

Ewing's Sarcoma of Spine-Current Concepts and Review of literature

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Abstract

Introduction: Ewing sarcoma (ES) is a malignant and aggressive bony tumor affecting the most common age group of 5-20 years. It constitutes 10%-15% of all bone sarcomas and is the second most common primary malignant bone tumor after osteosarcoma.

Methods: We undertook a review of the literature on Ewing's Sarcoma of spine to evaluate its etiology, the clinical presentations, differential diagnosis, imaging modalities and the management with chemotherapy, radiotherapy and surgical management. PubMed, EMBASE, Google Scholar and Cochrane key articles were searched. Key words like 'Ewing's Sarcoma', 'Spine', 'etiology', 'treatment', 'surgical management', 'en bloc resection' were used

Discussion: The current management of Ewing's sarcoma of the spine usually involves three main modalities: combination chemotherapy, surgery and/or radiotherapy. Recent improvements in combination chemotherapy (vincristine, doxorubicin, cyclophosphamide +/- Ifosfamide and etoposide) are one of the most significant factors for improving survival. Also, recent advancements in radiotherapy and instrumentation and fusion techniques in surgical management has also demonstrated to improve local disease control and overall survival.

Conclusion: Primary Ewing sarcoma of spine is a rare condition affecting most common age group of 5-20 years and accounting for 1-3 cases/million/year. About 5% cases have spine involvement. Recent improvements in combination chemotherapy have improved the overall survival rates. En block resection and/or radiotherapy has improved local control of the disease.

Keywords: Ewing's Sarcoma, Spine, etiology, Treatment, Surgical management, En-bloc resection

Introduction

Ewing sarcoma (ES) is a malignant and aggressive bony tumor affecting adolescents and young adults with most common age group 5-20 years [1,2]. It constitutes 10%-15% of all bone sarcomas and is the second most common primary malignant bone tumor after osteosarcoma. It arises from unique mesenchymal progenitor cells. It is characterised by distinctive small round cell sarcoma associated with a t(11:22) translocation. The most common anatomical sites include the metadiaphysis of long bones (~50%), the pelvis (~25%) and axial skeleton; however, it can originate in almost any bone or soft tissue [3-5].

Methods

We undertook a review of the literature on Ewing's Sarcoma of spine to evaluate its etiology, the clinical presentations, differential diagnosis, imaging modalities and the management with

chemotherapy, radiotherapy and surgical management. PubMed, EMBASE, Google Scholar and Cochrane key articles were searched. Key words like 'Ewing's Sarcoma', 'Spine', 'etiology', 'treatment', 'surgical management', 'en bloc resection' were used. Additional articles were identified by checking the references manually. Articles were reviewed by two independently reviewers.

Discussion

Etiology

The exact etiology of Ewing's Sarcoma unknown, however, it is thought to be of neuroectodermal origin and no associations with environmental, genetic, familial or radiation history has proven. The association of t(11;22) (q24;q12) translocation is found in 85% of tumors leading to EWS-FLI-1 formation, while t(21;12)(22;12) translocations seen in 10-15% of patients with EWS-ERG fusion formation [5].

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Epidemiology

Primary Ewing sarcoma of spine is a rare condition accounting for 1-3 cases/million/year. About 5% involve the spine. The most common age group 5-20 years, with approximately 30% of the cases described in children under the age of 10, and another 30% are in adults over the age of 20 [3]. There is a male predominance with a male to female ratio of 1.5-3 to 1. The incidence of Ewing sarcoma in the elderly is not well described in the literature.

Clinical Presentation

Localised pain, stiffness, or swelling for a few weeks or months are the presenting features. Late diagnosis is common as more than 50% of the patients present 6 months after initiation of symptoms [6].

Patients typically complain of intermittent pain that worsens at night, local erythema, mass or swelling could also be present. Systemic symptoms, including fever and weight loss is frequently seen and might indicate metastatic disease.

Metastatic lesions can occur in the lungs (50%), bone (25%), bone marrow (20%) and can present with asymmetric breath sounds, pleural signs, or rales. Petechia or purpura and thrombocytopenia may be present from bone marrow metastases. A neurologic examination is of critical importance in patients with spine involvement.

Delayed diagnosis more common in pelvis and axial skeleton due to the anatomic location, patients are likely to experience symptoms and notice it earlier when the tumor is even relatively small in size at the extremities and thus seek medical consultation at an earlier stage. As pelvis and axial skeleton have large cavities noticing the small sized tumors is difficult.

Although tumor size and location are debatable on prognosis, this could be one of the reasons for inferior overall survival and disease-free survival in axial and pelvic tumors as explained in several studies

Investigations

Primary investigations include an X-ray of the affected area demonstrating usual destructive confluent "moth-eaten" lesions, "Codman's triangle" of the elevated periosteum, or multilayered "onion-skin" or "sunburst" periosteal reaction. Recent guidelines from National Comprehensive Cancer Network (NCCN) 2017 [7], advises imaging of primary sites should include MRI with or without CT, with contrast is of prime importance. Rest imaging modalities such as CT thorax, positron emission tomography (PET)/CT, bone scan, and MRI of the spine/pelvis, to detect possible metastatic sites. MRI helps to identify soft-tissue extension, marrow involvement and relationship of lesion to adjacent neurovascular structures (Fig. 1). MRI can also help to assess recurrence after tumor resection, response to neoadjuvant chemotherapy and radiation. Lab investigations usually demonstrate elevated ESR, WBC and LDH with reduced Hemoglobin levels. Serum lactate dehydrogenase (LDH) carries prognostic significance. To establish the diagnosis core-needle biopsy is necessary either a fluoroscopy-guided or CT-guided or an open biopsy. Grossly it may appear grayish white with variable amount of necrosis, hemorrhage or cyst formation or may have liquid consistency mimicking pus. On histopathology it will

appears as monotonous small round blue cells with high nuclei: cytoplasm ratio and pseudo-rosettes appearance. Immunostaining demonstrates CD99 positivity in almost 95% [8].

Classification and Staging

The commonly used staging system for Ewing sarcoma developed by Musculoskeletal Tumor Society (MSTS)/Enneking [9, 10] classifies tumor by grade (low grade being stage IA-IB, high-grade stage IIA-IIB, distant metastasis stage IIIA-IIIB and subdivided by compartmental status (T1- Intra-compartmental -located in the bone cortex versus T2-extracompartmental - extended beyond the bone cortex). Grossly, Tumor size is categorized as small (≤ 8 cm) or large (> 8 cm).

Histologically, tumors are graded based on the percentage of cellular atypia-low metastatic potential tumours classified as low-grade tumour and low metastatic potential tumours with higher the percentage of cellular atypia are classified as high-grade tumour e.g., intramedullary osteosarcoma, Ewing's sarcoma. The majority of

AJCC STAGING SYSTEM						
Stage	Grade	Size	Depth	Node	Metastasis	5 yr. survival
IA	Low Grade	< 8 cm	Any	None	None	98%
IB	Low Grade	> 8 cm	Any	None	None	
IIA	High Grade	< 8 cm	Any	None	None	82%
IIB	High Grade	> 8 cm	Superficial	None	None	82%
III	Any	Discontinuous (skip) lesion	Deep	None	None	52%
IVA	Any	Any	Any	None	Lung	
IVB	Any	Any	Any	Present	Other than lung	30%

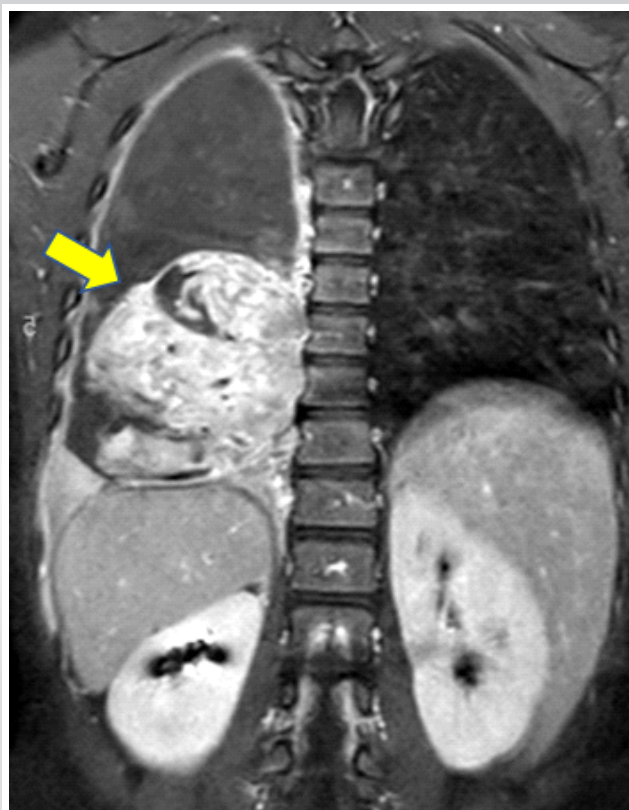


Figure 1: A] MRI Coronal image demonstrating large destructive left paraspinal and hemithoracic mass entering spinal canal predominantly through the neural foramina at T8/9 and T9/10, bony involvement of T8, T9 vertebrae with left 8th and 9th ribs involvement with mass measuring 67x72x103 mm

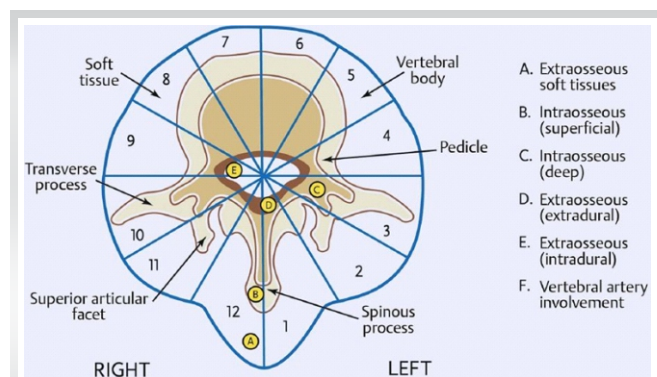


Figure 2: The Weinstein-Boriani-Biagini (WBB) classification assists surgical planning by establishing feasibility criteria and strategies to achieve oncological resection of tumors. The vertebra is divided into 12 equal radiating zones in an axial plane. The tumor is further divided into five concentric layers centered around the thecal sac, and the presence or absence of vertebral artery involvement: Soft tissue (A), Intraosseous superficial (B), Intraosseous deep (C), Extradural (D), Intradural (E), Vertebral artery involvement (F). Based on these stages, surgical procedures are proposed.

Table 1: Enneking staging system: linkage between stage and surgical margins

Tumor stage	Grade, location, metastases	Clinical evaluation	Control margin
1	G ₀ T ₀ M ₀	Latent	Intracapsular
2	G ₀ T ₀ M ₀	Active	Marginal or intracapsular plus effective adjuvant
3	G ₀ T ₁₋₂ M ₀₋₂	Aggressive	Wide or marginal plus effective adjuvant

G0-Benign, T0- Intracapsular, T1-Extracapsular, intracompartmental, T2- Extracapsular, Extracompartmental, M0-Absence of metastasis, M1-Presence of metastasis

Ewing's tumors are MSTs/Enneking stage IIB or III (Table 1). The American Joint Committee on Cancer (AJCC) classification method [11] is TNM by, which classifies tumour depending on tumor size, lymph node metastasis, distant metastasis, and tumor grade (cellular differentiation, mitotic rate, and extent of necrosis). The Weinstein-Boriani-Biagini (WBB) classification [12] assists surgical planning for spine tumours by establishing feasibility criteria and strategies to achieve oncological resection of tumors (Fig. 2). After the resection of the tumor, microscopic resection margin was defined as clear (R0) if the margin was reported as being wide or marginal, and as positive (R1 or R2) if the margin was assessed as intralesional [13].

R0- Microscopic margin free of tumor cells; R1- tumor cells microscopically present at resection margins; R2- Tumor tissue grossly present at resection margin -seen with naked eye

Differential Diagnosis

Differential diagnosis of ES that includes other small round cell tumors such as neuroblastoma, lymphoma, neuroectodermal tumors, and synovial sarcoma. Osteomyelitis, osteogenic sarcoma, and eosinophilic granuloma are the other differentials [14].

Management

Since its first description by James Ewing in 1921 [1], management options and survival of Ewing's sarcoma has significantly improved. The current management of Ewing's sarcoma of the spine usually involves three main modalities: combination chemotherapy, surgery and/or radiotherapy [14].

Multidisciplinary and interprofessional team approach is important to achieve best results in young patients of Ewing's sarcoma. The

skilled team should include pediatric oncologist, radiologists, orthopedic surgeons, radiation oncologists, pathologists, and pharmacists for best outcomes.

Recent improvements in combination chemotherapy (vincristine, doxorubicin, cyclophosphamide +/- Ifosfamide and etoposide) are one of the most significant factors for improving survival [15–18]. Also, recent advancements in radiotherapy and instrumentation and fusion techniques in surgical management has also demonstrated to improve local disease control and overall survival.

Radiotherapy is helpful as a mode of local therapy, although in spine tumors considering its proximity to the spinal cord, and in lumbar region, the renal structures, its use is restricted in dose [≥ 50.4 Gy] and extent to reduce radiation induced complications [19].

Recent research studies by the AO spine tumor oncology group suggested that en bloc resection may provide improved local control for Ewing's sarcoma of the spine, but not improved overall survival. They also recommended that RT may be used for local control either alone or to supplement incomplete resection [20].

Regarding resection margins, an en bloc resection is defined as a surgical resection aiming to excise a tumor, fully covered by a continuous shell of healthy tissue called the 'margin'.

The resection will be called as 'intralesional' when the surgeon incidentally or intentionally violates the tumor. Intentional intralesional resection comes in scenarios where a surgical margin requires resection of functional tissues like a nerve, nerve sheath, dura, thoracic duct, or a major vessel as it lies close to the tumor or is infiltrated by the tumor or patient presents with acute neurological deficit secondary to epidural compression [11–13, 21–23].

The decision to sacrifice the structure depends on the risk of local recurrence and the impact on the outcome, versus the functional impairment.

From an oncologic point of view, if wide margin resection is essential to accomplish local and systemic cure of the disease, then the surgeon should carefully assess and choose to disregard the functional role of tissue.

The more aggressive the tumor, the more important it becomes to obtain a margin that is sufficient. For more aggressive tumors, it is important to assess the tumor control and long-term survival option over sacrificing important anatomical structures and even paraplegia can be acceptable to achieve an oncologically appropriate resection. Also, it is to be noted by principle, that while dealing with a benign tumor or a metastasis, it is not advisable to sacrifice functionally important structures like nerve root as aim of the management is to improve or preserve function without unnecessary morbidity [21].

The decision-making process and understanding of the patient and guardians for the surgical procedure takes a vital importance when functional loss is expected. Their understanding, acceptance and consenting of the functional loss is necessary to execute the plan for the disease control and long-term survival.

Recent study by Harrop et al [24] in aggressive osteoblastomas and giant cell tumors of the thoracic and lumbar spine demonstrated that en bloc resection is strongly recommended to minimize the risk of local recurrence when anatomically achievable.

In 1992, Sharafuddin et al [25], demonstrated Ewing's Sarcoma case series of 7 patients and described 6 patients treated surgically of

which 4 had laminectomies with tumor excision, 1 had anterior decompression with tumor excision, and 1 had en bloc tumor excision. Also, all 7 patients were treated with systemic chemotherapy (VAC-A) and except one patient 6 patients received radiotherapy too. Local recurrence was noted in a patient who had undergone laminectomy and adjuvant radiotherapy. Three patients died of disease at 6 and 10 months and a 3rd patient died of urosepsis. The disease-free survival in the patient who underwent en bloc resection was 7 months.

In 2002 Talac et al [26] analyzed 30 primary spine sarcomas, with 7 cases of Ewing's sarcoma. Of 7 patients, 5 patients underwent piecemeal excision and 1 of 5 had developed local recurrence (20%). Rest 2 patients had en bloc resections and did not demonstrate local recurrence. The disease-free survival for the Ewing's sarcoma subgroup was unreported.

In 2011, Boriani et al [12, 27] studied 27 patients who were treated with systemic chemotherapy combined with radiotherapy and/or surgery in three different time periods 1979-1982, 1983-1990 and 1991-2008. The study suggested tumor-free margin en bloc resection provided better local control and longer survival, whereas the results of intralesional resection were worse than chemotherapy and radiotherapy alone.

Hesla et al [28] in 2018 retrospectively reviewed 24 patients diagnosed with Ewing's sarcoma between 1986 and 2012 through the Scandinavian Sarcoma Group registry. 19/23 patients had neurologic changes at the time of presentation. Regardless of whether emergency decompression surgery was performed, 13/19 patients recovered completely from their neurological condition. Definitive radiotherapy was primary mode of care in 18/24 of patients. 13/24 patients underwent spinal decompressive surgery due to spinal cord compression. The study concluded that urgent decompressive surgery without establishing the histological diagnosis may increase the risk for local recurrence and also suggested that urgent decompressive surgery does not have any clear advantage over non-surgical treatment in terms of neurologic recovery.

Conclusion

Primary Ewing sarcoma of spine is a rare condition affecting most common age group of 5-20 years and accounting for 1-3 cases/million/year. About 5% cases have spine involvement. Recent improvements in combination chemotherapy have improved the overall survival rates. En block resection and/or radiotherapy has improved local control of the disease.

Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the Journal. The patient understands that his/her name and initials will not be published, and due efforts will be made to conceal his/her identity, but anonymity cannot be guaranteed.

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