Ewing's sarcoma and primary osseous lymphoma: spectrum of imaging appearances

Reference:
Weber Marc-André, Papakonstantinou Olympia, Nikodinovska Violeta Vasilevska, Vanhoenacker Filip, Nikodinovska.- Ewing's sarcoma and primary osseous lymphoma: spectrum of imaging appearances.
Seminars in musculoskeletal radiology - ISSN 1089-7860 - 23:1(2019), p. 36-57
Full text (Publisher's DOI): https://doi.org/10.1055/S-0038-1676125
To cite this reference: https://hdl.handle.net/10067/1569870151162165141
Ewing’s sarcoma and primary osseous lymphoma: spectrum of imaging appearances.

Marc-André Weber¹, Olympia Papakonstantinou², Violeta Vasilevska Nikodinovska³, and Filip M. Vanhoenacker⁴

¹Institute of Diagnostic and Interventional Radiology, University Medical Center Rostock, Rostock/Germany
²Second Department of Radiology, National and Kapodistrian University of Athens “Attikon” Hospital, Athens/Greece
³Department of Radiology, University Surgical Clinic „St.Naum Ohridski“ University „Ss. Cyril and Methodius“, Skopje/Macedonia
⁴Department of Radiology, AZ Sint-Maarten Mechelen, University Hospital Antwerp, Ghent University, Mechelen/Belgium

Submitted as invited review article to Seminars in Musculoskeletal Radiology

Correspondence to:
Marc-André Weber, MD MSc
Institute of Diagnostic and Interventional Radiology
University Medical Center Rostock
Ernst-Heydemann-Str. 6, 18057 Rostock/Germany
Phone: +49 (0)381 494-9201, Fax: +49 (0)381 494-9202
E-mail: marc-andre.weber@med.uni-rostock.de
Abstract:

Ewing’s sarcoma is a rare, highly malignant anaplastic stem cell tumor. Histologically, the tumor consists of uniform, densely packed, small monomorphic cells with round nuclei. The typical appearance at hematoxylin-eosin staining is small, blue and round cells without any matrix formation. On conventional radiography, Ewing’s sarcoma typically presents as a permeative lesion in the diaphysis of a long bone in a child. A large soft tissue component is another characteristic feature, which is best depicted by MRI. Primary osseous lymphomas are most commonly high-malignant B-cell lymphomas. At hematoxylin-eosin histologic staining, the tumor stroma consists of diffuse round cell infiltrates, which resembles to the appearance of Ewing’s sarcoma. Although there is no typical imaging appearance of an osseous lymphoma, it should be considered in an adult presenting with a Lodwick-grade II or III lesion in the metaphysis or diaphysis of a large long bone, the pelvis or the vertebral column. Histological confirmation is mandatory.

Keywords: Ewing’s sarcoma, primary osseous lymphoma, radiography, magnetic resonance imaging, review.
Ewing’s sarcoma

Definition: Ewing’s sarcoma (ES) is a rare, highly malignant anaplastic stem cell tumor of neuroectodermal origin, also classified as round cell sarcoma – to which also the primitive neuroectodermal tumors (PNET) belong. It mainly arises from the bone.¹

Demography: It represents about 7-10% of all malignant bone tumors and affects mainly children and adolescents. The mean age is 15 years and the age peak is 9-25 years. However, rarely children and elderly people may be affected. In a series of 64 patients, patient’s age ranged between 7-67 years.² In Germany, the annual incidence is 120 new cases in a general population of 80 million. Boys are 1.5-2.4 times more often affected than girls are.² In children, ES is the second most common primary malignant bone tumor after osteosarcoma.

Clinical manifestations: Symptoms consist of nonspecific, non-exercise related pain in the area of the tumor and swelling. General symptoms such as fever, fatigue, loss of appetite and weight may appear more frequently than in other malignant bone tumors.¹

Localization: ES mainly is localized in the long bones of the extremities and most commonly within the diaphysis close to the metaphysis. The most commonly affected bone is the femur (25%) (Fig. 1), followed by tibia (11%) (Fig. 2), humerus (11%), and pelvic bones (11%) (Fig. 3).¹ Other localizations are the fibula (7%) (Fig. 4-5) and ribs (6%) (Fig. 5). ES can virtually involve all bones of the body and may also involve extra-skeletal sites (Fig. 1). An isolated involvement of the soft tissue (extra-skeletal ES) was observed seen in 1.5% of all cases in a series of 64 patients.² Compared to osteosarcoma, flat bones are more often affected in ES. Rarely, a bi-centric ES or synchronous involvement of multiple bones may be seen (Fig. 6), whereas transarticular spread can be rarely seen in sacroiliac joints.³ About up to 15% of all ES cases are localized in the vertebral column with the lumbar spine and the sacrum most commonly affected; the location of ES, tends to follow the distribution of red marrow. The mean age at initial clinical presentation is with 19.3 years slightly higher than the mean age of Ewing’s sarcomas of the extremity bones.⁴ Metastases of ES affecting the vertebral column are more common than a primary ES of the spine.⁵

Pathology: Macroscopically, the tumor has a fish-flesh like aspect. At histology, the tumor consists of uniform, densely packed, small monomorphic cells with round nuclei, which are generally larger than in primary osseous lymphoma. The typical appearance at hematoxylin-eosin staining is small, blue and round cells without any matrix formation (Fig. 2). At immunostaining, an expression of the cellular surface antigen CD99, a product of the MIC-2
gene is characteristic. The characteristic reciprocal translocation between chromosome 11 and 22 (t[11;22], which affects in 85% the EWS- and FLI1-gene, can be verified by using break apart FISH (fluorescence in situ hybridization) (Fig. 2).1,6,7

**Imaging:** Conventional radiography (CR) reveals an aggressive osteolytic lesion with a wide zone of transition and with a moth-eaten or permeative pattern in the majority of cases.8 In a series of 64 patients, most tumors were mixed lytic-sclerotic (75%), and purely lytic in 25%.2 Complex periosteal reactions like onion-skinned, spiculae, “sunburst”, or Codman’s triangle can be seen (Fig. 5) in 27-50% of all cases.2 Onion-skinned or multi-lamellated periosteal reactions may be encountered in 25% of cases. Computed tomography (CT) is more sensitive than CR to detect bony destruction in anatomically complex regions such as the vertebral column and the pelvic bones due to the lack of superimposition. In flat bones such as the pelvic bones Ewing’s sarcomas may have a predominantly sclerotic appearance (Fig. 3), which overall represent about 10% of cases. The reason for the sclerotic appearance is mainly necrotic bony changes, as tumor-related formation of new bone is not a histological feature of ES.1 Magnetic resonance imaging (MRI) is the method of choice for local staging, because it demonstrates the true tumor extension (Fig. 4-7). The MRI protocol has to cover the entire tumor extent as well as the adjacent joints and the entire bone the tumor originates, since skip lesions (Fig. 5), which when present have great influence on the treatment planning, are frequent. Skip metastases at initial presentation were present in 14% of all cases in a series of 64 patients.2 The signal intensity of the tumor tissue of the ES is hypointense on T1-weighted images (WI) and hyperintense on T2-WI. A large soft tissue component is highly characteristic (96% of all cases),8 showing marked contrast-enhancement.2 Focal areas of cortical destruction are frequent (92% of all cases),8 allowing continuity between the intraosseous and extraosseous components (Fig. 5-7). This continuity is also commonly seen as subtle channels extending through the cortex at MRI, a finding that reflects the underlying pathologic appearance,8 since the communication between the medullary canal and soft-tissue components may be through focal cortical destruction or more commonly through permeation of the cortical haversian canal system and along neurovascular channels with small nests of tumor cells.8 Extra-skeletal Ewing’s sarcomas commonly demonstrates a nonspecific radiologic appearance of a large soft-tissue mass affecting the paraspinal region or lower extremity,8 and they may be occult on CR (Fig. 1). Another imaging characteristic that may occur in ES as well as osseous lymphoma is the so-called “wrap around sign”. This means that the cortex at T2-weighted images appears regularly hypointense, although there is a large soft tissue component that appears to be wrapped around the bone. This is believed to be due to the permeative growth of the tumor so
that the calcified bone is not destroyed to a major extent (Fig. 4-7). Since ES most often metastasizes hematogenously into the lung (although lymphatic and osseous spread may also occur but is rare – the incidence of regional node involvement is about 3% in skeletal ES) staging consists of CT of the thorax and abdomen as well as a nuclear bone scan or a positron emission tomography using FDG as tracer to detect or exclude metastases. In 25% of all cases, there are metastases present at time of diagnosis of ES. According to the EWING 2008 study, initial imaging of ES consists of MRI for local staging, chest CT, whole-body scintigraphy and FDG PET. After completion of imaging, the final diagnosis will be verified at histology and by genetic markers from biopsy material. Biopsy should be performed in a dedicated sarcoma treatment center.

**Differential diagnosis:** In general, all other tumor consisting of small-, round, and blue cells may have a similar imaging aspect. The main differential diagnoses comprise of osteolytic osteosarcoma and small-cell osteosarcoma in children and adolescents, osteomyelitis in all age groups and Non-Hodgkin’s lymphoma in the adulthood. In children, unifocal Langerhans Cell Histiocytosis is another differential, but the periosteal reaction is often less aggressive and an eosinophilic granuloma may have a sequestrum. In the spine, ES may mimic spondylitis because of its high signal intensity in T2-WI, whereas in the rare case of sacroiliac joint involvement it should be distinguished from septic sacroiliitis (Fig. 7).

**Therapy and treatment monitoring:** Treatment is interdisciplinary and consists of induction chemotherapy and the local therapy with subsequent chemotherapy and/or radiation therapy within multicentric study protocols. Such multicentric study protocols are, for instance, the EURO-EWING 99 (6 cycles of induction chemotherapy followed by local therapy, and adjuvant chemotherapy using different regimens according to individual patient’s risk factors) or the EURO-EWING 2008 study (Fig. 4, 6). For the latter, neoadjuvant chemotherapy with histopathological assessment of tumor response to induction neoadjuvant chemotherapy, followed by local therapy like surgical tumor resection and reconstruction and optionally followed by radiation therapy is recommended. Radiation therapy alone as local therapy is the therapy of choice whenever surgery is not possible but has the drawback of a higher local recurrence rate. A second chemotherapy phase as adjuvant chemotherapy is followed in a risk-adapted way. The success of neoadjuvant chemotherapy is assessed locally by using CR and MRI and FDG PET (according to EURO-EWING 2008) to assess therapy response and local recurrence (Fig. 4). Dynamic-contrast enhanced MRI (DCE) may help in differentiating residual or recurrent tumor from post-therapeutic changes, since tumor tissue enhances early
and more rapidly during the first-pass of contrast, whereas reactive tissue resulting from post-therapeutic changes enhances later and more slowly.\textsuperscript{18} Low-dose CT of the chest is recommended in adults for pulmonary follow-up, in children a chest X-ray may be enough. Most relapses occur in the first 3 years of follow-up; late relapses have rarely been observed even after 15 years or longer. Follow-up intervals should be 2–3 months during the first 3 years, 6 months until 5 years and at least once yearly thereafter according to the clinical recommendations of the European Society for Medical Oncology (ESMO).\textsuperscript{19} Overall, the 5-year-survival rate is about 64\% (up to 75\% in those patients who present without known metastases).\textsuperscript{20,21} Age, tumor volume, and extent of metastatic spread are relevant risk factors.\textsuperscript{15}

**Primary osseous lymphoma**

**Definition:** Lymphomas are a heterogeneous group of primary neoplasms of the lymphoid tissue. Malignant lymphocytes normally accumulate in the lymph nodes, causing lymph node disease. Occasionally they may spread to the blood (leukemic phase) or infiltrate organs outside the lymphoid tissue. Lymphomas may be classified as Hodgkin disease or non-Hodgkin lymphoma. Among all cases of lymphoma, 40-50\% involve the skeletal system, generally from metastatic disease. Non-Hodgkin lymphoma affects bones more commonly than Hodgkin's lymphoma, either as primary or secondary. Hodgkin's lymphoma, characterized by involvement of Reed-Sternberg cells, most commonly presents with progressive painless enlargement of peripheral lymph nodes, especially around the cervical region. At the time of diagnosis, osseous involvement is uncommon and even in the late stages only 9-35\% of cases have any bony involvement. Rarely Hodgkin's lymphoma presents as an osseous lesion without involvement of lymph nodes.\textsuperscript{22} One has to distinguish primary osseous lymphoma (primary lymphoma of bone, PLB) from a secondary bone involvement by lymphomas arising from inner organs or lymph nodes. The primary Non-Hodgkin’s lymphoma of the bone is an aggressively growing tumor consisting of malignant lymphatic cells which affects a single bone with or without regional lymphadenopathy. The polyostotic PBL is defined as multifocal but exclusive involvement of the skeleton, whereas the disseminated lymphoma affects various organs with or without secondary involvement of the skeleton.\textsuperscript{23} Thus, for the correct categorization of an osseous lymphoma the radiologist’s role is to exclude simultaneous extra-osseous manifestations of lymphoma at other localizations. Primary osseous lymphomas are most commonly high-malignant B-cell lymphomas.\textsuperscript{24}

**Demography:** PLB is an uncommon clinical entity and a rare presentation of non-Hodgkin's lymphoma. It can occur at any age but it has a wide age peak between 30 and 60 years.\textsuperscript{24,25} An
overall median age of 45 years (range, 7-87 years) has been reported in a study on 119 patients with a female-to-male ratio of 1:1.53.25 PLBs represent 3-5% of all malignant bone tumors, 4-5% of extra nodal lymphoma and less than 1% of all non-Hodgkin's lymphoma.26 Diffuse large-B-cell lymphoma (DLBCL) accounts for the majority of cases of primary osseous lymphomas. DLBCL usually associates with single bone involvement, whereas the less frequent types like the B-lymphoblastic lymphoma associate with multifocal involvement. Primary osseous lymphoma is uncommon in children and adolescents.27

**Clinical manifestations:** The leading symptom is local pain. General symptoms such as fever, night sweat and fatigue that appear frequently in extra-skeletal lymphomas are typically not frequently observed in PLBs.

**Localization:** 50% of all PLBs are localized within the skeleton of the trunk and skull, the other 50% are situated in the long bones, especially the femur (Fig. 8); in general bones containing red marrow are affected. Of the latter, two thirds are localized at the metaphysis and one third at the diaphysis. Epiphyseal involvement is rare.28 80% of PLBs are observed unifocally within the bone (Fig. 9).24 In a recent study, the femur was the most commonly involved single site in PLBs, whereas those with multifocal bone lesions most frequently presented with spine disease (Fig. 8, 10).29 Secondary lymphomas also favor the spine and should be distinguished from primary multifocal lymphoma.30

**Pathology:** PLBs have an indistinct tumor margin and show an invasive diffuse growth pattern. The bony cortex nearly always is infiltrated, and also mostly penetrated. The pattern of extensive marrow disease and surrounding soft-tissue masses but without extensive cortical destruction has been reported nearly exclusively in round cell tumors such as PLB, multiple myeloma, and ES.31 An explanation for this finding is the spread of tumor cells from the marrow through small vascular channels that run through the cortex into the surrounding soft tissue.31 At hematoxylin-eosin histologic staining, the tumor stroma consists of diffuse round cell infiltrates. This aspect resembles to the appearance of Ewing’s sarcoma. The diffuse infiltrates cause secondary bone resorption. At immunohistochemical analysis, nearly all lymphomas will express common leukocyte antigen and B-cell markers like CD20 (Fig. 10).31

**Imaging:** On CR or CT, PLBs may appear as solitary osteolytic or multiple osteolytic lesions with an aggressive destruction pattern (Fig. 9). Similar to Ewing’s sarcoma, the permeative and moth-eaten destructive pattern is an indication of the presence of a tumor consisting of small or round cells. The periosteal reaction, which has been reported in about 60% of cases, is often aggressive and may be complex.31 CT may be useful to demonstrate bony destruction and, if
present, sclerosing pattern within the spine and pelvis (Fig. 11). Osteosclerotic changes may be observed as well, however, predominant osteosclerosis is unusual in primary osseous Non-Hodgkin’s lymphomas.\textsuperscript{24,32} A sequestrum within a lucent lesion occasionally is seen and is optimal visualized on CT, although it is a non-specific finding.\textsuperscript{31} In the spine, the often-multisegmental lesions may appear osteolytic or mixed osteolytic and –sclerotic (Fig. 10). Although osseous lymphoma has been classically considered in the differential diagnosis of an ivory vertebra, this is a relatively rare occurrence.\textsuperscript{33,34} The mixed sclerotic–lytic type is more common in secondary lymphomas and after treatment.\textsuperscript{30} However, radiographic findings may be very subtle even in the presence of aggressive appearance on other imaging modalities (Fig. 12).\textsuperscript{31,35} MRI, likewise to ES, is the method of choice for the work-up of symptomatic areas and especially in case of suspected compression of the spinal cord or spinal nerves. The signal behavior itself is nonspecific, and may also show a diffuse or focal replacement of normal bone marrow, as it could be seen in multiple myeloma (Fig. 12). Lymphoma of the deep soft tissues usually reveals long cones of intramuscular or intermuscular tumor again best depicted by MR imaging. Cortical destruction allowing communication between the intraosseous and soft tissue components may be subtle with small striations of extension.\textsuperscript{36} Similar to Ewing’s sarcoma a “wrap around”-sign may be observed consisting of an often large soft-tissue component encasing the bone while the cortical bone appears preserved on MRI (Fig. 13). In reality, the tumor has penetrated the cortex in a permeative way. Contrast-enhanced CT should be used for staging and detection of other organ manifestations (Fig. 14). A nuclear bone scan may demonstrate the local osseous involvement and other bony manifestations of the lymphoma, the sensitivity to detect multifocal disease is lower than that of whole-body MRI. FDG-PET is well suitable for staging and treatment monitoring, but also whole-body MRI (including diffusion-weighted imaging) may be used for this purpose (Fig. 9); both have similar performance for the detection of bone marrow involvement.\textsuperscript{37,38}

**Differential diagnosis:** For differential diagnosis, the patient’s age is the crucial parameter. Typical differential diagnoses comprise in young patients ES, unifocal Langerhans Cell Histiocytosis, and osteolytic osteosarcoma. In elderly patients, typical differential diagnoses comprise metastases (for instance of small-cell tumors like the bronchial carcinoma), fibrosarcoma, and osteomyelitis. In aggressive osteomyelitis with Lodwick-grade II or III appearance,\textsuperscript{39,40} clinical presentation may be in favor of inflammation. For verification of the final diagnosis, biopsy sampling and imaging correlation is always mandatory (Fig. 13, 15-16).
Therapy and treatment monitoring: The mainstay of treatment is polychemotherapy (Fig. 13) and radiotherapy.\textsuperscript{24,31} Surgery is only indicated in case of complications, such as for instance in case of pathologic fractures\textsuperscript{31} or spinal cord compression with neurological deficits. The most common chemotherapy scheme for aggressive Non-Hodgkin’s lymphoma is CHOP (cyclophosphamide, hydroxodaunorubicin (doxorubicin), oncovin (vincristine) and prednisone/prednisolone). It has recently been reported that primary osseous DLBCL had 3- and 5-year progression-free survival of 61.2% and 46.9%, respectively and 5- and 10-year overall survival of 81.1% and 74.7%, respectively. Multivariate analysis identified soft tissue extension and International Prognostic Index (IPI) score as the most important unfavorable prognostic factors.\textsuperscript{29} Also, multifocality was also highly significantly associated with a worse progression-free survival and overall survival and the authors concluded that multifocal bone involvement is more similar to secondary bone lymphoma in characteristics and survival rather than unifocal bone disease, and thus should be better classified and treated similar to the secondary bone lymphomas.\textsuperscript{41} Extraskeletal involvement and older age are adverse prognostic factors. For systemic lymphoma with bone involvement, disease-free 5-year survival is 44%.\textsuperscript{25,43}

Conclusion: The typical manifestation of ES is a permeative lesion in the diaphysis of a long bone in a child. However, the imaging appearance in projection radiography may be diverse and ES has been titled as chameleon of the bone tumors. Extra-skeletal Ewing’s sarcomas may be missed on CR and will best be depicted by MRI. There is no single characteristic imaging appearance of an osseous lymphoma. An osseous lymphoma should be considered in the differential diagnosis when encountering in an adult a Lodwick-grade II or III osteolytic lesion in the metaphysis or diaphysis of a large long bone, the pelvis or the vertebral column that may be accompanied to a greater or lesser extent by sclerotic bony changes. Similar to ES, also PLB may be titled as chameleon of the bone tumors. In general, permeative and moth-eaten destructive patterns of the bone are a hint for a small- or round-cell tumor. Histological confirmation should always be sought. Since cases with remarkably normal-appearing CR may show distinct abnormalities on MRI or bone scintigraphy, in patients with persisting symptoms but negative CR further assessment with a more sensitive modality, such as MRI, is essential.
References


Figure legends

Figure 1: Extra-skeletal Ewing’s sarcoma in a 26-year-old man. Projection radiographs in a.-p. (a) and lateral projection (b) performed after a swelling and increasing painfulness of his right thigh that he had observed for 5 days. No bony erosion is visible, but an increased opacification of the quadriceps femoris muscle. MRI (c) and (d): axial T2-weighted fat-saturated sequences) demonstrate the large soft-tissue tumor predominantly within the vastus intermedius muscle. The patient was included into the EURO-EWING 2008 study.

Figure 2: Predominantly extra-osseous Ewing’s sarcoma with histopathological correlation in a 25-year-old woman. MRI (a): axial T2-weighted fat-saturated sequence, (b): sagittal T2-weighted sequence) illustrates the infiltration of the dorsal tibia (arrows) and the large soft tissue mass ventral to the Achilles tendon. Histology (c): hematoxylin-eosin staining) demonstrates monomorphous cells with a relatively small, eosinophilic cytoplasma. The hematoxylin-eosin stained section with a lesser magnification (d-e) demonstrate that Ewing’s sarcoma stroma consist mainly of infiltrates of small, round and blue cells with small amounts of relatively cell-poor connective tissue (asterisk). The slightly higher magnification (f) better illustrates the monomorphous small, round and blue cells typical of Ewing’s sarcoma in hematoxylin-eosin staining. The MIB-1 immunostaining of Ki67 (g) illustrates mitotic activity of 20%. There was a homogeneous and strong, membranous expression of CD99, a p30/32 surface antigen, in the CD 99 immunostaining (h). The diagnosis of Ewing’s sarcoma could be confirmed by using break apart EWS-FISH analysis (FISH: fluorescence in situ hybridization) with a, the EWS-gene locus encompassing DNA probes combination (i). Tumor cell nuclei show besides an orthologous fused another dislocated hybridization pair (arrow) confirming the translocation t(11;22) of the EWS-gene locus.

Figure 3: Predominantly sclerotic Ewing’s sarcoma of the right os ilium (arrows) in a 26-year-old woman that was subsequently treated by polychemotherapy and radiotherapy. CT in axial (a) and coronal (b) plane; MRI using a coronal T1-weighted (c) and an axial T2-weighted sequence (d). These predominantly sclerotic Ewing’s sarcomas are not uncommon within the pelvis.

Figure 4: Ewing’s sarcoma in a 12-year-old boy. Projection radiography in a.-p. (a) and lateral (b) view demonstrate only a blurred cortical bone of the diaphysis of the fibula (arrow). MRI (c): coronal T1-weighted, (d): coronal contrast-enhanced T1-weighted, (e): axial T2-weighted, (f): axial ADC (apparent diffusion coefficient) map, and (g): axial contrast-enhanced fat-saturated T1-weighted sequence) illustrates the large soft tissue component surrounding the
fibula (arrows). The tumor’s stroma consisting of densely packed cells (at histology small, round, and blue cells with characteristic proof of EWSR1-ERG fusion) is reflected by the low ADC values of the tumor tissue (f). Six months after neoadjuvant polychemotherapy the tumor mass has substantially decreased as evidenced by MRI (arrows; (h): axial fat-saturated T2-weighted, (i): axial contrast-enhanced fat-saturated T1-weighted, (j): coronal STIR, (k): coronal T1-weighted, and (l): sagittal T2-weighted sequence). (m): FDG PET/CT shows slight tracer uptake within the left fibula but no metastases. After partial resection of the tumor bearing bone and complete resection of the tumor including the soft tissue component (n), therapy was proceeded with chemotherapy and radiotherapy of the lower leg.

**Figure 5:** Image gallery of Ewing’s sarcomas. Projection radiographs in a.-p. (a) and lateral view (b) as well as sagittal reformatted CT (c-d) of Ewing’s sarcoma of the diaphysis of the left radius in a 14-year-old girl. Note a hair-on-end periosteal reaction at the ulnar and palmar aspect of the diaphysis of the radius on plain radiographs. On CT, the extent of the periosteal reaction is more obvious and shows that both the palmar and dorsal side of the radius are involved. Note also focal irregular delineation of the dorsal cortex of the radius. Projection radiographs in a.-p. (e) and lateral view (f) of Ewing’s sarcoma of the left fibula in an 11-year-old boy. There is fusiform bone expansion of the diaphysis of the fibula with a distinct periosteal reaction with a variable pattern, consisting of partially onion-skinned and partially perpendicular (sunburst pattern) to the underlying cortex. The lesion has a mixed appearance with areas of osteolysis, cortical destruction and sclerotic areas. Ewing’s sarcoma of the left femur with onion-skin periosteal reaction (arrow), fusiform bone expansion of the diaphysis and ill-defined osteolysis with cortex permeation on projection radiography (g), large soft-tissue component (arrow) and wrap-around sign on axial T2-weighted fat-suppressed MRI (h), and skip-lesion (arrow) in the femur diaphysis depicted by unenhanced coronal T1-weighted MRI (i). Ewing’s sarcoma of the left lower thoracic rib cage in a 12-year-old boy. There is cortical destruction of the rib with large associated soft tissue mass extending in the pleura, left paravertebral muscles and left neuroforamen. The lesion is inhomogeneous on T2-WI with fat suppression with areas of low to intermediate signal intensity and hyperintense areas. There is vivid enhancement of the lesion (j): sagittal T2-weighted, (k): axial T1-weighted and (l): contrast-enhanced fat-saturated T1-weighted sequence).

**Figure 6:** Rare bicentric Ewing’s sarcoma in a 7-year-old boy. Projection radiography in a.-p. (a) and lateral (b) projection. Inhomogeneous lytic and sclerotic changes with blurred cancellous and cortical bone and a slight periosteal reaction of the first metatarsal bone are
visible (arrows), but no obvious changes in the calcaneus of the left foot are visible. The synchronous manifestation of two Ewing’s sarcomas within the calcaneus and first metatarsal bone is elucidated by MRI (arrows); (c): contrast-enhanced fat-saturated T1-weighted, (d): coronal T2-weighted, (e): axial T1-weighted, and (f): axial STIR (short tau inversion recovery) sequence). The large soft tissue component encompassing the first metatarsal bone and the cortical bone penetration is also well depicted in (d). Nuclear bone scan (g) as well as FDG-PET/CT (h) shows no other tracer uptaking tumors in the rest of the body. Therapy was according to the EURO-EWING 2008 study that was followed by an amputation at the mid lower leg level. The lateral projection radiograph three years later show a normal stump with slight ossifications at the end of the stump. The boy is satisfied with the situation, can do sports, and has no pain at all.

Figure 7: Image gallery of Ewing’s sarcomas. (a-c): 18-year-old woman with Ewing’s sarcoma and involvement of the left sacroiliac joint (arrows), presenting with low back pain, fever and malaise. Initial MR imaging shows transarticular infiltration of the left sacroiliac joint and in conjunction with clinical symptoms the findings were misinterpreted as osteomyelitis and the patient received antibiotic treatment for two months without any clinical improvement (coronal fat-saturated proton-density WI (a), coronal fat-saturated contrast-enhanced T1-WI and (c): axial T1-WI). (d-f): 37-year-old man with Ewing’s sarcoma presented with painful swelling. Projection radiograph in a.-p. view (d) shows cortical destruction and periosteal reaction at upper third of femoral diaphysis. An axial fat-saturated T2-WI (e) and a sagittal contrast-enhanced spoiled GRE fat-saturated T1-WI (f) reveals the large soft tissue component within the quadriceps compartment, which almost encircles the cortex. The cortex was affected only posteriorly, despite the large soft tissue mass (e, f), whereas bone marrow involvement of the femur was best seen after gadolinium administration (arrow in f).

Figure 8: Image gallery of bone lymphomas. (a-c): 74-year-old man with osseous Non-Hodgkin’s lymphoma, initially misdiagnosed as seronegative spondylarthrititis (a): sagittal T1-weighted and (b-c): sagittal proton-density weighted fat-saturated sequence). The inferior anterior and posterior corners of L2 are hypointense on T1-WI and hyperintense on fat-saturated T2-WI, respectively, whereas a lesion at the inferior end plate of L1 imitated an Andersson lesion. Repeat MRI after three months revealed more and larger focal lesions. (d-f): Multifocal Non-Hodgkin’s lymphoma in a 51-year-old woman presenting with intermittent back pain and infiltration of L4, L5 and S1 vertebral bodies as well as epidural infiltration at L5 level (arrow) (d): sagittal T1-weighted, (e): sagittal STIR, and (f): sagittal T2-weighted sequences). Please
note the different signal behavior on T2-weighted images of the osseous manifestations. There is mixed signal intensity of L5 vertebral body on STIR image (e) and low signal intensity on T1-WI and T2-WI, while a mild hyperintensity of L4 and S1 are shown only on STIR MR images. (g-i): Non-Hodgkin’s lymphoma of the right distal femur in a 39-year-old man with increasing pain in the left knee without a history of trauma (g): projection radiograph in a.-p. view, (h): nuclear bone scan, CT in coronal (i) and axial reformation (j), MRI using coronal STIR (k) and T1-weighted (l) sequences. The radiograph of the left knee demonstrated a radiopaque lesion at the distal metadiaphyseal region of the left femur, with associated periosteal reaction and the bone scintigraphy with technetium-99 MDP reveals intense radiotracer uptake. The coronal reformatted CT image shows, in addition to (f) cortical destruction (arrows) along with one more lytic lesion in the epiphysis. The two lesions have low signal intensity on T1-WI (l) and high signal intensity on STIR (k) images.

Figure 9: Primary osseous B-cell non-Hodgkin’s lymphoma in a 22-year-old man with painful swelling and tenderness of the right fibula head for 4 months, no prior trauma and no fever. Projection radiography in a.-p. (a) and lateral view (b) without obvious evidence of bony pathology. Projection radiography in a.-p. (c) and lateral view (d) 6 weeks later clearly show the destructive osteolysis of the fibular head (arrows). MRI (e): coronal T1-weighted, (f): sagittal T2-weighted, (g): coronal contrast-enhanced fat-saturated T1-weighted, (h): sagittal and (i): axial proton-density weighted fat-saturated, and (j): axial contrast-enhanced fat-saturated T1-weighted sequence) also illustrates the cortex exceeding infiltration and the wrap-around-sign (arrows). Staging was performed with scintigraphy (k) and contrast-enhanced CT (coronal reformation, (l)) of the trunk, both showing no evidence of other skeletal as well as extra-skeletal manifestations of lymphoma. 4 months after 6 cycles of R-CHOP chemotherapy, whole-body MRI was performed for follow-up assessment (m, n): coronal STIR, demonstration slight reduction of tumor size within the fibular head and no other manifestations of the lymphoma. Treatment was continued by radiotherapy with in total 32 Gray of the fibula.

Figure 10: Primary multifocal osseous diffuse large B-cell lymphoma in a 43-year-old man presenting with a three months history of back pain and pain of the left lower extremity. Hospitalization followed due to worsening of the symptoms and neurological findings. Sagittal CT (a) and sagittal T1-weighted MRI (b) of the lumbar spine illustrate several osseous predominantly lytic and marrow-replacing lesions asymmetrically located on vertebral bodies, pedicles and several laminae. Also, a well-defined glenoid lytic lesion is present with small cortical disruption without significant soft tissue mass (arrow on the chest CT (c)). Nuclear
bone scan (d) shows an intense tracer uptake of the vertebral column and the pelvis as well as some lesions within the ribs. There is absence of lymph node or visceral involvement. The hematoxylin-eosin staining (e), magnification x 100) illustrates that the tumor stroma consists of relatively monomorphous medium- to large-sized cells and rare multinuclear cells, with hyperchromatic nuclei, prominent nucleoli, and scarce cytoplasm. There also is diffuse, homogenous and strong CD 20 immunostaining (f), magnification x 200) supporting the diagnosis of diffuse large B-cell lymphoma. This case illustrates nicely the multifocal location on the spine with metastases as typical differential diagnosis.

Figure 11: Non-Hodgkin’s B-cell lymphoma in a 75-year-old woman presenting as both osteolytic and osteosclerotic lesion of the glenoid in axial CT sections (a-c). The scapular lesion was an incidental finding. CT-guided biopsy (d) revealed an aggressive Non-Hodgkin’s diffuse large-B-cell lymphoma (DLBCL).

Figure 12: Indolent Non-Hodgkin’s B-cell lymphoma in a 69-year-old man. Pain at both knee for one year, most pronounced around the right knee, no B symptoms. Projection radiographs in lateral views (a): right knee, (b): left knee) reveal no obvious bony destruction. MRI (c): axial T1-weighted, (d): axial fat-saturated proton-density weighted, and (e): coronal T1-weighted sequence on the left side; (f): coronal STIR on the right side) reveals the multifocal lymphomatous bone marrow infiltration confirmed at histology. MRI (g): axial contrast-enhanced T1-weighted fat-saturated sequence on the right side and (h) on the left side, (i): coronal T1-weighted sequence) performed 4 months after first MRI there is an increase of the diffuse lymphomatous infiltration of the bone marrow but no extra-osseous manifestation, as confirmed by an contrast-enhanced CT of the trunk (not shown).

Figure 13: Non-Hodgkin’s B-cell lymphoma in an 82-year-old man. Projection radiograph of the pelvis (a) performed because of increasing pain in the left groin for 3 weeks, weight loss, and B-symptoms, as well as a locally palpable lump. (b): axial CT, (c): coronal STIR, (d): axial contrast-enhanced fat-saturated T1-weighted sequence. The osteolysis of the iliac bone with partly calcified periosteal shell (arrows in (a) and (b)) presents at MRI with a large and homogeneous soft tissue component that penetrates the cortical bone (arrows in (e) and (d)). A wrap-around sign is also present. (e): CT-guided biopsy revealed an aggressive Non-Hodgkin’s diffuse large-B-cell lymphoma (DLBCL). The axial contrast-enhanced fat-saturated T1-weighted sequence (f) performed after 6 cycles of R-CHOP chemotherapy clearly demonstrates treatment response with nearly absent contrast-enhancement and nearly vanished soft tissue component (arrow).
**Figure 14:** Non-Hodgkin’s diffuse large-B-cell lymphoma (DLBCL) in a 59-year-old woman with multi-organ manifestation (stage IV). The left shoulder joint and upper arm were first to present with symptoms (swelling for 2 weeks, no pain medication). Projection radiograph (a) shows soft tissue opacification around the left shoulder, contrast-enhanced staging CT revealed large mass with enhancement of the left shoulder joint and scapula as well as infiltration of the anterior humerus (b), lung (arrow in (c)), and bilateral kidney infiltration visible as multiple hypodense lesions with blurred border (arrows in (d)), infiltration of the spinal canal and erector spinae muscle (arrows; (e): axial contrast-enhanced fat-saturated T1-weighted, and (f): coronal STIR sequence).

**Figure 15:** Non-Hodgkin’s B-cell lymphoma in a 69-year-old man with multifocal osseous manifestations. First symptom was an episode of sudden back pain without trauma for 2 months. MRI (sagittal T1-weighted (a), contrast-enhanced fat-saturated T1-weighted sequence (b)) demonstrated infiltration of the bone marrow of the 6th thoracic vertebra and a slightly wedge-shaped vertebra. Staging CT of the trunk revealed osseous lesions in the second rib of the right side (c), the 6th thoracic vertebra (d), and the acetabulum (e) and os pubis (not shown), as well as an enlarged lymph node within the right groin (f), no other enlarged lymph nodes. CT-guided biopsy of the 6th thoracic vertebra was performed (g) and histology revealed diffuse large-B-cell lymphoma (DLBCL).

**Figure 16:** Aggressive Non-Hodgkin’s diffuse large-B-cell lymphoma (DLBCL) at stage IV in a 76-year-old man with severe back pain and weight-loss for 2 months. MRI (a): coronal STIR, (b): sagittal T1-weighted sequence) revealed infiltration of 1st lumbar vertebra (arrow) and large paravertebral mass next to the right psoas muscle (arrow); CT in sagittal reformation (c) and CT-guided biopsy for histological and immunohistochemical verification (d).