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ORIGINAL ARTICLE

Male Health

The survival and prognostic factors of primary testicular lymphoma: two-decade single-center experience

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This study aims to investigate the effect of different local testicular treatments and validate common prognostic factors on primary testicular lymphoma (PTL) patients. We retrospectively reviewed the clinical records of 32 patients from 1993 to 2017 diagnosed with PTL and included 22 patients for analysis. The Kaplan–Meier method, Log-rank test, and multivariate Cox proportional hazard regression analysis were applied to evaluate progression-free survival (PFS), overall survival (OS), and determine prognosis predictors. The median follow-up time was 30 months. Median OS and PFS were 96 months and 49 months, respectively. In univariate analysis, advanced Ann Arbor stage (III/IV) ($P < 0.001$), B symptoms ($P < 0.001$), and extranodal involvement other than testis ($P = 0.001$) were significantly associated with shorter OS and PFS. In multivariate analysis, Ann Arbor stage was significantly associated with OS (OR = 11.58, $P = 0.049$), whereas B symptom was significantly associated with PFS (OR = 11.79, $P = 0.049$). In the 10 patients with the systemic usage of rituximab, bilateral intervention could improve median OS from 16 to 96 months ($P = 0.032$). The study provides preliminary evidence on bilateral intervention in testes in the rituximab era and validates common prognostic factors for Chinese PTL patients.

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Keywords: local treatment modalities; prognostic factors; prophylaxis contralateral orchiectomy; prophylaxis contralateral radiotherapy; testicular lymphoma

INTRODUCTION

Primary testicular lymphoma (PTL) is an uncommon form of extranodal non-Hodgkin lymphoma and accounts for 3%–9% of testicular malignancies.[1] The relative incidence increases with age. For patients older than 60 years, PTL is the most common testicular malignancy.[2] A typical clinical presentation is a firm, painless testicular mass associated with hydrocele in 40% of cases,[3] and urologists are often the first consultants that patients meet.

Ultrasonography (US) is the most widely used imaging method for testicular mass. PTL demonstrates focal or diffuse areas of hypoechogenicity with hypervascularity in an enlarged testis.[3] Considering its rarity, it is difficult to distinguish PTL from a germ cell tumor (GCT). Therefore, ipsilateral orchiectomy plays an important role in diagnosis and can achieve therapeutic effect through better local control for relapse.[4] Although the role of ultrasound-guided core needle biopsy was advocated in one study,[5] the reality of the study was confined by limited case number. What's more, concerns for sampling error, the threat of seeding, and missing carcinoma in situ (CIS) make it a rarely undertaken option.[6] For patients with equivocal malignant US features, frozen section examination is a better choice. Recently, magnetic resonance imaging (MRI) also has played a role in the diagnosis of testicular mass by allowing simultaneous evaluation of both testes, paratesticular spaces, and the spermatic cord.[3] Typical findings include T2 hypointensity and strong heterogeneous gadolinium enhancement.[7] One advantage of MRI is that it may distinguish PTL from seminoma or nonseminoma,[7] but high-cost limits it for routine application.

After orchiectomy, an adequate pathologic specimen should be presented to the pathologist. When it is difficult to distinguish PTL from seminoma,[8] an expert pathology review should be sought for the following appropriate staging and therapy.

For PTL patients, the Ann Arbor stage of lymphoma should be used.[3,9] Specifically, bilateral testes involvement occurs in 5%–6% of PTL patients, which is considered as stage I because these patients have outcomes similar as other stage I patients.[3,10] Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) was recommended to stage FDG-avid lymphomas.[11] Since the majority (77.8%) of PTL are diffuse large B-cell lymphoma (DLBCL) subtype,[12] which is FDG-avid, PET-CT should be utilized to determine the extent of involvement. It can determine whether the chest, abdomen, skin, bone marrow, or other sites of lymph nodes are involved.[11] A bone marrow biopsy (BMB) is only needed for DLBCL if the PET is negative and when identifying discordant histology is important for patient management.[11] PET-CT could not detect central nervous system (CNS) involvement because CNS is naturally FDG-avid. As a result, brain magnetic resonance imaging and lumbar puncture for cerebrospinal fluid analysis by cytology and

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flow cytometry (since it can improve sensitivity) should be performed to rule out CNS involvement.[11,13]

Unlike common GCT, of which first-line chemotherapy protocol is BEP (cisplatin, etoposide, and bleomycin), PTL needs chemotherapy containing anthracycline, even in stage I/II patients.[4] The most often used protocol is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) at 21-day intervals, on the basis of nodal DLBCL.[3] Prophylaxis contralateral scrotal radiation and intrathecal chemotherapy are also recommended because contralateral testis and CNS are the most common relapse regions.[3] However, these recommendations have been derived from either nonrandomized phase 2 studies or from retrospective series because of the rarity of PTL. Conflicts exist about the effect of the systemic use of rituximab,[1,14–17] and testicular local treatment in this special extranodal lymphoma type.[4,14,16,18] In addition, most of the studies were conducted in Caucasian populations, the results of which might differ in the Asian population. This study aims to validate common prognostic factors in Chinese population and investigate the effect of different local testicular treatments for PTL.

PATIENTS AND METHODS

Study cohort

After the approval of the Peking University Third Hospital Medical Science Research Ethics Committee, the information of 32 PTL patients diagnosed at Peking University Third Hospital (Beijing, China) from July 1993 to February 2017 was retrospectively collected through electronic medical record system. Ten patients were excluded for inadequate follow-up, and the final analysis included 22 patients. Clinical information, such as age, symptoms, and history, was collected before treatment. Standard workup included a normal laboratory examination and an imaging examination (ultrasound, computed tomography, magnetic resonance imaging, or PET/CT) for staging. Bone marrow biopsy/aspiration and examination of cerebrospinal fluid were performed depending on symptoms. Standard therapy included excision of the involved testicle and systemic chemotherapy containing anthracycline (at least one-cycle of CHOP-like protocol). Response after treatment was assessed according to the current recommendations.[11] Most patients were treated with rituximab after 2011. Prophylactic contralateral scrotal radiation and intrathecal injection were used depending on the physician's judgment.

Acquisition and definition of data

Ann Arbor stage was evaluated according to the Cotswolds modifications.[9] B symptoms included unexplained fevers of more than 101°F (38.3°C), drenching night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months before diagnosis. Patients with bilateral testicular involvement but without other site lesions were considered stage I.[4] Overall survival (OS) was measured from the time of diagnosis to the time of death for any cause. Progression-free survival (PFS) was measured from the time of diagnosis to that of disease progression. The patients who had not happened the endpoint event during follow-up were considered as censored.

Statistical analyses

The Kaplan–Meier method was used to calculate PFS and OS. The Log-rank test was used to compare survival between groups. Correlation between variables was calculated by Pearson's correlation coefficient. Multivariate Cox proportional hazard regression analyses were performed to evaluate significant variables associated with PFS and OS. Values of $P = 0.05$ or less (two-sided test) were considered to indicate statistical significance. The software SPSS version 24.0 (IBM Inc., Chicago, IL, USA) was used for analysis.

RESULTS

Patient characteristics

The median age at presentation was 64 years. Twelve (54.5%), 3 (13.6%), 2 (9.1%) and 5 (22.7%) patients were diagnosed with Ann Arbor stage I, II, III, and IV, respectively. Synchronous bilateral testicular involvement was reported in three (13.6%) patients; in two of them, the disease was limited within the testis, so these patients were considered stage I. The median maximal diameter of the testicular mass was 4.4 cm (range: 1.5–8.0 cm). Three (13.6%) patients had B symptoms; all of them had disseminated disease (stage III/IV). Twenty-two lymph node region involvement were documented in eight patients, including paraaortic (5), hilar (3), mediastinal (3), cervical (3), iliac (2), inguinal femoral (2), axillary or pectoral (2), mesenteric (1) and infraclavicular lymph nodes (1). Five patients had extranodal involvement other than the testis at presentation, including bone marrow (3), brain (1) and intestine (1). All the patients included in the study had non-Hodgkin lymphoma. Except for one patient with extranodal NK/T-cell lymphoma, the other 21 patients were all B-cell original; diffuse large B-cell lymphoma (DLBCL) was present in 19 patients, and two patients had undefined subtypes because of dated specimens. In the DLBCL patients, four patients were classified as germinal center B-cell-like subtype by Han's algorithm, 13 patients as activated B-cell-like subtype, and two patients as undefined. The main clinical characteristics are listed in **Table 1**.

Treatment modality

Nineteen patients received at least one cycle of chemotherapy. One of them with Ann Arbor stage III disease received chemotherapy without anthracycline in 1993. The other 18 patients received systemic CHOP protocol. Three patients did not receive systemic chemotherapy and these three patients all had limited disease and refused chemotherapy after thorough explanation. Most patients (10/12) were treated with rituximab after 2011. In contrast, only two out of ten patients were treated with rituximab before 2010.

Two patients did not receive total resection of testicular mass; one of them had a unilateral lesion and received scrotal radiotherapy (RT); the other one had bilateral testicular involvement and intestinal involvement. The remaining 20 patients received total resection of the testicular mass, including bilateral resection in three patients, in two of whom, both sides were involved. In the remaining case, one side was involved in presentation, and the patient underwent unilateral resection. Two years later, an abnormal contralateral testis was found and removed, but pathology confirmed chronic inflammation. In our analysis, we considered this patient as having a bilateral orchiectomy. Among 17 patients with unilateral resection, eight of them adopted prophylactic contralateral scrotal RT. The local treatment strategies are shown in **Figure 1**.

Among the whole cohort, three patients received therapeutic RT for brain, pelvis, and bilateral supraclavicular region, respectively. One patient received prophylactic RT for the pelvic region. Prophylactic intrathecal injection (ITH) was performed in 12 patients. Therapeutic ITH was performed in one patient with central nervous system (CNS) involvement.

Outcome and patterns of relapse

The median follow-up time was 30 months. Median OS was 96 months for all patients, 288 months for stage I/II and only 16 months for stage III/IV patients. The rates of 1-, 3-, and 5-year OS for all patients were 85.4%, 73.2%, and 57.6%, respectively (**Figure 2a**). Median PFS was 49 months for the whole group, 80 months for stage I/II, and

Table 1: Clinical characteristics and treatment modalities of patients in different Ann arbor stage

Characteristic	*Ann Arbor stage I/II[a], n (%)*	*Ann Arbor stage III/IV[b], n (%)*	*All patients[c], n (%)*
Age (year)			
≤60	5 (33.3)	2 (28.6)	7 (31.8)
>60	10 (66.7)	5 (71.4)	15 (68.2)
Side			
Left	7 (46.7)	4 (57.1)	11 (50.0)
Right	6 (40.0)	2 (28.6)	8 (36.4)
Bilateral	2 (13.3)	1 (14.3)	3 (13.6)
Pathology			
Natural-killer-cell lymphoma	0	1 (14.3)	1 (4.5)
Activated B-cell-like DLBCL	9 (60.0)	4 (57.1)	13 (59.1)
Germinal center B-cell-like DLBCL	3 (20.0)	1 (14.3)	4 (18.2)
Unknown	3 (20.0)	1 (14.3)	4 (18.2)
Maximal diameter ≥7 cm			
No	11 (73.3)	3 (42.8)	14 (63.6)
Yes	1 (6.7)	1 (14.3)	2 (9.1)
Unknown	3 (20.0)	3 (42.8)	6 (27.3)
B symptoms			
No	15 (100)	4 (57.1)	19 (86.4)
Yes	0	3 (42.9)	3 (13.6)
IPI			
0–2	10 (66.7)	0	10 (45.5)
3–5	4 (26.7)	2 (28.6)	6 (27.3)
Unknown	1 (6.7)	5 (71.4)	6 (27.3)
LDH			
1× normal	8 (53.3)	3 (42.9)	11 (50.0)
>1× normal	2 (13.3)	2 (28.6)	4 (18.2)
Unknown	5 (33.3)	2 (28.6)	7 (31.8)
β2-microglobulin			
1× normal	3 (20.0)	1 (14.3)	4 (18.2)
>1× normal	4 (26.7)	3 (42.9)	7 (31.8)
Unknown	8 (53.3)	3 (42.9)	11 (50.0)
Lymph nodes involvement			
No	11 (73.3)	3 (42.9)	14 (63.6)
Yes	4 (26.7)	4 (57.1)	8 (36.4)
Retroperitoneal lymph node enlargement			
No	13 (86.7)	4 (57.1)	17 (77.3)
Yes	2 (13.3)	3 (42.9)	5 (22.7)
Extranodal involvement other than testis			
No	15 (100)	2 (28.6)	17 (77.3)
Yes	0	5 (71.4)	5 (22.7)
Systemic chemotherapy			
None or without anthracycline	3 (20.0)	1 (14.3)	4 (18.2)
CHOP	5 (33.3)	1 (14.3)	6 (27.3)
R-CHOP	7 (46.7)	4 (57.1)	11 (50)
Unknown	0	1 (14.3)	1 (4.5)
Local treatment of testicles			
None or RT only	0	2 (28.6)	2 (9.1)
ULR	6 (40.0)	3 (42.9)	9 (40.9)
ULR plus contralateral RT	6 (40.0)	2 (28.6)	8 (36.4)
BLR	3 (20.0)	0	3 (13.6)
Other site radiotherapy			
No	13 (86.7)	5 (71.4)	18 (81.8)
Yes	2 (13.3)	2 (28.6)	4 (18.2)
ITH			
No	7 (46.7)	4 (57.1)	11 (50.0)
Prophylactic ITH	8 (53.3)	2 (28.6)	12 (45.5)
Therapeutic ITH	0	1 (14.3)	1 (4.5)

[a]*n*=15, [b]*n*=7, [c]*n*=22. CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab; RT: radiotherapy; ITH: intrathecal injection; BLR: bilateral resection; ULR: unilateral resection; DLBCL: diffuse large B-cell lymphoma; LDH: lactate dehydrogenase; IPI: international prognostic index

8 months for stage III/IV. The rates of 1-, 3-, and 5-year progression-free survival were 85.2%, 72.1%, and 46.7%, respectively (**Figure 2a**). Nine patients (40.9%) died from PTL. Seven of them died within 5 years (4–51 months) after diagnosis. However, PTL showed a continuous pattern of death up to 24 years. Eleven (50.0%) patients relapsed during the follow-up period. The median duration from relapse to death was 5 months (2–16 months). However, two patients survived for 32 months and 74 months respectively after relapse, and both received salvage chemotherapy.

Sites of initial failure of treatment included recurrence in nodal (4/10), contralateral testis (3/10), CNS (2/10), and bone marrow (1/10) (with data about three patients' specific site of relapse incomplete). Two patients had synchronous relapse: one patient with concurrent bone marrow and abdominal nodes relapse and another with concurrent central nervous system and contralateral testis relapse.

Analysis of prognostic factors

Table 2 lists the univariate survival analysis (log-rank test) based on different characteristics and treatment modalities for OS and PFS. Advanced Ann Arbor stage (III/IV) ($P < 0.05$, as shown in **Figure 2b** and **2c**), B symptoms ($P < 0.05$) and extranodal involvement other than testis ($P < 0.05$) were significantly associated with shorter OS and PFS. Compared to Ann Arbor stage I patients, Ann Arbor stage II patients were significantly associated with worse OS ($P = 0.015$) but not PFS ($P = 0.127$). Lymph node involvement or retroperitoneal lymph node enlargement (RPLNE) were not significantly associated with either OS or PFS.

We did not include extranodal involvement other than testis in multivariate Cox regression analysis, because the correlation between Ann Arbor stage and extranodal involvement other than testis was 0.79 ($P < 0.001$). In multivariate analysis, Ann Arbor stage was significantly associated with OS (OR = 11.58, 95% CI: 1.01–152.35, $P = 0.049$). B symptoms was significantly associated with PFS (OR = 11.79, 95% CI: 1.01–137.89, $P = 0.049$).

Local treatment of the testicle did not have a statistically significant difference on OS and PFS ($P = 0.440$ and $P = 0.483$, respectively, shown in **Figure 3a** and **3b**). However, no deaths or progression occurred in those three patients who selected bilateral orchiectomy. Median OS (96 *vs* 51 months, $P = 0.771$) and PFS (80 *vs* 22 months, $P = 0.425$) for patients with unilateral orchiectomy plus contralateral RT were longer than those in patients with unilateral orchiectomy, but statistical significances were not observed. Patients without resection of the testicle had the worst OS and PFS (median 20 and 17 months, respectively). Compared with unilateral resection, bilateral intervention (plus contralateral RT or resection) showed the potential to improve survival.

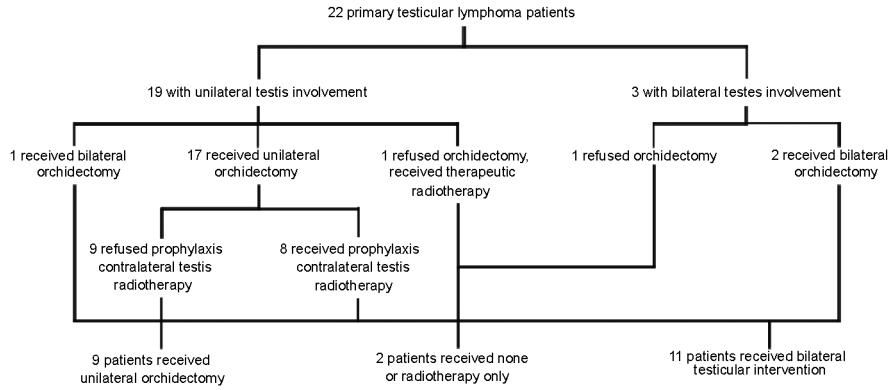

Figure 1: Local treatment strategies in our cohort.

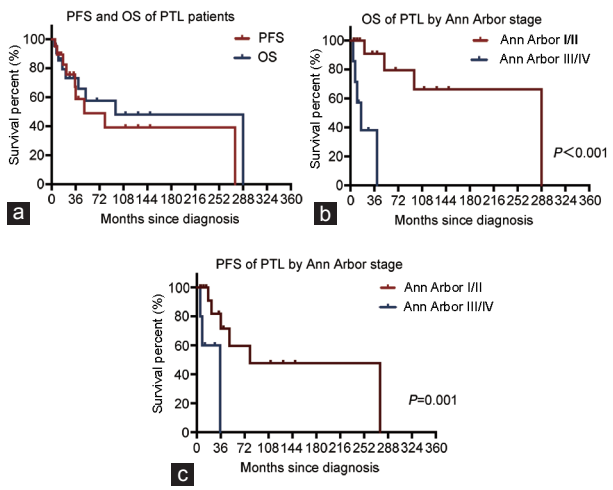

Figure 2: Kaplan–Meier log rank analysis of PTL patients. (**a**) OS and PFS of 22 PTL patients. (**b**) OS and (**c**) PFS classified by different Ann Arbor stages (I/II *vs* III/IV) are shown. Both OS and PFS of Ann Arbor stage I/II were significantly longer than advanced stage patients ($P < 0.001$ and $P = 0.001$, respectively). PTL: primary testicular lymphoma; OS: overall survival; PFS: progression-free survival.

Rituximab did not significantly improve median OS (288 *vs* 96 months, $P = 0.052$) or PFS (276 *vs* 80 months, $P = 0.455$), either in stage I/II or in stage III/IV patients. However, rituximab changed the predictive value of Ann Arbor stage. In ten patients who did not use systemic rituximab, Ann Arbor stage was significantly associated with OS ($P = 0.001$) and PFS ($P = 0.014$). In the eleven patients receiving systemic rituximab, Ann Arbor stage was not significantly associated with OS or PFS ($P = 0.159$ and $P = 0.143$, respectively) (**Figure 4a** and **4b**).

Rituximab also changed local treatment efficiency. In the eleven patients with systemic application of rituximab, bilateral intervention could improve median OS (16 *vs* 96 months, $P = 0.032$). In the ten patients who did not use rituximab, patients performed unilateral or bilateral intervention had a similar OS and PFS ($P = 0.772$ and $P = 0.901$, respectively).

DISCUSSION

Our study confirmed to some degree that advanced Ann Arbor stage (III/IV), B symptoms and extranodal involvement other than testis are poor prognostic markers for PTL in Chinese population. In addition, we showed that bilateral intervention (unilateral orchiectomy plus contralateral RT or orchiectomy) had the potential to improve survival, especially in patients receiving systemic rituximab treatment.

Multiple prognostic factors of PTL have been described, mainly from retrospective series because of its rarity.[1,4,14] In 2003, one of the largest retrospective studies in the prerituximab era was conducted by the International Extranodal Lymphoma Study Group (IELSG) including 373 cases. The study found that a worse international prognostic index score (IPI, including age >60-year, ECOG performance ≥2, Ann Arbor stage III/IV, high LDH, more than one extranodal involvement[19]), B-symptoms and nonuse of anthracyclines were significantly associated with shorter survival in multivariate analysis.[4] In 2009, another study including 769 cases based on the Surveillance, Epidemiology, and End Results (SEER) database, showed that older age, diagnosis before 1986, advanced stage and left testicular involvement were independent predictors of worse disease-specific survival (DSS).[1] In 2010, a case series from the MD Anderson Cancer Center found that advanced stage, elevated serum LDH, B-symptoms, and high IPI were poor prognostic markers. The 5-year OS and PFS for patients after 2000 were 86.6% and 59.3%, respectively. They were treated predominantly with R-CHOP, intrathecal chemotherapy (ITC), and scrotal RT. It is compared to 56.3% and 51.7% between 1977 and 1999 when patients were treated without rituximab and were not uniformly treated with ITC. Patients treated before 1977 had worst 5-year OS (15.4%) and PFS (15.4%) because of the lack of doxorubicin-based chemotherapy or ITC.[14]

We specifically searched the literature about PTL in Asian population and found four retrospective studies from China. In a study including 32 cases conducted in 2011, poor ECOG performance, left testicular involvement, and surgery alone were negative prognostic factors for overall survival.[20] Another study conducted in 2013 with 39 cases also validated ECOG performance status as a prognostic factor of survival in patients with primary testicular DLBCL, in addition to infiltration of adjacent tissues and bulky disease (tumor mass >9 cm).[21] In 2014, a retrospective study of 37 cases with primary testicular DLBCL between 2003 and 2012 found that patients who had a complete response (CR), primary tumor diameter <7.5 cm and IPI score ≤1 were significantly associated with longer PFS at multivariate analysis.[22] Another Chinese study on PTL reported a 3-year OS rate of 57%, without prognosis predictor analysis.[23]

In our study, median OS and PFS were 8 years and 4 years, respectively. The rate of 1-, 3-, and 5-year OS and PFS for all was 85.4%,

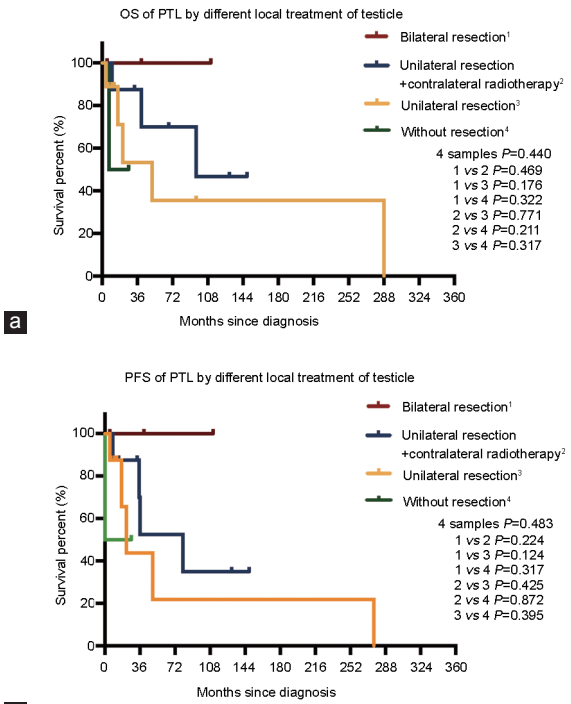

Figure 3: Kaplan–Meier log rank analysis of PTL patients divided by different local treatments. Different local treatment modalities did not significantly influence (**a**) OS or (**b**) PFS of PTL patients, but contralateral radiotherapy or resection had a potential to prolong PFS. PTL: primary testicular lymphoma; OS: overall survival; PFS: progression-free survival.

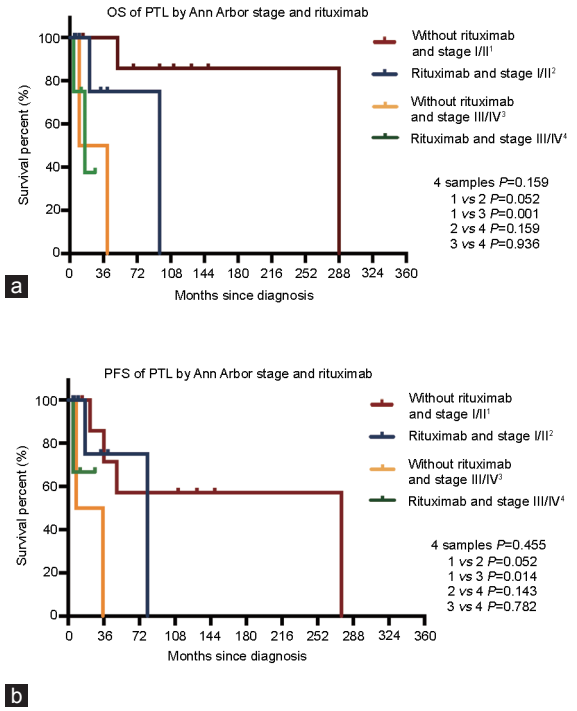

Figure 4: Kaplan–Meier log rank analysis of PTL patients divided by Ann Arbor stage and usage of rituximab. (**a**) OS and (**b**) PFS of PTL patients are shown. In patients without usage of rituximab, Ann Arbor stage was still a significant predictor of survival (OS: P =0.001; PFS: P =0.014). However, in patients with rituximab, Ann Arbor stage was not significantly associated with OS or PFS (P = 0.159 and P = 0.143, respectively). Also, rituximab failed to significantly improve survival in our cohort. PTL: primary testicular lymphoma; OS: overall survival; PFS: progression-free survival.

Table 2: Univariate analysis of prognostic factors for overall survival and progression-free survival

Features	*P value (log-rank test)*	
	OS	*PFS*
Ann Arbor stage (I/II *vs* III/IV)	<0.001	0.001
Age (>60 years *vs* ≤60 years)	0.776	0.367
Side (left, right and bilateral)*	0.074	0.232
Maximal diameter (≥7 cm *vs* <7 cm)	0.060	0.097
B symptoms (yes *vs* no)	<0.001	<0.001
IPI (3–5 *vs* 0–2)	0.367	0.369
LDH (>1× normal *vs* 1× normal)	0.691	0.909
β2-microglobulin (>1× normal *vs* 1× normal)	0.976	0.971
Lymph nodes involvement (yes *vs* no)	0.235	0.550
Retroperitoneal lymph node enlargement (yes *vs* no)	0.169	0.311
Extranodal involvement other than testis (yes *vs* no)	0.001	0.005
Systemic chemotherapy (without anthracycline, CHOP and R-CHOP)*	0.225	0.515
Locally treatment of testicle (none/RT only, ULR and bilateral intervention)*	0.351	0.237
Therapeutic radiotherapy (yes *vs* no)	0.059	0.190
Prophylactic intrathecal injection (yes *vs* no)	0.290	0.144

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab; RT: radiotherapy; ULR: unilateral resection; OS: overall survival; PFS: progression-free survival; LDH: lactate dehydrogenase; IPI: international prognostic index . *P value represents the overall comparison among three groups.

73.2%, 57.6% and 85.2%, 72.1%, 46.7%, respectively. This outcome is consistent with the studies mentioned above. In the analysis of outcome predictors, we confirmed that two indicators in IPI (advanced Ann Arbor stage [III/IV] and extranodal involvement other than testis) and B symptoms were associated with poor prognosis. However, we failed to validate left-testicle involvement or elevated serum LDH as predictors of poor prognosis. Furthermore, unlike testicular GCT, RPLNE was not a predictor of OS or PFS (both $P > 0.05$). This indicates that PTL is a totally different disease from other testicular tumors. Predictors for lymphoma (like factors in the IPI score) instead of GCT should be used to predict prognosis for this special testicular mass.

The risk of contralateral testicle relapse is up to 42% within 15 years when contralateral irradiation is not administered.[4] Multiple studies found that not having prophylactic contralateral irradiation is a poor predictor of prognosis.[1,4,14] Therefore, prophylactic contralateral irradiation is recommended.[2,3] However, in most cases, this procedure will destroy the germinal epithelium and lead to persistent Leydig cell dysfunction, resulting in infertility and hypogonadism.[24] Furthermore, even after irradiation, contralateral testicle failure could still be as high as 10% in the prerituximab era.[25] Performing prophylactic contralateral orchiectomy is an alternative, though the evidence is still lacking. In the rituximab era, local failure rates after prophylactic contralateral irradiation seem to fall, as reported in a case series that no case of contralateral relapse with a median follow-up of 32 months.[26]

Our study found that in patients treated with rituximab, bilateral testicle intervention could improve outcomes significantly compared to unilateral resection. However, in patients without rituximab, this effect disappeared. It is shown that in the rituximab era, contralateral irradiation, or resection may play a more important role in the management of PTL patients. This phenomenon could be explained by

the assumption that rituximab could eliminate tumor cells systemically but minimally pass through the blood-testicle-barriers.[14,16,17,27] Thus, rituximab (systemic control) plus bilateral testicle intervention (local control) could kill tumor cells to best extent and improve survival in PTL patients. Limited by relatively small case amount, we did not analyze specifically which kind of bilateral intervention is better. Therefore, we could not determine whether prophylaxis contralateral orchiectomy has a better outcome than RT.

Our study has several limitations. First, due to its retrospective nature, some data are missing, which meant that the analysis of some reported prognosis predictors (*e.g.*, infiltration of adjacent tissues) could not be included in our analysis. They remained confounding factors, which may affect the degree of confidence of this study. Second, the results mentioned above still need to be validated by larger studies because of the relatively small amount of cases. Finally, because our cohort covered 24 years, treatment modalities changed several times. Therefore, it is hard to analyze the best dose or protocol of chemotherapy or RT. However, considering the rarity of PTL, this study still provides useful information for clinical practitioners.

CONCLUSION

We validated that advanced Ann Arbor stage (III/IV), B symptoms and extranodal involvement other than testis are poor prognostic markers of PTL in the Chinese population. Furthermore, compared with unilateral resection, bilateral intervention (unilateral resection plus contralateral RT or resection) showed the potential to improve survival, especially in the era of rituximab. We provide preliminary evidence for the application of prophylactic contralateral radiotherapy in the era of rituximab. Whether prophylactic contralateral orchiectomy should be performed still needs to be studied. Nonetheless, prospective, randomized trials and comparative effectiveness studies are required to further explore the best local treatment modality in the rituximab era.

AUTHOR CONTRIBUTIONS

RZM collected the dataset, conceived the idea of the study, participated in data analysis, conducted statistical analyses and drafted the manuscript. LT collected the dataset and conceived the idea of the study. LYT participated in data analyses and conducted statistical analyses; HYH, ML and ML provided pathology review. LLM reviewed and polished the manuscript. JL and HJ participated in the design of the study and coordination. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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