ORIGINAL RESEARCH

Retrospective Study on Ewing Sarcoma

Dr.Tanya Aggarwal[1], Dr.Seerat Sangha[2], Dr.Chetan Verma[3]

[1]PG resident, Department of Radiodiagnosis MGUMST, Jaipur, India
[2]PG Resident, Department of Radiodiagnosis, Christian Medical College, Ludhiana, Punjab, India
[3]Senior Resident, Department of Orthopaedics, Esic Hospital, Baddi, Himachal Pradesh, India

Corresponding Author
Dr.Tanya Aggarwal
PG resident, Department of Radiodiagnosis Mgumst,Jaipur.

Received: 28 October, 2023 Accepted:24 November, 2023

Abstract

Background: Ewing sarcoma (EwS) represents a rare, highly malignant cancer, with most patients harboring a priori micrometastases. Hence, this study was conducted to evaluate site and stages of ewing sarcoma.

Materials & Methods:A total of 15 subjects were enrolled. The age of subject was between 10 to 16 years. The number of male subjects was 10 and remaining 5 were females. The results were recorded and analysed using SPSS software.

Results: The ewing sarcoma is predominantly common in males. Ewing cancer predominantly localizes in the limbs, with only a limited number of cases occurring in the rib region. The lower limbs exhibit the highest frequency of tumor occurrence.

Conclusion: Ewing sarcoma is more common in males and shows occurrence of highest frequency in lower limbs.

Keywords:ewing sarcoma, cancer, femur.

Introduction

Primary bone tumors are relatively rare types of cancer. Their relative frequency is not yet well established and still there is more information needed regarding the evolution and prognosis of those patients. Bone malignant tumors account for 0.2% of all cancers diagnosed in the United States and represent 10% of malignant diseases during infancy and adolescence. [1] In Romania, incidence varies between 1.5-2.5/100.000 infants, the most frequent being Ewing sarcoma and osteosarcoma. The peak of incidence present a bimodal distribution, first peak is in the second decade, while the second appears in the sixth decade and later. [1]Ewing sarcoma (ES) represents a rare, highly malignant cancer, with most patients harboring a priori micrometastases, since, without systemic therapy, over 90% of patients die from disseminated disease. [2-4] It is most commonly diagnosed in the second decade of life; however, patients have presented as early as newborn and as late as into the eighth decade, with tumors in almost every bodily location.Ewing's sarcoma is the second most common malignant bone tumour occurring in children and young adults, and accounts for 10–15% of all primary bone tumours. [5] The annual incidence is approximately 0.6/million total population, and it usually occurs between the ages of 10 and 20 years. It affects 13/million 0–24 year olds each year in the UK, and is slightly more common in males than females (ratio, 1.5 : 1). [6] It has been described in siblings, although this is rare and the disease does not appear to be implicated in familial cancer syndromes. Genetic influences may play some role in its aetiology because black Afro-Caribbean and Chinese populations are less frequently affected than the white population. [7]Ewing's sarcoma can affect any bone but the most common sites are the lower extremity (45%), followed by the pelvis (20%), upper extremity (13%), axial skeleton and ribs (13%), and face (2%). [8] The femur is the most frequently affected bone, with the tumour usually arising in the midshaft. Typically, by light microscopy, the tumour consists of small round cells with regular round nuclei containing finely dispersed chromatin and inconspicuous nucleoli, and a narrow rim of clear or pale cytoplasm. Ultrastructurally, the tumour contains primitive cells with a smooth nuclear surface, scanty organelles, and cytoplasmic glycogen in pools or aggregates. Ewing sarcoma (ES) is a highly malignant tumor composed of small round cells. The origin of this tumor was unclear until recently, when electron microscopic and immunohistochemical analyses suggested that it is of neurogenic origin. [9] ES tumors often express a balanced translocation involving the EWS gene on

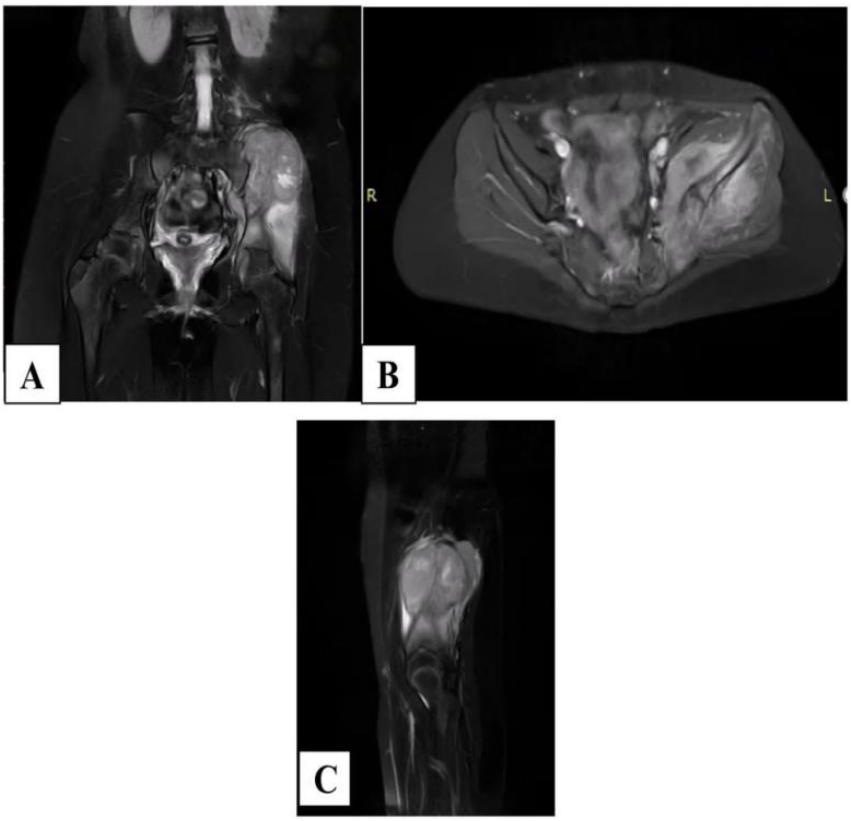
chromosome 22 and a member of the ETS family of transcription factors. [10] With the development of diagnostic radiological techniques such as magnetic resonance imaging (MRI), extraskeletal masses can be depicted clearly and the tumor area can be accurately evaluated. Due to improvements in intensive chemotherapy, the prognosis of ES patients has improved markedly. The current chemotherapy protocols used to treat ES include various combinations of the following six drugs: doxorubicin (DOX), cyclophosphamide (CPM), vincristine (VCR), actinomycin-D (ACT-D), ifosfamide (IFO), and etoposide (ETO). Local ES lesions are usually treated via surgical excision or radiotherapy, or a combination of both. In cases in which surgical excision is not possible due to the large size of the tumor, its anatomical location, or the fact that the acquired surgical margin is not sufficient to achieve local control, pre- or postoperative radiotherapy is usually selected. Better understanding of how local control can be achieved has helped to improve the oncological outcomes of ES. Although the survival rate of ES patients has improved, their prognosis remains unsatisfactory, and the treatment of ES is still challenging to the medical teams involved, which include orthopedic surgeons, pediatric oncologists, and radiotherapists. [11-13] Hence, this study was conducted to evaluate site and stages of ewing sarcoma.

Materials & Methods:

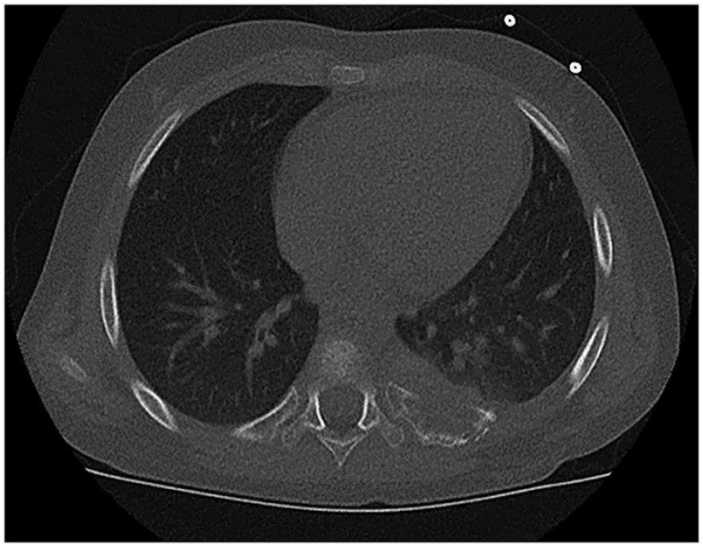
A total of 15 subjects were enrolled. The age of subject was between 10 to 16 years. The number of male subjects was 10 and remaining 5 were females. The individuals site and stage of cancer was recorded. The group based on clinical and laboratory data and followed-up the patients, to find out the unfavorable factors that induced death were analysed. The results were recorded and analysed using SPSS software.

Results:

The ewing sarcoma is predominantly common in males. Ewing cancer predominantly localizes in the limbs, with only a limited number of cases occurring in the rib region. The lower limbs exhibit the highest frequency of tumor occurrence. A prolonged duration from the onset of initial symptoms to the diagnosis negatively impacts prognosis, as evidenced by tumor staging, revealing that a majority of patients are diagnosed with stage III or IV tumors. Notably, 26.6% of cases are identified in advanced stage IV of the disease.



Sacral wings



Tumor arising from the paravertebral dorsal portion of the left 7th rib with infiltration of the transverse process and vertebral body.

Table 1: Distribution of ewing sarcoma according to gender

Ewing sarcoma	Number
Male	10
Female	5

Table 2: Distribution according to location of tumor

Location	Ewing sarcoma (%)
Humerus	20
Ribs	13.3
Sacrum	20
Femur	46.7

Table 3: staging of tumor

	TV<200cm^3	TV>200cm^3	No TV
II A	0%	0%	6.7
II B	6.7	6.7	0
III	20	6.7	6.7
IV	26.6	13.2	6.7

Discussion:

Extraskeletal Ewing sarcoma (EES) is a rare entity that belongs to the ES family of tumors (ESFT), which is a group of small round tumor cells that share a common neural histology and genetic mechanism. [14] In addition to EES, ESFT includes the classical ES of bone (ESB), which is the second most common primary bone malignancy in the pediatric population, peripheral primitive neuroectodermal tumor (pPNET) and Askin tumor of the chest wall, which is a subtype of pPNET. [15] EES was first discovered in 1969, but it remains an elusive pathology in the literature. [16] Hence, this study was conducted to evaluate site and stages of ewing sarcoma.In the present study, the ewing sarcoma is predominantly common in males. Ewing cancer predominantly localizes in the limbs, with only a limited number of cases occurring in the rib region. The lower limbs exhibit the highest frequency of tumor occurrence. A study by Burchill SA et al, identification of the non-random chromosome rearrangements between the EWS gene on chromosome 22q12 and members of the ETS gene family in Ewing's sarcoma, peripheral primitive neuroectodermal tumour, Askin tumour, and neuroepithelioma has been a key advance in understanding their common histogenesis and defining the Ewing's sarcoma family of tumours (ESFT). In addition to improvements in diagnosis and potentially the stratification of patients for risk, biological investigations of these gene fusions may define targets for much needed therapeutic strategies to eliminate minimal residual disease or metastatic disease. Insight into their relation with other oncogenic events in ESFT will advance risk group analysis and ultimately may improve clinical management and survival for patients with this disease. [17]In the present study, a prolonged duration from the onset of initial symptoms to the diagnosis negatively impacts prognosis, as evidenced by tumor staging, revealing that a majority of patients are

diagnosed with stage III or IV tumors. Notably, 26.6% of cases are identified in advanced stage IV of the disease. Another study by Zollner SK et al, ewing sarcoma, a highly aggressive bone and soft-tissue cancer, is considered a prime example of the paradigms of a translocation-positive sarcoma: a genetically rather simple disease with a specific and neomorphic-potential therapeutic target, whose oncogenic role was irrefutably defined decades ago. This is a disease that by definition has micrometastatic disease at diagnosis and a dismal prognosis for patients with macrometastatic or recurrent disease. International collaborations have defined the current standard of care in prospective studies, delivering multiple cycles of systemic therapy combined with local treatment; both are associated with significant morbidity that may result in strong psychological and physical burden for survivors. Nevertheless, the combination of non-directed chemotherapeutics and ever-evolving local modalities nowadays achieve a realistic chance of cure for the majority of patients with Ewing sarcoma. In this review, they focus on the current standard of diagnosis and treatment while attempting to answer some of the most pressing questions in clinical practice. In addition, this review provides scientific answers to clinical phenomena and occasionally defines the resulting translational studies needed to overcome the hurdle of treatment-associated morbidities and, most importantly, non-survival. [18] In over 85% of cases of Ewing sarcoma a translocation between chromosomes 11 and 22 was reported. The result of this translocation is a pathognomonic fusion gene, EWSR1/FLI1 that encodes the EWS/FLI protein.[19] Other types of chromosomal translocations were reported, such as t(21;22), EWSR1/ERG found in 10% of cases. [20] Different gene mutations were identified in ES patients: TP53 occur in 5%-20%, amplifications of MDM2 occur in 0%-10% of cases, deletions of the CDKN2A in 15% of patients. [21] Patients with ES exhibit local symptoms such as tumor mass formation, induration, pain, swelling, venous dilation, and hyperemia. Pathological fractures sometimes occur due to bone metastasis, and spinal metastasis-associated back pain can progress to spinal paralysis. In cases in which an ES originates in the chest wall, pleural infiltration combined with carcinomatous pleurisy is often observed. The interval between the onset of the initial symptom and diagnosis has become shorter; i.e., it was 4.7 months in 2003, whereas it was 9.6 months in 1984. [22] This change might have been due to improvements in diagnostic techniques. Anemia and leukocytosis are often observed in ES, as are increases in the white blood cell count, blood sedimentation rate; and the serum levels of lactate dehydrogenase (LDH), alkaline phosphatase, and C-reactive protein. An elevated LDH level is associated with a poor prognosis. [22] Physicians must be aware that ES patients often exhibit similar blood and serum biochemical findings to those displayed by patients with inflammatory conditions such as osteomyelitis. In ES of the bone, plain radiographs exhibit permeative and infiltrative destruction of the affected bone (often in the diaphysis of the long bone). In addition, an onion skin-like appearance and spiculae are indicative of periosteal reactions. The pelvis is the most commonly affected site; however, it is difficult to identify pelvic tumors on plain X-rays alone. Computed tomography (CT) is useful for depicting extraskeletal soft tissue masses, destruction of the bone cortex, and pulmonary metastasis. On MRI, ES of the bone exhibits low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, and appears as large extraskeletal soft tissue masses derived from bone. Skip lesions affecting the bone are often clearly depicted on MRI. On bone scans, ES of the bone demonstrates high ^{99m}Tc-MDP uptake. Similarly, it displays high ^{18}F-fluorodeoxy glucose (18F-FDG) uptake on 18F-FDG-positron emission tomography (PET). [23] To achieve significant improvement to overcome plateaued survival rates, especially for high-risk patients, innovative clinical strategies and novel therapeutic concepts are required. EwS provides a tumor-specific molecular target which is indispensable for tumor development. Characteristically, EwS carry a balanced translocation. In 85–95% of all EwS patients, this rearrangement fuses the Ewing sarcoma breakpoint region 1 gene (EWSR1) on chromosome 22 to the friend of leukemia virus integration site 1 gene (FLI1) on chromosome 11 t(11;22)(q24;q12). 19 The resulting EWSR1-FLI1 fusion product functions as an oncoprotein that is both necessary and presumably sufficient for tumorigenesis. [24] Consequently, inactivation of EWSR1-FLI1 function is desirable for effective therapy, although it is clinically not mandatory, as shown by effectiveness of non-targeted chemotherapy in a substantial proportion of patients with localized tumors.

Conclusion:

Ewing sarcoma is more common in males and shows occurrence of highest frequency in lower limbs.

References:

1. Franchi A. Epidemiology and classification of bone tumors. Clin Cases Min Bone Metab. 2012;2:92–5.
2. Wang C.C., Schulz M.D. Ewing's sarcoma; a study of fifty cases treated at the Massachusetts General Hospital, 1930-1952 inclusive. N. Engl. J. Med. 1953;248:571–576.
3. Dahlin D.C., Coventry M.B., Scanlon P.W. Ewing's sarcoma. A critical analysis of 165 cases. J. Bone Joint. Surg. Am. 1961;43-A:185–192.
4. Ewing J. The Classic: Diffuse endothelioma of bone. Proceedings of the New York Pathological Society. 1921;12:17. Clin. Orthop. Relat. Res. 2006;450:25–27.
5. Huvos AG. Ewing's sarcoma. In: Huvos AG, ed. Bone tumors: diagnosis, treatment and prognosis, 2nd ed. Philadelphia PA: Sanders, 1991:523–52.

6. Cotterill SJ, Parker L, Malcolm AJ, et al. Incidence and survival for cancer in children and young adults in the North of England, 1968–1995: a report from the Northern Region young persons' malignant disease registry. Br J Cancer 2000;83:397–403.
7. Joyce MJ, Harmon DC, Mankin HJ, et al. Ewing's sarcoma in female siblings: a clinical report and review of the literature. Cancer 1984;53:1959–62.
8. Grier HE. The Ewing family of tumors. Ewing's sarcoma and primitive neuroectodermal tumors. Pediatr Clin North Am 1997;44:991–1104.
9. Jaffe R, Santamaria M, Yunis EJ, Tannery NH, Agostini RM, Jr, Medina J, Goodman M. The neuroectodermal tumor of bone. Am J Surg Pathol. 1984;8(12):885–898.
10. de Alava E, Lessnick SL, Sorensen PH. Ewing sarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumours of soft tissue and bone. Lyon: WHO Press; 2013. pp. 305–309.
11. Paulussen M, Craft AW, Lewis I, Hackshaw A, Douglas C, Dunst J, Schuck A, Winkelmann W, Kohler G, Poremba C, Zoubek A, Ladenstein R, van den Berg H, Hunold A, Cassoni A, Spooner D, Grimer R, Whelan J, McTiernan A, Jürgens H. European Intergroup Cooperative Ewing's Sarcoma S. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol. 2008;26(27):4385–4393.
12. Cripe TP. Ewing sarcoma: an eponym window to history. Sarcoma. 2011;2011:457532.
13. Le Deley MC, Paulussen M, Lewis I, Brennan B, Ranft A, Whelan J, Le Teuff G, Michon J, Ladenstein R, Marec-Berard P, van den Berg H, Hjorth L, Wheatley K, Judson I, Juergens H, Craft A, Oberlin O, Dirksen U. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol. 2014;32(23):2440–2448.
14. Carpentieri DF, Qualman SJ, Bowen J, Krausz T, Marchevsky A, Dickman PS, Cancer Committee, College of American Pathologists Protocol for the examination of specimens from pediatric and adult patients with osseous and extraosseous Ewing sarcoma family of tumors, including peripheral primitive neuroectodermal tumor and Ewing sarcoma. Arch Pathol Lab Med. 2005;129:866–873.
15. Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. Jpn J Clin Oncol. 2007;37:79–89.
16. Tefft M, Vawter GF, Mitus A. Paravertebral 'round cell' tumors in children. Radiology. 1969;92:1501–1509.
17. Burchill SA. Ewing's sarcoma: diagnostic, prognostic, and therapeutic implications of molecular abnormalities. J Clin Pathol. 2003 Feb;56(2):96-102
18. Zöllner SK, Amatruda JF, Bauer S, Collaud S, de Álava E, DuBois SG, Hardes J, Hartmann W, Kovar H, Metzler M, Shulman DS, Streitbürger A, Timmermann B, Toretsky JA, Uhlenbruch Y, Vieth V, Grünewald TGP, Dirksen U. Ewing Sarcoma-Diagnosis, Treatment, Clinical Challenges and Future Perspectives. J Clin Med. 2021 Apr 14;10(8):1685.
19. Delattre O, Zucman J, Plougastel B, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992;359:162–5.
20. Khoury JD. Ewing sarcoma family of tumors. Adv Anat Pathol. 2005;12:212–20.
21. Randall RL, Lessnick SL, Jones KB, et al. Is There a Predisposition Gene for Ewing's Sarcoma? J Oncol. 2010;2010:1–6.
22. Patterson FR, Basra SK. Ewing's sarcoma. In: Schwartz HS, editor. Orthopaedic knowledge update: musculoskeletal tumors 2. Rosemont: American Academy of Orthopaedic Surgeons; 2007. pp. 175–183.
23. Gyorke T, Zajic T, Lange A, Schafer O, Moser E, Mako E, Brink I. Impact of FDG PET for staging of Ewing sarcomas and primitive neuroectodermal tumours. Nucl Med Commun. 2006;27(1):17–24.
24. Kovar H., Aryee D.N., Jug G., Henockl C., Schemper M., Delattre O., Thomas G., Gadner H. EWS/FLI-1 antagonists induce growth inhibition of Ewing tumor cells in vitro. Cell Growth Differ. 1996;7:429–437.