Primary lymphoma of bone: a population-based study of 2558 patients

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Abstract

Background: Primary lymphoma of bone (PLB) is an extremely rare malignancy arising in the skeletal system. There is no consensus over the best definition of PLB. Most of the published articles are single-institutional retrospective studies with a limited sample size. The rarity of PLB and discrepancies on diagnostic criteria has resulted in a vague understanding of PLB.

Methods: We retrospectively analyzed the clinical characteristics and prognostic factors of 2558 PLB patients who were registered in the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2016. Survival rates were calculated using the Kaplan–Meier method. The effects of various factors on survival outcomes were analyzed by using the log-rank test. Univariate and multivariate analyses were conducted by using the Cox proportional hazards model to determine independent prognostic factors.

Results: The median follow-up time of all eligible patients was 58 months. There seemed no sex preponderance in PLB incidence. The most involved sites are axial skeletons. The most common histological subtype was diffuse large B-cell lymphoma. The 3-, 5-, 10-, and 20-year overall survival (OS) rates were 70.70%, 65.70%, 54.40% and 39.50%, respectively. PLB patients whose primary tumor sites were appendicular and craniofacial skeletons had a significant survival advantage [hazard ratio (HR) = 0.694, 95% confidence interval (CI) 0.552–0.872; HR = 0.729, 95% CI 0.597–0.889, respectively] over those with axial skeletons as primary tumor sites. Patients with Hodgkin lymphoma, non-Hodgkin lymphoma (NHL)–mature B-cell lymphoma, and NHL-precursor-cell lymphoblastic lymphoma also had a significant OS advantage (HR = 0.392, 95% CI 0.200–0.771; HR = 0.826, 95% CI 0.700–0.973; and HR = 0.453, 95% CI 0.223–0.923, respectively). Patients with Ann Arbor stage III–IV at diagnosis were at higher risk of death than those with stage I–II (HR = 1.348, 95% CI 1.107–1.641). Chemotherapy was an independent favorable prognostic factor (HR = 0.734, 95% CI 0.605–0.890).

Conclusions: Primary anatomic site, histology type, higher Ann Arbor stage and chemotherapy were independent prognostic factors. Chemotherapy played a pivotal role in PLB treatment.

Keywords: primary lymphoma of bone, prognosis, SEER, survival, therapeutic modality

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Introduction

Primary lymphoma of bone (PLB), a rare hematological malignancy arising in the skeletal system, constitutes approximately 5% of extranodal lymphomas, less than 1% of all non-Hodgkin lymphomas (NHLs) and 3–7% of all malignant bone tumors.[1] PLB is putatively correlated with HIV infection, osteomyelitis, chemotherapy, and some autoimmune disease.[2] Diagnostic criteria for defining and classifying PLB have varied over time. According to World Health Organization classification of bone and soft-tissue tumors, PLB is defined as a single skeletal neoplasm composed of malignant lymphoid cells without regional

lymph-node invasion, or bone lesions without invasion on visceral tissue or lymph node. Up till now, there is no consensus on the best definition of PLB. The definition in previous studies varied depending on different authors. Some studies only enrolled patients with Ann Arbor stage I and stage II at diagnosis, while other studies also enrolled patients with stage III and stage IV.[1,3] PLB in pediatric patients is considered another clinical entity which is markedly different from its adult counterpart.[4,5]

The most commonly observed symptom is bony pain and swelling (80–95%), followed by tumor mass (30–40%) and pathological fracture (15–20%). The most frequently involved sites are the axial skeletons, yet every bone throughout the body is the potential place for PLB tumorigenesis.[2,6] It is difficult to distinguish PLB from other kinds of primary bone tumors including chondrosarcoma and Ewing's sarcoma in that radiographic results of PLB are not specific. Survival outcomes of PLB were considered brighter than other types of primary bone cancers. Moreover, previous studies reported that 5-year overall survival (OS) rate ranged from 36.0% to 88.3%, since different studies adopted different diagnostic criteria.[6–10] Due to the rarity of PLB, the existing relevant literature consists mainly of single-institutional studies with small sample sizes, thus leading to an ambiguous description of clinical features, management, and prognosis. Selecting the optimal therapeutic strategy remains enigmatic because there have been no prospective clinical trials conducted regarding PLB. Herein, we present a series of 2558 PLB patients who were registered in the Surveillance, Epidemiology and End Results (SEER) database to explore patient demographics, pathological characteristics, therapeutic options, survival outcomes, and prognostic factors, thus shedding more light on this rare bone cancer.

Methods

Information regarding PLB patients between 1973 and 2016 were extracted from the SEER database, which is a population-based cancer registry supported by the National Cancer Institute of the United States (US). The SEER database covers approximately 28% of the US population, holding annually uploaded data on patient demographics, tumor pathology, anatomic sites of tumor, stage at diagnosis, first course of treatment modalities and the follow-up vital status. Our present study was exempted from institutional review board because the SEER database is available to the public and contains completely anonymized patient information.

The flowchart of identification process is shown in Figure 1. A total of 3113 PLB patients were identified from the SEER database, of whom 2558 cases (82.17%) with complete survival information were eligible for further analysis. Inclusion criteria were as follows: (a) anatomic site of the primary tumor localized on the skeletal system [International Classification of Diseases (ICD)-O-3: C40.0–C41.9]; (b) histological type limited to lymphoma (ICD-O-3 histology codes: 9590–9738); (c) malignant behavior (ICD-O-3 behavior code: 3). Exclusion criteria contained: (a) patients without histological confirmation (diagnostic confirmation codes: 2, 4, 5, 6, 7, 8, 9); (b) patients with unclear information (stages, treatment modalities, age, sex, etc.); (c) patients aged under 18-years old (due to the potentially different natural history of disease). There were two endpoint events in this study. OS was calculated from pathological diagnosis to the date of last follow up, or death from any causes. Disease-specific survival (DSS) was defined as the time interval from diagnosis to the date of last follow up, or death caused by PLB.

All statistical analyses were performed with software SPSS (Version 26.0, SPSS Inc, Chicago, IL, USA). The influence of clinical and therapeutic variables on survival outcome was assessed by comparing the Kaplan–Meier survival curves through log-rank test. Multivariate analyses on DSS and OS were performed with a Cox proportional hazard regression model by incorporating variables that were statistically significant in univariate analysis. All significance tests were two tailed with $p < 0.05$ considered statistically significant.

Results

A total of 2558 patients with PLB were finally enrolled in our study, including 1251 men and 1307 women (0.957:1). The distribution of histologic subtypes of PLB was demonstrated in Table 1. The most frequently observed histological subtype was diffuse large B-cell lymphoma (DLBCL; $n = 1703$, 66.58%), followed
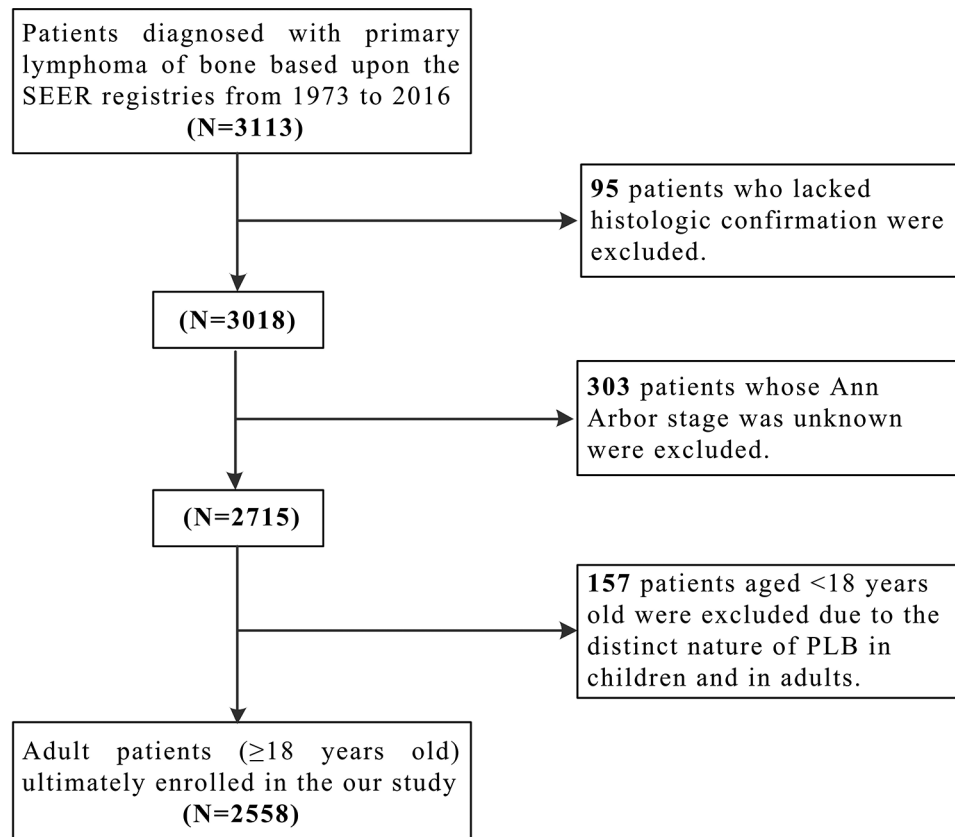
Figure 1. Flow diagram of the selection process for the patient cohort.
PLB, primary lymphoma of bone; SEER, Surveillance, Epidemiology, and End Results database.

by follicular lymphoma (*n* = 166, 6.49%). The distribution of primary involved skeletal sites of PLB is shown in Table 2. The most commonly involved site was vertebral column (*n* = 767, 29.98%), followed by the long bones of lower limb and associated joints (*n* = 597, 23.34%). Information about PLB patient demographic and variables is summarized in Table 3. Median age at diagnosis was 59.59 years old (range 18–100 years), and 86% of patients were White (*n* = 2189, 85.6%). The vast majority of PLB patients (*n* = 2534, 99.1%) suffered from NHL; 2082 of NHL–PLB patients were diagnosed with mature B-cell lymphoma (81.4%) and only 56 of NHL–PLB patients were diagnosed with mature T- and natural killer (NK)-cell lymphoma (2.2%). While patients who suffered from Hodgkin lymphoma (HL) accounted for merely 0.9% (*n* = 24). A total of 1430 cases (55.9%) had primary axial bone lesions (including vertebral column, rib, sternum, clavicle, pelvic bones, sacrum, coccyx, and associated joints), while 223 cases (8.7%)

had craniofacial bone lesions (including mandible, bones of skull and face and associated joints) and 905 cases (35.4%) had appendicular bone lesions (including long and short bones of upper and lower limbs, scapula, and associated joints). Based upon Ann Arbor stage at diagnosis, PLB patients were categorized into four groups. That was stage I (*n* = 1367, 53.4%), stage II (*n* = 285, 11.1%), stage III (*n* = 58, 2.3%) and stage IV (*n* = 848, 33.2%), respectively. Most of patients underwent radiation and/or received chemotherapy therapy as initial treatment (1391 and 1941 patients, respectively). Of all patients, merely 618 cases (24.2%) received surgery.

The median follow-up time for all eligible patients was 58 months (range 0–401 months). The Kaplan–Meier curves of OS and DSS are shown in Figure 2. The OS rates of 3, 5, 10 and 20 years were 70.70%, 65.70%, 54.40% and 39.50%, respectively. At the corresponding time point, DSS rates were 76.80%, 73.60%, 68.10% and

Table 1. The distribution of histologic subtypes in PLB.

Histologic type (ICD-O-3)	Number	Percentage
Diffuse large B-cell lymphoma, NOS (9680)	1703	66.58%
Non-Hodgkin lymphoma, NOS (9591)	314	12.28%
Follicular lymphoma (9698)	166	6.49%
Lymphoid neoplasm, NOS (9590)	111	4.34%
Chronic/small lymphocytic, NOS (9670)	49	1.92%
Anaplastic large cell lymphoma, T-cell and null cell type (9714)	44	1.72%
Burkitt lymphoma, NOS (9687)	34	1.33%
Marginal zone B-cell lymphoma, NOS (9699)	30	1.17%
Precursor NHL, NOS (9727)	29	1.14%
Lymphoplasmacytic lymphoma (9671)	24	0.94%
Classical Hodgkin lymphoma, NOS (9650)	17	0.66%
Peripheral T-cell lymphoma, NOS (9702)	12	0.47%
Mantle-cell lymphoma (9673)	9	0.35%
Nodular sclerosis classical Hodgkin lymphoma (9663)	7	0.27%
NHL, NOS, T-cell (9684)	5	0.20%
NK/T-cell lymphoma, nasal and nasal-type (9719)	2	0.08%
Primary effusion lymphoma (9678)	1	0.04%
Composite Hodgkin lymphoma and NHL (9596)	1	0.04%
Total patients with PLB	2558	100.00%

ICD, International Classification of Diseases; NHL, non-Hodgkin lymphoma; NK, natural killer (cell); NOS, not otherwise specified; PLB, primary lymphoma of bone.

61.00%, respectively. In the univariate assessment, sex ($p=0.005$), primary site ($p<0.001$), lateral position ($p=0.001$), histological records: broad grouping ($p<0.001$), Ann Arbor stage ($p<0.001$), the number of lesions ($p=0.027$), surgery ($p=0.004$), radiation ($p<0.001$), and chemotherapy ($p<0.001$) are the possible predictive factors of OS (Table 4).

As demonstrated in Figures 3 and 4, Kaplan–Meier survival curves gave a detailed description of the associations between various factors and PLB prognosis. According to our results, sex did not seem to be one of those factors. Primary site could influence the prognosis of PLB, since patients with axial neoplasm had a bleaker prognosis than patients whose primary tumor sites were at the appendicular and craniofacial skeletons. The actual laterality of primary sites (left/right or bilateral) did not seem correlated with prognosis. Patients with malignant lymphoma [not otherwise specified (NOS) or diffuse] have shorter survival period than those with mature B-cell lymphomas and HLs. Patients with lower Ann Arbor stage (stage I–II) at diagnosis exhibited a remarkable survival advantage over those with higher Ann Arbor stage (stage III–IV). As to therapeutic approaches, chemotherapy and radiation therapy benefited PLB patients, while surgery did not prove to extend patient survival.

Table 2. The distribution of primary anatomic sites in PLB.

Primary anatomic sites (ICD site code)	Number	Percentage
Vertebral column (C41.2)	767	29.98%
Long bones of lower limb and associated joints (C40.2)	597	23.34%
Pelvic bones, sacrum, coccyx and associated joints (C41.4)	356	13.92%
Long bones of upper limb, scapula, and associated joints (C40.0)	258	10.09%
Bone, NOS (C41.9)	181	7.08%
Bones of skull and face and associated joints (C41.0)	130	5.08%
Rib, sternum, clavicle and associated joints (C41.3)	104	4.07%
Mandible (C41.1)	93	3.64%
Short bones of lower limb and associated joints (C40.3)	41	1.60%
Overlap bones, joints, and cartilage (C41.8)	19	0.74%
Bone of limb, NOS (C40.9)	9	0.35%
Overlap of bones, joints, and cartilage of limbs (C40.8)	3	0.12%
Total patients with PLB	2558	100.00%

ICD, International Classification of Diseases; NOS, not otherwise specified; PLB, primary lymphoma of bone.

As revealed in Table 5, multivariate analysis showed that the primary site, histological classification, Ann Arbor stage, and chemotherapy were independent prognostic factors. As to classification of tumor, patients with HL, NHL–mature B-cell lymphomas and NHL-precursor-cell lymphoblastic lymphoma had a significant OS advantage [hazard ratio (HR) = 0.392, 95% confidence interval (CI) 0.200–0.771; HR = 0.826, 95% CI 0.700–0.973; and HR = 0.453, 95% CI 0.223–0.923, respectively]. In terms of primary sites, patients with primary appendicular and craniofacial tumor had a significant survival advantage (HR = 0.694, 95% CI 0.552–0.872; HR = 0.729, 95% CI 0.597–0.889, respectively) over those with axial tumor. Patients with higher stage (stage III– IV) at diagnosis were at higher risk of death than those with lower stage (stage I–II) at diagnosis, yielding an HR of 1.348 (95% CI 1.107–1.641). Surgical treatment and radiotherapy proved not to be a protective factor of patients' long-term survival ($p > 0.05$), but chemotherapy was an independent favorable prognostic factor (HR = 0.734, 95% CI 0.605–0.890). The multivariate analysis of DSS was similar to the results of OS analysis.

Discussion

PLB has the characteristics of non-specific clinical manifestations but responds well to chemotherapy. DLBCL accounts for approximately 80% of all PLB histological subtypes.[2] Due to the low incidence of PLB, clinicopathological characteristics and therapeutic options are yet to be further investigated. Our present study analyzed 2558 cases in the SEER database, where most of the patients are White. Compared with the previous studies,[6,10–16] our study achieved consistent conclusions. The majority of the PLB patients were those with NHL. The median age at diagnosis was over 50-years old. Axial skeletons were the most involved sites. Chemotherapy and radiotherapy are recognized as the main treatment options for PLB. In terms of prognosis, higher Ann Arbor stage and multifocal disease at diagnosis were the unfavorable factors. Previous studies reported that there were more male PLB patients than female patients,[10–16] but our results were based upon a larger sample size, and indicated that the ratio of male to female PLB patients was close to 1:1. That is to say, the incidence of PLB has no sex predilection. Meanwhile, through further log-rank test, we found that the prognosis of

Table 3. Demographic and clinical characteristics of the adult PLB patients.

Characteristic		Number	Percentage
Sex			
Female		1251	48.9%
Male		1307	51.1%
Marital status			
Unmarried		1152	45.2%
Married		1403	54.8%
Age			
20–40		462	18.1%
40–60		674	26.3%
60–80		1021	39.9%
80–		401	15.7%
Race			
White		2189	85.6%
Black		206	8.1%
American Indian/Alaska native		23	0.9%
Asian or Pacific Islander		140	5.5%
Lymphoma type			
Hodgkin lymphoma		24	0.9%
Non-Hodgkin lymphoma		2534	99.1%
Primary site			
Axial		1430	55.9%
Appendicular		905	35.4%
Craniofacial		223	8.7%
Laterality			
Bilateral, single primary		32	1.3%
Left: origin of primary		607	23.7%
Right: origin of primary		555	21.7%
Not a paired site		1364	53.3%
Histologic type: broad groupings			
ICD-O-3:9590-9599	Malignant lymphomas, NOS or diffuse	367	14.3%
ICD-O-3:9650-9669	Hodgkin lymphomas	24	0.9%
ICD-O-3;9670-9699	NHL– mature B-cell lymphomas	2082	81.4%
ICD-O-3:9700-9719	NHL–mature T- and NK-cell lymphomas	56	2.2%
ICD-O-3:9720-9729	NHL-precursor-cell lymphoblastic lymphoma	29	1.1%

(Continued)

Table 3. (Continued)

Characteristic	Number	Percentage
Ann Arbor stage		
Stage I	1367	53.4%
Stage II	285	11.1%
Stage III	58	2.3%
Stage IV	848	33.2%
Number of bone lesions		
Single	2328	91.0%
Multiple (≥2)	230	9.0%
Radiation sequence with surgery		
No radiation and/or cancer-directed surgery	2202	86.1%
Radiation after surgery	339	13.3%
Radiation prior to surgery	12	0.5%
Radiation before and after surgery	5	0.2%
Surgery		
No	1940	75.8%
Yes	618	24.2%
Radiation		
No	1167	45.6%
Yes	1391	54.4%
Chemotherapy		
No	617	24.1%
Yes	1941	75.9%
Overall survival		
Censored	1440	56.3%
Dead	1118	43.7%
Disease-specific survival		
Censored	1833	71.7%
Dead	725	28.3%
Year of diagnosis		
1975–1986	111	4.3%
1986–1996	340	13.3%
1996–2006	890	34.8%
2006–2016	1217	47.6%

ICD, International Classification of Diseases; NHL, non-Hodgkin lymphoma; NK, natural killer (cell); NOS, not otherwise specified; PLB, primary lymphoma of bone.
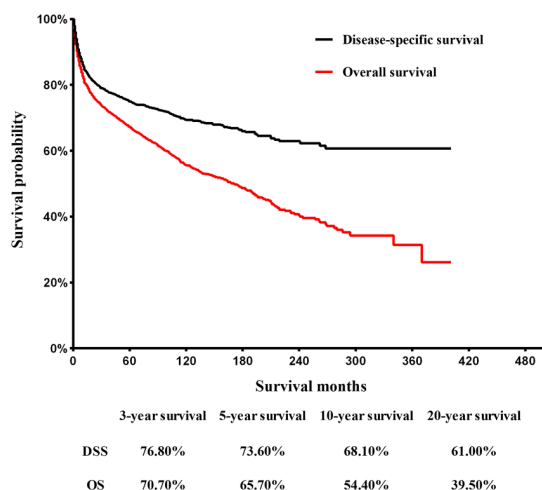
Figure 2. Kaplan–Meier curves of overall survival and disease-specific survival for adult patients with primary lymphoma of bone.
DSS, disease-specific survival; OS, overall survival.

female PLB patients seems to be worse than that of the male patients.

The past 2 decades witnessed the wide administration of anthracycline-containing chemotherapy with subsequent consolidative irradiation for the treatment of PLB.[6,11,14,17–19] A study conducted on 78 PLB patients with pathological fracture at presentation confirmed that anthracycline-based chemotherapy followed by irradiation proved to be the optimal treatment sequence, while the inverse sequence of these two modalities was correlated with bleaker survival outcome. Initial surgery did not help to inhibit the tumor and did not extend survival.[20] In clinical practice, surgery is often applied for diagnostic biopsy, pathological fractures, and spinal decompression with the aim of improving the quality of life. The role of surgery in PLB tumor control and treatment

Table 4. Univariate analysis of overall survival.

Characteristic	Median survival (95% CI)	HR (95% CI)	*p*
Sex			
Female	134.0 (160.3–107.7)	Reference	
Male	176.0 (149.4–202.6)	0.843 (0.750–0.949)	**0.005**
Age			0.143
20–39	157.0 (108.5–205.5)	Reference	–
40–59	136.0 (105.2–166.8)	1.073 (0.898–1.283)	0.437
60–79	162.0 (124.4–199.6)	1.010 (0.855–1.195)	0.903
>80	179.0 (143.2–214.8)	0.855 (0.693–1.055)	0.144
Race			0.108
White	157.0 (136.5–177.5)	Reference	–
Black	183.0 (150.5–215.5)	0.740 (0.583–0.941)	0.114
American Indian/Alaska native	131.0 (81.2–180.8)	0.965 (0.517–1.798)	0.910
Asian or pacific islander	144.0 (73.7–214.3)	0.967 (0.748–1.250)	0.798
Lymphoma type			
Hodgkin lymphoma	183.0 (95.1–270.9)	Reference	–
Non-Hodgkin lymphoma	162.0 (142.9–181.1)	1.478 (0.767–2.848)	0.243
Primary site			**0.000**
Axial	114.0 (93.6–134.4)	Reference	–
Appendicular	204.0 (112.7–295.3)	0.685 (0.515–0.860)	0.001
Craniofacial	219.0 (177.1–260.9)	0.697 (0.612–0.793)	0.000

(Continued)

Table 4. (Continued)

Characteristic	Median survival (95% CI)	HR (95% CI)	*p*
Laterality			**0.001**
Bilateral, single primary	113.0 (39.5–186.5)	Reference	–
Left: origin of primary	211.0 (175.6–246.4)	0.776 (0.460–1.307)	0.340
Right: origin of primary	163.0 (122.1–203.9)	0.835 (0.495–1.408)	0.498
Not a paired site	124.0 (101.6–146.4)	1.027 (0.615–1.713)	0.919
Histologic type: broad groupings			**0.000**
Malignant lymphomas, NOS or diffuse	92.0 (61.2–122.8)	Reference	/
Hodgkin lymphomas	183.0 (95.1–270.9)	0.520 (0.267–1.014)	0.055
NHL–mature B-cell lymphomas	167.0 (145.3–188.7)	0.740 (0.635–0.863)	0.000
NHL–mature T- and NK-cell lymphomas	181.5 (141.6–221.4)	0.618 (0.390–0.979)	0.040
NHL-precursor-cell lymphoblastic lymphoma	239.6 (186.8–292.4)	0.395 (0.195–0.800)	0.010
Ann Arbor stage			**0.000**
Stage I–II	191.0 (166.5–215.5)	Reference	–
Stage III–IV	107.0 (87.2–126.8)	1.078 (1.324–1.681)	**0.000**
Number of lesions			
Single	167.0 (144.9–189.1)	Reference	–
Multiple (≥2)	104.0 (75.0–133.0)	1.242 (1.024–1.505)	**0.027**
Surgery			
No	179.0 (157.3–200.7)	Reference	–
Yes	114.0 (87.8–140.2)	1.212 (1.064–1.379)	**0.004**
Radiation			
No	107.0 (89.7–124.3)	Reference	–
Yes	225.0 (119.8–244.3)	0.630 (0.559–0.710)	**0.000**
Chemotherapy			
No	80.0 (59.8–100.2)	Reference	–
Yes	202 (180.1–223.3)	0.619 (0.546–0.702)	**0.000**
Year of diagnosis			0.522
1975–1986	175.0 (95.8–254.2)	Reference	–
1986–1996	139.0 (101.7–176.3)	0.911 (0.665–1.247)	0.560
1996–2006	164.0 (128.0–200.0)	0.828 (0.619–1.106)	0.202
2006–2016	159.0 (129.3–188.7)	0.872 (0.656–1.159)	0.346

Bolded numerals indicate statistical significance.
CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma; NK, natural killer (cell); NOS, not otherwise specified.
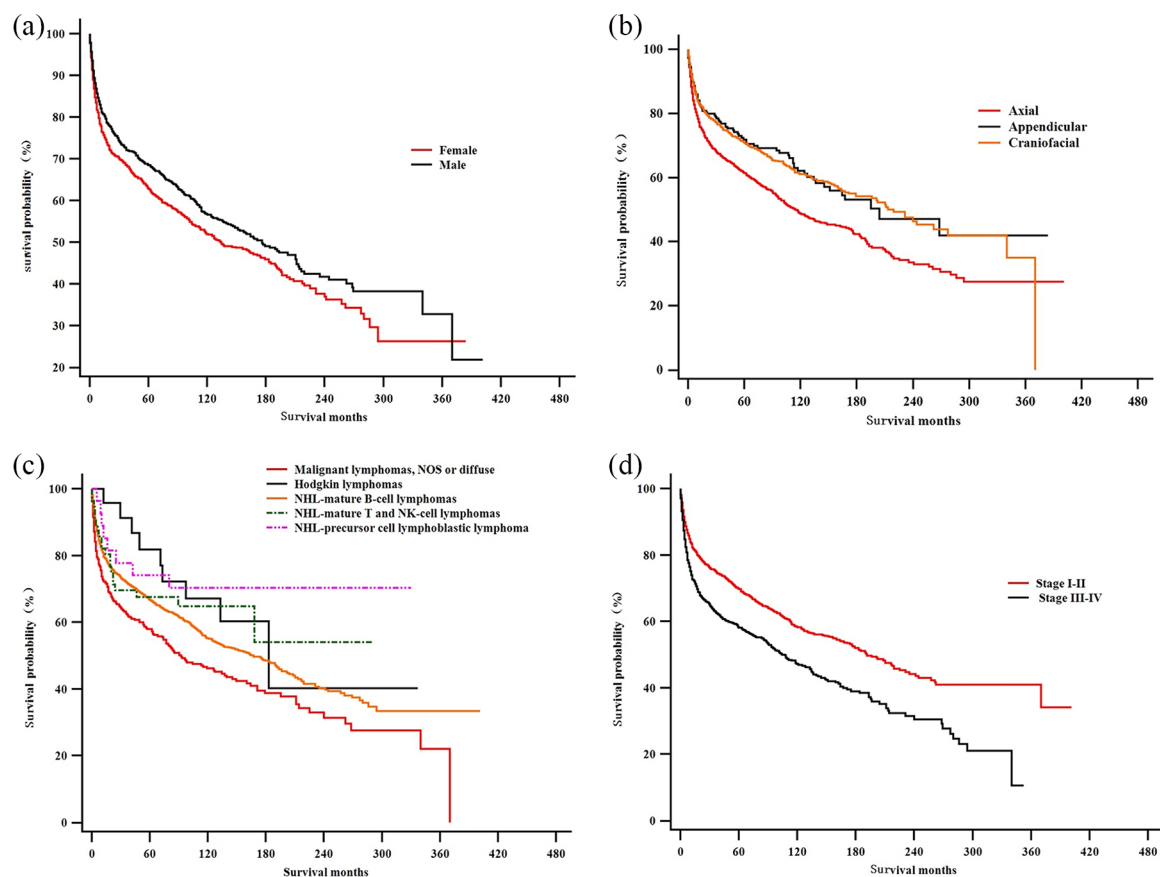
Figure 3. Kaplan–Meier estimate of overall survival by subgroup analysis: (a) sex; (b) primary anatomic sites; (c) histological subtype; and (d) Ann Arbor stage.
NHL, non-Hodgkin lymphoma; NK, natural killer (cell); NOS, not otherwise specified.

warrants further verification. Multiple studies have revealed that a combined regime can achieve a higher OS rate and have clarified that a combinative use of chemotherapy and radiotherapy might be the best therapeutic option for PBL.[7,13,21–23] A multicenter retrospective study verified that 116 PLB patients diagnosed at an early stage (stages I and II) had a brighter prognosis and can benefit greatly from adequate radiotherapy dose (40 Gy) alone, chemotherapy alone and the combined modalities.[11] Another retrospective study enrolled 102 PLB patients with DLBCL. In comparison with the non-radiotherapy group, patients who received consolidative radiotherapy after standard chemotherapy achieved excellent survival outcomes, yielding both markedly improved 5-year progression-free survival (PFS) rate (88% *versus* 63%, $p = 0.0069$) and OS rate (91% *versus* 68%, $p = 0.0064$).[24]

However, the IELSG-14 study concluded that whether they received subsequent radiotherapy or not, PLB patients with DLBCL subtype had an encouraging prognosis when administered with the anthracycline-based therapeutic regimen. The addition of subsequent consolidative radiotherapy with intensified doses and enlarged involved fields to initial chemotherapy was not correlated with improved survival outcome.[25] A retrospective study on 52 PLB patients demonstrated that the complete response rate in the radiotherapy-alone group and chemotherapy with/without radiation group were 64% and 85%, along with the relapse rate of 57% and 6%, respectively.[26] Beal *et al.* revealed that the 5-year OS rate of PLB patients treated with a combination of chemotherapy and radiotherapy was not superior to that of patients who received chemotherapy alone.[10] A retrospective study on 61
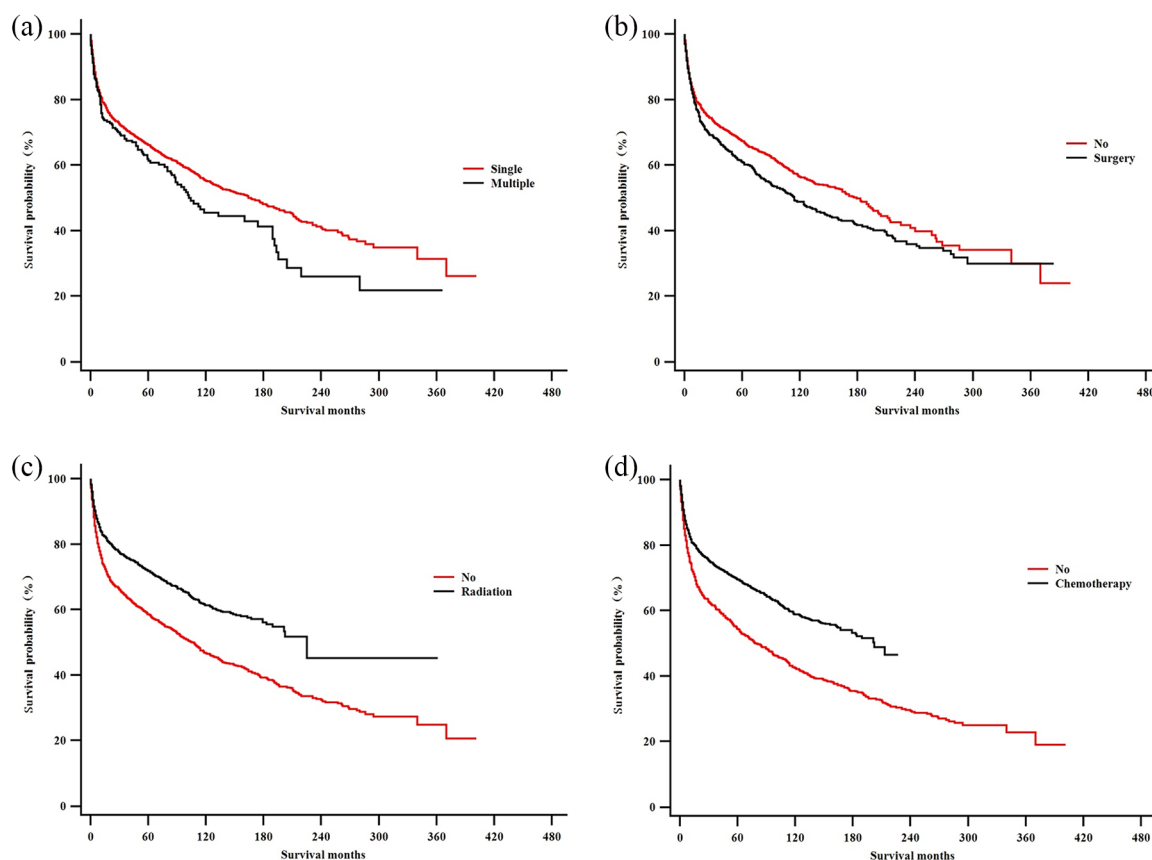
Figure 4. Kaplan–Meier estimate of overall survival by subgroup analysis: (a) number of osseous lesions; (b) Surgery; (c) radiotherapy; and (d) chemotherapy.

Chinese PLB patients demonstrated that chemotherapy played a pivotal role in PLB treatment, and chemotherapy alone was also not inferior to the combined therapeutic modality.[19]

Since the majority of PLB is pathologically categorized into DLBCL, cyclophosphamide, doxorubicin, vincristine, and prednisone or rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone are currently the main treatment regimens. Beal *et al.*[10] reported that PFS and OS of PLB subtype with CD20-positive B-cell lymphoma have been greatly improved by combining rituximab. Yuste *et al.*[15] found that PFS increased from 52% to 88% by adding rituximab into conventional chemotherapy. Bisphosphonates can inhibit the activity of osteoclast and are currently applied in multiple myeloma and metastatic bone lesions in prostate cancer, lung cancer, and prostate cancer. PLB patients have tendency toward osteolytic lesions,

and even pathological fracture. Bisphosphonates can also be used in the context of hypercalcemia to prevent bone destruction.[27]

There existed several limitations in our present study. First, lymphomas contain a series of highly heterogenous diseases and thus PLB consists of various histological subtypes. Second, the dates of information retrieval from SEER spanned a long period of time, ranging from 1973 to 2016, which witnessed the changes in diagnostic criteria and the rapid advancement of treatment approaches. Third, the inherent drawbacks of the SEER database are unavoidable. The SEER database neither collects nor records information regarding disease progression, relapse or recurrence, infection, comorbidities, and complications. Besides, the SEER database lacks the important information about individual patient, including Eastern Cooperative Oncology Group Performance Status, international prognostic

Table 5. Multivariate analysis of disease-specific survival and overall survival.

Characteristic	Disease-specific survival		Overall survival	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex				
Female	Reference		Reference	
Male	0.896 (0.749–1.072)	0.229	0.881 (0.763–1.017)	0.084
Primary site				
Axial	Reference	–	Reference	
Appendicular	0.626 (0.466–0.841)	0.002	0.694 (0.552–0.872)	0.002
Craniofacial	0.708 (0.553–0.908)	0.006	0.729 (0.597–0.889)	0.002
Laterality				
Bilateral, single primary	Reference	–	Reference	
Left: origin of primary	0.930 (0.489–1.771)	0.826	0.898 (0.532–1.519)	0.689
Right: origin of primary	0.853 (0.446–1.631)	0.631	0.953 (0.563–1.613)	0.859
Not a paired site	0.920 (0.486–1.744)	0.798	0.935 (0.555–1.577)	0.802
Histologic type: broad groupings				
Malignant lymphomas, NOS or diffuse	Reference	–	Reference	–
Hodgkin lymphomas	0.184 (0.058–0.583)	0.004	0.392 (0.200–0.771)	0.007
NHL–mature B-cell lymphomas	0.828 (0.676–1.014)	0.067	0.826 (0.700–0.973)	0.023
NHL–mature T- and NK-cell lymphomas	0.518 (0.269–0.999)	0.050	0.680 (0.424–1.090)	0.109
NHL-precursor-cell lymphoblastic lymphoma	0.536 (0.235–1.221)	0.137	0.453 (0.223–0.923)	0.029
Ann Arbor stage				
Stage I–II	Reference	–	Reference	–
Stage III–IV	1.635 (1.281–2.086)	0.000	1.348 (1.107–1.641)	0.03
Number of bone lesions				
Single	Reference	–	Reference	–
Multiple (⩾2)	1.122 (0.878–1.435)	0.357	1.201 (0.990–1.457)	0.064
Surgery				
No	Reference	–	Reference	–
Yes	1.162 (1.064–1.379)	0.101	1.129 (0.977–1.304)	0.101
Radiation				
No	Reference	–	Reference	–
Yes	0.996 (0.559–0.710)	0.981	0.934 (0.730–1.195)	0.587
Chemotherapy				
No	Reference	–	Reference	–
Yes	0.641 (0.546–0.702)	0.000	0.734 (0.605–0.890)	0.002

CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma; NK, natural killer (cell); NOS, not otherwise specified.

index score, tumor size, lactate dehydrogenase, and many other laboratory test results. Lastly, the specific therapeutic regimens, drug doses, administration frequency, and radiation doses were also not recorded in the SEER database.

Despite the abovementioned limitations, this study, to the best of our knowledge, represents the largest retrospective PLB cohort till now. We have found that there was no sex predilection in PLB occurrence. Multivariate analysis revealed that primary anatomic site, histological classification, Ann Arbor stage and chemotherapy were closely associated with PLB prognosis. Chemotherapy played a pivotal role in PLB treatment. It remains still controversial whether chemotherapy in combination with radiotherapy is superior to chemotherapy alone. The optimal treatment strategies, including agents with novel mechanisms of action and radiation doses and fields, warrant further verification in future studies and clinical trials.

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