Bone sarcomas

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Key words: sarcoma, bone, chondrosarcoma, Ewing sarcoma, osteosarcoma, giant cell tumor of bone, diagnostics, therapy, recommendations

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. The quality of scientific evidence

I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials

II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomized cohort studies)

III — Scientific evidence obtained from retrospective observational studies or case-control studies

IV — Scientific evidence obtained from clinical experiences and/or experts, opinions

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2. Category of recommendations
A — Indications confirmed unambiguously and absolutely useful in clinical practice
B — Indications probable and potentially useful indications in clinical practice
C — Indications determined individually

Correct diagnosis and effective combination therapy of primary malignant bone tumours (bone sarcomas) depend on the cooperation of radiologists and nuclear medicine specialists, pathologists, surgical oncologists and orthopaedic surgeons, medical oncologists, radiotherapists, and physiotherapists. Multidisciplinary treatment should necessarily be carried out in the centres of the respective experiment (III, A). Multi-centre cooperation is recommended within the framework of the Polish Bone Cancer Registry (prnk@coi.waw.pl). The introduction of combined treatment allows five-year survival in approximately 60–70% of patients and increases the percentage of patients in whom the limb can be preserved.

Epidemiology and aetiology

Bone sarcomas in adults are a diverse group of tumours of mesenchymal origin. They are rare, constituting less than 0.5% of new cases of all malignancies. In some cases, detailed histogenesis is unknown.

Clinically, bone sarcomas are divided into spindle cell and small cell. Osteosarcoma occurs most often among spindle-cell sarcomas — in Poland diagnosed annually in approximately 60–100 people (2–3 per 1,000,000), and more common in men (1.4 to 1) and young people (approx. 80% of cases in second and third decade and about 20% of cases in the sixth and seventh decades of life). The second most common in the incidence of spindle-bone sarcomas in adults is chondrosarcoma, and others (e.g. fibrosarcoma or undifferentiated pleomorphic sarcoma) are much rarer. Small cell sarcomas (e.g. Ewing's sarcoma or mesenchymal chondrosarcoma) occupy the third spot in the incidence of primary malignant bone tumours in adults. However, in the first and second decade of life, Ewing's sarcoma is second — after osteosarcoma — in terms of prevalence (3 cases per 1,000,000; about 40–60 cases per year) of primary malignant bone tumour (in about half of the patients between 10 and 20 years old, children under five years of age rarely, boys more often).

A small number of spindle cell sarcomas occur on the basis of predisposing diseases (e.g. Paget's disease or hereditary retinoblastoma — osteosarcoma, multiple osteochondral osteomas — chondrosarcoma) or may be induced by previous irradiation. Small cell sarcomas do not develop secondary to other conditions and do not occur in familial or hereditary cancer syndromes [1, 2].

Bone sarcomas in children and adolescents are 7–8.2% of all cancers in this age group. Annually about 75 new cases are diagnosed in Poland. The most frequently diagnosed is osteosarcoma — 56% of all bone tumours in children and adolescents (approximately 40 new cases per year), followed by Ewing sarcoma 34% (approximately 25 new cases per year). Other, much less frequent malignant bone tumours in children are chondrosarcoma and fibrosarcoma. In rare cases, the skeleton may also be the primary location of lymphoma [3, 4]. Primary bone lymphoma is not discussed in this paper.

Diagnostics

Medical history and physical examination

The most important and early symptom is pain, which is usually stronger at night and gradually increases in the following months of the disease (the exception being the majority of chondrosarcomas). In the later stages of the disease there may be observed a tumour and distortion of the limb — the symptoms are connected by some of the patients with trauma (in fact, the injury only draws attention to the disease, but does not cause cancer). About 40% of small cell sarcomas have a so-called inflammatory mask (symptoms of inflammation and fever), which makes proper diagnosis difficult. In about 60% of patients at the time of diagnosis there is soft tissue infiltration. Bone sarcomas are often accompanied by limb dysfunctions (limited mobility of the nearest joint with reflex saving) and permanent articular contractures and bone fractures in cases of local advancement. The diagnosis of early forms of bone sarcomas (volume less than 100 cm^3 and no crossing of the cortical bone) is very difficult and usually accidental. In the more advanced local stage of small cell sarcoma, general symptoms (fever, anaemia, weakness) may occur, which — apart from increased activity of lactate dehydrogenase (LDH) — are negative prognostic factors.

Osteosarcoma is most often located near the metaphyses of the long bones — mainly the distal femoral area (around the knee area — about 50%), the proximal part of the tibia or brachial bone, and the head of the fibula bone. Osteosarcoma develops most often on the basis of healthy and fast-growing bone (young people), but it can also arise at the site of previous benign lesions (e.g. fibrous dysplasia, bone infarction, or — in older people — Paget's disease). Chondrosarcomas occur more often

later in life and often affect differently shaped bones (pelvis, shoulder girdle) or proximal femur and can develop from pre-existing lesions (e.g. osteochondroma or enchondroma). Ewing sarcomas most often concern the shaft of long or flat bones, spine, and pelvis.

Imaging studies

The first and basic study is an X-ray of the entire bone in two projections together with the adjacent joint (classic forms of bone sarcoma give symptoms characteristic of each type of sarcoma).

In the group of small cell tumours, X-ray images are often atypical, especially in the early stages of the disease and in small children. The tumour usually destroys healthy bones through osteolytic defects or infiltration. Sometimes there are signs of pathological malignancy of calcified (bone or cartilage) tissue and malignant periosteal reactions (e.g. Codman's triangle or spikulae). In children and adolescents in Ewing sarcoma osteolysis foci are visible and sometimes sclerotic changes coexist. Periosteum reactions that can run parallel to the bones are very typical (image of "onion skins"). It is not uncommon for a bone fracture to coexist (around 15%). Depending on the type of sarcoma and the rate of tumour growth, infiltration can pass to the growth plate, and also damage to joint cartilage can occur.

In further diagnostics (assessment of the local stage of the cancer by determining the extent of changes in soft tissues and seizing the bony layer and spongy bone), magnetic resonance imaging (MRI) is helpful to visualise bone marrow, joints, and attitudes to surrounding structures, as well as computed tomography (CT). Bone scans help to exclude lesions in other parts of the skeleton. In the assessment of the stage of small cell sarcomas, it may be helpful to perform a positron emission tomography (PET) examination together with a CT scan (PET-CT). It is always necessary to perform a chest X-ray examination to exclude metastases (metastases in the lungs — about 20% of patients at the time of diagnosis of bone sarcoma) [5–7].

Pathomorphological assessment

Histological diagnosis is established on the basis of tissue examination of the material from the surgical biopsy or oligobiopsy. It is important to choose the place of material collection (based on the assessment of the surgeon and pathologist made on the basis of full diagnostic procedure), which should contain tumour cells intact necrotic. The place of material collection should be removed during the final excision by one group of doctors. In Ewing sarcomas in adults, bone marrow retrieval should be considered for histological examination, which in about 15% of patients contains cancer cells; in children, bone marrow examination is part of the compulsory testing before starting treatment.

The basic method of biopsy in bone sarcomas is an open biopsy, and only a part of experienced centres base on the examination of material obtained by trepanobiopsy or core-needle biopsy (in children and adolescents, the method of choice is an open biopsy). Biopsy incision should not interfere with subsequent surgery and leads to unfavourable expansion of irradiation fields and increases the risk of pathological fracture. The residual activity of the isotope (99Tc) given during bone scintigraphy can be used to select the best site and determine it intraoperatively using a manual (sterile) gamma-camera. Incisions for the open biopsy and for subsequent radical excision must coincide (scar after an open biopsy — an inseparable fragment of the pathological preparation). A biopsy should be performed away from the neurovascular bundle. When choosing a biopsy site the results of X-ray and bone scintigraphy need to be used and the principle of the shortest path between the skin and the tumour should be applied. A skin incision — long enough to reach deeply situated lesions — should be carried out in parallel to the long axis of the limb. During preparation, the limits of the muscle compartment should not be exceeded. The specimen from the tumour infiltration should be taken "sharply" from the periphery (the largest proliferation and the smallest necrosis). In tumours without crossing the cortical layer of long bones, one should cut the bone window in the thinnest place, in order not to weaken the bones and promote a pathological fracture. During the removal of the specimen, significant bleeding from the tumour may occur. Thorough haemostasis should be performed within the soft tissues and bones (e.g. wax). The wound should be thoroughly closed after drain removal (without drainage or with drainage — in this case the drain should be placed in the immediate vicinity of the biopsy wound), so as not to leave dead spaces (stitching of subsequent layers of muscle, fascia, subcutaneous tissue, and skin). It is also good practice to perform a smear on the slide from the collected slice to perform a cytological examination or tissue impression of a roller obtained during a thick-needle biopsy for the intraoperative evaluation of the material in terms of "diagnostics" and the appropriate volume for the proper examination. In case of bleeding lesions the tumour mass of the material taken by the surgeon may constitute the necrotic part of the tumour. Material from bone cancer should be submitted for pathological examination without fixation, while in the case of planned molecular testing with nucleic acid isolation, the material should be frozen at a temperature of at least –70°C. Consideration should also be given to collecting material for microbiological testing in order to exclude osteoarthritis. The protection of the material for molecular research is currently in force in children and adolescents with bone tumours.

The pathomorphological report should be based on the classification of the World Health Organisation

Table 1. Classification of primary malignant bone tumours according to the World Health Organisation (WHO)

Osteogenic tumours
Osteosarcoma
Conventional osteosarcoma
Chondroblastic subtype
Fibroblastic subtype
Osteoblastic sclerosing subtype
Telangiectatic osteosarcoma
Small cell osteosarcoma
Central low-grade
Secondary osteosarcoma
Parosteal osteosarcoma
Periosteal osteosarcoma
High-grade surface osteosarcoma
Chondrogenic tumours
Chondrosarcoma
Central, primary and secondary
Peripheral
Dedifferentiated
Mesenchymal
Clear cell
Fibrogenic tumours
Fibrosarcoma of the bone
Haemopoietic neoplasms
Plasma cell myeloma*
Primary non-Hodgkin lymphoma of the bone*
Osteoclastic giant cell rich tumours
Malignant giant cell tumour
Notochordal tumours
Chordoma
Vascular tumours
Angiosarcoma
Epithelioid haemangioendothelioma
Myogenic tumours
Leiomyosarcoma
Lipogenic tumours
Liposarcoma
Miscellaneous tumours
Ewing sarcoma
Undifferentiated high-grade pleomorphic sarcoma of the bone
Adamantinoma

*Myeloma and primary bone lymphoma are not discussed in this paper

(WHO) (Tab. 1) [8], and in the differential diagnosis of small cell tumours, the availability of immunohistochemistry and cytogenetic tests for the assessment of characteristic translocations is necessary.

Nonetheless, in order to plan treatment it is necessary to obtain information on histological diagnosis, local range, and stage of the tumour (locally advanced or metastatic).

The standards of pathomorphological reports including data from morphological, immunohistochemical, and molecular studies have been developed by the College of American Pathologists (CAP) and the Royal College of Pathologists (RCPath) (https://www.rcpath.org/resourceLibrary/dataset-for-histopathology-reports-on-primary-bone-tumours.html); Protocol for the examination of cancer patients (Cancer protocol templates: www.cap.org).

Differentiation

The first stage of differentiation — using X-ray — includes the exclusion of benign tumours and fibrous dysplasia and changes in the course of metabolic diseases (e.g. hyperparathyroidism). Differentiation of the aneurysmal bone cyst is difficult because the lesion can be secondary to fast-growing malignant bone cancer.

The next step is the histological differentiation of bone sarcoma based on the examination of the material obtained via an open biopsy. In the differentiation of sarcomas, the location is of secondary value (most often — the metaphyseal region in spindle cell sarcomas and bone stems in small cell sarcomas). The importance of sarcoma differentiation is due to the fact that spindle cell tumours are insensitive to irradiation. It is important to exclude bone lymphomas because they do not require surgical treatment. Metastasis of other cancers to the bone are more common than primary sarcomas, and in the differentiation the age of the patients is of additional importance (sarcomas are more common in younger people). In children and adolescents, all small cell malignancies of childhood (neuroblastoma, lymphoma, rhabdomyosarcoma, primitive neuroectodermal tumour, and small cell osteosarcoma) should be included in the differentiation.

In cases of osteosarcomas and Ewing's sarcomas the assessment of material after tumour resection or amputation involves the analyses of the proportion of cross-sectional area covered by the tumour tissue necrosis. The prognosis is better if necrosis accounts for 90% or more of tumour formation.

Staging

The basis for the classification of clinical stage is the assessment of a group of the most important prognostic factors, which include: histological malignancy, neoplastic infiltration through the cortical bone, size of the primary tumour, and condition (metastases) in distant organs (mainly lungs) and regional lymph nodes.

Determination of the stage of bone sarcoma is based on the TNM classification according to the American Joint Committee on Cancer (AJCC) of 2010 (Tab. 2, 3) with histological malignancy (G1–G4), primary tumour (T1–T3), regional lymph nodes (N), and distant organ metastases (M) [9]. In 2018, the eight edition of UICC--AJCC classification was introduced, in which bone sarcomas located in the pelvic bones and in the spine are classified separately.

Table 2. Staging of bone sarcomas according to TNM classification

Primary tumour (T)	
Tx	Tumour cannot be assessed
T0	No sign of the tumour
T1	Tumour 8 cm or less in greatest dimension
T2	Tumour more than 8 cm in greatest dimension
T3	Discontinuous tumours in the primary bone site "skipping metastases"
Regional lymph nodes (N)	
Nx	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastases (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites
Additional markings in the TNM classification — pT (m) NM — "m" defines the presence of several tumour foci in one location — rTNM — "r" defines the material that is the recurrence of a previously diagnosed tumour (after remission) — ypTNM — "y" determines the material that is evaluated after or during chemotherapy, radiotherapy or both methods	
Histology grade (G)	
Gx	Grade cannot be assessed
G1	Well differentiated — low grade
G2	Moderately differentiated — low grade
G3	Poorly differentiated — high grade
G4*	Undifferentiated — high grade

*Ewing sarcoma — G4

Treatment

All primary malignant bone tumours should be treated in multidisciplinary teams (IV, A), because over 70% of bone sarcomas require combination therapy [especially osteosarcomas and small cell sarcomas (I, A)] involving — primarily — surgical treatment and chemotherapy (Tab. 4) [1, 2, 6, 7, 10]. The primary goal is to obtain local control of the sarcoma through proper surgical radical treatment. The decision about the extent of this type of therapy should be made prior to initiation of combination therapy, and patients should agree to the planned extent of surgical excision before starting the initial chemotherapy (CTH). In the case of bone fracture before treatment, internal anastomoses are contraindicated due to the risk of local sarcoma cell shedding and disqualification from the limb-saving surgery.

In terms of treatment strategies, bone sarcomas can be divided into four basic groups: osteosarcomas and other, less frequent, spindle cell sarcomas, chondrosarcoma, small cell sarcomas and giant cell tumours of bone.

When deciding on the treatment of spindle cell sarcoma patients (mainly osteosarcoma) and small cell sarcomas, the following principles apply [1, 2, 6, 7, 10]:

— obtaining a reliable histological diagnosis before starting treatment;
— the use of combined treatment within the established therapeutic protocols (I, A), because they are high grade histological malignancy (results of exclusive surgical treatment are poor — less than 20% of five-year survival) beside of low grade parosteal osteosarcoma (subject of discussion — use of peri-operative CTH in patients with spindle cellar sarcomas over 50 years of age) — if possible, treat-

Table 3. Clinical staging of bone sarcomas according to the AJCC 2010 classification

	T	N	M	G
IA	T1	N0	M0	G1, G2 (low grade)
IB	T2, T3			
IIA	T1	N0	M0	G3, G4 (high grade)
IIB	T2			
III	T3	N0	M0	G3, G4
IVA	Any T	N0	M1a	Gx–G4 (any grade)
IVB	Any T	N1	Any M	
		Any N	M1b	

Table 4. General principles of treatment for particular types of bone sarcomas

	Preoperative chemotherapy	Surgical treatment	Radiotherapy	Postoperative chemotherapy
Osteosarcoma	Yes	Yes	No	Yes
Other spindle cell sarcomas				
Chondrosarcoma*	No	Yes	No	No
Ewing sarcoma (small cell sarcomas)	Yes	Yes	Yes	Yes
Giant cell tumour	No**	Yes	Yes	No

*Excluding mesenchymal and dedifferentiated subtypes, for which the schemes as for small cell sarcomas and osteosarcoma are used, respectively; **except for denosumab used to optimise resection

ment should be offered to patients under prospective clinical trials;
— decision about the extent of excision before commencement of combination therapy — patients should agree to planned surgery before starting preoperative CTH, because the effectiveness of initial treatment may cause unwarranted hopes of avoiding amputation or surgical treatment (lack of knowledge, understanding, and acceptance by the patient of initial surgical decisions lead to conflict and resignation from the proposed operation, which is the basis for treatment and cure of the patient);
— absence — standard — radiation therapy (RTH) in the radical treatment of osteosarcoma (II, A);
— patients with resectable metastases are treated according to similar principles as patients with localised tumour, although the prognosis is significantly worse. In the treatment plan, if possible, include dissection of metastases;
— use of three-stage procedures for the most common malignant bone tumours in children and adolescents:
  • stage I — initial CTH to reduce the primary tumour focus and destroy micrometastases (4–16 weeks depending on the CTH regimen used and the response to treatment — EURAMOS in osteosarcoma and EWING 2008 in Ewing sarcoma);
  • stage II — treatment of the primary tumour (surgical and/or irradiation depending on the type of sarcoma, location of the lesion and age of the patient) — the principle of removing the tumour with a margin of unaltered tissues applies (radical treatment in the histopathological assessment with the aspiration to preserve the limb — if possible — and completing the resulting defect with bone graft, endoprosthesis, or other form of reconstruction) and applying irradiation under the conditions of the planned three-dimensional conformal RTH (the possibility of using higher doses of targeted radiation in a shorter time and a significant reduction of the risk of complications — a dose of 40–65 cGy depending on the tolerance of tissues affected by irradiation and age of the patient);
  • stage III — postoperative CTH to increase the chance of cure [4–8 months depending on the type of tumour — treatment regimen depends on the response to initial CTH including the clinical response and the degree of necrosis in the excised tumour — with a favourable response (high degree of necrosis [11]) drugs from stage I are used, whereas in the unfavourable case — new CTH regimens with the use of other drugs should be used; in Ewing sarcoma in children and adolescents in case of poor response to initial CTH or in the case of multiple metastatic disease foci, consolidation of treatment with high-dose CTH followed by transplantation of stem cells taken from the patient during the first stage of treatment can be applied; in the case of tumour progression, it is necessary to change the scheme and/or earlier treatment of the primary tumour].

Surgical treatment

Greater efficiency of diagnostics, introduction of combination therapy principles, and technological progress have resulted in extending the indications for the use of treatment with the possibility of saving limbs. Surgical sparing treatment must provide a radical local excision of the tumour (R0 — microscopically without infiltration in the surgical incision line), cannot reduce the time free from relapse, and must result in better functional effects than after amputation and external prosthesis without deterioration of quality of life. Limb-sparing surgeries should only be planned when a stabilisation or partial response is obtained after the initial CTH. Possibilities of maintaining good limb fitness include: absence of pain, deep and superficial sensation, and limb functionality (upper limb — preservation of at least a grip function of the hand, lower limb — preserving the support function and the ability to walk). Indications for surgical sparing treatment in children and adolescents are determined taking into account the type of sarcoma (histological

diagnosis), the response to initial CTH, the anatomic location of the lesion, the location of the tumour biopsy, ratio to surrounding tissues and structures (blood vessels and nerves), age, and lifestyle.

Surgical procedure consists of three elements: tumour resection, bone reconstruction, soft tissue coverage.

Tumour should be removed with the periphery of completely unchanged tissues after the separation of vascular-nerve bunches. Along with the tumour, the scar should be removed after the biopsy and — if possible — the tumour should be removed outside the joint. The most frequently used forms of reconstruction are:

— tumour excision with subsequent joint immobilisation;
— excision of the tumour with enucleation in the joint and reconstruction with the help of an endoprosthesis or bone graft;
— extra-articular tumour excision with bone reconstruction graft.

Finally, the most difficult step in the surgical treatment is to supplement the resulting loss of soft tissue. Various techniques of reconstruction and microsurgery are used, enabling the movement of the muscle or skin-muscle flaps (e.g. the dislocation of the gastrocnemius muscle), which is particularly useful for extensive lesions in the proximal part of the lower leg (tibia).

The type of reconstruction performed depends on: size and location of the tumour, age and activity of the patient, as well as the knowledge and experience of the operating team.

The analysis of the test results and the response to the initial CTH allows us to determine the maximum tumour coverage and to determine the planned extent of excision with the necessary margin of normal bone. If, despite the extent of excision, the limb or its basic function can be preserved, the type of reconstruction should be determined taking into account the location of the tumour and the age of the patient (in this it is necessary to compare the calendar age with the bone age defined in the wrist X-ray). If there is a high probability of further growth of the patient and the table prediction of growth and the net body height percentile calculation indicates that the patient will grow more than 4 cm, it is indication for reconstruction with implantation of growing, expandalbe endoprostheses enabling extension of the extremity. Due to the need to continue CTH in the post-operative period, reduced immunity, and the possibility of infectious complications, a non-invasive, electromagnetic system that does not require operational intervention is preferred. In the remaining patients, a modular system (cementless) is used.

Implantation of the oncological endoprosthesis is associated with the possibility of complications throughout the patient's life, leading even to the need for amputation of the limb. The basic problems are maintaining the mechanical efficiency of endoprostheses and preventing bone atrophy in the vicinity of the endoprosthesis. In some cases, it is not necessary to replace the removed part of the bone (e.g. pelvic or shoulder girdle surgery). Sometimes, in addition to the reconstruction of bone fragments, reconstructions in the field of muscular ligamentous and sometimes also vascular structures are necessary. If there is no possibility of radical excision using limb-saving methods, it is necessary to perform amputation (Tab. 5) at the correct level (above the joint and proximally from the bone involved). Surgical treatment remains the only method of treatment in chondrosarcoma (exception — mesenchymal and dedifferentiated subtype).

Table 5. Contraindications for sparing surgery in bone sarcomas

Failure to use initial chemotherapy in osteosarcoma and small cell sarcomas
The lack of an adequate response to initial chemotherapy (stabilisation and/or partial response)
Extensive infiltration of soft tissues and vascular-nervous structures
Pathological bone fracture (relative contraindication)
Poor placement of an open biopsy
Inability to follow-up after treatment
Complications after endoprosthesis implantation

Some patients with metastatic bone sarcomas (mainly — M1a) have a chance to be cured under the condition of proper association of CTH with radical surgical treatment of metastases provided that adequate local control of the tumour is obtained.

Combination therapy

Spindle cell sarcomas

Spindle cell sarcomas (mainly osteosarcoma and chondrosarcoma) primarily require surgical treatment to control the disease locally. In cases of osteosarcoma, regardless of localisation, it is necessary to attach a complementary CTH before and after surgery (I, B) [schemes involving doxorubicin, cisplatin, ifosfamide, and methotrexate (I, A)] to improve survival without lung metastases and overall survival (Fig. 1) [1, 2, 5–7, 10, 12–17], and in the treatment of subsequent lines, ifosfamide with etoposide or gemcitabine with docetaxel (II, A) [18, 19] are used. Spindle-cell sarcomas usually are resistant to irradiation. Prognosis of patients with spindle cell sarcomas varies depending on the grade of histological malignancy and response to initial CTH, but overall five-year survival is around 70% or more on the condition of proper diagnosis and treatment.

The high degree of histological malignancy of osteosarcoma in children and young adults makes it

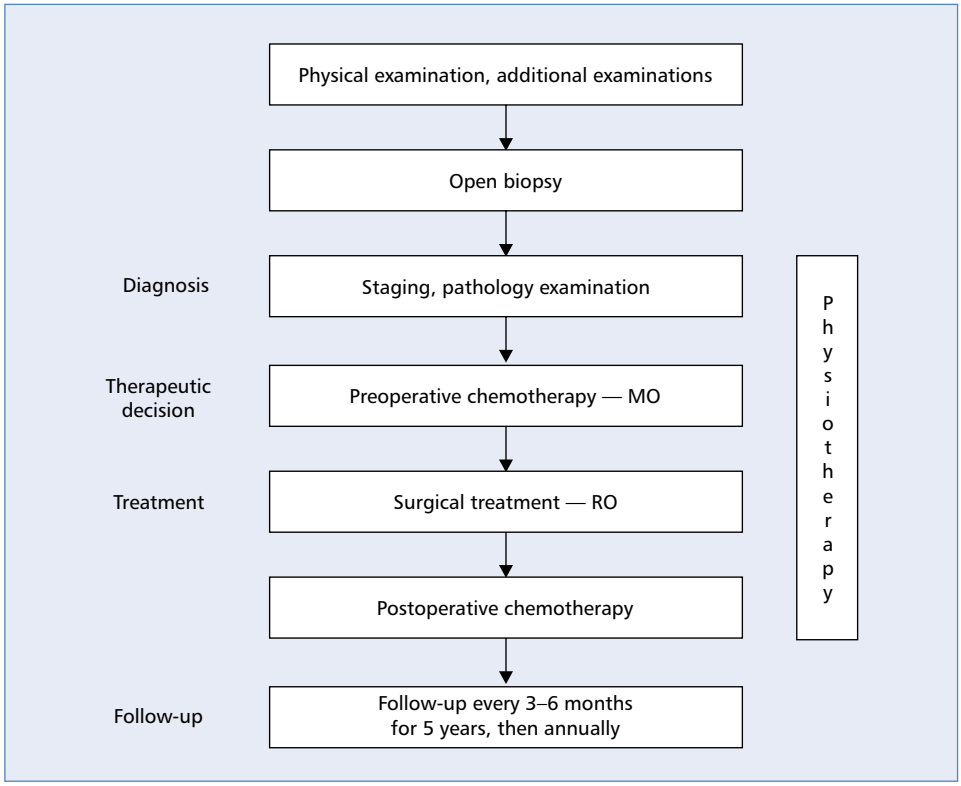

Figure 1. Diagram of the treatment for resectable osteosarcomas

necessary to use combined treatment with preoperative and postoperative CTH and surgical treatment (RTH is not used in radical treatment and is only used in the group of young patients under palliative procedure). The condition of starting the treatment is histological verification. Currently, there is no attempt to initially excise the tumour, which is most often associated with the need to perform a mutilating procedure (amputations or enucleation of the limb in the joint) and does not improve long-term results. The most important prognostic factors at the time of diagnosis include: size and location of the tumour, histological grade, and presence or absence of metastases. The size of the tumour correlates with the activity of LDH and alkaline phosphatase, and the finding of the concentration values of these enzymes constituting a multiple of the norm is a factor of poor prognosis (similarly as a significant size) [1, 10, 17]. Patients with limb localisation and distal tumour localisation have the best prognosis. Worse prognosis concerns patients with sarcomas located in the vertebrae and in the pelvic bones, where practically no radical resection is possible and attempts are being made to use protonotherapy (proton beam radiotherapy). The presence of metastases at the time of diagnosis of osteosarcoma is another factor of poor prognosis. The chance of getting a total cure in these patients depends among other things on the location and number of lesions, as well as the possibility of their radical resection (single metastasis — better prognosis, and multiple bilateral metastases — worse prognosis). The worst prognoses are for patients with dissemination to bones (rarely at the time of diagnosis) and to the brain (exceptionally at the beginning of the disease, more often with subsequent relapses). Currently, the most important prognostic factors are determined after excision of the tumour — non-radical resection and a low degree of tumour necrosis after initial CTH (more than 90% necrotic cells changed — better prognosis compared with 10% or more "live" cells — poor prognosis). The chance of five-year survival for a group with a favourable prognosis is 75–80% in contrast to the group with poor prognosis, in which 45–55% of patients survive for five years.

Management of adult patients with osteosarcoma begin with 3–4 cycles of preoperative CTH (usually doxorubicin and cisplatin and possibly a third drug, which is methotrexate) used in every three-week cycles. Methotrexate is not widely used in adult patients with osteosarcoma due to toxicity and lack of improvement in survival [20], but it is used as standard in therapeutic protocols in children and adolescents. It is now known that the escalation of CTH in the first line of treatment does not improve the survival and it is advisable to preserve ifosfamide for use in the second line of treatment. Currently, the absence of use preoperative CTH in patients with

osteosarcoma should be considered a mistake. At the time of 4 and 5. cycle (3 weeks after the 3rd CTH cycle) an operation should be carried out, the aim of which is to radically remove the primary sarcoma. Until recently, the choice of the post-operative CTH regimen was based on the assessment of histopathological response in the surgical preparation (in the case of a good response, the treatment was continued according to the program initially used for 2–12 cycles, while if an unsatisfactory pathological response was considered, other drugs was considered, e.g. ifosfamide and etoposide after previous use of doxorubicin and cisplatin). However, the results of studies conducted within EURAMOS-1 showed that the addition of ifosfamide and etoposide to the post-operative CTH (no benefit from intensification/change of treatment regimen) in patients with worse prognosis (no response) does not improve survival [21]. Only in the case of an parosteal variant of low-grade osteosarcoma, the basis of the treatment is a radical removal of the lesion only. Chemotherapy is used post-operatively in the case of high-grade dedifferentiation in pathology examination.

Muramyl tripeptide is an immunostimulant drug registered for adjuvant therapy in combination with multi-drug CTH in patients under 30 years after radical resection of non-metastatic osteosarcoma on the basis of results coming from one clinical study, which shows an improvement in overall survival (relative reduction of the risk of death by 28%, extension of six-year overall survival from 70% to 78%) [22] (II, C), but correct localisation of this drug in the therapeutic management requires further investigation.

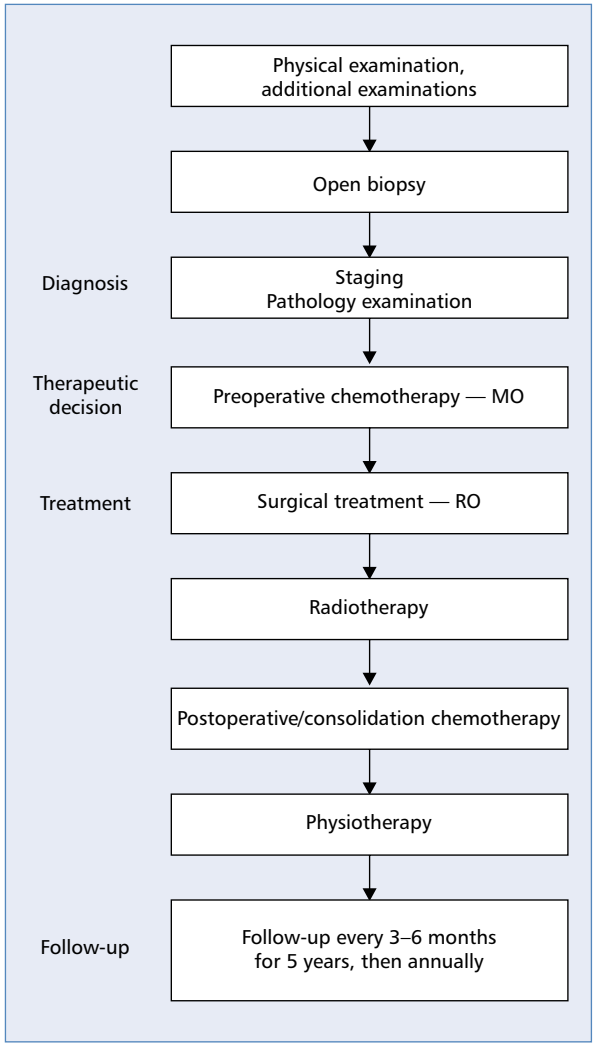

Figure 2. Scheme of the treatment of resectable small bone cell sarcomas

Small cell sarcomas

Small cell sarcomas (mainly Ewing sarcomas, as well as the mesenchymal form of chondrosarcoma) are low-differentiated and sensitive to irradiation (used to treat the primary focus) and are characterised by a high response rate to multidrug CTH [1, 2]. They require long-term combination therapy (started with CTH) (I, A), but prognosis is worse than in spindle cell sarcomas, and five-year survival in adults is 30–40%, and in children and adolescents 56–65%. The acceptance by the patients of the proposed type and course of treatment together with all the consequences is an essential condition for success. Patients should be informed about the duration of treatment (nearly 12 months), side effects of CTH and RTH (direct and long distant) and functional disability as a result of surgical treatment (both limb-sparing and amputation). Considering the relatively small number of patients with small cell sarcomas and significant difficulties in obtaining long-term experience, it is recommended to conduct treatment in oncology centres with extensive experience. Additional arguments are radiosensitivity of small cell sarcoma of bones (in contrast to spindle cell forms) and the important role of RTH in combination therapy.

Due to the chemosensitivity of small cell sarcomas, treatment starts with CTH (Fig. 2) regardless of the clinical stage (M0 or M1). Active drugs include: cyclophosphamide, ifosfamide, doxorubicin, dactinomycin, etoposide, and vincristine (I, A) [1, 2, 6, 7, 10, 23–27]. The doses and schedule of individual multi-drug programs depend on the local treatment protocols and toxicity occurring during treatment. The inclusion of ifosfamide and etoposide in the standard treatment (VCD regimen) in metastatic patients increases the duration of relapse-free survival and overall survival (I, A) [25]. The subject of a randomised trial of the third phase of Euro Ewing 2012, which is currently recruiting patients, is the comparison of the two most popular treatment programs (VIDE induction therapy + VAC/VAI post-operative treatment with the VCD/IE scheme). After inductive

CTH (3–5 cycles), local surgical treatment and perioperative RTH should be used (III, A) [10, 28–30]. If the size of the tumour exceeds 8 cm in the qualification and negative surgical margins are questionable, preoperative RTH or RTH and CTH should always be considered, which gives a chance for radical resection, and the area and radiation dose will be significantly lower than in the case of postoperative treatment (III, B). In clinical trials, it was not proven that irradiation of the whole bone was associated with an improvement of local control, and there was no significant advantage of doses above 60 Gy per patient survival compared to standard doses. RTH can be used on the initial sarcoma volume with a margin of 2–3 cm, which often makes it possible to reduce the field of irradiation and complications while maintaining the effectiveness of local treatment. It is necessary to provide a total dose of 40–60 Gy (depending on location) in fractions of 1.8–2.0 Gy per day. In the absence of radical local resection of sarcoma, radical RTH should be used, which — instead of mutilating surgery — is recommended especially for patients with the presence of M1 disease. In the EURO-EWING99 study in patients with primary metastatic disease who received local treatment, the three-year relapse-free survival was significantly longer compared with those who did not receive such treatment [31]. The certainty of a local cure, in turn, increases the percentage of patients who are qualified, if necessary, for the radical treatment of metastases. In the case of bone tumours of less than 8 cm in size and with a good response to the initial CTH, after radical resection, it is possible to omit the complementary RTH. There was no phase III randomised trial that would compare radical RTH with complete resection. The results of some studies indicate better local control without affecting long-term survival after surgery with or without RTH [29, 32]. After local treatment, the consolidating CTH is continued until the maximum dose of drugs is reached (in practice at least six months; in total 48–52 weeks) or the onset of grade 3 and grade 4 toxicity.

The implementation of the concept of initial combination therapy with CTH and postponed local treatment (Fig. 2) significantly improved long-term results of treatment of small cell sarcoma of bone in adults. Five-year survival increased from 5–10% to around 40%. The primary presence of metastases in distant organs reduces the percentage of cured patients to 30%. The prognosis of adult patients with small cell sarcoma is worse than in children due to the frequent occurrence of unfavourable prognostic factors, which are: metastases to distant organs, the longest tumour size over 8 cm or tumour volume above 100 cm^3, age over 17 years, and elevated LDH activity. Worse prognosis concerns localisation within the pelvis and spine as well as extra-osseous forms. The patients with recurrent disease have particularly bad prognosis.

In children and adolescents with Ewing sarcoma, the treatment includes the use of CTH according to the EWING 2008 schedule, and in the treatment of the primary focus, surgical procedures and/or irradiation. In the treatment of the primary focus, surgical procedures are recommended first. Radiotherapy is reserved for inoperable cases, after non-radical excision and axial location. Irradiation should be carried out under the conditions of three-dimensional RTH. This allows for higher doses of targeted radiation in a shorter time and a significant reduction in the risk of complications (dose of 40–60 Gy depending on the tolerance of the tissues affected by irradiation and age). In patients with an advanced process (high-risk group), high-dose CTH can be considered with transplantation of haematopoietic stem cells as part of the research protocols; this procedure improves treatment outcomes in patients with risk factors [50]. In children in the treatment of the second line (progression of disease, recurrence), topotecan and irinotecan are used [33]. The introduction of combination therapy significantly improved the results — currently, in the case of a localised tumour, about 65% of patients (in children) get a cure. However, in patients with metastases in distant organs (lungs and/or bones) after CTH and surgical treatment and/or RTH, five-year survival is achieved in individual cases.

In the management of patients with small cell sarcomas there are important early complications (toxicity grade 3 and 4 during long-term CTH) and long-term ones (including — in 10% of patients secondary malignancies, permanent infertility), which justifies the annual observation for their whole life after the treatment.

Palliative treatment

Treatment of recurrent bone sarcomas should be based on CTH and metastasis resection (metastasectomy). In the case of lung metastases, multiple metastases resections and multiple thoracotomy are often justified (III, B). The results of surgical treatment of lung metastases are quite good, provided that complete resection of all lesions is performed [34, 35]. The choice of the second-line CTH schema depends strictly on the drugs used in the initial treatment — often ifosfamide, etoposide is used (in some centres methotrexate in high doses with folinic acid, which concerns especially young patients).

Chemotherapy of patients with primary metastatic small cell sarcomas is based on the use of schemes identical to those used in the primary stage (ifosfamide or cyclophosphamide, doxorubicin, etoposide, and vincristine). In patients with pulmonary metastases who achieve a complete response after CTH, irradiation of the entire lung volume may be considered (III, B) [36], and in the case of a partial response, resection of persistent lesions is indicated [37].

As part of palliative care, RTH metastases in the bone play an important role.

Other primary bone tumours

The therapeutic treatment of choice in chondrosarcoma is a radical surgical procedure without perioperative treatment because in most cases (the exception is mesenchymal and dedifferentiated subtypes) there is resistance to conventional CTH and RTH. In the case of unresectable lesions, palliative RTH can be used (especially protonotherapy in skull base tumours) (III, B) [2, 6, 7, 10, 38].

Chordomas are very rare primary bone tumours developing usually within the sacrum or base of the skull. The treatment of choice is radical resection (rarely possible), and currently comparable results are obtained using proton RTH or carbon ions. Adjuvant RTH is indicated after R1 resection (with the margins occupied by the tumour in a microscopic examination) (III, B) [38–45]. Despite the lack of randomised trials, protonotherapy is the method of choice in postoperative therapy or as the onlytreatment in cases of unresectable cranial base tumours and recognised as a procedure guaranteed by the Polish Agency for the Evaluation of Medical Technology and Tariffs [46].

The giant cell tumours of bone are usually treated surgically, and in cases of recurrence or lack of possibility of excision, good results can be obtained using RTH [47]. Recent reports indicate high efficacy (> 95%) of anti-RANKL monoclonal antibody (denosumab) in the treatment of advanced giant cell tumours of bone [48] — denosumab is the standard treatment for unresectable giant cell tumours; in some patients neoadjuvant treatment with denosumab enables radical surgery with limb sparing (II, B) [49].

Rehabilitation

Rehabilitation (physiotherapy) is a necessary part of the management of patients with bone sarcoma because the beginning of treatment and is divided into:

— preoperative CTH period — prevention of muscle wasting as a result of saving the affected limb (higher weight of healthy tissue promotes healing of the postoperative wound regardless of the scope of the operation performed, which is important in relation to the use of preoperative CTH);
— postoperative period — conducting breathing and passive breathing exercises from the first day after surgery with the extension of the scope of exercises after removal of suction drains;
— post-operative CTH period — use of exercises at home and assessment of progress during the stay in the ward during subsequent CTH cycles and many months after the end of treatment (sometimes periodic intensive exercises are necessary in stationary conditions, which results in the necessary participation of a physiotherapist in a multidisciplinary diagnostic-therapeutic team).

Psychological support is important for the patient, the form of which is a patient support group [e.g. Association of Patients with Sarcomas "Sarcoma" (www.sarcoma.pl), Fulfilled Dreams Foundation, Heroes Foundation, the Foundation for Children with Cancer, and others].

Follow-up after treatment

Conducting follow-up after the end of combined treatment is an inevitable duty of teams conducting radical treatment. Teams are responsible for conducting long-term observation and correct treatment of failures. Most relapses in patients with bone sarcoma occur within 2–3 years after the end of treatment, which justifies more frequent (every three months) follow-up visits [6, 7, 10]. During visits, an X-ray examination of the area of the operated bone and chest should be performed. In subsequent years, control tests may be less frequent (every 6–12 months). The consequence of intensive combination treatment of patients with bone sarcomas may be the occurrence of secondary tumours (7–10% of patients treated for small cell sarcomas). Other late complications of combination therapy (e.g. cardiovascular failure, infertility, complications of total hip replacement) are also important, which justifies the need for long-term observation of patients. The risk of disease relapse depends on the degree of histological malignancy and primary sarcoma size, the radicality of the combination treatment and the time from primary sarcoma treatment. It is known that in low-grade bone sarcomas less than 5 cm in size, the risk of relapse after radical treatment is very low, so it is often enough to perform an X-ray examination every 6–12 months for the first three years, followed by a check each year. In turn, in high-grade sarcomas, whose risk of lung metastases and local recurrence is much higher, it is necessary to perform cyclic chest X-ray assessment and, in addition to a careful examination, imaging of the tumour area (Tab. 6).

Observation of children and adolescents with primary and malignant bone should be carried out in the first year every six weeks, in the second and third year, every three months, in the fourth year every six months, and from the fifth year after the end of treatment and in subsequent years 12 months (Tab. 7).

Table 6. Recommended follow-up tests in adult patients with bone sarcomas

Treatment stage	Examination type	Frequency of tests
After radical treatment of sarcoma in stage IA–IB (with low histological grade G1/G2)	Follow up visit and physical examination every 6 months for the first 2–3 years, then once a year Chest X-ray — every 6–12 months, chest CT only if there are suspected changes in RTG Evaluation of the place after resection by imaging (X-ray, MR, or CT) — regular controls every 6 months (for the first 2–3 years, then once a year) Need to educate the patient towards self-control	Every 6 months for the first 2–3 years, then every 12 months
After radical treatment of stage II–III sarcoma (higher grade G3/G4)	Follow-up and physical examination, especially of the scar of the sarcoma and regional lymph nodes X-ray or chest CT Evaluation of the resection site by imaging (X-ray, MR, or CT) regular controls every 3–4 months (for the first 2–3 years, then every 6–12 months), for patients after radical treatment of Ewing sarcoma, bone scintigraphy may be considered in control Need to educate the patient towards self-control	Every 3–4 months for the first 2–3 years, then every 6 months to 5 years after radical treatment, then once a year
After the treatment of distant metastases (grade IV)	Evaluation in imaging studies depending on the location of measurable metastatic foci	The follow-up visits scheduled for individual patients

Table 7. Scheme of follow-up after treatment of primary malignant bone tumours in children and adolescents

Months	Physical examination	Blood count, electrolytes with Ca/PO4, transaminases, creatinine, urine analyzes other tests depending on clinical situation	ECG, ECHO, RR, HR	Spirometry	Growth hormone, thyroid hormones, sex hormones	RTG og the primary site	USG of the primary site	Chest CT	Bone scan
1 and 2 year									
0	X	X	X	X	X	X	X	X	X
1.5	X					X			
3	X	X					X	X	
4.5	X					X			
6	X	X	X	X			X	X	X
7.5	X					X			
9	X	X					X	X	
10.5	X					X			
12	X	X	X	X	X		X	X	X
3 year									
3	X					X		X	
6	X	X					X	X	X
9	X					X		X	
12	X	X	X	X	X		X	X	X
4 year									
6	X	X				X	X	X	
12	X	X	X	X	X	X	X	X	X
5 year and next									
	X	X	X	X	X	X	X	RTG KLP	

ECG — electrocardiography; ECHO — echocardiography; RR — arterial blood pressure; HR — heart rate; RTG — roentgenography; CT — computed tomography; MR — magnetic resonance; USG — ultrasonography; KLP — chest; PET — positron emission tomography

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