Ewing's sarcoma of the bone: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Ewing tumors of bone are the second most common primary malignant bone cancer in children and adolescents, but are also seen in adults. The median age at diagnosis is 15 years and there is a male predilection of 1.5/1. Ewing’s sarcoma (ES)/peripheral neuroectodermal tumors (PNETs) are diagnosed in white Caucasians at an incidence of 3 per million population per year, but are very uncommon in African and Asian populations.

diagnosis

The first symptom is usually pain—often erroneously attributed to trauma. Plain radiographs in two planes, complemented by computed tomography (CT) and/or magnetic resonance imaging (MRI) are indicative of a malignant tumor. Patients with suggestive findings should be referred to a center with particular experience in bone sarcoma before performing a biopsy. The definitive diagnosis is made by biopsy, providing sufficient material for conventional histology and molecular biology (fresh, unfixated material). ES/PNETs are small blue round-cell tumors, PAS- and CD99 (MIC2)-positive. Confirmation of diagnosis by a pathologist with particular expertise in bone tumors is recommended [IV, C]. All ES/PNETs are high-grade tumors. While the degree of neurological differentiation used to be applied to differentiate classical ES from PNET, newer molecular biology studies have shown that all ES/PNETs share a common gene rearrangement involving the EWS gene on chromosome 22. In most cases, a reciprocal translocation t(11;22)(q24;q12) is found, but t(21;22)(q22;q12) and others may also be found.

staging and risk assessment

Before biopsy, the description of the local extent of the tumor requires radiographic and CT/MRI of the entire involved bone, including adjacent joints and soft tissues. For planning of local therapy, the precise involvement of bone, bone marrow and soft tissues including the relationship to critical structures like nerves or vessels, must be specified. A chest CT scan is required to rule out lung or pleural metastases. The assessment for bone and bone marrow metastases is to include ⁹⁹mTc bone scintigraphy, to detect osseous metastases, and light microscopic examination of bone marrow aspirates and biopsies taken at sites distant from the primary tumor. Positron emission tomography (PET) scanning for bone metastases and PCR techniques to investigate for bone marrow metastases are sensitive imaging methods currently under evaluation. Additional appropriate imaging studies and biopsies should be taken from suspicious sites, as the exact staging of the disease has impact on treatment and outcome [III, B].

About 20% of the patients have ES/PNETs of the pelvic bones, 50% show extremity tumors. ES/PNETs may involve any bone and (less commonly) soft tissues. Twenty to twenty-five percent of the patients are diagnosed with metastatic disease (10% lung, 10% bones, 5% combinations or others).

With surgery or radiotherapy alone, 5-year survival is <10%. With treatment in current multimodality trials including chemotherapy, survival approximates to 60–70% in localized and 20–30% in metastatic disease. Bone metastases confer a poorer outcome than lung/pleura metastases (<20% versus 20–40% 5-year survival) [IIa, B]. Other known prognostic factors are tumor size or volume, serum lactate dehydrogenase (LDH) levels, axial localization or older age (>15 years). Under treatment, poor histological response to preoperative chemotherapy, and incomplete or no surgery for local therapy are further adverse prognostic factors [IIa, B].

treatment plan

As ES/PNETs are rare cancers, and their management is complex, the accepted standard is treatment in specialized centers and in the framework of co-operative trials.

localized disease

Multimodal approaches within clinical trials, employing combination chemotherapy and surgery and/or radiotherapy, have raised 5-year survival rates from <10% to >60%. All
follow-up

Most relapses occur in the first 3 years of follow-up; late relapses have rarely been observed even after 15 years or longer. Beside the detection of relapse, long-term sequelae of treatment are the main concern in long-term follow-up. Impaired renal function may be observed early in follow-up, but cardiac or pulmonary damage may become apparent later. Secondary cancers may arise in irradiated sites. Secondary leukemia, particularly acute myeloid leukemia, may rarely be observed independent of previous irradiation as early as 2–5 years after treatment [III, B]. Follow-up intervals should be 2–3 months during the first 3 years, 6 months until 5 years and at least once yearly thereafter. Follow-up is more specifically detailed in concurrent clinical trial manuals, e.g. EURO-E.W.I.N.G, 99.

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