Cancer Association of South Africa (CANSA)

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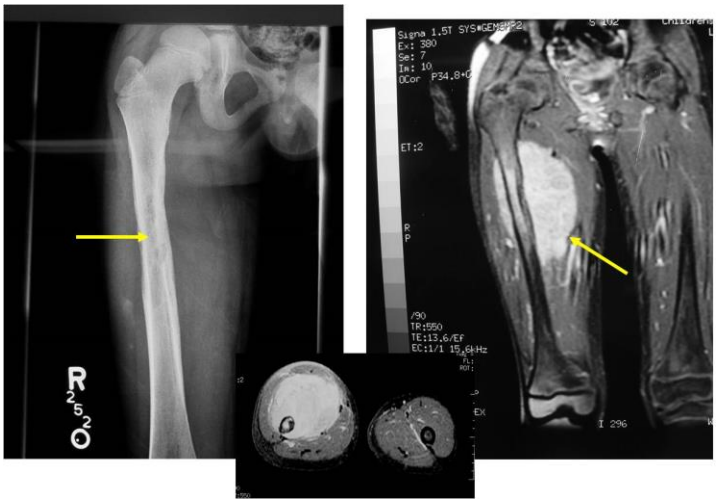
Fact Sheet
on
Ewing's Sarcoma in Children

Introduction

Ewing's sarcoma is a primary bone cancer that affects mainly children and adolescents. It is one of a group of cancers known collectively as the Ewing sarcoma family of tumours - ESFT or sometimes just EFT. It is the second most common bone cancer in children, but is also relatively uncommon. It accounts for only 1% of all childhood cancers. Although it can occur at any age, it very rarely occurs in adults over the age of 30.



[Picture Credit: Ewing's Sarcoma 1]

Because many illnesses can cause the same symptoms as Ewing's sarcoma, it is sometimes missed in its early stages. But early diagnosis and treatment is important. If found early enough, before it spreads to multiple organs, Ewing's sarcoma can be treated successfully in 50% to 75% of cases.

Ewing's Sarcoma

Ewing's sarcoma or Ewing sarcoma is a malignant small, round, blue cell tumour. It is a rare disease in which cancer cells are found in the bone or in soft tissue. The most common areas in which it occurs are the pelvis, the femur, the tibia, the humerus, the ribs and clavicle (collar bone).

Because a common genetic locus is responsible for a large percentage of Ewing's sarcoma and primitive neuro-ectodermal tumours, these are sometimes grouped together in a category known as the Ewing Family of Tumours (EFT). The diseases are, however, considered to be different: peripheral primitive neuro-ectodermal tumours are generally not associated with bones, while Ewing sarcomas are most commonly related to bone.

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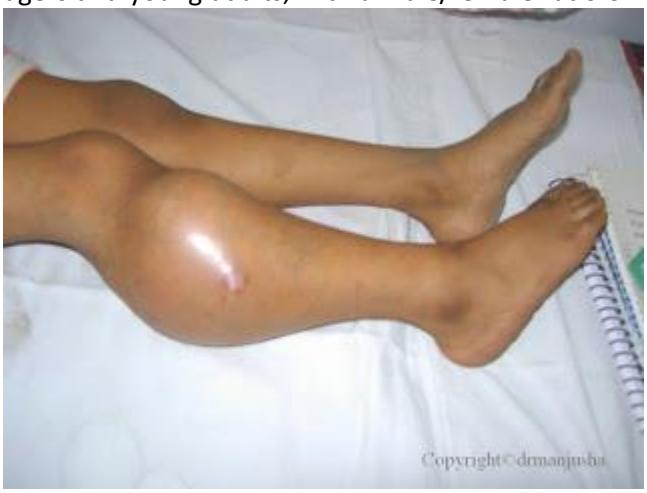
Ewing's sarcoma occurs most frequently in teenagers and young adults, with a male/female ratio of 1.6:1.



Although usually classified as a bone tumour, Ewing's sarcoma can have characteristics of both mesodermal and ectodermal origin, making it difficult to classify.

[Picture Credit: Ewing's Sarcoma 2]

Ewing's sarcoma is the second most common type of bone cancer in children, although very rare.

- Most of all Ewing's sarcoma tumours occur in children and young adults between ages 10 and 20
- This type of cancer is rarely found in African-Americans and Asian-Americans
- The racial incidence in South Africa is also not known
- It affects slightly more boys than girls
- It does not appear to be inherited (passed down in families)
- Although not often seen, Ewing's sarcoma can occur as a second cancer, especially in patients treated with radiation therapy

Pasha, A., Vignoli, M., Subbiani, A., Nocentini, A., Selleri, S., Gratteri, P., Dabraio, A., Casini, T., Filippi, L., Fotzi, I., Favre, C. & Calvani, M. 2019.
"Ewing Sarcoma (ES) is an aggressive paediatric tumour where oxidative stress and antioxidants play a central role in cancer therapy response. Inhibiting antioxidants expression, while at the same time elevating intracellular reactive oxygen species (ROS) levels, have been proposed as a valid strategy to overcome ES cancer progression. Flavonoid intake can affect free radical and nutritional status in children receiving cancer treatment, but it is not clear if it can arrest cancer progression. In particular, apigenin may enhance the effect of cytotoxic chemotherapy by inducing cell growth arrest, apoptosis, and by altering the redox state of the cells. Little is known about the use of apigenin in paediatric cancer. Recently, β3-adrenergic receptor (β3-AR) antagonism has been proposed as a possible strategy in cancer therapy for its ability to induce apoptosis by increasing intracellular levels of ROS. In this study we show that apigenin induces cell death in ES cells by modulating apoptosis, but not increasing ROS content. Since ES cells are susceptible to an increased oxidative stress to reduce cell viability, here we demonstrate that administration of β3-ARs antagonist, SR59230A, improves the apigenin effect on cell death, identifying β3-AR as a potential discriminating factor that could address the use of apigenin in ES."

Incidence of Ewing's Sarcoma in South Africa
The South African Cancer Registry (2017) does not provide any information on the incidence of sarcoma cases.

Causes and Risk Factors of Ewing's Sarcoma

There has been a lot of research into possible causes of Ewing's sarcoma but the exact cause remains unknown.

Like osteosarcoma, the development of Ewing's sarcoma may be related in some way to periods of rapid bone growth. This may explain why most cases of Ewing's sarcoma are seen in adolescents. Known risk factors include:

- Sex: more common in males than females (1.6 males to every female)
- Age: most cases are found between the ages of 10-20
- Race: Ewing's sarcoma tends to be rarer in some racial groups. It seems to be less common in black and Chinese children compared to other races. This suggests there may be a genetic factor involved.

Abbott, D., O'Brien, S., Farnham, J.M., Young, E.L., Yap, J., Jones, K., Lessnick, S.L., Randall, R.L., Schiffman, J.D. & Cannon-Albright, L.A. 2019.

Background: There are few reports of the association of other cancers with Ewing sarcoma in patients and their relatives. We use a resource combining statewide genealogy and cancer reporting to provide unbiased risks.

Methods: Using a combined genealogy of 2.3 million Utah individuals and the Utah Cancer Registry (UCR), relative risks (RRs) for cancers of other sites were estimated in 143 Ewing sarcoma patients using a Cox proportional hazards model with matched controls; however, risks in relatives were estimated using internal cohort-specific cancer rates in first-, second-, and third-degree relatives.

Results: Cancers of three sites (breast, brain, complex genotype/karyotype sarcoma) were observed in excess in Ewing sarcoma patients. No Ewing sarcoma patients were identified among first-, second-, or third-degree relatives of Ewing sarcoma patients. Significantly increased risk for brain, lung/bronchus, female genital, and prostate cancer was observed in first-degree relatives. Significantly increased risks were observed in second-degree relatives for breast cancer, nonmelanoma eye cancer, malignant peripheral nerve sheath cancer, non-Hodgkin lymphoma, and translocation sarcomas. Significantly increased risks for stomach cancer, prostate cancer, and acute lymphocytic leukemia were observed in third-degree relatives.

Conclusions: This analysis of risk for cancer among Ewing sarcoma patients and their relatives indicates evidence for some increased cancer predisposition in this population which can be used to individualize consideration of potential treatment of patients and screening of patients and relatives.

[Picture Credit: Ewing Sarcoma 3]

Signs and Symptoms of Ewing's Sarcoma

The signs and symptoms of Ewing's sarcoma will depend on the size of the cancer and where it is in the body. The main symptoms are:

- bone pain in the affected area; in many patients this grows more severe over time and is especially bad at night
- swelling and tenderness in the affected area.

Other less common symptoms include:

- fever
- a feeling of exhaustion
- weight loss

As tumours grow, they can also put pressure on the soft tissues around them, causing swelling and pain. Some Ewing's sarcomas cause no symptoms at all, but weaken the affected bone. This means it is at risk of fracturing.

These symptoms, however, can be caused by a wide range of conditions and many patients who experience them will not have Ewing's sarcoma. Pain and swellings, for example, can be the result of sports injuries.

Diagnosis of Ewing's Sarcoma

A definitive diagnosis is made almost always on biopsied material. This should be obtained incisionally rather than by needle core in order to provide sufficient material for pathologic interpretation and for biologic studies.

Frozen sections may be used to determine whether the biopsy has provided lesional tissue but should not be the basis for a final diagnosis. It is strongly preferred that the biopsy be obtained by an orthopaedic surgeon who will perform the operation to achieve local tumour control, adhering to the principles of surgical oncology (UICC).

Cesari, M., Righi, A., Colangeli, M., Gambarotti, M., Spinnato, P., Ferraro, A., Longhi, A., Abate, M.E., Palmerini, E., Paioli, A., Ferrari, C., Donati, D.M., Picci, P. & Ferrari, S. 2019.

BACKGROUND: Ewing sarcoma (ES) is the second most common bone tumor in adolescents and children. Staging workup for ES includes imaging and bone marrow biopsy (BMB). The effective role of BMB is now under discussion.

PROCEDURE: A monoinstitutional retrospective analysis reviewed clinical charts, imaging, and histology of patients with diagnosis of ES treated at the Rizzoli Institute between 1998 and 2017.

RESULTS: The cohort included 504 cases of ES of bone; 137 (27%) had metastases at diagnosis, while the remaining 367 had localized disease. Twelve patients had a positive BMB (2.4%). Eleven had distant metastases detected at initial workup staging with imaging assessment: six patients presented with bone metastases, five with both bone and lung metastases. Only one patient with ES of the foot (second metatarsus) was found to have bone marrow involvement with negative imaging evaluation (0.3%).

CONCLUSIONS: On the basis of our data, we suggest reconsidering the effective role of BMB in initial staging workup for patients with ES with no signs of metastases by modern imaging

techniques. In metastatic disease, the assessment of the bone marrow status may remain useful to identify a group of patients at very high risk who could benefit from different treatment strategies.

Treatment of Ewing's Sarcoma
The treatment of Ewing's sarcoma may include:

Chemotherapy - is usually the first step in treating Ewing's sarcoma.

Surgery - may be done after several weeks or months of chemo have reduced the cancer to the point where surgery can be most effective.

Radiation therapy - is used to kill or decrease cancer cells that cannot be removed surgically. This may be followed by more chemo to kill any remaining cells.

Standard treatment options for localised Ewing sarcoma usually include the following:
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Chemotherapy.
Local-control measures:

- Surgery
- Radiation therapy
- High-dose chemotherapy and autologous stem cell rescue

Because most patients with apparently localized disease at diagnosis have occult metastatic disease, multidrug chemotherapy and local disease control with surgery and/or radiation therapy is indicated in the treatment of all patients. Current regimens for the treatment of localized Ewing sarcoma achieve event-free survival (EFS) and overall survival (OS) of approximately 70% at 5 years after diagnosis.

Bhattacharjee, S., Venkata, S.R. & Uppin, M.S. 2018.
BACKGROUND: Ewing's sarcoma is a disease of children and young adults and occurs most often in bone and soft tissues. The intracranial and spinal manifestation of the disease is rare and reported incidence is 1%-6%.
AIMS AND OBJECTIVES: We conducted this study to determine the surgical outcome of children with skull and spine Ewing's sarcoma (SSES).
METHODS: This is a prospective analysis of 13 patients of SSES who reported to the Department of Neurosurgery, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, between 2014 and 2016. All cases after detailed examination, magnetic resonance imaging, and computed tomography scan were subjected to surgery followed by adjuvant therapy comprising chemotherapy and radiotherapy. Outcome was analyzed at 6 months as well at latest follow-up. Neurological function, local recurrence, primary or secondary nature of the disease, distant relapse, and treatment-related complications were analyzed in this study.
RESULTS: There were eight female and five male patients with a mean age of 12 years (ranging from 4 to 8 years). Pain was the common presenting feature in all cases. Focal neurological deficits corresponding to the anatomical location was seen in six patients. These 13 cases were distributed anatomically as four cases involving the cloves, two cases with occipital bone and lobe involvement,

one case of parietal bone and lobe involvement, and six cases of spinal involvement. Surgery was performed in all cases where gross total excision (Ozge C, Calikoglu M, Cinel L, Apaydin FD, Ozgür ES. Massive pleural effusion in an 18-year-old girl with Ewing sarcoma. Can Respir J 2004;11:363-5), near-total excision, and subtotal excision was achieved in these 13 cases (Steinbok P, Flodmark O, Norman MG, Chan KW, Fryer CJ. Primary Ewing's sarcoma of the base of the skull. Neurosurgery 1986;19:104-7). Subsequently all cases underwent multiagent chemoradiotherapy. Postsurgery pain subsided in 12 (92%) of patients. Ten patients maintained or improved motor function. In seven cranial cases and in six spinal cases, four cases showed improvement whereas three (23%) had deterioration of motor function.
CONCLUSIONS: Surgical outcome of SSES in short-term follow-up is good with current recommended management regimen of maximum excision followed by chemo and radiotherapy. However, metastasis is not uncommon.

Elshahoubi, A., Alnassan, A. & Sultan, I. 2019.
BACKGROUND: Children with Ewing sarcoma (ES) are subjected to an interval-compressed regimen with cycles of chemotherapy given every 2 weeks, which is nowadays considered to be the standard of care for individuals with such a case. We developed institutional clinical practice guidelines (CPG) applying outpatient administration in regard to this regimen. This study intends to evaluate our institutional experience with this regimen.
METHODS: We conducted a retrospective review of patients with ES who were treated using interval-compressed protocol of 14 cycles consisting of alternating cyclophosphamide, doxorubicin, vincristine (VDC) and ifosfamide, etoposide (IE) with a maximum dose of doxorubicin of 375 mg/m. Cycles were subsequently followed by G-CSF administration until count recovery was recorded. Patients treated using our guidelines from June 2013 to June 2015 were eligible for these guidelines. Patients younger than 3 years at the time of diagnosis were not eligible for outpatient administration of chemotherapy.
RESULTS: In total 12 patients with localized ES or lung-only metastasis were eligible. By the time of analysis, 153 cycles were administered to these patients. Eight cycles for 6 patients were administered on an inpatient basis while the rest (N=145) were administered in the outpatient chemotherapy unit. The median number of cycles per patient were 14 (with a range of 5 to 14). Ninety cycles (59%) were administered on time per CPG. The median interval between these cycles were 16 days (range, 12 to 36 days). The median interval between induction and consolidation cycles were 14 and 17 days, respectively. Neutropenia was reported at the time of each next cycle for 12 cycles. Transient gross hematuria was reported in 1 patient only. In addition, a cost saving of 21% (approximately US$ 4500) were achieved per patient.
CONCLUSIONS: Our study showed that the outpatient administration of interval-compressed regimen is safe and associated with acceptable adherence to this regimen.

Involvement of a Multidisciplinary Treatment Team

A multidisciplinary team consisting of all (or most) of the following specialities should preferably be involved in the treatment of a child with Ewing's Sarcoma:

- Paediatric oncologist
- Paediatric Surgical oncologist
- Radiation oncologist

Late Side Effects

A small number of children may develop other side effects, sometimes many years later. These include a reduction in normal bone growth, infertility, a change in the way the heart and lungs work, and a small increase in the risk of developing a second cancer later in life.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Dr James Ewing
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Ewing's Sarcoma 2
https://www.google.co.za/search?q=genetic+causes+of+Ewing+sarcoma&source=lnms&tbm=isch&sa=X&ei=HBnWU-OMEoKI7AaPzoCABA&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=1MgOnjuTZ3aHsM%253A%3BCUK6duxqC1ZVCM%3Bhttp%253A%252F%252F3.bp.blogspot.com%252F_QLnTCCtS6g0%252FRuLvXEVa-zI%252FAAAAAAAAADQ%252FtcwzsK9vfsw%252Fs320%252FES%252Bclinical%252B2.jpg%3Bhttp%253A%252F%252Fpaediatric-cancer.blogspot.com%252F%3B320%3B240

Ewing's Sarcoma 3
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http://ghr.nlm.nih.gov/condition/ewing-sarcoma

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