Bone sarcomas: ESMO–ERN PaedCan–EURACAN: Clinical Practice Guidelines for diagnosis, treatment and follow-up†


¹Fondazione IRCCS Istituto Nazionale dei Tumori & University of Milan, Milan, Italy; ²Instituto Portuges de Oncología de Lisboa Francisco Gentil, EPE, Lisbon, Portugal; ³University Hospital Essen, Germany; ⁴Department of Oncological Orthopedics, Musculoskeletal Tissue Bank, IFO, Regina Elena National Cancer Institute, Rome, Italy; ⁵Klinikum Stuttgart-Olgahospital, Stuttgart, Germany; ⁶Institut Curie, Paris, France; ⁷NORDIX, Athens, Greece; ⁸Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; ⁹Royal Manchester Children’s Hospital, Manchester, UK; ¹⁰Vienna General Hospital (AKH), Medizinische Universität Wien, Vienna, Austria; ¹¹Hospital Universitario Virgen del Rocio-CIBERONC, Seville, Spain; ¹²Gustave Roussy Cancer Campus, Villejuif, France; ¹³Centro di Riferimento Oncologico di Aviano, Aviano; ¹⁴Ospedale Regionale di Treviso “S.Maria di Cà Foncello”, Treviso, Italy; ¹⁵Integrated Unit ICO Hospitalet, HUB, Barcelona, Spain; ¹⁶Sarcoma Unit, University College London Hospitals, London, UK; ¹⁷Ghent University Hospital (Pediatric Hematology-Oncology & Stem Cell Transplantation Universitair Ziekenhuis), Ghent, Belgium; ¹⁸Skane University Hospital-Lund, Lund, Sweden; ¹⁹Azienda Ospedaliero, Universitaria Cita della Salute e della Scienza di Torino, Turin,
Italy; 20N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; 21Institute of Scientific Hospital Care (IRCCS), Regina Elena National Cancer Institute, Rome; 22Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; 23Istituto Ortopedico Rizzoli, Bologna; 24Azienda Ospedaliera Universitaria Careggi Firenze, Florence, Italy; 25Department of Medical Oncology, Leiden University Medical Centre, Leiden, The Netherlands; 26Institut Jules Bordet, Brussels, Belgium; 27Candiolo Cancer Institute, FPO IRCCS, Candiolo, Italy; 28Royal Orthopaedic Hospital, Birmingham Children`s Hospital NHS Foundation Trust, Birmingham, UK; 29Turku University Hospital (Turun Yliopistollinen Keskussairaala), Turku, Finland; 30NKI, Amsterdam, the Netherlands; 31Oxford University Hospitals NHS Foundation Trust, Oxford, UK; 32Mannheim University Medical Center, Mannheim, Germany; 33Department of Medicine III, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; 34Helsinki University Central Hospital (HUH), Helsinki, Finland; 35Royal Marsden Hospital, London; 36The Institute of Cancer Research, London, UK; 37University Medical Center Groningen, Groningen; 38Radboud University Medical Center, Nijmegen, The Netherlands; 39University Hospital Motol, Prague; 40Masaryk Memorial Cancer Institute, Brno, Czech Republic; 41St. Anna Children´s Hospital & Children´s Cancer Research Institute, Vienna, Austria; 42Maria Skłodowska Curie Institute, Oncology Centre, Warsaw, Poland; 43Tel Aviv Sourasky Medical Center (Ichilov), Tel Aviv, Israel; 44Medical Oncology, University Hospital of Lausanne, Lausanne, Switzerland; 45Azienda Ospedaliera, Universitaria, Policlinico S Orsola-Malpighi Università di Bologna, Bologna, Italy; 46Fundacio de Gestió Sanitaria de L'hospital de la Santa Creu I Sant Pau, Barcelona, Spain; 47Helios Klinikum Berlin Buch, Berlin, Germany; 48YCRCRC Department of Clinical Oncology, Weston Park Hospital NHS Trust, Sheffield, UK; 49Aarhus University Hospital, Aarhus, Finland; 50Leuven Cancer Institute, Leuven, Belgium; 51Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 52Fondazione Istituto di Ricostruzione e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; 53Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; 54Institute of Oncology of Ljubljana, Ljubljana, Slovenia; 55Netherlands Cancer Institute Antoni van Leeuwenhoek, Amsterdam, The Netherlands; 56University College Hospital, London, UK; 57Gerhard-Domagk-Institut für Pathologie, Universitätsklinikum Münster, Münster, Germany; 58Oslo University Hospital,
Norwegian Radium Hospital, Oslo, Norway; Centre Leon Bernard and UCBL1, Lyon, France.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland;
E-mail: clinicalguidelines@esmo.org
†Approved by the ESMO Guidelines Committee, ERN PaedCan and EURACAN: July 2017.

Incidence and epidemiology

Primary bone tumours are rare, accounting for < 0.2% of malignant neoplasms registered in the EUROCare database [1]. Different bone tumour subtypes have distinct patterns of incidence, and each has no more than 0.3 incident cases per 100 000 per year. Osteosarcoma (OS) and Ewing sarcoma (ES) have a relatively high incidence in the second decade of life, whereas chondrosarcoma is more common in older age.

OS is the first primary cancer of bone (incidence: 0.3 per 100 000 per year). The incidence is higher in adolescents (0.8–1.1 per 100 000 per year at age 15–19), where it accounts for > 10% of all solid cancers. The male: female ratio is 1.4:1. Most osteosarcomas of younger patients arise in an extremity, while the proportion of axial tumour sites increases with age. Risk factors for the occurrence of OS include previous radiotherapy, Paget disease of bone [2] and germ-line genetic abnormalities associated with Li–Fraumeni syndrome, Werner syndrome, Rothmund–Thomson syndrome, Bloom syndrome and hereditary retinoblastoma [3].

Chondrosarcoma (CS) is the most frequent bone sarcoma of adulthood. The incidence is about 0.2 per 100 000 per year, with a median age at diagnosis between 30 and 60 years. No gender predominance has been reported [4].

ES is the third most common primary malignant bone tumour. It occurs most frequently in children and adolescents, but is also seen in adults. Median age at diagnosis is 15 years and there is a male predominance (1.5:1). In white Caucasians > 25 years old,
ES has an incidence of 0.3 per 100 000 per year [5], and it is even rarer in the African and Asian population. The genetic basis for the difference between ethnical groups has been recently linked to a common genomic germline variant, which extends a microsatellite, thereby facilitating the binding of the EWSR1-FLI1 chimeric protein to the \textit{EGR2} gene locus, leading to higher expression of the transcription factor early growth response 2 (EGR2) and increased susceptibility to ES [6]. The most common ES primary sites are the extremity bones (50% of all cases), followed by pelvis, ribs and vertebra. However, any bone can potentially be affected, and a soft-tissue origin is also possible, especially in adults (30% of cases).

Chordomas are even rarer compared to other subtypes, with an incidence of \(\sim 0.5\) per million per year [7].

High-grade spindle/pleomorphic sarcomas of bone: spindle cell sarcomas of bone are a heterogeneous group of primary malignant bone tumours that do not fulfil the histological criteria for a diagnosis of osteosarcoma, chondrosarcoma or Ewing’s sarcoma [8].

Giant cell tumour of bone is a benign intramedullary bone tumour composed of mononuclear cells and osteoclast-like multinucleated giant cells, with a variable and unpredictable potential for aggressive growth. It represents approximately 5% of primary bone tumours and about 15%-20% of benign bone tumours [9].

\textbf{Diagnosis and pathology / molecular biology}

The medical history should focus on characteristic symptoms such as duration, intensity and timing of pain. The presence of persistent non-mechanical bone pain, predominantly at night, should prompt a radiological assessment. Swelling and functional impairment can be present if the tumour has progressed through the cortex and distended the periosteum, but they are often later signs. The differential diagnosis of a bone sarcoma includes osteomyelitis, benign tumours and bone metastases, all of which outnumber primary bone sarcomas [10-13]. The diagnosis can be strongly oriented by patient age. For patients < 5 years old, a destructive bone lesion could be
interpreted predominantly as either metastatic neuroblastoma or Langerhans cell histiocytosis (LCH). For patients aged ≥ 5 years old, the likelihood of a primary bone sarcoma is higher. In adult patients, after 40 years of age, bone metastases and myeloma will be the most common diagnoses [13].

Conventional radiograph in two planes is the first radiological investigation. When the diagnosis of malignancy cannot be excluded with certainty on radiographs, the next step should be magnetic resonance imaging (MRI) of the whole compartment with adjacent joints, which is regarded today as the best modality for local staging of extremity and pelvic tumours [14]. Computed tomography (CT) may provide additional information by allowing a better visualisation of calcifications, periosteal bone formation and cortical destruction. It is generally the imaging modality of choice of other primary sites.

All patients with a bone lesion which is likely to be a primary malignant bone tumour on a radiological basis should be referred to a bone sarcoma centre or to an institution belonging to a specialised sarcoma network [14-16]. Children and adolescents should be referred to centres which in addition provide age-specific expertise. The biopsy and the pathological diagnosis require expertise in the field and should be discussed in a multidisciplinary setting.

The biopsy of a suspected primary malignant bone tumour should be carried out at the reference centre by either the surgical team who will carry out the definitive tumour resection or by a dedicated interventional radiologist [15-18]. In most patients, a core-needle biopsy, taken under imaging control, can be an appropriate alternative to open biopsy. Contamination of surrounding tissue should be minimised, and adequate multiple sampling of representative areas must always be provided. To ensure that the tissue is representative of the tumour, X-rays of the biopsy location are recommended, and, in some circumstances, a frozen section may be required for diagnosis in some cases and recommended for research purposes. If osteomyelitis is a differential diagnosis, samples should be sent for microbiological culture. If required, an open biopsy should be carried out using a longitudinal incision. In aggressive and malignant tumours of bone, the biopsy tract and the channels through which drains have been placed must be considered to be potentially contaminated and must later be removed,
together with the resection specimen, in an effort to minimise the risk of a local recurrence. Therefore, biopsy tracts should be clearly marked by means of a small incision or an ink tattoo to ensure that the location is recognised at the time of the definitive procedure. In case of spinal column involvement, laminectomy or decompression should be avoided unless necessary to relieve spinal cord compression, and tissue sampling must be carried out whenever a bone sarcoma is suspected.

Samples must be interpreted by an experienced bone sarcoma pathologist, in collaboration with the radiologist, and discussed in a multidisciplinary team. The request form should be completed with all details that might be relevant for diagnosis, including patient’s age, the site of the tumour, radiological findings, if there are multiple lesions, family history and, for surgical specimens, preoperative treatments.

With the increasing capability for accurate molecular diagnosis and next-generation sequencing (NGS) technologies, samples should be quickly submitted for pathological assessment. The collection of fresh frozen tissue is strongly encouraged, to enable molecular diagnostics. As an alternative, decalcification in ethylenediaminetetraacetic acid (EDTA) instead of formic acid can be considered. Tumour imprints (touch preps) are used by some, but not all expert institutions: they might be useful for tumour-specific translocation by fluorescent in situ hybridisation (FISH) in some institutions. Informed consent for tumour banking should be routinely sought as for all rare malignancies, enabling later analyses for research, depending on local regulations. Similarly, a further option is to establish primary cell cultures for cytogenetics and other studies, such as patient-derived xenografts within research protocols with informed consent.

The nature of the bone specimen received for pathology reporting should be recorded, i.e. needle biopsy, curettage or excision (e.g. segmental resection, limb salvage amputation, or another complex resection, such as a hemipelvectomy). It is usually necessary to decalcify the bone tumour biopsy using specific standard operating procedures. The histological features of the tumour should be described and the tumour type (and subtype) specified according to the most recent version of the World Health Organization (WHO) Classification [19]. The results of relevant ancillary
investigations (e.g. immunohistochemistry or molecular assessments) should be accurately recorded [16]. Molecular diagnostic techniques currently available include FISH, RT-PCR and NGS technologies. Examples include translocation detection in ES and mesenchymal CS, isocitrate dehydrogenase (IDH1 and IDH2) mutations in conventional chondrosarcoma and MDM2 amplification in parosteal and intramedullary low-grade osteosarcoma [4].

NGS technologies carried out on tumour tissue have revealed diagnostic information for ES and other round cell sarcomas (translocations), mesenchymal chondrosarcoma {{(Hes-related family basic helix-loop-helix (bHLH) transcription factor with YRPW motif 1 - nuclear receptor coactivator 2 (HEY1-NCOA2), and conventional chondrosarcoma (IDH) and giant cell tumour of bone [H3 histone family member 3A (H3F3A)]).}}

At the time of the resection of the primary tumour, for surgical specimens, the size (measured in three dimensions in mm) of the tumour in the resected bone should be recorded. The pathology report should also describe the extent of local tumour spread, including involvement of specific anatomical soft tissue and bone compartments. It should be recorded whether the resection margins are either clear or infiltrated and the distance (in mm) of tumour from the nearest resection margin measured. Photographs should be taken of the intact specimen and of the tumour slabs after sawing. A complete, representative slab of the tumour, usually in the longitudinal axis as guided by the radiological images, should be embedded for microscopy in a grid manner. This is especially relevant after neoadjuvant chemotherapy to assess response. The tumour should be coded using Systematic Nomenclature of Medicine (SNOMED) or International Classification of Diseases for Oncology (ICD-O) codes.

**Staging and risk assessment**

All cases of suspected bone tumours should be formally discussed in a multidisciplinary team in a reference centre with the radiologist who has interpreted the imaging, the pathologist who has reviewed the biopsy material, the surgeon, the radiation and the medical and/or paediatric oncologist. The output of the multidisciplinary discussion must be recorded, in order to minimise the risk of errors in diagnosis, staging, risk assessment and treatment.
Several staging systems for bone tumours are in use [20-23]. However, none of them is perfect or generally accepted. Generally, tumour burden (volume) and the presence of detectable metastases are the two main factors that 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 [24]. Whole-body MRI and positron emission tomography (PET)-CT or PET-MRI are increasingly utilised for staging (including skip bone lesions) [25]. 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.

No specific laboratory tests for the diagnosis of bone sarcoma are routinely available. Baseline serum analysis in ES and OS should include alkaline phosphatase (AP) and lactate dehydrogenase (LDH) given their proven prognostic value [26-28]. Prognostic features also include clinical presentation: a pathological fracture may lead to the dissemination of tumour cells into surrounding tissues and increase the risk of local recurrence. In cases of fracture, internal fixation is contraindicated as it disseminates the tumour further into both bone and soft tissues and increases the risk of local recurrence. External splintage is recommended.

Chemotherapy can result in renal, cardiac and auditory dysfunction. Before starting the treatment, baseline renal function testing, assessment of cardiac function [left ventricular ejection fraction (LVEF)] and audiogram (in the case of platinum derivatives) should be carried out. Sperm storage is recommended for male patients of reproductive age. For female patients, a fertility physician is routinely consulted about potential ovarian sampling and cryopreservation in some countries, but not in all, reflecting a limited scientific knowledge on gonadotoxic effects of the different chemotherapy used and a variability of healthcare policies across nations [29].

**Treatment (locoregional and advanced disease)**

Given the rarity of the disease and the complexity of management, the accepted standard for bone sarcomas is treatment at reference centres and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise
In these centres/networks, therapy is usually given within either the framework of prospective, often collaborative, clinical studies or established treatment protocols. In the case of high-grade osteosarcoma, ES or pleomorphic sarcoma, following biopsy proven-diagnosis, primary chemotherapy is indicated.

**Osteosarcoma**

Osteosarcoma usually arises in the metaphysis of a long bone, most commonly around the knee in children and adolescents. Involvement of the axial skeleton and craniofacial bones is primarily observed in older patients. High-grade osteosarcoma frequently metastasises, the lung being the most frequent metastatic site by far, followed by distant bones.

Conventional osteosarcoma is always high-grade. Central and parosteal osteosarcoma are low-grade malignancies, although they may increase in size and invade the medulla of bone, and transform to high-grade sarcoma, whereas periosteal osteosarcoma is an intermediate-grade chondroblastic osteosarcoma, sometimes difficult to distinguish from high-grade surface osteosarcoma. Adverse prognostic or predictive factors for conventional osteosarcoma include detectable primary metastases, axial or proximal extremity tumour site, large tumour size, elevated serum AP or LDH and older age [III, B] [26]. As mentioned above, staging should include local imaging studies, specifically plain radiographs and MRI of the whole affected extremity [III, A].

Curative treatment of high-grade osteosarcoma consists of chemotherapy and surgery [II, A]. Compared with surgery alone, multimodal chemotherapy treatment of high-grade localised osteosarcoma increases disease-free survival probability from 10%–20% to > 60%. In general, chemotherapy is administered before and after surgery, although a formal proof that giving chemotherapy preoperatively improves survival is lacking. The extent of histological response to preoperative chemotherapy predicts survival [26-28, 30].

Low-grade central and parosteal osteosarcoma are malignancies with a lower metastatic potential, which are treated by surgery alone [IV, B]. Although chemotherapy has been used for periosteal osteosarcomas, no benefit for
Chemotherapy was shown in two retrospective analyses [31, 32], and its use is not routinely recommended in this setting [IV, D].

Surgery should be carried out by a surgical team familiar with the wide range of surgical reconstructive options. Paediatric and adolescent patients need to be treated by surgeons with great experience in the field of paediatric bone tumours, including age-specific reconstruction challenges, such as the reconstruction of growing bones. The goal of surgery is to safely remove the tumour and yet preserve as much function as possible, striving to obtain microscopically clear surgical margins [30]. Most patients should be considered candidates for limb salvage. Either intra-lesional or marginal margins increase the local relapse rate, which is associated with reduced overall survival. Thus, clear margins are the first goal of surgery [III, B]. Areas where there is suspicion of close margins should be marked on the surgical specimen sent to pathology.

Pathological fracture does not necessarily necessitate an amputation. In chemosensitive tumours, primary neoadjuvant chemotherapy can be used with the expectation that it will allow the fracture haematoma to contract and allow subsequent resection of the tumour and the involved soft tissues [33].

Doxorubicin, cisplatin, high-dose methotrexate (HD-MTX) and ifosfamide have antitumour activity in osteosarcoma [I, A] [34-37]. Doxorubicin, cisplatin and HD-MTX (MAP) are most frequently used as the basis of treatment in children and young adult patients [31]; however, HD-MTX can be difficult to manage in adults > 25 years old. In older patients, regimens combining doxorubicin, cisplatin and ifosfamide without HD-MTX can also be used in these patients [III, B]. These drugs should be administered with adequate supportive care by experienced paediatric oncologists or medical oncologists at reference institutions with appropriate infrastructure and a multidisciplinary treatment approach [35]. Most current protocols include a period of preoperative chemotherapy, to facilitate local surgical treatment and to allow the assessment of tumour response [38, 39]. The EURAMOS 1 prospective trial aimed to establish whether pegylated interferon alpha-2b (IFNα–2b), in addition to standard MAP chemotherapy given postoperatively, could improve outcome in patients with
good histological response to preoperative MAP. The results showed that many patients failed to start and complete interferon treatment, and there was no significant overall survival advantage [I, C] [40, 41]. Also, the study evaluated if altering postoperative chemotherapy in poor responders to preoperative systemic therapy might have any impact on outcome, and, again, no survival benefit was proven. In case of poor pathological response to the preoperative MAP regimen, the postoperative addition of ifosfamide and etoposide to MAP failed to improve the survival and increased the risk of secondary malignancy compared to those patients treated with the MAP regimen only [I, C] [34]. Whenever possible, patients with osteosarcoma should receive chemotherapy in the context of prospective studies.

Innate immune-modulation has been attempted in OS with some agents, e.g. interferon [35] and muramyl tripeptide. As described above, the use of interferon failed to show a survival advantage in patients with a good histological response to a MAP-preoperative regimen. Muramyl tripeptide added to postoperative chemotherapy was associated with a significant advantage in overall survival and a non-significant trend in event-free survival in one large randomised trial [II, C] [42, 43]. Muramyl tripeptide has been approved in Europe for patients < 30 years of age with completely resected localised osteosarcoma, but it is not reimbursed in all European countries. There is no consensus in the sarcoma community on the use of this drug, due to weaknesses in the data from the only trial currently available [42]. Further studies are needed to identify any subgroup of patients who could benefit from immune modifying agents.

Dynamic MRI is reliable to evaluate changes in tumour vascularity and to give additional information on tumour response to primary chemotherapy [44, 45]. Similarly, the value of diffusion MRI is currently under evaluation [45].

In general, there is no indication for radiotherapy, but there are anatomical locations in which the possibility of complete surgical resection is limited. In these cases, after a multidisciplinary discussion, radiotherapy may be an option to try to extend the progression-free interval. This must be discussed in a multidisciplinary team beforehand and with the patient, and it should be made clear at the time of surgery that the goal is not an R0 resection [V, C]. New radiotherapy techniques (e.g. proton
beam and carbon ion therapy) should be considered, particularly for unresectable primary tumours.

The multimodal treatment principles detailed above were generated in children, adolescents and young adults with high-grade central osteosarcoma, but also relate to adults [III, B] [46]. Adult patients may require tailored regimens, especially as far as HD-MTX is concerned, in particular for those aged > 40. Some studies have put a threshold of 25 to remove HD-MTX from the induction regimen [47], while others included HD-MTX for older patients [48]. Doxorubicin plus cisplatin and/or ifosfamide are commonly used with age-adapted doses. Recently, the addition of zoledronic acid was tested in a randomised setting and failed to demonstrate an improvement in relapse-free or overall survival or histological response. Its use is, therefore, not recommended outside clinical trials [I, D].

Primary metastatic osteosarcoma patients are treated with a curative intent following the same principles of non-metastatic osteosarcomas [49]. In fact, there are subsets of patients who can have a very similar prognosis to that of localised disease, provided surgical removal of all known metastatic deposits is achievable [III, B] [50]. Approximately 25% of all patients with primary metastatic osteosarcoma and > 40% of those who achieve a complete surgical remission may become long-term survivors.

High-grade craniofacial osteosarcoma should be treated the same way as high-grade osteosarcoma of other locations, although prospective evidence is lacking due to the absence of selective clinical studies in this patient population [IV, B]. The use of PET monitoring is under investigation [51]. Radiotherapy, preferably within clinical studies, can be proposed when complete surgery is not feasible [IV, B]. The value of proton beam/carbon ion radiotherapy in this setting is currently under study. Adjuvant RT follows the same recommendations that for other sites (see above).

The management of recurrent osteosarcoma needs to take into account the timing of recurrences/metastases, the number of metastases and the metastatic sites. CT scan can over- and under-estimate the number of pulmonary metastases, but the recent results have improved with spiral CT. The 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 complete second surgical remission survive for > 5 years [52]. Even patients with subsequent recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted [52]. For lung metastases, stereotactic radiotherapy, radiofrequency ablation or cryotherapy might be used as alternative options in patients unfit for surgery [IV, B]. Some groups also consider radiofrequency ablation [53, 54] and stereotactic radiotherapy [55] to be potential alternative local treatment options for small lung or bone metastases [53-55].

The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined. Treatment choice may take into account the prior disease-free interval, and often includes ifosfamide or cyclophosphamide, possibly in association with etoposide and/or carboplatin [III, B], and other active drugs including gemcitabine and docetaxel [IV, C], sorafenib [III, B] or regorafenib [II, B], as well as 153Sm [56-60]. 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 [50, 51]. However radiological responses and clinical benefit are commonly witnessed so that its use should be considered [IV, B].

Radiotherapy may have a role in palliation [61]. In general, despite second-line treatment, the prognosis of recurrent disease has remained poor, with a long-term post-relapse survival of < 20%.

**Ewing sarcoma**

ES is a small, blue, round cell tumour, periodic acid-Schiff positive and CD99 (MIC2)-positive. All ES are high-grade tumours. They can arise both from bone, soft tissues or visceral sites, displaying the same behaviour in principle.

The definitive diagnosis is made by biopsy, providing sufficient material for conventional histology, immunohistochemistry, molecular pathology and biobanking. Molecular biology studies have shown that almost all of these tumours share a common TET-ETS gene rearrangement involving the EWSR1 gene on chromosome
In most cases, this involves a reciprocal translocation \(t(11;22)(q24;q12)\) [48], but \(t(21;22)(q22;q12)\) [49, 50], and others may also occur \([t(7;22), t(17;22)\) and \(t(2;22)]\) [62-65]. In recent years, new small round cell sarcoma entities have been recognised, with novel translocations, among which BCOR-rearranged sarcoma preferentially affects the bone EWS RNA binding protein 1 - nuclear factor of activated T cells 2 (EWSR1-NFATc2), FUS RNA binding protein - nuclear factor of activated T cells 2 (FUS-NFATc2), capicua transcriptional repressor – forkhead box O4 (CIC-FOXO4) or capicua transcriptional repressor – double homeobox 4 (CIC-DUX4) translocations are other examples of recurrent molecular alterations found in these malignancies [66, 67] (see Table 1).

Current investigations have shown that tumour biology and prognosis of these tumours, which are probably different nosological entities rather than molecular variants actually differs from that of classical ES, making the diagnosis and identification of these cases mandatory. Since not all are recognised in routine, the patients presenting with these tumours are still treated within Ewing-like regimens. However, given the low incidence of these rare tumours, currently there is little evidence to support different approaches to their management. Inclusion in prospective registries is worthwhile (a EURACAN Domain 1 sarcoma project is underway for this purpose).

Although most ES tumours can be recognised with classical haematoxylin and eosin (H&E) stain and immunohistochemistry molecular confirmation is mandatory for the identification of the classical and distinct molecular subtypes as described above [III, A] [63-68]. The laboratory should be enrolled in an external quality assurance programme. When frozen tissue is available, techniques that identify both fusion partners [i.e. reverse transcription polymerase chain reaction (RT-PCR) or anchored, multiplex PCR-based, targeted NGS] are the techniques of choice. The latter can also be applied to non-decalcified or EDTA-decalcified, formalin-fixed paraffin-embedded (FFPE). FISH is a good choice when only FFPE tissue [or touch preps (imprints)] are available. There are several commercial sources for EWSR1 break-apart probes. Assays using EWSR1 break-apart probes do not detect EWS–FLI1 fusions, but only EWSR1 rearrangements, which should not be a problem when interpreted in the
appropriate clinical and pathological context. NGS should be considered when no typical translocation has been detected by conventional methods.

Bone marrow biopsies and aspirates (from sites distant to the primary or known metastatic lesions) may be considered in the staging, but several experts underline that there is a very low incidence of bone marrow metastases in localised disease if the PET scan is negative. 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) [69, 70]. Staging must be oriented to detect lung, bone and bone marrow metastases and should include biopsy in case of doubtful lesions. Multiple bone metastases confer a poorer outcome than lung/pleural metastases (< 20% compared with 20%–40% 5-year survival). Other known prognostic factors are tumour size or volume, serum LDH levels, axial localisation and older age (> 15 years). A poor histological response to preoperative chemotherapy and incomplete or no surgery for local therapy are further adverse prognostic factors [27, 71-75]. Molecular structure of the EWSR1 fusion transcripts has not been shown to be of prognostic value with current treatment protocols. Genomic analysis with the assessment of copy number variation has been shown to be of prognostic value [77, 78]. In addition, Stag2, TP53 and CDKN2A mutations confer poorer outcomes. With surgery or radiotherapy alone, i.e. without systemic treatments, 5-year survival was < 10%. With the currently recommended multimodal approaches including chemotherapy, 5-year survival is ~60%–75% in localised and ~20%–40% in metastatic disease, respectively, depending on metastatic sites and burden.

Current trials employ 3–6 cycles of initial combination chemotherapy after biopsy, followed by local therapy, and another 6–10 cycles of chemotherapy, usually applied at 2- to 3-week intervals. Treatment duration is thus 10–12 months. Agents considered to be most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide [79-83]. Almost all active protocols are based on five- to six-drug combinations of these substances [I, A]. Chemotherapy intensity (interval
compression) was positively associated with outcome in paediatric and adolescent (<18 years) patients in a prospective North American study [II, A] [84].

The use of high-dose chemotherapy with escalated alkylating agent dose and blood stem cell rescue has attracted much attention in ES since the 1970s. Only recently have the results of randomised studies with busulfan and melphalan (BuMel) indicated that this approach results in a survival advantage for tightly defined and highly selected patients with poor response to induction chemotherapy and/or tumour volume > 200mL [II, A] [85, 86]. No such advantage was evident for patients presenting with pulmonary metastases [II, D].

ES is a radiosensitive tumour at lower doses than OS. The goal of local therapy for the primary tumour is to ensure that the entire volume of tissue involved at diagnosis is treated. 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 of the primary tumour. Surgery must involve excision of all tissues originally involved with tumour (not just the tissue that is left after chemotherapy shrinkage) or be supplemented by radiotherapy. 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 tumour cells) [IV, B] [73]. The dose of postoperative radiotherapy is also 45–60 Gy, depending on margins, response and location. Intrallesional surgery must be avoided, as there is no benefit when compared with radiotherapy alone [73]. Change in the size of the soft tissue mass is easily evaluated on MRI and is a good predictor of tumour response [44, 45]. Dynamic MRI is not as reliable as in osteosarcoma [45], as remaining small tumour foci may not be detected. Sequential FDG-PET evaluation might be of additional value [87].

The 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 extraskeletal ES follows the same principles as for bone ES, thus incorporating chemotherapy in all cases as well as
postoperative radiotherapy in most cases, with the possible exception of superficial lesions. For extraskeletal ES, postoperative radiotherapy is generally used, with the possible exception of good prognosis, superficial ES.

Patients with metastases at diagnosis are treated with the same treatment approach as patients with localised disease but have a worse prognosis. In patients with lung metastases, whole-lung irradiation may confer a survival advantage [II, C] [74, 75]. The role of surgical resection of residual metastases is less well defined.

For patients presenting with extra-pulmonary metastases, survival is even worse (less than 20%) [88]. Chemotherapy is similar to that for localised disease but responses are less durable. Treatment of the primary tumour is often appropriate, especially in the presence of responding metastatic disease. There is no formal evidence either for or against high-dose chemotherapy in this situation, so that its uptake differs between centres. No randomised studies have been reported for this approach.

Recurrent ES, whether local or with distant metastases, is almost always fatal, even though further responses to chemotherapy are frequent and valuable. 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 [89]. Doxorubicin therapy is usually no longer feasible due to previously achieved cumulative doses. Chemotherapy regimens in relapse situations are not standardised and includes alkylating agents (cyclophosphamide and high-dose ifosfamide) in combination with topoisomerase inhibitors (etoposide and topotecan), irinotecan with temozolomide [III, B] or gemcitabine and docetaxel, or high-dose ifosfamide or carboplatin with etoposide [90, 91]. The relative advantages of these different regimens are currently being tested in an international randomised study (EORTC trial 1403 EudraCT 2014-000259-99 / ISRCTN36453794). Observational studies of high dose chemotherapy indicate that for selected patients (those with a disease-free interval above 18 months, with no extra-pulmonary disease and a complete remission before high-dose chemotherapy), use of high-dose chemotherapy is debated among experts.

**High-grade spindle/pleomorphic sarcomas of bone**
Pleomorphic sarcomas of bone comprise a diagnostically heterogeneous group of malignant tumours including undifferentiated pleomorphic sarcoma [8, 21]. 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 fractures at presentation. They represent between 2% and 5% of primary bone malignancies. 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. Therefore, the diagnosis should be established in a multidisciplinary setting and IDH mutation analysis should be considered when the radiological images suggest a chondrosarcoma.

Pleomorphic sarcomas typically present in older patients with a lytic lesion in bone. In many, the differential diagnosis will be against metastases. Full staging and biopsy are required to reach a diagnosis. Pathological fractures are common and, as mentioned in the introduction, should not undergo internal fixation. Treatment strategies mimic those of osteosarcoma, with chemotherapy and complete en bloc resection including any soft tissue component. Their sensitivity to chemotherapy is poorly known, and studies on specific histologies as currently defined [especially after reappraisal of histologies previously known as malignant fibrous histiocytoma (MFH)], are highly required. Radiotherapy may be considered in inoperable lesions. A global effort to collect these cases would be helpful to establish diagnostic and prognostic criteria as well as recommended treatments, for the whole group as well as for the different histologies.

**Chondrosarcoma**

Most chondrosarcomas arise as primary malignant tumours. The majority are low-grade, locally aggressive, non-metastasising tumours (atypical cartilaginous tumour / chondrosarcoma grade I), rather than high grade (grades II–III) [17, 92]. Grade I chondrosarcomas can be labelled atypical cartilaginous tumour, as it is currently defined by the WHO 2013, since they usually do not metastasise [2]. Grade I chondrosarcomas may be treated with radiotherapy when located at critical sites such as the skull base. 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 central chondrosarcoma and secondary peripheral chondrosarcomas, respectively. The majority of chondrosarcomas are of the conventional subtype, but rarer subtypes include mesenchymal and clear cell chondrosarcoma [93, 94]. In rare circumstances, conventional chondrosarcomas can ‘dedifferentiate’ into a very high-grade tumour with a dismal prognosis: the so-called dedifferentiated chondrosarcoma [93, 94]. Most chondrosarcomas are solitary, but they can occur as multiple lesions in syndromic patients with multiple osteochondromas and enchondromatosis.

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 [95]. For large axial and pelvic chondrosarcoma, heterogeneity is common, and most lesions contain high-grade elements. The differentiation between benign enchondroma or osteochondroma and atypical cartilaginous tumour / chondrosarcoma grade I can be difficult, but can be aided by the use of dynamic contrast-enhanced MRI [96]. In the phalanges of the hands and feet, malignancy is extremely rare, but in the other long bones central cartilaginous lesions should be considered atypical cartilaginous tumour unless proven otherwise [93].

Inoperable, locally advanced and metastatic high-grade chondrosarcomas have a poor prognosis [76, 77]. 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 and heterogeneity of grade elements within tumours [75]. Also, grade I tumours (atypical cartilaginous tumours) are not necessarily curable in all cases, mainly due to problematic local recurrence or progression to high grade. In particular, dedifferentiated chondrosarcomas are aggressive and frequently metastasise [76].

Assessing the grade of chondrosarcomas is difficult and discrepant diagnoses are common even among experts [92]. Atypical cartilaginous tumours are unlikely to
metastasise, but may recur locally. Atypical cartilaginous tumours in the long bones of the limbs can be managed by curettage with or without local adjuvant (e.g. phenol, cement and 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 (grade II and III) and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins [IV, B].

Evidence suggests that mesenchymal chondrosarcoma is more sensitive to chemotherapy and therefore usually considered for adjuvant or neoadjuvant therapy [IV, C] [97, 98]. Most authors suggest a Ewing-type chemotherapy regimen.

Dedifferentiated chondrosarcoma is often treated as a high-grade bone sarcoma, with systemic and local therapies that need to be adapted to patient’s age [V, C] [99, 100]. 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, 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 high-dose radiotherapy, including proton beam or carbon ion radiotherapy, achieving 80%–90% local control rates [101].

With regard to chemotherapy, drugs active in sarcomas such as doxorubicin and ifosfamide may prove active in chondrosarcoma, especially in high-grade lesions [99, 102]. The activity of gemcitabine in combination with docetaxel has been reported [103], and a potential role for mammalian target of rapamycin (mTOR) inhibitors in combination with cyclophosphamide has been suggested [IV, C].

**Giant cell tumour of bone**

Giant cell tumour (GCT) of bone is a rare [104], locally aggressive tumour of the skeleton. GCT is classified in the intermediate category, as GCT can be aggressive and recurs locally in up to 50% of cases [9]. Soft tissue extension is significantly
associated with the risk of local recurrence. Up to 5% of GCTs metastasise to the lungs, and transformation to a high-grade malignancy though debated, may occur in 1%–3% of patients. Giant cell tumours of bone contain mutations in the H3F3A gene (predominantly at the G34 position) which can be detected using mutation analysis or immunohistochemistry using mutation specific antibodies [104, 105].

Treatment options include intralesional curettage with or without adjuvant or en bloc excision [IV, A]. These have been assessed in a few prospective studies [106-109]. Denosumab, a human monoclonal antibody to receptor activator of nuclear factor kappa B ligand (RANKL), known to be overexpressed in GCT, is standard treatment in unresectable or metastatic GCT [III, A] [110]. Its use in the neoadjuvant setting is debated and should be carried out exclusively in expert centres, and ideally within a clinical trial. There is increasing evidence that, if being used preoperatively and prior to curettage, surgery is best carried out after a few months of treatment, as otherwise extensive ossification may take place, making it difficult to define the extent of the lesion [V, C]. It can also be used in unresectable disease and rare metastatic disease. In this setting, treatment interruption is usually followed by progression, so that treatment needs to be maintained [110]. Potential maxillar and skeletal side effects need to be monitored (osteonecrosis of the jaw, atypical fractures). The optimal schedule and duration of treatment with denosumab in surgically unsalvageable GCTs is still to be settled, and the possible long-term side effects are still largely unknown.

Radiotherapy can provide a satisfactory local control in GCT (5-year control rate of 80%) [109]. However, the use of radiotherapy can be associated with a risk of GCT transformation into a high-grade sarcoma and can make surgical resection challenging if required. Therefore, the use of radiotherapy in GCTs should always be discussed in a multidisciplinary setting and be limited to cases in which surgery leads to unacceptable morbidity and denosumab is ineffective or contraindicated [IV, D].

Chordoma
Chordomas are very rare tumours, arising from the remnants of the notochord into the sacrum (50%), skull base (30%) and mobile spine (20%). Extraskeletal cases have also been reported but are extremely rare.
Median age is 60 years, but skull base presentations can also affect a younger population, including children and adolescents. Chordoma is a low-grade but locally-invasive malignancy. Dedifferentiated cases are observed in 5% of patients. The metastatic potential of chordoma is ~30%. Metastases usually appear late in the natural history of the disease, mostly after local recurrence.

Chordoma prognosis is related more to local aggressiveness than to metastases. Chordoma is a tumour showing notochordal differentiation. Brachyury is a transcription factor involved in notochord differentiation and its expression is the diagnostic hallmark for conventional chordoma [111]. Immunohistochemistry positivity for brachyury is strongly recommended to confirm diagnosis. Dedifferentiated chordomas may lose brachyury expression. Genomic alterations of brachyury genes (duplications) are also frequent in familial and sporadic forms along with activating mutations of the \textit{PI3K} gene-activated mutations [112].

Due to the rarity and long natural history of the disease, the level of evidence available for more common tumour types is currently beyond reach for chordoma. In fact, only a few phase II trials are available and most published data are from case series and/or retrospective. Chordoma management needs to be carried out at referral centres and/or referral networks, with a multidisciplinary team including expert pathologists and radiologists, surgeons familiar with musculoskeletal tumours and site of surgery, expert radiation oncologists with access to hadron facilities, dedicated medical oncologists and a palliative care team. All diagnostic and therapeutic procedures should be discussed in a multidisciplinary expert team.

MRI is the best modality for local staging. CT scan should be used in the case of diagnostic doubt. Chordoma should be differentiated from benign notochordal lesions and, if radiological appearance is typical for these, biopsy is not recommended unless the lesion changes over time [113]. Preoperative core-needle biopsy is recommended as for sarcoma of the bones. The biopsy track needs to be included in the surgical resection. In the case of skull base chordoma, preoperative biopsy can be avoided in selected cases.
Tumour location is the most relevant variable to define the primary tumour treatment. The quality of surgical margins is the most important prognostic factor. *En bloc* R0 resection is standard treatment [IV, B], when it is feasible and sequelae are acceptable/accepted by the patient, with an expected 5-year recurrence-free survival of 50%. For sacral chordoma, surgery should definitely be offered as the first choice if the chordoma arises from S4 and below. Surgery should always be discussed in the context of other alternatives for tumours originating above S3, since surgery is always followed by important neurological sequelae. Surgery is the primary standard choice for tumours originating from S3, especially if the preservation of S2 roots is possible, as it may result in some neurological recovery (40% of cases) [115-117].

If *en bloc* R0 resection is not feasible, definitive radiotherapy alone should always be considered as a valid alternative [III, B] [118-121]. Local relapse has extremely poor survival rates and local control is rarely achievable. Supportive care should be incorporated into the treatment from the beginning.

For skull base and upper cervical tract chordoma, R1–R2 surgery plus high-dose radiotherapy is the treatment of choice [114, 118, 119].

Hadrons, i.e. high-dose protons or carbon ions, are superior to photons physically and in terms of sparing irradiation of non-target lesions, although no randomised trial is available at present to assess the benefit of hadrons compared with photons in chordoma. Since hadrons allow lower doses to be given to normal tissues, they should be considered the treatment of choice. Advanced technology photons could be used in the case of unavailability or non-accessibility of protons and ions, and every time they show similar dose distribution to the target and critical structures. Due to the relative radiation resistance of chordomas, a high-dose up to at least 74 GyE in conventional fractionation (1.8–2 GyE) for photon and proton therapy is required [101, 120, 121].

Indications for definitive radiotherapy include unresectable disease, inoperable patients and neurological impairment not accepted by the patient. Radiotherapy should be considered in the case of R2 or R1 resections. A randomised study comparing proton beam therapy and surgery is ongoing (NCT02986516). The use of
adjuvant/neoadjuvant radiotherapy needs to be discussed with the single patient and prospective studies encouraged.

In the case of local relapse, the choice of treatment can include surgery and/or radiotherapy and/or systemic treatment, balancing morbidity and quality of life.

For oligometastatic disease, surgery/radiofrequency ablations/stereotactic radiation of metastases can be considered in selected cases. Chemotherapy is inactive. An exception can be high-grade dedifferentiated chordoma, for which anecdotal responses to chemotherapy have been reported [V, C]. There is phase II evidence that imatinib or sorafenib can be beneficial in advanced chordoma in terms of progression-free survival and mainly non-dimensional tumour responses [122], and a randomised phase II study with regorafenib is ongoing (NCT02389244); its role within the treatment strategy deserves further evaluation. However, when other treatments are no longer possible, it could certainly be considered if available. Prospective studies are ongoing.

**Follow-up, long-term implications and survivorship**

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 could be a proposed strategy. Strict rules cannot be provided in the absence of any formal prospective studies, and in the context of differing opinions in this panel of experts. A recommended follow-up policy may foresee intervals between checks after the completion of chemotherapy, approximately every 3 months for the first 2 years; every 6 months for years 3–5; every 6-12 months for years 5–10, and thereafter every 0.5-1-2 years according to local practice and other factors. Chest CT, if used instead of chest X-rays, should be carried out with low-dose, radiation-sparing techniques, particularly in younger patients who will have a higher lifetime risk to experience second, radiation induced malignancies.
In the 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 tumour surveillance.

In ES, where osseous metastases are likely, isotope bone scanning can be used but should be weighed against the additional radiation exposure, particularly in younger patients. More modern techniques (e.g. PET or whole-body MRI) are increasingly being adopted into routine practice, but require further evaluation in clinical trials. This is a general priority for all cancers.

Importantly, there is lack of consensus on this chapter within this panel, taking into consideration the specific risk and performance of systematic imaging follow-up regarding the median and long-term risk of second cancers. Some panellists propose 6 monthly follow-up. Some propose interruption of systematic follow up at 5 years, while others maintain it beyond 10 years. National guidelines may also be different across countries [123]. The lack of consensus and the very limited number of prospective trials point to the need to generate prospective clinical trials on this topic in the future.

It is important to evaluate the long-term toxic effects of chemotherapy, surgery and radiotherapy for cured patients given the incidence of late complications. Monitoring for late effects should be continued for > 10 years after treatment, depending on the chemotherapy protocol and radiation used and in conjunction with late effects services when available. Long-term cardiac evaluation is of major importance since it has been shown that deterioration of cardiac function can still occur decades after anthracycline treatment [123, 124].

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. Developments in genetic understanding of bone sarcoma point to the importance of obtaining a detailed family history and of genetic evaluation in high-risk
families. Patients with cancer predisposition syndromes (e.g., Li-Fraumeni or Rothmund-Thomson syndromes) require special care and follow-up.

**Methodology**

These Clinical Practice Guidelines have been produced by ESMO in partnership with EURACAN, the European Reference Network for rare adult solid cancers. These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). They are conceived to provide the standard approach to diagnosis, treatment and survivorship on sarcomas, GISTs and bone sarcomas. Recommended interventions are intended to correspond to the ‘standard’ approaches, according to current consensus among the European multidisciplinary sarcoma community of experts. These are represented by the members of the ESMO Sarcoma Faculty and experts appointed by ERN PaedCan and all institutions belonging to the Sarcoma domain of EURACAN.

Experimental interventions considered to be beneficial are labelled as ‘investigational’. Other non-standard approaches may be proposed to the single patient as ‘options’ for a shared patient physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompany the text, covering the main typical presentations of disease, and are meant to guide the user throughout the text. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 2. Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts.

**Disclosure**

PGC has reported advisory roles for Deciphera Pharmaceuticals, Eisai, Eli Lilly, Nektar Therapeutics, speaker’s honoraria from Eisai, Eli Lilly, Pfizer, PharmaMar, and conducted studies sponsored by Amgen Dompé, AROG Bayer, Blueprint Medicines, Eli Lilly, Daiichi Sankyo Pharma, Epizyme, GlaxoSmithKline, Novartis, Pfizer, PharmaMar; SBa has reported research support from Novartis, Incyte, Blueprint Medicines, has received honoraria or consultation fees from Novartis, Lilly, Pfizer, PharmaMar and Bayer; SBi has reported advisory/consultant roles for Lilly,
Bayer, Pfizer, Novartis, Isolfol and Clinigen and conducted studies sponsored by Janssen-Cilag, Eisai and Loxo Oncology; SBo has reported honoraria and travel grants from Nanobiotix and Lilly and received travel grants from PharmaMar; IB has received research funds from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Amgen and has reported advisory roles for AstraZeneca, Roche, Merck Sharp & Dohme, LEO Pharma, Amgen, Bristol-Myers Squibb, Pfizer and Novartis; BB; TB has reported honoraria from Roche and PharmaMar and advisory board and honoraria from Amgen, Bayer, Novartis, Eisai and Eli Lilly; JMB has reported consulting advisory role for PharmaMar, Lilly, Bayer, Novartis and being a member of the speaker’s bureau for PharmaMar and received travel grants from PharmaMar and Lilly; LB; APDT is a member of the speakers’ bureau for Lilly, Pfizer and Merck Sharp & Dohme; XGDM has reported advisory role for Lilly, PharmaMar and Novartis; PD has reported conducted research sponsored by Eli Lilly; CD; ME has participated in advisory boards for Bayer, Sobi, Lilly, Eisai and Novartis; FF; AMF has conducted studies sponsored by Amgen Dompé, AROG Bayer, Blueprint Medicines, Eli Lilly, Daiichi Sankyo Pharma, Epizyme, GlaxoSmithKline, Novartis, Pfizer, PharmaMar; NG; SG has received research grants and honoraria from Novartis, Pfizer and Bayer; HG has received research grants from Novartis, Daiichi Sankyo Pharma and Pfizer; RG; AG has reported compensation for advisory boards from Novartis, Pfizer, Bayer, Lilly, PharmaMar and Nanobiotix, honoraria from Novartis, Lilly, PharmaMar and Nanobiotix, and research funds from PharmaMar and travel grants from PharmaMar and Nanobiotix; RH; BH has received research grants from EuroSarc and has conducted research with EIT Health in collaboration with GE Healthcare and Philips, he has received reagents from Takeda and Astellas to conduct clinical trials without direct funding; PH has reported conducting research sponsored by Novartis, Blueprint Medicines, Nanobiotix and Lilly and has received honoraria and travel grants from PharmaMar, Eisai and Lilly; HJ has reported co-appointment with Orion Pharma and holds stock in Sartar Therapeutics, Faron Pharmaceuticals and Orion Pharma; RLJ is a consultant for Adaptimmune, Blueprint Medicines, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunedesign, Lilly, Merck and PharmaMar; IJ has received honoraria from Lilly for lectures; PJ has reported being a consultant for Stryker for the design of a new tumour prosthesis; BK has reported honoraria from Novartis, Pfizer and Bayer and advisory role for Bayer; KK has received travel grants from Novartis and Pfizer; RL; ALC has received honoraria
from Pfizer, Novartis, Lilly, Amgen, Bayer and PharmaMar; IL has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis and Pfizer for scientific presentations or research; MAP has served on advisory boards for Bayer and Pfizer, and has received research grants from Novartis; PRe has served on advisory boards for Novartis, Pfizer, PharmaMar, Ariad, Merck, Deciphera, Roche, Clinigen and Lilly and has received honoraria from Novartis, Pfizer, Bayer, PharmaMar and Lilly; PRu has received honoraria for lectures from Novartis, Pfizer, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche and has served as a member of advisory board for Novartis, Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, Blueprint Medicines; PS has received honoraria from Daiichi Sankyo Pharma, Eisai, Eli Lilly, Medspace, Novartis, Swedish Orphan Biovitrium, has reported consulting or advising roles for Sixth Element Capital, Adaptimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Boehringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo Pharma, Eisai, Eli Lilly, Epizyme, Genzyme, Ipsen, Loxo Oncology, Medspace, Nektar, Novartis, Philogen, Piqur Therapeutics, Plexxikon, is a member of speaker's bureau of Bayer, Eisai, Eli Lilly, GlaxoSmithKline, Novartis, PharmaMar, Swedish Orphan Biovitrium, has received research grants from Bayer, Blueprint Medicines, CoBioRes, Exelixis, Bristol-Myers Squibb, Novartis, Plexxikon, and has received travel grants from Sixth Element Capital, Adaptimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Boehringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo Pharma, Eisai, Eli Lilly, Epizyme, Genzyme, GlaxoSmithKline, Ipsen, Loxo Oncology, Medspace, Nektar, Novartis, PharmaMar, Philogen, Piqur Therapeutics, Plexxikon, Swedish Orphan Biovitrium; SSSt has received honoraria from Eli Lilly and PharmaMar, research grants from Amgen Dompé, Advenchen, Bayer, Eli Lilly, Daiichi Sankyo Pharma, Epizyme Inc., Novartis, Pfizer and PharmaMar; travel grants from PharmaMar and has reported advisory/consultant roles for Bayer, Eli Lilly, ImmuneDesign, Maxivax and PharmaMar; WVdG has received research grants from Novartis; EW has reported travel/research grants and/or honoraria from Novartis Oncology, Milestone, Menarini, PharmaMar, Roche, Nanobiotix and Bayer; JYB has declared research grants and honoraria from Novartis, GlaxoSmithKline, Pfizer and Bayer; IL has received honoraria from Bristol-Myers Squibb, MDS, Roche, Novartis and Pfizer for scientific presentations or research; NA, RB, JVMGB, AB, EDA, AFed, VF, AFe, TG, RI, SK, DAK, OM, MM,
RP, PP, SP-N, ALP, MHR, AAS, SSI, KSH, MU, JW and FVC have declared no conflict of interest. SF, AH and OZ have not reported any potential conflicts of interest.
References

58. Duffaud F et al. ASCO 2018 (annual meeting of the American Society of Clinical Oncology), Abstract 11505


87. Shapeero LG, Vanel D. Imaging evaluation of the response of high-grade osteosarcoma and Ewing sarcoma to chemotherapy with emphasis on dynamic contrast-enhanced magnetic resonance imaging. Semin Musculoskelet Radiol 2000; 4: 137-146.

Table 1. Personalised medicine synopsis table

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Use</th>
<th>LOE</th>
<th>GOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic characterisation</td>
<td>PCR, FISH, NGS</td>
<td>Small round cell sarcoma</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

FISH, fluorescent *in situ* hybridisation; GoR, grade of recommendation; LoE, level of evidence; NGS, next-generation sequencing; PCR, polymerase chain reaction.
Table 2. Summary of recommendations

**Diagnosis and pathology / molecular biology**
- Management of bone sarcomas should be carried out in a reference centre for bone sarcomas by either a surgical team or dedicated interventional radiologist.
- Pathological diagnosis should be made according to the 2013 WHO classification.
- Medical history should focus on characteristic symptoms such as duration, intensity and timing of pain, persistent non-mechanical bone pain, swelling and functional impairment.
- Diagnosis can be strongly oriented by patient age, and bone metastases and myeloma will be the most common bone sarcoma diagnoses in adult patients > 40 years old.

**Staging and risk assessment**
- General staging should be carried out to assess the extent of distant disease, including bone scintigraphy, chest radiographs and CT, whole-body MRI and positron emission tomography (PET)-CT or PET-MRI.

**Treatment (locoregional and advanced disease)**

*Osteosarcoma*
- Adverse prognostic or predictive factors include detectable primary metastases, axial or proximal extremity tumour site, large tumour size, elevated serum AP or LDH and older age [III, B].
- Staging should include local imaging studies, specifically plain radiographs and MRI of the whole affected extremity [III, A].
- Curative treatment of high-grade osteosarcoma consists of chemotherapy and surgery [II, A]; multimodal chemotherapy treatment is preferred.
- Low-grade central and parosteal osteosarcoma are malignancies with a lower metastatic potential, which should be treated by surgery alone [IV, B].
- Doxorubicin, cisplatin, HD-MTX and ifosfamide have anti-tumour activity in osteosarcoma [I, A]. In older patients, preferred regimens combine doxorubicin, cisplatin and ifosfamide without HD-MTX [III, B].
- In limited cases, radiotherapy including new techniques (e.g. proton beam and carbon ion therapy) should be considered, particularly for unresectable primary tumours.
Primary metastatic osteosarcoma patients are treated with a curative intent following the same principles of non-metastatic osteosarcomas.

High-grade craniofacial osteosarcoma should be treated the same way as high-grade osteosarcoma of other locations, although prospective evidence is lacking [IV, B]. Radiotherapy, preferably within clinical studies, can be proposed when complete surgery is not feasible [IV, B].

The treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases, although stereotactic radiotherapy, radiofrequency ablation or cryotherapy might be used as alternative options in patients unfit for surgery [IV, B].

Radiofrequency ablation and stereotactic radiotherapy are potential alternative local treatment options for small size lung or bone metastases.

Second-line chemotherapy for recurrent osteosarcoma includes ifosfamide or cyclophosphamide, possibly in association with etoposide and/or carboplatin [III, B], and other active drugs including gemcitabine and docetaxel [IV, C], sorafenib [III, B] or regorafenib [II, B], as well as 153Sm.

**Ewing sarcoma**

ES is a rare tumour and is usually treated within Ewing-like regimens.

Treatment of patients with extraskeletal ES follows the same principles as for bone ES and incorporates chemotherapy in all cases, as well as postoperative radiotherapy in most cases.

Complete surgical excision, where feasible, rather than radiotherapy is regarded as the best modality of local tumour control.

Radiotherapy alone 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 [IV, B].

Preferred chemotherapy options include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin and etoposide, with most active protocols based on five- to six-drug combinations of these substances [I, A].

Current trials employ 3–6 cycles of initial combination chemotherapy after biopsy, followed by local therapy, and another 6–10 cycles of chemotherapy usually applied at 2- to 3-week intervals.
Recent studies recommend the use of BuMel for highly selected patients with poor response to induction chemotherapy and/or tumour volume > 200 mL [II, A]

For patients with metastases at diagnosis, chemotherapy is similar to that for localised disease, but responses are less durable and patients have a worse prognosis

Chemotherapy regimens in relapse situations are not standardised and include alkylating agents (cyclophosphamide and high-dose ifosfamide) in combination with topoisomerase inhibitors (etoposide and topotecan), irinotecan with temozolomide [III, B] or gemcitabine and docetaxel, or high-dose ifosfamide or carboplatin with etoposide

**High-grade spindle/pleomorphic sarcomas of bone**

- Treatment strategies mimic those of osteosarcoma and include chemotherapy and complete en bloc resection including any soft tissue component
- Radiotherapy may be considered in inoperable lesions

**Chondrosarcoma**

- Mesenchymal chondrosarcoma is usually considered to be sensitive to adjuvant or neoadjuvant therapy [IV, C] and is treated using a Ewing-type chemotherapy regimen
- Dedifferentiated chondrosarcoma is often treated as a high-grade bone sarcoma, with systemic and local therapies that need to be adapted to patient’s age [V, C]
- Skull base chondrosarcomas can be treated with high-dose radiotherapy including proton beam or carbon ion radiotherapy
- Doxorubicin and ifosfamide may prove active in chondrosarcoma, especially in high-grade lesions, and gemcitabine in combination with docetaxel has also been reported to be effective
- There is a potential role for mTOR inhibitors in combination with cyclophosphamide [IV, C]

**Giant cell tumour of bone**

- Treatment options for GCTs include intralesional curettage with or without adjuvant or en bloc excision [IV, A]
- Denosumab is standard treatment in unresectable or metastatic GCT [III, A], although its use in the neoadjuvant setting is debated
Radiotherapy can provide local control in GCT but can be associated with transformation into a high-grade sarcoma, and should be limited to cases in which surgery leads to unacceptable morbidity and denosumab is ineffective or contraindicated [IV, D]

Chordoma

Chordomas are very rare tumours, and management should be carried out at referral centres and/or referral networks with a multidisciplinary team

*En bloc* R0 resection is standard treatment [IV, B], if feasible; otherwise, definitive radiotherapy alone should be considered as a valid alternative [III, B]

For sacral chordoma, surgery should be offered if the chordoma arises from S4 and below or discussed in the context of other alternatives for tumours originating above S3. Surgery is preferred for tumours originating from S3, especially if the preservation of S2 roots is possible

R1–R2 surgery plus high-dose radiotherapy is the treatment of choice for skull base and upper cervical tract chordoma

Indications for definitive radiotherapy include unresectable disease, inoperable patients and neurological impairment not accepted by the patient. Radiotherapy should be considered in the case of R2 or R1 resections

In the case of local relapse, recommended treatment includes surgery and/or radiotherapy and/or systemic treatment

For oligometastatic disease, surgery/radiofrequency ablations/stereotactic radiation of metastases can be considered in selected cases

Imatinib or sorafenib may be beneficial in advanced chordoma in terms of progression-free survival and mainly non-dimensional tumour responses

Follow-up, long-term implications and survivorship

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 could be a proposed strategy

A recommended follow-up policy varies among experts and may foresee intervals between checks after the completion of chemotherapy, approximately every 3 months for the first 2 years; every 6 months for years 3–5; every 6-12 months for years 5–10, and thereafter every 0.5-1-2 years
• Chest CT, if used instead of chest X-rays, should be carried out with low-dose, radiation-sparing techniques
• For low-grade bone sarcoma, the frequency of follow-up visits may be lower (e.g. 6 months for 2 years and then annually)
• In ES, where osseous metastases are likely, isotope bone scanning can be used but should be weighed against the additional radiation exposure
• More modern techniques (e.g. PET or whole-body MRI) are increasingly being adopted into routine practice, but require further evaluation in clinical trials
• Long-term toxic effects of chemotherapy, surgery and radiotherapy should be evaluated, and monitoring for late effects should be continued for > 10 years after treatment, depending on the chemotherapy protocol and radiation used
• Long-term cardiac evaluation is important as it has been shown that deterioration of cardiac function can still occur decades after anthracycline treatment
• 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

AP, alkaline phosphatase; BuMel, busulfan and melphalan; CT, computed tomography; ES, Ewing sarcoma; GCT, giant cell tumour; HD-MTX, high-dose methotrexate; LCH, Langerhans cell histiocytosis; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin R0, no tumour at the margin; R1, microscopic tumour at the margin; R1, macroscopic tumour at the margin; PET-CT, positron emission tomography; WHO, World Health Organization.
Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System<sup>a</sup>)

**Levels of evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case–control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

**Grades of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

<sup>a</sup>By permission of the Infectious Diseases Society of America [126].
Figure 1. General diagnostic strategy for bone sarcomas

BM, bone marrow; CT, computed tomography; PET, positron emission tomography.

Figure 2. General therapeutic strategy for the three most frequent bone sarcomas

BuMel, busulfan-melphalan high-dose chemotherapy consolidation; ChT, chemotherapy.