Abstract. Primary lymphomas of bone are uncommon malignancies. The vast majority of them are non-Hodgkin lymphoma (NHL), whereas primary Hodgkin lymphoma (HL) of bone is extremely rare. Patients with primary NHL of bone commonly present with local bone pain, soft tissue swelling, and a mass or a pathological fracture. There is a slight male preponderance, and most patients are over 45-50 years of age. Primary NHL of bone can arise in any part of the skeleton, but long bones (femurs, tibia) are the most common sites of presentation. Comprehensive immunohistochemical studies are required to establish an accurate histological diagnosis of primary NHL of bone. Most cases of primary NHL of bone are classified as diffuse large B-cell lymphomas (DLBCL) in the World Health Organisation (WHO) classification of hematological malignancies. On full staging evaluation, most patients have disease of stage IE or IIE according to the Ann Arbor system. Several studies indicate that patients with primary NHL of bone have a favorable outcome, especially when treated by combined modality therapy. A number of studies reported that clinical stage is the most important prognostic variable in predicting overall survival. Interestingly, the rare occurrence of primary lymphoma of bone is in contrast with the frequency of plasma cell tumors in bone, which typically present as unique or multiple osteolytic lesions (multiple myeloma). The fact that the bone marrow is the normal site of homing of plasma cells during normal B-cell differentiation may provide an explanation for the preferential occurrence of plasma cell tumors in bone. Plasma cells are functionally defined as terminally-differentiated, immunoglobulin (Ig)-secreting post-germinal center B-cells, and the possibility that primary bone lymphoma represent tumors of post-GC B-cells might be suggested (31). Therefore, the present review summarizes data on the histogenesis of primary NHL of bone in view of the recent histogenetic classification of DLBCL on the basis of the B-cell differentiation gene expression profiles (germinal center vs. post-germinal center B-cell differentiation).

Primary lymphomas of bone are uncommon malignant neoplasms. Primary non-Hodgkin lymphoma (NHL) of bone comprises approximately 7% of malignant bone tumors, 5% of extranodal lymphomas and <1% of all NHL (1-71). Oberling first described primary lymphoma of bone in 1928 (7). The first series of cases was reported by Jackson and Parker (8) in 1939. They described 17 cases of so-called primary reticulum cell sarcoma of bone and established primary NHL of bone as a distinct clinical entity. The lymphoid nature of these lesions was subsequently recognized, and most cases have proven by immunohistochemistry to be of B-cell derivation (9-13, 25-36). Primary Hodgkin lymphoma (HL) of bone are extremely rare, and the majority of patients have concurrent nodal HL (mostly nodular sclerosis) detected at staging (3, 39, 72-85). The present review summarizes the clinical, epidemiological, radiological and histological features as well as the treatment modalities and the prognostic factors in primary lymphomas of bone (1-85). Little is known about the histogenesis of these extranodal lymphomas. Interestingly, the rare occurrence of primary lymphoma of bone is in contrast with the frequency of plasma cell tumors in bone, which typically present as unique or multiple osteolytic lesions (multiple myeloma). The fact that the bone marrow is the normal site of homing of plasma cells during normal B-cell differentiation may provide an explanation for the preferential occurrence of plasma cell tumors in bone. Plasma cells are functionally defined as terminally-differentiated, immunoglobulin (Ig)-secreting post-germinal center (GC) B-cells, and the possibility that primary bone lymphoma represent tumors of post-GC B-cells might be suggested (31). Therefore, the present review summarizes data on the histogenesis of primary NHL of bone in view of the recent histogenetic classification of DLBCL on the basis of the B-cell differentiation gene expression profiles (germinal center vs. post-germinal center B-cell differentiation).
of bone in view of the recent molecular and immuno-
histochemical histogenetic classification of B-cell neoplasms
on the basis of the B-cell differentiation gene expression
profiles (GC and post-GC B-cell differentiation profiles)
(86-105).

Non-Hodgkin’s Lymphomas of Bone

Clinical findings. Patients with primary NHL of bone
commonly present with local bone pain, soft tissue swelling
and a mass or a pathological fracture (18-20, 42). There is a
slight male preponderance, and most patients are over 45-50
years of age. Pediatric cases have also been reported (23).
Primary, NHL of bone can arise in any part of the skeleton,
but long bones (femurs, tibia) are the most common site of
presentation, followed by the pelvis and spine, with the
scapula, maxilla and mandible accounting for most of the
remaining cases (18-20, 42). On full staging evaluation, most
patients have disease of stage IE or IIE according to the
Ann Arbor system (17, 18, 26, 31, 32, 54, 68). Nodal
involvement is uncommon.

Radiological findings. If biopsy of a bone lesion reveals
NHL, the question arises whether this is a primary bone
NHL or a secondary localization of primary nodal NHL.
Thus, comprehensive lymphoma staging is required,
including conventional X-ray, abdominal ultrasound,
computed tomography (CT) scans, magnetic resonance
imaging (MRI), technetium bone scanning and a bone
marrow biopsy (45-67). There is a wide spectrum of findings
related to the radiographic appearance of primary bone
NHL, ranging from a near-normal bone appearance to a
focal lytic lesion with geographic margins or a diffusely
permeative lesion with bone destruction and soft-tissue
involvement. Despite these multiple imaging features, the
presence of a solitary, permeative osseous lesion located in
diaphysis of a long bone with layered periosteal
reaction and very little cortical destruction on plain X-rays
and a soft-tissue mass on CT and MR images is highly
suggestive of primary bone NHL (45-67).

On conventional X-ray examination, primary NHL of
bone shows variable changes, including lytic lesions or
blastic lesions (20, 22, 41, 44). Cortical erosion or
destruction may occur, but there is usually little periosteal
reaction (18). In younger patients, the differential diagnosis
of primary NHL of bone mainly includes osteosarcoma,
Ewing’s sarcoma and osteomylitis; in older patients, bone
metastasis of solid tumors should be considered (47, 55, 63).
Primary NHL of bone is frequently manifested as a
pathological fracture (51). Technetium bone scanning may
reveal increased uptake at the periphery of a primary NHL
of bone lesion, with a central area of decreased uptake (18).
Similar to conventional X-ray, the findings of bone scanning
are not specific for primary NHL of bone. CT is useful for
demonstrating soft tissue extension and may show marrow
or cortical involvement not apparent on plain
roentgenogram (17).

MRI is essential in the imaging investigation of primary
NHL of bone (53, 57) due to the excellent demonstration of
the following features: i) Bone marrow replacement, as
areas of low signal in T1-weighted images and bright signal
in T2-weighted images. Short time inversion recovery
(STIR) images also distinguish normal from abnormal
marrow. After Gadolinium administration, areas of
enhancement can be demonstrated within the lesion. ii) Soft-tissue mass. The combination of a lytic-permeative
lesion with a soft-tissue component is very usual in cases of
primary NHL of bone and MRI is the modality of choice in
order to depict soft-tissue involvement. Cortical destruction
is usually minimal. iii) Cortical erosion. Although this
finding can be depicted both by CT and MR imaging, the
erterm permits early detection. Although MRI was reported as
the most sensitive imaging technique in the diagnosis of
primary NHL of bone (53, 57), Charousset et al. (35)
reported that Technetium scintigraphy is more sensitive
than MRI and more specific for diagnosis of these tumors.
Moreover, based on their follow-up examinations, Misgeld
et al. (30) suggested that MRI may not reliably differentiate
between persistent lymphoma and healing bone and that
Positron Emission Tomography (PET) may be preferable
for assessing remission status. PET imaging is the most
recent modality that may be used in follow-up of
malignancies and it is considered the most sensitive method
available nowadays. Two cases of primary bone NHL have
been reported in the literature (65, 66), which compared the
follow-up between PET scan with F-18 Fluorodeoxyglucose
and MRI and suggested that PET is superior in the
evaluation of primary bone NHL. PET imaging in primary
bone NHL needs to be further investigated.

Krishnan et al. (47) reviewed 20 cases with regard to the
imaging features previously reported in the literature, and
presented the following classification of radiographic
patterns: i) The lytic-destructive pattern. It is the most
common and may be further differentiated into permeative
and moth-eaten pattern, depending on how poor the margins
of the lesion are and how uniform the radiolucent area is.
Lamellar or layered periosteal reaction has also been
reported in most of the cases with lytic primary bone NHL.
The above features may be accompanied by cortical
interruption, sequestra and soft-tissue mass, perhaps
suggestive of a more aggressive tumor which can be depicted
more clearly by computed tomography (CT). ii) The blastic-
sclerotic pattern. It is rare and sometimes a mixed lesion with
lytic and sclerotic areas can be depicted. The rare type of
primary HL of bone may have this appearance. In addition,
sclerotic areas may develop in PBL after radiation therapy
and chemotherapy. iii) Subtle or "near-normal" findings. In some cases plain X-rays are unable to demonstrate any remarkable findings despite the clinical symptoms. In those cases bone scintigraphy and MRI can depict the lesion clearly whereas CT is superior to plain X-rays but is not able to depict the full extent of the lesion.

Of particular interest is the finding that in primary bone NHL the soft-tissue mass and marrow changes are associated with surprisingly little cortical destruction (44, 47, 55). An explanation for the MR images of minimal cortical changes despite an accompanying soft-tissue mass (44, 55-57) is offered by one study in which MRI of primary intramedullary lymphomas of bone demonstrated penetrating channels that extended through the cortex in proximity to osteoclastic bone resorption (56). In this study, it was demonstrated by immunohistochemistry that the bone lymphoma cells are immunoreactive for cytokine mediators (interleukin-1, interleukin-6 and tumor necrosis factor) that may stimulate extensive osteoclastic activation (56). The authors suggested that tumor activation of osteoclastic resorption, with production of tumor channels through the cortex, may represent one of the mechanisms by which lymphoma escapes the intramedullary space and forms soft-tissue masses without extensive cortical destruction (56).

MRI is useful for the differential diagnosis between primary lymphoma of bone and other bone tumors. Haussler et al. (55) investigated the pattern and dimension of cortical bone abnormality on MRI as a feature to distinguish primary lymphoma of bone from osteosarcoma and Ewing’s sarcoma. They studied 46 patients with primary malignant bone lesions with a soft-tissue mass (16 osteosarcomas, 15 Ewing sarcomas, 15 lymphomas). Qualitative image analysis revealed no differences for signal characteristics and enhancement. Lymphomas showed significantly more often homogeneous appearance (47%; Ewing sarcoma 20%; osteosarcoma 6%), significantly less frequent cortical abnormality (60%; Ewing sarcoma 87%; osteosarcoma 100%), significantly less frequent complete penetration (13%; Ewing sarcoma 40%; osteosarcoma 81%) and significantly less frequent complete destruction (0%; Ewing sarcoma 13%; osteosarcoma 19%).

Precise knowledge of the radiological morphology and of the time-course of changes of successfully treated primary NHL of bone helps to differentiate residual tumor and recurrence from non-specific abnormalities. Although, the imaging appearance of primary NHL of bone before treatment is well documented (45, 56), the differentiation of residual tumor and treatment-associated changes, including tumor necrosis and granulation tissue, may be difficult on MR images of bone tumors after treatment (58, 59). There are some reports about MRI features of primary bone lymphoma after treatment (48, 60-62). In some patients, no significant size reduction of bone marrow abnormalities (61), prolonged persistence of signal abnormalities (62), or even progression of the MRI findings despite clinically complete remission (60) were reported.

Indeed, Stroszczynski et al. (61) investigated the value of MRI and Gallium scintigraphy for the staging and for the accuracy in detecting residual disease after first-line chemotherapy of 21 cases of bone lymphomas. They studied both primary lymphoma of bone and secondary involvement of bone by extraosseous NHL and HL. Dynamic contrast-enhanced MRI had a sensitivity of 90% and a specificity of 80%. Ga scintigraphy had a sensitivity of 70% and a specificity of 93% for evaluating tumor activity. The standard of reference was based on clinical, radiological (radiography, CT and bone scintigraphy) and histological data. The authors concluded that both methods are valuable but should be used as complementary diagnostic tools.

Yuki et al. (62) described a case of primary lymphoma of bone in complete remission, monitored with Ga citrate, 99m Tc hydroxymethylene diphosphonate, and 201Ti scintigraphy and MRI. Gallium-67 citrate scintigraphy detected the change in tumor activity very rapidly, whereas bone marrow signal abnormalities persisted on MRI after 6 cycles of chemotherapy.

Melamed et al. 1997 (60) described 5 cases of multifocal primary lymphoma of bone monitored with MRI after treatment. Despite complete remission, the authors described progression of most of the lesions on MRI. However, they did not describe the MRI criteria of progression in these patients. Mengiardi et al. (48) and Mulligan et al. (45) reported that the signal characteristics of primary lymphoma of bone before treatment were non-characteristic and uniform. During treatment, signal intensities and pattern of enhancement were not altered (48). Necrotic areas (as diagnosed on the basis of MRI criteria) were rarely observed before and during therapy. In two patients in whom histological examination of the bone marrow biopsy was available during therapy, necrosis and inflammatory changes were detected microscopically (48). The findings of Mengiardi et al. (48) underline the fact that MRI signal abnormalities may not differentiate bone marrow abnormalities after treatment from an active neoplasm (59). Mengiardi et al. (48) concluded that: a) MRI shows a rapid decrease of tumor volume with complete disappearance of the soft-tissue component; and b) minor MRI signal abnormalities of bone marrow without clinical relevance persist for up to 2 years.

CT of the chest and abdomen is often performed to monitor patients with lymphoma, and the involved bone is commonly visible on these scans. However, CT may not be able to differentiate treatment effects from residual tumor. CT is less commonly used than MRI in the follow-up of bone and soft-tissue neoplasms. However, it is important to know the CT appearance of primary NHL of bone because
CT is used for thoraco-abdominal staging and follow-up examinations that may include the bones most commonly involved in primary NHL of bone (18). Israel et al. (67) reported that CT abnormalities may persist even one year after treatment, with a tendency to show a decrease of initially predominant osteolysis accompanied by an increase of sclerosis. Mengiardi et al. (48) reported that even large osteolytic lesions with aggressive appearance showed, within 2 months, some remodeling of bone. In the ensuing months, this primitive type of bone showed slow differentiation into cortical and trabecular bone with persistence of a coarse pattern for the observed period of time (≤3 years). This appearance has some resemblance to the bone abnormalities seen in Paget’s disease. On the basis of their findings, Mengiardi et al. (48) concluded that CT showed bone remodeling within months with a persistent architecture similar to that of Paget’s disease of bone.

Conclusively, the imaging investigation in case of a bone lesion suspicious for primary NHL of bone requires plain X-rays and/or CT scan in order to depict the radiographic features of the lesion. The CT scan is more important in terms of a percutaneous guided-biopsy and as a baseline examination before treatment, since it is used for thoraco-abdominal staging and follow-up (46). MRI is the examination of choice for detection of the lesion and is also valuable in cases of multifocal primary NHL of bone (48). 67Ga scintigraphy and MRI are the most effective and widely available methods of follow-up, compared to CT whereas PET imaging is the most recent and sensitive method that needs further evaluation (45-48, 60, 63-67).

**Histological findings.** Histological and immunohistochemical evaluation revealed that most primary NHL of bone are classified as diffuse large B-cell lymphomas (DLBCL) (Figure 1) in the Revised European-American Lymphoma (REAL) classification and the WHO classification of hematologic malignancies (11, 14-36). According to the Kiel classification, primary NHL of bone has usually been classified as centroblastic-centrocytic lymphoma or centroblastic lymphoma (3). According to the Working Formulation, primary NHL of bone has usually been classified as B-cell lymphoma of follicular center cell origin with diffuse mixed or diffuse large cell histology (20, 22). It is noteworthy that large multilobated tumor cells can be observed in many cases of large cell lymphomas of bone (18-36). An accurate histological diagnosis of large cell lymphomas of bone may be difficult because of: a) the accompanying fibrosis that ranges from delicate reticulin fibrosis to collagen fibrosis and to abundant, dense sclerosis with ostoid formation; b) the decalcification and crush artifacts; and c) the observations that the large lymphoma cells may have spindle-shape appearance or may form small clusters that resemble carcinoma (3, 72). Thus, an extensive immunohistochemical study is required to establish the accurate diagnosis of primary DLBCL of bone.

A comprehensive immunohistochemical panel should include antibodies against B-cell (CD20 and CD79a) and T-cell antigens (CD3), the leucocyte common antigen (LCA/CD45), cytokeratins, vimentin, desmin and neurofilaments. In addition to DLBCL, other lymphoid malignancies may manifest with primary bone presentation, including atypical Burkitt’s lymphomas, follicular lymphoma, small B-cell lymphomas, B-cell lymphoplasmacytic lymphomas, anaplastic large cell lymphomas, peripheral T-cell lymphomas, HL and precursor B-cell lymphoblastic lymphomas (12, 25, 32, 37-41). Precursor B-cell lymphoblastic lymphoma of bone often manifests as a lytic lesion and should be differentiated from other small round cell tumors of bone, particularly Ewing’s sarcoma, which was the initial diagnosis in all four cases reported by Ozdemirli et al. (40). Thus, an extensive immunohistochemical study is required to establish the diagnosis of precursor B-cell lymphoblastic lymphoma of bone including antibodies directed against CD10, CD20, CD43, CD79a, CD99 (MIC2 gene product) and terminal deoxynucleotidyl transferase (Tdt) (40, 41). Small lymphocytic lymphoma with plasmacytic features (lymphoplasmacytic lymphoma) are more often described in Japan than in the West (37). Peripheral T-cell lymphomas occasionally arise in bone and have been reported in the mandible (12, 25); in Japan, 10% of primary NHL of bone have a T-cell immunophenotype (37).

Besides the aforementioned diagnostic immunohistochemical panel of antibodies, other immunohistochemical parameters, including the proliferation-associated protein Ki-67/MIB-1, the tumor suppressor protein p53 and the anti-apoptotic protein bcl2, were investigated in primary NHL of bone, (5, 31, 32, 34). The Ki-67/MIB-1 index was always high with a mean value of 70% in DLBCL of bone (32). p53 immunoreactivity was detected in 55% of cases of DLBCL of bone (5). Bcl2 immunoreactivity was detected in 35-60% of cases (5, 31, 32, 34), but no Bcl2/JH gene rearrangement was found by polymerase chain reaction in DLBCL of bone (5). In contrast, a clonal B-cell population was demonstrated by IgH gene rearrangement studies using polymerase chain reaction in 54-72% of DLBCL of bone (5, 34).

**Etiology.** The etiology of primary NHL of bone is unknown, although it has been reported that these extranodal lymphomas might be related to immunological disorders, viruses, karyotype disorders or traumas (36).

**Histogenesis.** The histogenesis of primary NHL of bone remains unclear. Histogenetic investigation with respect to the B-cell differentiation immunophenotypic profiles has been performed only in DLBCL (31, 32). De Leval et al.
(31) suggested that most cases of DLBCL of the bone probably arise de novo, with no evidence of a transformation of pre-existing small B-cell proliferation. The investigations of de Leval et al. (31) and Zinzani et al. (32) were based on the evidence that most nodal and extranodal DLBCL harbor somatic mutations in the variable regions of their immunoglobulin genes, a hallmark of the germinal center (GC) reaction, leading to the concept that most DLBCL derive from GC B-cells or their descendants (i.e., post-GC B-cells) (86). By analogy with normal B-cell differentiation, it has been hypothesized that the two major morphological variants of DLBCL (centroblastic and immunoblastic) might reflect, respectively, the GC and post-GC derivation of the tumors (31). The increased understanding of the pathobiology of DLBCL has been made possible by using cDNA and oligonucleotide microarrays for the analysis of the global gene expression profile of DLBCL (86-93). On the basis of the B-cell differentiation gene expression profiles, three molecularly distinct histogenetic groups of DLBCL have been identified: the GC B-cell-like DLBCL, the activated B-cell-like DLBCL and the type 3 DLBCL (88-93). The GC B-cell-like DLBCL were characterized by the expression of genes of the normal GC B-cells (e.g., bcl6, CD10, CD38), the activated B-cell-like DLBCL were characterized by the expression of genes that are normally induced during in vitro activation of peripheral blood B-cells, while the type 3 DLBCL did not express either set of genes at a high level (88-92). The DLBCL gene expression subgroups have distinct mechanisms of malignant transformation, which indicates that they are pathogenetically distinct diseases. Indeed, the translocation t (14;18), which involves the bcl2 gene, the amplification of the c-REL locus on the chromosome 2p and ongoing immunoglobulin somatic mutations, were observed in GC B-cell-like but not in activated B-cell-like DLBCL (88-92). By contrast, activated B-cell-like DLBCL are characterized by activation of the NF-κB pathway and high expression levels of NF-κB target genes, including those that encode the interferon regulatory factor 4 (IRF4/MUM1), the cell adhesion molecule CD44, the anti-apoptotic genes c-FLIP, bcl2, bcl-xL, TRAF1, TRAF2, c-IAP1 and c-IAP2 and the cell cycle-associated gene cyclin D2 (88-92). With respect to the clinical relevance of the molecular classification of DLBCL, patients with GC B-cell-like DLBCL had more favorable clinical outcome than those with activated B-cell-like or type 3 DLBCL (88-92). Since the cDNA microarray technology is not generally available, many studies have successfully used immunohistochemical analysis for the histogenetic classification of DLBCL in routine histopathology specimens (94-101). Of importance is the study of Hans et al., who correlated cDNA microarrays and immunohistochemistry in order to examine the reliability of bcl6/CD10/MUM1 B-cell differentiation immunophenotypes for classifying DLBCL (96). They showed that the classification of DLBCL into GC and non-GC B-cell-like groups, based on the bcl6/CD10/MUM1 B-cell differentiation immunophenotypes, is prognostically relevant and predicts the cDNA classification in 71% of GC B-cell-like and 88% of activated B-cell-like or type 3 DLBCL (96).

In view of the aforementioned information, it is interesting to analyze the contrast between the rare occurrence of bone lymphoma and the frequency of osseous plasma cell tumors such as multiple myeloma. Plasma cells are functionally defined as terminally differentiated, immunoglobulin (Ig)-secreting post-GC B-cells, and the fact that the bone marrow is the normal site of homing of plasma cells during normal B-cell differentiation may provide an explanation for the preferential occurrence of plasma cell tumors in bone (31). On this basis, De Leval et al. (31) hypothesized that DLBCL involving the bone are likely to be derived from B-cells at a post-GC stage of differentiation. To test this hypothesis this group analyzed the histogenesis of primary bone DLBCL by using the histogenetic panel bcl6, CD10, MUM1, CD138 and VS38c. Almost half of the tumors (14/29 cases) were bcl6+/CD10+ (GC-like immunophenotype), 9/29 cases were bcl6+/CD10- (indeterminate immunophenotype), and 6/29 cases were bcl6-/CD10- (post-GC immunophenotype). The indeterminate immunophenotype was seen only in primary bone lymphomas. MUM1 was frequently detected in GC-like and non-GC-like categories. No evidence for plasmacytic differentiation by CD138 and VS38c was found. CD44 expression was seen in 6/29 cases, all of them being of a non-GC signature. Although CD44 expression is thought to possibly reflect an increased capacity for dissemination of tumor cells, most CD44-positive tumors were localized to bone and none of them recurred. The authors concluded that: a) a GC-like B-cell differentiation immunophenotype characterizes roughly half of large cell lymphomas of bone and is associated with improved survival; b) the primary bone lymphoma had an immunophenotype suggesting a later stage of differentiation (indeterminate and post-GC) than the cases with disseminated disease, the majority of which had a GC-like differentiation immunophenotype; and c) true morphological or immunophenotypic plasmacytic differentiation was not detectable (31). Zinzani et al. (32) showed that among DLBCL involving bone 16/37 cases expressed the CD10 protein and 16/30 cases expressed the Bcl-6 protein. The CD138 protein was expressed by a small minority of the neoplastic cells in some cases, thus confirming the impression that none of the DLBCLs evaluated had immunoblastic morphology (32). Based on these findings, these authors stated that more than 50% of evaluable DLBCLs showed a immunophenotypic profile consistent with a GC cell derivation. However, neither the MUM1 immunostaining was performed nor the bcl6/CD10 immunophenotypic patterns were analyzed in order to gain more insight in the histogenesis of DLBCL of bone in this series. In addition, Huebner-Chan et
al. (5) and Gianelli et al. (34) reported bcl6 positivity in 6/20 and 22/32 DLBCL of bone, respectively, but the bcl6/CD10/MUM1/CD138 histogenetic immunophenotypic patterns were not analyzed.

**Treatment and prognosis.** Cure of primary NHL of bone by surgery alone is no longer considered appropriate. Unlike other bone tumors, the role of surgery in the treatment of primary NHL of bone is now limited to the diagnostic biopsies and the management of pathological fractures that either present at initial diagnosis or arise during the peri-or post-treatment period (18). For a long time, the therapy of localized stages IE and IIE according to the Ann Arbor classification was traditionally based on radiation therapy to the involved bone and local lymph drainage (3, 19, 21). In recent years, however, combined radiochemotherapy (combined modality treatment) has often been employed for localized as well as for advanced stages of primary NHL of bone (16-20, 28, 32, 35, 44, 54). With respect to prognosis, several studies indicate that patients with primary NHL of bone have a favorable outcome, especially when treated by combined modality therapy (26, 30, 32, 43, 68-71). Reported 5-year survival rates ranged from 60% to 90% (26, 30, 32, 43, 68-71). Because of the rarity of primary NHL of bone, the variability of histological criteria that have been used for classification and the variability in treatment strategies, no prognostic factors have been clearly identified or widely accepted. However, some studies reported that clinical stage is the single most important prognostic variable in predicting overall survival in patients with primary NHL of bone (3, 22).
The presence of a soft-tissue swelling has been suggested to indicate an increased risk of relapse with unfavorable prognosis (52). In addition, an immunoblastic morphology has been reported as predictive of an adverse prognosis (26). Furthermore, age at diagnosis has been reported as a predictive factor of survival with patients older than 60 years at presentation, with a worse overall survival and a worse progression-free period (26, 29, 70).

The treatment results of the large series of bone lymphomas are summarized below.

Dorsoretz et al. (21) evaluated 30 patients with primary NHL of bone (histological classification: cleaved, non-cleaved and pleomorphic lymphomas according to the Working Formulation). All patients received radiotherapy to a dose of 45-50 Gy. Disease-free survival and overall survival at 5 years were 53 and 63%, respectively. The cumulative incidence of local recurrence was 14% at 5 years. No local failures were observed when tumors received doses higher than 50 Gy. The authors recommended irradiating the entire affected bone to 45 Gy and the tumor and immediately adjacent soft-tissue to 55 Gy.

Mendenhall et al. (17) evaluated 21 patients with primary NHL of bone who received combined modality treatment (n=1), radiotherapy alone with a dose of 40-45 Gy (n=9), and chemotherapy alone (n=1). Chemotherapy involved either an anthracyclin-containing regimen or nitrogen mustard, oncovin, procarbazine and prednisone. The overall 5-year survival was 56% in these series. There was no clear-cut advantage for either combined modality treatment or radiotherapy. Fairbanks et al. (19) evaluated 63 patients with primary NHL of bone of stage IE disease (histological classification: 43 diffuse large cell, 13 diffuse mixed cell, 3 small non-cleaved and 4 unclassified according to the Working Formulation). They did not find any apparent differences between combined modality treatment (including CHOP or CHOP-bleomycin) and radiotherapy alone. They favored radiotherapy with a dose of at least 40 Gy, but recommended combined modality treatment for patients with bad prognostic features, i.e., bulky disease or pelvic involvement.

Dubey et al. (20) evaluated 45 patients with primary NHL of bone (histological classification: 41 diffuse large cell, 2 diffuse mixed cell, 1 lymphocytic and 1 lymphoblastic according to the Working Formulation). Chemotherapy was generally doxorubicin-based. Radiotherapy usually involved 40-60 Gy. No significant advantage of the combined modality treatment (with<50 Gy) vs. radiotherapy alone (with >50 Gy) was proven for the patients with stage IE or IIIE. However, the authors recommended combined modality treatment (with irradiation in the range of 45 Gy) for intermediate grade primary NHL of bone because they observed a higher rate of relapse without chemotherapy.

Heyning et al. (26) retrospectively analyzed 60 cases of primary NHL of bone to determine clinical factors affecting prognosis in relation to the histological subtype and treatment outcome. All 33 cases that could be immunophenotyped were of B-cell origin. According to the REAL classification, most tumors were large B-cell lymphomas (92%) and according to the Kiel classification 45% of the tumors were centroblastic multiloblated. Primary NHL of bone 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 older than 60 at presentation 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 worse survival than the centroblastic subtype (p=0.015).

Suryanarayan et al. (23) reported the treatment results of 31 cases of localized primary NHL of bone in children (histological classification: 21 large cell lymphomas, 5 lymphoblastic lymphoma, 2 small non-cleaved cell lymphoma and 3 unclassified lymphoma according to the Working Formulation). Seven patients received radiotherapy and the remaining patients chemotherapy. Since there have been no deaths, the authors concluded that localized primary NHL of bone is curable in most children and adolescents with chemotherapy of modest intensity and radiotherapy is an unnecessary adjunct.

Brousse et al. (29) evaluated 28 patients with NHL of bone and compared the outcome of primary and secondary NHL of bone; they found that the overall 5-year survival was better in the primary bone lymphoma group (65%) than in the secondary lymphoma group (40%).

Zinzani et al. (32) evaluated 52 patients with primary NHL of bone (histological classification: 44 diffuse large B-cell lymphomas, 2 atypical Burkitt's lymphomas, 2 anaplastic large cell lymphoma of T-cell derivation, 2 follicular lymphoma and 2 small B-cell lymphoma according to the REAL classification). They observed a complete response in 35/41 (85%) patients treated with chemotherapy with/without radiation therapy and in 7/11 (64%) patients who received radiation therapy alone. Relapses were observed in only 2/35 (6%) patients after chemotherapy (with/without radiation therapy), as compared with 4/7 (57%) patients after radiation therapy alone (p=0.004); the relapse-free survival curves of these two subsets were significantly different. At both univariate and multivariate analysis only the type of front-line therapeutic approach (chemotherapy with/without radiation therapy vs. radiation therapy alone) turned out to have a significant prognostic influence. The data from this study indicated that in primary NHL of bone the use of chemotherapy or combined-modality therapy seems to
provide more durable complete responses than radiation therapy alone. On the other hand, the prognostic value of various immunohistochemical parameters was evaluated in DLBCL of bone but no significant differences, regarding response to therapy, overall survival and relapse-free survival, were observed on the basis of CD10, Bcl6 and Bcl2 immunopositivity.

De Leval et al. (31) evaluated 29 patients with DLBCL presenting with bone involvement (18 localized primary lymphoma of bone, 2 multifocal primary lymphoma of bone and 9 with extraskeletal disease). Most patients were treated with combined modality treatment. Most cases had a good outcome; 6 patients died during follow-up, and the 5-year mortality rate was 26%. In this study the overall disease course and prognosis were not worse for the patients with extraskeletal bone involvement compared with those with disease limited to the skeleton; indeed, all deaths occurred in patients with no evidence of extraskeletal involvement. It must be emphasized, however, that this study was restricted to cases in which a bone lesion was the presenting sign of NHL. Thus, the reported cases with extraskeletal dissemination differ from the secondary bone NHL reported in the majority of the other series, most of which occurred as osseous dissemination in the setting of a previously known NHL.

Barbieri et al. (68) reported the largest series of primary NHL of bone with treatment results and analysis of prognostic factors for stage I and stage II disease. They evaluated 77 patients with primary NHL of bone. Most cases had B-cell high-grade histology. The median follow-up was 149 months. Forty-four patients had a solitary bone lesion (stage I); and in 33 patients, the tumor was spread to the locoregional lymphatic area (stage II). All patients were treated with radiotherapy with a median dose of 40 Gy (range 36-54 Gy), and 67 received an additional anthracyclin-based regimen of chemotherapy (combined modality therapy). After therapy, 73 out of 77 patients (94.8%) reached a complete remission. At a median time of 23 months, 14 out of 77 (18.2%) patients had a disease relapse. Four of them were treated with radiotherapy alone and 10 patients were treated with combined modality therapy. Actuarial disease-free survival and overall survival at 15 years were, respectively, 76.6% and 88.3%. Prognostic factors such as age, sex, stage and bulky lesions were analyzed. Age (<40 vs. >40 years) was the only significant factor for disease-free survival (85.3% vs. 66.6%, p=0.03).

Based on this large series, the authors stated that, in primary NHL of bone, the combined modality treatment seemed to produce a better outcome than radiotherapy alone, which still remains the best treatment for local disease control. Radiation therapy alone should be reserved for mandibular tumors, which are usually very small and diagnosed earlier.

Misgeld et al. (30) summarized the results from the literature with respect to treatment strategies for primary NHL of bone. The treatment strategy in low-grade primary NHL of bone should probably be similar to that applied to low-grade nodal NHL. Localized stages of primary NHL of bone can be treated with 45-50 Gy involved-field radiotherapy alone, completely covering the bone that is affected, as well as the regional lymph nodes. Radiotherapy is also indicated in all patients endangered by pathological fractures. Combined modality treatment should be started if constitutional symptoms or progressive disease are observed. In intermediate or high-grade primary NHL of bone, the combined modality treatment is preferred for all stages. Since assessment of remission status can be rather difficult in primary NHL of bone, even with the use of PET (18), chemotherapy should involve a sufficient number of treatment cycles, i.e., 6 or 8 cycles. Adequate intensity of chemotherapy is also important in view of the decreased perfusion of bone in comparison with lymph nodes. After chemotherapy, consolidation therapy consists of involved-field radiotherapy with 45-50 Gy. High-dose chemotherapy with autologous stem cell support is an option if there is no satisfactory response to conventional chemotherapy or if early relapse occurs.

Hodgkin Lymphomas of Bone

HL very rarely presents as a primary bone tumor, and the majority of patients have concurrent nodal HL (mostly nodular sclerosis) detected at staging (39, 72-85). Bone HL present with bone pain and many patients have B-type symptoms (39). Most lesions are localized in the axial and proximal appendicular skeleton (39). The radiographic features of bone HL are non-specific but indicate a destructive malignant process with osteosclerotic, osteolytic, and mixed lytic/sclerotic patterns; cortical destruction, periosteal new bone formation and soft-tissue masses were also reported (39, 72-85).

The histological diagnosis of bone HL may be very problematic, undoubtedly related to the rarity of its presentation. Immunohistochemical study using a comprehensive panel, which includes CD45, CD15, CD30, B-cell and T-cell antigens, is necessary for the diagnosis of bone HL (39). HL should be included in the histological differential diagnosis of bone lesions in cases in which osteomyelitis, eosinophilic granuloma, a lesion with cellular spindling or a lesion with fibrous component is considered (39, 72-85). Osteomyelitis is a particularly difficult differential diagnostic entity, as the clinical and radiological features of this entity and bone HL may be quite similar (82). Ozdemirli et al. (82) reported four cases of bone HL, all of which were described as diagnostic

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problems with osteomyelitis. Ostrowski et al. (39) reported that necrosis and extensive polymorphonuclear cell infiltration (similar to that sometimes noted in nodal HL) were present in two cases initially misdiagnosed as osteomyelitis. Eosinophilic granuloma is also a particularly difficult differential diagnostic entity and the misdiagnosis of eosinophilic granuloma has been noted in bone HL (83, 84). Chan et al. (85) reported on four adolescent patients who presented with "primary" bone lesions (all of whom had lymph node disease at diagnosis); eosinophilic granuloma was initially suspected or favored in all cases, based on histological assessment. Eosinophilic granuloma may be associated with fever and the sites of presentation of this entity may overlap with those of bone HL. Radiographically, however, eosinophilic granuloma usually shows well-delineated osteolytic lesions, a feature which is helpful in distinguishing this from bone HL. Bone HL should also be distinguished from bone NHL (3, 29-35, 39). Most cases of NHL of bone are B-cell neoplasms with a significant large-cell component. In addition, NHL of bone may be associated with fibrosis or sclerosis. Ostrowski et al. (3) reported that fibrosis with spindling of cells contributed significantly to diagnostic dilemmas in 2% of lymphomas of bone (39). The same group reported that fibrosis was part of the reactive background in most cases of bone HL, but was not a prominent feature. However, Ozdemirli et al. (82) reported that the initial diagnosis in one case of bone HL was malignant fibrous histiocytoma. Thus, HL should be included in the differential diagnosis of bone lesions with cellular spindling or a fibrous stromal component.

Ostrowski et al. (39) reported the largest series of bone HL (25 cases) with extensive immunohistochemical analysis. Five of the 25 patients had primary bone HL (3 patients had solitary, bone HL and 2 had primary, multifocal, bone HL without involvement of extra-bone sites). Twelve of the 25 patients who presented with lesions in bone sites also had extra-bone tumors detected at staging, and the remaining 8 out of 25 patients had recurrent HL that presented in bone. Three patients with primary solitary bone HL received radiation treatment only; at last follow-up 2 patients were alive at 22 months and 10 years, respectively. Patients with concurrent bone and extra-bone tumors exhibited a 60% overall survival rate, but at last follow-up all 4 patients diagnosed after 1986 still were alive; those with HL that recurred as bone lesions had a 60% survival rate at 8 years, but only 1 of the 5 patients diagnosed since 1984 had died of the disease. Based on their findings, Ostrowski et al. (39) concluded: a) that primary, solitary bone HL is extremely rare; b) that a few cases were cured with radiation therapy; and c) that the long-term prognosis of patients with bone HL appears good with current chemotherapeutic regimens. The presence of bone lesions in HL, at either presentation or recurrence, should not be interpreted as implying a worse prognosis than HL without involvement of bone sites (39).

**Conclusion**

Primary lymphomas of bone are uncommon malignancies. The vast majority of them are NHL, whereas primary HL of bone are extremely rare. Primary NHL of bone can arise in any part of the skeleton, but long bones (femurs, tibia) are the most common site of presentation. Most cases of primary NHL of bone are classified as DLBCL in the WHO classification of hematological malignancies. On full staging evaluation, most patients have disease of stage IE or IIE according to the Ann Arbor system. Several studies indicate that patients with primary NHL of bone have a favorable outcome, especially when treated by combined modality therapy. A number of studies reported that clinical stage is the most important prognostic variable in predicting overall survival. Interestingly, the rare occurrence of primary lymphoma of bone is in contrast with the frequency of plasma cell tumors in bone. This could be due to the fact that, during normal B-cell differentiation, the bone marrow is the normal site of homing of plasma cells, which are terminally-differentiated, immunoglobulin-secreting post-GC B-cells. In this regard, the possibility that primary NHL of bone represent tumors of post-GC B-cells might be suggested. In order to gain further insight in the pathogenesis of primary lymphoma of bone, it would be interesting to undertake immunohistochemical and molecular studies based on previous investigations on other types of lymphomas (102-115), to analyze in detail the expression patterns of major cell cycle and apoptosis regulators and to correlate them with the B-cell differentiation gene expression profiles (GC vs. post-GC B-cell differentiation).

**References**


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