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ORIGINAL ARTICLE

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Malignant lymphoma of bone

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Abstract Malignant lymphoma of bone is rare. In many cases, its diagnosis is delayed because of unspecific clinical signs and equivocal radiographs. Therapy in general is multimodal, including surgery and radio- and chemotherapy. Our objective was to demonstrate the clinical and radiological aspects of the lesion to optimize diagnostic approaches and to evaluate treatment and prognostic factors. Thirty-six patients with malignant lymphoma of bone who were surgically treated over a 15-year-period were retrospectively reviewed. Seventeen of them showed a singular bone non-Hodgkin's lymphoma (NHL) which was classified as primary lymphoma of the bone (PLB). In 13 cases, dissemination of the disease with multiple bone or visceral involvement was apparent (dNHL). Six patients suffered from bone involvement due to Hodgkin's disease (HD). Surgical treatment was indicated for diagnostic reasons or complications due to the disease. Radiation and chemotherapy were part of the oncological treatment. The patients' mean age was 57 years.The main symptom in malignant bone lymphoma in 33 patients was pain, with an average duration of 8 months. In the secondary cases, bone involvement appeared on average 57 months after the initial diagnosis. An osteolytic pattern was seen in 58% of the lesions. Soft-tissue involvement was seen in 71% of cases (PLB 80%, dNHL 73%, HD 40%) and was the primary diagnostic sign associated with this disease. The 5-year survival rate was 61% (PLB 88%, dNHL 38%, HD 50%). Multiple vs solitary bone involvement was the most significant factor in the prognosis. Extraskeletal involvement significantly decreased survival. No correlation was found between gender, age, location, or histological subtypes and survival. Bone involvement in NHL appears late in the extraskeletal disease. The clinical appearance is nonspecific, and the delay between the onset of symptoms and diagnosis is often long. One of the major radiologic signs is the existence of a soft-tissue tumor surrounding the bone with little or no bone involvement on plain films. Treatment generally is conservative, based on the stage of the disease. Local radiation with or without systemic chemotherapy should be used. The long-term survival is favorable, but dependent on the stage of the disease and the amount of bone involvement.

Keywords Lymphoma · Bone · Magnetic resonance imaging · Surgical therapy · Prognosis

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Introduction

Malignant lymphoma of bone is a well-recognized but rather rare entity, accounting for about 5% of all patients with primary bone tumors [1]. In advanced stages of the disease, it may be impossible to determine whether the lymphoma developed within the bone (primary) or invaded it (secondary) [2]. Approximately 4% of all patients with NHL present with an obvious skeletal lesion [3], but in two well-documented series of NHL patients, routinely performed bone-marrow biopsies were positive in 18% and 23% of non-Hodgkin's lymphomas [4, 5]. In a large group of 422 patients with bone lymphomas at the Mayo Clinic, 38% showed extraskeletal involvement at the time of detection of bone involvement [6]. In many patients with localized primary lymphoma of the bone (PLB), diagnosis is delayed due to unspecific clinical signs and equivocal radiographs. Using magnetic resonance imag-

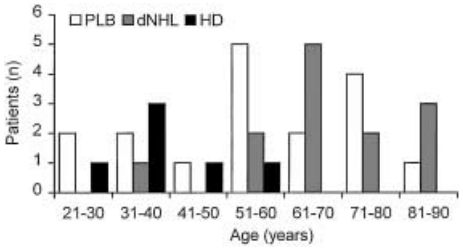

Fig. 1 Ages of 17 patients with primary lymphoma of the bone (PLB), 13 patients with multiple bone or visceral involvment in non-Hodgkin's lymphoma (dNHL), and 6 patients with Hodgkin's disease (HD) prior to surgery

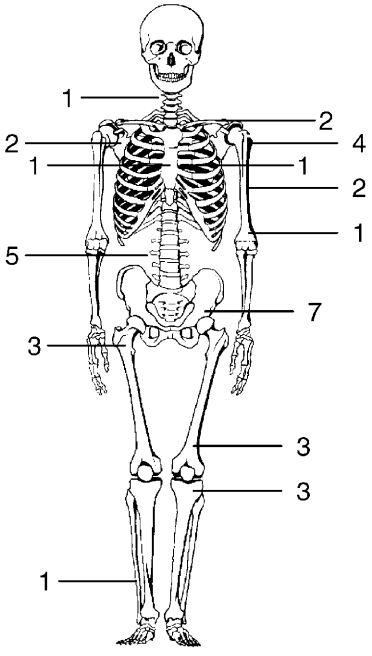

Fig. 2 Anatomical sites of the lesions in 36 surgical procedures

ing (MRI), early diagnosis is possible, although malignant lymphoma is not usually considered before biopsy [7]. Therapy in general is multimodal, including surgery and chemo- and radiotherapy. The prognosis is comparable to that of a localized Ewing's sarcoma (which sometimes has been confused with this tumor entity) [8].

This retrospective report includes 36 malignant lymphomas of bone demonstrating the typical clinical and radiological findings. We are well aware that lymphoma is not a primarily surgically treated disease but demonstrating the typical clinical and radiological aspects of the lesion may optimize diagnostic approaches. Second, we evaluated treatment and prognostic factors, thus optimizing therapeutic approaches.

Patients and methods

Between 1980 and 1998, 36 patients (16 men, 20 women) were surgically treated for malignant lymphoma of bone at our institution. These patients are the subjects of this report. Their mean age was 57 years (range 20–90 years) (Fig. 1). The mean observation period was 64 months (range 1–170 months).

Clinical findings and evaluation

Thirty-three patients showed persistent localized pain, 13 patients a growing palpable tumor. Neurological symptoms caused by spinal involvement were seen in 5 patients. A pathological fracture of the proximal femur or the humerus occurred in 3 cases. In one patient with known NHL, the routine investigation showed a bone manifestation. In 6 patients, diagnosis of lymphoma had already been established before the orthopedic evaluation, clearly defining bone involvement as being metastatic disease. Seven additional patients showed a disseminated disease with extraosseous lesions at presentation. All 6 patients with HD showed additional visceral involvement. Twenty-three of the 30 patients with NHL showed only skeletal involvement, and in 17 of them, this involvement was a solitary bone lesion (PLB). The mean duration of symptoms was 8 months (range 1–48 months). In the metastatic cases, the period was 57 months (range 9–160 months) between primary diagnosis and secondary bone involvement. The anatomical distribution of the lesions is shown in Fig. 2. In 9 patients, a non-neoplastic initial diagnosis of spondylitis, osteomyelitis, arthritis, endoprosthetic loosening, menisceal tears, or ischialgia caused a delay in the diagnosis of malignant bone lymphoma. Routine laboratory evaluations were not very helpful. Eleven patients had an increased C-reactive protein, 8 patients had a mild or moderate anemia, 7 patients had an increased LDH, and 4 patients had a raised alkaline phosphatase level. Staging included standard radiographs, bone scans (technetium-99m methyldiphosphonate) and, in most of the early cases, computed tomography (CT) of the skeletal lesions. More recently, MRI was used to evaluate the extent of the tumor. In addi-

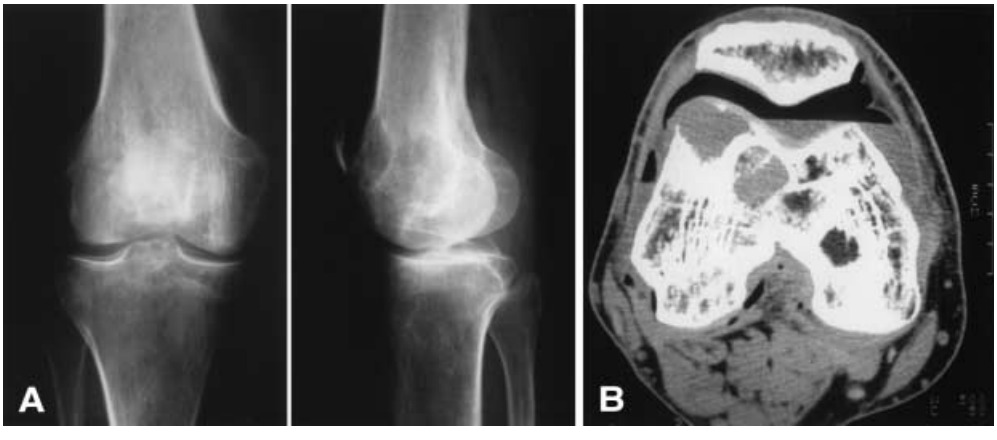

Fig. 3A,B Plain radiograph (**A**) and computed tomography (CT) scan (**B**) of a 55-year-old patient with an 8-month history of pain and swelling in the knee. Multiple moth-eaten-like osteolytic lesions with destruction of the cortex were found during arthrographic meniscus evaluation. At 53 months after chemotherapy and radiotherapy, there is no evidence of disease

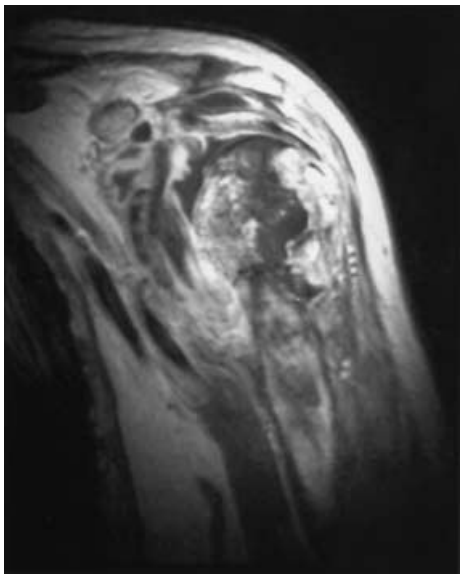

Fig. 4 Magnetic resonance imaging (MRI) of a 59-year-old patient with a known history of NHL. The coronal, T1-weighted, contrast-enhanced SE image of the proximal humerus shows a disseminated tumor infiltration of the bone with a pathologic fracture. The patient underwent resection and implantation of a tumor prosthesis. At 59 months after chemotherapy and radiotherapy, there is no evidence of disease

tion, chest radiographs, sonography of the abdomen, and CT scans were performed to determine the spread of the disease.

Radiographic patterns

The radiological pattern of the lesions was inhomogeneous. No radiological signs of tumor infiltration, multiple small intraosseous osteolytic zones (Fig. 3), extensive bone destruction (Fig. 4), or osteosclerosis were seen. Soft-tissue infiltration could be examined by CT or MRI in 31 patients. In 22 of these patients (71%), an often large soft-tissue tumor was found adjacent to the bone lesion (Fig. 5) (Table 1).

Histology

The histological results were as follows: 25 had B-cell lymphoma, 1 had T-cell lymphoma, 2 had low-malignant lymphoma, 2 had highly malignant polymorphous lymphoma, and 6 had Hodgkin‘s disease.

Surgery

To establish the diagnosis, 26 biopsies were performed: 25 incisional biopsies and 1 needle. In these cases, the stability of the affected bone was not compromised to such an extent that surgical stabilization was required. In one patient (Fig. 4) with extended disease of the proximal humerus and localized pain, resection of the tumor and implantation of a tumor prosthesis were necessary. In 2 patients with pathological fractures, a standard or tumor-endoprosthesis was implanted in the proximal femur. Resection of a destroyed lumbar vertebra was necessary in 2 cases to prevent further neurological complications, and reconstruction was carried out using either a fibular graft or a vertebral prosthesis. Four patients with spinal cord compression received dorsal decompression with an additional stabilization. Osteosynthesis was necessary in one patient. In all patients, intralesional or marginal margins were obtained.

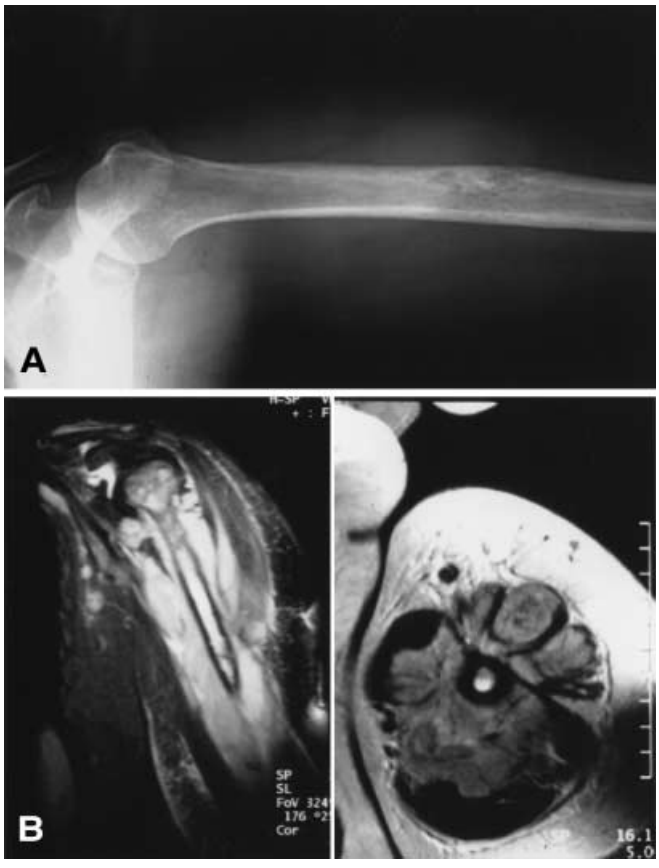

Fig. 5A,B Plain radiograph (**A**) and MRI (**B**) of a 77-year-old patient with a large soft-tissue infiltration from NHL. The radiograph shows a mixed osteosclerotic and osteolytic pattern. On MRI (coronal STIR image left, axial T2-weighted, spin-echo image right), the soft-tissue component is localized around the involved bone marrow, showing the typical growth pattern. At 18 months after chemotherapy and radiotherapy, there is no evidence of disease

Adjuvant treatment

Before surgery, 4 patients had already received some form of chemotherapy, and 1 patient had undergone radiotherapy, although not at the site of the acute lesion. After surgery, chemotherapy was necessary in 28 additional cases, while radiotherapy was necessary in 34 cases. Four patients received either chemotherapy or radiotherapy.

Results

Postoperative complications occurred in 7 patients. Two patients showed delayed wound healing, and in one case a patient with a deep infection needed to be revised. In 2 patients, secondary fractures occurred at the lesion sites. One patient with spinal involvement showed a progressive paralysis despite decompression and stabilization. One 83-year-old patient with a proximal femur resection and prosthetic replacement died 3 weeks after the intervention during chemotherapy. Overall survival is shown in Fig. 6 (Kaplan-Meier survival analysis). Survival rates were the same for non-Hodgkin’s and Hodgkin’s lymphoma (Fig. 7), but nearly all patients with Hodgkin’s dis-

Table 1 Radiologic signs of tumor involvement in 26 patients with non-Hodgkin's lymphoma and 5 patients with Hodgkin's lymphoma of the bone. In 5 patients, CT scan or MRI was not performed

	No radiographic bone lesion	Osteolysis	Osteolysis and sclerosis	Osteosclerosis	Soft-tissue tumor
Non-Hodgkin's lymphoma	7	15	3	1	20
Hodgkin's lymphoma	0	3	1	1	2
Total	7	18	4	2	22

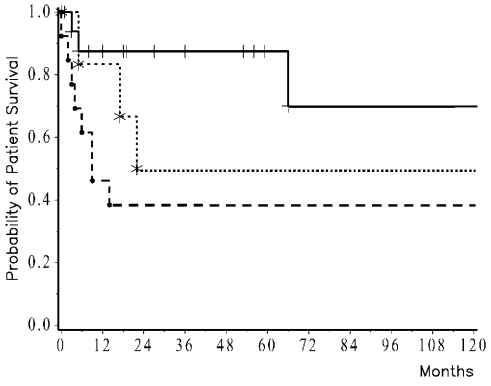

Fig. 6 Survival time after surgery in 17 patients with primary lymphoma of the bone (PLB) (+), 13 patients with multiple bone or visceral involvement by non-Hodgkin's lymphoma (dNHL) (●), and 6 patients with Hodgkin's disease (HD) (*) (p=0.0391)

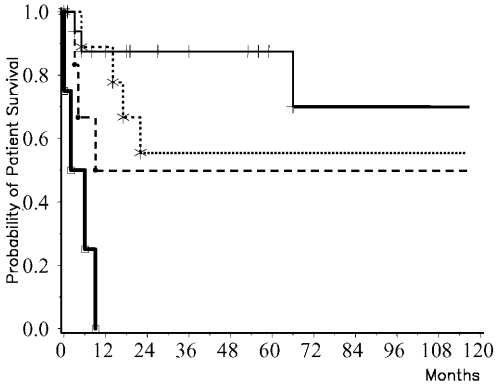

Fig. 8 Survival time in 17 patients with solitary skeletal lesions of lymphoma of the bone (+), 6 patients with multiple skeletal lesions (●), 9 patients with simultaneous extraskeletal and solitary skeletal lesions (*), and 4 patients with multiple skeletal lesions and extraskeletal involvement (❑) (p=0.0001)

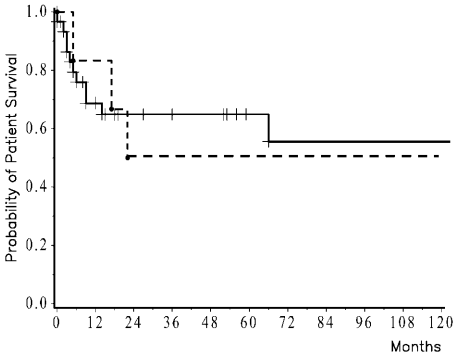

Fig. 7 Survial time in 30 patients with NHL (+) and 6 patients with Hodgkin's disease of the bone (●) after surgery

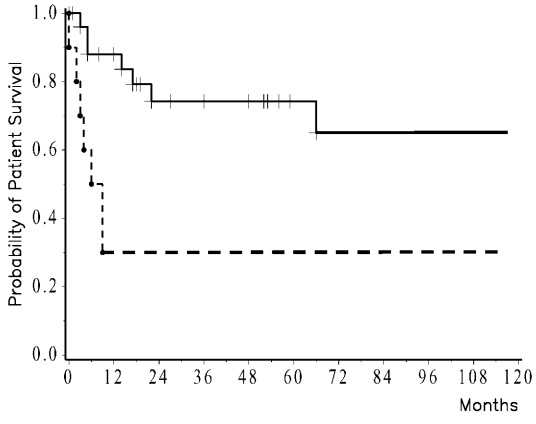

Fig. 9 Survival time in 26 patients with solitary skeletal lesions (+) and 10 patients with multiple skeletal lesions (●) of lymphoma of the bone (p=0.020)

ease showed an extensive dissemination with extraskeletal involvement. Extraskeletal involvement and skeletal dissemination proved to be highly significant prognostic factors (Fig. 8). However, the most significant one was skeletal dissemination at surgery (Fig. 9) (Table 2). Multivariant analysis using the log-rank method adjusted for gender, age, location (trunk or extremeties), skeletal dissemination (more than one lesion), and extraskeletal involvement showed significant correlations between the extent of the disease (skeletal dissemination and extraskeletal involvement) and prognosis (Table 2).

Table 2 Multivariant analysis of presumed factors influencing survival in 36 patients treated surgically for lymphoma of the bone (*SE* standard error)

Factor	Parameter	SE	Risk Ratio	P
Gender	0.911	0.607	2.488	0.1331
Age	0.030	0.021	1.030	0.1648
Location[a]	0.033	0.018	1.033	0.9577
Extraskeletal[b]	1.497	0.637	4.468	0.0188
Solitary bone[c]	1.705	0.629	5.499	0.0067

[a]Trunk, extremities
[b]Bone only, additional visceral involvement
[c]Solitary osseous, multiple osseous

Discussion

First described by Oberling in 1928 and presented in a larger series by Parker and Jackson in 1939, malignant

lymphoma of the bone has been recognized as a separate clinicopathological entity [9, 10, 11]. According to the WHO, 'primary' lymphoma of the bone (PLB) is defined as a solitary osseous lesion without involvement of other osseous or nonosseus sites within 6 months of the onset of symptoms [11]. The involvement of regional lymph nodes does not rule out the diagnosis of PLB. The classification by Rappaport has been widely accepted but is being replaced by new classification systems including modern aspects of the immune system [12, 13, 14]. As a consequence of a case study including 1177 subjects completed by the National Cancer Institute, a working formulation of non-Hodgkin's lymphoma was described in 1992 [15]. In addition to the routinely performed histological staining, the development of immunohistochemical methods has proved to be of use not only for the characterization of the lymphoma subtypes, but also for the differential diagnosis [16, 17].

Bone involvement in Hodgkin's disease is rare [18, 19]. 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. Of these patients, only 13 (3.1%) had Hodgkin's lymphoma, and none, as in our study, was limited to a single bone lesion [6].

The distribution of age and sex in the current study was similar to that in the literature. Malignant bone lymphoma was seen in all decades of life with the majority of patients being between 50 and 70 years of age and, in contrast to the literature, primarily affecting women [20, 21, 22]. PLB in children is rare, and differentiation, especially from Ewing's sarcoma, is important [23, 24]. The treatment is analogous to that for adults [25]. The differential diagnosis generally considers all round-cell lesions of bone [26]. Histological typing may be difficult and sometimes impossible in high-grade malignant lymphomas [27]. In 2 of our cases, the primary histological diagnois was undifferentiated sarcoma, revised after discussing the typical radiological aspects of the cases.

All bones may be affected, but a central location is common. Nonspecific symptoms, such as local pain and swelling, may be the only signs of the disease. The duration of these symptoms is usually over a long period of time (as shown above), with a mean of more than 1 year. B-symptoms including fever, sweating, or weight loss occur as in any other lymphoma condition [28]. Pathologic fractures are, as shown here, not uncommon.

In more than two-thirds of the cases, PLB is seen as an osteolytic bone lesion (58% in our study). Osteoblastic or mixed appearences (sometimes with sequestra [29]) are possible as shown [30, 31]. Even a normal bone pattern may occur, despite a disseminated long-lasting disease. The metaphyseal location is predominantly affected, due to the distribution of bone marrow [32]. Nuclear bone scans may produce false-negative results due to the predominantly osteolytic character of the lesions [33]. But as shown in ^{99m}Tc-methylene diphosphonate bone imaging, the accuracy of site identification was 98% in a series of 107 examinations [34]. Simultaneous use of bone-scintigraphy and plain films is most helpful in distinguishing solitary and multiple bone involvement. Bone marrow scintigraphy with ^{99m}Tc-marked microcolloid in combination with MRI followed by a guided bone-marrow biopsy has proven to be more sensitive than a biopsy alone [35, 36]. ^{67}Ga-scintigraphy may also be useful, especially in lymphomas with soft-tissue involvement. ^{67}Ga has not been shown to be superior to ^{99m}Tc for bone lesions [37]. Radioimmunoimaging with ^{99m}Tc-labelled murine monoclonal IgG_1 antibody was established as a cost-effective, sensitive and easy to perform method for evaluating metastatic spread [38, 39].

Soft-tissue involvement in PLB is common, affecting 71% of the patients in our study. As shown in Fig. 6, despite moderate bone destruction, a huge soft-tissue mass may be present. This is a major indication for using MRI in PLB. In our experience, a large soft-tissue tumor extending concentrically around the bone with infiltration of the bone marrow in the typical age group of patients is the major clue to the diagnosis. One could call it an 'Ewing-like' pattern in adults aged 50 years or older. MRI is also effective in determinating bone marrow involvement in PLB [40, 41]. However, the imaging characteristics of bone marrow in MRI vary depending on vascularity and fibrosis [42, 43]. Staging should be completed by using CT or sonography to evaluate the possible systemic spread of the lymphoma. As mentioned by Schajowicz and proved in our study, systemic spread has a much worse prognosis than PLB, although morphologically they are indistinguishable [11].

The treatment is primarily conservative in nature. Surgical intervention is restricted to cases with neurological complications, impending fracture, or fracture [44, 45]. As shown at Mount Sinai Hospital in a thoroughly performed analysis of 15 consecutive patients, 7 needed more than one biopsy in order to obtain enough material for the histological diagnosis [46]. Immunohistochemical workups especially require adequate, well-prepared biopsy material. In our cases, incisional biopsy was therefore used, with only one exception.

Surgical complications are linked to the patients' occasionally poor preoperative general condition and immune status. This explains our results of 8% delayed wound healing or deep infection and one death shortly after surgery during chemotherapy.

At the present time, there are no general protocols or sound data for applying chemotherapy or radiotherapy. The optimal timing of radiation and chemotherapy in PLB 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 [47]. This procedure is used in our clinic. In some institutions, local radiation alone is recommended [48, 49]. In contrast, adjuvant chemotherapy, mainly used to prevent systemic disease, may also reduce the incidence of local recurrence in PLB and improve the prognosis in children and adults with disseminated disease [50, 51, 52]. Despite the lack of an adequate phase III trial, the combined treatment modality is sup-

ported by the strong evidence that this provides a significant therapeutic benefit for localized extraskeletal NHL [53, 54, 55]. Assessment of the response to therapy in PLB is a major concern [56]. All forms of nuclear scans, as well as MRI, are not entirely adequate to differentiate between residual or persistent tumors and healing bones.

In defining the prognosis of PLB, several prognostic factors have been established. In their large study of 422 patients, Ostrowski et al. were able to demonstrate the most predictable positive value of single bone involvement [6]. The 5-year survival rate was 58% compared with 42% in multifocal osseous disease. That is in accordance with our own data of a 5-year survival of 70% in single bone involvement and 50% in multifocal osseous disease (Fig. 9). The correlation between the site of the primary lesion and the prognosis is controversial. Having found no correlation in one study [57], Ostrowski was able to reveal highly significant differences. 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 this study, a significant influence of trunk vs extremity lesions could not be shown. This might be a result of the advances obtained in the past few decades of radiotherapy in critical locations. Advanced age was also negatively associated with a reduced chance of survival. Despite a trend in our data in this same direction, a significant influence of age could not be shown.

The lack of prognostic significance of the histological typing in the above-mentioned study and our own series is not surprising, considering that data for the present series were collected over a relatively long period of time with different methods of diagnoses and treatments. Even in detailed pathohistological studies, the influence of grade and type has remained unclear [58, 59]. Surprisingly, in the Mayo Clinic study, no influence of different treatment modes on recurrence and survival rates could be found [60].

In conclusion, primary lymphoma of bone is a rare clinical entity. As shown, bone involvement appears late in the course of the extraskeletal disease. Thorough investigation of systemic manifestations is therefore highly recommended. The clinical appearance is not specific, and the delay between onset of symptoms and diagnosis is often long. One of the major radiologic signs is a large soft-tissue tumor surrounding the bone with little or no bone involvement on plain films. The treatment in general is conservative, based on the stage of the disease. There is no definite therapeutic scheme. Local radiation is recommeded, and additional systemic chemotherapy seems to be effective. The long-term survival is based on the stage of the disease, favoring patients with solitary bone lesions.

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