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Diagnostic imaging of primary malignant bone tumors in children (osteosarcoma, Ewing`s sarcoma) – part I

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Summary

Background: Neoplastic conditions of developmental period are an important problem in oncology and pediatrics. Multi-agent chemotherapy introduced in the 1970's significantly improved the results of treatment but still these tumors are the 2nd cause of death in children and adolescents.

Primary malignant bone tumors account for 1-1.5% of all neoplasms and for 7% of developmental period tumors. Depending on the kind of tissue, bone tumors demonstrate various patterns of growth, infiltration and internal architecture. Imaging methods are an important part of diagnostics and the most effective tool of monitoring response to treatment.

Plains films were the only imaging technique for many years. In the 2nd half of 20th century, angiography was introduced. Despite invasiveness, it showed malignant character of the tumor and its extension in soft tissues.

In the 7th decade of the last century, ultrasound and computed tomography started being routinely used in clinical practice. After a few years, resolution of these modalities was improved so that they could better visualize musculoskeletal tumors.

Magnetic resonance imaging was the next step, this method came into use in Poland 16 years ago. MRI is the best modality to show the extent of marrow involvement.

All the imaging techniques have their place in the diagnostic algorithm of bone tumors. Scintigraphy plays an important role in detecting skeletal metastases and disseminated disease. Fusion of radiological and nuclear medicine methods, PET-CT, brings new possibilities to musculoskeletal tumor diagnostics.

Key words: **Bone tumors • osteosarcoma • Ewing`s sarcoma • diagnostics • radiographs • ultrasound • computed tomography • magnetic resonance imaging**

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Introduction

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Developmental age tumors have always ben an important problem in pediatrics as they still are the second most frequent cause of mortality among children and adolescents after accidents and traumas [1].

Primary malignant bone tumors account for 1-1.5% of all neoplasms [2] and for 7% of developmental period tumors [1]. It means ca. 100 new cases a year among Polish children. The incidence of bone tumors increases with age to reach the peak in the second decade of life [3, 4].

Current oncological diagnostics is a multidisciplinary area, involving many branches of medicine. In order to establish the diagnosis and to assess the stage and extent of the bone tumor, all the available imaging modalities are used (plain radiography, ultrasonography, computed tomography, magnetic resonance, scintigraphy) as well as laboratory tests, including biochemical, hormonal, immunological and genetic investigations.

Despite advances in the therapy, the results of treatment of some bone tumors are still unsatisfactory. Most frequently this is due to too late detection (diagnosis) of the tumors and, consequently, too late institution of the therapy.

The primary factors explaining late detectability of bone tumors include:
a) atypical, discrete symptoms, especially at early stages of the disease, which may pass unnoticed by the child's parents or a physician, or misinterpreted,
b) insufficient knowledge among both general practitioners and pediatricians concerning the possibility of neoplastic disease in children.

Imaging diagnostics may also constitute an element delaying identification of the tumor. In view of the above, it is very important that the patient should be diagnosed in a center with experience in this field, or at least that the results of examinations performed elsewhere should be consulted with such a center, which can contribute to shortening of the diagnostic period. Such an algorithm is implemented in the Institute of Mother and Child. Diagnostic examinations performed on the spot are preferable because consultation of results obtained in other centers ends in some cases with recommendations to repeat some of the investigations, often for the reason that the images do not cover the whole region of interest involved by the detected lesion. Therefore, a paper discussing in detail the specific issues associated with imaging diagnostics of the most common malignant bone tumors is important from the point of view of an oncological surgeon and cooperation between oncologists and radiologists.

Background

Depending on the tissue type, bone tumors demonstrate various tendencies with respect to growth, infiltrations and internal transformations. Growing in the bone, they cause its destruction, leading to pathologic osteogenesis and chondrogenesis, abnormal calcifications and ossifications, and various periosteal reactions. Therefore, imaging modalities constitute an important element in the diagnostics of bone tumors, as well as the most effective tool for monitoring the response to treatment [4, 5, 6].

Only a few months after the discovery of the properties of radiation by W.K. Roentgen in 1895, X-ray films of the bones were introduced into the diagnostics, becoming the fundamental method of detection of bone tumors, and they have held this position to date. For several decades, plain radiography was the only method of X-ray examination. In the second half of the 20th century, investigations of the vasculature – angiography – were introduced to assist tumor diagnostics. Despite invasiveness of this method, it often allowed assessment of tumor malignancy and its extent in soft tissues.

At the end of the 1970's, the computed tomography (CT) technique was introduced and since that time it has been improved so that it has became useful for imaging bone structures and their tumor-related changes in more detail than conventional X-ray. At the same time, ultrasonography (USG) came into routine clinical use, but with respect to tumors of the locomotor system it needed a few years more to develop the method so that it provided appropriate image resolution and the advantages of color Doppler technique.

Further advance immensely significant for the possibility of visualization of soft tissue lesions was the application of magnetic resonance imaging (MRI) method, which has been used in Poland during the last sixteen years. MR is the method providing the best visualization of abnormalities within the marrow cavity. Clinical experience demonstrates that all these imaging modalities have their places in the diagnostic algorithm applied in case of tumors of the bones and soft tissues, and that their results are complementary, providing clinicians with more information concerning the characteristics and extent of the neoplastic process and effects of treatment.

These methods allow precise determination of the site of biopsy or specimen collection for histopathologic investigations. The biopsy should be performed after MRI as potential bleeding that may follow changes the intensity of the tumor signal [7]. Detailed information concerning the tumor size, borderlines, topography, relation to adjacent organs and tissue structures is a prerequisite for radical resection of the lesion for the surgeon [8].

Nuclear medicine techniques supplement the information obtained with radiological methods. They allow to visualize the whole skeleton, and despite higher sensitivity of MRI scintigraphy is indispensable for detection of bone metastases and multifocal lesions, especially in case of lack of unequivocal morphological abnormalities [1]. The most recent scintigraphic image fusion technique, based on both positron emission tomography (PET) and computed tomography, referred to as PET-CT, is important in the search for the primary tumor in cases where metastatic lesions are detected and their origin is impossible to establish by means of other methods [9]. PET, enabling quantitation of fluorodeoxyglucose (FDG) uptake, allows to compare its level before and after chemotherapy. In such investigations, a significant correlation between the extent of tumor necrosis (osteogenic sa, Ewing sa in children) induced by the therapy with the results of histopathology was demonstrated. However, the results of PET/PET-CT may be misleading in assessment of the character of bone tumors because dome benign lesions such as non-ossifying fibroma or fibrous cortical defects may demonstrate metabolic activity and imitate a malignant process by radioligand uptake [10]. On the other hand, some malignant tumors demonstrate only limited FDG uptake.

It seems, however, that the future of diagnostics of metastatic foci belongs to MRI (quick, single-sequence, screening

MRI of the whole body in STIR sequence) [11], although the results obtained with PET-CT utilizing 11C-choline are also promising. According to the first published reports, the accuracy of this method in staging of sarcomatous lesions of the bone and soft tissue in the TNM system is superior to that of "conventional" imaging, including scintigraphy of the skeletal system, chest CT and MR of the region of the primary tumor [12].

The paper discusses in detail four imaging modalities routinely used in the diagnostics of bone and soft tissue tumors of the locomotor system. They include:
- X-ray – plain radiograms
- Ultrasonography – using conventional and Doppler technique
- Computed tomography of the musculoskeletal system and the chest
- Magnetic resonance, especially for assessment of bone marrow cavities and soft tissue tumors, including contrast-enhanced MRI.

These methods are applied at all stages of diagnostics and treatment of the tumor, such as:
- the diagnostic period, in which the tumor is detected, and its location, size, character, outline, etc. are determined;
- the therapeutic period, in which the changes taking place as a result of the instituted treatment, most commonly induction chemotherapy, are monitored;
- the preoperative period, in which the aim of imaging examinations is to determine the operability parameters of the tumor;
- the follow-up period after treatment, in which the aim of imaging examinations is to assess the course of healing, occurrence of potential complications, and to detect potential relapses of the disease.

The diagnostic efficacy of these methods depends on the familiarity with, and observance of some principles, including:
- properties and diagnostic potential of the method,
- indications for use of the appropriate method at appropriate time (diagnostic algorithm),
- correct technique of the investigation, based on a uniform standard,
- quality control of the technique.

CLASSIFICATION AND PATHOMORPHOLOGY OF MALIGNANT BONE TUMORS

The current classifications of bone tumors are based on the tissue type, from which the tumor originates. According to the international WHO classification of 1972, amended in 1990 and used up to the present [13], bone tumors are divided as follows:
I. osteogenic tumors
II. chondrogenic tumors
III. giant cell tumors
IV. tumors of myeloid origin
V. tumors of vascular origin
VI. connective tissue tumors
VII. other tumors
VIII. non-classifiable tumors
IX. tumor-like lesions

The most common malignant bone tumors of developmental age include osteogenic sarcoma (sarcoma osteogenes) and Ewing's sarcoma (sarcoma Ewingi). Others, like chondosarcoma or malignant tumors of vascular origin and fibrohistiocytic hyperplasias, are less frequent. These tumors occur typically in older age groups. Giant cell tumors (osteoclastoma) occur sporadically below the third decade of life. Myeloid tumors (myeloma) practically do not occur in children. A common tumor of the second decade of life is a benign lesion (osteoblastoma), which may also take a clinically malignant form, osteoblastoma agressivum, forming metastases in the lungs [3, 13].

The first documented reports concerning sarcomas of the bone date back to the 19th century. In 1866, Lucke described a case corresponding to the characteristics of Ewing's sarcoma, and Samuel Gross listed in 1879 the typical clinical and pathological features of sarcomas of the long bones. The first scientific papers concerning the most common bone tumors were published by James Ewing, an American pathologist (1866-1943) [14]. In 1921, he described the clinical course and pathomorphology of a non-osteogenic tumor, originating, in his opinion, from the endothelium of bone marrow blood vessels. Therefore, he called it „diffuse endothelial tumor of bone", and then „endothelial myeloma". Today, the tumor is referred to as Ewing's sarcoma. In 1929, Ewing described the pathological features of a bone tumor arising from the mesenchymal tissue and capable of generating abnormal osseous tissue, called sarcoma osteogenes – osteosarcoma [6].

Sarcoma osteogenes, osteosarcoma

Sarcoma osteogenes (osteogenic sa) accounts for ca. 50% of all bone tumors. It occurs predominantly in the second decade of life – in 60% of all cases, with the peak of incidence in the 13-14 age group [1, 3, 5]. It is rare below 10 years of age, sporadic in infancy and elderly age [15]. Males are affected more frequently. It occurs in various populations, irrespectively of race [7]. In the pathogenesis of osteogenic sa, the role of genetic factors is emphasized – familial occurrence and increased risk of developing the disease in patients with hereditary form of retinoblastoma. In such cases, a mutation of retinoblastoma suppressor gene RB1 located in chromosome 13 is found [16]. Mutations of RB1 are also seen in sporadic oteogenic sarcomas. Induction of the sarcoma by ionizing radiation [13] or previously existing bone lesions such as aneurysmal bone cysts and chondro-osseous exostoses in children, or fibrous dysplasia and Paget's disease in adults has been documented [13, 17]. The fact that osteogenic sarcoma occurs mainly in adolescents during the pubescence period, prompts consideration of the relationship between rapid growth and the development of this tumor [3].

Osteogenic sarcoma arises from mesenchymal tissue [3, 7]. It is the only tumor capable of osteogenesis, belonging to group I according to WHO classification. The formation of osteoid or osseous tissue is effected directly from the mesenchymal stroma, without the mediation of cartilage. Osteogenic sarcomas demonstrate considerable variability of histological structures. Apart from osseous and osteoid tissue, the tumor cells can produce cartilage, fibrous and myxomatous tissue, or non-differentiated structures.

Two classifications of osteogenic sarcomas are commonly used: one, taking into account the histological maturity corresponding with histological grades of malignancy G1, G2 and G3 and the second, more complex one, considering the similarities of the neoplastic tissue to the particular mesenchymal tissue structures [3]. Depending on the predominance of individual structures, the following types are distinguished:
– osteoblastic, which is the most common one,
– chondrosarcomatous, in which the sarcoma demonstrates capability of metaplastic tissue formation,
– fibrohistiocytic with scarce osteoid and osseous trabeculae formation,
– microcellular,
– anaplastic,
– teleangiectatic,
– mixed, in which no type of histological texture predominates. The first three types are considered as classic forms of osteogenic sarcoma [3]. Most histopathological diagnostic problems are associated with the chondrosarcomatous, fibrohistiocytic and microcellular types. The capability of osteoid and osseous trabeculae formation by the tumor is the feature most important for differential diagnosis.

The primary osteogenic sarcoma may develop inside the bone – central type (75% of cases), as well as juxtacortically. The central type develops predominantly in the metaphyses of long bones, most frequently in the distal femoral metaphysis [5]. Among all osteosarcoma cases, 50% is located in the region of the knee [1, 7, 15, 17]. The tumor also often develops in the humerus and in the pelvic bones, less frequently in the scapula, fibula, carpal and tarsal bones, facial and cranial skeleton [7]. Growth cartilage usually constitutes a barrier for tumor spread. Locations limited exclusively to bone epiphyses or diaphyses are rare [7]. There are also primary multifocal forms of osteosarcoma [7, 13].

Osteogenic sarcoma is characterized by distant, mainly blood-borne, metastases, primarily to the lungs. In ca. 30% of cases they are detected on diagnostics [1, 17]. According to some authors, micrometastases are present at the onset of the disease in 80% of cases [18]. Metastases to the bones and other organs are less frequent.

Juxtacortical form of osteogenic sarcoma (osteosarcoma juxtacorticale), is classified as a separate entity [13, 19]. It usually represents a well-differentiated sarcoma type with less aggressive course, developing on the bone surface. It usually occurs in young adults at the turn of the 2nd and 3rd decade of life as well as in the 3rd-5th decade of life. It presents two classic growth variants: paraosteal, originating from the external layer of the periosteum, and periosteal, developing most often in bone shafts and in children. Radiographic images show a tumor with irregular areas of calcifications and ossifications on the bone surface or involving the cortical layer, which is then thickened and uneven. With rare exceptions, the bone marrow cavity is not involved [19]. In some aggressive forms, which also occur, the features of malignancy typical of all sarcomas are observed. Juxtacortical osteosarcomas show a lesser tendency to metastize. The prognosis is better than in the central type of osteosarcoma [13].

The first clinical symptom of osteosarcoma is most frequently pain, aggravating at night, limited mobility and in ca. 50% of cases edema of the extremity, dependent on the involvement of bones and soft tissue [5, 7]. Often it follows a history of a trauma [5], rarely pathologic fracture is the first symptom [1, 17]. Laboratory tests demonstrate elevated alkaline phosphatase (AP) in patients with advanced osteoclastic process and increased level of lactate dehydrogenase (LDH) in cases of soft tissue infiltration [1, 17].

The particular forms of osteosarcoma require differentiation with tumors originating from the tissue observed in the given tumor, such as chondrosarcoma, fibrohistiocytoma malignum and benignum, angiosarcoma, other mesenchymal tumors and microcellular tumors such as Ewing's sarcoma, PNET (primitive neuroectodermal tumor), lymphoma or metastases of sympathoblastoma.

Differential diagnosis should also take into consideration many benign processes involving osteogenesis and ossification of bone texture, such as aneurysmal bone cysts, osteoblastoma, osteogenic fibroma, fibrous dysplasia. The juxtacortical form requires differentiation with non-neoplastic osteogenic reactions, associated e.g. with healing of fractures, as well as with paraosteal lesions which undergo calcification, e.g. myositis ossificans [7].

Ewing's sarcoma (sarcoma Ewingi)

Ewing's sarcoma is the second most frequent bone tumor in children and adolescents, accounting, according to various authors, for from 10 to 25% of all bone tumors [14]. It reaches the peak of incidence in the 2nd decade of life, but also frequently occurs between 5 and 10 years of age [3, 17]. 90% of cases of Ewing's sarcoma is diagnosed between 4 and 25 years of age [13, 14]. Boys are affected significantly more often (1.5 – 2 times), girls less frequently and with better prognosis [17].

Most clinical characteristics and microscopic pattern of the tumor described by Ewing are still valid, however, the views concerning the pathogenesis of the tumor have changed many times. Recent cytogenetic investigations seem to confirm the thesis that Ewing's sarcoma originates from primitive neural tissue. An identical translocation between chromosomes 11 and 22 - t (11;22)(q24;q12) – is found both in Ewing's sarcoma and in primitive neuroectodermal tumors (PNET). It is currently believed that Ewing's sarcoma and PNET belong to the same group of sarcomas [16].

The most frequent locations of Ewing's sarcoma include long bone shafts, mainly that of the femur (22%), and the tibia (11%) and flat bones, including the pelvis (12%). Ewing's sarcoma of the facial and cranial bones is rare (1.5%) [17]. Some authors link the prognosis with the location of Ewing's sarcoma, presenting the view that central localization (sarcomas located in the pelvis, ribs, vertebrae, scapula, clavicle and skull bones) and proximal peripheral localization (the femur and humerus) are associated with worse prognosis than sarcomas located on the distal periphery (in the carpal and tarsal bones, lower leg and forearm) [14, 17]. Since 1975, an extraosseous form of Ewing's sarcoma, i.e. Ewing's sarcoma of soft tissues, has been known.

It accounts for 15% of bone sarcoma cases and affects mainly the extremities. It is a soft tissue tumor demonstrating no bone lesions or lesions limited to the periosteum only. It never infiltrates the bone marrow cavity. The diagnosis is possible exclusively on the basis of microscopic investigations [13, 14].

Ewing's sarcoma is a microcellular, blastemic neoplasm of the marrow cavity with not very specific texture. Histologically it is characterized by cellular monomorphism, fine reticulin stroma and presence of glycogen in the cytoplasm. It does not undergo ossification [3]. The presence of glycogen, regarded some time ago as a factor of considerable significance, has a limited diagnostic value as it is not pathognomonic for Ewing's sarcoma. Histopathological diagnosis is associated with considerable difficulty; in many cases it has to be established, in addition to conventional methods, on the basis of immunohistochemical and cytogenetic investigations [3].

The dominant clinical symptoms of Ewing's sarcoma are aggravating pain at the site of the primary focus and local edema, indicating the involvement of soft tisue. In ca. 40% of cases, local symptoms are accompanied by generalized ones, such as asthenia, loss of appetite, elevated body temperature, and in laboratory investigations increases erythrocyte sedimentation rate and leukocytosis. This „inflammatory mask" causes a delay of correct diagnosis in some cases [1, 17].

Like in osteogenic sarcoma, increased levels of LDH and AP are observed. In 5 to 15% of cases, pathological fractures occur [17]. Ewing's sarcoma belongs to the group of tumors producing early metastases, mainly to the lungs (40%) and bones. In 15-35% of cases, they are detected before the institution of treatment [14, 17].

In the radiological images of Ewing's sarcoma, the signs of bone tissue destruction and periosteal reactions are predominant [13, 14, 15, 17]. A soft tissue tumor is present in most cases.

Radiological differentiation of Ewing's sarcoma should take into account other tumors giving similar bone destruction patterns (PNET, osteosarcoma, lymphoma, reticulosarcoma, metastases of neuroblastoma), juxtacortical tumors infiltrating the bone (rhabdomyosarcoma, fibrohistiocytoma malignum, sarcoma synoviale), as well as non-neoplastic processes associated with osteolytic changes and periosteal reactions, and, first of all, inflammatory conditions [13].

Morphology of neoplastic lesions

In pathologic, neoplastic tissue, various biological and chemical processes detectable in radiological images are going on. The character of these changes can vary, presenting osteolysis, sclerotization and periosteal reactions [13].

The following types of osteolysis can be distinguished:
a) geographical (map-like) type – well-delineated bone loss areas of varied size and shape, formed as a result of replacement of normal bone by pathologic tissue, presenting as sinus-like defects of the bone structure;
b) osteolysis presenting "moth-eaten appearance" (macular type) – small foci of decreased bone density; such a pattern appears as a result of presence of multiple osteolytic foci scattered within normal tissue,
c) permeative type – diffuse, permeating destruction pattern, with inhomogeneous decrease of trabecular structure density; formed as a result of development of tumor tissue between the trabeculae, not all of which undergo destruction at the same time.

The geographical type is observed both in malignant and benign lesions, the macular type sometimes occurs also in non-neoplastic, e.g. inflammatory processes, whereas the permeative type is practically pathognomonic for malignant tumors [4].

Sclerotization demonstrated by imaging investigations may result from:
a) calcification of osseous and osteoid tissue formed in the neoplastic osteogenesis process,
b) mineralization of necrotic lesions,
c) periosteum-derived osteogenesis of new bone formations.

Periosteal reactions observed in bone tumors – various forms of proliferation and osteogenesis manifested by stimulated periosteum, depend on the location of hyperplastic growth, aggressiveness of the tumor and duration of the disease. The periosteum may also be directly affected by tumor aggression [4]. We propose the following classification of periosteal reactions [6]:
1. Lamellar (laminar) reactions
a) thickening of the periosteum
b) periosteal detachment
c) periosteal proliferation

2. Infiltration of the periosteum
a) changes of shape without disruption of periosteal integrity (thickening or thinning)
b) disruption of periosteal integrity
c) Codman's triangle (also referred to as Codman's spur or angle) – disruption of periosteal integrity by an infiltrate and wedge-like desquamation of the periosteum in the peripheral parts of the tumor

3. Spicular reactions – osteogenic reactions in the form of processes perpendicular to the bone surface, referred to as spicules; they have varied thickness and length, and regular or chaotic arrangement [13].

Lamellar reactions without disruption of periosteal integrity are not characteristic of malignant tumors only. They are observed in inflammatory processes, systemic diseases, deficiency and autoaggression syndromes, in syphillis, benign tumors and after traumas as well [4, 13]. Disruptions of periosteal integrity and Codman's triangle are seen mostly in malignant tumors. Spicular reactions are regarded as pathognomonic for malignancies, because they are extremely rare in other pathologic processes [4]. Spicular reactions are particularly frequent in osteosarcoma and Ewing's sarcoma [10, 20].

Typical radiological image of osteosarcoma:
– osteolysis of predominantly macular type, „moth-eaten appearance"

– neoplastic osteogenesis in the tumor, varied patterns of abnormal bone tissue calcification: flocculate, cloud-like, small and large spots, to complete sclerotization,
– periosteal reactions, of all types, spicules most frequently very short, „velvet-like" or arranged „like sunrays".

Typical radiological image of Ewing's sarcoma:
– osteolysis in long bones predominantly of permeative and macular type, in flat bones large foci of desctruction with permeative osteolysis,
– calcifications as a result of osteoid accumulation in the necrotic foci and mineralization of necrotic lesions,
– periosteal reactions, all types, sometimes onion-like layers, the predominant spicule type forming a "hair-end" pattern, with alternating shorter and longer ones.

Assessment of response to treatment

The only objective method of assessment of tumor response to treatment is histopathology. Usually a 4-grade scale according to Huvos is applied, which is based on percentage determination of necrotic areas in the tumor [21]: grade I - 0-49%; grade II - 50-89% , III - 90-99%, IV - 100% necrosis, i.e. no neoplastic cells in the investigated material. Pathomorphological assessment is possible only in postoperative specimens, and the possibility of monitoring tumor reactions during chemotherapy is indispensable for appropriate management. For this purpose, besides clinical examination, all imaging modalities are used. They assess the tumor size, its vascularization, structure, periosteal reactions, bone marrow cavity. Symptoms indicating favorable response to treatment include reduction of the bone and soft tissue tumor size, marked restriction of its area, calcification of neoplastic tissue, remodeling of periosteal reactions, reduced extent of changes in the marrow cavity or their remodeling, changes in tumor vasculature. The assessment of tumor response to chemotherapy with imaging examinations is subjective. For clinical purposes, on the basis of Huvos scale, the response is assessed as good (grade IV-III), average (grade III-II), no reaction (grade II-I) and progression. Grade III included both the responses good from histological point of view (over 95% of necrosis) and bad ones. Grades II and I correspond to histologically bad response.

RADIOGRAPHY (X-ray)

Conventional radiography of the skeletal system and the thoracic cavity (lungs) is the essential method applied at each stage of diagnostic and clinical management [4, 5, 22, 23, 24, 25].

Apparatus

Plain radiography can be performed in all departments (surgeries) equipped with basic X-ray apparatus (a table for skeletal radiography and a till unit for chest X-ray).

Radiograms of the skeletal system are obtained on a so-called skeletal table, equipped with X-ray grid.

Chest radiograms are obtained on a till unit with Bucky grid) in vertical position. In case of non-ambulant patients, chest X-ray can be also performed on the skeletal table.

Examination methodology

Standard X-ray examination in case of a bone tumor must be always performed in two projections: anteroposterior and lateral. The film should cover the area of pathologic change with the largest possible margin of normal bone. For bone tumors located in long bone shafts, the film should also show two adjacent joints.

Radiography should always be performed according to the same standards, both with respect to technical conditions and to positioning of the patient for the examination. Control X-rays performed in positions different from the baseline one are useless for monitoring changes obtained as a result of treatment [22].

Conventional chest X-ray is performed from 1.5 m distance in erect position with maximum inspiration. In small children and non-ambulant patients, the examination can be performed in horizontal position observing the standards applicable to this method (distance between the radiation source and the cassette - 1 m, also with maximum inspiration). The X-rayed area must cover the apices of the lungs, the pleurodiaphragmatic sinuses, and the adjacent elements of chest wall. The examination is routinely performed in two projections: posteroanterior (in horizontal position anteroposterior) and lateral. In children below 3 years of age, only P-A projection is used because of technical difficulties associated with obtaining good quality images in lateral projection, and of the fact that CT is included in the diagnostic protocol. X-rays of the lungs are obtained with hard technique (lower mA level, shorter time, resulting in a lower dose of radiation and sharper image of the pulmonary tissue and the mediastinum).

Special radiograms

In dubious cases, comparative radiograms are obtained (for comparison with the coresponding contralateral structure, e.g. for differentiation of hyperplastic and developmental changes). For instance, comparative radiograms of both knees or elbow joints in children are mandatory.

In rare cases, it is necessary to obtain additional radiograms, e.g. in magnification – if small-size lesions of the skeletal system are suspected.

In the diagnostics of pulmonary lesions, besides typical posteroanterior and lateral projections, oblique ones can be used, as well as targeted radiography; with CT available, they are performed very rarely.

Angiography techniques

Up to recent times, angiographic studies supplemented plain radiography, providing information about the vascularization and extent of the lesions, and making it possible to assess their malignancy [5]. They have been used to date in case of tumors with rich vasculature, requiring preoperative embolization [25].

The method has higher value in investigation of soft tissue tumors than of bone tumors. An improved method

of angiographic investigations is Digital Subtraction Angiography (DSA) [13]. It is less invasive than classic angiography, visualizes better the vasculature of the tumor and its surroundings, eliminating images of other structures. At present, CT, MRI and US considerably limit the use of angiography in the diagnostics of bone tumors.

Examination in the diagnostic period

Neoplastic tissue causes destruction and remodeling of bone structure. The normal structure of bone tissue is obscured, or completely disappears (fig. 1 and 2).

On the basis of conventional X-ray, the following characteristics can be determined:

Location of the process
a) which bone and which part of it (epiphysis, metaphysis, diaphysis) is affected,
b) whether the neoplastic infiltration reaches the growth cartilage, extends beyond it, and what is its distance from the nearest articular space. X-ray cannot show the articular capsule or determine the extra- or intracapsular location of the tumor (for surgical purposes).
c) radiograms obtained in two positions make it possible to assess the tumor location in the bone (central, eccentric, cortical or juxtacortical). Some bone tumors tend to develop in particular locations, so detailed analysis of the location largely facilitates the diagnosis.

On the basis of conventional X-ray, the best site for histopathology specimen collection is selected. US is helpful in determination of the biopsy site (relation to blood vessels, assessment of non-calcified tissue [22].

Extent of neoplastic process

a) Assessment of tumor size on the basis of conventional X-ray is approximate and carries considerable error. As it follows from our experience, CT is the most objective method of tumor size evaluation. The infiltration area assessed on the basis of X-ray often does not correlate with its size assessed by radioligand uptake studies. This is due to microinfiltrations, which have not altered the bone structure yet, but demonstrate activity in scintigraphy. Therefore, scintigraphy should constitute an integral part of the diagnostic algorithm.
In the everyday practice of tumor chemotherapy monitoring, the lesion size is expressed in centimeters. The measurements are performed in three perpendicular planes, always at the same sites. The X-ray film of the affected extremity before the first chemotherapy cycle is always done with a scale, so that it shows the nearest joints.
b) Assessment of the size of non-calcified juxtacortical soft tissue tumors is often difficult due to edema, venous or lymphatic congestion accompanying the lesion. Also no signs of the tumor on the radiogram do not exclude its presence. MRI is the most favorable method of soft tissue assessment, but CT is more commonly used and cheaper.
c) X-ray does not allow to evaluate the extent of bone marrow cavity infiltration by the tumor. For this purpose, MRI is recommended, and if it is unavailable – CT.

The outline of the tumor and the structure of its periphery also have considerable diagnostic and prognostic significance. Regular shape and well-defined contours (e.g. sclerotic margin) suggest a slowly growing lesion, in contrast to

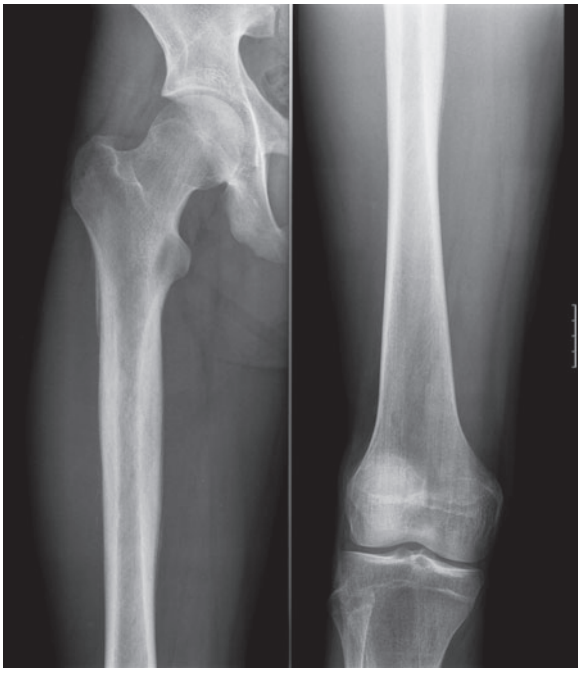

Figure 1. Ewing sa, femur. Thickening of cortex, patchy (moth-eaten-appearance) and permeative osteolysis, lammelar periosteal rection, periosteal breakthrough, Codman's triangle.

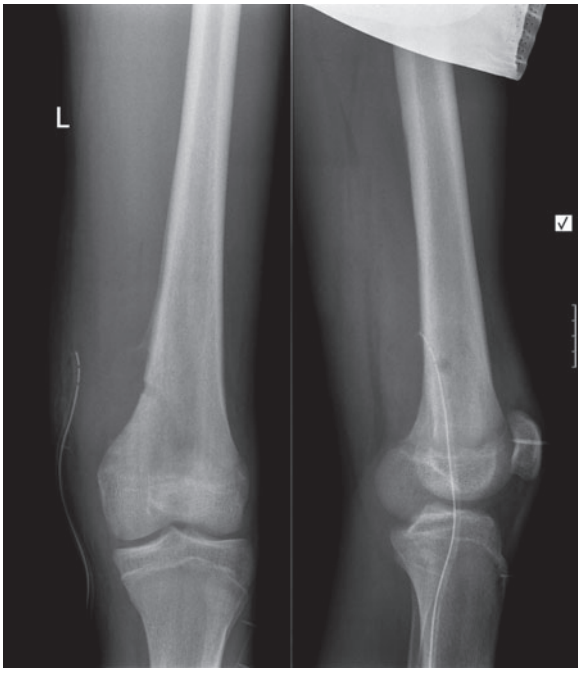

Figure 2. Osteogenic sa, femur. Patchy osteolysis, radiopaque areas of bone involvement, periosteal breakthrough, Codman's triangle, extracorticalal tumor with delicate calcifications. Biopsy canal.

an irregular area destroyed by an infiltrating tumor. On the basis of a conventional radiogram, it is possible to assess whether the tumor mass destroys the cortical layer, permeates it and infiltrates the paraosteal tissues.

Bone destruction patterns can be helpful in assessment of radiological malignancy grade. A three-grade scale was developed by Lodwick. Now it is already a historical method. Ultimate diagnosis and grading of the lesion is established by a histopathologist.

In ca. 80% of bone tumor cases, ossification and calcification areas present in the pathologic tissue are clearly visible in radiograms. Pathologically calcified tissue reveals more or less compact trabecular structure. It may show a regular pattern, and chaotic arrangement of the osseous trabeculae evidences varied grades of tissue malignancy. Lobular calcification pattern is characteristic of calcified normal and pathologic chondrous tissue [13]

Calcifying neoplastic tissue presents different patterns of calcification. The changes may show significant polymorphism, from point-like calcifications, through macular ones, to complete. In the diagnostic period, conventional X-ray is also used for assessment of periosteal reactions (fig. 1 and 2).

Therapeutic and preoperative period

Radiological investigations are repeated periodically throughout the whole treatment period (before each chemotherapy course and in case of complications and adverse clinical signs), in addition to clinical examinations and laboratory tests. In the consecutive examinations, effects of chemotherapy are assessed (good or average response to treatment, no response to treatment, progression).

On the basis of X-ray, similarly to the diagnostic period, the following parameters are assessed:

a) Tumor size. It is very important to maintain the same conditions and methodology during each consecutive examination. Different positioning of the examined extremity, or tumor measurement at a different level may lead to incorrect conclusions concerning the effects of treatment. Conventional radiography often reveals an increase of the tumor size in the course of treatment, it seems, however, to be apparent. Increases of tumor size on conventional radiograms obtained during chemotherapy can be explained by higher saturation of the tumor mass with calcium salts, which results in its better visibility [26]. An increase of tumor size is regarded as an unfavorable outcome of the therapy, but, as it has been emphasized above, reliable assessment of tumor size is possible with MRI or CT [23]. The preoperative radiogram of the affected extremity is obtained in the same way as that before the first chemotherapy course – with a measuring tape (fig. 3), which makes it easier for the surgeons to make a decision concerning the type of surgery (sparing or radical - mutilating).
b) Conventional X-ray does not allow assessment of the extent and grade of necrosis. Progressive calcification of neoplastic tissue present in the bone and remodeling of its structure, as well as a restriction of the process area with good delineation of tumor borders is a favorable sign (fig. 4).
c) Calcification of periostal reactions is also a symptom expected in the course of cytostatic treatment. The grade of calcification, incorporation and limitation of osteogenic periosteal reactions should be assessed [23] (fig. 4).

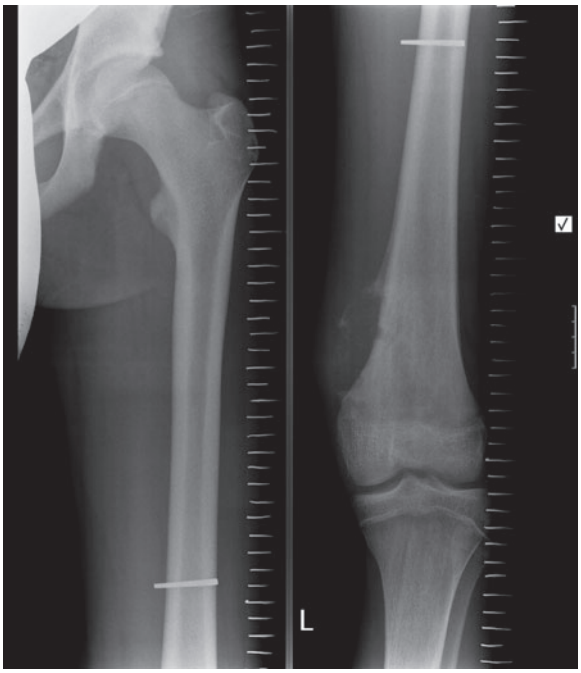

Figure 3. Osteogenic sa, femur. Radiogram with measurement.

Each periodic assessment includes also chest X-ray, performed according to the applicable standards.

Postoperative and follow-up period

Immediately after the surgery, according to the aforementioned principles, the extent of the procedure depending on its type (sparing, mutilating) is assessed. In case of amputation of the extremity, its level is determined and the structure of the bone stump and soft tissue is assessed.

After sparing surgery with the use of an allograft, its type is defined (bone splints or fragments) and its extent is assessed (fig. 5).

After implantation of an endoprosthesis, its positioning and fixing is assessed (fig. 6).

If the postoperative period is uncomplicated, radiography, like before the surgery, is performed before each adjuvant chemotherapy course (according to the adopted treatment protocol), and after the completion of treatment with the frequency dependent on the follow-up period: for 2 years at 2-month intervals, up to 5 years at 6-month intervals; the freuency of further control exminations is disputable: once a year? depending on the clinical symptoms? The structure of the stump, remodeling and incorporation of allografts, periosteal reactions and their character, type of potential complications or relapses are assessed then (fig. 7 and 8).

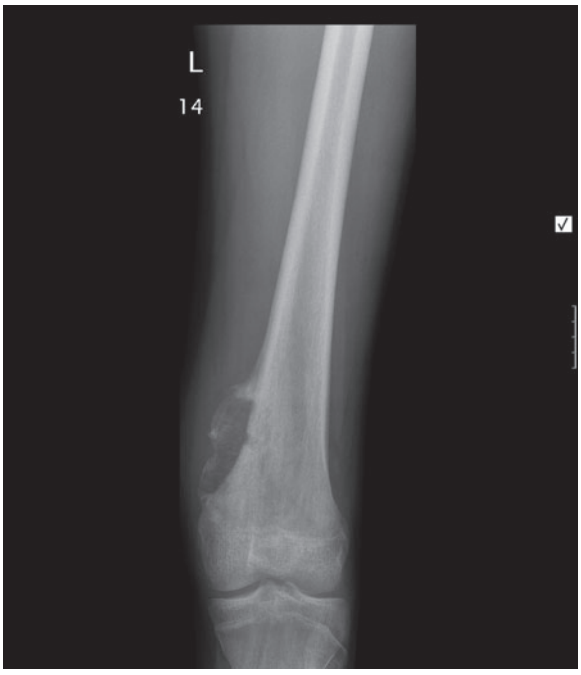

Figure 4. Osteogenic sa after initial chemotherapy (the same patient as in fig. 2). Sclerotic bone remodeling, calcification of periosteal reactions and ectracortical tumor.

ULTRASONOGRAPHY (US)

Ultrasonography (US) is a complementary method in the diagnostics of tumors of the musculoskeletal system in children and adolescents, used in order to obtain the images of soft tissues, as well as superficial osseous, chondrous and articular structures.

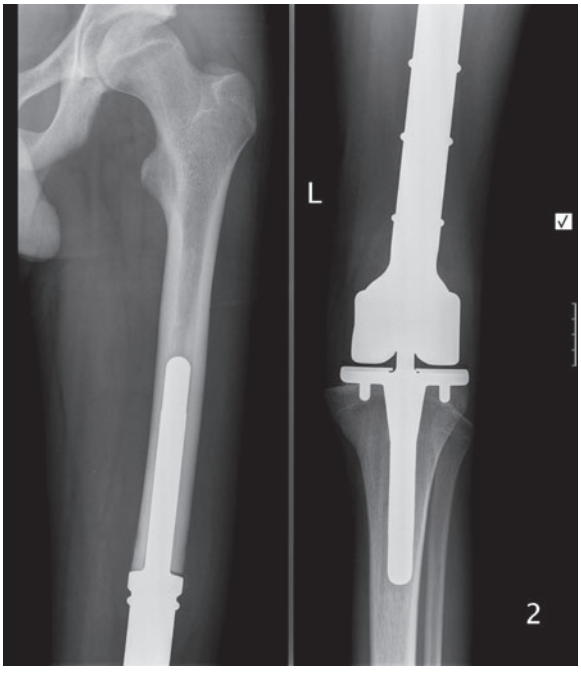

Figure 6. Patient after the resection of osteogenic sa. Correct position of the endoprosthesis. Regular edges of the stump of femur, normal bone structure.

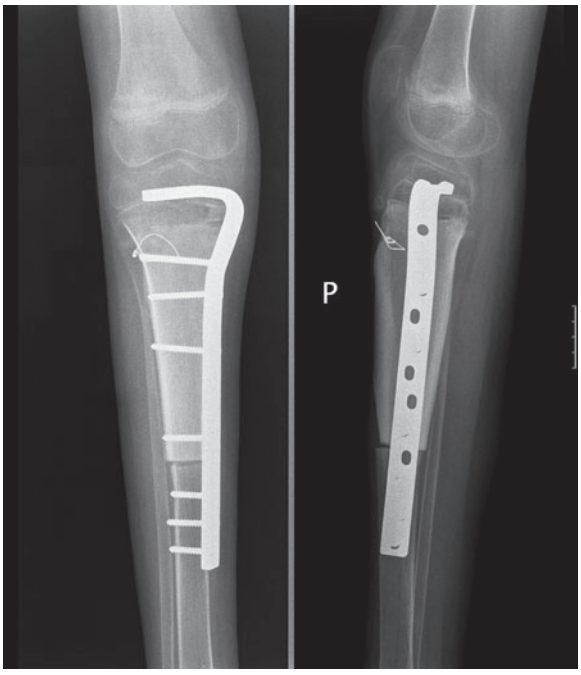

Figure 5. Patient after the resection of osteogenic sa. Allogenous osseous implant with a metallic stabilizing element. Trace of bone union in the proximal part, lack of the union in the distal end.

US is performed in the diagnostic and therapeutic period (pre- and postoperative) as well as for assessment of postoperative complications.

This method is also used for localization of diagnostic biopsy sites [2, 8] or puncture of pathologic fluid-containing spaces.

The examination is cheap and safe for the patient. It provides dynamic images with high resolution. It can be performed at the bedside and in the operation room.

The disadvantage of the method is its considerable dependence on the investigator's experience and his/her interpretation of the images, physical stature of the patient, and to a large extent also on the equipment quality. The presence of artifacts may make the assessment of the image more difficult.

Apparatus

The prerequisite for obtaining diagnostic US images of musculoskeletal structures is the use of digital equipment with high technical parameters, specialist software for soft tissue and with both Color Doppler and Power Doppler angio options. Measurement software must enable calculations of the basic quantitative flow parameters, as well as PI and RI coefficients.

The following transducer types are used:
1. linear wide-band transducer with variable frequency from 5 to 12 MHz (most often 7.5MHz frequency is used).
2. convex type transducer with 5 MHz frequency – for preliminary assessment of large tumor masses, located deep and affecting a larger area.

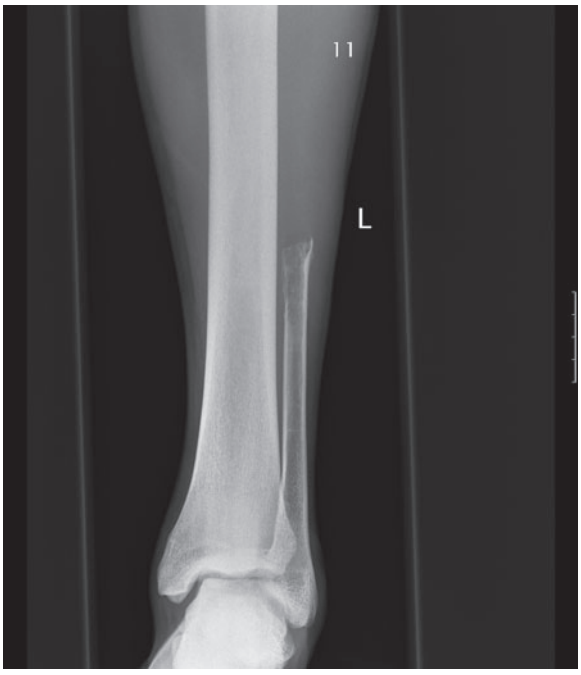

Figure 7. Patient after the resection of osteogenic sa of the fibula. Recurrence in the proximal part of the stump – osteolysis, periosteal breakthrough and spicular reactions.

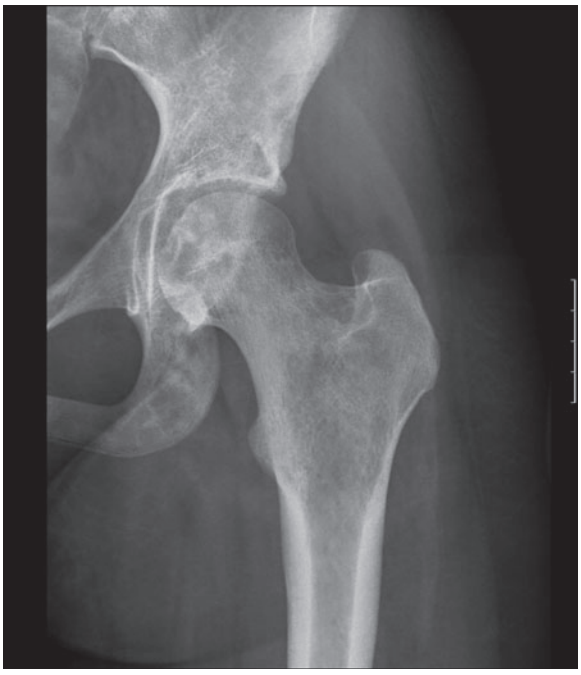

Figure 8. PNET of the 3rd metatarsal bone of the left foot. Lytic metastases in the pelvis and femur.

3. linear or microconvex transducers with higher frequency, exceeding 10 MHz, are used for the assessment of lesions in the skin and subcutaneous tissue, as well as superficial changes on flat bones and in very small children. They need not be routinely used in diagnostics of the locomotor system tumors, but they are useful in investigation of some tumor types.

Additional options

For imaging of larger tumors, the technique of extended visual field obtained with linear transducers with pseudoconvex option is extremely useful, or panoramic imaging used for investigation of extensive tumors, exceeding the transducer width.

In three-dimensional US technique, numerous conventional 2D images are collected in sequences lasting a few seconds each, and then reconstructed. Activation is effected by the transducer movement induced by the operator's hand or by a special probe kept immobile above the object. 3D colored images of pathologic vasculature in the tumor is particularly important for the assessment of angiogenesis [2, 27].

The use of contrast enhancement increases US sensitivity. Enhancement of the echo effect is enhanced by the presence of gas microbubbles [28, 29, 30, 31]. The results of US should be recorded and archived using at least two methods. The basic method is printing the images on photosensitive paper, black-and-white, or colored. Digital archiving of images in the DICOM format on CD's or DVD's is becoming a standard.

Examination methodology

The examination is performed in B type presentation, in two dimensions and true time.

– The basic investigation should be performed in two perpendicular planes, taking the largest dimension of the tumor or the axis of the involved bone as an axis. The investigation may be modified depending on the character of plane changes;
– In order to standardize the investigation, the proximal and medial structures should be located on the left side of the image, and the distal and lateral ones – on the right side;
– The examination should start from the normal tissue area
– The site of transducer application should be determined accurately in relation to some landmarks of bony structures;
– To obtain the preliminary image for determination of the tumor location and size, a convex type 5 MHz head is used;
– 7.5–10 MHz and higher frequency transducers are used for precise assessment of the tumor mass structure [32]. Attention should be paid to appropriate adhesion of the probe to the skin surface. If it is impossible, using more gel or distance rings is recommended.

In order to obtain an optimal image, the setting of the image appropriate for the investigated tissue and their depth should be considered.

Regulation can be applied to:
– appropriate enhancement for the whole image and its individual layers (TGC/ZRW potentiometers),
– dynamics changes from 50-60dB (more details) to 45-50 dB (reduction of artifacts),
– appropriate depth setting to cover the whole extent of the lesion,
– location and number of the foci – better image quality with better focused depth,
– changes of emitted wave intensity – especially in superficial tissues.

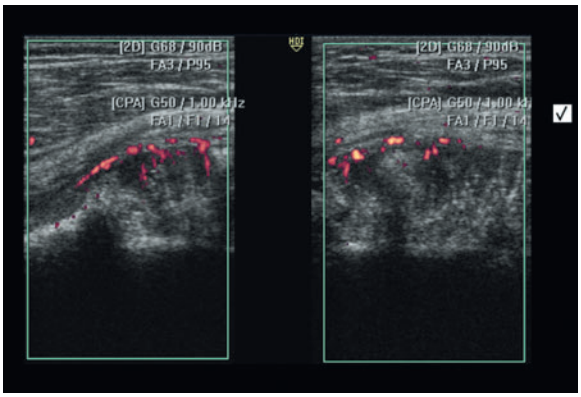

Figure 9. Osteogenic sa of femur. US with PD: infiltration of the periosteum with its breakthrough, Codman's triangle, spicules. Inhomogenous extracortical tumour with hypo- and hyperechoic parts.

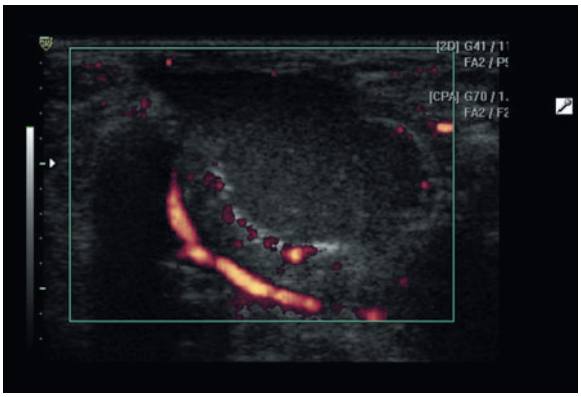

Figure 10. PNET of the 3rd metatarsal bone. Cortical destruction, pathological vascularization.

The next stage is an examination utilizing the Doppler phenomenon for assessment of the tumor vasculature and relation of the blood vessels to the tumor. The most useful and the most frequently used technique is Power Doppler (PD), used for demonstration of low-velocity flow in the tissues, irrespectively of its direction. The examination can determine the diameter, morphology and topography of blood vessels [31]. The technique with color flow imaging (Color Doppler) allows to demonstrate the presence of flow, its direction and effect of vascular changes (e.g. compression) on blood flow. Duplex Doppler in combination with color flow imaging visualizes the course of the blood vessel with flowing blood, and at the same time allows precise selection of the site where Doppler spectrum and PI and RI coefficients are measured. Some units have the Triplex option, in which 2D images, color Doppler and impulse Doppler are obtained at the same time.

The image of vasculature depends on the equipment and the individual parameters set in the laboratory; they should always be identical, both with respect to examinations of the same patient and of all patients with tumors examined with the same apparatus.

Diagnostic period

The aim of the baseline examination is to assess tumor parameters:
– determination of tumor location in relation to the nearest joint and assessment of its relation to the growth cartilage, surfaces, muscles, fascial and vascular structures.

US enables precise localization of the tumor with assessment of its distance from the nearest joint. In case of lesions localized close to the joints it allows to determine whether the articular elements are involved. It can also be assessed whether the tumor extends beyond the growth cartilage (when it is still present).

– assessment of tumor size: transverse, longitudinal and sagittal dimensions, size of the tumor in soft tissues, extent of destruction of the cortical bone layer.

Precise measurements of the tumor are possible in case of small lesions. Both linear measurements and volume estimation can be performed. Accurate measurements of large tumors are difficult and often impossible, limited by too small area visualized by the transducer. A certain progress has been achieved owing to the introduction of panoramic imaging function, which allows to visualize a larger area with the same transducer size. Besides assessment of soft tissue tumors, US provides information concerning the lesions present in the superficial bone layers – US is not designed for assessment of lesions of the osseous tissue; however, defects of the cortical layer are visible (fig. 10). The character of osteolysis can be assessed, and the lesions formed as a result of external compression or infiltration can be differentiated.

– character of bone lesions: osteolysis – well delineated, poorly delineated, focal, multifocal, disintegration – bone debris, destruction as a result of external compression or infiltration.

It is impossible to investigate the infiltration of bone marrow cavity with US.

– assessment of periosteal abnormalities:

Normal periosteum is not visible.
US is exceptionally useful for investigation of periosteal lesions. It is the method providing the best images of changes in the periosteum (undermining by infiltration, disruption of integrity, Codman's triangle, spicular reactions) before it calcification (fig. 9, 18b). Assessment of the periosteum and its reactions plays an important role in diagnostics and monitoring of treatment. Observation of the changes in periosteal vasculature is one of the bases for evaluation of tumor response to treatment [27].

– assessment of tumor structure: homogeneous, inhomogeneous, solid masses, cyst-like lesions, areas of disintegration, fibrosis, calcifications, etc. (fig. 9, 17b, 17c, 18b).

The value of US in assessment of tumor structure is comparable to that of MRI. This method can demonstrate the presence of solid masses, cyst-like lesions, signs of disintegration, and in the course of treatment determine the presence of regression, necrotic, fibrous areas, and, to a lesser extent, calcifications of the lesion.

– determination of the tumor echostructure – always in relation to the surrounding normal tissue: muscular and adipose – normoechogenic, hypoechogenic, hyperechogenic, mixed;

The structure of neoplastic lesions is usually inhomogeneous with varied echogenicity. Echogenicity assessment of the tumor must not be the basis for determination of its character. Changes in echogenicity in the course of chemo- or radiotherapy can be an indicator of the tumor reaction to treatment [2].

– assessment of edema: in the vicinity of the tumor and generalized

Edema of the tissues surrounding the tumor makes it difficult to assess the extent of the lesion, because it can be treated as tumor-affected tissues.

– assessment of tumor borderlines: expansion growth: sharp, regular, encapsulated, partially encapsulated
– infiltration growth: obscured, irregular, non-encapsulated, invading the surrounding tissues (muscles, adipose tissue, subcutaneous tissue and skin)

Ultrasonography allows to determine the character of tumor growth and its borderlines, which largely facilitates differentiation of malignant and benign lesions. Infiltration growth patterns suggest a malignancy, whereas expansion growth is more typical of benign tumors [2].

US does not allow assessment of neoplastic osteogenesis.

– determination of vascular pattern of the tumor:
– according to subjective criteria: absent, scarce, moderate and abundant, homogeneous or inhomogeneous, central, peripheral and mixed or interstitial
– measurement of blood flow in the selected blood vessels.

More and more attention is paid to the assessment of pathologic vasculature of the tumors. Blood vessels supplying the tumor are pathologic by nature and formed as a result of neoangiogenesis. Development of pathologic vasculature, from little venules to arteries, can be helpful in assessment of the malignancy grade of the tumor according to differentiation of its angioarchitecture. The blood vessels are usually arranged chaotically, forming an irregular network [11, 17c]. Because of poorly developed and unevenly thick tunica media, their lumen is irregular, with numerous stenosed sites and obliterations, sinuses and sinusoids lined only with endothelium, or even with tumor cells. Larger blood vessels can form up to three branches. Arteriovenous shunts are also common. Such vascular structure has certain hemodynamic results, the blood flow is irregular, often turbulent, with congestion in the sinuses and smaller vessels and drainage through arteriovenous shunts [27]. The flow recorded from pathologic tumor vessels has low resistance, lower maximum systolic velocity and relatively high flow velocity persistent throughough the whole diastolic phase [29]. Combination of color Doppler and power Doppler techniques can help to assess tumor malignancy [2]. In many cases, qualitative assessment is difficult, or impossible. The subjective assessment of vascularization, i.e. subjective evaluation of the number, topography

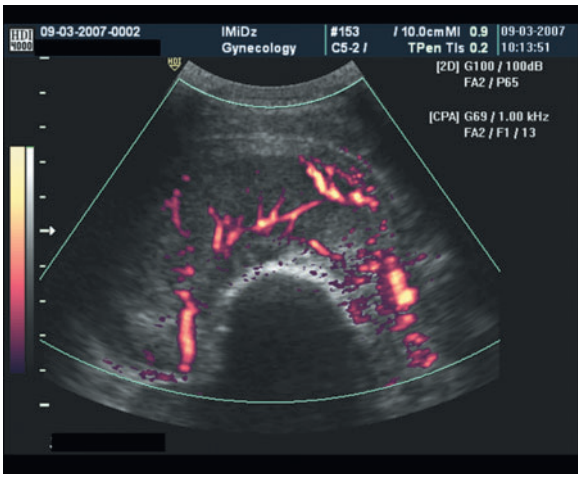

Figure 11. Ewing sa of femur. US with PD. Pathological vascularization within the tumor.

and size of blood vessels, plays an important role in such cases. Tumor vascularization can be assessed subjectively as: absent, scarce, moderate and abundant, homogeneous or inhomogeneous, central, peripheral and mixed or interstitial. Histopathological investigations demonstrate that the variations of vascular patterns are dependent on the grade of malignancy [2]. Limitations of the technique result from too small tumor size, or total necrosis and avascularity.

– assessment of lymph nodes in the vicinity of the tumor: determination of size, echogenicity, structure, signs of disintegration, vascularization (of hilar, capsular origin).

This is almost the only reproducible method of assessment of the regional lymph nodes because of the accuracy and resolution of the image. Some problems may be associated with retroperitoneal and abdominal lymph nodes, obscured by gases.

Therapeutic period (preceding the subsequent chemotherapy course)

Assessment of the lesions after chemotherapy (radiotherapy):
overall tumor size
size of necrotic areas
size of regression areas
size of neoplastic texture areas
assessment of periosteal reaction
assessment of vascularization.

The above parameters are used in evaluation of the tumor reaction to treatment. The necrotic foci are anechoic, badly delineated, avascular areas. The presence of regression areas and areas with viable neoplastic texture can be assessed by observation of changes in their vascular pattern during the diagnostic and therapeutic period. Reduction or lack of vascularization, changes in flow parameters in previously richly vascularized locations are important diagnostic signs [33].

Preoperative period

Repeated assessment after the subsequent cycle of chemotherapy (radiotherapy) and determination of tumor response to treatment.

Assessment of the aforementioned parameters (together with CT and MRI results) in the preoperative period assists the surgeon in planning of the extent of the procedure. It is important to determine the tumor size, its distance from the nearest joint and relations with the adjacent structures. Particular attention should be paid to precise determination of the relations between the tumor and the neurovascular bundle.

Postoperative period
– assessment of radicality of the surgery
Detection of the presence of potential pathologic tissue based on their morphologic features (echogenicity abnormalities) and pathologic vascularization is not easy. It requires differentiation with inflammatory conditions and processes of normal healing after the surgery.
– assessment of soft tissues:
normal healing and cicatrization;
complications: edema, exudate, hematoma
– assessment of bone healing
– assessment of local recurrences
– assessment of metastatic lesions.

Differentiation of the lesions developed as a result of complicated healing and potential tumor relapse is difficult. Ultrasonographic images are not pathognomonic for these pathologic processes. Nevertheless, US plays an important role in the detection of local recurrences, especially in patients with implanted endoprostheses, in whom artifacts produced by metal elements make other methods (CT and MRI) less useful [25].

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