Bone sarcomas: ESMO–EURACAN–GENTURIS–ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

Version of Record: https://www.sciencedirect.com/science/article/pii/S0923753421042800
Manuscript_b7b290aaf05cfa632e9d52ba43d1841b

Bone sarcomas: ESMO–EURACAN–GENTURIS–ERNPaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up†

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[†]Approved by the ESMO Guidelines Committee, EURACAN, GENTURIS and ERNPaedCan: August 2021.This publication supersedes the previously published version – Ann Oncol. 2018:29(suppl 4): iv79-iv95.

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Word count: 11214 (excluding title page, acknowledgements, funding and disclosures). Tables: 0; Figures: 2; References: 89; Supplementary tables: 4; Supplementary figures: 0.

Keywords: Bone sarcoma, clinical practice guideline, diagnosis, treatment, follow-up, management

Highlights:

- This Clinical Practice Guideline provides key recommendations on the management of bone sarcomas.

- Recommendations have been agreed following a consensus meeting of representatives from ESMO, EURACAN, GENTURIS and ERNPaedCan.
- Authorship includes a multidisciplinary group of experts from different institutions and countries worldwide.

INCIDENCE AND EPIDEMIOLOGY

Primary bone sarcomas (BSs) account for <0.2% of malignant neoplasms across all ages.[1] The overall incidence rate ranges between 0.8-0.9 cases per 100,000/year, with single BS types having no more than 0.3 incident cases per 100,000/year. Osteosarcoma and Ewing sarcoma (ES) have a relatively high incidence in the second decade of life, whereas conventional chondrosarcomas are more common in older age.[2]

Osteosarcoma is the most common BS (incidence: 0.3/100,000/year). The incidence is higher in adolescents (0.8-1.1/100,000/year at age 15-19 years) but there is a significant second peak in the seventh and eighth decades of life.[1,2] The male to female ratio is 1.4:1. In younger patients, most osteosarcomas arise in extremities, while the proportion of axial tumour sites increases with age. Risk factors for the occurrence of osteosarcoma include previous radiotherapy (RT), Paget disease of the bone and germline genetic abnormalities associated with Li–Fraumeni syndrome, Werner syndrome, Rothmund–Thomson syndrome, Bloom syndrome and hereditary retinoblastoma.[3]

ES is a round cell sarcoma (RCS) marked by a gene fusion involving a member of the FET family and a member of the ETS family of transcription factors. ES is the third most common BS (incidence: ~0.1/100,000/year) and 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. The most common ES primary sites are the extremity bones (50%), 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).

ES is currently regarded as distinct from rarer and recently identified entities such as RCS with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcomas and sarcomas with *BCOR* alteration[4]. Among RCSs with *EWSR1* non-ETS fusions, *EWSR1-NFATC2* is the commonest, has a strong male predominance, affects an older population and occurs mainly in bone.[5] *CIC*-rearranged sarcomas mostly arise from soft tissues and are rare in bone.[6] Among RCSs with *BCOR* alterations, the *BCOR-CCNB3* variant occurs mainly in the bones and predominantly affects paediatric patients, whereas

BCOR with internal tandem duplication has been described in soft tissue tumours of infancy.[7,8]

Conventional chondrosarcoma is the most frequent BS of adulthood (incidence: ~0.2/100,000/year), with a median age at diagnosis between 30 and 60 years and no gender predominance.[1] Dedifferentiated chondrosarcoma (DCS), mesenchymal chondrosarcoma (MCS) and clear-cell chondrosarcoma are ultra-rare chondrosarcoma subtypes, with an incidence of <0.1/100,000/year. Extraskeletal myxoid chondrosarcoma, although originally thought to be a cartilaginous neoplasm, does not show cartilage differentiation and is classified as a mesenchymal tumour of uncertain differentiation and covered by the European Society for Medical Oncology-European Reference Network for Rare Adult Solid Cancers-European Reference Network for Genetic Tumour Risk Syndromes (ESMO-EURACAN-GENTURIS) Clinical Practice Guidelines on soft tissue sarcomas (STSs).[9]

Conventional chordomas are even rarer than other types of BSs, with an incidence of approximately 0.08/100,000/year and a median age at diagnosis of 60 years. There is a slight male predominance. Dedifferentiated and poorly differentiated chordomas are ultra-rare subtypes.[1,10]

Giant cell tumour of bone (GCTB) is locally aggressive, rarely metastasising and represents 5% of primary bone tumours, with an incidence of approximately 1/1,000,000/year.[1]

High-grade spindle/pleomorphic 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 ES.[11]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

A general diagnostic strategy for BS is shown in Figure 1. The presence of persistent and often progressive 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

these are often later signs. The differential diagnoses of a BS include osteomyelitis, benign tumours and bone metastases, all of which outnumber primary BS. 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. For patients aged ≥5 years, the likelihood of a primary BS is higher. After 40 years of age, bone metastases and myeloma will be the most common diagnoses.

Conventional radiography in two planes is the first radiological investigation. When the diagnosis of malignancy cannot be definitely excluded on radiographs, magnetic resonance imaging (MRI) of the whole compartment with adjacent joints should be carried out. MRI is currently regarded as the best modality for local staging for tumours of the extremities, spine and pelvis. Computed tomography (CT) may provide additional information on bone involvement (presence of calcification, periosteal bone formation and cortical destruction) and can be chosen as preferred imaging modality for other primary sites.

All patients with a bone lesion which is suspected to be a primary BS on a radiological basis should be referred to a BS reference centre or to an institution belonging to a sarcoma network.[12] Children and adolescents should be referred to centres that, in addition, provide age-specific expertise.

The biopsy of a suspected primary BS should be carried out by either the surgical team who will carry out the definitive tumour resection or by a dedicated interventional radiologist after discussing with the surgeon.[12] For those patients whose pathological diagnosis was obtained outside a reference network, an expert pathological review in a sarcoma reference centre is mandatory. In most patients, a core-needle biopsy, taken under imaging guidance, represents an appropriate alternative to open biopsy. Contamination of surrounding tissue should be minimised, and adequate multiple sampling of representative areas must always be provided. If required, an open biopsy should be carried out using a longitudinal incision. In aggressive and malignant bone tumours, the biopsy tract and the channels through which drains have been placed must be considered potentially contaminated and must later be removed, together with the resection specimen, in an effort to minimise the risk of a local recurrence (LR).

Therefore, biopsy tracts should be clearly marked 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 BS is suspected.

Histology specimens must be interpreted by an experienced bone tumour pathologist, in collaboration with the radiologist, and discussed in a multidisciplinary team.

With the increasing capability for accurate molecular diagnosis, samples should be quickly submitted for pathological assessment.[13] The collection of fresh snap frozen tissue is encouraged to overcome damage to nucleic acids resulting from decalcification, and to allow subsequent molecular assessment.

The nature of the bone specimen received for pathology reporting should be recorded (i.e. needle biopsy, curettage or excision). It is usually necessary to decalcify the bone tumour biopsy. Ethylene-diamine-tetra-acetic acid (EDTA) is preferred over acid-based methods; in case of the latter, sampling frozen tissue is essential to allow molecular diagnostics. Tumour type must be diagnosed according to the most recent version of the World Health Organization (WHO) classification for tumours of soft tissue and bone (2020).[4] It is important to note that for BS, the histotype determines the histological grade, with few exceptions.[4] The results of ancillary investigations (e.g. immunohistochemistry or molecular assessments) should be accurately recorded whenever relevant. Examples include translocation detection in RCS and MCS, isocitrate dehydrogenase (*IDH1* and *IDH2*) mutations in conventional chondrosarcoma and *MDM2* amplification in parosteal and intramedullary low-grade osteosarcoma.

At the time of the resection of the primary tumour, for surgical specimens, the size of the tumour in the resected bone should be recorded (at least the maximal diameter, but preferably three-dimensional measurement, in mm). The pathology report should 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 (R0) or microscopically (R1) or macroscopically (R2)

involved. In case of negative margins, the distance (in mm) of tumour from the nearest resection margin as well as the distance to the closest osteotomy margin should be measured. A complete, representative slab of the tumour, usually through its largest dimension 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 (ChT) to assess response. The percentage of viable tumour/percentage of histological response (including necrosis, fibrosis and calcification) should be documented, as this has prognostic value, especially in ES and osteosarcoma. In osteosarcoma, a cut-off of 10% viable tumour cells or ≥90% response is used to indicate a good response.[14] For ES the cut-off is less well-defined. Recent studies suggest that 100% response is most optimal to define a good tumour response in ES.[15] However, earlier reports define good response between 90% and 100% necrosis, fibrosis and calcification.[16,17]

Recommendations

- The initial work-up of a suspected primary BS tumour should be carried out at a sarcoma reference centre, and should include medical history, physical examination, radiological assessment and biopsy [IV, B].
- Pathological diagnosis should be made by a bone tumour expert dedicated pathologist according to the 2020 WHO classification and should be supported by ancillary investigations whenever relevant [IV, A].
- For surgical specimens, tumour size and local extent of spread, site, status of surgical margins and percentage of pathological response to preoperative ChT should be described [V, B].

STAGING AND RISK ASSESSMENT

Several staging systems for BS are in use, with no unifying system accepted as standard.[18-20] Tumour burden and the presence of detectable metastases are the two main factors 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 and dedicated chest CT. Whole-body (WB)-MRI and [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT or PET-MRI are

increasingly utilised for staging of bone and bone marrow metastases (including skip bone lesions). Additional appropriate imaging studies and biopsies can be taken from suspicious sites.

No specific laboratory tests for the diagnosis of BS are routinely available. Baseline serum analysis in ES and osteosarcoma should include alkaline phosphatase (AP) and lactate dehydrogenase (LDH) given their proven prognostic value and their use as response monitoring during treatment. 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 recurrence, especially in osteosarcoma.

ChT for BS can result in renal, cardiac and auditory dysfunction. Prior to starting therapy, baseline renal function testing, assessment of cardiac function 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, consultation with a fertility physician about potential ovarian sampling, cryopreservation, gonadotrophin-releasing hormone agonists and other means of ovarian suppression for fertility preservation should be considered, where available. However, there is still limited scientific knowledge on gonadotoxic effects of the different ChT used and variability of health care policies across nations.
Additional guidance on germline *TP53* testing in osteosarcoma is provided in the Supplementary Material and in Supplementary Table S1.

Recommendation

- General staging should be carried out to assess the extent of distant disease, including chest CT, bone scintigraphy and/or WB-MRI and and/or FDG-PET-CT/MRI as clinically indicated. Baseline serum analysis in ES and osteosarcoma should include AP and LDH [III, B].

TREATMENT

Given their rarity and the complexity of management, the accepted standard for BS is treatment at reference centres and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise [III, A]. In these

centres/networks, therapy is usually given within either the framework of prospective, often collaborative, clinical studies or established treatment protocols.
Supplementary Table S2 lists systemic agents that have been associated with preliminary or partial evidence of activity in BS; however, they have not entered standard practice and/or they are not approved/reimbursed in all European countries. Thus, if available, their use may be considered depending on the clinical context with individualised patient–physician shared decisions. The principles for the treatment of osteosarcoma and ES are summarised in Figure 2.

Osteosarcoma

Osteosarcoma usually arises in the metaphysis of a long bone, most commonly around the knee, in children and adolescents.[2] Involvement of the axial skeleton and craniofacial bones is primarily observed in adult patients. High-grade osteosarcoma patients frequently develop metastases with the lung being the most frequent metastatic site by far, followed by distant bones.

The diagnosis of osteosarcoma is based on morphological findings, and no specific diagnostic molecular tests are available. Conventional osteosarcoma is always high-grade. Periosteal osteosarcoma is intermediate-grade and often chondroblastic. Low-grade central osteosarcoma and parosteal osteosarcoma are low-grade malignancies, arising intramedullary and from the bone surface, respectively. These malignancies can sometimes show high-grade components.[21] In the case of parosteal osteosarcoma with limited low-grade component, the differential diagnosis with conventional osteosarcoma can be helped by the detection of *MDM2* amplification, which is present in >85% of cases.[22]

Adverse prognostic factors for conventional osteosarcoma include primary metastases, axial or proximal extremity tumour site, large tumour volume, elevated serum AP or LDH levels and older age [III, B].[23]

Curative treatment of high-grade osteosarcoma consists of ChT and surgery [II, A]. Compared with surgery alone, multimodality management with ChT and surgery for high-grade, localised osteosarcoma increases disease-free survival (DFS) probability

from <20% to >60%. In general, ChT is administered before and after surgery, although there is no evidence that giving preoperative ChT improves survival, as long as ChT is administered. However, it allows the assessment of histological response to preoperative ChT, which predicts survival.[23]

Surgery should be carried out by a surgical team familiar with the wide range of surgical reconstructions. Paediatric and adolescent patients need to be treated by surgeons with experience in the field of paediatric bone tumours, including age-specific reconstruction challenges, such as the reconstruction of growing bones. Most patients should be considered candidates for limb salvage. R1 and R2 margins both increase the LR rate, which is associated with reduced overall survival (OS). 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. 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 LR. External splintage is recommended. Pathological fracture does not necessarily require an amputation. Primary neoadjuvant ChT 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.

Doxorubicin, cisplatin, high-dose methotrexate (HD-MTX) and ifosfamide have anti-tumour activity in osteosarcoma [I, A].[24-27] The doxorubicin/cisplatin/HD-MTX (MAP) regimen is most frequently used as front-line ChT in children and young adult patients;[24-26] however, HD-MTX can be challenging to administer in adults.[27,28] In patients aged over 40 years, the use of MTX (8 g/m^2) after a poor response to non-MTX induction ChT was proved to be feasible, and regimens combining doxorubicin, cisplatin and potentially ifosfamide are an alternative.[24-26,29]

Most current protocols for localised disease include a period of preoperative ChT, to facilitate local surgical treatment and to allow the assessment of histological response, although there is no evidence to support a change in ChT based on this alone .[24-26,29] The use of post-operative PEGylated interferon-α2b in addition to MAP in patients with good histological response to preoperative ChT, of ifosfamide and etoposide in poor responders and the preoperative use of zoledronic acid in newly diagnosed

osteosarcoma patients failed to improve outcome in large randomised studies; therefore, their use is not recommended outside clinical trials [I, D].[24,30,31]

Innate immune modulation has been attempted in osteosarcoma with some agents, in particular muramyl tripeptide (MTP). In one large, randomised trial where patients with localised osteosarcoma were treated with MAP and randomly assigned to receive ifosfamide and/or MTP or not, MTP added to post-operative ChT was associated with a significant advantage in OS. On this basis, MTP 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. However, there is no consensus for its use within the sarcoma community, due to the availability of only one randomised study and the lack of a statistical significance for the improvement in event-free survival and, at a subgroup analysis, the fact that the difference was apparently confined to arms adding ifosfamide to MAP [II, C].[32]

RT may be considered in osteosarcoma patients with unresectable primary tumours where surgery would be unacceptably morbid, or as adjuvant treatment for tumours at high risk of local recurrence and with limited option for further surgery [IV, B]. Modern RT techniques [including heavy particles and intensity-modulated RT (IMRT)] may offer a technical advantage to deliver high doses and should be considered where appropriate, especially in paediatric patients or young adults.[33,34]

High-grade craniofacial osteosarcomas mostly occur in older adults, are mainly represented by the chondroblastic subtype and seem to have a lower risk for distant metastases.[35] Although the value of ChT remains unclearly defined, there is no reason today not to manage high-grade craniofacial osteosarcomas in the same way as high-grade osteosarcoma of other locations [IV, B]. Given the site, surgery can prove challenging, and therefore the administration of all ChT before surgery with close monitoring may be advantageous [IV, B].[36] RT can be proposed when complete surgery is not feasible and in patients undergoing resection with positive margins, after discussion within a multidisciplinary team [IV, B]. Modern RT techniques (including heavy particles and IMRT) may offer a technical advantage to deliver high doses and could be considered.

Primary metastatic osteosarcoma patients may be treated with a curative intent following the same principles as applied in non-metastatic osteosarcomas. Retrospective data suggest that 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].[37]

MTP does not offer a survival benefit in this group and should not be used outside clinical trials.[38] For patients with widely disseminated disease, who are deemed incurable, quality of life should always be balanced against potential treatment benefits and toxicity.

The management of recurrent osteosarcoma needs to take into account the timing of recurrences and the number and sites of metastases. The treatment of recurrent osteosarcoma is primarily surgical in patients with isolated lung metastases or LR. Complete removal of all resectable metastases must be attempted [III, B], as more than a third of patients with a complete second surgical remission survive for >5 years.[39] Even patients with subsequent recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted.[39] For lung metastases, stereotactic RT, radiofrequency ablation (RFA) or cryotherapy might be used as alternative options in patients unfit for surgery [IV, B]. Some groups also consider RFA and stereotactic RT as potentially alternative local treatment options for bone metastases.[40]

In a retrospective review including patients with LR as first event, no benefit from ChT administration was demonstrated, while the achievement of a second complete surgical remission was found to be of major importance.[41] A disease-free interval >18 months was confirmed as an important prognostic factor.

In the largest reported series, the use of second-line ChT correlated with limited prolongation of survival in patients with inoperable metastatic recurrences, while a positive correlation with operable disease was observed in only one study.[37] However, radiological responses and clinical benefit are commonly witnessed, so ChT use should be considered [IV, B].

Treatment choice may take into account prior DFS, ChT regimens previously used 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].[42] Data on cabozantinib and regorafenib are detailed in Supplementary Table S2.[43-45] RT may have a role in palliation.

In general, despite second-line treatment, the prognosis of recurrent disease has remained poor, with a 5-year post-relapse survival rate of <20%.[37,46]

Extra-osseous osteosarcoma is exceedingly rare, and there is no consensus about whether treatment should be in accordance with skeletal osteosarcoma or soft-tissue sarcomas.[47]

Low-grade central and parosteal osteosarcomas are malignancies with a lower metastatic potential, treated by surgery alone [IV, B]. The use of ChT could be considered for cases with a high-grade component [V, C].[21] ChT is not routinely recommended in periosteal osteosarcomas, as no benefit was shown in retrospective studies [IV, D].[48]

Ewing sarcoma

ES is the second most common malignant bone tumour in children and young adults. It can arise from bone, soft tissues or visceral sites, displaying the same behaviour in principle, and lungs, bone and bone marrow are the most common metastatic sites. There is retrospective evidence suggesting that cutaneous and subcutaneous ES have a better prognosis compared with other localised soft tissue ES.[49]

The definitive diagnosis is made on biopsy. ES is a RCS, marked by a gene fusion involving a member of the FET family (usually *EWSR1*) and a member of the ETS family of transcription factors.[4] All cases are high-grade. In 85% of cases a reciprocal translocation t(11;22)(q24;q12), resulting in *EWRS1-FLI1* fusion, can be detected, whereas the t(21; 22)(q22; q12), resulting in *EWSR1-ERG* fusion, can be found in approximately 10% of cases.[50] Other translocations can also occur, involving other ETS genes (*FEV, ETV1, E1AF*).

Molecular confirmation is mandatory for the distinction between ES and other RCSs [V, A].[4] Assays using *EWSR1* break-apart probes do not detect fusion partners, but only *EWSR1* rearrangements, which should not be a problem when interpreted in the appropriate clinical and pathological context. Massive parallel sequencing should be considered when no translocations have been detected by conventional methods [IV, B].

Staging must be performed to detect lung, bone and bone marrow metastases and should include biopsy in case of doubtful lesions. FDG-PET-CT or WB-MRI are preferred over bone scan for skeletal imaging if available [V, B]. Bone marrow biopsies and aspirates (from sites distant to the primary or known metastatic lesions) are not mandated if a FDG-PET/CT is done [V, C], since several studies demonstrate a very low incidence of bone marrow metastases in patients with localised disease and negative FDG-PET/CT.[51]

Metastatic disease at presentation is the most significant predictor of survival. Approximately 25% of patients are diagnosed with metastatic disease (10%: lung; 10%: bones/bone marrow; 5%: combinations or others). Multiple bone metastases confer a poorer outcome than lung/pleural metastases (<20% compared with 50%-60% 5-year survival).[52,53] Other adverse known prognostic factors are tumour volume, LDH levels, axial localisation, older age (>15 years), a poor histological response to preoperative ChT and incomplete or no surgery for primary site.[52] With the currently recommended treatment protocols, patients with ES have similar outcome, independently from the type of gene fusion detected.[54,55] Without systemic treatments, 5-year survival was <10% in historical series. With the current recommended multimodal approaches including ChT, 5-year survival is ~60%-75% in localised and ~20%-40% in metastatic disease, respectively, depending on metastatic sites and tumour burden.

Multiagent regimens including vincristine (V), doxorubicin (D), cyclophosphamide (C)/ifosfamide (I) and etoposide (E) have proven activity in ES in large collaborative trials.[56-58] A recent large, randomised study enrolling localised or metastatic ES patients aged 5-50 years compared the European regimen of VIDE induction and VAI

or VAC (V, actinomycin D and I or C) consolidation with the USA regimen of compressed VDC/IE induction and IE/VC consolidation. The interval-compressed VDC/IE regimen showed superiority to VIDE for both event-free survival and OS, with similar toxicity, and it is currently the preferred first-line treatment in ES [I, B].[59]

The use of high-dose ChT with escalated alkylating agent dose and autologous blood stem cell rescue has attracted much attention in ES since the 1970s. The results of randomised studies with busulfan and melphalan (BuMel) indicated that this approach results in a survival advantage for patients with poor response to VIDE induction ChT and/or tumour volume >200 ml [II, A].[60] No such advantage was evident for patients presenting with pulmonary metastases, treated with standard ChT and whole lung irradiation [II, D].

For poor-responding patients treated with interval compressed VDC/IE, the role of high-dose ChT has not been evaluated. The selection of the most appropriate consolidation should take into account the ChT regimen received and need for RT, whose feasibility can be limited in patients receiving BuMel due to expected toxicity.

Generally, up to nine cycles of induction ChT is delivered after biopsy, followed by local therapy, and consolidation thereafter. Overall treatment duration is 10-12 months. The optimal timing for local control must be discussed at a multidisciplinary level, taking into account primary site, size, response, anticipated morbidity from surgery and tolerability. Change in the size of the soft tissue mass is easily evaluated on MRI, a good predictor of tumour response. Sequential FDG-PET evaluation might be of additional value.[61]

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 LR when RT is used as the sole treatment [IV, A].[56,62] Surgery must involve excision of all tissues originally involved prior to induction ChT (not just the tumour tissue remaining following dimensional shrinkage on ChT). Intralesional surgery must be avoided, as there is no benefit compared with RT alone.[56]

RT with definitive intent alone should be used instead of surgery if complete surgical excision is not possible and in cases with challenging local sites such as axial or spinal tumours where surgery will be unacceptably morbid [IV, A].[56,63] Adjuvant RT (45-60 Gy) significantly reduces local recurrence in patients with large-volume tumours (>200 ml), poor-histological response or inadequate surgical margins and should be recommended in these circumstances [IV, B].[56,64] Also, adjuvant RT should be considered in patients with non-sacral pelvic ES regardless of surgical margins, tumour volume or histological response, as this was shown to have superior local control and survival outcomes compared with surgery alone [II, B].[65] If RT is agreed to be indicated at the time of diagnosis, preoperative RT should be considered. Lower doses to a smaller volume of tissue are required, and homogeneity of radiation dose is improved in the absence of metal artefact from internal fixation, thereby potentially reducing long-term morbidity. The use of modern RT techniques with the ability to deliver high doses and minimise dose to normal tissues, including heavy particles, should be considered whenever felt to be technically more appropriate, especially in paediatric patients and young adults.[66]

The treatment of adult patients follows the same principles as for ES in typical age groups. However, the tolerability of ChT schedules developed for children and patients ≤40-50 years, needs to be accounted for in the management of older patients.

Treatment of patients with extraskeletal ES follows the same principles as for bone ES, thus incorporating ChT in all cases as well as RT in most cases [IV, B]. Given their favourable prognosis, the number of cycles in cutaneous and subcutaneous ES is to be discussed case by case, at a multidisciplinary level and with the patient [V, C]. Prospective registration of cases, in Europe, in the framework of EURACAN–European Reference Network for Paediatric Oncology (ERNPaedCan) should be encouraged.

Patients with metastases at diagnosis are treated with the same treatment approach as patients with localised disease but have a worse prognosis. Local treatment, especially in the presence of responding metastatic disease, has been proved to be associated with outcome improvement, and should therefore be attempted [II, B].[67]

Whole-lung irradiation, particularly when achieving complete remission of all lung metastases, can be used in this setting, although data demonstrating an improvement in outcome are lacking [III, C].[68] In patients with oligometastatic bone disease, local control at metastatic sites with RT should be considered [IV, B].[67] The role of high-dose ChT in patients with extra-pulmonary metastases remains controversial, with no randomised evidence to support its use [III, D].

Recurrent ES, whether local or with distant metastases, is almost always fatal, even though further responses to ChT are frequent and potentially valuable. The most consistent prognostic factor is time to relapse (>2 years from initial diagnosis have a better outcome).[69] ChT regimens for relapsed ES are not standardised and include alkylating agents (cyclophosphamide and ifosfamide) in combination with topoisomerase inhibitors (etoposide and topotecan), irinotecan with temozolomide, gemcitabine and docetaxel, high-dose ifosfamide or carboplatin with etoposide [III, B].[70,71] Preliminary results from the rEECur study, the first randomised controlled trial in this setting, suggest gemcitabine and docetaxel to be the inferior regimen, with temozolomide plus irinotecan also inferior to topotecan plus cyclophosphamide and high-dose ifosfamide.[72] Data for cabozantinib and regorafenib are detailed in Supplementary Table S2.[43]

For selected patients with a long disease-free interval of ≥2 years achieving a complete remission through medical therapy and/or surgery, consolidation with high-dose ChT may be considered [V, C].

RCSs with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcoma and sarcoma with *BCOR* alterations

RCS with *EWSR1* non-ETS fusions, *CIC*-rearranged sarcoma and sarcoma with *BCOR* alterations are currently recognised as distinct entities, with distinctive molecular, immunohistochemical, clinical and epidemiological features, as detailed earlier.[4] The clinical behaviour of these entities remains uncertain, and there is no consensus on whether they should be treated with an ES-like approach, as currently done by most sites, or regarded as high-grade STS. When feasible, combination

regimens including anthracycline and alkylating agents should be favoured [V, B]. Registration within clinical trials and prospective registries is recommended.

Chondrosarcoma

Chondrosarcoma becomes more frequent with increasing age, with approximately 80% of cases diagnosed after 40 years. The most common primary sites are the long bones, especially the lower limb, followed by the pelvis and ribs.[1,73]

The majority of conventional chondrosarcomas are locally aggressive or low-grade, non-metastasising tumours (atypical cartilaginous tumour/chondrosarcoma grade I), rather than high-grade chondrosarcoma (grades II–III). The label atypical cartilaginous tumour is currently in use for tumours arising in long and tubular bones of the appendicular skeleton, while tumours of the axial skeleton (flat bones including pelvis, scapula and skull base) should be called chondrosarcoma grade I.[4] Most low-grade and high-grade conventional chondrosarcomas are primary and originate in the medulla of bone (central chondrosarcoma), although a proportion can arise secondary within an enchondroma (secondary central chondrosarcoma) or at the surface of the bone from the cap of a pre-existing osteochondroma (secondary peripheral chondrosarcoma). Most chondrosarcomas are solitary, but they can occur as multiple lesions in syndromic patients with multiple osteochondromas and enchondromatosis. Rarely (2% of cases), chondrosarcoma can arise from the periosteum at the surface of bone (periosteal chondrosarcoma). Conventional chondrosarcomas can occasionally dedifferentiate into a very aggressive high-grade sarcoma with a dismal prognosis, the so-called DCS.[4] Rarer chondrosarcoma subtypes include MCS and clear-cell chondrosarcoma.[4,74]

The diagnosis of chondrosarcoma is based on morphology. Approximately 50% of central chondrosarcomas carry *IDH1* or *IDH2* mutations; however, molecular analysis is not required routinely.[75] MCS is marked by the presence of a highly specific gene fusion between *HEY1* and *NCOA2.*[76]

Metastatic disease at presentation, histological grade, axial primary site and size have been reported as prognostic factors in conventional chondrosarcomas.[77] Metastatic

disease at presentation is more common in DCS (20% of cases) and MCS (10%).[78] Pain at the site of a cartilaginous lesion may be an indicator of malignancy. A contrast-enhanced MRI can reveal high-grade areas, providing a useful guide to the site of biopsy. For large axial and pelvic chondrosarcoma, heterogeneity is common, and most lesions contain high-grade elements. The distinction 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.[78]

Atypical cartilaginous tumours in the long bones of the limbs can be managed by curettage with or without local adjuvant therapy (e.g. phenol, cement and cryotherapy), with a high chance of success [IV, B].[79] Alternatively, some reference centres now recommend active surveillance, with close radiological monitoring, for now-progressive and asymptomatic lesions [V, C].[80] Low-grade peripheral chondrosarcomas (arising from osteochondromas) should be surgically excised, aiming to excise the tumour with a covering of normal tissue over it [IV, B]. Higher-grade chondrosarcomas (grade II-III) and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins [IV, B]. There is a very high risk of distant metastasis and LR following excision of DCS, particularly in the presence of a pathological fracture. If wide margins cannot be reliably achieved with limb salvage, amputation should be considered.

RT can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptoms palliation [IV, B]. Modern RT techniques with the ability to safely deliver high doses, including heavy particle RT, should be considered whenever felt to be technically appropriate. High-dose RT is currently recommended for patients with skull base chondrosarcomas [III, B], on the basis of the excellent outcome reported (80%-90% local control rates).[81]

Evidence suggests that MCS and DCS are more sensitive to ChT.[82,83] Localised MCSs are usually treated with adjuvant/neoadjuvant ChT combining anthracycline and alkylating agents [IV, C]. Adjuvant/neoadjuvant ChT can also be considered for localised DCS [V, C].

Inoperable, locally advanced and metastatic high-grade chondrosarcomas have a poor prognosis.[83] For patients with oligometastatic, resectable, lung disease, surgery, RT or local ablation can be considered, especially for conventional chondrosarcomas [V, C]. In patients with widely metastatic disease, ChT is of limited benefit, with higher responses seen in patients receiving combination anthracycline-based therapy and those with DCS or MCS. The activity of gemcitabine and docetaxel has been reported.[84] In MCS, trabectedin may be an option [V, C].[85] Data on pazopanib are detailed in Supplementary Table S2.[86] Preliminary data on the activity of immunotherapy and inhibitors of mutant *IDH1* (i.e. ivosidenib) are available. Prospective trials are ongoing.

Chordoma

Chordoma arises from the persistent notochordal elements in the spine (sacrum 50%, mobile spine 20%) and in the skull base (30%). Extraskeletal cases are extremely rare. Median age of diagnosis is 60 years, but skull base presentations can affect a younger population, including children and adolescents. More than 40% of patients with chordoma will develop metastases, usually late in the natural history, and mostly after LR.

Conventional chordoma is marked by nuclear expression of brachyury and its diagnostic assessment is highly recommended [V, B].[4] Dedifferentiated chordomas account for <5% of cases and behave more aggressively than the conventional counterpart. In the high-grade dedifferentiated component, loss of brachyury expression is often observed. Poorly differentiated chordoma is a high-grade, exceedingly rare subtype, typically affecting children and adolescents, marked by brachyury expression and loss of *INI1* (usually associated with deletions in *SMARCB1*).[4]

Chordoma should be differentiated from benign notochordal cell tumours, benign lesions with peculiar radiological features believed to be chordoma precursors. If radiological appearance is typical for benign notochordal cell tumours, biopsy is not recommended unless the lesion changes over time. For chordoma, preoperative core-

needle biopsy is recommended, and the biopsy track needs to be included in the surgical resection. For skull base chordoma, preoperative biopsy is not recommended if the tumour cannot be reached easily or safely, or if there is a high risk of tumour cell seeding [V, C].[87] Initial staging should include primary site imaging, MRI of axial spine and chest-abdominal-pelvic CT.

En-bloc R0 resection is the recommended treatment for primary localised disease when feasible and sequelae are accepted by the patient [IV, B].

For sacral chordoma, surgery should be offered as a first choice in case of lesions arising from levels of sacral spinal nerve 4 and below. Surgery should always be discussed in the context of other alternatives for tumours originating above sacral spinal nerve 3, given the neurological sequelae associated to surgical resection [IV, B].

For skull-base and upper-cervical tract chordoma, resection with negative margins can rarely be done, and microscopically positive margins should be the goal of surgery [V, B].

Adjuvant RT should always be considered for skull-base and cervical-spine chordomas, and for sacral and mobile spine chordoma with R1 resection margins.

If *en-bloc* R0 resection is not feasible, the patient is inoperable or surgical sequelae are unacceptable to the patient, definitive RT alone (without debulking) is an alternative [V, C]. Due to the relative radiation resistance of chordomas, high-doses (at least 74 Gy) are required. Particle therapy allows dose escalation, with improved local control and survival, and should be considered the treatment of choice [II, B].[88,89] Conformal-photon irradiation may be proposed when similar dose uniformity within the target volume and dose to organs at risk can be achieved [V, B]. RT may be given post-operatively or preoperatively with a post-operative boost.

LR has extremely poor survival rates and local control is rarely achievable. In the case of LR, possible salvage treatment can include surgery and/or RT and/or RFA and/or

cryotherapy and/or systemic treatment, balancing morbidity, quality of life and expected disease control.[90]

For oligometastatic disease, surgery, RFA, cryotherapy or stereotactic RT can be considered in selected cases. ChT is inactive and is generally not recommended [V, D]. In conventional chordoma there are preliminary data on the activity of epidermal growth factor receptor inhibitors, and these agents are currently under investigation in clinical studies. Enhancer of zeste homolog 2 (EZH2) inhibitors have shown preliminary activity in *INI1*-negative, poorly differentiated chordoma.

Giant cell tumour of bone

GCTB is a locally aggressive, rarely metastatic tumour, typically affecting the end of long bones, but also arising in the axial skeleton, especially from sacrum or vertebral bodies.[4]

LR in GCTBs occurs in up to 50% of cases, with soft tissue extension being the most relevant prognostic factor. Up to 5% of GCTBs metastasise to the lungs, often maintaining the classical morphology, while transformation to a high-grade malignancy may occur in 1%-3% of patients. Primarily, malignant GCTBs are exceedingly rare. Both conventional and malignant GCTBs are marked by a mutation in the *H3F3A* gene, whose detection can help in differential diagnosis, especially with osteosarcoma enriched in giant cells.[91] Demonstration of nuclear expression of G34W mutant H3F3A protein using immunohistochemistry offers optimal support to diagnosis.

Treatment options include intralesional curettage with or without adjuvant therapy and *en-bloc* excision [IV, A], balancing risk for LR and long-term functional outcome. These have been assessed in a few prospective studies.[92,93] Denosumab, a human monoclonal antibody to receptor activator of nuclear factor kappa B (RANK)-ligand (RANK-L), known to be overexpressed in GCTB, is the standard treatment in unresectable or metastatic GCTBs [III, A].[93-95] Its use in the preoperative setting for GCTBs that are potentially resectable with high morbidity is debated and should be reserved for complex cases [II, C].[96] There is increasing evidence that, if used preoperatively and before curettage, surgery is best carried out after a few months of

treatment, although the most appropriate length of preoperative treatment has not been established yet [V, C].[93,94] The optimal schedule and duration of treatment with denosumab in metastatic or surgically unsalvageable GCTs is also undefined, and the possible long-term side-effects are still largely unknown. Preliminary evidence suggests that denosumab interruption can be followed by disease progression. Potential side-effects need to be monitored [osteonecrosis of the jaw (ONJ) and atypical fractures]. ONJ is an infrequent but severe and treatment-limiting adverse event of denosumab. Denosumab rechallenge in patients with progressive advanced GCTB after the resolution of ONJ can be considered [IV, C].[97] Systemic treatment for metastatic GCTB refractory to denosumab should follow osteosarcoma protocols.

High-grade spindle/undifferentiated pleomorphic sarcomas of bone

Undifferentiated pleomorphic sarcomas of bone are a diagnosis of exclusion as they have no identifiable line of differentiation.[4] Expert pathology review should be performed to exclude other rare or recently described sarcoma types. They typically present in older patients with a lytic lesion in bone and represent <2% of primary bone malignancies.

Their sensitivity to ChT is poorly known. Treatment strategies mimic those of osteosarcoma, with ChT and complete *en-bloc* resection including any soft tissue component [IV, B].[98,99] RT may be considered in inoperable lesions.

Recommendations

Osteosarcoma

- Low-grade central and parosteal osteosarcoma are malignancies with a low metastatic potential that should be treated by surgery alone [IV, B].
- Curative treatment of high-grade osteosarcoma consists of multimodal ChT and surgery [II, A].
- Doxorubicin, cisplatin, HD-MTX and ifosfamide have anti-tumour activity in osteosarcoma [I, A]. In patients >40 years, preferred regimens combine doxorubicin, cisplatin and ifosfamide [III, B].
- High-grade craniofacial osteosarcoma should be treated the same way as high-grade osteosarcoma of other sites [IV, B]. In this location, RT can be proposed

when complete surgery is not feasible and in patients undergoing resection with positive margins [IV, B].

- Heavy-particle RT and IMRT can be considered, particularly for unresectable primary tumours [IV, B].
- Primary metastatic osteosarcoma patients are treated with a curative intent following the same principles of non-metastatic osteosarcomas [III, B].
- The treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases or local recurrence [IV, B].
- RFA and stereotactic RT are potential alternative local treatment options in patients unfit for surgery and for small lung or bone metastases [IV, B].
- Second-line ChT 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].

Ewing sarcoma

- Molecular confirmation is mandatory for the distinction between ES and other RCSs [V, A].
- The interval-compressed VDC/IE regimen is currently the preferred first-line treatment in ES [I, B].
- The use of BuMel could be considered for selected patients with poor response to VIDE induction ChT and/or tumour volume >200 ml [I, B].
- The role of high-dose ChT has not been evaluated with interval compressed VDC/IE. The selection of the most appropriate consolidation should take into account the ChT regimen received and need for RT.
- Complete surgical excision, when feasible, rather than RT as a sole modality is regarded as the best modality of local tumour control [IV, A].
- RT alone should be used if complete surgical excision is not possible and in primary sites where surgery will lead to unacceptable morbidity [IV, A].
- Adjuvant RT (pre- or post-operative) is indicated where the original involved tissues cannot be completely resected with adequate surgical margins, for large-volume tumours or poor histological response [IV, B]. It should be considered in patients with non-sacral pelvic ES regardless of surgical margins, tumour volume or histological response [II, B].

- Treatment of patients with extraskeletal ES follows the same principles as for bone ES [IV, B].
- For cutaneous/subcutaneous ES the number of ChT cycles should be discussed on an individual case basis [V, C].
- For patients with metastases at diagnosis, ChT is similar to that for localised disease [III, B].
- ChT regimens for relapsed disease include alkylating agents in combination with topoisomerase inhibitors, irinotecan with temozolomide, gemcitabine and docetaxel, high-dose ifosfamide or carboplatin with etoposide [III, B].

RCS with EWSR1 non-ETS fusions, CIC-rearranged sarcoma and sarcoma with BCOR alterations

- There is no consensus on whether they should be treated with an ES-like approach or regarded as high-grade STS. Combination regimens including anthracycline and alkylating agents should be favoured when feasible [V, B].
- Registration within clinical trials and prospective registries is recommended.

Chondrosarcoma

- Atypical cartilaginous tumours can be managed by curettage with or without local adjuvant therapy [IV, B].
- High-grade chondrosarcomas and all chondrosarcomas of the pelvis or axial skeleton should be surgically excised with wide margins [IV, B].
- RT can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptoms palliation [IV, B].
- High-dose RT is currently recommended for skull base chondrosarcomas [III, B].
- Localised MCSs are usually treated with neoadjuvant/adjuvant ChT combining anthracycline and alkylating agents [IV, C].
- Neoadjuvant/adjuvant ChT can also be considered for localised DCS [V, C].

Chordoma

- The assessment of brachyury nuclear expression in conventional chordoma is highly recommended to confirm diagnosis [V, B].

- 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 [IV, B].
- R1–R2 surgery plus high-dose RT is the treatment of choice for skull base and upper cervical tract chordoma [V, B].
- Indications for definitive RT include disease for which R0 or R1 resection cannot be achieved according to an expert centre, inoperable patients and neurological impairment not accepted by the patient [III, B].
- For relapse, treatment includes surgery and/or RT and/or systemic therapies [III, B].

Giant cell tumour of bone

- Treatment options for GCTB include *en-bloc* excision [IV, A] and intralesional curettage with or without adjuvant therapy in carefully selected cases [IV, C].
- Denosumab is standard treatment in unresectable or metastatic GCTB [III, A].
- Denosumab use in the preoperative setting for GCTB that are potentially resectable with high morbidity is debated and should be individualised and reserved for complex cases following multidisciplinary discussion [II, C].

High-grade spindle/undifferentiated pleomorphic sarcomas of bone

- Treatment strategies mimic those of osteosarcoma and include ChT and complete *en-bloc* resection [IV, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Follow-up of high-grade BS should include a physical examination, cross sectional imaging and plain radiograph of the primary site (or MRI or CT) together with chest X-ray/CT scan. Strict guidance cannot be provided in the absence of any formal prospective studies, and in the context of differing opinions within the expert panel. A recommended follow-up policy could include evaluation after the completion of ChT, approximately every 2-3 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.

In the case of low-grade BS, 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.

It is important to evaluate the long-term toxic effects of ChT, surgery and RT for cured patients given the incidence of late complications, particularly for patients treated as children, adolescents and young adults, dependent on the protocol and follow-up should be in conjunction with a survivorship clinic when available.

Secondary cancers may arise in survivors of BS, either related to, or independent of, irradiation. Secondary leukaemia, particularly acute myeloid leukaemia, may rarely be observed following ChT, as early as 2-5 years after treatment. Patients with cancer predisposition syndromes require specialised follow-up in conjunction with a genetics clinic.

Recommendations

- Follow-up of high-grade BS could include physical examination, cross sectional imaging and plain radiograph of the primary site together with chest X-ray/CT scan [IV, B].
- A recommended follow-up may foresee intervals of 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 [V, B].
- For low-grade BS, the frequency of follow-up visits may be lower (e.g. 6 months for 2 years and then annually) [V, B].
- Long-term toxic effects of ChT, surgery and RT should be evaluated, and monitoring for late effects should be continued for >10 years after treatment, depending on the protocol used [V, B].

METHODOLOGY

This CPG has been developed by ESMO in partnership with EURACAN, GENTURIS and ERNPaedCan during a virtual consensus meeting that was held on 5th December 2020. The CPG was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). Recommended interventions are intended to correspond to the 'standard' approaches for diagnosis, treatment and survivorship on bone sarcomas, according to current consensus among the European multidisciplinary sarcoma community of experts. This community was represented by the members of the ESMO Sarcoma Faculty and experts appointed by all institutions belonging to the Sarcoma domain of EURACAN-GENTURIS-ERNPaedCan.

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, just covering the main and typical presentations of disease, and are exclusively meant to guide the user reading the text. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S3.[100] Statements without grading were considered justified standard clinical practice by the experts.

ACKNOWLEDGEMENTS

Patient representatives Markus Wartenberg and Gerard van Oortmerssen from Sarcoma Patients EuroNet (SPAEN) who attended the consensus meeting as observers and contributed the valuable perspectives of patients to the consensus process. The authors thank Louise Green and Richard Lutz of the ESMO Guidelines staff for their support throughout the whole consensus process and Jackie Jones of JJ Medical Communications Ltd for her project management support during the virtual consensus meeting. This support was funded by ESMO. Manuscript editing support was provided by Louise Green and Catherine Evans (ESMO Guidelines staff).

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

SJS has received honoraria for participation in advisory board for GlaxoSmithKline (GSK); NA Non-remunerated leadership and advisory roles for Sociedade Portuguesa de Cirurgia; JB has no personal financial disclosure, received research grants (Institutional) from Eli Lilly, Novartis, Roche, Samsung Bioepis, Paxman Coolers Ltd., Sun Pharma and non-remunerated advisory role for Novartis, non-remunerated leadership activities for Immuno-oncology society of India, Indian society of Medical and Paediatric Oncology, Teenage and Young Adult Cancer Foundation and Indian cooperative oncology network; SB has received honoraria for participation in advisory boards for Deciphera, Blueprint Medicines, Lilly, Novartis, Daiichi-Sankyo, Plexxikon, Roche, GSK, invited speaker fees from Pfizer and PharmaMar, institutional research grant from Novartis, institutional research as principal investigator (PI) for Daiichi-Sankyo, Roche, Deciphera, Lilly, Novartis, Blueprint Medicines, Bristol Myers Squibb (BMS), Incyte, non-renumerated activities for Federal Institute for Drugs and Medical Devices (BfArm) and founding member of German Sarcoma Foundation; RB reports non-renumerated activities as PI for IRCSS Galeazzi Orthopedic Institute and IRE-ISG Regina Elena Institute, participation at the Clinical Experience Exchange Meeting, III IDBN National Congress 2019, Italian Association of Medical Oncology (AIOM), IRE-ISG Regina Elena Institute and Lazio Association of Orthopaedic Hospital Traumatologists (ALOTO); SBi has received honoraria for participation in advisory boards from Bayer Healthcare, Boehringer Ingelheim, Clingen, Hofmann La Roche, Ipsen, Eli Lilly and Sensorion, non-remunerated activities for Bayer and membership of the German Pediatric Oncology Society and European Musculoskeletal Oncology Society; JYB received research support from Merck Sharp & Dohme (MSD), Roche, GSK, Novartis, Bayer, PharmaMar outside the present work; SBon has received honoraria for advisory board from Nanobiotix and as invited speaker for PharmaMar, trial research grant from the Institut National du Cancer (INCa); IB has received honoraria for participation in advisory boards for Roche, Lilly, Sanofi, Pierre Fabre,

Ipsen, and as invited speaker for Amgen, BMS, Novartis, Leo Pharma, AstraZeneca and Genesis, member of Board of Directors for Hellenic Society of Medical Oncology, Hellenic Society of Sarcomas and Rare Tumors, Hellenic Oncology Research Group (HORG), PI trial research support from Novartis, BMS, Regeneron, MSD, Lilly and Roche; JVMGB receives royalties from UpToDate and Wolters Kluwer, and direct research funding from TRACON pharmaceuticals; KB has received honoraria for expert testimony and advisory boards for Bayer, invited speaker fees and research grant from Eli Lilly, PI for Deciphera and Novartis; TB has received honoraria for participation in advisory boards for Bayer and Eli Lilly, invited speaker fees from PharmaMar and Novartis; EDÁ has received honoraria for participation in advisory board for Bayer, invited speaker for Lilly, PharmaMar and Roche, Institutional research support from Pfizer, Roche and AstraZeneca; APDT has received honoraria for participation in advisory boards for Bayer and Roche, invited speaker for PharmaMar and Novartis; XGDM has received honoraria for participation in advisory boards for Ipsen, EusaPharma, BMS, Pfizer, Roche and PharmaMar, invited speaker for Lilly, Astellas Pharma, Eisai and Pfizer and Institutional research grant from AstraZeneca; ME has received honoraria for participation in advisory boards for Clinigen and Bayer, consulting fees from Blueprint Medicines, institutional research funding from Novartis; AF has received honoraria for participation in advisory board for Novartis and invited speaker fees for MSD and Amgen; VF has received honoraria for participation in advisory boards and speaker fees for BMS, Novartis and MSD and speaker fees from Pierre Fabre; NG has received honoraria as invited speaker for Eisai and reports membership of the European Society for Paediatric Oncology (SIOPE), ACCELERATE, Societe Francaise de lutte contre les cancers et leucemies de l'enfant et de l'adolescent (SFCE) and Groupe Onco- hématologie Adolescents et Jeunes Adultes (GO-AJA); SG has reported institutional research for Blueprint Medicines and member of American Society of Clinical Oncology (ASCO) and AIOM; HG has reported PI research for Daiichi, Deciphera and Novartis, Co-ordinating PI for Boehringer Ingelheim and AmMax Bio; FG has received honoraria for participation in advisory board for Amgen and expert testimony for Deciphera, stock ownership for Atlanthera, licencing fees from Zimmer, non-renumerated activities for 3D-Side and INCa DGOS funding and member of the board of NetSarc the French clinical reference network for soft tissue and visceral sarcomas; GG has received honoraria for participation in

advisory boards for Lilly, Eisai, Merck, Bayer and GSK, invited speaker fees from PharmaMar and Novartis, Institutional grants from PharmaMar,Bayer and Novartis; AG has received honoraria for participation in advisory boards for Novartis, Pfizer, Bayer, Lilly, PharmaMar, SpringWorks and Nanobiotix, invited speaker for Lilly, PharmaMar and research grant from PharmaMar; RH has received Honoraria from GSK; ABH is a member of Board of Directors for EIT health UK and Ireland, received or currently receives direct research funding as a PI from Roche, performs work in clinical trials or contracted research for the Institution and Clinical Director of the Oncology and Haematology Directorate, Oxford Cancer Centre; SHN reports institutional research role as deputy PI for Eisai, non-remunerated activity for Harmonization International Bones Sarcoma Consortium (HIBISCus), membership of SIOPE, German, Swiss, Austrian Society of Paediatric Oncology and Hematology (GPOH) and German Society of Pediatrics and Adolescent Medicine (DGKJ); NH has received honoraria as expert testimony and invited speaker from PharmaMar, performs work in clinical trials or contracted research for which his/her institution received financial support from PharmaMar, Lilly, Adaptimmune Therapeutics, AROG Pharmaceuticals, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GSK, Novartis, Blueprint Medicines, Nektar Therapeutics, Forma, Amgen and Daiichi-Sankyo, non-remunerated leadership roles for Grupo Español de Investigación en Sarcomas (GEIS) and SELNET, and has non-remunerated membership or affiliation with ESMO, Sociedad Española de Oncología Médica (SEOM), ASCO, Connective Tissue Oncology Society (CTOS) and European Organisation for Research and Treatment of Cancer (EORTC); PH has received honoraria for participation in advisory boards for Pfizer, Roche and GSK, invited speaker fees from PharmaMar and Lilly, clinical expert fees from Boehringer Ingelheim, institutional research funding for clinical trials from Siemens, Novartis, Blueprint medicines and meeting sponsorship from PEKKIP Oncology, non-remunerated activities for the German Sarcoma Foundation (DSS), German Interdisciplinary Sarcoma Group (GISG) and Interdisciplinary Working Party on Sarcomas (IAWS) of the German Cancer Society (DKG), advisory role for the German Cancer Aid (DKH) Committee on Health Technology Assessment and Sarcoma Patients EuroNet (SPAEN); HJ has received honoraria for participation in advisory boards for Orion Pharma, Neutron Therapeutics and Maud Kuistila Memorial Foundation, had full time or part time employment at Orion Pharma, until Aug. 31, 2020, stocks in Orion Pharma and

Sartar Therapeutics; RLJ has received honoraria for expert testimony consultancy for Adaptimmune, Bayer, Boehringer Ingelheim, Blueprint Medicines, Clinigen, Eisai, Epizyme, Daiichi, Deciphera, Immunedesign, Lilly, SpringWorks, Tracon, UpToDate, PharmaMar , advisory board for Athenex, Institutional research grant from MSD; CJ has received travel grants from Ipsen and PharmaMar; LK has received honoraria for participation in advisory boards for Bayer, Novartis and Agios; BK has received honoraria for participation in advisory boards for Bayer, Blueprint Medicines, Boehringer Ingelheim, SpringWorks, GSK and PharmaMar, Institutional research support from PharmaMar and SpringWorks, member of EORTC and Chair of the EORTC soft tissue and bone sarcoma group (STBSG); AK has received honoraria for participation in advisory boards for Daiichi-Sankyo and Otsuka and invited speaker fees from Novartis, Taiho and Eisai; KK has received honoraria for participation in advisory board for Bayer and expert testimony for Eli Lilly and Roche; ALC has received honoraria for participation in advisory boards for Deciphera and Lilly, invited speaker fees from PharmaMar and Bayer; EL received honoraria from SpringWorks Therapeutics for scientific advisory board participation. Member of the European Reference Network GENTURIS; AL has received Institutional research grants from Johnson & Johnson, Alphamed, Medacta and Implantec, non-remunerated activities for European Musculoskeletal Society (EMSOS), Austrian Society of Orthopaedic Surgeons (OGO) and membership of CTOS; ALP has received honoraria as invited speaker for PharmaMar, institutional research funding from the Spanish Health Ministry, reported non-renumerated activities as PI for PharmaMar, Cebiotex, Deciphera, Lilly, GSK, Daiichi, Epizyme, Advenchen Laboratories, Novartis, Karyopharm, Blueprint medicines, GEIS and other activity for EORTC; JMB has received honoraria for expert testimony for Lilly, PharmaMar, Eisai, Bayer, invited speaker fee from PharmaMar, Institutional research for PharmaMar, Eisai, Novartis, Immix Biopharma, Lixte, Karyopharm, Bayer, Celgene, Pfizer, BMS, Blueprint Medicines, Deciphera, Nektar Therapeutics, Forma, Amgen, Daiichi-Sankyo, Lilly, AROG Pharmaceutcials, Adaptimmune and GSK; OM has received honoraria for participation in advisory boards for MSD, Megapharm, AstraZeneca, Takeda and Progenetics, invited speaker fees from MSD and Roche; CM has performed non-remunerated activities for International Cancer Imaging Society and EORTC STBSG; OMi has received honoraria for participation in advisory boards for Bayer, Blueprint Medicines, MSD, Pfizer, invited speaker fees

from BMS, Eli-Lilly, Ipsen, Roche and Servier, institutional research for Blueprint Medicines, Bayer, Epizyme and Eli-Lilly; BM has received honoraria from Clinigen as invited speaker; EP has received honoraria for participation in advisory boards for SynOx, Daiichi-Sankyo and Deciphera Pharmaceuticals and invited speaker fees from Peer View Educational; MAP has received honoraria for participation in advisory boards for Roche, invited speaker fees from Eli- Lilly, Pfizer, and Novartis, expert testimony from Blueprints Medicine and institutional research grant from Novartis; SPN has received honoraria for participation in advisory board for Immunocore; PR has received honoraria for participation in advisory boards for Bayer, Clinigen, Roche, MSD, Deciphera, Mundibiopharma, PharmaMar, Blueprint Medicines, invited speaker fees from Lilly, PharmaMar, institutional research for PharmaMar, Karyopharm, SpringWorks, AROG Pharmaceuticals , Blueprint, Deciphera, Amgen, Astellas, Epizyme, Lilly, MSD, Pfizer, Novartis and Philogen, membership of German Sarcoma Foundation; PRu has received honoraria for participation in advisory boards for MSD, BMS, Pierre Fabre, Merck, Sanofi, Blueprint Medicines, invited speaker fees from MSD, BMS, Pierre Fabre, Merck, Sanofi, Novartis, institutional research funding from Pfizer, BMS and non-remunerated activities for the Polish Society of Surgical Oncology and ASCO; MS has received honoraria for travel grant from PharmaMar and writing engagement for Lilly; SS has reported a research grant from Johnson & Johnson and research funding from Roche Austria; PS has received honoraria for participation in advisory boards for Deciphera, Blueprint Medicines, Boehringer Ingelheim, Ellipses Pharma, Transgene, Exelixis, Medscape, Guided Clarity, Ysios, Modus Outcomes, Studiecentrum voor Kernenergie, Curio Science, institutional honoraria for advisory boards for Blueprint Medicines, Ellipses Pharma, Intellisphere, expert testimony for Advanced Medical/Teladoc Health, institutional research funding from CoBioRes NV, Eisai, G1 Therapeutics, Novartis and PharmaMar; SSl Chair of Centre for Personalised Cancer Treatment and Route Personalised Medicine, Dutch Science Agenda, Member of supervisory board for SkylineDX and Scientific advisory committee Pan-Cancer T BV; KSH reports non-renumerated activity for CTOS as President 2020 and membership of the Scandinavian Sarcoma Group; MAJvdS has performed work in clinical trials or contracted research for which the institution received financial support from Daiichi-Sankyo, Implantcast and Carbofix; WTAvdG has received institutional honoraria for participation in advisory boards for Bayer and

GSK, institutional research grants from Novartis and Lilly and consultancy work for SpringWorks; WJvH has received institutional honoraria for participation in advisory board for Belpharma, invited speaker fees from Amgen, expert testimony for Sanofi and MSD, personal travel grant from Novartis and institutional research grant from BMS; TF Reported institutional research funding from the Foundation ARC and Ligue Régionale contre le Cancer, leadership role for ERN GENTURIS; PGC has received honoraria for participation in advisory board for Bayer, institutional research funding from Amgen Dompé, Advenchen, Bayer, Blueprint, Deciphera, Eli Lilly, Epizyme, Daiichi, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks, AROG Pharmaceuticals and Eisai, non-remunerated activities for the Italian Sarcoma Group, European School of Oncology, Federation of Italian Cooperative Groups and Rare Cancers Europe; SSta has received honoraria for participation in advisory boards for Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, Novartis, invited speaker fees from GSK and PharmaMar, expert testimony fee from Bavarian Nordic and Epizyme, institutional research funding from Amgen Dompé, Advenchen, Bayer, Blueprint Medicines, Deciphera, Eli Lilly, Epizyme, Daiichi, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks and Hutchinson MediPharma International Inc., non-remunerated activities for CTOS, Chordoma Foundation, Epithelioid Haemagioendothelioma Foundation, Desmoid Foundation, EORTC STBSG and Italian Sarcoma Group Onlus; AMF, AB, SBo, BB, AD, FF, AFer, PJ, DAK, FLG, ABM, MM, CMo, RP, AAS, CS, DS, AT, MU and RL have declared no conflicts of interests.

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Figure 1. General diagnostic strategy for bone sarcomas

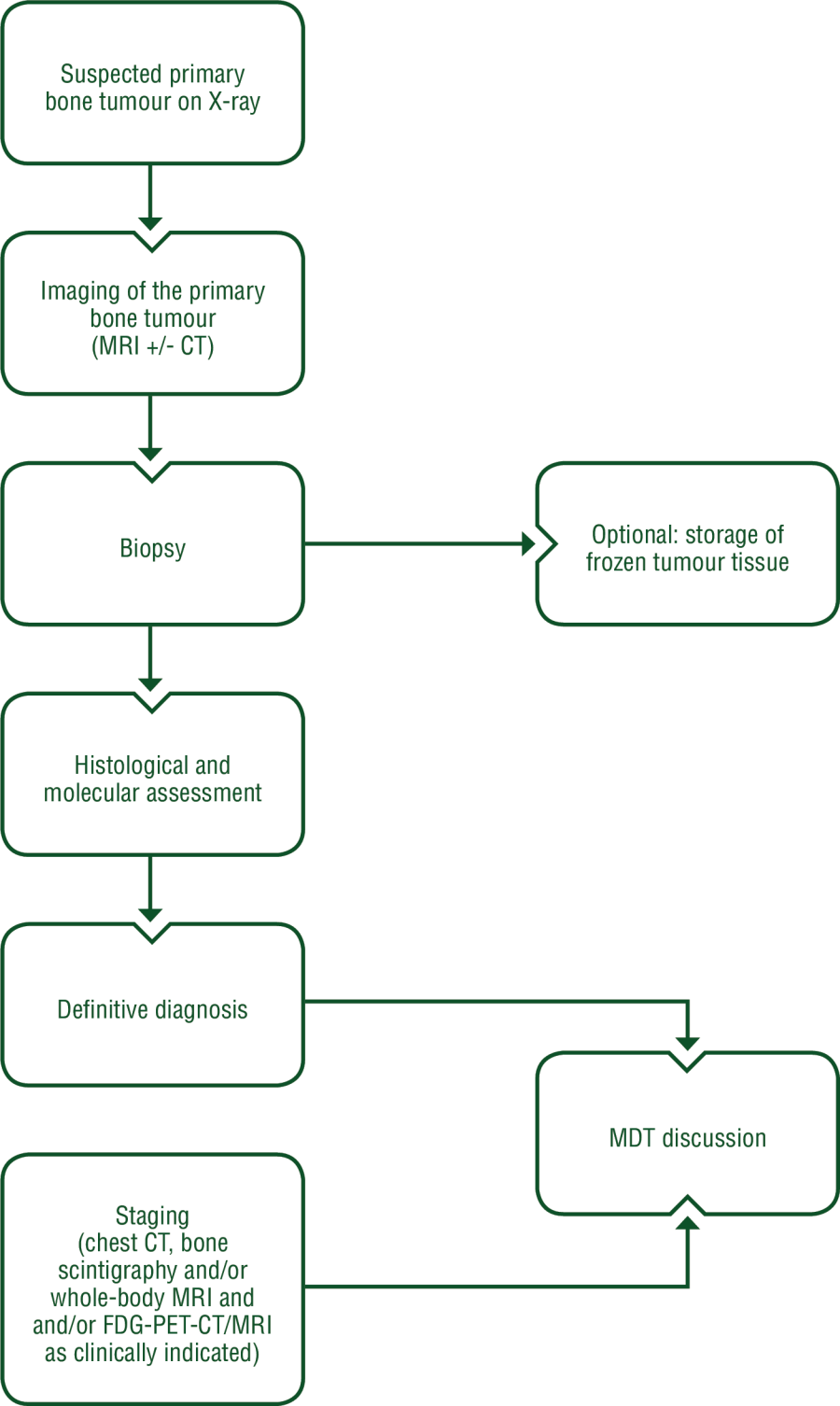
CT, computed tomography; FDG-PET-CT, [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography-computed tomography; MDT, multidisciplinary team; MRI, magnetic resonance imaging.

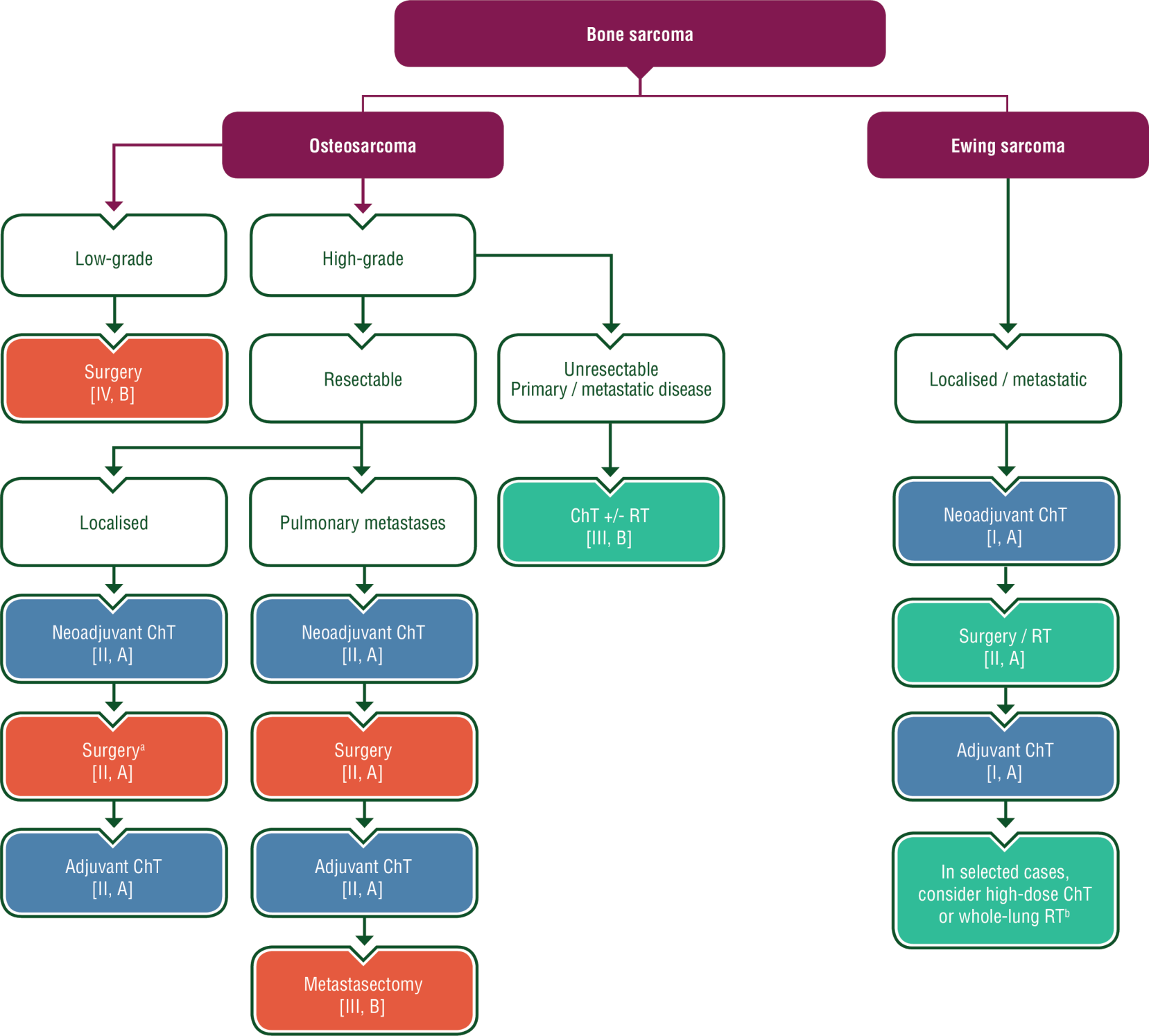
Figure 2. General therapeutic strategy for osteosarcoma and Ewing sarcoma

Purple; general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

ChT, chemotherapy; RT, radiotherapy.

[a] Surgery can be offered upfront, followed by adjuvant ChT.
[b] See section on Ewing sarcoma under Treatment section.


Suspected primary bone tumour on X-ray
Imaging of the primary bone tumour (MRI +/- CT)
Biopsy
Optional: storage of frozen tumour tissue
Histological and molecular assessment
Definitive diagnosis
MDT discussion
Staging (chest CT, bone scintigraphy and/or whole-body MRI and and/or FDG-PET-CT/MRI as clinically indicated)


Bone sarcoma
Osteosarcoma
Ewing sarcoma
Low-grade
High-grade
Surgery
[IV, B]
Resectable
Unresectable
Primary / metastatic disease
Localised / metastatic
Localised
Pulmonary metastases
ChT +/- RT
[III, B]
Neoadjuvant ChT
[I, A]
Neoadjuvant ChT
[II, A]
Neoadjuvant ChT
[II, A]
Surgery / RT
[II, A]
Surgery[a]
[II, A]
Surgery
[II, A]
Adjuvant ChT
[I, A]
Adjuvant ChT
[II, A]
Adjuvant ChT
[II, A]
In selected cases,
consider high-dose ChT
or whole-lung RT[b]
Metastasectomy
[III, B]