# Cancer Association of South Africa (CANSA)

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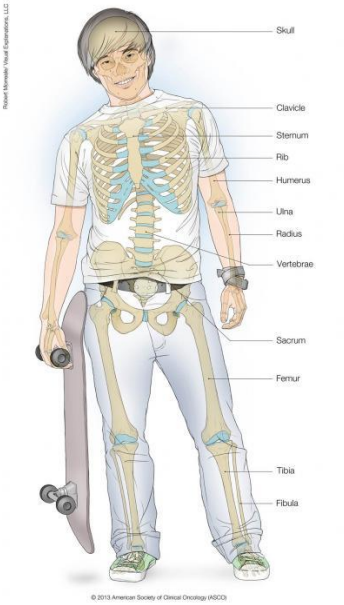
Fact Sheet
on
Ewing's Sarcoma

**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.

**Durer, S. & Shaik, H.** 2020. Cancer, Ewing sarcoma. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2020 Jan. 2020 Jun 23.

"Ewing sarcoma (ES) is an aggressive tumor of adolescents and young adults, which constitutes 10% to 15% of all bone sarcomas. James Ewing first described it in 1921, and it represents 'classic' Ewing sarcoma of bone, extra-skeletal Ewing sarcoma, malignant small cell tumor of the chest wall (Askin tumor), and soft tissue-based primitive neuroectodermal tumors (PNET). These sarcomas originate from unique mesenchymal progenitor cells due to their similar histologic and immunohistochemical characteristics. Ewing sarcoma family tumors (ESFT) are characterized by the presence of non-random chromosomal translocations producing fusion genes that encode aberrant transcription factors. The t(11;22)(q24;q12) translocation is associated with 85% of tumors and leads to EWS-FLI-1 formation, whereas t(21;12)(22;12) and other less common translocations induced EWS-ERG fusion comprises the remaining 10% to 15% of cases. The most common anatomical sites include the pelvis, axial skeleton, and femur; however, it may occur in almost any bone or soft tissue. Typically, patients present with pain and swelling over the site of involvement. Over the last 40 years, both local therapy and multiagent adjuvant chemotherapy have achieved considerable progress in the treatment of localized disease that improved 5–year survival rate from less than 20% to greater than 70% but the recurrence rate remains high. Although most present locally, subclinical metastatic disease is present in almost all. Approximately 25% of patients with initially localized disease ultimately relapse. No standard therapy exists for relapsed and refractory ES, with survival rates being less than 30% in

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those with isolated lung metastases and less than 20% in those with bone and bone marrow involvement. Given these considerations of toxicity and suboptimal survival from metastatic disease, there is an urgent unmet need to develop novel therapies for ES."

**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.
**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 (2017) 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.

**Gargallo, P., Yáñez, Y., Juan, A., Segura, V., Balaguer, J., Torres, B., Oltra, S., Castel, V. & Cañete. A.** 2020.
"Ewing sarcoma is a rare tumor developed in bone and soft tissues of children and teenagers. This entity is biologically led by a chromosomal translocation, typically including EWS and FLI1 genes. Little is known about Ewing sarcoma predisposition, although the role of environmental factors, ethnicity and certain polymorphisms on Ewing sarcoma susceptibility has been studied during the last few years. Its prevalence among cancer predisposition syndromes has also been thoroughly examined. This review summarizes the available evidence on predisposing factors involved in Ewing sarcoma susceptibility. On the basis of these data, an integrated approach of the most influential factors on Ewing sarcoma predisposition is proposed."

**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.

**Italiano, A., Mir, O., Mathoulin-Pelissier, S., Penel, N., Piperno-Neumann, S., Bompas, E., Chevreau, C., Duffaud, F., Entz-Werlé, N., Saada, E., Ray-Coquard, I., Lervat, C., Gaspar, N., Marec-Berard, P., Pacquement, H., Wright, J., Toulmonde, M., Bessede, A., Crombe, A., Kind, M., Bellera, C. & Blay, J.Y.** 2020
**Background:** Patients with Ewing sarcoma or osteosarcoma have a median overall survival of less than 12 months after diagnosis, and a standard treatment strategy has not yet been established. Pharmacological inhibition of MET signalling and aberrant angiogenesis has shown promising results in several preclinical models of Ewing sarcoma and osteosarcoma. We aimed to investigate the activity of cabozantinib, an inhibitor of MET and VEGFR2, in patients with advanced Ewing sarcoma and osteosarcoma.
**Methods:** We did a multicentre, single-arm, two-stage, phase 2 trial in patients with advanced Ewing sarcoma or osteosarcoma recruited from ten centres in the French Sarcoma Group. Key eligibility criteria were aged 12 years or older, Eastern Cooperative Oncology Group performance status of 0-1, and documented disease progression (according to Response Evaluation Criteria in Solid Tumors version 1.1) before study entry. The number of previous lines of treatment was not limited. Patients received cabozantinib (adults 60 mg, children [<16 years] 40 mg/$m^2$) orally once daily in 28-day cycles until disease progression, unacceptable toxicity, the investigator's decision to discontinue, or participant withdrawal. The primary endpoint for Ewing sarcoma was best objective response within 6 months of treatment onset; for osteosarcoma, a dual primary endpoint of 6-month objective response and 6-month non-progression was assessed. All enrolled patients who received at least one dose of cabozantinib were included in the safety analysis, and all participants who received at least one complete or two incomplete treatment cycles were included in the efficacy population. This study was registered with ClinicalTrials.gov, number NCT02243605.
**Findings:** Between April 16, 2015, and July 12, 2018, 90 patients (45 with Ewing sarcoma 45 with osteosarcoma) were recruited to the study. Median follow-up was 31·3 months (95% CI 12·4-35·4) for patients with Ewing sarcoma and 31·1 months (24·4-31·7) for patients with osteosarcoma. 39 (87%) patients with Ewing sarcoma and 42 (93%) patients with osteosarcoma were assessable for efficacy after histological and radiological review. In patients with Ewing sarcoma, ten (26%; 95% CI 13-42) of 39 patients had an objective response (all partial responses) by 6 months; in patients with osteosarcoma, five (12%; 4-26) of 42 patients had an objective response (all partial responses) and 14 (33%; 20-50) had 6-month non-progression. The most common grade 3 or 4 adverse events were hypophosphataemia (five [11%] for Ewing sarcoma, three [7%] for osteosarcoma), aspartate aminotransferase increase (two [4%] for Ewing sarcoma, three [7%] for osteosarcoma), palmar-plantar syndrome (three [7%] for Ewing sarcoma, two [4%] for osteosarcoma), pneumothorax (one [2%] for Ewing sarcoma, four [9%] for osteosarcoma), and neutropenia (two [4%] for Ewing sarcoma, four [9%] for osteosarcoma). At least one serious adverse event was reported in 61 (68%) of 90 patients. No patients died from drug-related toxic effects.
**Interpretation:** Cabozantinib has antitumor activity in patients with advanced Ewing sarcoma and osteosarcoma and was generally well tolerated. Cabozantinib could represent a new therapeutic option in this setting, and deserves further investigation.

**Funding:** Institut Bergonié; French National Cancer Institute; Association pour la Recherche contre le Cancer.

**Thanindratarn, P., Dean, D.C., Nelson, S.D., Hornicek, F.J. & Duan, Z.** 2019.
"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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https://www.cancer.net/cancer-types/ewing-sarcoma-childhood-and-adolescence/symptoms-and-signs

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

**Gargallo, P., Yáñez, Y., Juan, A., Segura, V., Balaguer, J., Torres, B., Oltra, S., Castel, V. & Cañete. A.** 2020. Review: Ewing sarcoma predisposition. *Pathol Oncol Res*. 2020 Oct;26(4):2057-2066. doi: 10.1007/s12253-019-00765-3. Epub 2019 Oct 26.

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