

EWING'S SARCOMA: APPROACHING CENTURY SINCE THIS BONE CANCER MADE NEWS

A 100 years have gone by since James Stephen Ewing published the first edition of 'Neoplastic Diseases: A Text-Book on Tumours,' in 1919.^[1] This landmark publication formally laid down the foundations of the discipline of oncology. James Ewing's contribution to modern-day oncological diagnosis and research has been immense. He cofounded the American Association for Cancer Research in 1907 and was its first president. He was also the first Professor of Pathology at Cornell and later became the director of Memorial Sloan-Kettering Cancer Center. In 1921, Ewing reported a new bone cancer and called it 'a diffuse endothelioma of the bone.' This discovery was later named after the maestro himself and since has been known to the world as Ewing's sarcoma.^[2,3]

Ewing's sarcoma is a small, round, blue cell malignancy arising from bone or soft tissue and most commonly affects adolescents and young adults. Although the histogenesis remains debatable, the genetic abnormality is characterised by the pathognomonic EWSR1-ETS gene fusions (EWSR1-FLI1) which serve as the oncogenic transcription factor, driving this cancer.^[4]

Globally, Ewing's sarcoma is the third most common primary malignant bone tumour, preceded by multiple myeloma and osteosarcoma and is the most frequent type in population under the age of 15 years.^[5] In Pakistan, this tumour is most prevalent under the age of 30 years with a predilection toward males and is found commonly in vertebrae, tibia, femur and the hip bone.^[6] Local studies show that Ewing's sarcoma is the second most prevalent aggressive bone and/or soft-tissue sarcoma in children, following rhabdomyosarcoma with pelvis, femur and ribs being the most common sites.^[7,8]

Till today, the strongest predictor of survival for Ewing's sarcoma is the stage at the time of initial diagnosis, thus suggesting that the earlier the detection, the favourable

the outcomes. The diagnostic algorithm consists of magnetic resonance imaging and/or computed tomography (CT) scan of the primary site, chest CT scan, positron-emission tomography and/or bone scan and bone marrow biopsy. However, as molecular diagnostic techniques are refined, it is evident that a significant proportion of patients with apparently localised disease may have micrometastatic involvement in the bone marrow.^[9]

The treatment regimen consists of aggressive chemotherapy with radiation and surgery. With the establishment of this multimodal approach, there has been an improvement in the survival rate from 20% in the non-chemotherapy era to 70% in modern times. Worldwide, three strategies are commonly used for chemotherapy. In North America, the combination of vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide and etoposide used in a time intense schedule, is considered the standard. In Europe, there is predilection toward the use of vincristine, ifosfamide and doxorubicin and etoposide (VIDE) as the initial chemotherapy regimen. In adult patients, the regimen VIDE has also been used including the use of dactinomycin in some regimens. To minimize therapy related toxicity, risk stratification is used in Euro-Ewing-99 protocol dividing patients into three risk groups based on tumour volume, presence and pattern of metastatic disease and histologic response to induction therapy. The treatment is then modified based on these three risk groups.^[10]

Amid the advances in treatment, a quarter of the patients will experience recurrence, majority of them within 2 years of initial diagnosis and with more than two third relapses occurring at distant sites most commonly the lungs and/or bones. These recurrences bear poor outcomes, despite the progress made in the management of patients with localised ES, patients with recurrent or metastatic disease have very few options. Treatment intensification, often including consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue, has not

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proven to improve survival and has shown no benefit over standard chemotherapeutic regimens.^[10]

The enhanced understanding of Ewing's pathophysiology has enabled the introduction of more selective, effective, and less toxic 'targeted' agents for antitumor activity. The EWSR1-FLI1 target genes are very specifically expressed in Ewing's sarcoma relative to normal tissues, and hence, experimental immunotherapeutic interventions have been targeted at this signalling pathway to achieve favourable outcomes. Biochemical evaluation has shown a high expression rate of insulin-like growth factor 1 receptor (IGF-1R) on the surface of the Ewing's sarcoma tumour cells which has been hypothesised to drive tumour growth. Hence, ganitumab (an IGF-1R antibody) is being used in conjunction with conventional chemotherapy for patients with newly diagnosed metastatic Ewing's sarcoma.^[11]

Extensive research is underway in an attempt to find predictive biomarkers for early diagnosis and specific prompt treatment of Ewing's sarcoma. Among these biomarkers for antibody-directed therapy are placenta growth factor, which may be implicated in invasiveness and metastatic potential of Ewing's sarcoma and poly ADP-ribose polymerase 1, which has been shown to exponentially increase in Ewing's tumour and carry a positive feedback loop with the EWS-FLI1 fusion transcript. The exciting new insights in immunotherapy of Ewing's sarcoma and other paediatric sarcomas introduce the novel concept of integrating antibody-based and cell-based immunotherapy into an overall treatment strategy.^[12]

The Western world has benefitted massively with the increased knowledge and novel therapeutic regimens; however, the low- and middle-income countries, where the large bulk of this cancer is prevalent, still have not gained much. The success of therapy is based on multimodal approach and interdisciplinary efforts of oncologist, surgeons, radiation oncologists, pathologist and radiologist in effectively treating these solid tumours and sarcomas.^[13] With scarce health-care resources and inadequate finances, there is an inability to accumulate all the required expertise in an attempt to cater to large populations in the low socioeconomic countries such as Pakistan.

There are limited data available on the long-term survival of Ewing's sarcoma patients managed in Pakistan. However,

unpublished data (abstracts presented) from two paediatric oncology centres in Karachi show that there are at least 60% overall survival rates for localised Ewing's disease, but this is limited to patients who complete their treatment according to standard guidelines and who reached paediatric oncology centres where oncologist, surgeons and radiation oncologist could give treatment in a multidisciplinary approach. Among the issues faced in Pakistan, the most important factors influencing poor outcomes are late referrals, followed by inadequate diagnosis and treatment.^[14]

Perhaps, one of the most significant barriers in the advancement of therapy is the lack of cancer registries at national level which makes it difficult to gauge the burden of disease and short-/long-term outcomes.^[15] The way forward is to utilize the hospital-based registries and provincial data to form minimum diagnostic and therapeutic guidelines, tailored to the needs of our own population. This includes deciding the chemotherapy regimen to accommodate the needs of our community and exploring surgical innovations to accommodate local needs.

In conclusion, there has been tremendous progress in understanding the pathophysiology, therapy and diagnosis of Ewing's sarcoma in the past 100 years. The next decade will be an era of 'precision medicine,' with each individual being treated, based on his/her own risks and desired outcomes. A lot of work still needs to be done in developing 'cure,' especially in areas of metastatic and recurrent disease. Being a developing nation with double burden of disease, we have to start from scratch and strengthen our basic skills with specific focus on spreading awareness, appropriate referrals, capacity building, supportive care and proper documentation, including the advent of national disease registries and national protocols.

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