

# Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

The ESMO / European Sarcoma Network Working Group\*

## incidence

Primary bone tumors are rare, accounting for <0.2% of malignant tumors registered in the EUROCARE database [1]. Different tumors have distinct patterns of incidence. Osteosarcoma and Ewing sarcoma (ES) have a relatively high incidence in the second decade of life, while chondrosarcomas are more common in older age groups (Figure 1).

Osteosarcoma is the most frequent primary cancer of bone (incidence: 0.2–0.3/100 000/year). The incidence is higher in adolescents (0.8–1.1/100 000/year at age 15–19), where it accounts for >10% of all solid cancers. The male–female ratio is 1.4:1. Risk factors for the occurrence of osteosarcoma include previous radiation therapy, Paget disease of bone [2], and germline abnormalities such as the Li–Fraumeni syndrome, Werner syndrome, Rothmund–Thomson syndrome, Bloom syndrome, and hereditary retinoblastoma [3].

ES is the third most common primary malignant bone-associated sarcoma. It occurs most frequently in children and adolescents, but is also seen in adults. The median age at diagnosis is 15 years and there is a male predilection of 1.5/1. ES is diagnosed in white Caucasians under the age of 25 at an incidence of 0.3/100 000 per year [4], but it is very uncommon in the African and Asian population. About 25% of patients have ES of the pelvic bones, while 50% have extremity tumors. Also the ribs and vertebral column are frequently affected. ES may involve any bone and (less commonly in children) soft tissues.

Chondrosarcoma is the most frequently occurring bone sarcomas of adulthood. The incidence is about 0.2/100 000 per year, with the most common age at diagnosis being between 30 and 60 years and the male–female ratio is ~1 [5].

Chordomas are rare; arising with an incidence of ~0.5/million population per year.

## diagnosis

The presence of persistent non-mechanical pain in any bone lasting more than a few weeks should cause concern and lead to further immediate investigation. Swelling will only be present if the tumor has progressed through the cortex and distended the periosteum. Regarding differential diagnosis, malignant bone tumors in children may be confused with benign tumors or in adults with metastatic disease, both of which outnumber primary malignant bone tumors [6–8]. The likely diagnosis of a suspected bone tumor is related to age. Before 5 years of age, a destructive bone lesion is most commonly metastatic neuroblastoma or eosinophilic granuloma; above 5 years, it is often a primary bone sarcoma; after 40 years of age, it tends to be metastasis or myeloma [9].

Bone sarcomas are frequently difficult to recognize as malignant by clinicians, radiologists as well as pathologists. Therefore, all patients with a suspected primary malignant bone tumor should be referred to a bone sarcoma reference center or an institution belonging to a specialized bone sarcoma network before biopsy [10–13] [III, A].

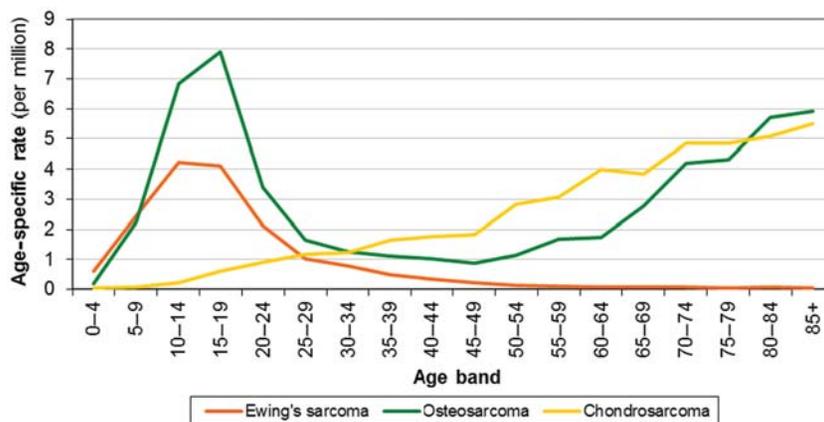
The medical history should focus on symptoms such as duration, intensity and timing of complaints, for example night pain or fracture. Moreover, specific events for bone tumors include prior benign/malignant lesions, family history, and previous radiotherapy. A recent injury does not rule out a malignant tumor and must not prevent appropriate diagnostic procedures. All patients should have a full physical examination. Specific attention should be given to the size, consistency of the swelling, its location and mobility, the relation of swelling to the involved bone, and the presence of regional/local lymph nodes.

Conventional radiographs in two planes should always be the first investigation. When the diagnosis of malignancy cannot be excluded with certainty on radiographs, the next imaging step is magnetic resonance imaging (MRI) of the whole compartment with adjacent joints, which is the best modality for local staging of extremity and pelvic tumors [14]. Computed tomography (CT) should be used only in case of diagnostic problems or doubt, to visualize more clearly calcification, periosteal bone formation, cortical destruction, or soft tissue involvement.

The biopsy of a suspected primary malignant bone tumor should be carried out at the reference center, by the surgeon who

\*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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**Figure 1** Age specific incidence rates by morphology, England, 1979–2004. Data from National Cancer Intelligence Unit, UK; [http://www.ncin.org.uk/publications/data\\_briefings/bone\\_sarcomas\\_incidence\\_and\\_survival.aspx](http://www.ncin.org.uk/publications/data_briefings/bone_sarcomas_incidence_and_survival.aspx).

is to carry out the definitive tumor resection or a radiologist member of the team [10–13]. The principles of the biopsy are:

- (i) there should be minimal contamination of normal tissues;
- (ii) in many situations, core needle biopsies (preferably taken under imaging control) are an appropriate alternative to open biopsy;
- (iii) adequate sampling of representative areas for histology must be assured;
- (iv) samples should always be sent for microbiological culture in all cases entailing a potential differential diagnosis;
- (v) samples must be interpreted by an experienced pathologist;
- (vi) the request form should contain sufficient details for the pathologist including the site of the tumor, the patient's age, and the radiological differential diagnosis.

If an open biopsy is done, it should be carried out using a longitudinal incision. To be sure that the biopsy location is adequate and the tissue is representative for the resulting analysis, it is recommended to make X-rays of the biopsy location and sometimes undertake a frozen section in case more material is required. In aggressive and malignant tumors of bone, the biopsy tract must be considered to be contaminated with tumor and must be removed together with the resection specimen to avoid local recurrences, including the possible channels through which drains have been placed. Biopsy tracts should be clearly marked by means of a small incision or ink tattoo to ensure that the location can be recognized at the time of the definitive procedure. In cases of spinal column involvement, laminectomy or decompression should be avoided unless necessary to relieve spinal cord compression. Samples should be quickly submitted for pathological assessment, ideally within half an hour; upon arrival, and before formalin fixation, tumor imprints (touch preps) can be taken (useful for tumor-specific translocation by FISH), and tissue/cell suspensions should be kept frozen in cryomolds. A further option is to establish primary cell cultures for cytogenetics and other studies. Collection of fresh frozen tissue and tumor imprints (touch preps) is encouraged, because new molecular pathology assessments could be made

at a later stage in the patient's interest. Informed consent for tumor banking should be sought, enabling later analyses and research, as long as this is allowed by local and international rules. The nature of the bone specimen received for pathology reporting should be recorded, i.e. needle biopsy, curettage, excision (e.g. segmental resection, limb salvage amputation or other complex resection, such as a hemipelvectomy). It is usually necessary to decalcify a bone tumor biopsy. The pathologist should receive information regarding the clinical/radiological context in which the tumor has arisen, relevant observations made at the time of surgery and whether the patient has received preoperative chemotherapy. The size (measured in three dimensions in mm) of the tumor in the resected bone should be noted.

The histological features of the tumor should be described and the tumor type (and subtype) specified according to the 2002 World Health Organization (WHO) Classification [15] (see Table 1).

The pathology report should note the extent of local tumor spread, including involvement of specific anatomical compartments. It should be noted whether the resection margins are clear or involved by tumor and the distance (in mm) of tumor from the nearest resection margin measured. The results of relevant ancillary investigations (e.g. immunohistochemistry) should be recorded [16]. The tumor should be classified using SNOMED or ICD-0 codes.

## stage classification and risk assessment

Ideally, all cases of suspected bone tumors should be discussed at a multidisciplinary team meeting that includes the radiologist who has interpreted the imaging and the pathologist who has reviewed the biopsy material and the surgeon and oncologist undertaking treatment. This will minimize the risk of errors in diagnosis, staging, risk assessment, and treatment.

Several staging systems for bone tumors are in use [17, 18]. However, none of them is perfect or generally accepted. Generally, tumor burden and the presence of detectable

**Table 1.** 2002 WHO classification of malignant bone tumors

Osteogenic tumors	
Osteosarcoma	9180/3
Conventional	9180/3
Chondroblastic	9181/3
Fibroblastic	9182/3
Osteoblastic	9180/3
Telangiectatic	9183/3
Small cell	9185/3
Low-grade central	9187/3
Secondary	9180/3
Parosteal	9192/3
Periosteal	9193/3
High-grade surface	9194/3
Ewing sarcoma/primitive neuroectodermal tumor	
Ewing sarcoma	9260/3
Cartilage	
Chondrosarcoma	9220/3
Central, primary, and secondary	9220/3
Peripheral	9221/3
Dedifferentiated	9243/3
Mesenchymal	9240/3
Clear cell	9242/3
Fibrogenic tumors	
Fibrosarcoma	8810/3
Fibrohistiocytic tumors	
Malignant fibrous histiocytoma <sup>a</sup>	8830/3
Giant cell tumor	
Malignancy in giant cell tumor	9250/3
Notochordal tumors	
Chordoma	9370/3
Vascular tumors	
Angiosarcoma	9120/3
Smooth muscle tumors	
Leiomyosarcoma	8890/3
Lipogenic tumors	
Liposarcoma	8850/3
Miscellaneous tumors	
Adamantinoma	9261/3

<sup>a</sup>In the new WHO classification, the entity MFH of the bone will disappear.

metastases are the two main factors which are taken into consideration in the clinical staging of these diseases.

General staging should be carried out to assess the extent of distant disease, including bone scintigraphy, chest radiographs, and CT [19]. Whole-body MRI and positron emission tomography (PET)/CT or PET/MRI are under evaluation both for staging and treatment response evaluation [20]. Additional appropriate imaging studies and biopsies can be taken from suspicious sites, as the exact staging of the disease has an impact on treatment and outcome [III, B].

No specific laboratory tests for the diagnosis of bone sarcoma are available. However, some are useful in the follow-up in ES and osteosarcoma and may also be of prognostic value, such as alkaline phosphatase (AP) and lactate dehydrogenase (LDH) [21, 22].

A pathological fracture may lead to the dissemination of tumor cells into surrounding tissues and increase the risk of local recurrence. In case of an existing pathological fracture in a possible primary malignant bone tumor, adequate imaging should be carried out, including MRI followed by biopsy. In cases of fracture, internal fixation is contraindicated as it disseminates tumor further into both bone and soft tissues and increases the risk of local recurrence. External splintage is recommended, along with appropriate pain control. In patients with weakened bone apparent at presentation, there may be a strong case for immobilizing the part following the biopsy, usually by application of an external splint. In chemosensitive tumors, primary neoadjuvant chemotherapy can be used with the expectation that a good response will allow the fracture hematoma to contract and allow subsequent resection of the tumor and the involved soft tissues. In patients with a poor response to chemotherapy or in tumors unlikely to respond to chemotherapy, early surgery obtaining wide margins should be considered; in some cases this may require amputation [23].

Chemotherapy treatment can result in renal, cardiac, and auditory dysfunction, and patients undergoing this treatment must have baseline renal function testing and assessment of cardiac function as well as an audiogram (in case of treatment with platinum derivatives).

Sperm storage is recommended for male patients of reproductive age. For female patients, consult a fertility physician for available options and, if options are available, discuss with the patient.

## treatment

As malignant primary bone tumors are rare cancers, and as management is complex, the accepted standard is treatment either in reference centers or within reference networks able to provide access to the full spectrum of care [IV, A]. In these centers, therapy is usually given within the framework of prospective, often collaborative, clinical studies, or established treatment protocols. In case of high-grade osteosarcoma, ES, or pleomorphic sarcoma, following biopsy proven-diagnosis, primary chemotherapy is indicated, preferably within the framework of (inter)national trials.

### osteosarcoma

Osteosarcoma usually arises in the metaphysis of a long bone, most commonly around the knee. Involvement of the axial skeleton and craniofacial bones is primarily observed in adults.

Conventional osteosarcoma, a high-grade malignancy, accounts for 75% of all high-grade osteosarcomas. Low-grade central and parosteal osteosarcoma are low-grade malignancies, while periosteal osteosarcoma is an intermediate-grade chondroblastic osteosarcoma.

Adverse prognostic or predictive factors include detectable primary metastases, axial or proximal extremity tumor site, large tumor size, elevated serum AP or LDH, and older age [21] [III, B]. Staging should include local imaging studies, as outlined in what follows.

Curative treatment of high-grade osteosarcoma consists of chemotherapy and surgery [I, A]. Compared with surgery

alone, multimodal treatment of high-grade localized osteosarcoma increases disease-free survival probabilities from only 10%–20% to >60%. In general, chemotherapy is administered before and after surgery, although a formal proof is lacking that giving chemotherapy preoperatively improves the outcome *per se*. The extent of histological response to preoperative chemotherapy predicts survival [21, 24, 25]. Current prospective trials evaluate whether altering postoperative chemotherapy in poor responders to preoperative systemic therapy improves treatment outcome.

Surgery should be carried out by a surgical team familiar with the wide range of surgical reconstructive options. The goal of surgery is to safely remove the tumor and yet preserve as much function as possible, striving to obtain adequate surgical margins as narrower margins are associated with an increased risk of local recurrence [25]. Most patients should be considered candidates for limb salvage. In principle, intralesional or marginal margins increase the local relapse rate, which is associated with reduced overall survival (OS). The consequences for function should be considered when obtaining wide tumor-free margins [III, B]. Areas where there is suspicion of close margins should be marked on the surgical specimen sent to pathology.

Doxorubicin, cisplatin, high-dose methotrexate, ifosfamide, and etoposide have antitumor activity in osteosarcoma [26–29] [I, A]. Doxorubicin, cisplatin, and high-dose methotrexate are frequently used as the basis of treatment [29] [II, A]. These drugs should be administered with adequate supportive care by experienced pediatric oncologists or medical oncologists in reference institutions with appropriate infrastructure and a multidisciplinary treatment approach [27]. A variety of pre- and postoperative combinations are used in common practice and in clinical trials, and the ideal combination scheme and the optimal treatment duration are yet to be defined. Most current protocols include a period of preoperative chemotherapy, to facilitate local surgical treatment and allow assessment of tumor response, although this has not been proven to add survival benefit over postoperative chemotherapy alone [30, 31] [I, B]. Treatment is commonly given over periods of 6–10 months [29]. Whenever possible, patients with osteosarcoma should receive chemotherapy in the context of prospective trials, which is regarded as standard of care. Immune modulation has been attempted with some agents, e.g. interferon [32] and muramyl tripeptide. Muramyl tripeptide added to postoperative chemotherapy was associated with a substantial advantage in OS and a non-significant trend in event-free survival in one large randomized trial [33, 34] [II, C]. Muramyl tripeptide has been approved in Europe for patients <30 years of age with completely resected localized osteosarcoma. There is no consensus in the sarcoma community on the use of this drug, because of weaknesses in the single trial available [33]. Further studies are definitely needed to identify the subgroup of patients who could benefit.

When tumor response assessment before surgery is clinically doubtful and relevant for clinical decision making, dynamic MRI is reliable, but requires sequential scans to evaluate change in tumor vascularity [35, 36] [III B]. Tumor response is often apparent only after several cycles of chemotherapy. Assessment of MRI peri-tumoral edema is helpful: its

disappearance is a sign of good treatment response [35]. Changes in the size and ossification of the tumor are not reliable criteria of tumor response to neoadjuvant chemotherapy.

In general, there is no indication for radiation therapy, but there are anatomical locations in which the possibility of complete surgical resection is limited. In these cases, radiation therapy may be an option to try to extend the progression-free interval. New radiation therapy techniques (e.g. proton beam therapy) may extend the indications for this.

The multimodal treatment principles detailed above were generated in children, adolescents, and young adults with high-grade central osteosarcoma, but also relate to adults at least up to the age of 60 [37] [III, B]. Older patients (>40 years) may require tailored regimens, especially as far as high-dose methotrexate is concerned. Doxorubicin and cisplatin are the most active drugs, with the cumulative dose of anthracycline being a critical factor.

Low-grade central and parosteal osteosarcoma are malignancies with a lower metastatic potential, which are treated by surgery only [III, B]. Careful analysis of the resected tumor may show areas of high-grade change, in which case the patient should be treated as for a conventional osteosarcoma.

Although chemotherapy has been used for periosteal osteosarcomas, no benefit for chemotherapy was shown in two retrospective analyses [38, 39].

High-grade cranio-facial osteosarcoma should be treated the same way as high-grade osteosarcoma of other locations, although evidence is lacking due to the absence of selective clinical studies in this patient population [V, B].

Primary metastatic osteosarcoma patients are treated with a curative intent along the principles of non-metastatic osteosarcomas [40]. In fact, there are subsets of patients who can have a very similar or even identical prognosis to that of localized disease, provided surgical removal of all known metastatic deposits is achievable [41] [III, B]. In lung metastases, this will usually require exploratory thoracotomy including palpation of both lungs. Approximately 30% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission become long-term survivors.

The management of recurrent osteosarcoma needs to take into account the timing of recurrence/metastases, number of metastases, and site of metastases. Treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases. Complete removal of all metastases must be attempted [III, B], as the disease is otherwise almost universally fatal, while more than a third of patients with a second surgical remission survive for >5 years [42]. Even patients with multiple recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted [42] [III, B]. CT scan can both over- and underestimate the number of metastases.

The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery and there is no accepted standard regimen. Treatment choice may take into account the prior disease-free interval, and often includes ifosfamide ± etoposide ± carboplatin, and other active drugs. In the two largest reported series, the use of second-line

chemotherapy correlated with limited prolongation of survival in patients with inoperable metastatic recurrences, while a positive correlation in operable disease was observed in only one of the two [41, 42].

Radiation therapy (including Samarium) may have a role in palliation [43].

In general, despite second-line treatment, the prognosis of recurrent disease has remained poor, with long-term post-relapse survival of <20%.

### Ewing sarcoma

ES is a small, blue, round-cell tumor, PAS+ and CD99 (MIC2)-positive. All ESs are high-grade tumors. The definitive diagnosis is made by biopsy, providing sufficient material for conventional histology, immunohistochemistry, molecular pathology, and biobanking (fresh, unfixed material). Molecular biology studies have shown that almost all these tumors share a common gene rearrangement involving the EWS gene on chromosome 22 [44, 45]. In most cases, this involves a reciprocal translocation t(11;22)(q24;q12) [46], but t(21;22)(q22;q12) [47, 48] and others may also occur [t(7;22), t(17;22) and t(2;22) translocations and inv(22)]. Although most ES can be recognized with classical hematoxylin and eosin (H&E) and immunohistochemistry, including CD99, EWS translocation detection is mandatory when the clinical-pathological presentation is unusual, or the histological diagnosis is doubtful [II, B]. A reference laboratory for ES diagnosis should have both FISH and reverse transcription polymerase chain reaction (RT-PCR) available [48]. The laboratory is strongly recommended to be enrolled in an external quality assurance program. RT-PCR is the investigation of choice when frozen tissue is available, and FISH is a good choice only when formalin-fixed paraffin-embedded tissue or touch preps (imprints) are available. There are several commercial sources for EWS break-apart probes. Assays using EWS break-apart probes do not detect EWS-FLI1 fusions, but only EWS rearrangements, which should not be a problem when interpreted in the appropriate clinical and pathological context. However, differential diagnosis versus other sarcomas carrying EWS rearrangements may be challenging.

Bone marrow biopsies and aspirates from sites distant to the primary or known metastatic lesions are mandatory. The added prognostic value of molecular positivity over light microscopic evaluation has not yet been proven [IV, C].

Between 20% and 25% of patients are diagnosed with metastatic disease (10% lung, 10% bones/bone marrow, 5% combinations or others) [49, 50]. Staging must be oriented to detect lung, bone, and bone marrow metastases. Multiple bone metastases confer a poorer outcome than lung/pleura metastases (<20% compared with 20%–40% 5-year survival). Other known prognostic factors are tumor size or volume, serum LDH levels, axial localization or older age (>15 years). A poor histological response to preoperative chemotherapy, and incomplete or no surgery for local therapy are further adverse prognostic factors [II, B] [22, 51–55]. Molecular structure of fusion transcripts has not been shown to be of prognostic value with current treatment protocols. Genomic analysis with copy

number variation assessment has been shown to be of prognostic value [56, 57].

With surgery or radiotherapy alone, 5-year survival was <10%. With treatment in current multimodality trials including chemotherapy, survival is ~60%–70% in localized and ~20%–40% in metastatic disease, depending on metastatic sites and burden.

All current trials employ 3 to 6 cycles of initial combination chemotherapy after biopsy, followed by local therapy and another 6 to 10 cycles of chemotherapy usually applied at 2–3-week intervals. Treatment duration is thus 10–12 months. Agents considered most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, and etoposide [58–62]. Virtually all active protocols are based on six-drug combinations of these substances [I, A]. Chemotherapy intensity is positively associated with outcome. High-dose chemotherapy with hematopoietic stem cell transplantation is still investigational in high-risk localized ES [63].

Complete surgical excision, where feasible, is regarded as the best modality of local control given the higher risk of local recurrence when radiotherapy is used as the sole treatment for the primary tumor. Radiotherapy alone (in the range of 45–60 Gy, depending on location) should be applied if complete surgical excision is impossible. Postoperative radiotherapy should be given in cases of inadequate surgical margins and discussed when histological response in the surgical specimen was poor (i.e. >10% viable tumor cells) [53, 64] [IV, B]. The dose of postoperative radiation therapy is also 45–60 Gy, depending on margins, response, and location. Intralesional surgery must be avoided, as there is no benefit when compared with radiation therapy alone [53].

Change in the size of the soft tissue mass is easily evaluated on MRI, and is a good predictor of tumor response [35, 36]. Dynamic MRI is not as reliable as in osteosarcoma [36], as remaining small tumor foci may not be detected. Sequential FDG PET evaluation might be of additional value [65].

Treatment of adult patients follows the same principles as for ES in typical age groups. However, tolerability of therapies in older patients needs to be taken into account when transferring treatment protocols conceived for children and patients of age ≤40–50 years.

Treatment of patients with extraskelatal ES follows the same principles as for bone ES, thus incorporating chemotherapy in all cases.

Patients with metastases at diagnosis are treated with the same treatment approach as patients with localized disease, although the disease has a definitely worse prognosis. Several non-randomized trials have assessed the value of more intensive, time-compressed or high-dose chemotherapy approaches, followed by autologous stem cell rescue, with promising result, but evidence of benefit, resulting from trials, is pending [66] [III, C].

In patients with lung metastases, whole-lung irradiation may confer a survival advantage [III, B] [54]. The role of surgical resection of residual metastases is less well defined. Patients with multiple bone or bone marrow metastases and patients with recurrent disease still fare poorly, with 5-year survival rates of ~20%. Despite this, local control of bone

metastases with either surgery or radiation therapy is recommended [67].

The only prognostic factor identified in relapsed patients seems to be time to relapse: patients relapsing later than 2 years from initial diagnosis have a better outcome [68] [III, B]. Doxorubicin therapy is usually no longer feasible due to previously achieved cumulative doses. Chemotherapy regimens in relapse situations are not standardized and are commonly based on alkylating agents (cyclophosphamide, high-dose ifosfamide) [69] in combination with topoisomerase inhibitors (etoposide, topotecan) or irinotecan with temozolomide [III, B] [70, 71]. IGFR (insulin growth factor receptor) targeting appears promising in advanced ES [72, 73].

### high-grade undifferentiated pleomorphic sarcomas of bone

Pleomorphic sarcomas of bone comprise a diagnostically heterogeneous group of malignant tumors including fibrosarcoma (FS), the so-called malignant fibrous histiocytoma (MFH), leiomyosarcoma, and undifferentiated sarcoma [16, 74, 75]. They arise in a similar age group to chondrosarcoma but the skeletal distribution is more like osteosarcoma. They typically present with pain and have a high incidence of fracture at presentation. They represent between 2% and 5% of primary bone malignancies. The true incidence is hard to establish as the two entities (MFH/FS) exhibit a substantial degree of morphological overlap, also reflected by an inconsistent use of terminology. Males are more frequently affected than females. An association with pre-existing disease (Paget's disease or bone infarct) or history of previous irradiation has been reported. It is not unusual for a spindle cell sarcoma to be found to be either a dedifferentiated chondrosarcoma or osteosarcoma after examining further different sections of the resection.

Pleomorphic sarcomas typically present in older patients with a lytic lesion in bone. In many, the differential diagnosis will be a metastasis. Full staging and biopsy are required to reach a diagnosis. Pathological fractures are common and should be investigated before fixation.

Treatment strategies mimic those of osteosarcoma, with chemotherapy and complete *en bloc* resection including any soft tissue component.

Anecdotal evidence suggests that prognosis may be better than that for osteosarcoma. A global effort to collect these cases would be helpful to establish diagnostic and prognostic criteria as well as recommend treatment.

### chondrosarcoma

Most chondrosarcomas arise as primary malignant tumors; the majority are low grade, locally aggressive, non-metastasizing tumors (grade I) rather than high grade (grades II–III) [76]. Most chondrosarcomas arise centrally in the metaphyseal region of long bones, but they can also develop in flat bones such as pelvis, rib, and scapula. High-grade chondrosarcoma frequently arises in the axial skeleton and long bones. Chondrosarcoma can arise in pre-existing benign lesions such as enchondroma and osteochondroma. In these circumstances, they are referred to as secondary chondrosarcoma and

secondary peripheral chondrosarcomas, respectively. The majority of chondrosarcomas are of the conventional subtype, but rarer subtypes include mesenchymal and clear-cell chondrosarcoma [77, 78]. In rare circumstances, conventional chondrosarcomas can 'dedifferentiate' into a very high-grade tumor with a dismal prognosis: so-called de-differentiated chondrosarcoma [77, 78]. Most chondrosarcomas are solitary, but they can occur as multiple lesions in patients with multiple osteochondromas and enchondromatosis.

Most chondrosarcomas present with a painless mass. Pain at the site of a cartilaginous lesion may be an indicator of malignancy. In the case of chondrosarcoma, a contrast-enhanced MRI can reveal high-grade areas. This provides a useful guide to the site of biopsy [79]. The differentiation between benign enchondroma or osteochondroma and malignant grade I chondrosarcoma can be difficult. In the phalanges of the hand and feet, malignancy is extremely rare, but in the other long bones central cartilaginous lesions should be considered low-grade chondrosarcoma till proven otherwise [77].

Inoperable, locally advanced and metastatic high-grade chondrosarcomas have a poor prognosis because of resistance to conventional treatments such as radiotherapy and chemotherapy [77, 78]. Prognosis depends on histological grade. However, histological classification is subject to variability in interpretation, with grade II and III chondrosarcomas often grouped together even though there is a wide spectrum of outcome [76]. Also, grade I tumors do not have 100% survival, mainly due to problematic local recurrence or progression to high grade upon occurrence. In particular, dedifferentiated chondrosarcomas are aggressive and frequently metastasize [77].

Assessing the grade of chondrosarcomas is difficult and variations in opinions even among experts are common [76]. Low-grade cartilage tumors are unlikely to metastasize but may recur locally. Grade I central chondrosarcomas in the long bones of the limbs can be managed by curettage with or without adjuvant (e.g. phenol, cement, cryotherapy) with a high chance of success. Low-grade peripheral chondrosarcomas (arising from osteochondromas) should be surgically excised, aiming to excise the tumor with a covering of normal tissue over it. Higher grade chondrosarcomas and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins.

Recent evidence suggests that mesenchymal chondrosarcoma may be chemotherapy sensitive, and may be considered for adjuvant or neoadjuvant therapy [80, 81] [V, B]. Most authorities suggest an Ewing-type chemotherapy regime.

There remains uncertainty about chemotherapy sensitivity of dedifferentiated chondrosarcoma, which is often treated as a high-grade bone sarcoma, with therapies which need to be adapted to patient's age [82, 83] [V,C]. There is a very high risk of local recurrence following excision of dedifferentiated chondrosarcoma, particularly in the presence of a pathological fracture. If wide margins cannot be reliably achieved with limb salvage, then amputation should be considered.

The role of radiotherapy in chondrosarcoma is limited, but may be appropriate in highly selected cases or for palliation. Excellent outcomes have been reported for skull base

chondrosarcomas with proton beam radiotherapy, achieving 80%–90% local control rates [84].

### chordoma

Chordomas typically arise in the sacrum, mobile spine, or skull base recapitulating histologically notochord remnants. Extra-axial cases have been occasionally reported.

Surgery is the treatment of choice, but the most frequent sites of origin make treatment of primary disease challenging. Local relapses affect >50% of cases, with a minority of patients being cured by further surgery [85]. There are now encouraging results from high-dose radiotherapy using proton beams or carbon ion facilities [86]. Assessment in a specialist center with expertise in managing these tumors is essential to define the role of surgery and/or radiotherapy.

Metastases are more common than previously believed (>20%), and therefore should be looked for on staging (lungs, liver, bone, soft tissues). For patients with advanced disease, there is evidence of some effectiveness of molecular targeted agents (imatinib) and studies are ongoing.

### giant cell tumor of bone

Giant cell tumor of bone (GCT) is a relatively rare, benign tumor of the skeleton. Although classified as benign, GCTs can be aggressive and recur locally in up to 50% of cases. Up to 5% of GCT metastasize to the lungs and spontaneous transformation to a high-grade malignancy occurs in 1%–3% of patients.

They are typically treated at specialist bone tumor treatment centers.

Treatment options include intralesional curettage with or without adjuvant or *en bloc* excision.

Recent work has suggested that denosumab, a human monoclonal antibody to RANKL that is overexpressed in GTC, may obtain substantial tumor responses in large or unresectable or metastatic GCT. Further results are awaited [87].

### follow-up

Follow-up is designed to detect either local recurrence or metastatic disease at a time when early treatment is still possible and might be effective. Follow-up of high-grade tumors should include both a physical examination of the tumor site and assessment of the function and possible complications of any reconstruction. Local imaging and chest X-ray/CT should be the norm. Though strict rules cannot be provided in the absence of any formal validation, a recommended follow-up policy may foresee intervals between checks after the completion of chemotherapy every 2–3 months for the first 2 years; every 2–4 months for years 3–4; every 6 months for years 5–10 and thereafter every 6–12 months according to local practice and other factors.

In case of low-grade bone sarcoma, the frequency of follow-up visits may be lower (e.g. 6 months for 2 years and then annually). Late metastases as well as local recurrences and functional deficits may occur >10 years after diagnosis and

there is no universally accepted stopping point for tumor surveillance.

In ES, where osseous metastases are likely, isotope bone scanning can be used in addition. More modern techniques (e.g. PET or whole-body MRI) require further evaluation.

It is important to evaluate the long-term toxicity effect of chemotherapy and radiotherapy if appropriate. Monitoring for late effect should be undertaken for >10 years after treatment, depending on the chemotherapy protocol and radiation used and in conjunction with late effects services when available.

Secondary cancers may arise in survivors of bone sarcomas, either related to or independent of irradiation. Secondary leukemia, particularly acute myeloid leukemia, may rarely be observed following chemotherapy, as early as 2–5 years after treatment [III, B].

### note

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Milan, Italy in January 2012 and refined afterward. This involved experts from the community of the European sarcoma research groups, sarcoma networks of excellence, and ESMO Faculty. Their names are indicated hereafter. The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The panel worked on the text of ESMO Guidelines of previous years, whose authorship should also be credited.

### Consensus Panel ESMO Guidelines 2012

Jean-Yves Blay, France (Moderator)  
 Carl Blomqvist, Finland  
 Sylvie Bonvalot, France  
 Ioannis Boukovinas, Greece  
 Paolo G. Casali, Italy  
 Enrique De Alava, Spain  
 Angelo Paolo Dei Tos, Italy  
 Uta Dirksen, Germany  
 Florence Duffaud, France  
 Mikael Eriksson, Sweden  
 Alexander Fedenko, Russian Federation  
 Andrea Ferrari, Italy  
 Stefano Ferrari, Italy  
 Xavier Garcia del Muro, Spain  
 Hans Gelderblom, Belgium  
 Robert Grimer, United Kingdom  
 Alessandro Gronchi, Italy  
 Kirsten Sundby Hall, Norway  
 Bass Hassan, United Kingdom  
 Pancras Hogendoorn, The Netherlands  
 Peter Hohenberger, Germany  
 Rolf Issels, Germany  
 Heikki Joensuu, Finland  
 Lorenz Jost, Switzerland  
 Heribert Jurgens, Germany  
 Leo Kager, Austria  
 Axel Le Cesne, France

Serge Leyvraz, Switzerland  
 Javier Martin, Spain  
 Ofer Merimsky, Israel  
 Toshiro Nishida, Japan  
 Piero Picci, Italy  
 Peter Reichardt, Germany  
 Piotr Rutkowski, Poland  
 Marcus Schlemmer, Germany  
 Stefan Sleijfer, The Netherlands  
 Silvia Stacchiotti, Italy  
 Antoine Taminiau, The Netherlands  
 Eva Wardelmann, Germany

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## conflict of interest

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