Ministry of Higher Education
and Scientific Research
University of Diyala
College of Medicine

Review article in:

Ewing sarcoma

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

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2021/2022

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Abstract:

It is the second most frequent bone tumour of childhood and adolescence that can also arise in soft tissue. Ewing sarcoma is a highly aggressive cancer, with a survival of 70–80% for patients with standard-risk and localized disease and ~30% for those with metastatic disease. Treatment comprises local surgery, radiotherapy and polychemotherapy, which are associated with acute and chronic adverse effects that may compromise quality of life in survivors. Histologically, Ewing sarcomas are composed of small round cells expressing high levels of CD99. Genetically, they are characterized by balanced chromosomal translocations in which a member of the FET gene family is fused with an ETS transcription factor, with the most common fusion being EWSR1–FLI1 (85% of cases). Ewing sarcoma breakpoint region 1 protein (EWSR1)–Friend leukaemia integration 1 transcription factor (FLI1) is a tumour-specific chimeric transcription factor (EWSR1–FLI1) with neomorphic effects that massively rewires the transcriptome. Emerging studies on the molecular mechanisms of Ewing sarcoma hold promise for improvements in early detection, disease monitoring, lower treatment-related toxicity, overall survival and quality of life.

Introduction:

Ewing sarcoma is a malignant bone tumour (occurring predominantly in the pelvis, femur, tibia and ribs) or soft-tissue tumour (occurring predominantly in the thoracic wall, gluteal muscle, pleural cavities and cervical muscles) that mainly affects children, adolescents and young adults.

It is the second most frequent bone tumour of childhood and adolescence that can also arise in soft tissue. Ewing sarcoma is a highly aggressive cancer, with a survival of 70–80% for patients with standard-risk and localized disease and ~30% for those with metastatic disease. Treatment comprises local surgery, radiotherapy and polychemotherapy, which are associated with acute and chronic adverse effects that may compromise quality of life in survivors. Histologically, Ewing sarcomas are composed of small round cells expressing high levels of CD99. Genetically, they are characterized by balanced chromosomal translocations in which a member of the FET gene family is fused with an ETS transcription factor, with the most common fusion being EWSR1–FLI1 (85% of cases). Ewing sarcoma breakpoint region 1 protein (EWSR1)–Friend leukaemia integration 1 transcription factor (FLI1) is a tumour-specific chimeric transcription factor (EWSR1–FLI1) with neomorphic effects that massively rewires the transcriptome.

Etiology:

Ewing sarcomas are thought to derive from cells of the neural crest, possibly mesenchymal stem cells, via a pathway that might include postganglionic cholinergic neurons. However, the exact cell of origin of the Ewing sarcomas is unknown.

Translocation of EWSR1 (Ewing sarcoma breakpoint region 1) with an ETS (E26 transformation-specific) transcription factor gene occurs in more than 95% of Ewing sarcomas. (Some argue that without a translocation, the tumor does not belong to Ewing sarcoma). The most common translocation seen in about 85% of all Ewing tumor is the t(11;22) translocation. This translocation joins the Ewing sarcoma gene EWS on chromosome 22 to a gene of the ETS family, friend leukemia insertion (FLI1), on chromosome 11 (i.e, t[11;22]).
No data regarding the cause of the chromosomal translocation are available. Downstream targets and protein

partners responsible for EWS-FLI1 transformation of cells are numerous; however, any one of these downstream pathways is neither adequate to create a Ewing sarcoma nor is its inhibition adequate to lead to Ewing sarcoma cell death.
So the cause of tumors in Ewing sarcoma is unknown. Cases are thought to be sporadic, although it has been found that relatives of patients with Ewing sarcoma have an increased incidence of neuroectodermal and stomach malignancies. In rare cases, Ewing sarcomas have been reported as a second malignancy, being found after a patient has been treated for another neoplasm. [1]

Pathogenesis:

The EWS-FLI1 fusion transcript encodes a 68-kd protein with 2 primary domains. The EWS domain is a potent transcriptional activator, whereas the FLI1 domain contains a highly conserved ETS DNA-binding domain. The EWS-FLI1 fusion protein thus acts as an aberrant transcription factor and has been found to transform mouse fibroblasts if both the EWS and the FLI1 functional domains are intact. The protein has consequently been implicated in the pathogenesis of Ewing sarcoma.
EWS-FLI1 remains the singular most direct target to eliminating Ewing sarcoma tumor cells. A small molecule that binds to EWS-FLI1, YK-4-279, blocks its interaction with a key partner protein, RNA Helicase A (RHA), leading to apoptotic cell death.[2]

Epidemiology:

The overall annual incidence of Ewing sarcoma is approximately 1 case per 1 million per year in the United States. The incidence from birth to age 20 years is 2.9 cases per million population. Approximately half of all patients are aged 10-20 years at the time of first diagnosis, making this the second most common primarily malignant bone tumor in children and adolescents. Cases have been reported from birth through 80 years, although very infrequently.

The incidence of these tumors in Whites is at least 9 times higher than it is in Blacks. This finding contrasts with that observed in osteosarcoma, which has a relatively equal racial distribution. African countries report similar incidences, with a paucity of Ewing sarcoma.
The incidence of Ewing sarcoma in females is 2.6 cases per million population, compared with 3.3 cases per million population in males.
The incidence of these tumors peaks in the late teenage years. Overall, 27% of cases occur in the first decade of life, 64% of cases occur in the second decade, and 9% of cases occur in the third decade.

Clinical presentation

Patient History:

Patients with Ewing sarcoma can present with localized disease or clinically overt metastases. The majority of patients present with a history of locoregional pain, which may be intermittent, sometimes nocturnal and worsens over time. Pain is often mistaken for 'bone growth' or injuries resulting from sports or daily life activities (such as tendinitis, muscle pain, muscle injuries or osteomyelitis). In a substantial number of patients, pain is followed by a palpable soft-tissue mass, which may be indiscernible for a long time in patients with pelvic, chest wall or femoral tumours. Pain without an adequate event to explain the symptoms and pain lasting>1 month should prompt further investigation.[3]

Back pain may indicate a paraspinal, retroperitoneal, or deep pelvic tumor.

Systemic symptoms of fever and weight loss: As initially nonspecific 'B symptoms' (such as moderate fever, night sweats and loss of appetite) are mostly absent except in advanced stages or metastatic disease, diagnosis of Ewing sarcoma can be delayed; the median time to diagnosis is 3–9 months [4]

As Ewing sarcoma usually arises in the diaphysis of virtually any bone or in soft tissues, symptoms vary depending on the affected site. Additionally, tumour sites vary with age; an analysis focusing on children and AYA patients with bone Ewing sarcoma[4] showed that older AYA patients (20–24 years of age) had more pelvic and axial primary tumours, larger tumours and worse outcomes than children (0–9 years of age) [5]

Ewing sarcomas in older patients tend to occur more frequently in soft tissues [6]

Physical examination:

Because patients can present with disease close to bone, tumors can result in neuropathic pain. Therefore, a comprehensive neurologic examination to evaluate asymmetrical weakness, numbness, or pain is critical. Patients with lesions of the long bones can present with a pathologic fracture

Clinically significant bone marrow metastases can result in petechiae or purpura due to thrombocytopenia, while patients with lung metastases can present with asymmetrical breath sounds, pleural signs, or rales.

Ddx[7]:

Diagnostic Considerations:

Because Ewing sarcomas are rare, they are often not considered in a differential diagnosis until biopsy reveals a neoplasm known as a small round blue cell tumor. Malignancy is usually in the differential diagnosis before biopsy. For this reason, consultation with a pediatric oncologist is critical.

Ewing sarcoma should be considered in the differential diagnosis if a patient aged 10-30 years has a soft tissue or bony mass that causes the physician to consider the presence of a neoplasm.

Ewing sarcoma can occur in virtually any location. Careful examination of painful sites with inspection and palpation is critical.

Differential Diagnoses:

Nonrhabdomyosarcoma Soft Tissue Sarcomas
Pediatric Neuroblastoma
Pediatric Non-Hodgkin Lymphoma
Pediatric Osteomyelitis
Pediatric Osteosarcoma
Pediatric Rhabdomyosarcoma
Rickets

Investigations:

Laborotary tests:

Currently, no blood or urine markers are available for the routine diagnostics of Ewing sarcoma. Nonspecific markers of bone involvement such as elevated alkaline phosphatase may be detected. High lactate dehydrogenase (LDH) is usually correlated with tumour burden and has been shown to be associated with inferior outcome. [3]

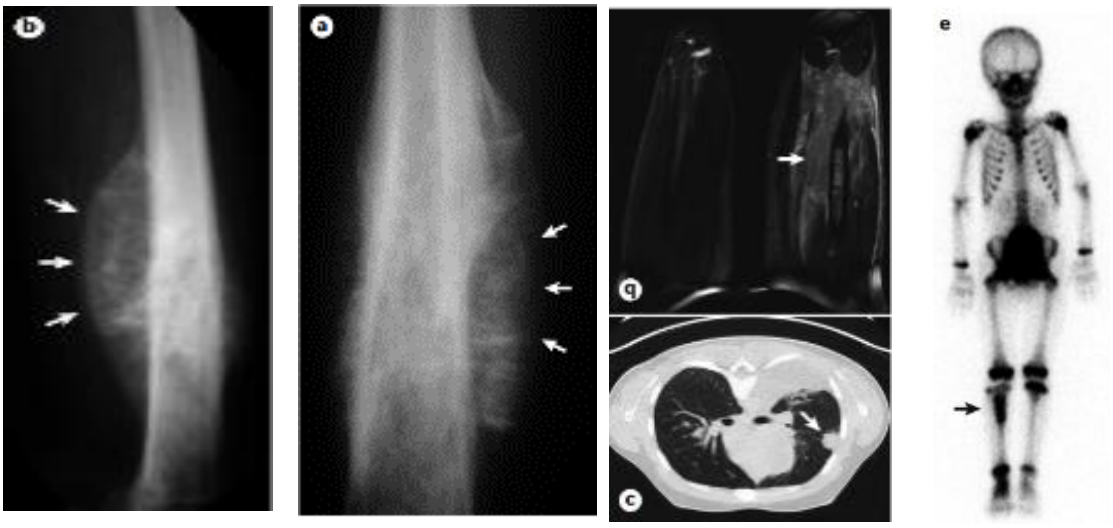
Radiographic imaging:

An effective evaluation for the staging and treatment of patients with Ewing sarcoma relies mainly on the correct identification of the primary tumour extension and the accurate detection of metastatic disease. Tumour imaging and metastatic evaluation include an initial radiological evaluation, successive CT of the lungs and bone scintigraphy for the detection of metastases[8].

- On radiographs, Ewing sarcoma shows tumour-related osteolysis as a destructive mass arising from the diaphyseal–metaphyseal bone with a multilayered appearance ('onion skin') (fig. 5a,b)

- Additional CT scans enable the detection of small lesions in the lungs (fig. 5c) and the assessment of bone destruction and periosteal involvement[9]
- MRI provides higher definition images to evaluate the extent of the disease and is used if the tumour does not arise in the bone (fig. 5d)

- 18F-fluorodeoxyglucose (FDG) PET– CT, can be used to determine tumour regression or progression before the identification of morphological alterations by anatomical imaging methods such as CT and MRI 127. recent RCTs study has been shown that FDG PET–CT can assess the presence of metastases in the bone marrow [10]
Moreover, two recent US studies suggested that invasive bone marrow aspiration can be omitted in standard-risk patients with Ewing sarcoma if there is no evidence of bone marrow involvement on FDG PET–CT [11,12]



radiological presentation of ewing sarcoma. Anteroposterior (panel **a**) and lateral (panel **b**) X-ray images showing an osteolytic lesion of a Ewing sarcoma and involvement of the periosteal soft tissue (arrows) in the right femur of a 14-year-old boy. CT scan of the lungs showing a pulmonary metastasis (arrow) in a 19-year-old male patient (panel **c**). MRI scan (T2-weighted) showing the primary tumour in the right femur with accompanying soft-tissue oedema (arrow) of the patient shown in panel **a** (panel **d**). Bone scintigraphy of a 6-year-old male patient highlighting a Ewing sarcoma tumour mass comprising his right tibia (arrow; panel **e**)

- The definitive diagnosis of Ewing sarcoma should be made by biopsy, providing sufficient material for conventional histology, immunohistochemistry, molecular pathology and biobanking. [13]

Regarding molecular pathology --> it include the detection of FET–ETS fusions and rearrangements by fluorescence in situ hybridization (FISH) and/or reverse transcription PCr (rt-PCr). (targeted) RNA sequencing for rare gene fusions in some patients.
Of note, After induction chemotherapy, Ewing sarcoma cells show a variable degree of necrosis and are replaced by loose connective tissue on Gross examination **5**. Histopathological assessment of tumour necrosis after therapy correlates with overall survival.

Metastasis:

Metastasis is the most powerful adverse prognostic factor in Ewing sarcoma. However, its underlying mechanisms remain poorly understood, although molecular pathways that correlate with metastasis have been identified through comparison of primary and metastatic Ewing sarcoma cell lines and tumours Ewing sarcoma predominantly spreads via the bloodstream. The most common metastatic sites are the lungs, bones or bone marrow, whereas other sites are rare Bone marrow metastasis occurs in approximately 10% of patients [14,15]

affect of microenviroment on tumor metastasis:
harsh conditions and hypoxia within the tumour microenvironment can lead to cell stress in Ewing sarcoma, which induces the synthesis of stress-adaptive proteins via two processes. First, primary Ewing sarcoma cells alter EWSR1–ETS protein levels to favour transcription and expression of EWSR1–FLI1 targets such as DKK2, STEAP1, CAV1 and CD99. Alternatively, primary tumours increase expression of RNA-binding proteins such as nuclease-sensitive element-binding protein 1 (YB1) which either directly enhances translation of stress-adaptive messages, such as hypoxia-inducible factor 1α (HIF1α), or indirectly enhances translation of stress-adaptive messages through stress granule (dense aggregations in the cytosol composed of proteins and RNAs) formation and translational reprogramming. Both of these pathways result in enhanced synthesis of stress-adaptive proteins, potentially leading to cells with increased metastatic capacity [16]

Staging and risk classification:

The clinical stage at diagnosis is one of the major predictors of survival. The accurate determination of tumour burden at diagnosis is a critical factor in planning treatment and predicting outcome.
For the detection of bone marrow metastases, bone marrow aspirates and trephine biopsies from sites that are tumour negative by imaging are typically performed[14,15]. However, modern imaging techniques such as FDG PET–CT scans have the potential to replace invasive bone marrow aspirates and trephine biopsies[11,12]

Risk groups in ewing sarcoma

staging of malignant disease in ewing sarcoma is of general importance as the stage at diagnosis is one of the major predictors of survival. with the advent of structured clinical trials for the treatment of ewing sarcoma, prognostic factors are used as stratification criteria with consecutive adjustment of treatment intensity213, including metastases, histological response to chemotherapy, tumour volume and age at diagnosis119.

standard risk

• Patients with localized disease, small tumours and good histological response (<10% vital tumour cells)
• Patients with small tumours <200 ml in whom histological response cannot be assessed
• in european trials, histological response to induction chemotherapy has been reported as a significant biomarker in the group of patients with localized disease70,214–216

High-risk localized

• unfavourable histological response
• More than 10% vital tumour cells
• Patients with large tumours (≥200ml) in whom histological response cannot be assessed are also stratified in the high-risk group in european trials70,144,217
• The North American study groups do not substratify patients with localized disease147

Very high-risk metastatic

• Disseminated disease
• Patients with lung metastases have been reported to have a better outcome than patients with other metastases142

Management:

The management of patients with Ewing sarcoma requires a multidisciplinary team that includes paediatric, medical and radiation oncologists; orthopaedic and general surgeons; and nurses. Patients with newly diagnosed localized standard-risk Ewing sarcoma can expect a survival of 70–80%. However, this high survival emerges from intensified cytotoxic drug regimens, which are associated with late effects. Furthermore, primary disseminated disease and relapse are associated with extremely poor outcomes and novel treatment strategies are urgently required.

Induction chemotherapy:

Patients with newly diagnosed Ewing sarcoma are treated with a combination of multi-agent cytotoxic chemotherapy and local control measures (surgery and/or radiotherapy).

Induction chemotherapy is given before local treatment to reduce the size of the primary tumour and address micrometastatic disease because micrometastatic disease is expected in all patients. Cooperative group clinical trials have demonstrated that multidrug treatment and treatment intensity are important factors of therapy and that intensity of chemotherapy is important for outcome. Modern protocols consist of intense induction chemotherapy with vinca alkaloids, alkylating agents and anthracyclines. For example, the randomized clinical trial

study used an intensive multidrug induction chemotherapy regimen containing vincristine, ifosfamide, doxorubicin and etoposide (VIDE); this intense regimen was tolerated by the patients at intervals of 21–28 days[17]
Moreover, long consolidation chemotherapy is an important element in the treatment of Ewing sarcoma to destroy slowly proliferating remaining tumour cells. The EE99 trial showed that standard-risk patients do not differ in outcome if cyclophosphamide-based or ifosfamide-based consolidation chemotherapy is used[18]. While High-risk localized patients (localized disease, poor histological response and large tumours) benefited more from high-dose busulfan and melphalan chemotherapy followed by transplantation of autologous haematopoietic stem cells (survival at 3 years of 67%) than from an eight-cycle standard dose of vincristine, actinomycin D and ifosfamide consolidation chemotherapy (survival at 3-year of 53%)[19].

The US Children's Oncology Group (COG) assessed the value of dose intensity by comparing 3-weekly (so-called uncompressed regimen) versus 2-weekly (called compressed) regimens of vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide. The 5-year survival was significantly better in patients who received the compressed regimen (73% versus 65%)[20].

Metastatic disease Tx:

Patients with metastatic Ewing sarcoma are treated either following regimens utilized in the care of patients with localized disease[20] or on randomized clinical trials seeking to improve outcomes for this group of patients. Early studies in patients with Ewing sarcoma and pulmonary metastases by the European Inter-Group Cooperative Ewing studies (EICESS-92) showed that whole lung irradiation (WLI) could improve a 5-year EFS compared with no WLI (49% versus 36%)[21]. In parallel, other studies have demonstrated a possible benefit from high-dose busulfan and melphalan chemotherapy and autologous stem cell transplantation (SCT) for metastatic disease[22].

Radiotherapy:

Definitive radiotherapy (radiotherapy as the only local treatment) in sacral tumours was comparable to combined surgery and radiotherapy in terms of local relapse and overall survival, whereas the combined local treatment in non-sacral tumours was associated with an improved local relapse and overall survival compared with surgery alone[23]

Benefit from postoperative radiotherapy was observed in patients with marginal or intralesional resections[24]. Thus, patients with narrow margins should receive postoperative radiotherapy

An early study of high-dose chemotherapy and total body irradiation in patients with newly diagnosed disseminated Ewing sarcoma was conducted by a cooperative trial group in the United States. The 2-year EFS was 20% for the entire cohort and 24% for patients who received myeloablative therapy160. Additionally, a European study retrospectively investigated the role of total body irradiation in two groups of patients. One group was treated with high-dose chemotherapy plus total body irradiation, and the second group was treated with tandem high-dose chemotherapy. The 5-year EFS was similar in both groups (22% versus 29%)[25].

Relapsed Ewing sarcoma

Ewing sarcoma relapse is associated with very poor outcomes; patients who relapse within 24 months after diagnosis have a 5-year survival of <10%3. Favourable prognostic factors at relapse are local relapse, younger age, isolated pulmonary recurrence and low LDH levels[26]. Additionally, a structured follow-up imaging protocol in which patients undergo routine imaging may enable a longer overall survival in recurring patients[27]. The vast majority of the value of different therapeutic approaches in relapsed Ewing sarcoma is drawn from retrospective analyses[28,29]. The first large investigator-initiated clinical trial in relapsed Ewing sarcoma was initiated in the European consortium and compares standard chemotherapy regimens in terms of survival, safety and quality of life[30].

Special disease complications:

Patients with Ewing sarcoma may present with pathological fracture or develop pathological fractures during treatment (14% of patients). Fractures in patients with Ewing sarcoma are the result of bone destruction and are more likely to occur in those with larger tumours (≥200 ml or ≥8 cm in the largest dimension). The main site for a pathological fracture is the femur, followed by the tibia (>50%). Despite these complications, survival in patients with pathological fractures is similar to those without these complication [31]. Approximately 6% of patients are diagnosed with Ewing sarcoma of the spine; thus, spinal cord compression may occur and warrants immediate decompression in most of the patients to prevent long-term neurological sequelae. In patients without severe neurological symptoms, systemic treatment plus steroids may be used to reduce tumour burden. Decompression at diagnosis positively affects the outcome in patients with Ewing sarcoma of the spine[32].

Complications related to treatment:

Patients with Ewing sarcoma are at risk of substantial and treatment-induced acute and long-term toxicity. Although prospective studies on late effects with a large and well-documented cohort of patients are still lacking, the chemotherapy agents commonly used in the management of Ewing sarcoma are known to be associated with a number of late effects in survivors. Chemotherapy regimens widely used in the treatment of Ewing sarcoma mainly rely on anthracyclines, alkylating agents and etoposide. Cardiomyopathy, renal insufficiency, renal Fanconi syndrome and reduced fertility have been described[33].
Furthermore, patients are at risk of secondary malignancies due to chemotherapy and/or radiotherapy[13]. Secondary malignancies occur in ~9% of Ewing sarcoma survivors[34].
As expected, radiotherapy is associated with an important risk of developing secondary cancers, mainly comprising osteosarcoma, acute myeloid leukaemia, breast cancer and thyroid cancer[34].
All local treatment modalities put Ewing sarcoma survivors at risk of treatment-related late sequelae in the form of neuromusculoskeletal complications and reduced functional capacity. However, a recent study showed that — independently of the different treatment modalities — the majority of patients had active lifestyles without major limitations decades after treatment[35].

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