clinical recommendations

Osteosarcoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

S. Bielack¹, D. Carre³ & P. G. Casali²
On behalf of the ESMO Guidelines Working Group*

¹Cooperative Osteosarcoma Study Group, Department of Pediatric Oncology and Hematology, Olgahospital, Stuttgart, Germany; ²Department of Cancer Medicine, Istituto nazionale dei Tumori, Milan, Italy

incidence

Osteosarcoma is the most frequent primary cancer of bone (incidence: 0.2–3/100 000/year). The incidence is higher in adolescents (0.8–11/100 000/year at age 15–19), where it accounts for >10% of all solid cancers. The male:female ratio is ~1.4. It usually arises in the metaphysis of a long extremity bone, most commonly around the knee. Involvement of the axial skeleton or craniofacial bones is observed primarily in adults.

diagnosis

Typical signs and symptoms are: history of pain, followed by localized swelling and limitations of joint movement and typical findings on X-rays. Definitive diagnosis requires histological examination of tumor material, which is generally obtained by open biopsy. Patients with findings suggestive of osteosarcoma should be sent to a reference center before biopsy [IV, C], as inappropriate techniques can irrevocably compromise chances for limb salvage or even cure.

By definition, the malignant cell population must produce osteoid for a tumor to be classified as osteosarcoma. Conventional osteosarcoma, a high-grade malignancy, accounts for 80–90% of all osteosarcomas. Its most frequent subtypes are osteoblastic, chondroblastic, and fibroblastic. Other high-grade types are teleangectasic, small cell osteosarcoma, and high-grade surface osteosarcoma. Low-grade central osteosarcoma and paraosteal osteosarcoma are low-grade malignancies, while periosteal osteosarcoma is an intermediate-grade chondroblastic osteosarcoma. Secondary osteosarcoma is a generally high-grade malignancy occurring in bone affected by pre-existing abnormalities, mainly Paget disease and radiation-therapy-induced changes. Confirmation of diagnosis by a pathologist with particular expertise in bone tumors is recommended [IV, C].

staging and risk assessment

The primary tumor must be evaluated by plain radiographs in two planes, which are mainly helpful to describe osseous changes, complemented by cross-sectional imaging, ideally magnetic resonance imaging (MRI), both of which should be performed before biopsy. MRI is considered the most useful tool to evaluate an osteosarcoma’s intramedullary and soft tissue extension and its relation to vessels and nerves. The region assessed by MRI should include the whole involved bone as well as the neighboring joints, so as to not miss skip lesions (intramedullary tumor foci without direct contact with the primary lesion).

Systemic staging must focus on the lungs and the skeleton, in which the majority of metastases arise, and should include chest X-rays, a CT scan of the thorax (preferably using a spiral technique performed with ≤5 mm collimation and obtained during a single breathhold) and a radionuclide bone scan, complemented by X-rays and/or MRI scans of affected areas. Appropriate imaging must be repeated before surgery of the primary tumor or of known metastases.

For many years, the Musculoskeletal Tumor Society staging system, which distinguishes between two grades of malignancy (low versus high) and intra- and extracompartmental extension, has been the one most widely used. There, the vast majority of osteosarcomas are classified as stage IIB. The current 6th edition of the UICC-TNM is an advancement of this system.

There are no specific laboratory tests for osteosarcoma, alkaline phosphatase (AP) and lactate dehydrogenase (LDH) are non-specific. Elevated levels correlate with adverse outcomes.

A variety of laboratory tests is required before interdisciplinary treatment is started. These are directed towards assessing organ function and general health. Recommended tests include a complete blood count and differential, blood group typing, a coagulation profile, tests for serum electrolytes including magnesium and phosphate, renal and liver function tests as well as hepatitis and HIV testing. Since chemotherapy treatment for osteosarcoma can result in cardiac and auditory dysfunction, patients should also have
baseline assessment by echocardiogram or radionuclide ventriculography as well as an audiogram. Sperm storage is recommended for male patients of reproductive age.

Adverse prognostic factors include proximal extremity or axial tumor site, large tumor volume, elevated serum AP or LDH, and foremost detectable primary metastases and poor histological response to preoperative chemotherapy [III, B].

treatment plan

localized tumors

Patients with osteosarcoma should be treated in reference centers able to provide access to the full spectrum of care or shared with such centers within reference networks [IV, C]. There, therapy is usually given within the framework of prospective, often collaborative, clinical studies, or established treatment protocols.

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

The goal of surgery is to safely remove the tumor and yet preserve as much function as possible. Most patients should be considered candidates for limb salvage. Surgical margins at least wide by Enneking’s definition, implying complete removal of the tumor (including the biopsy tract) surrounded by an unviolated cuff of normal tissue, must be attempted, as narrower margins are associated with an increased risk of local recurrence [III, B]. Radiotherapy has a limited role and should be reserved for inoperable situations [IV, C].

Currently, doxorubicin, cisplatin, high-dose methotrexate with leucovorin rescue and ifosfamide are considered the most active agents against osteosarcoma [Ib, A], but the ideal combination remains to be defined. Effective regimens employ several of the aforementioned drugs, usually over a period of 6–12 months. The use of growth factors either to allow dose escalation to maximal doses of all agents [III, C] or an increase in dose intensity [Ib, A] does not appear to improve survival expectations further. Addition of the immune modulator muramyl tripeptide (MTP) to postoperative chemotherapy correlated with a statistically significant advantage in overall survival and a non-significant trend in event-free survival in a recently published randomized trial. Following its approval by EMEA, the addition of MTP to the standard regimens for localized osteosarcoma, outside clinical trials, is therefore an option for a shared decision making with the patient in conditions of uncertainty.

Most current protocols include a period of preoperative chemotherapy, although this has not been proved to add survival benefit over postoperative chemotherapy alone [Ib, B]. The extent of histological response to preoperative chemotherapy, however, offers important prognostic information [Ib, A]. Current prospective trials evaluate whether altering postoperative chemotherapy in poor responders improves outcomes. As yet, the benefit of such an approach remains to be proved.

The multimodal treatment principles detailed above were generated in children, adolescents and young adults with high-grade central osteosarcoma, but also relate to adults at least up to the age of 60 [III, B] and to rarer variants of high-grade osteosarcoma, such as high-grade surface, secondary [III, B]. Low-grade central and parosteal osteosarcoma are variants with lower malignant potential which are treated by surgery only [III, B], and the exact role of chemotherapy has not been defined for periosteal osteosarcoma, while craniofacial osteosarcoma may display a low or a high malignancy grade and is generally approached accordingly [III, B].

metastatic disease and recurrent disease

Curative treatment for primary metastatic osteosarcoma is similar or even identical to that of localized disease, with the mandatory addition of surgical removal of all known metastatic deposits [III, B], usually by exploratory thoracotomy including palpation of the lung. Approximately 30% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission become long-term survivors.

Treatment for recurrent osteosarcoma is primarily surgical. Prognosis is poor, with long-term post-relapse survival in <20%. Complete removal of all metastases must be attempted [III, B], as the disease is otherwise almost universally fatal, while more than a third of patients with a second surgical remission survive for >5 years. Even patients with multiple recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted [III, B].

Overall, CT scans tend to underestimate the number of pulmonary metastases and may also fail to detect contralateral involvement in patients with seemingly unilateral pulmonary metastases [III, B]. Bilateral exploration by open thoracotomy, including palpation of both lungs, is therefore recommended [IV, C].

The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery and there is no accepted standard regimen. Choice may take into account the prior free interval, and often includes ifosfamide ± etoposide ± carboplatin, etc. In the two largest reported series, the use of second-line chemotherapy correlated with limited prolongation of survival in patients with inoperable metastatic recurrences, while a positive correlation in operable disease was observed in only one of the two. Radiotherapy to inoperable sites can be indicated for palliation and may be associated with limited prolongation of survival.

follow-up

Follow-up intervals recommended in current multinational trials are every 6 weeks to 3 months in years 1 and 2 after diagnosis, every 2–4 months in years 3 and 4, every 6 months in years 5–10 and every 6–12 months thereafter. Each visit should include a history and physical examination and a chest X-ray [IV, C]. X-rays of the primary tumor site are recommended every 4 months until the end of year 4 [IV, C]. Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumor surveillance.

Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory and reproductive function, orthopedic problems and other late
effects including secondary malignancies, and appropriate investigations should be included during regular follow-up [IV, C].

**note**

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

**literature**