Universiteit
Leiden
The Netherlands

Primary diffuse large B-cell lymphoma of bone

Heyning, F.H.

Citation
Heyning, F. H. (2011, December 1). *Primary diffuse large B-cell lymphoma of bone*. Retrieved from https://hdl.handle.net/1887/18170

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/18170

Note: To cite this publication please use the final published version (if applicable).

Chapter 2

Primary non-Hodgkin's lymphoma of bone: a clinicopathological investigation of 60 cases

F.H. Heyning[1], P.C.W. Hogendoorn[1,5], M.H.H. Kramer[1], J. Hermans[3], J.C. Kluin-Nelemans[4], E.M. Noordijk[2,5] and Ph.M. Kluin[1]

Departments of [1]Pathology, [4]Haematology, [2]Radiation Oncology and [3]Medical Statistics, Leiden University Medical Centre and [5]Netherlands Committee on Bone Tumours, Leiden, The Netherlands

Leukemia, 1999; 13; 2094-8

Abstract

A retrospective analysis of patients presenting with primary lymphoma of bone (PLB) was performed to determine clinical factors affecting prognosis in relation to histological subtype and treatment outcome. Data from 106 patients, presenting witha PLB between 1943 and 1996, were retrieved from the files of the Netherlands Committee on Bone Tumours and Leiden University Medical Centre. The lymphomas were reclassified according to the REAL and updated Kiel classification. The clinical presentation, survival and prognostic factors were investigated. Sixty patients had sufficient clinical information and adequate follow-up to be included in the study. All 33 PLB that could be immunophenotyped were of B cell origin. According to the REAL classification, most PLB were large (B) cell lymphomas (92%) and according to the Kiel classification 45% of the tumours were centroblastic multilobated. PLB presented most often in the long bones (48%), with Ann Arbor stage I (46%), II (16%), IV (16%) and unknown (20%). Stage IV disease was exclusively caused by the presence of multiple bone lesions. Notwithstanding the heterogeneous treatment, the 5 year overall survival was 61%; 46% of patients were progression free at 5 years. Patients at presentation older than 60 had a worse overall survival (76% vs 37%, $P = 0.0002$) and a worse progression free period (58% vs 28%, $P = 0.0073$). Patients with the immunoblastic subtype had a worse survival than the centroblastic mono/polymorphic subtype or the centroblastic multilobated subtype ($P = 0.015$). Primary lymphoma of bone represents an uncommon bone tumour with a relatively homogeneous morphology and clinical behaviour. Compared to other aggressive lymphomas, PLB have a favourable prognosis.

Introduction

Primary lymphoma of bone (PLB) is a rare disease, first described by Oberling in 1928.[1] It was not until 1939 that Parker and Jackson[2] described 17 cases of 'primary reticulum cell sarcoma of bone' and established PLB as a distinct clinical entity. Even today the diagnosis of PLB can be difficult due to the relatively non-specific radiographic appearance and the sometimes profound proliferation of reactive fibroblasts at the histological level.[3] Thus, PLB can be erroneously interpreted as a primary skeletal tumour of non-lymphoid origin such as Ewing's sarcoma or malignant fibrous histiocytoma.

Most studies on PLB published so far describe small groups of patients. In many studies stage IV tumours were excluded and patients were only treated with radiotherapy.[4–11] Uniform directives for classification, treatment and prognosis are still lacking. We describe a relatively large group of 60 patients with clinico-radiologically and histologically documented PLB, collected from the files of the Netherlands Committee on Bone Tumours and the Leiden University Medical Centre. Our objective was to document patient and tumour characteristics of this cohort with emphasis on histological subtype, substantiated by immunohistochemistry and to define factors affecting prognosis for PLB.

Materials and methods

Patients

The files from the registry of the Netherlands Committee on Bone Tumours with diagnosis codes 'malignant lymphoma', 'reticulum cell sarcoma' or 'lymphosarcoma' involving bone were reviewed. This registry contains more than 11000 cases, collected between 1943 and 1996 and includes clinical data at presentation, histological slides of the tumour and complete radiographic documentation. In addition to these cases, patients registered at the Leiden University Medical Centre with a diagnosis of primary non-Hodgkin's lymphoma of bone were selected. A total number of 106 patients were identified. Of this group 30 patients were excluded because of a different diagnosis after review of the histological slides, combined with new immunohistochemical data or clinical data obtained at follow-up. These cases included Ewing's sarcoma (n = 8), acute lymphoblastic leukaemia/lymphoma (n = 5) or Burkitt's lymphoma/leukaemia (n = 3), acute myeloid -leukaemia (n = 3), multiple myeloma (n = 3), secondary bone involvement of NHL (n = 3), Hodgkin's lymphoma (n = 2) or inappropriate histological material for review (n = 3). For a diagnosis of PLB, patients had to present with a histologically proven lymphoma arising within the medullary cavity of a bone, with or without regional lymph node involvement. Multiple bone lesions were acceptable as long as there was no evidence of earlier lymphomatous involvement elsewhere.

A questionnaire was sent to the collaborating hospitals to obtain follow-up data for the 76 selected patients. Follow-up data were successfully collected for 60 patients, whereas 16 patients were lost to follow-up. The last date of follow-up was December 1996. From these

60 cases, 54 were retrieved from the Netherlands Committee on Bone Tumours and six from the Leiden University Medical Centre. The patient records were reviewed for the following parameters: sex, tumour localisation, tumour diameter (5 cm, 5 cm as measured on the radiographs), treatment, response to treatment, date and site of relapse or progression if applicable, date of last follow-up or date of death and cause of death. The clinical parameters age, stage, serum LDH level, number of extranodal sites and performance status according to the Eastern Cooperative Oncology Group scale of the International Prognostic Index (IPI) for aggressive non-Hodgkin's lymphoma[12] were used. Stage was defined according to the Ann Arbor staging classification. Serum LDH level was recorded as 1.5× normal or 1.5 × normal. The number of extranodal sites was defined as the number of all extranodal sites including the bone localisations. According to the IPI12 performance status was grouped as 0 or 1 (the patient was ambulatory) or 2, 3 or 4 (the patient was not ambulatory).

Histological classification and immunohistochemistry

The pathological diagnosis was established according to the REAL classification[13] and updated Kiel classification[14] using standard histological criteria and, if possible, immunohistochemistry. Immunohistochemical studies were performed on paraffin-embedded material, and could be interpreted in 33 of 60 cases. In the remaining 27 cases the material was not available or inappropriate due to decalcification artefacts. The antibodies used in this study included leukocyte common antigen (CD45) (Dakopatts, Copenhagen, Denmark), L26 as a B cell marker (CD20) (Dakopatts), and a T cell marker (CD3) (Dakopatts). In some cases BerH2 (CD30) (Dakopatts) was also used. Immunohistochemical procedures were performed as detailed previously.[15]

Staging

Staging investigations performed varied over time and patients were staged retrospectively according to the Ann Arbor staging classification. For the purpose of this study, staging was defined as complete if it included: (1) a chest X-ray or a CT scan of the chest; (2) lymph-angiography or CT-scan or echography of the abdomen and pelvis; (3) bone marrow biopsy; and (4) total body bone scintigraphy or MRI. Defined as such 20 patients were completely staged and 40 were not. The investigation most frequently missing in the incompletely staged patients was a bone marrow biopsy.

Treatment

Since 1943 a wide variety of therapies has been used, including radiotherapy, chemotherapy and surgery in various combinations. The patients receiving chemotherapy were subdivided into a group treated with CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or CHOP-like therapy and a remaining group with mostly non-adriamycin containing single agent therapy. Surgery consisted of either resection or amputation. As patient numbers were too small to perform statistical analysis on all the different treatment combinations, we selected

the following groups (Table 1): group 1 (n = 5) was treated with radiotherapy alone (c–r+s–), group II (n = 24) was treated with radiotherapy and chemotherapy (c+r+s–), and group III (n = 11) was treated with radiotherapy, chemotherapy and surgery (c+r+s+). The remaining 20 patients received either other combinations of therapy or inadequate therapy (for example radiotherapy <30 Gy). In group II, 15 of 24 patients and in group III, six of 11 patients received adriamycin containing (CHOP or CHOP-like) chemotherapy.
Response to treatment was recorded as complete remission, partial remission (>50% reduction of tumour), no change or progressive disease.

Survival analysis

For the whole cohort (n = 60) the overall survival time was calculated from time of diagnosis until time of death or until date of last follow-up (December 1996). The progression-free period was calculated from the date of diagnosis to the date of progression or relapse or to last contact in case the patient was progression free. Patients who had progressive disease in response to treatment were considered to have a progression free period of 0 months. The five patients of whom the response to treatment could not be determined were excluded from the progression-free period analysis. Survival curves were calculated according to the Kaplan and Meier method; survival analysis was performed using the log-rank test. We performed univariate analysis on the following factors: sex, tumour localisation, tumour diameter, histological subtype, treatment, age, stage, and the level of serum LDH.

Results

Patient characteristics

Patient characteristics are summarised in Table 1. The group consisted of 39 males and 21 females, a ratio of 1.8 consistent with other studies.[8] The age of the patients varied from 13 to 86 years (median 48). The PLB most often presented in the long bones (29 localisations, 48%), of which seven localisations (12%) presented in the upper limb and 22 localisations (36%) in the lower limb (Figure 1). In 10 patients (16%) more than one bone localisation was found. The symptoms at presentation were local pain and/or a palpable mass. Three patients presented with a pathologic fracture. No B symptoms were reported in this cohort.

Clinical staging

In 48 patients the stage could be assigned. Twenty-eight patients presented with stage I disease, 10 with stage II, and 10 with stage IV (Table 1). Twenty-eight out of all 48 patients and 21 out of 38 patients with stage I or II disease had undergone an incomplete staging procedure. All stage II tumours had lymph node involvement near the site of the bone localisation. All stage IV tumours had more than one bone localisation and none had bone marrow or other distant organ involvement. Three of the 20 completely staged and seven of the 28 incompletely staged

Table 1. Summary of clinical, histological and therapeutical para¬meters

Parameter	No. of patients ()[a]	Percentage
Sex		
Male	39	65
Female	21	35
Stage		
I	28	46
II	10	16
III	0	0
IV	10	16
Unknown	12	20
Completely staged	20	33
Incompletely staged and unknown	40	67
Histology		
Follicle center cell, diffuse	2 (1)	3
Large B cell	55 (32)	92
Centroblastic mono/polymorphic[b]	18 (12)	30
Centroblastic multilobated[b]	27 (15)	45
Immunoblastic[b]	10 (5)	16
Anaplastic large cell	2 (0)	3
Immunocytoma	1 (0)	2
Therapy		
Radiotherapy only	5	8
Radiotherapy and chemotherapy	24	40
Radiotherapy, chemotherapy and surgery	11	18
Other combinations	20	33
Chemotherapy		
CHOP or CHOP-like	23	38
Other chemotherapy	15	25
Response to therapy		
Complete remission	29	48
Partial remission	5	8
No change	1	2
Progressive disease	20	33
Unknown	5	8

[a]Immunohistochemistry performed.
[b]Updated Kiel classification.[14]

patients had stage IV disease. This makes understaging in the latter group somewhat unlikely. In the remaining 12 patients the stage could not be determined.

Histological classification and immunohisto-chemistry

The results of the histological analysis and immunohistochemistry are given in Table 1. All 33 out of 60 lymphomas that could be immunophenotyped were of B cell origin. Based on the routine histological slides and limited immunophenotypic data available, almost all lymphomas (92%) were large (B) cell lymphomas according to the REAL classification.[13] According to the updated Kiel classification[14] 45% of the PLB were of the centroblastic multilobated subtype. The two anaplastic large cell lymphomas could not be immunophenotyped, and therefore, it cannot be excluded that they belonged to a subset of large B cell lymphomas with anaplastic morphology.[14]

Response to treatment, survival and prognostic factors

Forty-eight percent (n = 29) of 60 patients achieved complete remission, 8% partial remission, 2% showed no change, 33% had progressive disease and in 8% of the patients response to therapy could not be determined (Table 1).

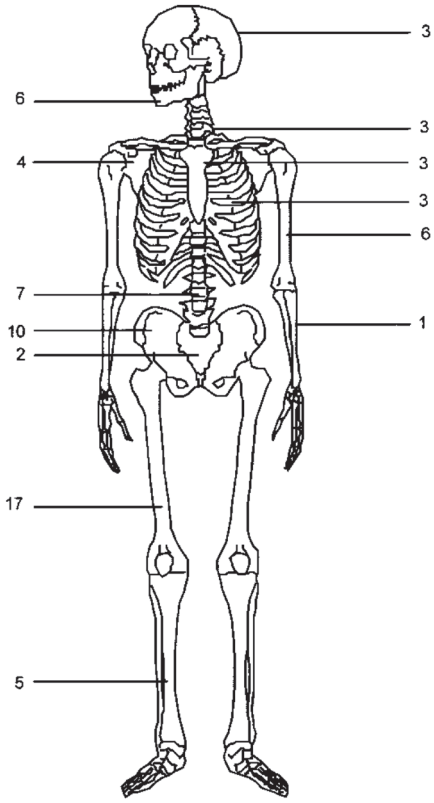

Figure 1. Tumor localisation. PLB most often presented in the long bones (50%): in the upper limb (12%) and in the lower limb (38%). Ten patients presented with more than one bone localisation. The site of these multiple localisations are included in the figure (70 localisations in total).

The mean follow-up for the whole cohort was 174 months, ranging from 1 to 296 months. At 5 years after diagnosis 46% of the patients were free of progression. The 5-year overall survival was 61% for all patients, 66% for patients with stage I and II and 50% for patients with stage IV (Figure 2). Nine out of 29 patients relapsed. The localisation of the relapses were bone (n = 3), lymph nodes (n = 3), liver (n = 1), lungs (n = 1) and breast (n = 1). Twenty-three patients died during follow-up. The cause of death was primary refractory disease in 18 patients, relapse in four patients and unrelated to NHL in one patient.

For statistical purposes we only included the three largest histological groups (centroblastic mono/polymorphic, centroblastic multilobated and immunoblastic) in the survival and

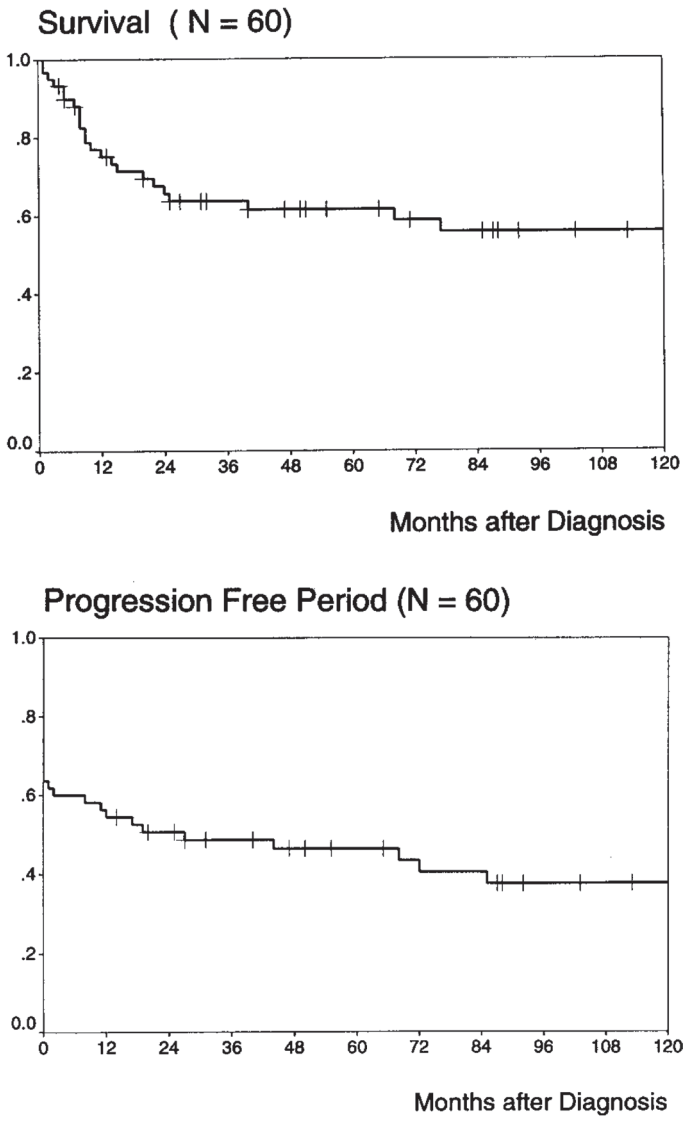

Figure 2. Survival in primary NHL ofbone. The 5 year overall survival was 61% for all patients (n = 60; upper-panel). At 5 years after diagnosis 46% of patients were free of progression (n = 60 patients, lower panel).

progression-free survival analysis. The immunoblastic subtype (as defined by the Kiel classification[14] containing 90% or more immunoblasts) had a statistically significantly shorter overall survival and progression-free period than the other subtypes (P = 0.015 and P = 0.05, respectively; Figure 3).

As a consequence of often incomplete clinical data the risk groups defined in the International Prognostic Index could not be determined. We analysed the influence of the individual factors age, sex, primary localisation, tumour size, stage and serum LDH on survival. To prevent bias, only the cases with sufficient data for all six parameters were included in the univariate analysis. Age was a significant prognosticator, with a 5 year overall survival of 76% for patients younger than 60 years and 37% for patients of 60 years and older (P = 0.0002; Figure 4) and a 5-year progression-free period of 58% vs 28% (P = 0.0073). As there was no difference in survival between stage I and stage II patients, we analysed stage I and II against stage IV. Although there was a trend towards worse survival for stage IV, it was not statistically significant (P = 0.56). An elevated serum LDH was associated with decreased overall survival (P = 0.25) but this did not reach statistical significance, probably because of the relatively small numbers of patients who could be analysed (n = 38). No statistically significant effect on survival was found after univariate analysis of the other prognostic factors such as sex, tumour localisation, and tumour size.

Survival was not statistically different for the three selected treatment combinations. The overall survival of patients treated with CHOP or CHOP-like chemotherapy was not significantly better than the survival of patients treated with other types of chemotherapy (P = 0.17). The progression-free period, however, was significantly longer for patients treated with CHOP or CHOP-like therapy, with a 5 year progression-free period of 58% vs 27% (data not shown). A confounding factor is that adequate staging and treatment are related: after 1975 both staging procedures (introduction of CT scan) and treatment modalities (introduction of CHOP or CHOP-like chemotherapy) improved. To investigate the possible impact of accuracy

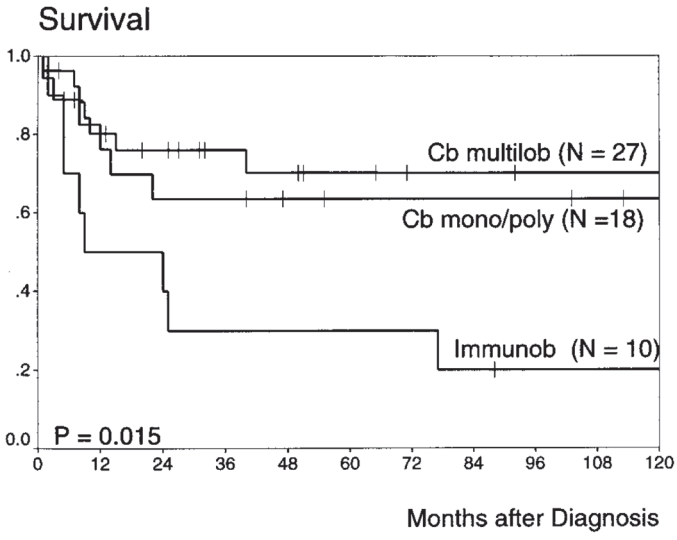

Figure 3. Comparison of tumor subtype related to overall survival. Patients with the immunoblastic subtype had a worse overall survival than the centroblastic multilobated subtype or the centroblastic mono/polymorphic subtype.

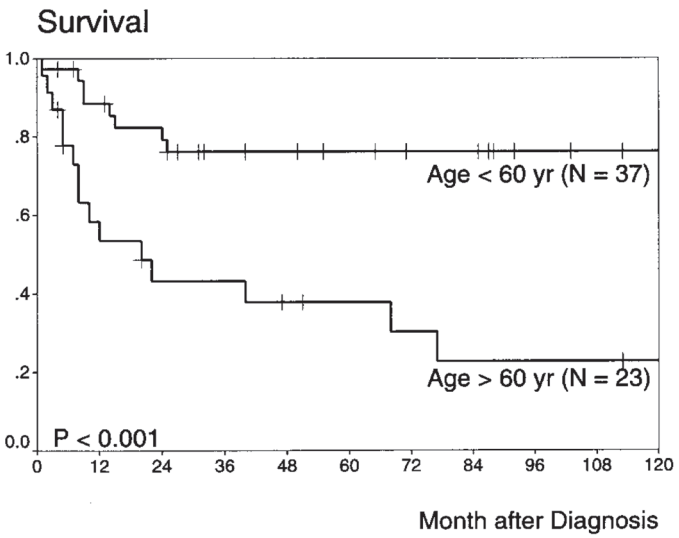

Figure 4. Comparison of age groups under and over 60 years related to overall survival. The 5-year overall survival was 76% for the patients younger than 60 years (n = 37) and 37% for the patients of 60 years and older (n = 23).

of diagnostic procedures on survival we analysed the role of complete staging: patients with complete staging had a slightly better prognosis with respect to overall survival, but it did not prove statistically significant in univariate analysis (P = 0.48).

Discussion

The presentation of NHL as a localised bone tumour is relatively uncommon. Any study of the pathophysiology of PLB and on prognostic factors is complicated by the small patient numbers and by the fact that the results of earlier studies are often not comparable to each other.[4-6] We studied a relatively large and representative group of patients, diagnosed and treated between 1943 and 1996. Patients were selected by reviewing all cases previously diagnosed as malignant lymphoma, lymphosarcoma or reticulum cell sarcoma. Since we did not review all primary bone tumours, we cannot exclude that especially in the early years of the registry, a few tumours were misdiagnosed as Ewing's sarcoma or, in case of excessive fibrosis, as sarcoma not otherwise specified, and thus were not included here.

We show that the patients display a homogeneous pathological and clinical presentation as well as clinical behaviour. Histologically, almost all PLBs were of the large B cell type, and half of these tumours were of the multilobated centroblastic subtype. The very high frequency of this latter subtype had been reported previously.[16] The majority of patients presented with pain and/or a palpable mass, most often at a single localisation in one of the long bones. Approximately one quarter of the patients presented with multiple bone lesions, which is in accordance with other studies.[9] Of note, these patients made up the entire group of stage IV patients. In line with a specific pattern of dissemination and homing of tumour cells in PLB, three of nine patients had bone localisations upon relapse.

The initial treatment for these tumours, before chemotherapy became available, was radiotherapy or surgery. Several studies suggest that the combination of chemotherapy and radiotherapy is the best treatment, as a consequence of which resection or amputation can be prevented.[4,17,18] In this cohort the overall 5 year survival was 61%. This is surprisingly high when the heterogeneous treatment schedules over the years of the study and the inclusion of stage IV patients are taken into account. Although survival was not statistically different for the three selected treatment combinations, patients treated with CHOP or CHOP-like therapy had a longer progressionfree period than patients treated with other types of chemotherapy.

Although our data are derived from a retrospective analysis of a very heterogeneous study group, some conclusions may be drawn with respect to prognostic factors. Consistent with previous reports,[10,11] immunoblastic lymphoma as defined by the updated Kiel classification,[14] had a worse prognosis than other large B cell lymphoma subtypes. In the past, the clinical parameters used to predict prognosis in PLB, were tumour stage and localisation.[7,8,10,11] We found these prognostic factors not easily applicable to PLB. Furthermore, as in other extra-nodal lymphomas, in PLB prognosis is not strongly affected by regional lymph node involvement: there was no difference in survival between stage I and stage II tumours and just a trend towards worse prognosis in stage IV tumours. This underlines that the Ann Arbor classification is not suitable for staging and predicting prognosis in PLB. Of note, many studies on PLB excluded patients with stage IV disease, partly in an effort to eliminate malignancies in which bone involvement is secondary.[4–6,19] This exclusion is not supported by our data that stage IV disease is mostly determined by multiple, osseous localisations.

Tumour localisation was no significant prognostic factor, neither could we confirm the suggestion that tumour localisation within the pelvis, ribs or vertebra is associated with a worse prognosis.[8] It is interesting that more than 50% of the stage IV tumours had at least one localisation in the pelvis, the vertebra or the ribs.

In conclusion, we propose that primary non-Hodgkin's lymphoma of bone be acknowledged as a specific clinicopathologic entity. Morphologically, PLB forms a homogeneous group and dissemination is often restricted. Furthermore, PLB patients seem to have a better survival than other NHL patients, even with therapy that is considered inadequate nowadays. Finally, this study suggests that age at presentation and tumour subtype are prognostic factors in PLB.

References

1 Oberling C. Les reticulosarcomes et les reticuloendotheliosarcomes de la moelle osseuse (sarcomes d'Ewing). *Bull Assoc Fr Etude Cancer* (Paris) 1928; 17: 259–296.

2 Parker F Jr, Jackson H Jr. Primary reticulum cell sarcoma of bone. *Surg Gynecol Obstet* 1939; 68: 45–53.

3 Kluin PM, Slootweg PJ, Schuurman HJ, Go DMDS, Rademakers LHPM, Van der Putte SCJ, Van Unnik JAM. Primary B-cell malignant lymphoma of the maxilla with a sarcomatous pattern and multilobated nuclei. *Cancer* 1984; 54: 1598–1605.

4 Rathmell AJ, Gospodarowicz MK, Sutcliffe SB, Clark RM. Localised lymphoma of bone. Prognostic factors and treatment recommendations. *Br J Cancer* 1992; 66: 603–606.

5 Fairbanks RK, Bonner JA, Inwards CY, Strickler JG, Habermann TM, Unni KK, Su J. Treatment of stage IE primary lymphoma of bone. *Int J Radiat Oncol Biol Phys* 1994; 28: 363–371.

6 Bacci G, Jaffe N, Emiliani E, Van Horn J, Manfrini M, Picci P, Bertoni F, Gherlinzoni F, Campanacci M. Therapy for primary non-Hodgkin's lymphoma of bone and a comparison of results with Ewing's sarcoma. Ten years' experience at the Instituto Ortopedico Rizzoli. *Cancer* 1986; 57: 1468–1472.

7 Dosoretz DE, Raymond AK, Murphy GF, Doppke KP, Schiller AL, Wang CC, Suit HD. Primary lymphoma of bone. The relationship of morphologic diversity to clinical behavior. *Cancer* 1982; 50: 1009–1014.

8 Ostrowski ML, Unni KK, Banks PM, Shives TC, Evans RG, O'Connell MJ, Taylor WF. Malignant lymphoma of bone. *Cancer* 1986; 58: 2646–2655.

9 Mendenhall NP, Jones JJ, Kramer BS, Hudson TM, Carter RL, Enneking WF, Marcus RB Jr, Million RR. The management of primary lymphoma of bone. *Radiother Oncol* 1987; 9: 137–145.

10 Clayton F, Butler JJ, Ayala AG, Ro JY, Zornoza J. Non-Hodgkin's lymphoma in bone. Pathologic and radiologic features with clinical correlates. *Cancer* 1987; 60: 2494–2501.

11 Vassallo J, Roessner A, Vollmer E, Grundmann E. Malignant lymphomas with primary bone manifestation. *Path Res Pract* 1987; 182: 381–389.

12 The Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *New Engl J Med* 1993; 329: 987–994.

13 Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC et al. A revised European-American classification of lymphoid neoplasms. A proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–1392.

14 Stansfeld AG, Diebold J, Noel H, Kapanci Y, Rilke F, Kelenyi G, Sundstrom C, Lennert K, Van Unnik JAM, Mioduszewska O et al. Updated Kiel classification for lymphomas. *Lancet* 1988; i: 292–293.

15 Kramer MHH, Hermans J, Parker J, Krol ADG, Kluin-Nelemans JC, Haak HL, Van Groningen K, Van Krieken JHJM, De Jong D, Kluin PM. The clinical significance of BCL2 and P53 protein expression in diffuse large B-cell lymphoma: a population-based study. J Clin Oncol 1996; 14: 2131–2138.

16 Pettit CK, Zukerberg LR, Gray MH, Ferry JA, Rosenberg AE, Harmon DC, Harris NL. Primary lymphoma of bone. A B-cell neoplasm with a high frequency of multilobated cells. Am J Surg Pathol 1990; 14: 329–334.

17 Baar J, Burkes RL, Bell R, Blackstein ME, Fernandes B, Langer F. Primary non-Hodgkin's lymphoma of bone. A clinicopathologic study. Cancer 1994; 73: 1194–1199.

18 Dubey P, Ha CS, Besa PC, Fuller L, Cabanillas F, Murray J, Hess MA, Cox JD. Localised primary malignant lymphoma of bone. *Int J Radiat Oncol Biol Phys* 1997; 37: 1087–1093.

19 Case 21–1996. Hodgkin's disease, nodular-sclerosis type, involving multiple bones. *New Engl J Med* 1996; 335: 115–122.