

# Cancer Association of South Africa (CANSA)

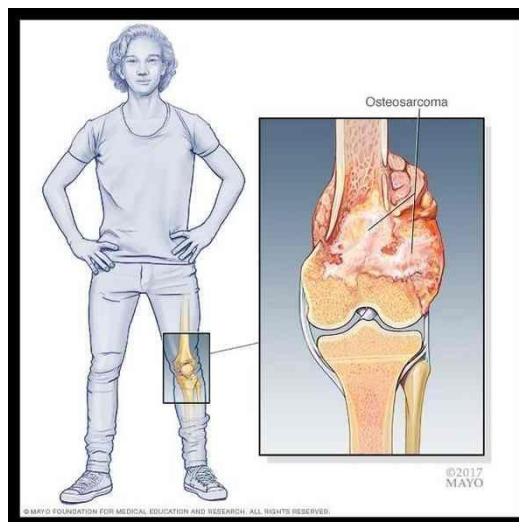


## Fact Sheet on Bone Sarcoma

### Introduction

The second largest group of sarcoma is bone sarcomas or bone cancer. There are three types of bone sarcoma: osteosarcoma; Ewing's sarcoma; and chondrosarcoma. Bone sarcomas very rare with approximately 2,890 new cases diagnosed in the United States each year, and approximately 1,410 deaths. The incidence is slightly higher in males than females and no race has a higher incidence than another, although, Ewing's sarcoma is higher among Americans of European descent. Bone sarcomas are very likely to be diagnosed in children; and due to the rarity and severity of bone cancer, a bone cancer specialist such as a paediatric oncologist or an orthopaedic oncologist should be consulted in the treatment of the disease.

[Picture Credit: Bone Sarcoma]



Bone consist of three types of tissue: compact tissue (the hard outer portion of the bone), cancellous tissue (spongy tissue inside the bone containing the bone marrow), and subchondral tissue (the smooth bone tissue of the joints). Cartilage surrounds the subchondral tissue to form a cushion around the joints.

Bone tumours can be benign (non-cancerous) or malignant (cancerous). Benign bone tumours are rarely life threatening and do not spread within the body; however, they can grow and compress healthy bone tissue. Cancer that develops in the bone is called primary bone cancer. It is differentiated by secondary bone cancer which spreads to the bone from another part of the body.

Primary bone cancer is rare with approximately 2 500 new cases diagnosed each year in the United States (this figure includes bone cancer which is not sarcoma).

The most common type of primary bone cancer is osteosarcoma. Because it occurs in growing bones, it is most often found in children. Another type of primary bone cancer is chondrosarcoma which is found in the cartilage. This cancer occurs more often in adults. Ewing's sarcoma can occur as either a bone sarcoma or a soft tissue sarcoma depending upon the original location in the tumour.

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Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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Page 1

## **Bone Sarcoma**

Bone sarcoma is an extremely rare type of bone neoplasm that starts in the bone. Sometimes a bone sarcoma is called a primary bone cancer. It is an uncommon form of cancer. Bone sarcoma can affect any bone in the body but the most common area it affects is the legs.

### **Rosenberg, A.E. 2017.**

“The pathologic interpretation of malignant bone tumors is one of the more challenging areas in surgical pathology. This is based on the reality that primary bone sarcomas are uncommon, demonstrate significant morphologic heterogeneity, and have a broad spectrum of biology. Accordingly, it is difficult for pathologists to acquire the necessary experience to confidently and accurately diagnose bone sarcomas. The task is further complicated by the fact that it requires the integration of clinical and radiologic information into the diagnostic process. Lastly, molecular aberrations in sarcomas are being newly discovered and their identification is often critical to make specific diagnoses. The pathologist's role in guiding optimal treatment in biopsy specimens is to make an accurate diagnosis and provide the grade and molecular aberrations when appropriate. The pathology report of resected tumors must confirm this information and assess the surgical resection margins and the percentage of necrosis if the sarcoma has been treated with neoadjuvant systemic therapy.”

## **Bone Sarcoma Sub-Types**

The following is a list of bone sarcoma sub-types:

- Chondrosarcoma
- Craniofacial Osteosarcoma
- Ewing's Sarcoma
- Multifocal Sclerosing Osteosarcoma
- Osteosarcoma
- Osteosarcoma in Paget's Disease
- Parosteal Osteosarcoma
- Periosteal Osteosarcoma
- Post-irradiation Osteosarcoma
- Malignant fibrous histiocytoma (MFH)

## **Incidence of Bone Sarcoma in South Africa**

The outdated National Cancer Registry (2016), known for under reporting, does not provide any information regarding the incidence of bone sarcoma.

The incidence of primary bone sarcomas is higher in males than in females, regardless of histologic type. A low-grade variant of osteosarcoma (parosteal osteosarcoma) is observed more frequently in females.

Age - Osteosarcoma and Ewing sarcoma develop primarily in children and adolescents. A biphasic pattern of incidence of osteosarcoma has been observed; peaks have been noted among adolescents (rapid growth of long bones) and in patients over 60 years of age (secondary tumours arising in association with Paget's disease or within previously irradiated tissue). Chondrosarcomas are rarely seen in skeletally immature patients. They usually develop in middle-aged and older adults. MFH is observed in adults.

Race - No predilection has been noted in any particular race. However, Ewing's sarcoma is extremely rare in American and African blacks.

Disease Site - Any bone and any site within a given bone may be affected. Most osteosarcomas occur in the metaphyseal region of skeletally immature long bones (i.e., distal femur, proximal tibia, and proximal humerus), which have the greatest growth potential. Ewing's sarcoma is classically described as a diaphyseal

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(main or midsection of a long bone) lesion, but it may arise in any region within an involved long bone. It commonly arises in the flat bones of the pelvis and scapula. Primary bone tumours of any histologic type are extremely rare in the spine and sacrum.

### **Signs and Symptoms of Bone Sarcoma**

Symptoms of bone sarcoma can vary depending on the size and location of your tumour.

- Bone pain, particularly occurring at night
- A mass or swelling
- Restricted movement in a joint

Symptoms can sometimes be confused with more common problems such as a sports injury or in children and young people, so-called growing pains.

When a bone tumour grows, it presses on healthy bone tissue and can destroy it, which causes the following symptoms:

- Pain - The earliest symptoms of bone cancer are pain and swelling where the tumour is located. The pain may come and go at first. Then it can become more severe and steady later. The pain may get worse with movement, and there may be swelling in nearby soft tissue.
- Joint swelling and stiffness - A tumour that occurs near or in a joint may cause the joint to swell and become tender or stiff. This means a person may have a limited and painful range of movement.
- Limping - If a bone with a tumour breaks, or fractures, in a leg, it can lead to a pronounced limp. Limping is usually a symptom of later-stage bone cancer.
- Other less common symptoms - Rarely, people with bone cancer may have symptoms such as fever, generally feeling unwell, weight loss, and anaemia.

### **Risk Factors for Bone Sarcoma**

In most cases, the cause of bone cancer is unknown. Most cancers begin with an error or mutation in the bone cell DNA, the control region and building blocks of the cells. Changes in the cellular DNA can lead to problems with the cells dividing and multiplying into new cells, potentially causing an uncontrolled growth of abnormal cells.

There are certain known risk factors for developing some types of bone cancer. Osteosarcoma is more common in people who previously have received radiation therapy or treatment with certain chemotherapy medications.

Osteosarcoma is also more common in children who have had hereditary retinoblastoma, which is a rare cancer of the eye.

Ewing's sarcoma is more common in children with hereditary cancer syndromes, including Li-Fraumeni syndrome or Rothmund-Tomson Syndrome, multiple exostoses, or other bone conditions, including Paget's Disease of bone.

**Montgomery, C., Park, K.J., Gardner, J., Majors, I. & Nicholas, R. 2019.**

“Patients often cite a history of trauma prior to the diagnosis of a sarcoma. Sparse literature suggests that there may be a link between sarcoma development and trauma. A 10-year review of academic tertiary-referral sarcoma center database was examined to identify patients who developed a sarcoma after having a history of a significant musculoskeletal trauma. A total of 501 patients were treated for a sarcoma during this time period. Six patients were identified as previously having a significant musculoskeletal trauma at the site of sarcoma development. Half of the sarcomas arose in bone and the other half in soft tissue. Five (83%) patients had multiple operations for the injury with 3 (50%) patients having a postoperative wound infection. The average time from injury to development of the sarcoma was 19.8 years. Survival after diagnosis was poor, and 4 (67%) of the patients died due to their metastatic disease within 3 years of diagnosis. Our findings suggest the possibility of post-traumatic sarcomas.”

**Li, G., Zhang, P., Shang, W., Lei, Z., He, J., Meng, J., Di, T. & Yan, W. 2019.**

**Background:** Ewing sarcoma (ES) is the second commonest primary malignant bone neoplasm. Metastatic status at diagnosis strongly predicted poor prognosis of Ewing sarcoma patients. Yet little was known about the underlying mechanism of ES metastasis.

**Purpose:** This study intended to identify the relationship between key genes/pathways and metastasis/poor prognosis in Ewing's sarcoma patients by using bioinformatic method.

**Methods:** In this study, multi-center sequencing data were obtained from the GEO database, including gene and miRNA expression profile and prognosis information of ES patients. Differentially expressed genes (DEGs) were identified between primary and metastasis ES samples by the GEO2R online tool. Gene ontology (Go) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses of DEGs were performed. And PPI network analyses were conducted. The ES patient's prognostic information was employed for survival analysis, and the potential relationship between miRNAs and key genes was analyzed.

**Results:** The results showed that a total of 298 and 428 DEGs were screened out in metastasis samples based on GSE17618 and GSE12102 dataset compared to primary samples respectively. The most significantly enriched KEGG pathway was the mismatch repair (MMR) pathway. MSH2, MSH6, RPA2, and RFC2 that belong to the MMR pathway were identified as key genes. Moreover, the expression of key genes was increased in metastasis samples compared with primary ones and was associated with poor event-free and overall survival of ES patients. The negative correlation of the expression level of the key genes with patients prognosis also supported by TCGA sarcoma database. Furthermore, knockdown of EWSR/FLI1 fusion in ES cell line A673 down-regulates the expression of the 4 key genes was revealed by GDS4962.

**Conclusion:** In conclusion, the present study indicated that the key genes promote our understanding of the molecular mechanisms underlying the development of ES metastasis, and might be used as molecular targets and diagnostic biomarkers for the treatment of ES.

## **Diagnosis of Bone Sarcoma**

Diagnosis of bone sarcoma commences with a complete medical history, family history, and physical examination.

Certain blood tests may be ordered that can help with the diagnosis. Alkaline phosphatase and lactate dehydrogenase are often elevated in the blood of patients with Osteosarcoma and Ewing's Sarcoma.

Imaging studies:

- Plain X-ray of the affected bone
- A bone scan can identify areas of increased bone activity that can occur with fracture, growth, and tumours. It can be used to localise a bone cancer and look for other areas of involvement.

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Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

June 2020

Page 4

- A computed tomography (CT) scan can provide a three-dimensional picture of the bones that can provide a better view of the cancer.
- A Magnetic Resonance Imaging (MRI) scan may be ordered to evaluate the soft tissues or bones involved by a cancer.
- A Positron Emission Tomography (PET) scan involves injecting a small amount of radioactive glucose into the bloodstream and scanning the entire body to look for other areas of increased bone activity. This scan can often be combined with the CT scan for improved detail.

Bone biopsy - after an abnormality has been identified in the bone, the physician may want to obtain a biopsy of the bone. This involves taking a small piece of the bone that can be studied by a pathologist to determine what type of cancer is present.

**Vieth, V. 2019.**

**Background:** Reliable diagnostic assessment of malignant bone lesions remains a challenge in all the medical disciplines involved. The high incidence of benign (mainly pediatric) bone lesions needs to be distinguished from the rare malignant counterparts. If clinical presentation and patient history are unable to exclude a malignant tumour, adequate imaging of the affected region is necessary.

**Objectives:** This article focuses on giving implementable advice in dealing with problems and questions arising in the diagnostic process of treating patients with suspected or confirmed bone sarcoma. Also, follow-up recommendations from a radiological point of view are presented.

**Methods:** Review and discussion of relevant literature against personal experiences in the medical imaging of patients with bone sarcomas.

**Results:** Interpretation of projection radiographic images usually succeeds in assessing a bone tumour's dignity by evaluating periosteal reaction, the formation of a tumour matrix and consideration of the Lodwick classification. A current adaptation of the classic Lodwick classification incorporates diagnostic possibilities of more recent imaging techniques (magnetic resonance imaging (MRI), positron emission tomography (PET)) and is presented in this article. Plain radiographs are superseded by MRI as the primary imaging performed when depicting bone lesions with increasing frequency. The role of MRI in terms of primary diagnostics, staging, planning of biopsy tracts and tumour resections, evaluation of treatment response and follow-up are discussed. All diagnostic imaging techniques, including whole-body imaging methods, relevant in the diagnosis and therapy of bone sarcomas are presented in the sequence in which they appear during treatment.

**Conclusions:** Radiological imaging and expertise are important pillars in diagnosis and treatment of bone sarcomas. A variety of complementing imaging techniques provide a treatment-relevant basis significant for all medical disciplines involved.

### **Treatment of Bone Sarcoma**

Treatment for bone sarcoma may include chemotherapy, radiation therapy and surgery.

Surgery is the most common treatment for bone cancer. The goal of surgery is to remove the entire area of cancer and a surrounding layer of normal bone to help prevent recurrence of the cancer. Depending on the amount of bone removed, the surgeon may replace some of the bone with other normal bone grafts, bone cement, or artificial joints.

**Cirstoiu, C., Cretu, B., Serban, B., Panti, Z. & Nica, M. 2019.**

“Modern surgical management of extremity bone sarcomas is governed by limb-sparing surgery combined with adjuvant and neoadjuvant chemotherapy. All the resection and reconstruction techniques have to achieve oncologic excision margins, with survival rates and functional results superior to amputation. The main

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June 2020

Page 5

reconstruction techniques of bone defects resulted after resection are: modular endoprosthetic reconstruction; bone graft reconstruction; bone transport; resection arthrodesis; and rotationplasty. Oncologic resection and modular endoprosthetic reconstruction are the generally approved surgical options adopted for the majority of cases in major specialized bone sarcoma centres. Good basic principles, efficient multidisciplinary approach and sustained research in the field can provide a better future for the challenge posed by extremity bone sarcoma treatment. Cite this article: *EFORT Open Rev* 2019;4:174-182. DOI: 10.1302/2058-5241.4.180048."

**Zeller, J., Kiefer, J., Braig, D., Winninger, O., Dovi-Akue, D., Herget, G.W., Stark G,B, & Eisenhardt, S.U.** 2019. **Background:** Sarcomas are tumors of mesenchymal origin with high variation in anatomical localization. Sarcomas affecting the bone often require an interdisciplinary resection and reconstruction approach. However, it is critical that microsurgical reconstruction strategies do not negatively impact tumor safety and overall survival, as limb salvage is only the secondary goal of tumor surgery. Here, we analyzed the efficacy and safety of microsurgery in interdisciplinary treatment of sarcoma affecting the bone. **Patients and Methods:** We performed a retrospective chart review of all patients treated for soft-tissue and bone sarcoma at the senior author's institution with a focus on bone affection and microsurgical reconstruction between 2000 and 2019. This particular subgroup was further investigated for tumor resection status, 5-year survival rate, length of hospital stay, as well as overall complication and amputation rates. **Results:** Between 2000 and 2019, 803 patients were operated for sarcoma resection and reconstruction by the Department of Plastic and Hand Surgery. Of these, 212 patients presented with sarcoma of the extremity affecting the bone. Within this subgroup, 40 patients required microsurgical reconstruction for limb salvage, which was possible in 38 cases. R0 resection was achieved in 93.8%. The 5-year survival was 96.7%, and the overall complication rate was 25%, of which 40% were microsurgery associated complications. **Conclusion:** Safe and function-preserving treatment of soft-tissue and bone sarcoma is challenging. Primary reconstruction with microsurgical techniques of sarcoma-related defects enables limb-sparing and adequate oncosurgical cancer treatment without increasing the risk for local recurrence or prolonged hospital stay. The treatment of sarcoma patients should be reserved to high-volume centers with experienced plastic surgeon embedded in a comprehensive treatment concept.

Chemotherapy may be used in some cases of bone cancer. The medications are used to help kill the cancer cells. It may be used to help shrink the cancer cells prior to surgery to allow for a less extensive surgery. It may be used after surgery to help kill any remaining cancer cells left behind following surgery.

**Tamura, A., Yamamoto, N., Nino, N., Ichikawa, T., Nakatani, N., Nakamura, S., Saito, A., Kozaki, A., Kishimoto, K., Ishida, T., Yoshida, M., Akasaka, Y., Hasegawa, D. & Kosaka, Y.** 2019.

"The dismal prognosis of patients with disseminated Ewing sarcoma necessitates the development of novel treatment strategies. Pazopanib is an oral multi-targeted tyrosine kinase inhibitor that is active against advanced soft tissue sarcoma. However, the clinical activity and feasibility of pazopanib for treating Ewing sarcoma remain poorly understood. Moreover, clinical information on the use of tandem high-dose chemotherapy for Ewing sarcoma is limited. A 14-year-old boy with Ewing sarcoma was transferred to our hospital for treatment. Magnetic resonance imaging, computed tomography scans, and bone scintigraphy revealed multiple lesions in the pubis, ilium, ischium, femur, rib, cranial bone, thoracic vertebrae, sacrum, obturator muscle, adductor magnus muscle, testicular cord, and lungs. Bone scintigraphy after intensive chemotherapies confirmed that multiple abnormal accumulations were still present in the cranial bone and pubis. Subsequently, the patient received tandem high-dose chemotherapy including topotecan, and radiotherapy. Abnormal accumulations have disappeared in bonescintigraphy. Subsequently, pazopanib maintenance therapy was initiated. Despite the presence of innumerable lesions at diagnosis, the patient has been in near-complete remission for the past 1 year with pazopanib administration. This confirms that adding

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Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

June 2020

Page 6

pazopanib maintenance therapy after tandem high-dose chemotherapy is a therapeutic option for cases with disseminated Ewing sarcoma.”

Radiation therapy involves using high energy X-ray beams to help kill the cancer cells. This is often given through a series of treatments over weeks or months. As with chemotherapy, radiation therapy can be used either before or after surgery.

**Reed, D.R., Hayashi, M., Wagner, L., Binitie, O, Steppan, D.A., Brohi, A.S., Shinohara, E.T., Bridge, J.A., Loeb, D.M., Borinstein, S.C. & Isakoff, M.S. 2017.**

“When pediatric, adolescent, and young adult patients present with a bone sarcoma, treatment decisions, especially after relapse, are complex and require a multidisciplinary approach.”

**Czyzewski, K., Galazka, P., Zalas-Wiecek, P., Gryniewicz-Kwiatkowska, O., Gietka, A., Semczuk, K., Chelmecka-Wiktorczyk, L., Zak, I., Salamonowicz, M., Fraczkiewicz, J., Zajac-Spychala, O., Bien, E., Plonowski, M., Wawrykow, P., Pierlejewski, F., Gamrot, Z., Malas, Z., Stolpa, W., Musial, J. & Styczynski, J. 2019.**

**Objectives:** The analysis of epidemiology, risk factors and outcome of infections in children with malignant bone tumors (MBT) undergoing chemotherapy.

**Methods:** In this retrospective nationwide multicenter cross-sectional study, a total number of 126 children with MBT including 70 with Ewing sarcoma (ES) and 56 with osteosarcoma (OSA) were screened for infections over a period of 72 consecutive months.

**Results:** The risk of infection was 7.15-fold higher in patients with ES as compared to the OSA group, especially concerning bacterial infections (4.1-fold increase risk). Bacterial infections occurred in 74.3% patients with ES and in 41.1% with OSA. The median time from diagnosis to first infection was 4.9 months. 33.0% of bacterial episodes were diagnosed as bloodstream (BSI), 31.1% as gastrointestinal tract, 30.1% as urinary tract infection. Infection-related mortality (IRM) from bacterial infection was 6% and 15% in ES and OSA patients, respectively. Cumulative incidence was 7.1% for invasive fungal disease and 6.3% for viral infections. The only significant risk factor for IRM was time to infection  $\geq 5$  months since the beginning of chemotherapy. All patients who have died from infection had BSI and were in neutropenia.

**Conclusions:** Infections in the children with MBT in our study occurred with high frequency, especially in patients with ES. The most frequent were bacterial infections, while fungal and viral infections were episodic. Among the bacterial infections, bloodstream, urinary tract and gastrointestinal tract infections occurred with similar frequency. All deceased patients died due to BSI. Bacterial infection occurring  $\geq 5$  months since the beginning of chemotherapy was a risk factor for death.

### **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

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June 2020

Page 7

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/](http://www.sanctr.gov.za/)

### Medical Disclaimer

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#### Bone Sarcoma Picture

<https://za.pinterest.com/pin/445223113157484589/?lp=true>

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Page 8



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