Cancer Association of South Africa (CANSA)

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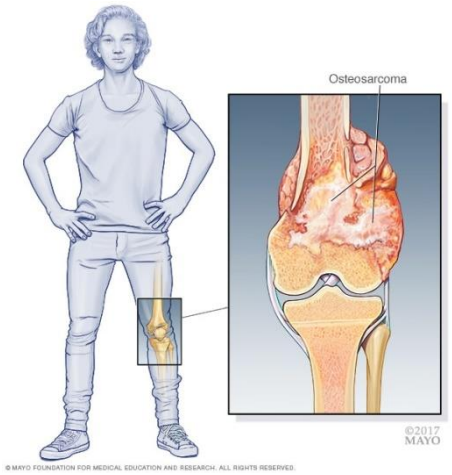
Fact Sheet
on
Osteosarcoma

Introduction

Cancerous (malignant) tumours of connective tissues are called 'sarcomas'. Sarcoma arises in the connective tissue of the body. Normal connective tissue includes, fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.



[Picture Credit: Osteosarcoma]

Sarcomas are divided into two main groups, bone sarcomas and soft tissue sarcomas. They are further sub-classified based on the type of presumed cell of origin found in the tumour. They all share certain microscopic characteristics and have similar symptoms.

Sarcomas can develop in children and adults. For children under 20 approximately 15 percent of cancer diagnoses are sarcomas.

Osteosarcoma

Osteosarcoma (also referred to as osteogenic sarcoma) is a type of cancer that produces immature bone. The cancer cells in these tumours look like early forms of bone cells that normally help make new bone tissue, but the bone tissue in an osteosarcoma is not as strong as that of normal bones. It is the most common type of cancer that arises in bones, and it is usually found at the end of long bones, often around the knee. Most people diagnosed with osteosarcoma are under the age of 25, and it is thought to occur more often in males than females. Without appropriate treatment, the disease is fatal.

Research has shown that one in five (1:5) individuals diagnosed with Osteosarcoma already have metastasis (micrometastasis) to the lungs at diagnosis. These so-called micrometastases may not be detected at diagnosis due to their small size.

Osteosracoma spreads mainly through the bloodstream although some metastasis may occur via the lymphatic system.

Several different sub-types of osteosarcoma have been identified. Criteria used is based on how the tumours appear on X-ray and under the microscope following biopsy (taking a specimen of tissue for study).

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Identifying a patient's sub-type of osteosarcoma is important since each sub-type progresses differently and responds differently to treatments.

Osteosarcomas are divided into the following:
High-Grade Osteosarcomas

- Conventional Osteosarcomas – the most common sub-type which most often occurs near the knee
  - Osteoblastic osteosarcoma (primarily composed of osteoid)
  - Chondroblastic osteosarcoma (primarily composed of cartilage)
  - Fibroblastic osteosarcoma (primarily composed of spindle cells)
- Telangaiectatic Osteosarcoma – they are vascular tumours with a small amount of osteoid – lloking at it with the naked eye, it is described as looking like "a bag of blood"
- Small Cell Osteosaroma – under the microscope it is made up of small, round blue cells (very similar to Ewing Sarcoma)
- High-Grade Surface Osteosaroma – these tumours arise from the surface of bone
- Paget's Osteosarcoma – iat occurs in patients with Paget's Disease of the bone, mostly in patients over the age of 60
- Postradiation Osteosarcome – high-dose radiation in the treatment of other cancer may result in Postradiation Osteosarcoma
- Extraskeletal osteosarcoma - these tumours arise in the body's soft tissues, rather than bone and is more common in older adults

Intermediate-Grade Osteosarcomas

- Periosteal osteosarcoma – which arises from the surface of bone, most often in the diaphysis, or shaft portion, of the tibia (shinbone) - the tumours produce both cartilage and osteoid

Low-Grade Osteosarcomas – these tumours occur in the shaft of the body's long bones

- Parosteal Osteosarcoma – they arise on the surface of long bones

Zhang, Y., Li, J., Wang, Y., Jing, J. & Li, J. 2019.
"Osteosarcoma is a malignant tumor that occurs most commonly in the metaphysis of the long bones in the limbs in children and adolescents. Even with surgery and neoadjuvant chemotherapy, the therapeutic effect has reached a peak with 60-70% survival rates. Therefore, new biological targets or molecular mechanisms that enhance the efficacy of osteosarcoma treatments are needed. Circular RNAs (circRNAs) are useful biomarkers that have recently been recognized clinically and in medical research and have been of interest due to the use of next-generation sequencing and bioinformatics analysis. CircRNAs are involved in many diseases, including cancer. Therefore, this review aims to summarize the roles of circRNA in the diagnosis, progression, and prognosis of osteosarcoma."

Toki, S., Kobayashi, E., Yoshida, A., Ogura, K., Wakai, S., Yoshimoto, S., Yonemori, K. & Jawai, A. 2019.
Aims: The purpose of this study was to clarify the clinical behaviour, prognosis, and optimum treatment of dedifferentiated low-grade osteosarcoma (DLOS) diagnosed based on molecular pathology.
Patients and methods: We retrospectively reviewed 13 DLOS patients (six men, seven women; median age 32 years (interquartile range (IQR) 27 to 38)) diagnosed using the following criteria: the histological coexistence of low-grade and high-grade osteosarcoma components in the lesion, and positive immunohistochemistry of mouse double minute 2 homolog (MDM2) and cyclin-dependent kinase 4 (CDK4) associated with MDM2 amplification. These patients were then compared with 51 age-matched consecutive conventional osteosarcoma (COS) patients (33 men, 18 women; median age 25 years (IQR 20 to 38)) regarding their clinicopathological features.

Results: The five-year overall survival (OAS) rates in the DLOS and COS patients were 85.7% and 77.1% (p = 0.728), respectively, and the five-year progression-free survival (PFS) rates were 57.7% and 44.9% (p = 0.368), respectively. A total of 12 DLOS patients received chemotherapy largely according to regimens for COS. Among the nine cases with a histological evaluation after chemotherapy, eight showed a poor response, and seven of these had a necrosis rate of < 50%. One DLOS patient developed local recurrence and five developed distant metastases.
Conclusion: Based on our study of 13 DLOS cases that were strictly defined by histological and molecular means, DLOS showed a poorer response to a standard chemotherapy regimen than COS, while the clinical outcomes were not markedly different. Cite this article: *Bone Joint J* 2019;101-B:745-752.

Incidence of Osteosarcoma in South Africa
The outdated South African National Cancer Registry (2017) does not provide any information regarding the incidence of Osteosarcoma.

Causes and Risk Factors of Osteosarcoma
The cause(s) of Osteosarcoma are not known. Some risk factors have been identified:

- Rapid bone growth – it has a higher incidence during a child's growth spurts
- Exposure to previous radiation – often from treatment for another type of cancer
- Genetic factors – it may be related to the retinoblastoma gene with a mutation of the p53 gene
- Age – it is most common between the ages of 10 and 30 and over the age of 60
- Sex – it is most seen among teenage boys
- Li-Graumeni Syndrome – an inherited genetic mutation

Sadykova, L.R., Ntekim, A.I., Muyangwa-Semenova, M., Rutland, C.S., Jeyapalan, J.N., Blatt, N. & Rizvanov, A.A. 2020.
"Osteosarcoma is a rare tumor diagnosed at any age; however younger age is a common risk factor. In addition, multiple factors are believed to contribute to higher rates of osteosarcoma, particularly race and gender. Although diagnosed worldwide, osteosarcoma is found to be more prevalent in Africa with high numbers of cases reported in Nigeria, Uganda, and Sudan. Additionally, higher rates are detected in African Americans, suggesting a genetic predisposition linked to race. This review focuses on identifying high risk factors of osteosarcoma with an emphasis on sarcoma epidemiology and risk factors in African countries."

Signs and Symptoms of Osteosarcoma
Signs and symptoms may include:

- Pain – the most common symptom. It may come and go at first, but, gradually, it becomes constant
- A swelling mass in the area of the tumour
- Redness at the site of the tumour
- Development of a limp if the tumour is located in the leg
- Limited movement if the tumour affects a joint
- Occurrence of a pathologic bone fracture in the area of the tumour

Diagnosis of Osteosarcoma

The following tests may be used:

- Complete blood count (there is not blood marker to detect Osteosarcoma)
- Tests to determine how well the kidneys and liver and functioning
- X-rays to look for abnormal growths on the bones
- Chest X-ray to see whether the disease has spread to the lungs – it is one of the first sites of metastasis
- Computed tomography (CR scan) – also used to look for signs of spread of the disease to the lungs
- Magnetic Resonance Imaging – used if X-ray pictures are not clear
- Bone scan – used to identify bone disorders
- PET scan – uses a special glucose tracer and shows areas in the body where the glucose uptake is extra high
- Biopsy – taking a piece of tissue for examination under a microscope

Wang, J., Liu, S., Shi, J., Li, J., Wang, S., Liu, H., Zhao, S., Duan, K., Pan, X. & Yi, Z. 2019.

"Osteosarcoma (OS) is one of the most common malignant tumors derived from mesenchymal tissue and is highly invasive, mainly in children and adolescents. Treatment of OS is mostly based on standard treatment options, including aggressive surgical resection, systemic chemotherapy, and targeted radiation therapy, but the 5-year survival rate is still low. MicroRNA (miRNA) is a highly conserved type of endogenous nonprotein-encoding RNA, about 19-25 nucleotides in length, whose transcription process is independent of other genes. Generally, miRNAs play a role in regulating cell proliferation, differentiation, apoptosis, and development by binding to the 3' untranslated region of target mRNAs, whereby they can degrade or induce translational silencing. Although miRNAs play a regulatory role in various metabolic processes, they are not translated into proteins. Several studies have shown that miRNAs play an important role in the diagnosis, treatment, and prognosis of OS. Herein, the authors describe new advances in the diagnosis, prognosis, and treatment of miRNAs in OS."

Grading of Osteosarcoma

The tumour is usually "graded" during the biopsy - the higher the grade, the more aggressive the tumour is suspected to be.

Low-grade (less aggressive) tumours typically look more like normal cells than intermediate- or high-grade tumours. High-grade (more aggressive) tumours look almost nothing like the surrounding tissue and are often associated with a poorer prognosis.

Treatment of Osteosarcoma

Osteosarcoma is a surgical disease. Once discovered, the tumour must be removed if cure is to be achieved. Most commonly, this is done after a period of chemotherapy. The main goal of surgery is to safely and completely remove the tumour.

- Treatment of Osteosarcoma usually comprises of:
- Surgery – removal of the tumour utilising limb-salvage surgery
- Chemotherapy – usually given before surgery to attempt to shrink the tumour and again after surgery to kill any remaining cancer cells
- Radiation therapy – especially in cases of Osteosarcoma involving the spine, sacrum, skull, face, and ribs

Chen, C., Xie, L., Ren, T., Huang, Y., Xu, J. & Guo, W. 2021.
"Osteosarcoma (OS) is the most common primary malignancy of the bone and has a high propensity for local invasion and metastasis. Although combining surgery with chemotherapy has immensely improved the outcomes of osteosarcoma patients, the prognosis of metastatic or recurrent osteosarcomas is still unsatisfactory. Immunotherapy has proven to be a promising therapeutic strategy against human malignancies and improved understanding of the immune response to OS, and biomarker development has increased the number of patients who benefit from immunotherapies in recent years. Here, we review recent advances in immunotherapy in osteosarcoma and discuss the mechanisms and status of immunotherapies in both preclinical and clinical trials as well as future therapies on the horizon. These advances may pave the way for novel treatments requisite for patients with osteosarcoma in need of new therapies."

Tsukamoto, S., Errani, C., Angelini, A. & Mavrogenis, A.F. 2020.
"Approximately one-fourth of osteosarcoma patients have metastases at presentation. The best treatment options for these patients include chemotherapy, surgery, and radiotherapy; however, the optimal scheme has not yet been defined. Standard chemotherapy for osteosarcoma metastatic at presentation is based on high-dose methotrexate, doxorubicin, and cisplatin (the MAP regimen), with the possible addition of ifosfamide. Surgical treatment continues to be fundamental; complete surgical resection of all sites of disease (primary and metastatic) remains essential for survival. In patients whose tumors do not respond to neoadjuvant chemotherapy, early surgical resection of the primary tumor with limb-salvage surgery or amputation and multiple metastasectomies, if feasible, after the completion of adjuvant chemotherapy is a reasonable option, as the reduction of the tumor volume could probably increase the effect of chemotherapy. Advanced radiotherapy techniques, such as carbon ion radiotherapy and stereotactic radiosurgery, and molecular targeted chemo-therapy with drugs such as pazopanib or apatinib have improved the dismal prognosis, especially for patients who are medically inoperable or who refuse surgery. Given that the presence of metastatic disease at diagnosis of a patient with osteosarcoma is a poor prognostic factor, a multidisciplinary approach by surgeons, medical oncologists, and radiotherapists is important. [Orthopedics. 2020;43(5):e345-e358.]."

Wang, Z., Wang, A., Li, B., Wang. S., Chen, T. & Ye, Z. 2019.
"Advanced, recurrent, or metastasized osteosarcomas remain challenging to cure or even alleviate. Therefore, the development of novel therapeutic strategies is urgently needed. Cancer immunotherapy has greatly improved in recent years, with options including adoptive cellular therapy, vaccination, and checkpoint inhibitors. As such, immunotherapy is becoming a potential strategy for the treatment of osteosarcoma. Innate immunocytes, the first line of defense in the immune system and the bridge to adaptive immunity, are one of the vital effector cell subpopulations in cancer immunotherapy. Innate immune cell-based therapy has shown potent antitumor activity against hematologic malignancies and some solid tumors, including osteosarcoma. Importantly, some immune checkpoints are expressed on both innate and adaptive immune cells, modulating their functions in tumor immunity. Therefore, blocking or activating immune checkpoint-mediated downstream signaling patZZhways can improve the therapeutic effects of innate immune cell-based therapy. In this review, we summarize the current status and future prospects of innate immune cell-based therapy for the treatment of osteosarcoma, with a focus on the potential synergistic effects of combination therapy involving innate immunotherapy and immune checkpoint inhibitors/oncolytic viruses."

Li, S., Chen, P., Pei, Y., Zheng, K., Wang, W., Qiu, E. & Zhang, X. 2019.
BACKGROUND: Zoledronate has anti-bone resorption activity and is reported to reduce skeletal-related events. The objective of this study was to test the hypothesis that addition of zoledronate in chemotherapy is safe and effective in osteosarcoma.

MATERIAL AND METHODS: A total of 798 patients, age 25 years and above, with newly diagnosed high-grade surgically salvageable malignant osteosarcoma, were included in the trial. All patients had received standard chemotherapies (n=399). In addition, in a standard chemotherapy regimen, patients enrolled in the zoledronate group also received 10 courses of 4 mg intravenous infusions of zoledronate (n=399). Limb-sparing surgery was performed by orthopedic surgeons (n=798). Clinical assessment, laboratory monitoring, overall survival, event-free survival, and treatment-emergent adverse effects were evaluated. The chi-square independence-samples test was used for statistical analysis at 95% confidence level.
RESULTS: The histopathological response was the same for both groups (p=0.12). Addition of zoledronate to chemotherapy improved skeletal event-free survival (p=0.04) but decreased overall survival (p=0.02). Zoledronate induced hypocalcemia (p<0.0001), hypophosphatemia (p<0.0001), cardiotoxicity (p<0.0001), lung metastases (p=0.03), flu-like syndrome (p<0.0001), and ototoxicity (p=0.02), and elevated serum aspartate aminotransferase (p<0.0001) and serum alanine aminotransferase (p<0.0001).
CONCLUSIONS: The addition of zoledronate to standard chemotherapy in high-grade resectable osteosarcoma is detrimental and is not advised.

Miwa, S.,Shirai, T., Yamamoto, N., Hayashi, K., Takeuchi, A., Igarashi, K. & Tsuchiya, H. 2019.
"Osteosarcoma is the most common primary malignancy of bone. Although outcomes of patients with osteosarcoma have improved since the introduction of chemotherapy, outcomes of metastatic or unresectable osteosarcomas are still unsatisfactory. To improve osteosarcoma outcomes, the development of novel systemic therapies for osteosarcoma is needed. Since the 1880s, various immunotherapies have been utilized in patients with osteosarcoma and some patients have shown response to the treatment. Based on recent studies about the role of the immune system in malignancies, immunotherapies including immune modulators such as interleukin-2 and muramyl tripeptide, dendritic cells, immune checkpoint inhibitors, and engineered T cells have been utilized in patients with malignancies. Although there are limited reports of immunotherapies for osteosarcoma, immunotherapy is thought to be a promising treatment option for treating osteosarcomas."

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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https://rarediseases.org/rare-diseases/osteosarcoma/

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https://orthoinfo.aaos.org/en/diseases--conditions/osteosarcoma/

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