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REVIEW

Diagnosis and treatment of bone sarcomas

Andreas F. Mavrogenis, Panayiotis D. Megalooikonomos,
Christos Th. Vottis, Vassilios G. Igoumenou, Ioannis P. Galanopoulos,
Georgios N. Panagopoulos, Panayiotis J. Papagelopoulos

First Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, ATTIKON University Hospital, Athens, Greece

ABSTRACT

Bone sarcomas are primary, non-epithelial, malignant neoplasms that present a variety of malignancy grades; usually high-grade. Some bone sarcomas are purely osteolytic, while other produce bone or cartilaginous tissue, or mixed osteolytic/osteoblastic matrix. The most common bone sarcomas are osteosarcoma, Ewing's sarcoma and chondrosarcoma. They usually occur in children or young adults and develop in the extremities; mainly the distal femur and the pelvis. The most common symptoms are pain and the presence of a palpable enlarging mass. Plain radiographs are important at the primary work-up in every patient with prolonged bone pain. Magnetic resonance imaging (MRI) is the imaging modality of choice for the diagnostic evaluation of the tumor, its exact location, its relation with the adjacent anatomical structures, intramedullary progression and outside of bone expansion. Except from the local identification of the tumor, disease staging also includes computer tomography (CT) of the chest, of the upper and lower abdomen and the retroperitoneal space, and bone scintigraphy. Wide surgical resection (with tumor-free margins) is the main therapeutic approach, in combination with adjuvant treatment (pre- and postoperative) individualized for each patient. Multidisciplinary approach to these patients is necessary.

KEY WORDS: sarcoma; bone; osteosarcoma; chondrosarcoma; ewing sarcoma; wide resection; chemotherapy; radiation therapy

Introduction

Bone sarcomas include a wide variety of primary, non-epithelial neoplasms of mesenchymal origin that arise from bone and present different grades of malignancy; usually high grade. Some are purely osteolytic, while other produce bone or cartilaginous tissue, or mixed osteolytic/osteoblastic matrix. The most common bone sarcomas are osteosarcoma, Ewing's sarcoma and chondrosarcoma. Osteosarcomas account for approximately 50% of bone sarcomas and they typically occur in young patients, or in older patients secondary to Paget disease[1,2]. Ewing's sarcoma is the third most common primary malignant bone sarcoma in adults, and the second

CORRESPONDING AUTHOR, GUARANTOR

Andreas F. Mavrogenis, First Department of Orthopaedics National and Kapodistrian University of Athens, School of Medicine, 41 Ventouri Street, 15562 Holargos, Athens, Greece
Tel/fax: 0030-210-6542800, E-mail: afm@otenet.gr

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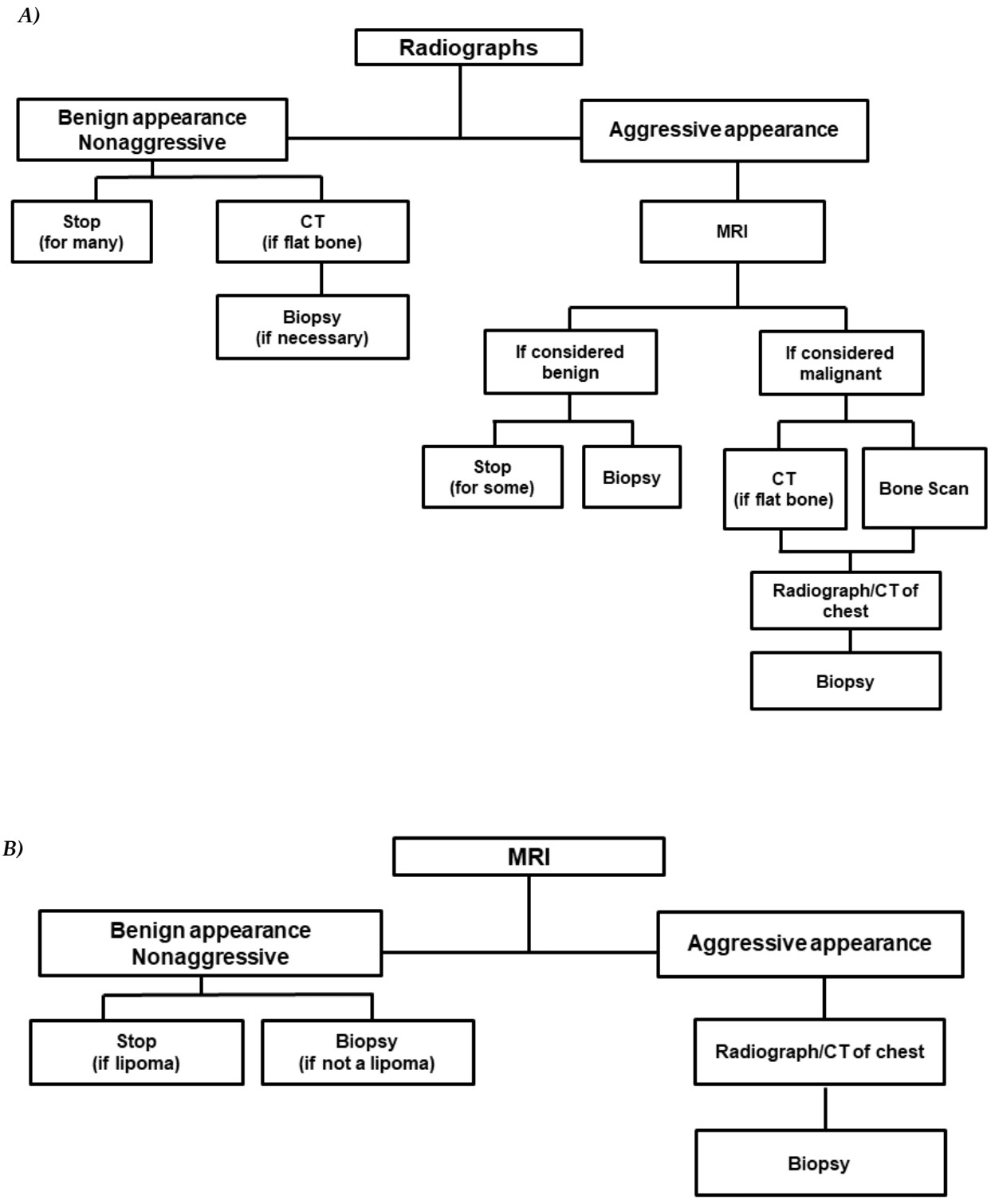

Fig. 1A+B. *Algorithm of diagnostic approach for patients with bone (A) and soft-tissue (B) tumors*

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most common in children. Chondrosarcomas develop later, between the third and the sixth decade of life. Osteosarcomas and chondrosarcomas may result from dedifferentiation of mesenchymal stem cells, while Ewing's sarcoma is represented by a specific phenotypic implication of EWS genes and seems to have a neuroectodermal origin [3].

Epidemiology

Most bone sarcomas occur in children and young adults and develop in the extremities, especially the distal femur, or the pelvis. The most common symptoms are pain and the presence of a palpable mass. Pain is deep, constant, at rest or during the night, not associated with any activities, while it usually initiates several weeks or a few months before diagnosis. The presence of a palpable mass will be identified when the tumor will destroy the cortex and the periosteum and will progress to the soft tissues [4-6].

Staging

The overall approach of a patient with a tumor, from the initial presentation until diagnosis, is termed as disease staging. Staging should include (1) medical history and clinical examination, (2) plain radiographs, MRI and eventually CT scan of the tumor region (local evaluation), (3) bone scintigraphy (evaluation of the skeleton), plain radiograph of the chest and CT scan of the chest (evaluation of the lungs), CT scan of the upper and lower abdomen and retroperitoneal space (evaluation of visceral organs and retroperitoneum), (4) blood tests and (5) biopsy (final assessment during staging). Classification (histological and surgical) and treatment will follow.

Medical history

During documentation of medical history, attention should be given to information as patient's age, initiation, duration and intensity of symptoms (e.g. night pain), family history, history of other benign or malignant lesions and previous treatments; especially radiation therapy. A history of local injury is reported in over 80% of patients with musculoskeletal tumors and should not mislead diagnosis [4-6]. During clinical evaluation patient's age should be taken into consideration. In children, an osteolytic lesion may represent an osteosarcoma, a metastatic neuroblastoma, an eosinophilic granuloma, or osteomyelitis. In the elderly, the potential diagnosis of such an osteolytic lesion tends to be a metastasis or myeloma and rarely a primary tumor (usually chondrosarcoma) [7-13].

Imaging

Radiographs are necessary in the initial diagnostic approach of patients with tumor. A bone sarcoma is almost always obvious in radiographs, while negligence to perform them at the first symptoms is associated with a significant delay in diagnosis. The imaging modality of choice for diagnosis and evaluation of the lesion and its relation with the adjacent anatomical structures (vessels and nerves) is MRI. CT is used supplementary to demonstrate the calcification, the periosteal reaction and bone formation, the cortical involvement or/and destruction and preoperative planning [5,6,14]. These imaging modalities should be always enhanced with intravenous contrast agents (paramagnetic substance or iodinated contrast, respectively) [5,6,14,15]. There are quite few lesions that present certain MRI features with which diagnosis may be safely established by means of imagine alone (**Fig. 1A+B**). In all other instances, staging should end up with tumor biopsy [15].

The role of positron emission tomography (PET/CT) in disease staging is under evaluation [16]. Additional imaging studies (and biopsy) can be conducted in additional suspicious regions for the documentation of metastatic disease or/and the exclusion of a second cancer [17].

Blood tests

Complete blood count (CBC) and serum biochemistry including all routine tests, as well as prostatic specific antigen (PSA) (prostate cancer evaluation in men) and serum protein electrophoresis (paraproteinaemia evaluation) should be included in the basic work-up. Tumor markers are not helpful in disease staging in patients with musculoskeletal tu-

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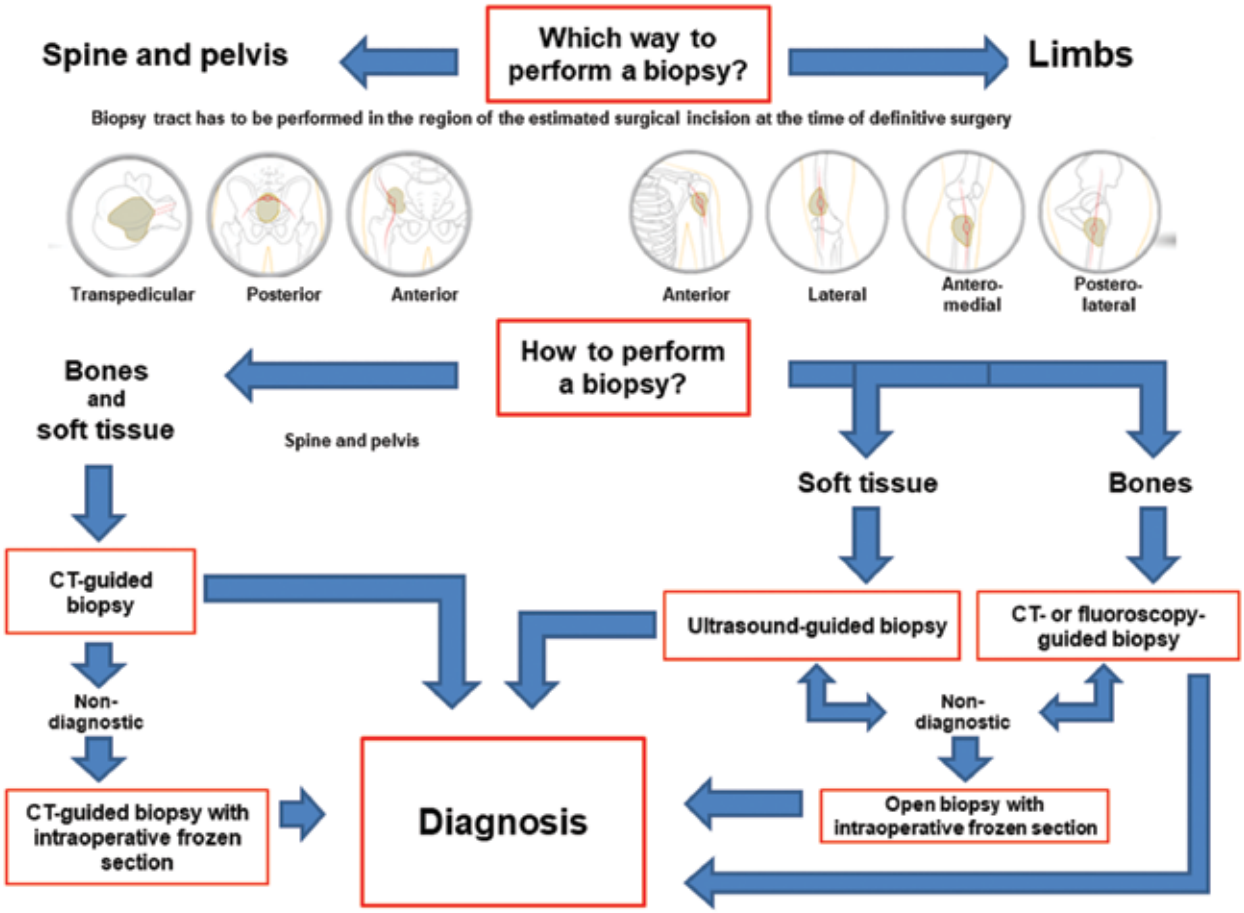

Fig. 2. *Principles of biopsy according to tumors' location*

mors. Alkaline phosphatase and lactate dehydrogenase may be useful in the follow-up of patients with Ewing's sarcoma, osteosarcoma and Paget disease and may have prognostic value [5,18,19].

Biopsy

Biopsy represents tumor tissue sampling for histological identification. Biopsy can be closed (percutaneous) or open (surgical). Closed biopsy may be performed with the guidance of an imaging modality (ultrasonography, fluoroscopy, CT, MRI, PET/CT) or non-guided. Open biopsy may be resectional biopsy (removal of the whole tumor) or segmental biopsy (removal of a tumor segment). Today, closed biopsy is the gold standard for the histological identification of musculoskeletal tumors (ideally guided with CT or ultrasonography), considering the significant lower complication rates and the limited risk for dissemination of the adjacent area with tumor cells, and its superior diagnostic yield. Open biopsy is indicated when closed biopsy is not diagnostic (in this case it is indicated to repeat closed biopsy using imaging guidance after communication and collaboration with an interventional radiologist in order to introduce the biopsy needle in the most suspicious regions of the tumor) and when the histological findings are not in accordance with the clinical and imaging characteristics of the lesion and the clinical experience. For this reason, biopsy of musculoskeletal tumors should be carried out at a reference center, ideally by the surgeon who is going to perform the definitive tumor resection (or a specialized radiologist), according to the oncological biopsy principles [20-22].

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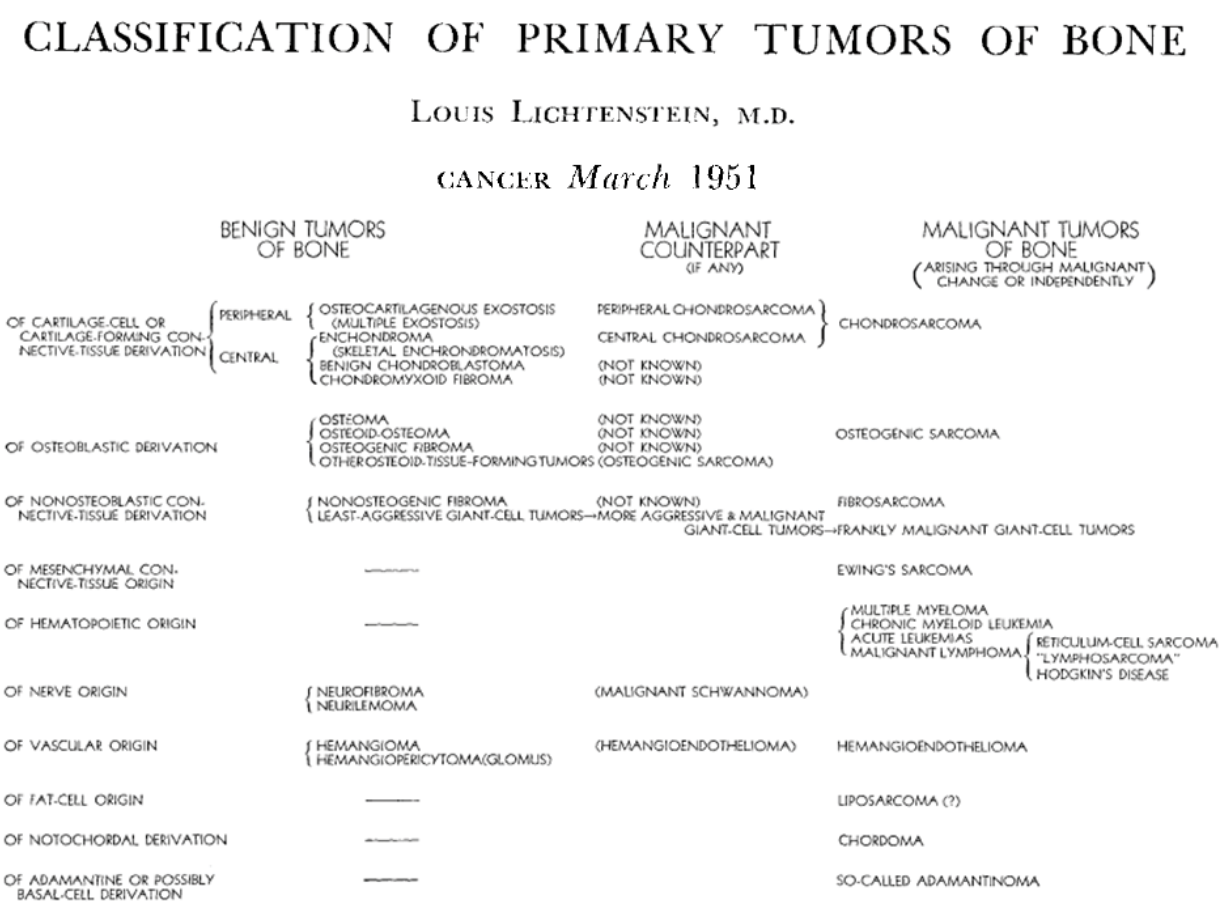

CLASSIFICATION OF PRIMARY TUMORS OF BONE

LOUIS LICHTENSTEIN, M.D.

CANCER *March* 1951

		BENIGN TUMORS OF BONE	MALIGNANT COUNTERPART (IF ANY)	MALIGNANT TUMORS OF BONE (ARISING THROUGH MALIGNANT CHANGE OR INDEPENDENTLY)
OF CARTILAGE-CELL OR CARTILAGE-FORMING CONNECTIVE-TISSUE DERIVATION	PERIPHERAL	OSTEOCARTILAGENOUS EXOSTOSIS (MULTIPLE EXOSTOSIS)	PERIPHERAL CHONDROSARCOMA	CHONDROSARCOMA
	CENTRAL	ENCHONDROMA (SKELETAL ENCHRONDROMATOSIS)	CENTRAL CHONDROSARCOMA	
		BENIGN CHONDROBLASTOMA	(NOT KNOWN)	
		CHONDROMYXOID FIBROMA	(NOT KNOWN)	
OF OSTEOBLASTIC DERIVATION		OSTEOMA	(NOT KNOWN)	OSTEOGENIC SARCOMA
		OSTEOID-OSTEOMA	(NOT KNOWN)	
		OSTEOGENIC FIBROMA	(NOT KNOWN)	
		OTHER OSTEOID-TISSUE-FORMING TUMORS	(OSTEOGENIC SARCOMA)	
OF NONOSTEOBLASTIC CONNECTIVE-TISSUE DERIVATION		NONOSTEOGENIC FIBROMA	(NOT KNOWN)	FIBROSARCOMA
		LEAST-AGGRESSIVE GIANT-CELL TUMORS	→ MORE AGGRESSIVE & MALIGNANT GIANT-CELL TUMORS	→ FRANKLY MALIGNANT GIANT-CELL TUMORS
OF MESENCHYMAL CONNECTIVE-TISSUE ORIGIN		———		EWING'S SARCOMA
OF HEMATOPOIETIC ORIGIN		———		MULTIPLE MYELOMA
				CHRONIC MYELOID LEUKEMIA
				ACUTE LEUKEMIAS
				MALIGNANT LYMPHOMA: RETICULUM-CELL SARCOMA; "LYMPHOSARCOMA"; HODGKIN'S DISEASE
OF NERVE ORIGIN		NEUROFIBROMA	(MALIGNANT SCHWANNOMA)	
		NEURILEMOMA		
OF VASCULAR ORIGIN		HEMANGIOMA	(HEMANGIOENDOTHELIOMA)	HEMANGIOENDOTHELIOMA
		HEMANGIOPERICYTOMA (GLOMUS)		
OF FAT-CELL ORIGIN		———		LIPOSARCOMA (?)
OF NOTOCHORDAL DERIVATION		———		CHORDOMA
OF ADAMANTINE OR POSSIBLY BASAL-CELL DERIVATION		———		SO-CALLED ADAMANTINOMA

Fig. 3. *Lichtenstein's histological classification of bone tumors*

Biopsy principles suggest minimal dissemination of tissues (needle biopsy, introduction of the needle through a single anatomical compartment and to the course of the estimated surgical resection), imaging guidance (closed core needle biopsy [trucut®] or bone trocar), sampling of representative regions of the tumor (guidance is very important), collection of at least 3 samples from representative regions of the tumor, introduction of the needle (closed biopsy) or skin incision (open biopsy) to the course of the estimated surgical resection, meticulous coagulation (open biopsy), avoidance of suction drains (meticulous coagulation), or when necessary drain tubes should be placed in the proximity to the skin incision of the biopsy, dissemination to a single anatomical compartment (the shortest route of the biopsy needle is not always the best) and the closed biopsy incision should be marked with tattoo ink in order to be recognized and resected at the time of definitive surgery (**Fig. 2**) [20-22].

Patients should limit their activities and the overuse of the limb, in which biopsy was performed, for several days after the procedure to reduce the risk of hematoma formation [6]. Biopsy specimens should be quickly submitted for pathological assessment, ideally within half an hour. Biopsy samples for cultures should be always collected and submitted, as the possibility of infection (osteomyelitis) is prominent, especially in certain patient groups as children. The request form sent to histopathology department should contain sufficient details regarding tumor site and patient's history [5,6,23]. To the laboratory, before formalin fixation, tumor imprints can be taken (useful for tumor-specific translocation

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TABLE 1. *MSTS (Enneking) staging system for bone sarcomas*

Stage	Grade	Site	Metastasis
IA	**G1**	**T1**	M0
IB	**G2**	**T2**	**M0**
IIA	G2	**T1**	**M0**
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

G1=low grade; G2=high grade; T1=intracompartmental; T2=extracompartmental; M0=without metastasis; M1=with metastasis

by FISH), and tissue suspensions should be kept frozen in cryomolds [6]. The histological features of the tumor should be described and the tumor type should be specified according to World Health Organization (WHO) classification [23].

Classification

The objectives of tumor classification and patient staging, as defined by the International Union Against Cancer (IUAC), are to define treatment, to estimate prognosis, to assess the results of treatment, and to facilitate to the easier and more effective communication between different institutions and scientists [21].

The classic histologic tumor classification according to cellular origin has been reported by Lichtenstein in 1951 (**Figure 3**) [24] Since its establishment in 1959, the American Joint Committee for Cancer (AJCC) has undertaken the development of clinically useful staging systems for various histological types of cancer. In 1980, the Musculoskeletal Tumor Society (MSTS) proposed a system for surgical staging of musculoskeletal tumors that was subsequently adopted by the AJCC. This system was initially established at the University of Florida in 1977 based on data collected between 1968 and 1976 by Orthopaedic Surgeon William Enneking. The MSTS staging system (also known as Enneking's system) includes two different classifications; one is addressed to benign musculoskeletal tumors (includes 3 stages which are represented with arabic numbers; 1,2 and 3) and another to bone sarcomas (also includes 3 stages that are represented with latin numbers; I, II and III) that is most frequently used in Orthopaedic oncology.

MSTS staging system takes into account the histological grade of malignancy (stage I: low grade and stage II: high grade) and the presence of metastases (stage III), and it is divided into 2 subcategories (A and B) according to the extent of the tumor within the anatomical compartment (A: intercompatrimental and B: extracompartimental- the bone is considered as an anatomical compartment) (**Table 1**) [25].

The AJCC staging system is according to the TNM system (tumor, nodes, metastasis) that mostly applies to soft-tissue sarcomas [26]. This system takes into account the size of the tumor (T) (with a threshold of 8 cm), the histopathologic grade (G), the presence of regional lymph node metastases (N) and the presence of distant metastases (M) (**Table 2**). However, the implication of this system to surgical planning is limited, due to lack of consideration to anatomy and local tumor extent [27].

Treatment

The treatment of patients with bone sarcomas require a multidisciplinary approach from a team of physicians with expertise in bone tumors that should include orthopaedic surgeon, medical and radiation oncologist, plastic surgeon, pathologist, radiologist and physiatrist, physical therapist, psychiatrist and psychologist, and in some cases vascular surgeon, urologist and general surgeon. Surgical treatment is the main therapeutic modality.

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TABLE 2. *AJCC (TNM) staging system for bone sarcomas*

Stage	Grade	Primary tumor	Regional lymph nodes involvement	Distant metastasis
IA	G_1 or G_2	T_1	N_0	M_0
IB	G_1 or G_2	T_2	N_0	M_0
IIA	G_3 or G_4	T_1	N_0	M_0
IIB	G_3 or G_4	T_2	N_0	M_0
III	Not defined			
IVA	Any G	Any T	N_1	M_0
IVB	Any G	Any T	Any N	M_1

G_1=well differentiated; G_2=moderately differentiated; G_3=poorly differentiated; G_4=undifferentiated; T_1=tumor confined within the cortex; T_2=tumor extends beyond the cortex; N_0=no regional lymph nodes involvement; N_1=regional lymph nodes involvement; M_0=without metastasis; M_1=with metastasis.

The aim of surgery is complete, wide (in tumor-free margins) tumor removal. The role of chemotherapy and radiation therapy is individualized according to the histological type of the tumor and in some instances the stage of disease and the general status of the patient. In some bone sarcoma types, as osteosarcoma and Ewing's sarcoma, preoperative chemotherapy aiming to treat the potential micrometastatic disease and reduce the soft tissue mass around the bone tumor to allow easier resection has been shown that significantly increases survival and local control of the disease and should not be neglected.

Surgical treatment; Limb salvage surgery and amputation

Before the 1970s, the standard (and often the only) treatment for musculoskeletal sarcoma patients was limb amputation or disarticulation [28] Nevertheless, patients' survival was not satisfactory. The evolution of imaging modalities, surgical techniques, and especially chemotherapy (specifically preoperative chemotherapy for sarcomas such as osteosarcoma) and radiation therapy during the 1970s led to significant advances in the treatment of patients with bone sarcomas resulting in the development of limb salvage surgery and significant increase of their survival.

The goal of surgery in bone sarcoma patients, as in all malignant tumors, is complete tumor resection with tumor-free (microscopically negative) margins. During surgery the specimen of the tumor should include skin incision and the track of the previous biopsy [22,25]. Surgical resection may be radical, wide, marginal or intralesional (**Figure 4**). Limb amputation and disarticulation are considered radical procedures, however even after such operations microscopically negative margins may not be achieved (e.g. removal with microscopically negative margins of a sarcoma in the inguinal area or the pelvis is not always feasible, even after hip disarticulation). Wide resection of bone tumors represents the removal of the lesion including at least 2-3 cm of healthy bone distally and proximally, accordingly. Considering soft tissue involvement (as in soft-tissue sarcomas), the margins of wide resection remain controversial (some authors suggest up to 5 cm of healthy tissue to cover the soft-tissue mass of a bone sarcoma or a soft-tissue sarcoma). However, it is common sense that such margins are generally difficult to be achieved considering the proximity of the tumor to important anatomical structures. As such, in the majority of cases tumor resection is marginal (in the whole surface or in some parts) comprising less than 2-3 cm healthy tissue margins around the tumor, or resection through

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the tumor capsule (in cases of a soft-tissue mass). In this setting, marginal resection should be considered by definition as microscopically positive in tumor cells [15,29-31,34-36].

Intralesional excision should be avoided in sarcoma patients because it is related to a high risk of local recurrence, regardless the conduction of adjuvant chemotherapy or radiation therapy. In cases of incorrect or inevitable intralesional excision, reoperation and wide resection should be performed aiming the total resection of the surgical bed of the previous operation [32]. In low-grade chondrosarcomas, that arise from the distal part of large joints (below the knee and the elbow), intralesional resection is acceptable considering the latent biological course of these entities and their low local recurrence rate. It has to be mentioned though, that after intralesional resection, even in these sites, recurrence rate is bigger in comparison with wide resection, however postoperative morbidity is considerably lower than the one after wide resection [12].

Limb salvage surgery has widely replaced amputation as the primary surgical approach in bone sarcoma patients, without limiting patients' survival. However, the differences of these procedures in terms of survival and risk of local recurrence are still under discussion due to the lack of long-term comparative studies, as they are difficult to be conducted in sarcoma patients and generally in cancer patients. Amputation often consists a more preferable treatment option, mainly because of its significantly lower risk of postoperative complications and should be considered and suggested to the patient as treatment of choice when it may achieve total tumor removal. Limb amputation consists absolute indication when the major arteries and nerves of the limb are encased by the tumor, in the condition that they cannot be surgically reconstructed.[15] In general, local recurrence constitutes relative indication for amputation (and contraindication for limb salvage surgery), but not when removal of the recurrent tumor can be achieved in tumor-free margins; however, in these cases this is usually quite difficult [33].

Nowadays, pathological fracture incidence in patients with primary bone sarcomas is not considered as an absolute indication for amputation. In these cases, the fracture should be immobilized (ideally with a plaster cast, traction, or external fixator), biopsy should be performed (ideally closed guided biopsy) for histological tumor identification and the patients should be treated with preoperative chemotherapy. Subsequently, resection of the tumor in negative margins should be attempted. If tumor resection in negative margins (wide resection) is considered impossible, limb amputation should be conducted. The response of the tumor to chemotherapy is a predictive index not only for fracture healing but also for patient's survival and local disease control. The extent of pathological fracture displacement is not related with patients' prognosis. The development of a pathological fracture in patients with chemo-resistant bone sarcomas consists a relative contraindication for limb salvage surgery [34,35]. Postoperatively (regardless the conduction of limb salvage surgery or amputation) chemotherapy or/and radiation therapy should follow, depending on the histological type of the sarcoma and the corresponding oncological treatment protocols [35,36].

Reconstruction after limb salvage surgery

After limb salvage surgery, in most of cases reconstruction of the bone defect needs to be addressed using megaprostheses, massive grafts (diaphyseal or osseocartilaginous allografts, vascularized or non-vascularized fibula autografts), or combination of methods [37-41]. Distraction histogenesis may be also applied in such defects, however the postoperative rehabilitation period is prolonged in such cases and the patient are usually scheduled for additional therapies that may influence histogenesis [42]. Pelvic resections and reconstructions consist demanding procedures with significant related complications, that may justify external (with limb amputation) or internal (without limb amputation) hemipelvic resection without subsequent reconstruction of the hemipelvis [12,43].

In children, biological reconstruction techniques are usually preferred (allografts or vascularized fibula autografts, epiphysis sparing techniques and

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distraction of the growth plate), however, expandable prostheses or rotationplasty (Van Ness procedure) in the very young children (below 6 years old) may be also applied [44,45]. In selected cases, in children with active growth plates, maintenance of the epiphysis and articular surface may be achieved with the application of distraction to the growth plate [5,46].

Computer-assisted surgery

Today, computer-assisted oncologic surgery allows the combination of computer technology and appropriate software, with modern imaging modalities and surgical instrumentation in a more precise and effective fashion [47]. The goals of computer-assisted surgery in bone sarcoma patients include the easier conduction of tumor resection with microscopically negative margins, and the optimal reconstruction. Preoperatively, this technology offers improved visualization of the operative field and facilitates surgical planning. Intraoperatively, real-time data are collected creating a virtual map of the operative field. After tumor resection, during reconstruction of the bone defect, computer-assisted surgery has been shown to be associated with improved accuracy in the application of prostheses, providing better positioning and function [47-49]. The increased surgical time, learning curve and cost are considered as limitations of computer-assisted surgery. However, for a surgeon that is familiar with the computer-assisted surgery systems, surgical time may not be significantly increased. Finally, as the use of computer-assisted surgery becomes more popular, it is expected that the costs and time of the procedure will decrease [6] In all circumstances, the optimal surgical treatment option should be selected for the patients each time with the minimal risk for complications, as complications in cancer patients are unacceptable.

Chemotherapy

Chemotherapy consist an important role in the treatment of osteosarcoma and Ewing sarcoma patients, considering that patients with seemingly localized disease, if treated with local tumor resection alone, will develop metastases and die from end-stage disease in a percentage of 80-90% if chemotherapy (pre- and postoperative) is not included in their treatment [5,50-56]. On the other hand, treatment of patients with chondrosarcoma is surgical in the majority of cases, although chemotherapy may have a role in patients with dedifferentiated and mesenchymal chondrosarcomas [8-10,12,13,57].

In general, chemotherapy agents do not differ between adults and children [50,58]. Doxorubicin, cisplatin, methotrexate and ifosfamide are considered the most active agents against osteosarcoma, whereas standard chemotherapy against Ewing's sarcoma is usually vincristine, adriamycin, cyclophosphamide and actinomycin D (VACA) [50,52,53,58-62]. Other chemotherapy agents have also been used in different combinations and protocols. Further reference to chemotherapy agents and schemas is not the subject matter of the present manuscript.

In patients with high-grade sarcomas, with metastases at the time of diagnosis, local recurrence, locally extended tumor (inoperable), and in poor responders to the first line treatment, modern target treatments are indicated, according to the suggestions of the treating medical oncologist. The application of these treatments implies the combination of therapeutical protocols that focus on different molecules, pathways, or targets (receptors) in the same pathway [5,63-69]. Recently described therapeutic approaches target RANKL. These include osteoprotegerin, denosumab, and RANK-Fc [70,71]. Gene, cell and immune therapies aim to down-regulate oncogenes or to overexpress the genes of therapeutic interest in the microenvironment and as immunotherapy [8,10,72,73].

Except from the less important side effects as alopecia, nausea and mucositis, chemotherapy treatment can result in more serious side effects as renal, cardiac and auditory dysfunction, hepatotoxicity, pneumonitis, enteritis, neuritis, and urogenital and central nervous system disorders [74]. Infertility is another chemotherapy complication. Preventive sperm cryopreservation is recommended to male patients of reproductive age, while female patients should be referred to specialized gynecologists for

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the assessment of the available preventive options for reproduction after treatment (e.g. oocyte or ovarian tissue cryopreservation) [5,6].

Radiation therapy

Radiation therapy can be useful for local disease control in patients with bone sarcomas in difficult locations such as the spine, the head and the pelvis, as well as in cases of inoperable tumors (locally extended or after multiple local recurrences) [75-77]. Radiation therapy can be administered before surgery, after surgery, or as the main therapeutic modality (usually palliative), depending on the site and the histological type, the surgical margins of resection, the response to chemotherapy and the radiosensitivity of the tumor. Preoperative radiation therapy can be administered to patients with sarcomas of the spine or the pelvis aiming to limit the tumor margins. Postoperative radiation is administered to those patients that wide resection (microscopically negative) was not possible, in cases of pathologic fractures, patients with poor response to chemotherapy, or when biopsy was not performed respecting the oncologic principles and has possibly caused local dissemination of the tumor. Ewing's sarcoma is usually radiosensitive [77].

In these patients, radiation therapy is administered as adjuvant treatment after surgical tumor removal, or as primary treatment in cases of inoperable tumors, and usually in spinal tumors or when patients do not consent with surgical treatment (due to comorbidities or when they do not accept amputation) and as palliative treatment [77,78]. Chondrosarcomas and osteosarcomas are not radiosensitive tumors and require doses of approximately 66 Gy for the control of microscopically residual disease and doses of ≥70 Gy in cases of macroscopically residual disease, when reoperation for total tumor removal is not possible [77,78]. The description of classic and modern radiation therapy techniques is not the subject matter of the present manuscript.

Treatment for metastatic and recurrent disease

Osteosarcomas most often metastasize to the lungs, while 10-15% of patients already present pulmonary metastases at the time of initial diagnosis (MSTS stage III) [53] In these patients, the same treatment principles apply with those with isolated local disease and no metastases (chemotherapy and surgical removal of the primary tumor and metastases) [5,79,80]. In patients with Ewing's sarcoma and solitary lung metastases radiation therapy of the pulmonary lesions and chemotherapy seem to improve prognosis [5,81]. However, the total survival of patients with metastatic disease is generally poor. The efficacy of second-line chemotherapy is limited (especially in osteosarcoma than Ewing's sarcoma) [5,82,83].

The local recurrence rate even after appropriate surgical management and optimal treatment with complete response is approximately 9%, while previously undetectable metastatic disease may become detectable in the postoperative period [15]. For this reason, the appropriate follow-up of these patients through time is critical.

Follow-up

Patients with bone sarcomas should be followed at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and yearly thereafter. In patients with low-grade sarcomas, the frequency of follow-up visits may be lower [6]. The clinical follow-up of these patients should include physical examination of tumor resection area and regional lymph nodes. The radiological follow-up should include imaging of the tumor area (ideally with MRI). Chest CT should be performed at 6-month intervals for the first 3 years, and yearly thereafter. Clinically suspicious areas for metastatic disease (skull, pelvis, spine) should be further examined with additional imaging (ideally MRI) and with biopsy when it is necessary for the exclusion of a second cancer.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Τα σαρκώματα των οστών είναι πρωτογενή, μη επιθηλιακά νεοπλάσματα ποικίλου βαθμού κακοήθειας, συνήθως υψηλής. Κάποια είναι αμιγώς οστεολυτικά, ενώ άλλα παράγουν οστίτη ή χονδρικό ιστό, ή εμφανίζουν μικτό οστεοβλαστικό/οστεολυτικό κυτταρικό στρώμα. Τα συχνότερα σαρκώματα των οστών είναι το οστεοσάρκωμα, το σάρκωμα Ewing και το χονδροσάρκωμα. Εκδηλώνονται συχνότερα σε παιδιά ή νέους ενήλικες και αναπτύσσονται στον περιφερικό σκελετό, κυρίως στο περιφερικό μηριαίο οστό και την πύελο. Η κλινική εικόνα συνήθως χαρακτηρίζεται από πόνο και ψηλαφητή μάζα αυξανόμενου μεγέθους. Οι απλές ακτινογραφίες είναι σημαντικές για την αρχική εκτίμηση κάθε ασθενή με επίμονο οστικό πόνο. Η μαγνητική τομογραφία είναι η απεικονιστική μέθοδος εκλογής για τη διαγνωστική αξιολόγηση του όγκου, την ακριβή εντόπιση και σχέση με τις γειτνιάζουσες ανατομικές δομές και την ενδομυελική έκταση και εξωοστική επέκταση του όγκου. Εκτός από τον τοπικό έλεγχο του όγκου, η σταδιοποίηση περιλαμβάνει επιπλέον αξονική τομογραφία θώρακα, άνω και κάτω κοιλίας και οπισθοπεριτοναϊκού χώρου και σπινθηρογράφημα των οστών. Η ευρεία χειρουργική αφαίρεση του όγκου (επί υγιών ιστών) είναι η κύρια θεραπεία, σε συνδυασμό με επικουρικές θεραπείες (προ- και μετεγχειρητικά) κατά περίπτωση. Η διεπιστημονική προσέγγιση των ασθενών αυτών είναι απαραίτητη.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: σάρκωμα, οστά, οστεοσάρκωμα, χονδροσάρκωμα, σάρκωμα Ewing, ευρεία εκτομή, χημειοθεραπεία, ακτινοθεραπεία