clinical practice guidelines

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Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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introduction

Primary bone tumours are rare, accounting for <0.2% of malignant tumours registered at the EUROCARE database. They have a relatively high incidence in children and adolescents, but are still numerically outnumbered by benign bone tumours, which clinically may have a similar presentation. They are also frequently difficult to recognize as malignant by clinicians, radiologists as well as pathologists and this leads to major diagnostic difficulties in non-specialized centres. One of the main recommendations of this guideline is that all patients with a suspected primary malignant bone tumour should be referred to a bone sarcoma reference centre or an institution belonging to a specialized bone sarcoma network before biopsy.

Primary bone tumours are considerably outnumbered by metastases to the bone in older patients, which in some instances might mimic the presentation of a primary bone tumour. The presence of non-mechanical pain or night pain around the knee of a person in this or indeed any age group should cause concern and lead to further immediate investigation. Swelling will only be present if the tumour has progressed through the cortex and distended the periosteum.

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background

A general overview of the histological types of primary malignant bone tumour according to the World Health Organization (WHO) classification is given in Table 1. Several staging systems for bone tumours are in use; however, none of them are perfect or generally accepted.

osteosarcoma

Osteosarcoma is the most frequent primary cancer of bone (incidence: 0.2–0.03/100 000/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. 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 80%–90% of all osteosarcomas. Its most frequent subtypes are osteoblastic, chondroblastic and fibroblastic. Other high-grade types are telangiectatic, small cell and high-grade surface osteosarcoma. Low-grade central and parosteal osteosarcoma are low-grade malignancies, while periosteal osteosarcoma is an intermediate-grade chondroblastic osteosarcoma. Risk factors for the occurrence of osteosarcoma include previous radiation therapy, Paget's disease of bone and germ line abnormalities such as the Li–Fraumeni syndrome, Werner syndrome, Rothmund–Thomson syndrome, Bloom syndrome and hereditary retinoblastoma.

Table 1. 2002 WHO classification of malignant bone tumours

Osteogenic tumours	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 tumour	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 tumours	Fibrosarcoma	8810/3
Fibrohistiocytic tumours	Malignant fibrous histiocytoma	8830/3
Haematopoietic tumours	Plasma cell myeloma	9732/3
	Malignant lymphoma, NOS	9590/3
Giant cell tumour	Malignancy in giant cell tumour	9250/3
Notochordal tumours	Chordoma	9370/3
Vascular tumours	Angiosarcoma	9120/3
Smooth muscle tumours	Leiomyosarcoma	8890/3
Lipogenic tumours	Liposarcoma	8850/3
Miscellaneous tumours	Adamantinoma	9261/3

Although listed by the WHO as bone tumours, plasma cell myeloma, as well as primary malignant lymphoma of bone are not dealt with by these guidelines.

Ewing sarcoma

Ewing sarcoma (ES) (including primitive neuroectodermal tumour of bone) is the second most common primary malignant bone cancer. 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, 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 tumours. Also the ribs and vertebral column are frequently affected. ES may involve any bone and (less commonly in children) arise purely in soft tissues

chondrosarcoma

Chondrosarcoma is one of the most frequently occurring bone sarcomas of adulthood. The incidence is ~0.1/100 000 per year, with the most common age being between 30 and 60 years and the male–female ratio is ~1. Most chondrosarcomas arise as primary malignant tumours, and the majority are low grade (grade I) rather than high-grade (grade II–III). Most chondrosarcomas arise centrally in the diametaphyseal 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. Chondrosarcomas can arise in pre-existing benign lesions such as enchondroma and osteochondroma. In these circumstances they are referred to as secondary chondrosarcomas and secondary peripheral chondrosarcomas, respectively. The majority of chondrosarcomas are of the conventional subtype, but rarer subtypes include mesenchymal and clear cell chondrosarcoma. In rare circumstances conventional chondrosarcomas can 'dedifferentiate' into a very high-grade tumour with a dismal prognosis, so-called dedifferentiated chondrosarcoma. Most chondrosarcomas are solitary, but they can occur as multiple lesions in patients with multiple osteochondromas and enchondromatosis.

spindle cell sarcomas of bone

Spindle cell sarcomas of bone (e.g. malignant fibrous histiocytoma/fibrosarcoma of bone) comprise a diagnostically heterogeneous group of malignant tumours including fibrosarcoma (FS), malignant fibrous histiocytoma (MFH), leiomyosarcoma and undifferentiated sarcoma. 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 significant 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 different sections of the resection.

other bone sarcomas

These include such entities as adamantinoma and chordoma, malignancy in giant cell tumour, angiosarcoma and liposarcoma, that have specific clinical presentations and management.

clinical presentation

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 tumours include prior benign/malignant lesions, family history and previous radiotherapy. A recent injury does not rule out a malignant tumour 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.

imaging

The likely diagnosis of a suspected bone tumour is related to age. Before 5 years of age, a destructive bone lesion is most

commonly metastatic neuroblastoma or eosinophilic granuloma; >5 years, it is often a primary bone sarcoma; >40 years of age, it tends to be metastasis or myeloma.

diagnosis and local staging

Conventional radiographs in two planes should always be the first investigation. CT should only be used in the case of a diagnostic problem or doubt, to visualize more clearly calcification, periosteal bone formation, cortical destruction or soft tissue involvement. When the diagnosis of malignancy cannot be excluded with certainty on radiographs, the next imaging step is MRI of the whole bone with adjacent joints, which is the best modality for local staging.

General staging should be carried out to assess the extent of distant disease including bone scintigraphy and chest radiographs and CT; small nodules are not specific for malignancy. Whole body MRI and PET are under evaluation for both staging and treatment response evaluation. Additional appropriate imaging studies and biopsies should be taken from suspicious sites, as the exact staging of the disease has an impact on treatment and outcome [III, B].

In the case of chondrosarcoma contrast-enhanced MRI can reveal high-grade areas: this provides a useful guide to the site of biopsy.

biopsy

The biopsy of a suspected primary malignant bone tumour should be carried out at the reference centre, by the surgeon who is to carry out the definitive tumour resection, a radiologist, or a member of the team. The principles of the biopsy are:

- there should be minimal contamination of normal tissues;
- in many situations core needle biopsy will be more than adequate, often controlled by ultrasound, X-ray or CT;
- samples should preferably be taken for microbiological culture as well as histology;
- in the tumour centre samples should be snap-frozen for future studies;
- samples must be interpreted by an experienced pathologist;
- the request form should contain sufficient detail for the pathologist including the site of the tumour, the patient's age and the radiological differential diagnosis.

It is advised in the case of tumours and tumour-simulating lesions of the skeleton, to determine the staging of the lesion before the biopsy. An important advantage of staging studies obtained before the biopsy is the possibility of choosing the location of the biopsy, taking into account possible future surgery, especially when it concerns limb salvage surgery. Imaging studies can also indicate the most representative part of the lesion. Core needle biopsy (multiple) (for example Jamshidi, but not fine-needle aspiration) or open biopsy (depending on the location of the lesion and local expertise, difficult cases) is preferred. An excision biopsy is contraindicated for all cases that present the possibility of an aggressive–benign or malignant lesion, because an excision without oncologically adequate margins will contaminate more tissue compartments than necessary. If an open biopsy is done, it should be performed using a longitudinal incision. To be sure that the biopsy location is adequate and the tissue is representative for the resulting process, it is recommended that X-rays be taken of the biopsy location and the pathologist consulted directly (by frozen section) after taking the biopsy in case more material is required. In aggressive and malignant tumours of bone, the biopsy tract should be considered to be contaminated with tumour 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 definitive procedure.

In cases of spinal column involvement, laminectomy or decompression should be avoided unless necessary to relieve spinal cord compression.

general comment on tumour handling. Material should be quickly, ideally within half an hour, submitted for pathological assessment; upon arrival, and before formalin fixation, tumour imprints (touch preps) can be taken (useful for tumour-specific translocation by FISH), and tissue/cell suspensions should be kept frozen in cryomoulds. A further option is to establish primary cell cultures for cytogenetics. Tumour banks are useful for diagnosis and translational research into the molecular pathology of cancer; therefore informed consent for tumour banking should be sought that allows for later analysis and research according to local practice.

reporting pathology

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 tumour biopsy. The pathologist should receive information regarding the clinical/radiological context in which the tumour 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 tumour in the resected bone should be noted. The histological features of the tumour should be described and the tumour type (and subtype) specified according to the latest WHO criteria. The extent of tumour necrosis in response to preoperative therapy should be assessed as being more or less than 90% necrosis. The pathology report should note the extent of local tumour spread, including involvement of specific anatomical compartments. Whether the resection margins are clear or involved by tumour should be noted and the distance (in mm) of tumour from the nearest resection margin measured. The results of relevant ancillary investigations (e.g. immunohistochemistry) should be recorded. The tumour should be classified using SNOMED or ICD-0 codes.

staging and risk assessment

Ideally all cases of suspected bone tumour 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.

laboratory tests

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

osteosarcoma. Staging: 75% of all osteosarcomas arise around the knee. Typically there is pain, which begins insidiously and gradually becomes constant; pain may be present at night and is often non-mechanical in nature. Localized swelling and limitation of joint movement are later findings.

Risk assessment: adverse prognostic or predictive factors include detectable primary metastases, poor histological response to preoperative chemotherapy, axial or proximal extremity tumour site, large tumour volume, elevated serum AP or LDH, and older age [III, B]. Staging should include local imaging studies, as outlined below.

Ewing sarcoma. Staging and molecular pathology: ES is a small blue round-cell tumour, PAS+ and CD99 (MIC2) positive. All ESs are high-grade tumours. 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 all these tumours share a common gene rearrangement involving the EWS gene on chromosome 22. In most cases, this involves a reciprocal translocation t(11;22)(q24;q12), but t(21;22)(q22;q12) and others may also occur [t(7;22), t(17;22) and t(2;22) translocations and inv(22)]. Although most Ewing sarcoma can be recognized with classical haematoxylin–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 Ewing sarcoma diagnosis should have both FISH and RT–PCR available. The laboratory is strongly recommended to be enrolled in an external quality assurance programme. RT–PCR is the investigation of choice when frozen tissue is available, and FISH is a good choice when only 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.

Some staging practices such as light microscopic analysis of bone marrow aspirates, and biopsies from sites distal to the lesion (metastases) are mandatory. The use of RT–PCR of bone marrow aspirate (metastases) is under investigation. The added value in prognostic sense over light microscopic evaluation has not been proved yet [IV, C].

Cytogenetic analysis by chromosome banding applying Multicolour FISH/Spectral FISH can be helpful to detect multichromosomal rearrangements in cases in which more conventional molecular techniques (FISH, RT–PCR) cannot help to get to the diagnosis.

Risk assessment: between 20% and 25% of patients are diagnosed with metastatic disease (10% lung, 10% bones/bone marrow, 5% combinations or others). Staging must be oriented to detect lung, bone and bone marrow metastases. All patients should have a bone marrow biopsy and aspirate performed before starting treatment. PCR techniques to investigate for bone marrow metastases are currently under evaluation. Bone metastases confer a poorer outcome than lung/pleura metastases (<20% compared with 20%–40% 5- year survival). Other known prognostic factors are tumour 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].

chondrosarcoma. Staging: most chondrosarcomas present with a painless mass. Pain at the site of a cartilaginous lesion may be an indicator of malignancy.

Risk assessment: the differentiation between benign enchondroma or osteochondroma and malignant grade I chondrosarcoma can be difficult. In the phalanges of the hands and feet malignancy is extremely rare, but in the other long bones central cartilaginous lesions should be considered low-grade chondrosarcoma till proved otherwise. Inoperable, locally advanced and metastatic high-grade chondrosarcomas have a poor prognosis because of resistance to conventional treatments such as radiotherapy and chemotherapy. 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. Also grade I tumours do not have 100% survival, mainly due to problematic local recurrence or progression into high grade upon occurrence. In particular, dedifferentiated chondrosarcomas are aggressive and frequently metastasize.

spindle cell sarcomas of bone (MFH/FS). Spindle cell sarcomas typically present in an older patient 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

prevention and management of pathological fracture

In the case of an existing pathological fracture in a possible primary malignant bone tumour, adequate imaging should be performed including MRI followed by biopsy. A pathological fracture may lead to dissemination of tumour cells into surrounding tissues and increase the risk of local recurrence. Thus 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 the case of an existing pathological fracture in a possible primary malignant bone tumour, adequate imaging should be performed

including MRI followed by biopsy. In cases of fracture, internal fixation is contraindicated as it disseminates tumour further into both bone and soft tissues and increases the risk of local recurrence. External splintage is recommended, along with appropriate pain control. Neoadjuvant chemotherapy should be used in the expectation that a good response will allow the fracture haematoma to contract and allow subsequent resection of the tumour and the involved soft tissues. In patients with a poor response to chemotherapy or in tumours unlikely to respond to chemotherapy then early surgery obtaining wide margins should be considered; in some cases this may require amputation. Postoperative radiotherapy may be considered to try to decrease the risk of local recurrence in radioresponsive tumours. Resection could be considered if feasible.

systemic therapy

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

baseline assessments. 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 the case of treatment with platinum derivates). Sperm storage is recommended for male patients of reproductive age. For female patients: consult fertility physician for available options (usually investigational) and if available discuss with the patient.

treatment evaluation by imaging

osteosarcoma. Changes in the size and ossification of the tumour are not reliable criteria of tumour response to neoadjuvant chemotherapy. Assessment of MRI peritumoral oedema is helpful: its disappearance is a sign of good treatment response. Dynamic MRI is reliable, but requires sequential scans to evaluate change in tumour vascularity. Assessment of response is usually only apparent after several cycles of chemotherapy. It is therefore useful in rare difficult cases to plan surgery, but not to change early a chemotherapy regimen.

Ewing sarcoma. Change in the size of the soft tissue mass is easily evaluated on MRI, and is a rather reliable indicator of tumour response. Dynamic MRI is not as reliable as in osteosarcoma, as remaining small tumour foci may not be detected. Sequential FDG-PET evaluation might be of additional value.

surgery

Surgery should be performed only after adequate preoperative staging and—depending on the tumour entity—primary chemotherapy, striving to obtain adequate surgical margins as narrower margins are associated with an increased risk of local recurrence. If possible a wide *en-bloc* resection should be performed, in general intracompartmental, but in the case of clear indications (easily removable bone, muscle) the entire bone/muscle compartment (extracompartmental) can be removed. One should consider the consequences for the remaining usefulness of the limb when obtaining wide tumour-free margins [III, B].

In the case of an indication for postoperative radiotherapy during surgery the risk areas and marginal margins should be identified with titanium (MRI-inert) haemo-clips. Areas suspicious for close margins should also be marked on the surgical specimen sent to pathology. The type of surgical reconstruction will depend on patient and surgeon choice and experience following open discussion of the risks and benefits of different options.

requirements for the surgical report. Describe the entire procedure, including the approach, relation to vital structures (vessels, nerves) resection margins, anatomical proportions (draw resection), risk areas (marginal borders) in relation to the resection specimen. Describe the placement of haemo-clips on the risk areas and vital structures, related to the wound area, give proportions in centimetres and describe the reconstruction. Questions to the pathologist related to the resection specimen: does the diagnosis from the resection specimen confirm the diagnosis of the biopsy? Can the surgery be considered a success based on the resection margin (risk locations marked by the surgeon)? Special attention should be given to the different compartments bone, nerves, muscle, joint, growth plate cartilage vessels, etc.

radiotherapy

The role of radiotherapy in osteosarcoma and chondrosarcoma is limited but may be appropriate in highly selected cases or for palliation [IV, C]. Further boost techniques to increase the local dose may be considered in osteosarcoma, including intensity-modulated radiotherapy (IMRT), proton therapy or samarium. Excellent outcomes have been reported for skull base chondrosarcomas with proton beam radiotherapy achieving 80%–90% local control rates.

Ewing sarcoma is a radiation-responsive tumour. Radiotherapy can, in combination with chemotherapy, achieve local control, but complete surgery when feasible has to be regarded as the first choice of local therapy. Incomplete surgery, even when combined with postoperative radiotherapy, is not superior to radiotherapy alone and should be avoided. If, however, incomplete surgery has occurred, it should be followed by postoperative radiotherapy.

specific treatment recommendations

osteosarcoma

localized disease. Curative treatment for high-grade osteosarcoma consists of surgery and chemotherapy [I, A]. Compared with surgery alone, multimodal treatment of high-grade osteosarcoma increases disease-free survival probabilities from only 10%–20% to >60%.

The goal of surgery is to safely remove the tumour and yet preserve as much function as possible. Most patients should be considered candidates for limb salvage. Doxorubicin, cisplatin, high-dose methotrexate and ifosfamide have antitumor activity in osteosarcoma [I, A]. These drugs should be administered with adequate supportive care by experienced paediatric oncologists or medical oncologists in reference institutions with appropriate infrastructure with a multidisciplinary treatment approach. Doxorubicin and cisplatin are frequently used as the basis of treatment, and there is evidence that combinations with methotrexate and/or ifosfamide might provide additional benefit over two-drug schedules [II, A]. 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, although this has not been proven to add survival benefit over postoperative chemotherapy alone [I, B]. Treatment is commonly given over periods of 6–12 months. Current prospective trials evaluate whether altering postoperative chemotherapy in poor responders to preoperative systemic therapy improves outcome of treatment. The use of haematopoietic growth factors has not consistently resulted in improved survival of osteosarcoma patients. The immune modulator muramyl tripeptide added to postoperative chemotherapy was associated with a statistically significant advantage in overall survival and a non-significant trend in event-free survival in one large randomized trial [II, B]. Muramyl tripeptide has been approved in Europe for patients <30 years of age with completely resected localized osteosarcoma, but has not been implemented in ongoing prospective clinical trials in Europe. Whenever possible, patients with osteosarcoma should receive chemotherapy in the context of prospective trials, which is regarded as standard of care.

The extent of histological response to preoperative chemotherapy, however, offers important prognostic information [I, A]. 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 [III, B] and to rarer variants of high-grade osteosarcoma, such as high-grade surface, secondary [III, B]. Chemotherapy is also recommended for older patients with osteosarcoma using adapted protocols.

Extraosseous osteosarcoma may be treated according to the regimens of high-grade soft tissue sarcomas or osteosarcoma schedules. There is no consensus on this point amongst experts. Low-grade central and parosteal osteosarcoma are variants with lower malignant potential, which are treated by surgery only [III, B]. Careful analysis of the resected tumour may show areas of high-grade change in which case the patient should be treated as for a conventional osteosarcoma. The exact role of chemotherapy has not been defined for periosteal and jaw osteosarcoma.

metastatic disease and recurrent disease. Primary metastatic osteosarcoma patients are treated with curative intent along the principals of non-metastatic osteosarcomas. There are subsets of patients who can have a very similar or even identical prognosis to that of localized disease, with the mandatory addition of surgical removal of all known metastatic deposits [III, B], usually by exploratory thoracotomy including palpation of the lung. 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, site of metastases. Treatment for recurrent osteosarcoma is primarily surgical. Prognosis is poor, with long-term post-relapse survival <20%. 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. Even patients with multiple recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted [III, B]. CT scan can both overestimate 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. Choice may take into account the prior disease-free interval, and often includes ifosfamide ± etoposide ± carboplatin, etc. 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.

Ewing sarcoma

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

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

Despite lively debate, complete surgery, where feasible, is regarded as the best modality of local control given the higher risk of local recurrence when radiotherapy is used as sole treatment for the primary tumour. Radiotherapy alone should be applied if complete surgery is impossible. Postoperative radiotherapy should be given in cases of inadequate surgical margins and discussed where histological response in the surgical specimen was poor (i.e. >10% viable tumour cells) [IV, C]. Intralesional surgery must be avoided as in one large series it was found that this was of no benefit when compared with radiotherapy alone. Treatment of adult patients follows the same principles. However, tolerability of therapies in adults needs to be taken into account when transferring treatment

protocols conceived for children and patients of age ≤30–40 years. Treatment of patients with extraskeletal Ewing sarcoma follows the same principles as for bone Ewing sarcoma.

metastatic and recurrent disease. Patients with metastases at diagnosis treated with the same treatment approach as patients with localized disease have a 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 results but evidence of benefit, resulting from trials, is pending [III, B]. In patients with lung metastases, whole lung irradiation may confer a survival advantage [III, B]. The role of surgical resection of residual metastases is less well defined. Patients with bone or bone marrow metastases and patients with recurrent disease still fare poorly, with 5-year survival rates of ∼20%.

The only prognostic factor identified in relapse seems to be time to relapse: patients relapsing later than 2 years from initial diagnosis have a better outcome [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) in combination with topoisomerase inhibitors (etoposide, topotecan) or irinotecan with temozolomide [III, B].

chondrosarcoma

Assessing the grade of chondrosarcoma is difficult and variations in opinion, even among experts, are common. Low-grade cartilage tumours 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 tumour with a covering of normal tissue over it. Higher-grade chondrosarcomas (including clear cell chondrosarcoma) 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. There remains uncertainty about chemotherapy sensitivity of dedifferentiated chondrosarcoma but it is often treated like osteosarcoma, with poorer outcome. 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. Chondrosarcomas in the skull are often not resectable. On these occasions proton beam radiotherapy could be considered following debulking.

spindle cell sarcomas of bone (MFH/FS) treatment

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

treatment of other bone tumours

Chordomas are rare, arising with an incidence of ∼0.5/million population per year. They typically arise in the sacrum or base of the skull recapitulating histologically notochord remnants. Although conventional therapy has in the past been used to complete surgical resection, there are now encouraging results from high-dose radiotherapy using proton beams or carbon ion facilities. Assessment in a specialist centre with expertise in managing these tumours is essential to define the role of surgery and/or radiotherapy. Metastases are rare but local recurrence common. There is evidence of some effectiveness of molecular targeted agents.

Adamantinoma of bone typically arises in the anterior cortex of the diaphysis of the tibia. The osteofibrous dysplasia-like subtype is low grade but will recur if not completely resected. The other subtypes have a propensity to metastasize in a substantial amount of cases, typically becoming clinically evident after a prolonged period of time.

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 tumours should include both a physical examination of the tumour site and assessment of the function and possible complications of any reconstruction. Local imaging and chest X-ray/CT should be the norm. Recommended intervals for follow-up after completion of chemotherapy are every 6 weeks to 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.

In the case of low-grade bone sarcoma the frequency of follow-up visits may be less and may be 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 tumour surveillance.

In Ewing sarcoma, where osseous metastases are likely, isotope bone scanning can be used in addition. More recent 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 leukaemia, particularly acute myeloid leukaemia, may rarely be observed following chemotherapy as early as 2–5 years after treatment [III, B].

notes

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were

considered justified standard clinical practice by the experts and the ESMO faculty.

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Lugano in November 2009. This involved experts from the community of the European sarcoma research groups, sarcoma networks of excellence and ESMO Faculty. The names of the Writing Committee and the Consensus Panel 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 EU-funded network of excellence CONTICANET (CONnective TIssue CAncers NETwork) and EUROBONET (EUROpean BOne NETwork) also supported financially the consensus process.

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