVA was used to analyze continuous variables and the x^2 test (or Fisher's exact test) aimed at comparing categorical variables. Competing risk analysis was calculated using cmprsk_v2.2-7 packages [10] to estimate the cumulative incidence of PT-DLBCL progression with early deaths due to any cause in the absence of progression. Statistical analyses were performed using R and SPSS 23.00 (IBM, Armonk, NY, USA) based on actual needs. Two-sided p value ≤0.05 was defined as statistical significance. The complete questionnaire did not take into account the value of missing variables.

Results

Baseline characteristics

A total of 30 newly diagnosed PT-DLBCL patients in our department from January 1st, 2007 to June 30th, 2017 were included. Table 1 lists their baseline characteristics. The median age at diagnosis was 60 years (28-82), with 50.0% aged under 60, and the other half over 60 years. All the pa-

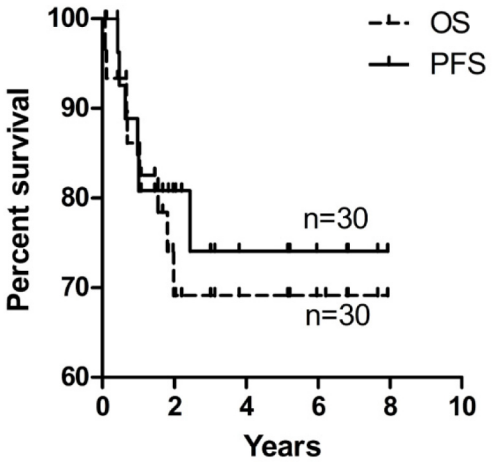

Figure 1. OS and PFS in 30 PT-DLBCL patients.

tients were diagnosed with unilateral testicular involvement, with 18 cases (60.0%) originating from the left testis and 12 cases (40.0%) from the right. Eighteen patients were categorized into the non-germinal center B-cell-like (non-GCB) type and the rest were germinal center B-cell-like (GCB) type. Moreover, 12 patients (40.0%) were in stage I and the same proportion were in stage IV, thus presenting a polarized situation. Furthermore, at the time of diagnosis, CNS involvement had already been established in 3 patients. The IPI exhibited low-risk (low and low intermediate) in 18 patients and high-risk (high intermediate and high) in 12 patients. Of the 16 cases tested, CMV IgG expression was positive in 14 cases (87.6%), out of which 3 had high IgG titers over 500 U/mL, making it impossible to measure accurate values.

Treatment and outcome

For the whole group, the median follow-up time was 24.230 months (range, 0.960 to 95.280), the median OS was 6.18 years and median PFS was 5.82 years (Figure 1). The estimated 5-year OS rate was 69.0%.

As shown in Table 2, 27 patients (90.0%) first underwent radical orchiectomy during therapy. Twenty-two patients (73.3%) were treated with rituximab-based immunochemotherapy, while the remaining patients (26.7%) did not receive rituximab-containing regimens. Less than two fifths of patients (11/29, 37.9%, 1 missing data) received prophylactic scrotal RT after completion of chemotherapy. Besides, one patient underwent prophylactic scrotal RT after disease progression. About 56.7% of patients (17/30) achieved CR and 30.0% (9/30) PR after the initial treatment. Therefore, the ORR was 86.7%. During the follow-up period, there were 8 deaths and 3 censored cases. According to analysis, 6 patients (20.0%) suffered disease progression, and presented new lesions in the ipsilateral testis (1), unilateral adrenal gland (1), CNS (2), skin (1) and liver and spleen (1), respectively. The estimated 5-year recurrence risk was 24.7%.

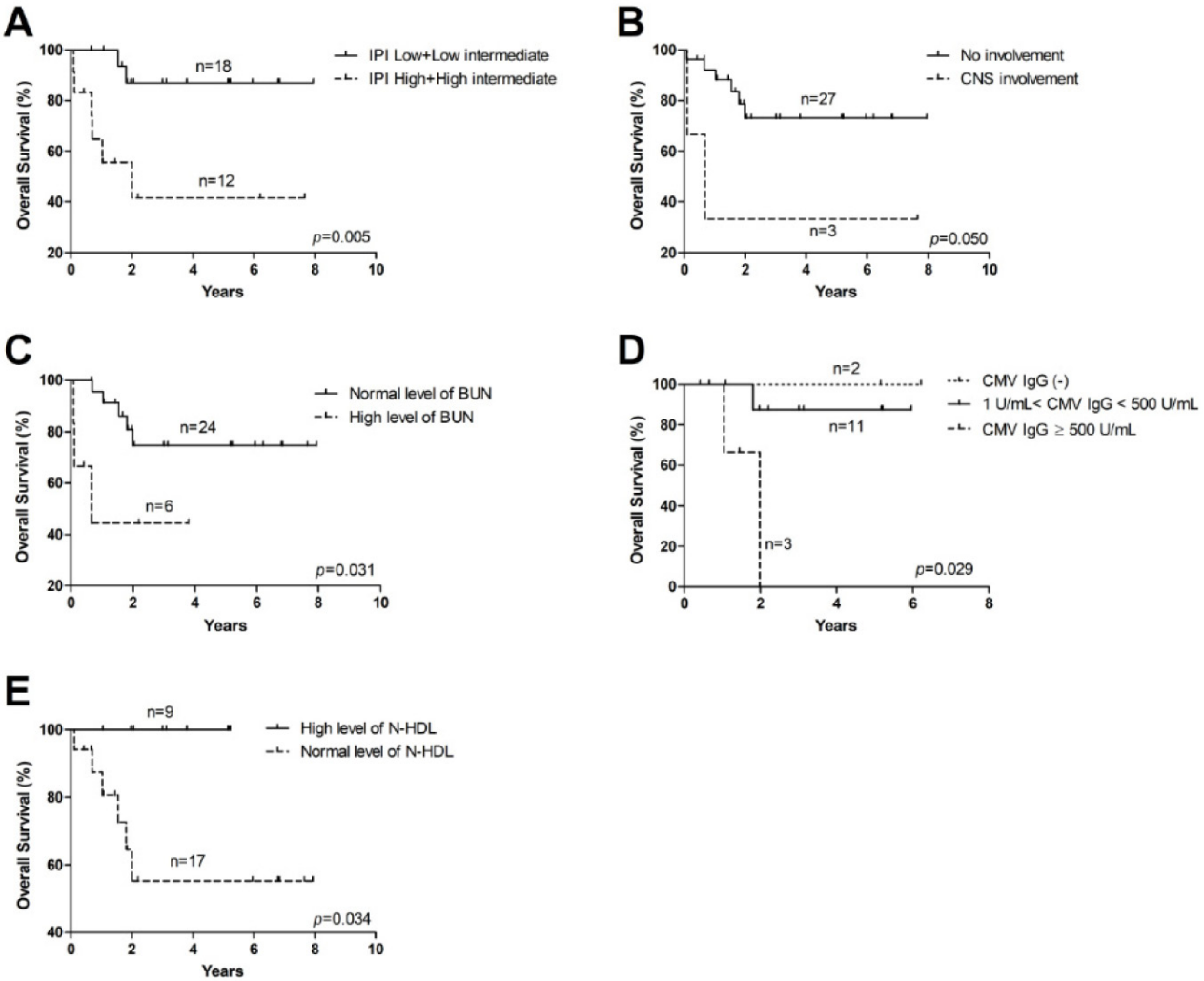

Figure 2. Significant prognostic factors for OS in PT-DLBCL patients in univariate analysis. **(A):** IPI risk groups. **(B):** CNS involvement. **(C):** BUN level at diagnosis. **(D):** CMV IgG level at diagnosis. **(E):** N-HDL level at diagnosis.

Prognostic factors for OS and PFS

To determine the clinical prognostic factors, univariate survival analysis was performed on PT-DLBCL patients using the Kaplan-Meier method (plus log-rank test) together with Cox regression analysis. High IPI risk (high and high-intermediate) (Figure 2A, p=0.005), CNS involvement (Figure 2B, p=0.050), high level of blood urea nitrogen (BUN) at diagnosis (Figure 2C, p=0.029) and high level of CMV IgG titer at diagnosis (Figure 2D, p=0.029) were defined as significant adverse factors for OS. In addition, high level of non-high density lipoprotein (N-HDL) at diagnosis (Figure 2E, p=0.036) was evidently associated with better OS. Also, high IPI risk (high and high-intermediate) (Figure 3A, p=0.037) and BM involvement (Figure 3B, p=0.021) were defined as significant adverse prognostic factors for PFS.

Based on the results presented above, the significance of these covariates in multivariate analysis (stepwise Cox regression, Table 3) was further evaluated. Since 14 patients (nearly 50%) were not tested for CMV IgG totally, this variable was excluded from the multivariate analysis to avoid statistical bias. Finally, IPI was identified as the only independent prognostic factor for both OS (p=0.025, HR 1.675, 95%CI:1.065-2.634) and PFS (p=0.037, HR 1.669, 95%CI: 1.032-2.700).

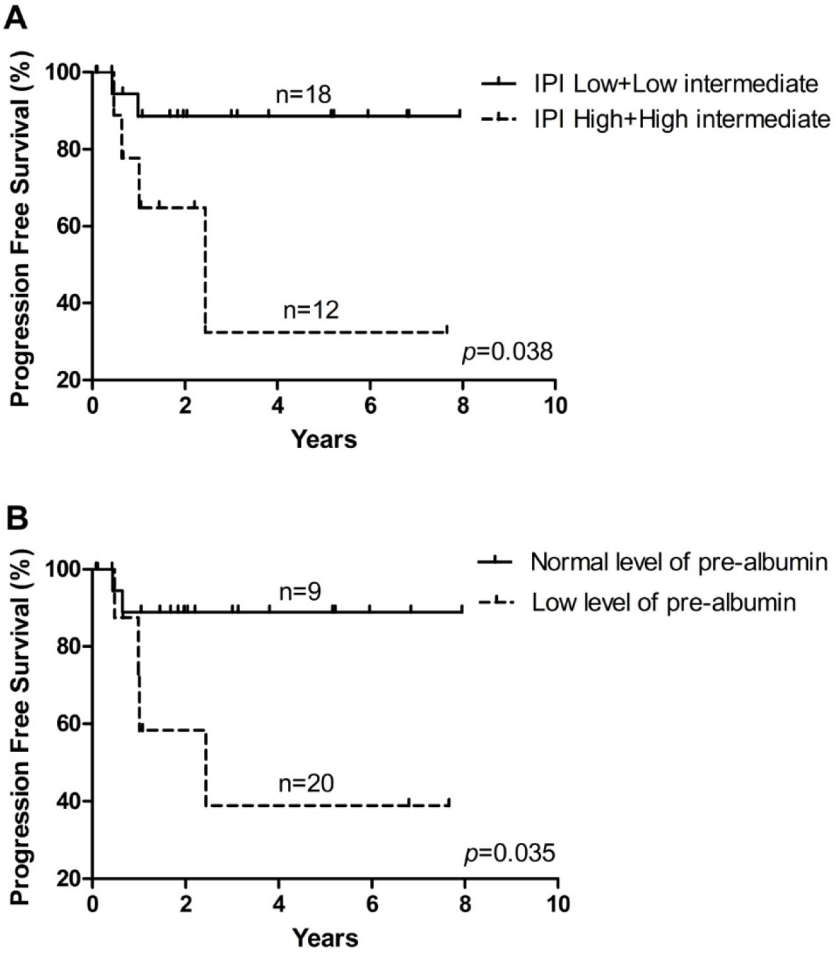

Figure 3. Significant prognostic factors for PFS in PT-DLBCL patients in univariate analysis. **(A):** IPI risk groups. **(B):** Pre-albumin level at diagnosis.

Table 3. Multivariate analysis of OS and PFS in PT-DLBCL patients

	*Variables**	*B*	*HR*	*95% CI*	*p*
OS	IPI	0.516	1.675	1.065-2.634	0.025
PFS	IPI	0.512	1.669	1.032-2.700	0.037

B: regression coefficient; CI: confidence interval; HR: hazard ratio. *Variables not entered in the equations: OS–CNS (p=0.275), BUN at diagnosis (p=0.441), N-HDL at diagnosis (p=0.302), PFS- pre-albumin (p=0.680)

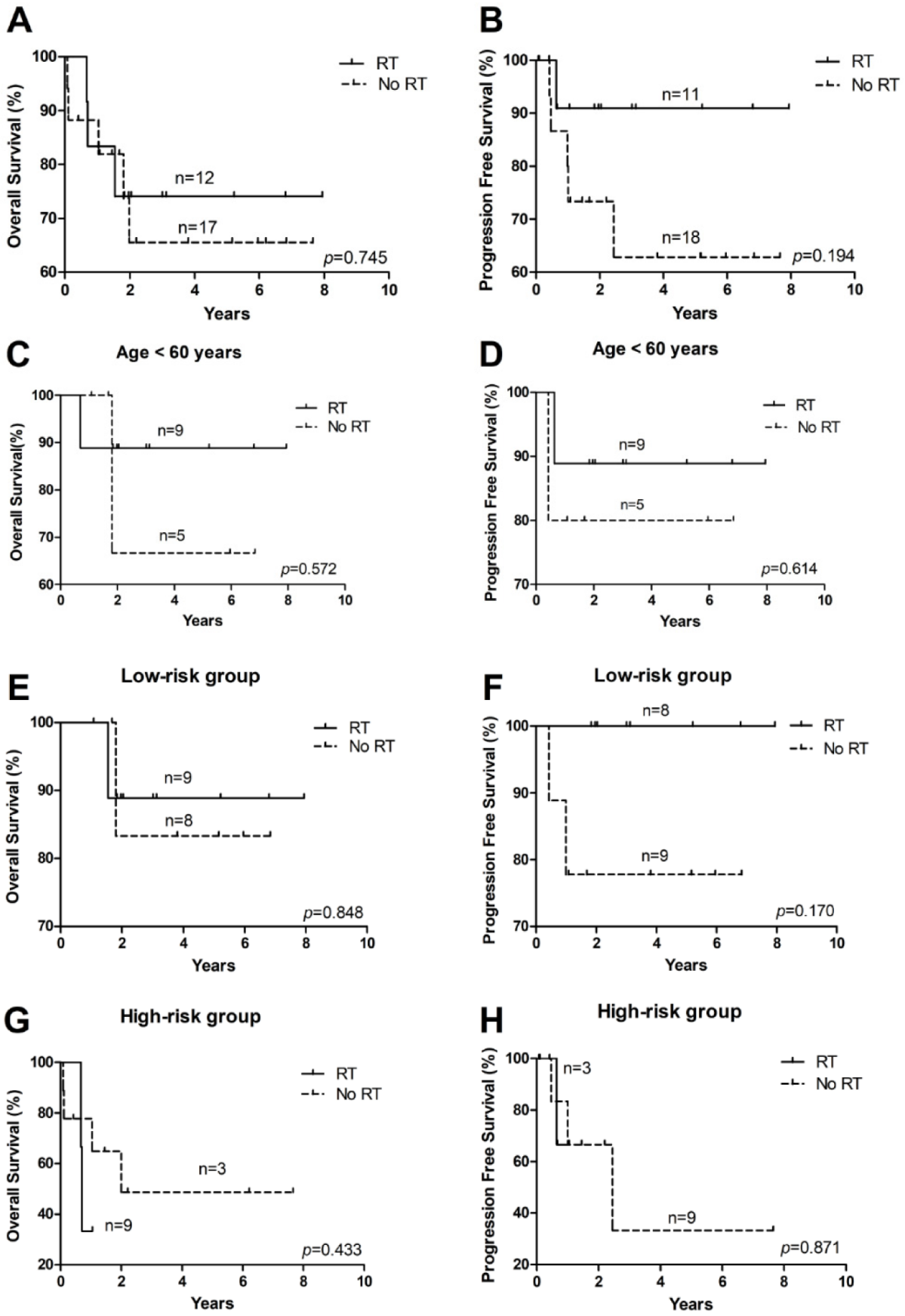

Figure 4. Role of prophylactic RT in PT-DLBCL patients. **(A)** and **(B):** No correlation was established between RT and superior OS or PFS. **(C)** and **(D)**: RT exerted no statistically significant effect on OS or PFS in young patients. **(E)** and **(F):** No significant correlation was found between RT and better OS or PFS in the low-risk group. **(G)** and **(H):** No significant correlation was found between RT and better OS or PFS in the high-risk group.

Roles of RT

Out of the 18 patients who were not treated with RT after the initial treatment, 5 (27.8%) suffered disease progression and 13 (72.2%) did not. Out of the 11 patients who received RT, 1 suffered disease progression (PD) (9.1%) and 10 did not (90.9%). Out of the 6 relapsed patients, 1 (16.7%) received scrotal RT after the initial treatment and 5 (83.3%) did not. Out of the 23 patients who did not relapse, 10 (43.5%) received scrotal RT and 13 (56.5%) did not. According to Fisher's exact test, there was no significant difference in the odds of recurrence between the two groups (p=0.362, p=0.362).

Moreover, no correlation was established between RT and superior OS or PFS, respectively (Figure 4A, p=0.745, Figure 4B, p=0.194). Since in our cohort the proportion of young patients (<60 years old) receiving RT was significantly higher than that of elderly patients (Table 1, p=0.025), the role of RT in young patients was further explored. Unfortunately, RT proved not to have a statistically significant effect on OS (Figure 4C, p=0.572) or PFS (Figure 4D, p=0.614) in this group. Based on multivariate analysis, the 30 patients were divided into 2 risk groups: low-risk (0-2 points) and high-risk (3-5 points). Further comparison showed that in neither the low-risk nor the high-risk group, a significant correlation was established between RT and better OS (Low-risk: Figure 4E, p=0.848; High-risk: Figure 4G, p=0.433) or PFS (Low-risk: Figure 4F, p=0.170; High-risk: Figure 4H, p=0.871).

When early death was considered as a competing risk, in all patients (Figure 5A, p=0.198), in younger patients (Figure 5B, p=0.620), or in the 2 risk sub-groups (Low-risk: Figure 5C, p=0.169; High-risk: Figure 5D, p=0.821), the cumulative incidence of disease progression exhibited no significant difference.

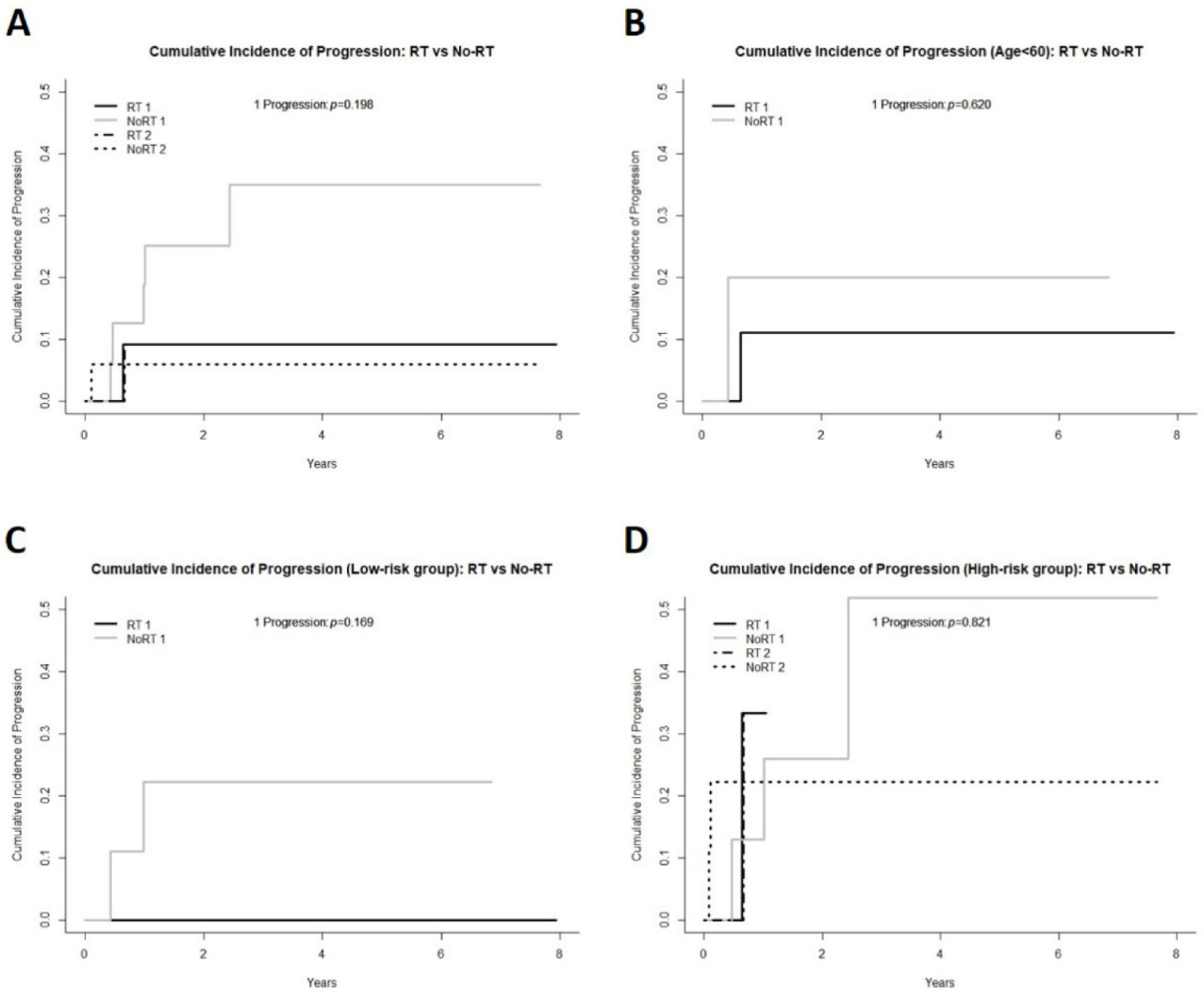

Figure 5. The cumulative incidence of disease progression exhibited no significant difference. **(A):** All patients (p=0.198). **(B):** Younger patients (p=0.620). **(C):** Low-risk sub-group (p=0.169). **(D)**: High-risk sub-group (p=0.821).

Discussion

A retrospective analysis was performed on the clinical features and role of RT in 30 PT-DLBCL cases. PT-DLBCL patients do not usually present obvious symptoms and signs at the time of onset. A painless testicular lump/mass is mostly the first symptom. According to previous studies, the median age at diagnosis of testicular lymphoma patients is 66-70 years [11,12]. The median age in our cohort was 60, which was much younger, thus indicating that Chinese patients may have an earlier onset age. In several large retrospective studies, 60-79% of patients were in stage I or II [4,8,9,13]. According to the findings of the present study, the number of patients in stage I/II and stage III/IV accounted for about 50%, thus suggesting that the disease status of Chinese patients at the time of diagnosis was poorer and more advanced than in other countries. The majority of reported PT-DLBCL cases exhibited an activated B-cell-like (ABC) (86.0%) gene expression profile (GEP) subtype or a non-GCB (84.0%) immunophenotype [14]. According to the findings of the present study, the proportion of the non-GCB type was only 60%, lower than reported in the previous literature, while the GCB type had a relatively higher proportion (40%).

Several retrospective analyses have been conducted to investigate the adverse prognostic factors for PT-DLBCL patients [7,15-17]. In a retrospective survival analysis of 769 PT-DLBCL patients over 60 years old, no prophylactic scrotal RT, CNS involvement, large lump/mass (>10 cm) and no anthracycline were recognized as the adverse variables that predict shorter OS [7]. In the study of Touroutoglou et al. [17] and Mazloom et al. [18], the presence of B symptoms, high IPI, high level of lactate dehydrogenase (LDH), and stage III/IV were significant independent adverse prognostic factors for OS in PT-DLBCL. In our study, multivariate analysis identified high IPI as the only adverse prognostic factor for OS and PFS, which confirmed the findings of previous studies.

In the study of Deng et al. [13], despite the addition of rituximab, a continuous relapse was the major failure pattern in PT-DLBCL patients, which most commonly involves the CNS as well as the contralateral testis. Unlike patients with PT-DLBCL, the CNS relapse incidence of pure DLBCL patients was only 5% and became lower after adding rituximab [19]. It is difficult for chemotherapy drugs to reach the contralateral testis, restricted by the "blood-testis barrier". Therefore, limited-stage patients are advised to simultaneously receive prophylactic bilateral scrotal RT. Tokiya et al. [20] have demonstrated that prophylactic RT is indeed an essential treatment measure for patients with stage I/II PT-DLBCL. The prospective trial in PTL (IELSG-10) also confirmed that contralateral testis relapses can be avoided by RT and combination of RCHOP21 and CNS, and RT testicular prophylaxis is a promising method [9]. The 5-year PFS was 74% and the 5-year OS was 85%. The 5-year risk of recurrence in the contralateral testicle and CNS was 0% and 6%, respectively. However, our study failed to confirm the significant role of prophylactic RT in Chinese patients with PT-DLBCL. For the whole group, the median PFS was 5.82 years and the median OS was 6.18 years. The estimated 5-year survival rate was 69.0%. In the patients receiving RT, the estimated 5-year risk of recurrence was 9.1%. Perhaps, this is because Chinese patients are not sensitive enough to prophylactic RT due to their inherent physical characteristics, or because of their late presentation, more advanced stages, and poor physical status, which decreases the effectiveness of prophylactic RT.

Given its retrospective nature, our study has some limitations regarding the interpretation of results. First, the relatively small sample size (only 30 PT-DLBCL patients) may understate the role of RT and may have potential bias. Therefore, further studies with more samples are needed. Second, clinical data including cytogenetic abnormalities and gene mutations were not available in our department before 2012. Third, the results came from a single-center cohort study, which has not been validated in other centers. Finally, for a more effective administration of RT, long-term treatment strategies for PT-DLBCL patients should be formulated by both radiation oncologists and hematologists. Prospective studies and multicenter studies should be proposed in the future to better understand PT-DLBCL patients.

Conclusions

In conclusion, the onset age of PT-DLBCL in Chinese patients was much younger and the proportion of advanced stage patients was higher. Moreover, the effect of prophylactic RT was not as good as expected. Therefore, more specific and powerful therapies should be explored.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interests.

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