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Clinical Investigation: Lymphoma

Early-Stage Primary Bone Lymphoma: A Retrospective, Multicenter Rare Cancer Network (RCN) Study

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Summary

Primary bone lymphoma (PBL) is a rare form of extranodal lymphoma. This study by the Rare Cancer Network retrospectively analysed patients treated with radiotherapy and /or chemotherapy, in Stage I and II disease. Local recurrence was observed in only 10% and distant recurrence in 17% of patients. IPI score, RT dose, complete response to treatment, and use of chemotherapy were independent favorable prognostic

Purpose: Primary bone lymphoma (PBL) represents less than 1% of all malignant lymphomas. In this study, we assessed the disease profile, outcome, and prognostic factors in patients with Stages I and II PBL.

Patients and Methods: Thirteen Rare Cancer Network (RCN) institutions enrolled 116 consecutive patients with PBL treated between 1987 and 2008 in this study. Eighty-seven patients underwent chemoradiotherapy (CXRT) without (78) or with (9) surgery, 15 radiotherapy (RT) without (13) or with (2) surgery, and 14 chemotherapy (CXT) without (9) or with (5) surgery. Median RT dose was 40 Gy (range, 4−60). The median number of CXT cycles was six (range, 2−8). Median follow-up was 41 months (range, 6−242).

Results: The overall response rate at the end of treatment was 91% (complete response [CR] 74%, partial response [PR] 17%). Local recurrence or progression was observed in 12 (10%) patients and systemic recurrence in 17 (15%). The 5-year overall survival (OS), lymphoma-specific survival (LSS), and local control (LC) were 76%, 78%, and 92%, respectively. In univariate analyses (log−rank test), favorable prognostic factors for OS and LSS were International Prognostic Index (IPI) score ≤ 1 ($p = 0.009$), high-grade histology ($p = 0.04$), CXRT ($p = 0.05$), CXT ($p = 0.0004$), CR ($p < 0.0001$), and RT dose >40 Gy ($p = 0.005$). For LC, only CR and Stage I were favorable factors. In multivariate analysis, IPI score, RT dose, CR, and CXT were independently influencing the outcome (OS and LSS). CR was the only predicting factor for LC.

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factors. Early stage PBL treated with combined RT and chemotherapy has an excellent prognosis.

Conclusion: This large multicenter retrospective study confirms the good prognosis of early-stage PBL treated with combined CXRT. An adequate dose of RT and complete CXT regime were associated with better outcome. © 2012 Elsevier Inc.

Keywords: Primary bone lymphoma, Early stage, Radiotherapy, Combined treatment modality

Introduction

Primary bone lymphoma (PBL), either in adults or children (1), is a rare presentation of non-Hodgkin lymphoma, accounting for less than 1% of all malignant lymphomas, for about 5% of all primary malignant bone tumors, and for 4−5% of all extranodal non-Hodgkin lymphomas (2−4). PBL was first described as a distinct clinical entity by Parker and Jackson in 1939 (5), and defined in the 2002 World Health Organization (WHO) classification of tumors of soft tissue and bone, as a single skeletal tumor with, or without regional lymph node involvement, or multiple bone lesions, without visceral or lymph node involvement (6).

Almost 90% of PBL patients present with diffuse large B-cell lymphoma histological subtype, which may have a better prognosis than that of the less common T-cell lymphoma subtype (7−9). The most commonly affected parts of the skeleton are within the metaphysis and diaphysis of the long bones (10). The clinical characteristics are nonspecific, making a proper diagnosis difficult at the outset. Pain, swelling, and pathologic fractures are the most common presenting symptoms.

Local radiotherapy (RT) was established as the standard treatment in the 1960s with a local relapse rate of 10−20%, but with a distant relapse rate of about 50% and a 5-year survival rate ranging between 55% and 65% (11−13). The 5-year survival rate has been improved to about 70−90% with the addition of chemoradiotherapy (CXRT) in early-stage disease (11, 14−17).

The role of RT was recently challenged (18, 19), as chemotherapy alone appeared to be quite effective, especially with the development of new agents such as rituximab. The purpose of our Rare Cancer Network (RCN; http://www.rarecancer.net) study was to collect substantial information from a large number of patients to more properly define the disease profile, therapeutic approach, and outcome and prognostic factors of this disease.

Patients and Methods

Patients

We collected 116 eligible patients from a total of 136 cases of PBL treated between 1987 and 2008 in 13 institutions of the RCN. Inclusion criteria included: age >16 years, confirmed pathological diagnosis of bone involvement, Stages I and II according to the Ann Arbor staging system (20), and a minimum of 6 months' follow-up after treatment. After a review of all clinical and pathological records, 20 cases were excluded from the analysis because of disseminated disease (12 cases) and multiple bone involvement (8 cases). All the medical records were reviewed for age, gender, symptoms, physical examination, laboratory examination, imaging, pathological diagnosis, involved sites, stage, International Prognostic Index (IPI) (21), treatment modality, response, site of relapse, treatment-related complications, time to death, and date of last follow-up. In this study, all investigators obtained their own Institutional Review Board approval for patients' data collection.

All pathology reports were reviewed and "translated" into the WHO classification. The workup of individual patients included medical history, physical examination, complete blood count, lactate dehydrogenase, erythrocyte sedimentation rate, complete metabolic profile, bone marrow biopsy and plain bone X-ray in all patients. Bone computed tomography, magnetic resonance imaging, positron-emission tomography, or whole body computed tomography scan were performed according to each institution's policy. Stage was established with the Ann Arbor staging system. Single localized bone lesions were classified as Stage IE, and in case of lymph node involvement on the same side of the diaphragm, patients were considered to have Stage IIE. IPI score was established based on the medical records.

Patients were treated according to each hospital's local policy. The modality of treatment included chemotherapy, RT, surgical resection, or a combination of these. Most patients had a biopsy only (100); however, 16 underwent surgery. Of these, 13 had some form of local excision or curettage, 2 had a laminectomy with partial excision, and 1 had a total hip replacement.

Response was evaluated according to lymphoma-adapted Response Evaluation Criteria in Solid Tumors (22, 23). Early and late treatment toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) V3.0 (24).

Statistical methods

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Lymphoma-specific survival (LSS) was calculated from the date of diagnosis to the date of lymphoma-related death. Local control (LC) was calculated from the date of diagnosis to the date of local recurrence. Survival curves were constructed using the Kaplan-Meier method, differences were considered significant if the p value was ≤ 0.05 (two-tailed log−rank test). Multivariate analysis (Cox model) was used to determine the independent prognostic factors. All prognostic factors identified in the univariate analyses with p value <0.20 were included in the multivariate analyses.

Results

Patient and treatment characteristics are presented in Table 1.

Median age was 51 years (range, 17−93 years), and there were 69 males (59%) and 47 females (41%).

The majority of patients (75%) received combined CXRT. Treatment sequences were chemotherapy followed by

Table 1 Clinical and treatment characteristics of patients

Parameter	Patients (*n*)	%
Clinical characteristics		
Median age (50)		
<50	63	54
≥50	53	46
Gender		
M	69	59
F	47	41
Histology subtype		
Diffuse large B cell	91	78
Follicular B cell	7	6
Anaplastic large cell	6	5
Other	12	11
Histological grade		
High	100	86
Intermediate	7	6
Low	9	8
Stage		
Stage IE	93	80
Stage IIE	23	20
Initial symptoms		
Pain	106	91
Mass/swelling	46	40
Neurologic symptoms	28	24
Pathological fracture	20	17
B symptoms	20	17
LDH level		
Normal	70	60
High	30	26
Not done	16	14
Site involved		
Spine	33	28
Pelvis	23	20
Femur	16	14
Face bone	15	13
Humerus	12	10
Other sites	17	15
IPI score		
≤1	81	70
>2	35	30
Treatment characteristics		
Combined treatment and sequence		
CT-RT	74	64
RT-CT	9	8
Concomitant CXRT	4	3
CXT alone	14	12
RT alone	15	13
Chemotherapy regimens		
R-CHOP	32	28
CHOP or CHOP-like	69	60
No CXT	15	12
Treatment modality with surgery		
Yes	16	14
No	100	86

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT-RT = chemotherapy followed by radiotherapy; CXT = chemotherapy; CXRT = combined chemoradiotherapy; IPI = international prognostic index; LDH = lactate dehydrogenase; RT-CT = radiotherapy followed by chemotherapy; RT = radiotherapy; R-CHOP = rituximab with CHOP.

radiotherapy (CT-RT) in 64%, radiotherapy followed by chemotherapy (RT-CT) in 8%, and concomitant CXRT in 3%. Eighty-eight percent received chemotherapy (CXT) in combination or alone. Of these, 68% were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy, and 32% with rituximab plus CHOP (R-CHOP) chemotherapy.

Response to treatment was evaluated in all patients. After initial therapy, 74% patients had a complete remission (CR), 20% partial remission (PR), 1% stable disease (SD), and 5% progressive disease (PD). One patient who experienced progressive disease, died during salvage treatment. Among patients achieving a CR, 81% were treated with combined CXRT, 10% with RT alone, and 9% with CXT alone.

The 5- and 10-year LC probability was 92% (95% CI 86−98) and 80% (95% CI 68−92), respectively. Local failure was observed in 10% of the patients. Of the 74% patients with CR, 6% had a local relapse, whereas of the 20% of patients who were in PR, 30% presented a further local progression ($p = 0.008$).

Of the patients who received an RT dose of less than 40 Gy, 12% recurred locally versus 8% of those receiving more than 40 Gy ($p = 0.75$). In the patients with local failure, 50% occurred within the planning target volume and 50% outside.

Distant progression was observed in 15% of the patients after a median time of 7 months (range, 2−72). Thirteen (13%) of the 101 patients who received chemotherapy suffered from systemic failure versus 4 (27%) of the 15 patients who did not ($p = 0.23$). Thirteen percent of the 67 patients treated with more than six cycles of chemotherapy developed systemic progression versus 16% of the 49 patients treated with fewer than six cycles ($p = 0.79$).

With a median follow-up of 41 months (range, 6−242 months), 63% patients were alive without evidence of disease, 12% were alive with disease, 19% patients died of lymphoma, and 6% patients died from other causes: 5 from unrelated disease, 1 from lung cancer, 1 from tonsil cancer. Overall, the 5- and 10-year OS was 76% (95% CI 67−84) and 72% (95% CI 61−84), respectively. The 5- and 10-year LSS probability was 78% (95% CI 70−86) and 78% (95% CI 70−86), respectively.

On univariate analyses, statistically significant factors favorably influencing OS were patient age (<50 years), IPI score 0 or 1 (Fig. 1a), RT dose (>40 Gy) (Fig. 1b), high histological grade subtype, combined CXRT, CXT for more than six cycles (Fig. 1c), and CR (Fig. 1d) at the end of treatment. For LSS, the previously mentioned parameters (Fig. 2a−c), except for age and number of CXT cycles, were also favorable factors. RT and Stage I were favorable factors with regard to LC (Fig. 2d; Table 2).

After multivariate analysis, the remaining independent prognostic factors for OS and LSS were IPI score <2, RT dose >40 Gy, CR, and administration of CXT. For LC, CR at completion of treatment remained the only independent prognostic factor (Table 3).

Grade 1−3 leukopenia was observed in 13% patients, Grade 1 lymphocytopenia in 2%, and Grade 1 thrombocytopenia in 2%. Grade 5 leukopenia occurred in 1% of patients after salvage chemotherapy. Late side effects were rare: Grade 1 toxicity in 3% patients (edema in 3 and pain in 1), Grade 2 toxicity in 2% patients (myositis in 1 and osteonecrosis in 1), Grade 3 toxicity in 3% patients (joint effusion in 1, osteonecrosis in 1 and pain in 2), and Grade 4 osteonecrosis in 1%. The latter patient died of a secondary lung cancer.

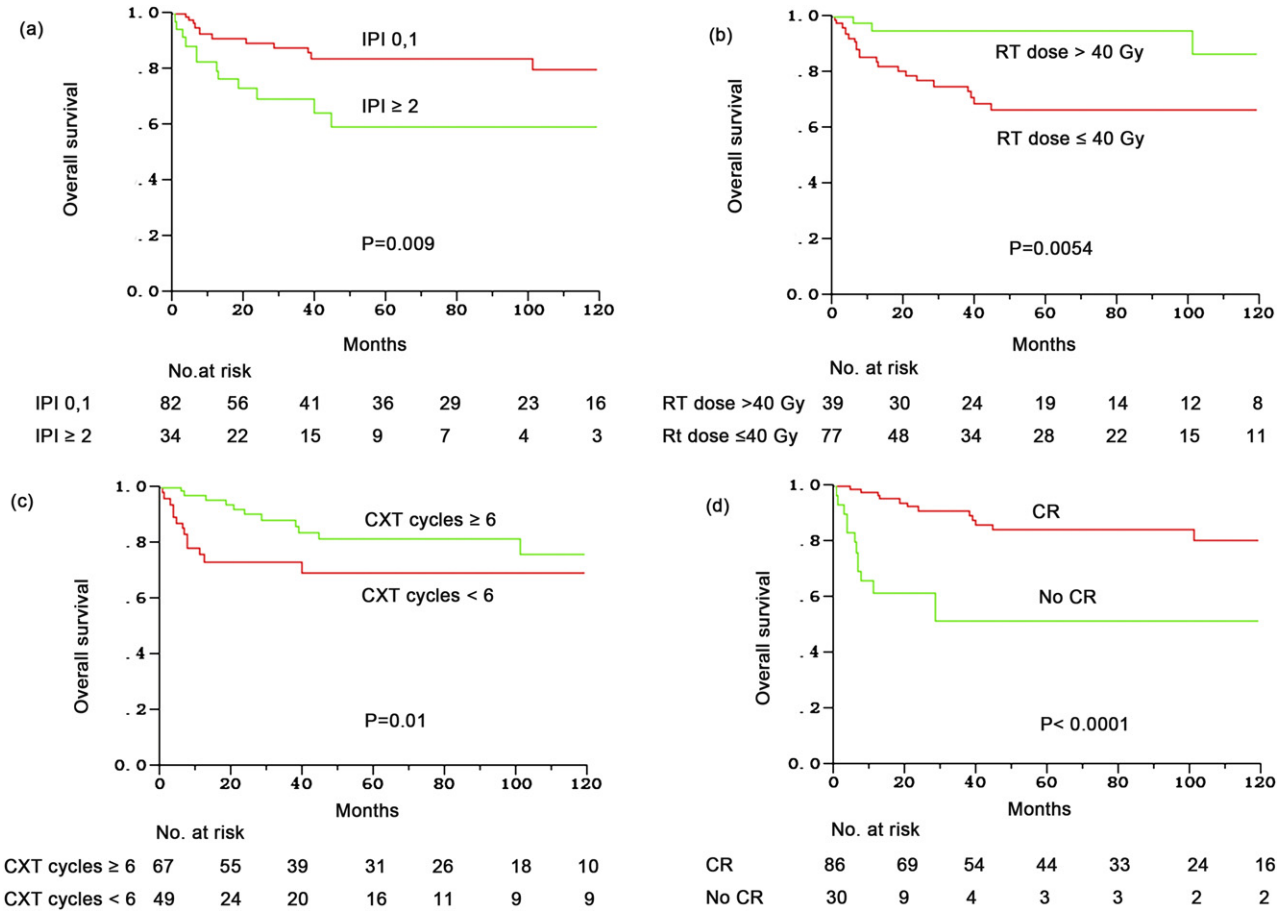

Fig. 1. Univariate analyses for prognostic factors on overall survival (OS). (a) OS according to international prognostic index (IPI) score; IPI 0,1 improved survival compared with IPI $\geq$2 ($p = 0.009$). (b) OS according to radiotherapy (RT) dose; RT dose >40 Gy improved survival compared with RT dose $\leq$40 Gy ($p = 0.0054$). (c) OS according to chemotherapy (CXT) cycles; CXT cycles $\geq$6 improved survival compared with CXT cycles <6 ($p = 0.01$). (d) OS according to response rate; patients with complete response (CR) had an improved survival compared with those without CR ($p < 0.0001$).

Discussion

To our knowledge, the current study from 13 institutions of the RCN is the second largest report on early stage PBL.

It has demonstrated relatively similar patient characteristics compared with other published series. A male predominance (male to female: 1.43:1) was found, and median age was 51 years, compared with 30−60 years in other series. Pain was the most common presenting symptom, followed by a mass or swelling. The most common sites of pathological fracture were usually located in the long bones, similar to other reports (7, 25). As in other reports (26), most of our patients presented with Stage IE (ratio between Stage IE and IIE: 4:1).

The overall outcome of patients in this study (5-year OS of 76%, LSS of 78%) was similar to that found in the literature (5-year OS ranging between 70% and 90%) (11, 14−17, 27).

Univariate analysis for OS in our study revealed that younger age (<50 years) predicted a better outcome, as reported in other series (11, 26). Normal lactate dehydrogenase level was considered to be a favorable prognostic factor in the report of Beal *et al.* (11), but in our series we could not confirm this observation. Patients with IPI scores 0−1 had a markedly better outcome compared with those with an IPI score 2−4, as previously found by Ramadan *et al.* (4), but not by Alencar *et al.* (27). In contrast to the study of Ostrowski *et al.* (13) and Horsman *et al.* (26), high-grade histology was slightly beneficial compared with low-grade histology for OS and LSS. Previously published papers using Surveillance, Epidemiology, and End Results (SEER) database analysis (28) have reported that patients with local disease had a better survival than those with extensive disease. However, we could not find a significant difference in 5-year OS and LSS between Stages I and II (78% vs. 67%, $p = 0.19$), which confirms the findings seen in previous series (4, 17). This might be explained by patient selection. Soft-tissue involvement was observed in 41% of the patients, and patients with extraosseous involvement did not show a significantly worse outcome in 5-year OS, compared with those without extraosseous involvement (62% vs. 85%, $p = 0.12$). According to some authors, soft-tissue involvement may just reflect an inflammatory process and not real tumor infiltration (29−31).

RT was established in the 1960s as the treatment of choice with a high local control rate and overall cure rates ranging from 44−63% (11, 27). However, the role of RT alone was challenged over recent years because of the 50% systemic progression rate

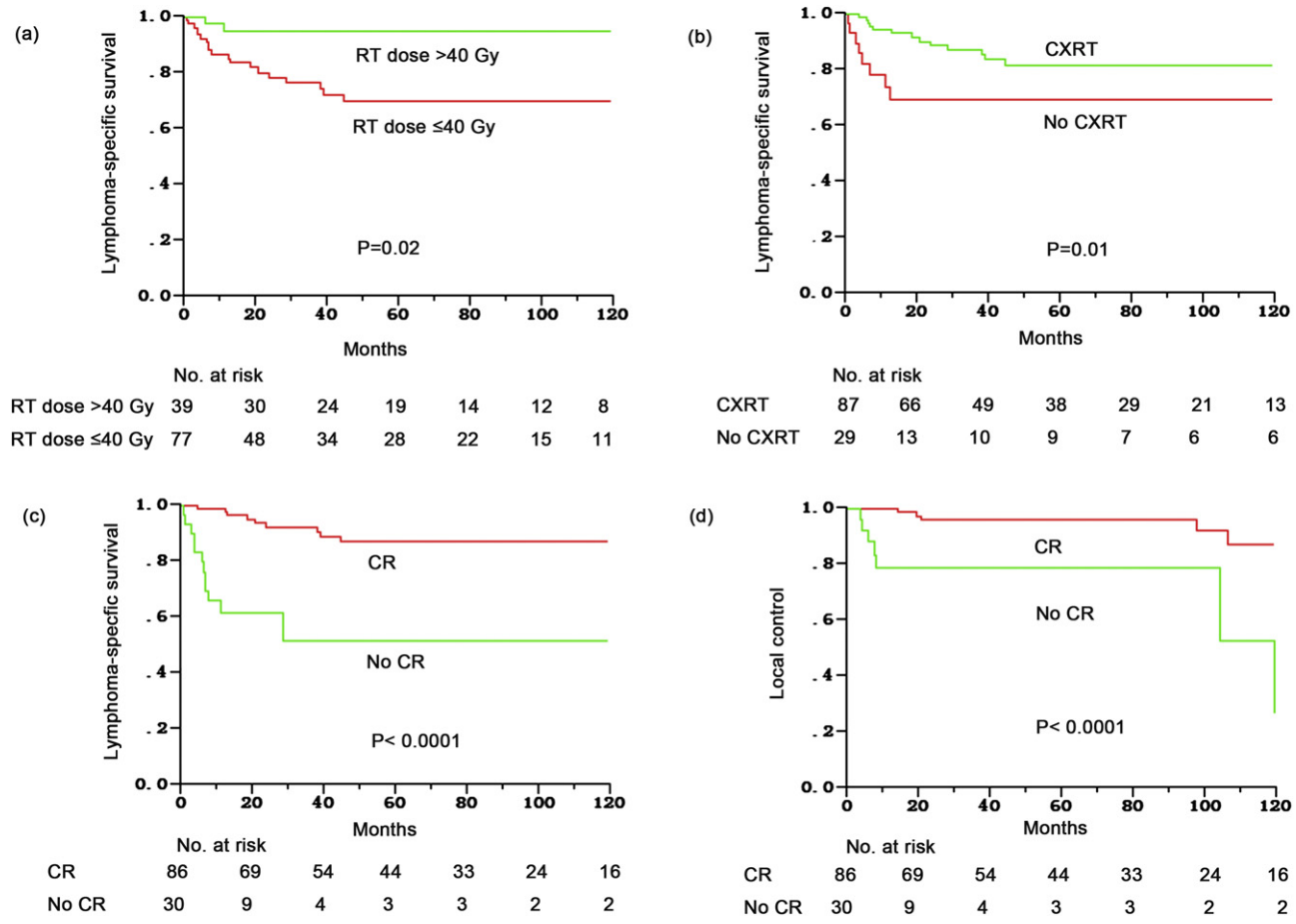

Fig. 2. Univariate analyses for prognostic factors on lymphoma-specific survival (LSS) and local control (LC). (a) LSS according to radiotherapy (RT) dose; RT dose >40 Gy improved LSS compared with RT dose ≤40 Gy ($p = 0.02$). (b) LSS according to chemoradiotherapy (CXRT); patients with CXRT had an improved LSS compared with those without CXRT ($p = 0.01$). (c) LSS according to response rate; patients with complete response (CR) had an improved LSS compared with those without CR ($p < 0.0001$). (d) LC according to response rate; patients with complete response (CR) had an improved LC compared with those without CR.

(11, 30). Barbieri *et al.* reported that an RT dose of 40 Gy with a limited RT volume in combination with CXT seemed to be adequate for local control (17). Our study addressed the issue of RT dose and volume. Radiation of the entire bone did not yield a superior outcome compared with partial bone radiation (74% vs. 77%, $p = 0.54$). However, both univariate and multivariate analyses showed that RT dose >40 Gy was associated with a significantly better 5-year OS and LSS than ≤40 Gy (95% vs. 66%, $p = 0.0054$, and 95% vs. 69%, $p = 0.02$ respectively) and a nonsignificant trend toward a better local control (96% vs. 89%, $p = 0.32$).

CXRT already demonstrated its superiority compared with single therapeutic approaches with 5-year OS between 60–90% in recent studies (11, 16, 31–33). Interestingly, Alencar *et al.* (27) recently reported no benefit with CXRT. Although there is no consensus regarding the optimal timing between either RT or chemotherapy, chemotherapy followed by RT was suggested to be the standard approach (34).

With the advent of highly effective chemotherapy, the role of RT has been questioned by some authors. In advanced-stage disease, Ramadan *et al.* found that patients who received chemotherapy and RT had a worse outcome compared with those who received chemotherapy alone (4). In the Southwestern Oncology Group 8736 study update, which was on non-PBL lymphoma, there was no difference between CXRT and chemotherapy alone (18, 19). Similar results were reported in some studies (11, 35, 36), and also in a report on children (37). Rituximab is now used in association with CHOP or a CHOP-like regimen in the treatment of lymphoma, and studies have demonstrated its positive impact on survival (38). In our series, the proportion of patients treated with R-CHOP was lower (3:7) than with CHOP alone, and we could not find any significant differences in survival between the two regimens.

Acute side effects were moderate. Leukopenia was the most common early toxicity after chemotherapy. The only reported late toxicity cases involved a limited occurrence of osteonecrosis.

In conclusion, early-stage PBL has a fairly good prognosis. Local control is excellent, and systemic failure occurs infrequently. Young age (<50) and a good IPI score (<2) were positive prognostic factors at diagnosis. The role of chemotherapy is central in the treatment of PBL. Chemotherapy followed by RT is superior for OS and LSS to a sequence of radiotherapy followed by chemotherapy. Although chemotherapy was superior to radiotherapy alone, radiotherapy still plays a role in local control. An RT dose of more than 40

Table 2 Univariate analyses (log–rank test)

Variable	*n*	5-y OS (%)	95% CI	*p*	5-y LSS (%)	95% CI	*p*	5-y LC (%)	95% CI	*p*
All patients	116	76	67–85		78	70–86		92	86–98	
Age										
<50	57	86	76–96	0.008	86	76–96	0.09	94	87–101	0.99
≥50	59	67	53–81		71	58–84		90	81–99	
Gender										
Female	47	72	58–86	0.18	74	60–88	0.10	93	85–101	0.38
Male	69	79	67–91		81	70–92		91	84–98	
IPI score										
≥2	34	59	40–78	0.009	64	46–82	0.02	93	83–103	0.62
<2	82	84	75–93		85	76–94		91	84–98	
Histological grade										
High	100	78	69–87	0.04	80	71–89	0.05	92	86–98	0.26
M/L	16	64	38–90		64	38–90		90	73–107	
Clinical symptoms										
B symptoms										
Yes	20	62	36–88	0.22	62	36–88	0.13	92	76–108	0.38
No	96	78	69–88		81	72–90		92	86–98	
Pathological fracture										
Yes	20	76	54–98	0.94	85	79–101	0.76	94	83–105	0.94
No	96	76	66–86		77	67–87		91	85–97	
LDH level										
High	30	93	83–103	0.10	93	83–103	0.17	83	68–98	0.10
Normal	70	72	60–84		75	64–86		93	86–100	
ND	16	72	48–96		72	48–96		100	100	
Extraosseous involvement										
Yes	48	62	46–78	0.12	68	52–84	0.06	93	85–101	0.81
No	68	85	76–94		85	76–94		91	83–99	
Stage (Ann Arbor)										
IE	93	78	69–88	0.19	81	72–90	0.13	92	86–98	0.04
IIE	23	67	43–91		67	43–91		90	77–103	
Treatment modality										
CXRT	87	79	69–89	0.001	81	72–90	<0.001	93	87–99	0.13
CXT	14	92	78–106		92	78–106		77	54–100	
RT	15	49	22–76		49	22–76		100	100	
CXRT vs. RT and CXT										
CXRT	87	79	69–89	0.05	81	72–90	0.01	93	87–99	0.66
RT and CXT	29	69	51–87		69	51–87		87	73–101	
Treatment modality of CXRT and RT vs. CXT										
CXRT and RT	102	75	66–84	0.27	94	89–99	0.08	94	89–99	0.08
CXT	14	92	78–106		77	54–100		77	4–100	
Treatment modality of CXRT and CXT vs. RT										
CXRT and CXT	101	80	71–89	0.004	82	73–91	<0.0001	91	85–97	0.24
RT	15	49	22–76		49	22–76		100	100	
Subgroup for CXRT vs. CXT alone										
CXRT	87	79	69–89	0.47	81	72–90	0.63	93	87–99	0.12
CXT	14	92	78–106		92	78–106		77	54–100	
Subgroup for CXRT sequence (not including the 4 concomitant cases)										
CT-RT	74	83	72–94	0.001	86	77–95	0.0006	95	89–101	0.02
RT-CT	9	39	6–72		39	6–72		78	51–105	
R-CHOP chemoradiotherapy (RCXRT) vs. CHOP or CHOP-like chemoradiotherapy (CCXRT)										
RCXRT	23	89	74–104	0.11	89	74–104	0.04	93	80–106	0.87
CCXRT	64	77	66–88		80	69–91		93	86–100	
No CXRT	29	69	51–87		69	51–97		87	73–101	
CXT regimen comparison (R-CHOP vs. CHOP vs. no CXT)										
R-CHOP	32	81	63–99	0.002	81	63–99	<0.0001	88	75–101	0.27
CHOP	69	80	69–91		83	73–93		92	85–99	
No CXT	15	49	22–76		49	22–76		100	100	

(*continued on next page*)

Table 2 (*continued*)

Variable	*n*	5-y OS (%)	95% CI	*p*	5-y LSS (%)	95% CI	*p*	5-y LC (%)	95% CI	*p*
Subgroup for RCXRT vs. CCXRT										
RCXRT	23	89	74–104	0.41	89	74–104	0.56	93	80–106	0.57
CCXRT	64	77	66–88		80	69–91		93	80–100	
Subgroup for comparison within CXT regimens (R-CHOP vs. CHOP or CHOP-like)										
R-CHOP	32	81	63–99	0.84	81	63–99	0.92	88	75–101	0.27
CHOP	69	80	69–91		83	64–102		92	88–99	
Cycles of CXT										
<6	49	69	55–83	0.01	75	62–88	0.06	88	77–99	0.87
≥6	67	81	70–92		81	70–92		93	87–99	
RT dose (Gy)										
>40	39	95	88–102	0.0054	95	88–102	0.02	96	89–103	0.32
≤40	77	66	54–78		69	57–81		89	81–97	
RT treatment volume (partial bone vs. entire bone)										
Partial	60	77	65–89	0.54	79	68–90	0.65	91	82–100	0.18
Entire	42	74	59–89		76	62–90		97	90–104	
No RT	14	92	78–106		92	78–106		77	54–100	
Response group (CR vs. no CR)										
CR	86	84	75–93	<0.0001	87	79–95	<0.0001	96	91–101	<0.0001
No CR	30	51	28–74		51	28–74		79	62–96	

Abbreviations: CCXRT = CHOP regimen with chemoradiotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CR = complete response; CT-RT = chemotherapy followed by radiotherapy; CXRT = chemoradiotherapy; CXT = chemotherapy; IPI = international prognostic index; LC = local control; LDH = lactate dehydrogenase; LSS = lymphoma-specific survival; M/L = intermediate/low; ND = not done; OS = overall survival; R-CHOP = rituximab plus CHOP; RCXRT = RCHOP regimen with chemoradiotherapy; RT = radiotherapy; RT-CT = radiotherapy followed by chemotherapy.

Table 3 Multivariate analyses

	OS		LSS		LC	
Variable	RR	*p*	RR	*p*	RR	*p*
IPI score (<2)	1.68	0.014	1.73	0.02	–	NS
RT dose (>40 Gy)	1.97	0.005	1.72	0.05	–	NS
Response (CR)	2.17	0.0004	2.56	<0.0001	2.96	0.00
CXT (yes)	2.46	0.0002	2.91	<0.0001	–	NS

Abbreviations: CR = complete response; CXT = chemotherapy; IPI = international prognostic index; LC = local control; LSS = lymphoma-specific survival; NS = not significant; OS = overall survival; RR = risk ratio; RT = radiotherapy.

Gy and more than six chemotherapy cycles are associated with a better outcome. Although our results need to be interpreted with caution because of a relatively limited follow-up (41 months) and its retrospective nature, we believe that our findings are important, especially because it is unlikely that a prospective study will be done, given how rare this cancer is.

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