Cancer Association of South Africa (CANSA)

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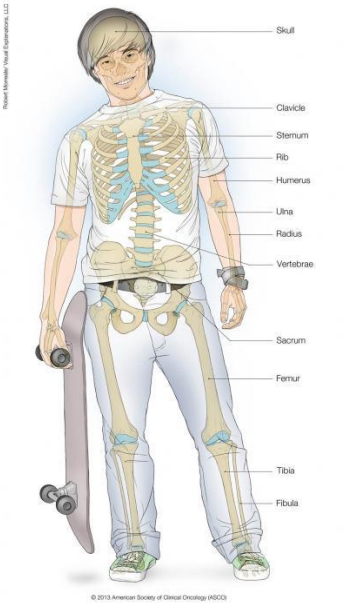
Fact Sheet
on
Ewing's Sarcoma

Introduction

A carcinoma forms in the skin or tissue cells that line the body's internal organs, such as the kidneys and liver, whereas a sarcoma grows in the body's connective tissue cells, which include fat, blood vessels, nerves, bones, muscles, deep skin tissues and cartilage. Carcinomas are the most common type of cancer.



[Picture Credit: Ewing's Sarcoma]

Sarcoma, on the other hand, is an uncommon group of cancers which arise in the bones and connective tissue such as fat and muscle. In most cases, it's not clear what causes sarcoma. Family history and exposure to chemicals or radiation may increase risk. Symptoms depend on tumour type and location. They may include a noticeable lump or pain.

White, V.M., Orme, L.M., Skaczkowski, G., Pinkerton, R., Coory, M., Osborn, M., Bibby, H., Nicholls, W., Conyers, R., Phillips, M.B., Harrup, R., Walker, R., Thompson, K. & Anazodo, A. 2019.

BACKGROUND: While overall survival (OS) for cancer in adolescents and young adults (AYA) has improved, there has been little change in AYA survival for several types of sarcomas. Using national data for Australia we describe (1) the treatment centers caring for AYA sarcoma, (2) treatments provided, and (3) survival outcomes.

PROCEDURE: National population-based study assessing treatment of 15-24 year-olds diagnosed with soft tissue sarcoma(STS), bone sarcoma (BS), and Ewing family tumors (ET) between 2007 and 2012. Treatment details were abstracted from hospital medical records. Treatment centers were classified as pediatric or adult specialist AYA/sarcoma center, or other adult. Cox proportional hazard regression analyses examined associations between type of treatment center and OS.

RESULTS: Sixty-one hospitals delivered treatment to 318 patients (135 STS; 91 BS, 92 ET), with 9%, 22%, and 17% of STS, BS, and ET, respectively, treated at pediatric and 62%, 59%, and 71% at adult specialist hospitals. Of 18-24 year-olds, 82% of BS, 90% of ET, and 73% of rhabdomyosarcomas at adult specialist centers were on a trial or standard protocol, compared with 42%, 89%, and 100%, respectively, at nonspecialist adult hospitals. After adjusting for disease and patient characteristics, survival was not associated with treatment center type for any disease type. However, ET survival was poorer for patients not receiving a standard chemotherapy protocol.

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CONCLUSIONS: Around 10% of AYA sarcoma patients attending adult hospitals were not on a standard protocol. Poorer survival for ET patients not on a standard protocol highlights the importance of ensuring all patients receive optimal care.

Ewing's sarcoma is a malignant tumour that arises in a primitive nerve cell within bone or soft tissue and mostly affects children and adolescents, especially between ages 10 and 20, but it can occur at any age. Ewing's sarcoma usually appears in the large bones of the arms and legs and the flat bones of the pelvis, spine, and ribs.

Berger, G.K., Nisson, P.L., James, W.S., Kaiser, K.N. & Nurlbert, R.J. 2019. Outcomes in different age groups with primary Ewing Sarcoma of the spine: a systematic review of the literature. *J Neurosurg Spine*. 2019 Feb 15:1-10. doi: 10.3171/2018.10.SPINE18795. [Epub ahead of print]
OBJECTIVE: Ewing sarcoma (ES) is among the most prevalent of bone sarcomas in young people. Less often, it presents as a primary lesion of the spine (5%-15% of patients with ES).
METHODS: A systematic literature search was performed, querying several scientific databases per PRISMA guidelines. Inclusion criteria specified all studies of patients with surgically treated ES located in the spine. Patient age was categorized into three groups: 0-13 years (age group 1), 14-20 years (age group 2), and > 21 (age group 3).
RESULTS: Eighteen studies were included, yielding 28 patients with ES of the spine. Sixty-seven percent of patients experienced a favorable outcome, with laminectomies representing the most common (46%) of surgical interventions. One-, 2-, and 5-year survival rates were 82% (n = 23), 75% (n = 21), and 57% (n = 16), respectively. Patients in age group 2 experienced the greatest mortality rate (75%) compared to age group 1 (9%) and age group 3 (22%). The calculated relative risk score indicated patients in age group 2 were 7.5 times more likely to die than other age groups combined (p = 0.02).
CONCLUSIONS: Primary ES of the spine is a rare, debilitating disease in which the role of surgery and its impact on one's quality of life and independence status has not been well described. This study found the majority of patients experienced a favorable outcome with respect to independence status following surgery and adjunctive treatment. An increased risk of recurrence and death was also present among the adolescent age group (14-20 years).

Incidence of Ewing's Sarcoma in South Africa
The National Cancer Registry (2014) does not provide any information on Ewing's Sarcoma.

Risk Factors of Ewing's Sarcoma
Doctors and researchers do not know what causes most cancers in children and teens, but the following factors may raise a person's chance of developing Ewing sarcoma:

- Genetic changes - Changes in a tumour cell's chromosomes appear to be responsible for Ewing's sarcoma, but the disease is not inherited. This means that it is not passed down from a parent to a child. The genetic changes occur for no known reason. A high percentage of Ewing's sarcoma cells have a chromosomal translocation, which means that small pieces of genetic material have swapped places inside the tumour cell. Usually the translocation is between chromosomes 11 and 22, although it may also occur between chromosomes 21 and 22, 7 and 22, and 17 and 22. The fusion of these bits of genetic material results in the out-of-control growth of Ewing's sarcoma cells.

- Age – Ewing's sarcoma can occur at any age. More than half of people with Ewing's sarcoma are between the ages of 10 and 20, with a median age of 15 years.
- Gender – Ewing's sarcoma is more common among boys than girls.
- Race/ethnicity – Ewing's sarcoma occurs most frequently in white people and is rare in black people in the United States and Africa. Ewing's sarcoma has been reported in Japan but is uncommon in China.

Signs and Symptoms of Ewing's Sarcoma

Signs and symptoms of Ewing's sarcoma may include:

- Pain, swelling or tenderness near the affected area - about 85% of children and teens with Ewing's sarcoma have pain that can come and go and sometimes is less severe at night
- Bone pain, which may worsen at night or with physical activity
- Stiffness or tenderness in the bone or in the tissue surrounding the bone
- Unexplained tiredness
- Fever with no known cause
- Unintended weight loss
- Broken bone without any known cause

Because the above signs and symptoms are non-specific and could be the result of another illness or condition, Ewing's Sarcoma tumours may not be suspected or found right away. It is important to monitor for these symptoms, recognise when they are persisting, and to follow up with one's doctor for further investigations.

Diagnosis of Ewing's Sarcoma

In addition to a physical examination, the following tests may be used to diagnose Ewing sarcoma:

Blood Tests

- a complete blood count (CBC)
- liver function test
- kidney function tests

Imaging Tests

- X-ray to create a picture of the organs and tissues of the body
- Computed Tomography (CT or CAT) scan
- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET) or Pet-CT scan
- Bone scan

Surgical Tests

- Biopsy
- Bone Marrow Aspiration

Other Tests

- Immunohistochemistry tests
- Cytogenic Tests
- Reverse Transcription Polymerawse Chain Reaction (RT-PCR)

Rizk, V.Y., Walko, C.M. & Brohl, A.S. 2019.
"Advancements in molecular and genetic techniques have significantly furthered our biological understanding of Ewing sarcoma (ES). ES is typified by a driving TET-ETS fusion with an otherwise relatively quiet genome. Detection of one of several characteristic fusions, most commonly *EWSR1-FLI1*, is the gold standard for diagnosis. We discuss the current role of precision medicine in the diagnosis, treatment, and monitoring of ES. Continued efforts toward molecularly guided approaches are actively being pursued in ES to better refine prognosis, identify germline markers of disease susceptibility, influence therapeutic selection, effectively monitor disease activity in real time, and identify genetic and immunotherapeutic targets for therapeutic development."

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
Treatment of Ewing's Sarcoma may include surgery, radiation and chemotherapy or a combination of all three.

Yu, H., Ge, Y., Guo, L. & Huang, L. 2017. Potential approaches to the treatment of Ewing's Sarcoma. *Oncotarget*. 2017 Jan 17;8(3):5523-5539. doi: 10.18632/oncotarget.12566.
"Ewing's sarcoma (ES) is a highly aggressive and metastatic tumor in children and young adults caused by a chromosomal fusion between the Ewing sarcoma breakpoint region 1 (EWSR1) gene and the transcription factor FLI1 gene. ES is managed with standard treatments, including chemotherapy, surgery and radiation. Although the 5-year survival rate for primary ES has improved, the survival rate for ES patients with metastases or recurrence remains low. Several novel molecular targets in ES have recently been identified and investigated in preclinical and clinical settings, and targeting the function of receptor tyrosine kinases (RTKs), the fusion protein EWS-FLI1 and mTOR has shown promise. There has also been increasing interest in the immune responses of ES patients. Immunotherapies using T cells, NK cells, cancer vaccines and monoclonal antibodies have been considered for ES, especially for recurrent patients. Because understanding the pathogenesis of ES is extremely important for the development of novel treatments, this review focuses on the mechanisms and functions of targeted therapies and immunotherapies in ES. It is

anticipated that integrating the knowledge obtained from basic research and translational and clinical studies will lead to the development of novel therapeutic strategies for the treatment of ES."

Thanindratarn, P., Dean, D.C., Nelson, S.D., Hornicek, F.J. & Duan, Z. 2019. Advances in immune checkpoint inhibitors for bone sarcoma therapy. *J Bone Oncol*. 2019 Jan 29;15:100221. doi: 10.1016/j.jbo.2019.100221. eCollection 2019 Apr.
"Bone sarcomas are a collection of sporadic malignancies of mesenchymal origin. The most common subtypes include osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma. Despite the use of aggressive treatment protocols consisting of extensive surgical resection, chemotherapy, and radiotherapy, outcomes have not significantly improved over the past few decades for osteosarcoma or Ewing sarcoma patients. In addition, chondrosarcoma and chordoma are resistant to both chemotherapy and radiation therapy. There is, therefore, an urgent need to elucidate which novel new therapies may affect bone sarcomas. Emerging checkpoint inhibitors have generated considerable attention for their clinical success in a variety of human cancers, which has led to works assessing their potential in bone sarcoma management. Here, we review the recent advances of anti-PD-1/PD-L1 and anti-CTLA-4 blockade as well as other promising new immune checkpoint targets for their use in bone sarcoma therapy."

Ren, Y., Zhang, Z., Shang, L. & You, X. 2019.
BACKGROUND: Metastatic Ewing's sarcoma (ES) of bone has a poor prognosis. Because there have been few previous studies on the prognostic factors and clinical outcome in patients with ES who have metastases at presentation, the aim of this study was to use the Surveillance, Epidemiology, and End Results (SEER) database to compare the clinical outcome following single and combined radiation treatment and surgery.
MATERIAL AND METHODS: The SEER database was used to identify patients with ES who presented with bone involvement and metastasis between 1973 to 2015. Prognostic analysis was performed using the Kaplan-Meier method and the Cox proportional hazards regression model.
RESULTS: There were 643 patients identified from the SEER database. The 5-year overall survival (OS) and cancer-specific survival (CSS) rates were 33.1% and 34.3%, respectively and the median OS and CSS were 29.0±1.9 and 29.0±2.1 months, respectively. Multivariate analysis identified age <20 years and surgical resection of the primary tumor to be significantly associated with improved OS. Radiation therapy was not an independent predictor of OS or CSS. Radiation therapy alone resulted in a significantly reduced the OS and CSS compared with surgical resection alone. Combined surgery and radiation therapy of the primary tumor did not significantly improve the OS or CSS of patients with ES and metastatic disease when compared with surgery alone.
CONCLUSIONS: Age <20 years and surgical resection of the primary tumor were significantly associated with improved OS in patients with primary ES of bone who presented with metastasis.

Borrego-Paredes, E., Prada-Chamorro, E., Chacón-Cartaya, S., Santos-Rodas, A., Gallo-Ayala, J.M. & Hernández-Beneit, J.M. 2019.
PURPOSE: The purpose of this study is to present our series of Ewing sarcoma cases and the survival data obtained in the medium term, using a multidisciplinary therapy protocol.
MATERIAL, METHODS AND RESULTS: Forty-one Ewing sarcomas were diagnosed, treated and followed-up in our hospital between 2004 and 2009 with an average age of 18.29 years. Seventy-eight percent were to Ewing sarcoma of the bone, the femur being the most frequent location. Sixty-eight percent had a localized stage at the time of diagnosis. At the end of follow-up, 40% of the patients did not survive, most died within the first 5 years of follow-up.

DISCUSSION: In Spain, Ewing sarcoma is the most common primary malignant bone tumour in childhood, ahead of osteosarcoma. Its survival rate has increased greatly in the last 40 years, improvement attributable mainly to the aggressive use of chemotherapy and to multidisciplinary treatment, but its prognosis remains very poor, especially for those with metastasis at diagnosis, the main adverse prognostic factor. Because of its high mortality, many authors consider it a disseminated disease from the beginning, with non-detectable micrometastasis that condition final survival.
CONCLUSIONS: Early diagnosis and multidisciplinary therapy in referral centres are the best strategies currently available to us to provide these patients the maximum possibilities of cure of this disease.

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.

Medical Disclaimer

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Ewing's Sarcoma
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Ewing's Sarcoma (Picture)
https://www.cancer.net/cancer-types/ewing-sarcoma-childhood/view-all

Ren, Y., Zhang, Z., Shang, L. & You, X. 2019. Surgical resection of primary Ewing's Sarcoma of bone improves overall survival in patients presenting with metastasis. *Med Sci Monit*. 2019 Feb 16;25:1254-1262. doi: 10.12659/MSM.913338.

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