Primary testicular lymphoma: A SEER analysis of 1,169 cases

HAITAO XU and FUSHENG YAO

Department of Hematology, Anqing Municipal Hospital, Anqing, Anhui 246003, P.R. China

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Abstract. Primary testicular lymphoma (PTL) is a rare lymphoid malignancy. The present retrospective study aimed to investigate the demographic characteristics and survival of patients with PTL, as well as the associated prognostic factors, using a population-based database. All adults diagnosed with PTL in the Surveillance, Epidemiology, and End Results database were identified between 1973 and 2013. The Kaplan-Meier method was used to estimate cause-specific survival (CSS). Log-rank test or multivariate Cox regression model was used to assess the influence of demographic and clinical parameters on CSS. A total of 1,169 patients with PTL were identified from the database, and the median age was 70 years. The predominant histological subtype was diffuse large B-cell lymphoma, which affected 82.9% (970/1,169) of patients, and 68.6% (802/1,169) of patients had early stage disease (stages I-II). Patients >70 years, those diagnosed at the earlier time period, or those who had advanced-stage symptoms had the worst 5-year CSS rates; however, treatment with rituximab significantly improved the 5-year CSS. In conclusion, this retrospective study presented data from the largest cohort of patients with PTL and described the effects of rituximab on the CSS of patients with PTL.

Introduction

Primary testicular lymphoma (PTL) is an uncommon extranodal lymphoma that accounts for 1-9% of testicular malignancies and 1-2% of non-Hodgkin's lymphomas (NHLs) (1,2). The median age at diagnosis of PTL is 67 years old, and the annual incidence is 0.09-0.26 per 100,000 individuals (3). The most common histological subtype of PTL is diffuse large B-cell lymphoma (DLBCL) (4). PTL presents clear extranodal tropism, mainly infiltrates the contralateral testis and commonly reaches the central nervous system (CNS) (5). These locations have immune privilege because of the presence of blood-testis and blood-brain barriers, which can lead to reduced concentrations of chemotherapy agents and evasion from host antitumor responses (6,7). Although the prognoses of PTL and secondary testicular involvement are similar, it is crucial to differentiate them in order to provide the most effective therapies to patients (1).

At present, a standard treatment for PTL has yet to be established. This can be explained by the rare nature of the disease and by the absence of prospective randomized controlled trials available. In previous studies, orchiectomy has been used as a diagnostic and a therapeutic tool; however, the outcomes of patients with PTL who undergo this surgery alone or in combination with radiotherapy are poor (8). Following the introduction of rituximab, prognosis of patients with PTL has significantly improved. A retrospective review including 75 patients with PTL from the MD Anderson Cancer Center revealed that the addition of rituximab to anthracycline-based chemotherapy significantly improves the 5-year overall survival (OS; 56 vs. 87%; P=0.019) of patients (9). Nevertheless, a retrospective analysis by the British Columbia Cancer Agency demonstrated that the 5-year progression-free survival (PFS) and OS of patients treated with rituximab were similar to those of patients who received no treatment, as determined by univariate analysis; however, rituximab provides better OS and PFS after adjustment by the International Prognostic Index (IPI) (10). Therefore, the effects of rituximab on the outcomes in patients with PTL are still unclear.

The present study aimed to investigate the demographic and clinical characteristics, and outcomes of patients with PTL using the Surveillance, Epidemiology, and End Results (SEER) registry, which is supported by the National Cancer Institute. The role of rituximab in the treatment of PTL was also examined, as well as the potential predictive factors for OS and cause-specific survival (CSS) in patients treated with rituximab.

Materials and methods

Data source. Patient data were obtained from the SEER database. The SEER program collects and publishes the
incidence, prevalence and survival data from 18 population-based cancer registries, covering >28% of the US population (www.seer.cancer.gov). The present study investigated the SEER database in April 2016 to identify all patients with PTL diagnosed between 1973 and 2013 using codes from the International Classification of Diseases (ICD) (11). ICD for Oncology, 3rd Edition (ICD-O-3) (12) morphological (9590-9738 and 9811-9975) and topographical (C620, C621 and C629) codes were used to identify cases of PTL. There were three exclusion criteria for the study: i) Diagnosis by autopsy or death certificate; ii) no microscopic confirmation of their disease; and iii) previous or coexisting malignancy. Fig. 1 presented the detailed screening procedure. To carry out analysis of CSS, the user-defined variable ‘Cause-specific Death Classification’ was selected in the SEER database. Using this variable, patients who succumbed to other unrelated causes were considered to be alive for the analysis. Patients with missing or unknown causes of mortality were excluded from the analysis.

The following information was obtained from the SEER database: Age at diagnosis, ethnicity, year of diagnosis, laterality, Ann Arbor stage, histotype, type of surgery, radiotherapy, cause of mortality and survival time. OS was defined as the length of time from the date of PTL diagnosis to the date that patients remained alive.

**Statistical analysis.** The incidence of PTL increases with age, and the median age of patients at diagnosis is 67 years old (3). In the present study, the age at diagnosis was categorized into four groups: <60 years, 60-69 years, 70-79 years and ≥80 years. Ethnicity was categorized as Caucasian, African descent, other and unknown. Ethnicities that were categorized as other or unknown were grouped together for analysis. The cohort was divided into three groups according to the year of diagnosis (1973-1997, 1998-2005 and 2006-2013). In the SEER database, two codes are given for resection surgery. Prior to 1997, the code ‘RX Summ-Surg Prim Site’ was used; after 1998, the code ‘RX SUMM-SURG PRIM SITE’ was used. To minimize the effects of coding on the study, patients were initially divided into two groups (prior to 1997 and after 1998). Since most patients suffered from primary testicular DLBCL (PT-DLBCL) and since rituximab was approved by the United States (US) Food and Drug Administration (FDA) after 2006, the post-1998 group was further divided into two groups (1998-2006 and after 2006) to understand the effects

| Table I. Demographic and clinical characteristics of 1,169 patients with primary testicular lymphoma. |
| --- |
| Variable | n (%) |
| **Ethnicity** |  |
| Caucasian | 1,005 (86.0) |
| African descent | 47 (4.0) |
| Other/unknown | 117 (10.0) |
| **Age (years)** |  |
| <60 | 359 (30.7) |
| 60-69 | 283 (24.2) |
| 70-79 | 335 (28.7) |
| ≥80 | 192 (16.4) |
| **Year of diagnosis** |  |
| 1973-1997 | 347 (29.7) |
| 1998-2005 | 368 (31.5) |
| 2006-2013 | 454 (38.8) |
| **Laterality** |  |
| Right | 574 (49.1) |
| Left | 523 (44.7) |
| Bilateral | 62 (5.3) |
| Unknown | 10 (0.9) |
| **NHL subtypes** |  |
| Other aggressive B-NH<sup>b</sup> | 29 (2.5) |
| DLBCL<sup>c</sup> | 970 (82.9) |
| Indolent B-NHL<sup>d</sup> | 39 (3.3) |
| Malignant lymphoma, NHL | 79 (6.8) |
| Others | 37 (3.2) |
| T-NHL | 15 (1.3) |
| **Treatment** |  |
| Resection + radiation | 408 (34.9) |
| Resection alone | 761 (65.1) |
| **Stage** |  |
| Stage I | 643 (55.0) |
| Stage II | 159 (13.6) |
| Stage III | 59 (5.0) |
| Stage IV | 185 (15.9) |
| Unknown | 123 (10.5) |

<sup>a</sup>Includes Native American individuals, Alaska Natives and Asian-Pacific Islanders. <sup>b</sup>Includes Burkitt’s lymphoma, Mantle-cell lymphoma, precursor B-cell lymphoblastic lymphoma and B lymphoblastic leukemia/lymphoma, not otherwise specified. <sup>c</sup>Includes ML, mixed small and large cell, diffuse; ML, large B-cell, diffuse; and ML, large B-cell, diffuse, immunoblastic, and not otherwise specified. <sup>d</sup>Includes follicular lymphoma, small B-cell lymphocytic lymphoma, marginal zone B-cell lymphoma and lymphoplasmacytic lymphoma. ML, malignant lymphoma; NHL, non-Hodgkin’s lymphoma; PTL, primary testicular lymphoma; T-NHL, T-cell non-Hodgkin lymphoma.
of rituximab on prognosis. However, information regarding the treatment of patients with rituximab was not available on the SEER database. Laterality was categorized as right, left, bilateral or unknown. The stage was established according to the 1983+ Ann Arbor classification criteria (13). Patients diagnosed between 1973 and 1983 were excluded from the data used for Ann Arbor stage statistics.

Statistical analyses were performed with R software (https://www.r-project.org). Two-tailed P<0.05 was considered to indicate a statistically significant difference. The Kaplan-Meier method was used to estimate differences in the CSS of patients with PTL, which was calculated between date of diagnosis and date of mortality caused by PTL. The log-rank test and multivariate Cox regression model were used to assess differences in CSS and OS according to age at diagnosis, ethnicity, laterality, year at diagnosis, Ann Arbor stage and histotype. P-values were computed by likelihood ratio tests.

Results

Baseline demographics and tumor characteristics. The SEER database included 1,169 patients diagnosed with PTL between 1973 and 2013 whose clinical features were summarized in Table I. The median age of patients was 70 years (range, 2-98 years). The majority of patients were Caucasian (1,005/1,169; 86%), and ~38.8% (454/1,169) of patients were diagnosed in the years following introduction of rituximab (2006 or later). Based on the Ann Arbor staging system, ~55% of patients with PTL had stage I disease (n=643), 13.6% had stage II disease (n=159), 5% had stage III disease (n=59) and 15.9% had stage IV disease (n=185). All patients underwent surgical intervention, and only 34.9% (408/1,169) of patients received radiotherapy after surgery. The most prevalent tumor histological subtype was DLBCL (970/1,169, 82.9%), followed by follicular lymphoma (21/1,169, 1.80%; Table II) and Burkitt’s lymphoma (15/1,169, 1.3%). T-cell lymphomas, including mature T-cell lymphoma, anaplastic large cell lymphoma, NK/T-cell lymphoma, and precursor T-cell lymphoblastic lymphoma, accounted for only a small number of cases (15/1,169, 1.3%). Table II summarizes the distribution of all PTL histological subtypes in the study cohort.

Survival and prognostic factors. Kaplan-Meier analyses were used to calculate CSS. Younger patients (<70 years) presented a significantly better prognosis than those ≥70 years (P<0.001). The estimated 5-year CSS rates during the periods of 1973-1997, 1998-2005 and 2006-2013 were 44% (194 patients succumbed), 62.4% (137 patients succumbed) and 70.4% (136 patients succumbed), respectively (P<0.001). The 5-year CSS rate was also associated with the PTL
Table III. Univariate and multivariate analyses for CSS and OS of patients with primary testicular lymphoma.

| Variable                  | 5-year CCS |  | 5-year OS |  |  |
|---------------------------|------------|----------|-----------|----------|----------|----------|----------|
|                           |            |          | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |          |          |
|                           |            |          | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Ethnicity                 |            |          |            |         |            |         |            |         |            |         |
| Caucasian                 | 58.5       | 0.214    | 54.1-61.7 | NI       | 57.6       | 0.227    | 54.3-61.2 | NI       |            |         |
| African descent           | 56.4       |          | 41.0-71.2 |           | 54.8       |          | 42.3-72.1 |           |            |         |
| Other                     | 63.5       |          | 54.3-75.6 |           | 65.0       |          | 55.4-76.0 |           |            |         |
| Age (years)               |            |          |            | <0.001   |            |         |            | <0.001   |            |         |
| <60                       | 71.5       |          | 66.5-76.7 |           | 71.2       |          | 66.4-76.5 |           |            |         |
| 60-69                     | 61.0       |          | 54.2-67.5 |           | 60.3       |          | 54.0-67.3 |           | 1.351     | 0.021    |
| 70-79                     | 53.8       |          | 47.7-60.0 |           | 52.9       |          | 47.1-59.6 |           | 1.883     | <0.001   |
| ≥80                       | 39.0       |          | 31.8-47.9 |           | 37.6       |          | 30.0-47.0 |           | 2.891     | <0.001   |
| Year of diagnosis         |            |          |            | <0.001   |            |         |            | <0.001   |            |         |
| 1973-1997                 | 44.0       |          | 38.7-50.0 |           | 44.0       |          | 38.7-50.0 |           |            |         |
| 1998-2005                 | 62.4       |          | 56.8-67.2 |           | 61.1       |          | 56.1-66.6 |           | 0.642     | <0.001   |
| 2006-2013                 | 70.4       |          | 64.9-75.8 |           | 69.8       |          | 64.6-75.4 |           | 0.453     | <0.001   |
| Laterality                |            |          |            | 0.129     |            |         | 0.096     |          |            |         |
| Right                     | 62.7       |          | 56.8-65.7 |           | 61.7       |          | 56.4-65.4 |           |            |         |
| Left                      | 56.5       |          | 54.0-63.3 |           | 57.1       |          | 54.2-63.7 |           |            |         |
| Bilateral                 | 52.8       |          | 32.9-64.2 |           | 51.9       |          | 32.7-63.9 |           |            |         |
| NHL subtypes              |            |          |            | <0.001   |            |         |            | <0.001   |            |         |
| Other aggressive B-NHL    | 40.4       |          | 27.5-59.4 |           | 40.3       |          | 27.6-59.8 |           | 2.072     | <0.001   |
| Malignant NHL, NOS        | 53.4       |          | 42.3-67.3 |           | 52.9       |          | 42.0-67.8 |           | 1.067     | 0.687    |
| DLBCL                     | 60.2       |          | 56.8-63.8 |           | 61.7       |          | 58.3-65.3 |           |            |         |
| Indolent B-NHL            | 57.8       |          | 44.8-77.4 |           | 58.8       |          | 44.8-77.4 |           | 1.071     | 0.753    |
| Others                    | 51.3       |          | 36.5-72.2 |           | 52.8       |          | 36.2-77.1 |           | 1.156     | 0.545    |
| T-NHL                     |            |          | NA         | <0.001   |            |         | NA        | <0.001   |            |         |
| Treatment                 |            |          |            | <0.001   |            |         |            | <0.001   |            |         |
| Surgery+Radiation         | 67.5       |          | 62.8-72.8 |           | 67.6       |          | 62.8-72.8 |           | 0.766     | 0.007    |
| Surgery                   | 54.3       |          | 49.2-57.5 |           | 53.7       |          | 49.0-57.2 |           |            |         |
| Stage                     |            |          |            | <0.001   |            |         |            | <0.001   |            |         |
| Stage I                   | 70.9       |          | 66.6-74.8 |           | 70.5       |          | 66.5-74.7 |           |            |         |
| Stage II                  | 58.2       |          | 50.0-67.4 |           | 58.1       |          | 50.0-67.4 |           | 1.514     | 0.003    |
| Stage III                 | 48.1       |          | 36.1-65.7 |           | 49.0       |          | 36.4-66.1 |           | 2.292     | <0.001   |
subtypes. The 5-year CSS rates were 60.2% (386 patients succumbed) for DLBCL, 57.8% (16 patients succumbed) for indolent B-NHL, 40.4% (17 patients succumbed) for other aggressive B-NHL and 53.4% (37 patients succumbed) for malignant NHL that was not otherwise specified (P<0.001). All patients underwent surgical intervention, and patients who had received radiotherapy had a 5-year CSS rate of 67.5% (133 patients succumbed) compared with 54.3% (348 patients succumbed) for patients who did not undergo radiation therapy (P<0.001). The 5-year CSS rates were 70.9 (187 patients succumbed), 58.2 (67 patients succumbed), 48.1 (30 patients succumbed) and 34.7% (119 patients succumbed) for patients with stage I, II, III, and IV tumors, respectively (P<0.001; Table III and Fig. 2). The 5-year OS rates were 70.5% (190 patients succumbed), 58.1% (67 patients succumbed), 49.0% (30 patients succumbed) and 35.5% (119 patients succumbed) for patients with stage I, II, III, and IV tumors, respectively (P<0.001; Table III and Fig. 3); this trend was similar to that of 5-year CSS. Multivariable Cox regression analysis of the study population revealed that age, period of diagnosis, some specific NHL subtypes, radiotherapy and Ann Arbor stage were independent prognostic factors. Ethnicity and laterality however did not represent independent prognostic factors (Table III).

Impact of rituximab on CCS in patients with PTL based on cancer stages and patient age.

Rituximab was first tested in a clinical trial in 1994 (14) and SEER Medicare-based studies by Hamlin et al. (15) revealed that the use of rituximab for the treatment of DLBCL has increased in older patients since 2000. Between 2005 and 2006, a large proportion of elderly patients with DLBCL were treated with rituximab-based regimens (16). In 2006, the US FDA approved rituximab for the treatment of DLBCL (17).

The effects of rituximab treatment on survival, according to cancer stage and age, were also explored. For this analysis, patients with PT-DLBCL were the primary focus, as they constituted the largest subgroup of PTL patients (4). Rituximab treatment was revealed to be an independent prognostic factor according to cancer stage, in univariate and multivariate analyses (P<0.05; Table IV). Compared with patients diagnosed prior to the introduction of (1973-2005), patients who received the treatment (2006-2013) had an improved survival rate [stages I-II, hazard ratio (HR) 0.608, 95% confidence interval (CI) 0.453-0.815, P<0.001; stages III-IV, HR 0.681, 95% CI 0.477-0.972, P=0.046; unknown stage, HR 0.674, 95% CI 0.453-1.057, P=0.007]. The association between rituximab treatment and age is complex. The survival benefit of rituximab treatment was observed in the two groups for patients <70 years (<60 years, HR 0.500, 95% CI 0.317-0.789, P=0.003; 60-69 years, HR 0.305, 95% CI 0.167-0.559, P<0.001). For patients >80 years, rituximab treatment did not present any survival advantage. Patients with DLBCL after 2006 were further analyzed (Table V, Figs. 4 and 5). Results revealed that age, Ann Arbor stage and treatment were significant factors affecting CSS and OS outcomes.

Discussion

To the best of our knowledge, the present study was the largest to explore the epidemiology and prognosis of PTL
The results revealed that DLBCL was the predominant histological subtype of PTL, and that 68.6% of cases were diagnosed in the early stages of the disease (stages I-II). In addition, age, year of diagnosis, specific NHL subtypes, radiotherapy and Ann Arbor stage were demonstrated as independent prognostic factors for PTL. Furthermore, patients >70 years, those that were diagnosed in the earlier time period, patients with T-NHL histotype, or patients with more tumors at stage III/IV exhibited the worst 5-year CSS rates. The introduction of rituximab in the scheme treatment significantly improved the 5-year CSS.

The median age at diagnosis of PTL was 70 years, which was slightly older than the age reported in the literature (67 years) (5,18). The present analysis revealed that B-cell NHL accounted for ~88.7% of all PTL cases, compared with T-cell NHL in 1.3% of PTL cases. The predominant histopathological type was DLBCL, which was observed in 82.9% (970/1,169) of cases, whereas follicular lymphoma was the second most prevalent subtype observed, followed by Burkitt's lymphoma. These were unique findings compared to previous studies (4,19).

In addition, earlier reports demonstrated that 60-79% of patients have stage I/II disease at the time of diagnosis (1,5,20), which is comparable to the 68.6% reported in the present study.

The age at diagnosis was an important predictor of survival, and patients <60 years old presented better survival outcomes than those >60 years old. These findings were consistent with previous studies (1,3,9). In addition, diagnosis...
at a later time period was a good prognostic factor of survival in PTL, due to the availability of radiotherapy and rituximab. Although orchiectomy is indicated for both diagnostic and therapeutic purposes, prognosis is considered to be poor in patients treated with orchiectomy alone (8), even for stage I disease (18). Furthermore, in a survey by the International Extranodal Lymphoma Study Group, the addition of adjuvant radiotherapy was associated with significant improvement in 5-year PFS (70 vs. 36%; $P=0.00001$) and OS (66 vs. 38%; $P=0.00001$) (21). In the present study, the 5-year CSS rate of PTL was improved from 54.3 to 67.5% when patients underwent radiotherapy. In addition, tumor histological types were associated with survival in patients with PTL. The 5-year CSS of patients with DLBCL was similar to that of those with indolent B-NHL (60.2 vs. 57.8%). This finding was consistent with a Dutch study, which demonstrated no significant improvement in survival rates for marginal zone lymphoma (22). Due to the low frequency of non-DLBCL histology, only

Figure 3. Overall survival of patients with primary testicular lymphoma. Kaplan-Meier survival curves by (A) age, (B) year of diagnosis, (C) NHL subtypes, (D) treatment, (E) stage and (F) laterality. DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma.
little amount of studies have reported the survival rates for these cases. However, the analysis performed in the present study revealed that patients with other aggressive B-NHLs had worse survival outcomes, with a 5-year CSS of 40.4%. Bacon et al. (23) described five cases of primary follicular lymphoma of the testes in adult men who, following initial treatment, remained free from disease 4 years after diagnosis. However, the lymphomas did not express B-cell lymphoma 2 gene or carry t(14;18) (q32; q21)/immunoglobulin heavy chain translocations, which is different from traditional follicular lymphoma. Liang et al. (24) summarized 13 cases of primary extranodal nasal-type natural killer/T-cell lymphoma of the testes, among which four patients survived for ≥1 year.

The relevance of laterality in the prognosis of PTL is controversial. Gundrum et al. (1) reported that lymphoma involvement of the right testis is associated with improved DSS. Conversely, Roychoudhuri et al. (25) revealed that testicular lymphoma with left-side involvement is associated with better outcomes. In the present study, the 5-year CSS rates with right-side, left-side and bilateral involvement were 62.7, 56.5 and 52.8%, respectively, with no significant difference among them (P=0.129). In addition, the prognostic impact of the Ann Arbor stage is still controversial. Numerous studies (1,8,9) have reported that early stage disease (I or II) is associated with improved survival in patients with PTL; however, other studies on PTL (26,27) did not identify Ann Arbor stage as a prognostic factor. In the current study, the overall 5-year CSS rates were 70.9, 58.2, 48.1 and 34.7% for patients with PTL diagnosed in stages I, II, III and IV, respectively. Patients with advanced-stage PTL had therefore a significantly inferior CSS compared to patients with early stage PTL.

Several studies have revealed that the outcome of patients with nodal DLBCL is improved greatly with the addition of rituximab to chemotherapy (28-31), although the effect of rituximab on PT-DLBCL is still debatable. A population-based retrospective study in the US (1) exhibited no difference in PT-DLBCL outcomes before and after addition of rituximab to therapy. Avilés et al. (32), demonstrated that the outcome of patients with early stage PTL is improved with the addition of rituximab to chemotherapy. In the present study, the introduction of rituximab also prolonged the 5-year CSS, independently of Ann Arbor stage and age. Rituximab is also used to treat patients with primary CNS lymphoma due to the positive effects seen in patients with extra-CNS DLBCL (33,34). However, as it is a large protein, it has a poor capacity to penetrate the CNS (35) and its ability to prevent the dissemination.
Table V. Univariate and multivariate analyses of primary testicular diffuse large B-cell lymphoma CSS and OS during the post-rituximab time period.

| Variable | 5-year CCS | 5-year OS |
|----------|------------|-----------|
|          | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|          | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Ethnicity |            |        |            |        |            |        |
| Caucasian | 71.5 (65.5-78.0) | <0.001 | 70.3 (64.2-77.7) | <0.001 |            |        |
| African descent | NA |        | NA |        |            |        |
| Other | NA |        | NA |        |            |        |
| Age (years) |        |        |            |        |            |        |
| <60<sup>b</sup> | 82.7 (74.0-92.5) | 0.516 | 82.5 (73.7-92.3) | 0.064 |            |        |
| 60-69 | 64.0 (53.5-76.5) | 3.056 (1.614-5.788) | <0.001 | 63.2 (52.6-76.0) | 0.039 |            |        |
| 70-79 | 40.8 (28.7-63.2) | 6.844 (3.561-13.152) | <0.001 | 40.3 (28.1-62.4) | 0.042 |            |        |
| ≥80 |             |        |            |        |            |        |
| Laterality | 0.552 | NI | 0.413 | NI |            |        |
| Right | 72.4 (64.7-81.1) | 0.726 (0.324-1.761) | 0.516 | 71.6 (63.8-80.4) | 0.011 |            |        |
| Left | 71.7 (62.3-80.5) | 3.016 (1.614-5.788) | <0.001 | 69.5 (60.1-78.4) | 0.005 |            |        |
| Bilateral | NA |        | NA |        |            |        |
| Treatment | 0.011 |        | 0.005 |        |            |        |
| Surgery+radiation | 76.5 (67.5-86.5) | 0.439 (0.189-0.748) | 0.046 | 76.5 (67.5-86.5) | 0.599 (0.365-0.981) | 0.042 |
| Surgery<sup>a</sup> | 68.5 (61.6-76.2) | 67.2 (60.1-75.1) |        |            |        |
| Stage | <0.001 |        | <0.001 |        |            |        |
| Stage I<sup>b</sup> | 80.2 (74.7-87.8) | 0.516 | 79.8 (65.7-74.1) | 0.001 |            |        |
| Stage II | 62.0 (47.8-80.4) | 2.735 (1.514-4.940) | <0.001 | 61.8 (47.2-80.0) | 2.844 (1.583-5.110) | <0.001 |
| Stage III | NA |        | NA |        | 5.268 (2.507-11.071) | <0.001 |            |        |
| Stage IV | 51.9 (38.6-69.9) | 4.462 (2.610-7.626) | <0.001 | 51.8 (38.5-69.8) | 4.288 (2.493-7.375) | <0.001 |
| Unknown | NA |        | NA |        | 0.824 (0.110-6.152) | 0.850 |            |        |

<sup>a</sup>Includes Native American, Alaska Native and Asian-Pacific Islander. <sup>b</sup>Reference group.CSS, cause-specific survival; DLBCL, diffuse large B-cell lymphoma; NA, not available; NI, not included; OS, overall survival.
Figure 4. Cause-specific survival of patients with diffuse large B-cell lymphoma after rituximab availability. Kaplan-Meier survival curves by (A) age, (B) stage, (C) laterality and (D) treatment.

Figure 5. Overall survival of patients with diffuse large B-cell lymphoma after rituximab availability. Kaplan-Meier survival curves by (A) age, (B) stage, (C) laterality and (D) treatment.
of DLBCL in the CNS remains questionable. Furthermore, rituximab treatment did not have any survival advantage for patients >80 years in the present study, which may be due to the poor physical condition and presence of additional comorbidity in these patients. Kemmerling et al (36) revealed that PT-DLBCL can be further subdivided into an activated B-cell (ABC) phenotype and a germinal center (GC) phenotype, and reporter that patients with the GC phenotype had a better OS than those with the ABC phenotype. Therefore, the differences in patients outcomes presented by numerous studies may be associated with the various subtypes of PT-DLBCL.

Although the present study was a large population-based study, it presented several limitations. Firstly, the SEER database provided no information regarding chemotherapy and rituximab use, which may affect the results. Secondly, the sites of relapse were not precisely described. Thirdly, not enough clinical data were available for risk stratification according to the IPI; therefore, survival analysis according to IPI risk was not assessed. Only 38.8% of patients were diagnosed after 2006, which may represent an unknown bias in the selection. This was however a population-based study and the data presented were very close to real-world conditions. Although knowledge from the current literature is not very critical, it remains a valuable guide to further investigate PTL and identify novel treatment schemes.

To the best of our knowledge, the present study was the largest study of patients with PTL, and exhibited that age, year of diagnosis, Ann Arbor stage and histological type were independent predictors for PTL prognosis. In addition, the multiple analyses revealed that adjuvant radiotherapy and the addition of rituximab to chemotherapy may provide survival benefits. A prospective study must however be performed to confirm these findings. In conclusion, determination of independent predictors and treatments efficiency may aid practitioners in their decision of therapy regimens and improve PLT prognosis.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors’ contributions
XH designed the study, performed the statistical analysis and drafted the manuscript. FX performed the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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