Primary bone lymphoma: Clinical presentation and therapeutic considerations

Annika Müller[a], Martin Dreyling[b], Falk Roeder[c,d], Andrea Baur-Melnyk[e], Thomas Knösel[f], Alexander Klein[a], Christof Birkenmaier[a], Volkmar Jansson[a], Hans Roland Dürr[a,*]

[a] Musculoskeletal Oncology, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Germany
[b] Department of Medicine III, University Hospital, LMU Munich, Germany
[c] Department of Radiation Oncology, Paracelsus Medizinische Privatuniversität, Landeskrankenhaus, Salzburg, Austria
[d] CCU Molecular Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[e] Institute of Radiology, University Hospital, LMU Munich, Germany
[f] Institute of Institute of Pathology, University Hospital, LMU Munich, Germany

ARTICLE INFO

ABSTRACT

Background: Primary lymphoma of bone (PBL) is a rare entity. Due to unspecific clinical signs and equivocal radiographs diagnosis may be delayed. This retrospective report of 109 PBL cases demonstrates typical aspects of the lesion. Treatment and prognostic factors are evaluated.

Methods: Retrospectively patient records were reviewed. All patients were followed for evidence of local or distant recurrence. Overall survival (OS) was used as clinical outcome.

Results: The median age of the 109 patients was 62.8 years. The most common symptoms were pain (76%), swelling (29%), neurologic symptoms and pathological fracture (16% each). Mean duration of symptoms was 8 months (0–197 months).

19% of patients had indolent NHL subtypes, 72% aggressive NHL subtypes and 7% cases Hodgkin disease. Cyclophosphamid, doxorubicin, vincristine and prednisone (CHOP) or CHOP plus rituximab (RCHOP) were given in 88 (81%) of patients. Radiotherapy was delivered in 67 (61%) of cases. 51 (47%) patients received both. Surgical interventions were restricted to cases with complications as fractures.

The 5-year OS was 66%. The 5-year OS was 66%. In the subgroup of 78 patients with aggressive NHL subtype there was a highly significant benefit for chemotherapy or chemotherapy and radiation in comparison to no treatment or radiation alone. Raised LDH, age, IPI and ECOG performance were prognostic factors. In multivariate analysis, age and raised LDH levels only kept significance.

Conclusions: In our series of primary bone lymphoma, chemotherapy resulted in a better outcome than Radiotherapy alone. Long-term survival is based on the stage of the disease, favoring younger (< 60 years) patients with solitary bone lesions, low level of LDH and favourable ECOG performance status and IPI scores.

1. Background

Primary lymphoma of bone is a well-recognized but rather rare entity, accounting for about 5% of all patients with primary bone tumors [1,2]. It was initially described by Oberling in 1928 [3]. In 1939 this subtype of lymphoma was described as a distinct entity with infiltration of the bone or the adjacent soft tissues [4]. In advanced stages of the disease, it may be impossible to determine whether the lymphoma developed within the bone (primary) or invaded it (secondary) [5]. However, in general lymph node or visceral involvement is excluded by definition [6]. Whereas in some studies regional lymph node involvement is permitted [7,8]. According to the WHO classification (2013), PBL is defined as a neoplasm composed of malignant lymphoid cells, producing one or more masses within bone, without any

supraregional lymph-node involvement or other extranodal lesions. In general it has a single skeletal lesion with or without regional lymph-node involvement and should be distinguished from secondary bone involvement in systemic lymphoma [9]. Affecting 1.7/1 Mio patients in the US [10] approximately 4% of all patients with NHL present with an obvious skeletal lesion [11], comprising 5% of all extranodal lymphomas [1]. In two series of NHL patients, routinely performed bone-marrow biopsies were positive in 18% and 23% of non-Hodgkin's lymphomas [12,13]. In a group of 422 patients with primary or primary and secondary bone lymphomas at the Mayo Clinic, 38% showed extraskeletal involvement at the time of detection of bone involvement [14]. Continued observation for 3 to 6 months, to ensure that visceral sites are not identified, prior to classifying as PBL may be considered.

The occurrence of a primary Hodgkin's lymphoma of bone is exceedingly rare. In many patients with localized primary lymphoma of the bone (PBL), diagnosis is delayed due to unspecific clinical signs and equivocal radiographs [15]. Magnetic resonance imaging (MRI) allows an early diagnosis, but due to the rareness of the lesion it is often not considered before biopsy [16,17]. Therapy is multimodal, mainly based on chemo- and radiotherapy. Surgery is only used in cases of skeletal complications [15]. The prognosis is superior to that of a localized Ewing's sarcoma (which sometimes has been confused with this tumor entity) [18].

This retrospective report includes 109 primary lymphomas of bone, updating also 36 cases published in 2002 [15].

2. Patients and methods

A retrospective review was done of 109 patients with PBL treated in our institution between 1980 and 2015. Patient records of these 109 patients were reviewed including presenting symptoms, sites of involvement and imaging. Staging included the results of physical examination noted in the medical records, routine laboratory check-up and bone marrow biopsy. Depending on the location of the lesion and skeletal radiographs, computed tomography (CT) scans and magnetic resonance imaging (MRI) were analysed. This is a retrospective analysis going back to 1980. A standardized staging using advanced imaging methods as PET-CT scans has only been introduced in the last years.

2.1. Statistical analysis

All patients were followed for evidence of local or distant recurrence in general by regional MRI scans and CT scans of the thorax and abdomen. Overall survival (OS) was defined as the time from surgery to death from any cause and was calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank, the Chi-Square test or the Cox proportional-hazards regression model. A p value of ≤0.05 was considered statistically significant.

3. Results

109 patients could be evaluated (61 males, 48 females). The median age was 62.8 years (mean 59.9, range 20–100). The most common location was the trunk in 61% of the cases, the most common symptoms were pain in 76% and a swelling distinct from lymph nodes as a soft-tissue tumor in 29% (Table 2). Median duration of symptoms was 8 months, but a wide variation was observed (0–197 months), median 3.3 months.

Diagnosis was established by incisional biopsies in 54 cases and true-cut biopsies in 50 patients. Five patients had biopsies with first surgery. 72 patients got no surgical intervention, spinal surgery was performed in 14 patients, conservative therapy including ortheses in 12 patients and a spectrum of osteosynthesis and endoprosthetic reconstructions in the remaining patients.

Histologically 21 (19%) patients had an indolent NHL subtyp, 78 (72%) patients had an aggressive NHL subtype and 7 (6%) cases

Table 1
Distribution of histopathologic subtypes of indolent, aggressive lymphomas and Hodgkin's disease.

Type	Number
Indolent	21 (19%)
CLL	3
Follicular	11
Marginal zone	1
Waldenström	6
Aggressive	78 (72%)
B-cell	76
T-cell	2
Hodgkin	7 (6%)
No subtype	3 (3%)

showed Hodgkin's lymphoma (Table 1). In 3 (3%) cases a subgroup analysis could not be established retrospectively.

The lactate dehydrogenase (LDH) level could be evaluated in 69 patients and was raised in 33 (48%). 49 (45%) of the patients showed an involvement of regional lymph nodes. In the subsequent clinical course involvement of liver (n = 8), bone marrow (n = 13), lung (n = 11), kidneys (n = 8) and spleen (n = 7) were observed.

The Eastern Cooperative Oncology Group (ECOG) performance status [19] was 0 (fully active) in 42 (38%), 1 (mild restriction) in 53 (49%), 2 (restricted but able for selfcare) in 11 (10%) and 3 (limited selfcare, 50% confined to bed or chair) 3 (3%).

The International Prognostic Index (IPI) (Age > 60 years, stage III or IV, elevated serum LDH, ECOG performance status > 1, more than 1 extranodal site) was found to be 0 in 9%, 1 in 24%, 2 in 27%, 3 in 27% and 4 in 13% of cases.

Non-surgical therapy consisted in the following forms of chemotherapy. CHOP scheme (4–6 cycles) alone or CHOP plus rituximab (RCHOP) was given in 88 (81%) of patients. Radiotherapy was delivered in a typically dose of 46 Gy in 67 (61%) of cases, 51 (47%) patients received both (CHOP + Radiotherapy). 4 patients got surgery alone and received neither CTX nor RTX.

At the time of latest follow-up 46 (42%) of the patients had deceased by death of any course. In the surviving 63 patients, the follow-up was 1–421 months (mean 102, median 64 months, 2 patients less than 12 months, 7 others 12–24 months). 56 (89%) of surviving patients were without evidence of disease. For all patients the 5-year OS as shown in Fig. 1 was 66% (mean OS 197, median OS 178 months. There was a trend for a worse survival in aggressive lymphomas, but without significance (Fig. 2). In the subgroup of 78 patients with an aggressive NHL subtype there was a highly significant benefit for those patients receiving chemotherapy (Fig. 3, p = 0,003). Also shown in this figure there was a trend for better overall survival in combined chemotherapy and radiation treatment but in a detailed analysis no significance for that. Rituximab was used in 49 patients. Interestingly, compared to 37 patients receiving CTX without rituximab no difference in overall survival was seen. Raised LDH (Hazard ratio 1.92, 95% CI 2.29–6.26, p = 0.01) or age below 60 years (Hazard ratio 0.51, 95% CI 0.28–0.93, p = 0.027) could be proven as prognostic factors. Accordingly, the International Prognostic Index (IPI) showed a significant better overall survival in patients with scores 0 or 1 (Hazard ratio 1.45, 95% CI 1.12–1.87, p = 0.005), with ECOG scale of performance status also a clear dependence was proven (p = 0.028). Regional lymph node involvement did not change the prognosis. Local relapse was observed in 11 (10%) patients. In the event of local relapse, overall survival was significantly reduced (p = 0.0478). Using Cox regression for multivariate analysis, age, raised LDH levels and the subtype only kept significance (Table 3).

Table 2

Clinical presentation, performance status, therapy and outcome in 109 patients with PLB. *Only available in 69 cases.

	Indolent	Aggressive	Hodgkin's disease	No subtype	Total
Clinical presentation					
Number	21 (19%)	78 (72%)	7 (6%)	3 (3%)	109 (100%)
Age (mean, years)	62.0	61.2	47.8	29.9	59.9
Location					
Trunk	13	46	6	2	67 (61%)
Upper extremity	3	17	0	0	20 (18%)
Lower extremity	6	14	0	0	20 (18%)
More than one	0	1	0	1	2 (2%)
Symptoms					
Fracture	5	11	0	1	17 (16%)
Pain	17	60	5	1	83 (76%)
Swelling	4	26	1	1	32 (29%)
Neurology	2	12	3	1	18 (17%)
Lymph nodes	13	29	7	0	49 (45%)
Perfomance status					
ECOG (mean)	0.81	0.74	0.86	1.0	0.77
IPI (mean)	2.1	2.2	2.0	0.5	2.1
Raised LDH*	4 (27%)	28 (55%)	1 (50%)	0 (0%)	33 (48%)
Therapy					
Radiotherapy	14	47	4	2	67 (62%)
Chemotherapy	13	70	5	1	89 (82%)
Rituximab	9	40	0	0	49 (56%)
Outcome					
5-year OS (%)	81.9 ± 8.2	59.2 ± 6.0	68.6 ± 18.6	–	65.6 6 ± 4.8

4. Discussion

This study represents a retrospective monocentric analysis in a large group of 109 patients with PBL and continues a study we published in 2002 [15].

The distribution of age and gender in the current study was similar to that in the literature as shown in a large population based study based on the SEER database [20]. Malignant bone lymphoma was seen in all decades of life with the majority of patients being between 50 and 70 years of age. PBL in children is rare, and differentiation, especially from Ewing's sarcoma, is important [21]. The differential diagnosis is long and generally considers all small blue round-cell lesions of bone. In addition from imaging analysis metastases, as well as chronic osteomyelitis, primary bone sarcomas, Ewing sarcoma, rhabdomyosarcoma, neuroectodermal tumors as PNET, small cell lung carcinoma, small-cell osteosarcomas, but also leukemic infiltrates have to be considered.

Ostrowski et al. published a large study of 422 patients with malignant lymphoma of the bone seen at the Mayo Clinic from 1907 to 1982 [14]. Histological typing may be difficult especially in high-grade malignant lymphomas [22]. The initial histological diagnosis in some of our cases was primarily undifferentiated sarcoma. This was later revised after discussing the radiological aspects of the cases and
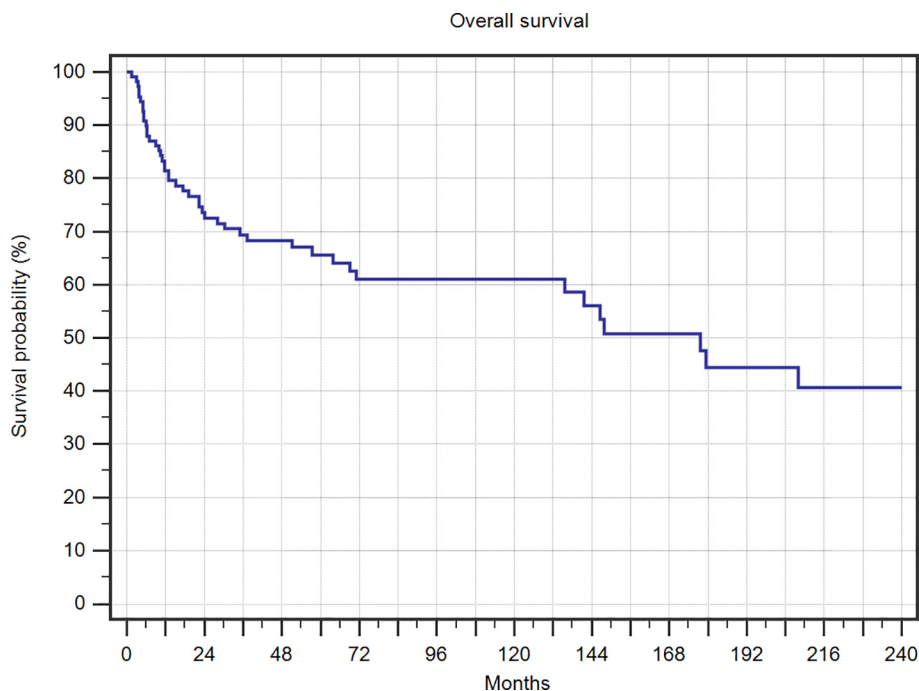

Fig. 1. Overall survival in 109 patients with primary lymphoma of bone.
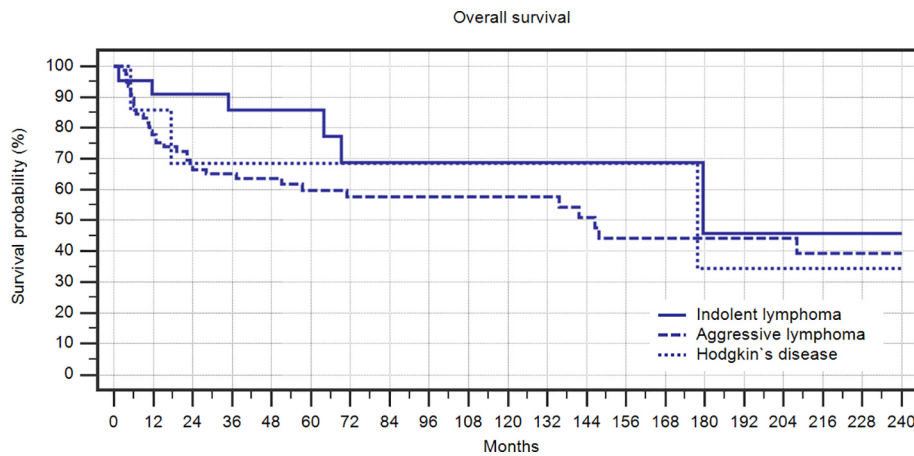
Fig. 2. Overall survival in 106 patients with either indolent lymphoma (n = 21), aggressive lymphoma (n = 78) or Hodgkin's disease (n = 7) n.s.

additional immunostaining resulting in the correct diagnosis.

In PBL all bones may be affected, but the axial skeleton is the main site of involvement. This reflects the distribution of red marrow. For the same reason the metaphyseal location is predominantly affected. The most common location in our series was the affection of the pelvis, the spine was the second most common location. The lesions are most commonly osteolytic. However they can also show an osteoblastic or mixed osteolytic/blastic bone change [23]. Pathologic fractures occurred in 16% of our patients. In the literature a pathological fracture was described as an independent adverse prognostic event [24]. In our group of patients this could only be proven as a trend but without significance.

In many cases in lymphoma only slight changes are seen in bone imaging despite a large soft tissue tumor in MRI. This is a major criteria for the diagnosis. This is due to the fact that the tumor sometimes shows such a rapid growth that it overruns the bony host response. Nuclear bone scans may produce false-negative results due to the predominantly osteolytic character of the lesions [25]. PET scans were first used in lymphomas in 1990 [26]. In a large number of studies PET-CT has been established as the most sensitive current imaging study not only for response assessment but also for staging of the disease [26–28].

Table 3

Cox proportional-hazards regression for overall survival of raised LDH, age, IPI, ECOG, histopathologic subtyps (indolent, aggressive, Hodgkin's disease), local relaps, chemotherapy (CTX) and radiotherapy (RTX), in 106 patients with PBL. 3 patients due to missing subtypes excluded.

Factor	P	HR	95% CI
Raised LDH	**0,0232**	4,6303	1,2327–17,3919
Age	**0,0112**	1,0426	1,0095–1,0767
IPI	0,1240	0,6658	0,3964–1,1181
ECOG	0,1642	0,5840	0,2737–1,2461
Histopathologic subtype	**0,0349**	3,2039	1,0858–9,4538
Local relapse	0,9267	1,0681	0,2627–4,3429
CTX	0,8924	1,0974	0,2855–4,2177
RTX	0,1859	0,5005	0,1794–1,3959

HR indicates hazards ratio; CI 95% confidence interval.

Soft-tissue involvement in PBL is common, affecting more than 70% of the patients [15]. Thus a large soft-tissue tumor extending concentrically around the bone with infiltration of the bone marrow in the typical age group of patients may be the major clue to the diagnosis. One could call it an 'Ewinglike' pattern in adults aged 50 years or older
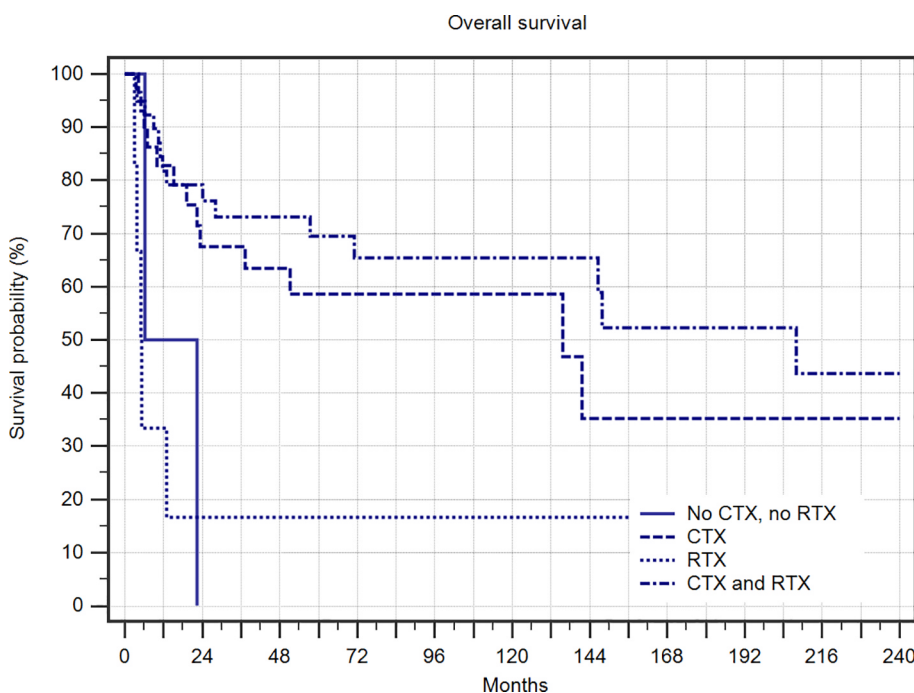

Fig. 3. Overall survival in 78 patients with primary lymphoma of bone (aggressive NHL subtype) in respect to no radiotherapy/chemotherapy (n = 2), radiotherapy only (n = 6), chemotherapy alone (n = 29) and combined modality treatment (n = 40); p = 0.0034. If compared patients with chemotherapy only (n = 29) and combined modality treatment (n = 41), there was just the shown trend but no significance.

[29].

Local pain and swelling, may be the only signs of the disease. The duration of these symptoms was in some cases long, more than one year, but many patients described also a rapid growth of the lesions. This is reflected by the difference between the mean of 8 months and the median of 3.3 months. B-symptoms including fever, sweating, or weight loss may occur as described by Govi et al. in 16%, but are missing in many cases [24]. So first suspect is often bone or soft tissue sarcoma in younger and metastatic disease in older patients.

Treatment is based on systemic therapy. Surgical intervention is restricted to cases with neurological complications, impending fracture, or fractures [15]. At present, there are no general protocols for applying and timing chemotherapy or radiotherapy. The optimal timing of radiation and chemotherapy in PBL is also unknown. As proposed by Mendenhall et al., radiotherapy should be delayed in monostotic and polyostotic diseases until chemotherapy is completed, in order to reduce the amount of radiotherapy and include only those sites of original gross involvement [30]. In some institutions, local radiation alone was recommended [31]. Chemotherapy seems to produce a better outcome than Radiotherapy alone; that still remains the best treatment for local disease control. Radiation therapy alone should be reserved for mandibular tumors, which are usually very small and earlier diagnosed [32]. In the IELSG-14 study, patients managed with primary chemotherapy, whether followed by radiation or not, had a better OS compared with patients treated with primary radiotherapy, whether followed by chemotherapy or not [33]. This was also described by Govi et al. [24] Chemotherapy may also reduce the incidence of local recurrence in PBL and improve the prognosis in children and adults with disseminated disease. Our own results may strengthen this by a trend to better survival in patients with combined modality treatment (Fig. 3). In a large analysis including 9 prospective trials of the German High-Grade Non-Hodgkin lymphoma study Group with 3.840 patients (from which 292 had skeletal involvement) also Rituximab failed to improve the outcome of those patients [34]. This underlines our own results with no effect of Rituximab in patients with aggressive forms of PBL on overall survival.

Several prognostic factors in PBL have been established. Unifocal versus multifocal disease at presentation was a weak but significant result. In their large study of 422 patients, Ostrowski et al. were able to demonstrate [14] a 5-year survival rate of 58% in unifocal disease versus 42% in multifocal osseous disease. This was also seen by Wu et al. comparing 81 cases of unifocal PBL with 35 cases of multifocal disease [35]. In our patients we found a overall 5-year survival of 66%, there was no difference between multifocal or unilocular osseous disease. The correlation between the site of the primary lesion and the prognosis is controversial. Having found no correlation in one study [36], Ostrowski showed local recurrence was higher in malignant lymphoma of the jaw, and systemic recurrence had a higher incidence in pelvic and spinal lesions. The 5-year overall survival rate was also very low in this group (24%) as compared with the extremities, such as the femur (79%). In our study, a significant influence of trunk vs extremity lesions could not be shown. This might be contributed to advances obtained in radiotherapy of critical locations. Advanced age was significantly associated with a reduced overall survival, as found also by others [37]. ECOG status, age, LDH levels, IPI stage are known significant factors of OS consistently seen in many larger studies of PBL [24,38–41]. Regarding the IPI stage which proved in our own group significant with 0/1 vs all olthers, there are studies showing no influence on OS, maybe attributed to a smaller sample number [42].

5. Conclusion

In summary PBL is a rare clinical entity. Clinical symptoms are unspecific, and the delay between onset of symptoms and diagnosis may either be short or long. Roentgenmorphology is heterogenous, one of the typical radiologic signs is large soft-tissue involvement surrounding the bone with little or no bone changes on radiographs. Treatment is based on systemic chemotherapy. Surgical intervention is restricted to cases with complications as fractures. Chemotherapy seems to produce a better outcome than radiotherapy alone; that still remains the best treatment for local disease control in unifocal cases. Long-term survival is based on the stage of the disease, favoring younger (< 60 years) patients with solitary bone lesions, low level of LDH and favourable ECOG and IPI scores.

6. Declarations

All authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work. This study was not supported by any grants or external funding.

7. Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all surviving patients included in this study. For non-surviving patients data were irreversibly anonymized as recommended by the ethics committee.

8. Competing interests

The authors declare that they have no competing interests.

Funding

This study was not supported by any grants or external funding.

10. Authors' contributions

A.M. Student doing her thesis on PBL. She contacted the patients and acquired the data, involved in drafting and revising of the manuscript.
M.D. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.
F.R. Reviewing the radiotherapy and deciding which patient to treat or not to treat, involved in drafting and revising of the manuscript.
A.B. Radiologist reviewing the radiologic investigations, involved in drafting and revising of the manuscript.
T.K. Pathologist reviewing the pathologic investigations, involved in drafting and revising of the manuscript.
A.K. Surgeon on many of the cases, involved in drafting and revising of the manuscript.
C.B. Surgeon, involved in drafting and revising of the manuscript. Final manuscript approval for submission and publication.
V.J. Surgeon on many of the cases, reviewer of the manuscript, involved in drafting and revising of the manuscript.
H.R.D. Corresponding author. Developed the study concept, did the final data analysis and provided the major clinical input in writing and revising of the manuscript.

Each author has contributed significantly to, and is willing to take public responsibility for this study: its design, data acquisition, and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

References

[1] C. Freeman, J.W. Berg, S.J. Cutler, Occurrence and prognosis of extranodal lymphomas, Cancer 29 (1972) 252–260.
[2] A. Jain, K. Alam, V. Maheshwari, R. Khan, H. Nobin, V. Narula, Primary bone

lymphomas-Clinical cases and review of literature, J. Bone Oncol. 2 (2013) 132–136.

[3] C. Oberling, Les réticulosarcomes et les réticuloendothéliosarcomes de la moelle osseuse (sarcomes d'Ewing), Bull. Assoc. Fr. Etud. Cancer 17 (1928) 259–296.

[4] J. Parker, J. Higinbotham, Primary reticulum cell sarcoma of bone, Surg. Gynecol. Obstet. 68 (1939) 45–53.

[5] A.J. Rathmell, M.K. Gospodarowicz, S.B. Sutcliffe, R.M. Clark, Localised lymphoma of bone: prognostic factors and treatment recommendations. The Princess Margaret Hospital Lymphoma Group, Br. J. Cancer 66 (1992) 603–606.

[6] H.C. Boston Jr., D.C. Dahlin, J.C. Ivins, R.E. Cupps, Malignant lymphoma (so-called reticulum cell sarcoma) of bone, Cancer 34 (1974) 1131–1137.

[7] H. Shoji, T.R. Miller, Primary reticulum cell sarcoma of bone. Significance of clinical features upon the prognosis, Cancer 28 (1971) 1234–1244.

[8] M.P. Glotzbecker, L.S. Kersun, J.K. Choi, B.P. Wills, A.A. Schaffer, J.P. Dormans, Primary non-Hodgkin's lymphoma of bone in children, J. Bone Joint Surg. Am. 88 (2006) 583–594.

[9] P.C.W. Hogendoorn, P.M. Kluin, Primary non-Hodgkin Lymphoma of bone, in: C.D. M. Fletcher, J.A. Bridge, P.C.W. Hogendoorn, F. Mertens (Eds.) WHO classification of tumours of soft tissue and bone. Lyon: International Agency for Research on Cancer (IARC), 69372 Lyon Cedex 08, France, (2013):316–318.

[10] M.U. Jawad, M.M. Schneiderbauer, E.S. Min, M.C. Cheung, L.G. Koniaris, S.P. Scully, Primary lymphoma of bone in adult patients, Cancer 116 (2010) 871–879.

[11] S.A. Rosenberg, H.D. Diamond, B. Jaslowitz, L.F. Craver, Lymphosarcoma: a review of 1269 cases, Medicine (Baltimore) 40 (1961) 31–84.

[12] M.G. Conlan, M. Bast, J.O. Armitage, D.D. Weisenburger, Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group, J. Clin. Oncol. 8 (1990) 1163–1172.

[13] J.M. Bennett, K.C. Cain, J.H. Glick, G.J. Johnson, E. Ezdinli, M.J. O'Connell, The significance of bone marrow involvement in non-Hodgkin's lymphoma: the Eastern Cooperative Oncology Group experience, J. Clin. Oncol. 4 (1986) 1462–1469.

[14] M.L. Ostrowski, K.K. Unni, P.M. Banks, et al., Malignant lymphoma of bone, Cancer 58 (1986) 2646–2655.

[15] H.R. Dürr, P.E. Müller, E. Hiller, et al., Malignant lymphoma of bone, Arch. Orthop. Trauma Surg. 122 (2002) 10–16.

[16] M. Salter, R.J. Sollaccio, W.K. Bernreuter, B. Weppelmann, Primary lymphoma of bone: the use of MRI in pretreatment evaluation, Am. J. Clin. Oncol. 12 (1989) 101–105.

[17] A. Krishnan, A. Shirkhoda, J. Tehranzadeh, A.R. Armin, R. Irwin, K. Les, Primary bone lymphoma: radiographic-MR imaging correlation, Radiographics 23 (2003) 1371–1383 discussion 1384–1377.

[18] G. Bacci, N. Jaffe, E. Emiliani, et al., Therapy for primary non-Hodgkin's lymphoma of bone and a comparison of results with Ewing's sarcoma. Ten years' experience at the Istituto Ortopedico Rizzoli, Cancer 57 (1986) 1468–1472.

[19] M.M. Oken, R.H. Creech, D.C. Tormey, et al., Toxicity and response criteria of the Eastern Cooperative Oncology Group, Am. J. Clin. Oncol. 5 (1982) 649–655.

[20] A.J. Jacobs, R. Michels, J. Stein, A.S. Levin, Socioeconomic and demographic factors contributing to outcomes in patients with primary lymphoma of bone, J. Bone Oncol. 4 (2015) 32–36.

[21] M.J. Coppes, C. Patte, D. Couanet, et al., Childhood malignant lymphoma of bone, Med. Pediatr. Oncol. 19 (1991) 22–27.

[22] S. Bhagavathi, K. Fu, Primary bone lymphoma, Arch. Pathol. Lab. Med. 133 (2009) 1868–1871.

[23] B. Edeiken-Monroe, J. Edeiken, E.E. Kim, Radiologic concepts of lymphoma of bone, Radiol. Clin. North Am. 28 (1990) 841–864.

[24] S. Govi, D. Christie, C. Messina, et al., The clinical features, management and prognostic effects of pathological fractures in a multicenter series of 373 patients with diffuse large B-cell lymphoma of the bone, Ann. Oncol. 25 (2014) 176–181.

[25] L. Janoskuti, I. Szilvasi, G. Papp, E. Rona, S. Benedek, S. Fekete, Bone scanning and radiography in the evaluation of patients with malignant lymphoma, Rofo 149 (1988) 427–428.

[26] B.D. Cheson, Staging and response assessment in lymphomas: the new Lugano classification, Chin. Clin. Oncol. 4 (2015) 5.

[27] L.J. Wang, H.B. Wu, M. Wang, et al., Utility of F-18 FDG PET/CT on the evaluation of primary bone lymphoma, Eur. J. Radiol. 84 (2015) 2275–2279.

[28] Y. Liu, The role of 18F-FDG PET/CT in staging and restaging primary bone lymphoma, Nucl. Med. Commun. 38 (2017) 319–324.

[29] C.Y. Lim, K.O. Ong, Imaging of musculoskeletal lymphoma, Cancer Imaging 13 (2013) 448–457.

[30] N.P. Mendenhall, J.J. Jones, B.S. Kramer, et al., The management of primary lymphoma of bone, Radiother. Oncol. 9 (1987) 137–145.

[31] K. Suryanarayan, J.J. Shuster, S.S. Donaldson, R.E. Hutchison, S.B. Murphy, M.P. Link, Treatment of localized primary non-Hodgkin's lymphoma of bone in children: a Pediatric Oncology Group study, J. Clin. Oncol. 17 (1999) 456–459.

[32] E. Barbieri, S. Cammelli, F. Mauro, et al., Primary non-Hodgkin's lymphoma of the bone: treatment and analysis of prognostic factors for Stage I and Stage II, Int. J. Radiat. Oncol. Biol. Phys. 59 (2004) 760–764.

[33] M. Bruno Ventre, A.J. Ferreri, M. Gospodarowicz, et al., Clinical features, management and prognosis of an international series of 161 patients with limited-stage diffuse large B-cell lymphoma of the bone (the IELSG-14 study), Oncologist 19 (2014) 291–298.

[34] G. Held, S. Zeynalova, N. Murawski, et al., Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement, J. Clin. Oncol. 31 (2013) 4115–4122.

[35] H. Wu, M.M. Bui, D.G. Leston, et al., Clinical characteristics and prognostic factors of bone lymphomas: focus on the clinical significance of multifocal bone involvement by primary bone large B-cell lymphomas, BMC Cancer. 14 (2014) 900.

[36] F. Clayton, J.J. Butler, A.G. Ayala, J.Y. Ro, J. Zornoza, Non-Hodgkin's lymphoma in bone. Pathologic and radiologic features with clinical correlates, Cancer 60 (1987) 2494–2501.

[37] E. Demircay, F.J. Hornicek Jr., H.J. Mankin, H. Degroot 3rd., Malignant lymphoma of bone: a review of 119 patients, Clin. Orthop. Relat. Res. 471 (2013) 2684–2690.

[38] H. Wu, L. Zhang, H. Shao, et al., Prognostic significance of soft tissue extension, international prognostic index, and multifocality in primary bone lymphoma: a single institutional experience, Br. J. Haematol. 166 (2014) 60–68.

[39] J.M. Horsman, J. Thomas, R. Hough, B.W. Hancock, Primary bone lymphoma: a retrospective analysis, Int. J. Oncol. 28 (2006) 1571–1575.

[40] K.M. Ramadan, T. Shenkier, L.H. Sehn, R.D. Gascoyne, J.M. Connors, A clinicopathological retrospective study of 131 patients with primary bone lymphoma: a population-based study of successively treated cohorts from the British Columbia Cancer Agency, Ann. Oncol. 18 (2007) 129–135.

[41] X. Zhang, J. Zhu, Y. Song, L. Ping, W. Zheng, Clinical characterization and outcome of primary bone lymphoma: a retrospective study of 61 Chinese patients, Sci. Rep. 6 (2016) 28834.

[42] K. Beal, L. Allen, J. Yahalom, Primary bone lymphoma: treatment results and prognostic factors with long-term follow-up of 82 patients, Cancer 106 (2006) 2652–2656.