Cancer Association of South Africa (CANSA)

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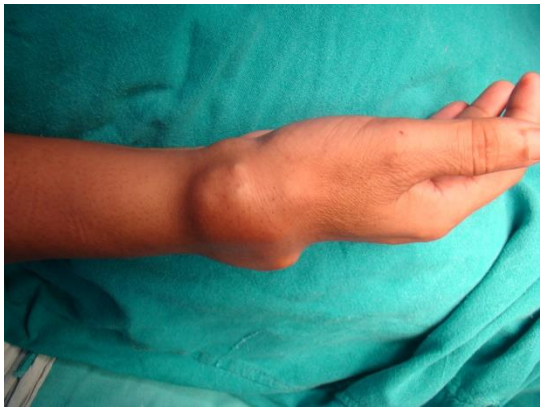
Fact Sheet
on
Chondrosarcoma

Introduction

Chondrosarcoma is a rare type of cancer (malignant tumour) that usually begins in the bones, but can sometimes occur in the soft tissue near bones. The most common locations for chondrosarcoma tumours are in the pelvis, hip and shoulder. More rarely, the base of the skull is affected.



[Picture Credit: Chondrosarcoma of the radius]

The defining characteristic of a chondrosarcoma is that its cells produce cartilage. Some types of chondrosarcomas grow slowly and, provided they are removed completely, have a low risk of spreading to other organs and bones. Others grow rapidly and have a high risk of metastasis.

There are several types of chondrosarcoma that are named based on the way that they appear under the microscope. These include:

- Conventional chondrosarcoma
- Clear cell chondrosarcoma
- Myxoid chondrosarcoma
- Mesenchymal chondrosarcoma
- Dedifferentiated chondrosarcoma

Kaneuchi, Y., Fujiwara, T., Tsuda, Y., Yoshida, S., Stevenson, J.D., Abudu, A.J. 2020.
Purpose: Chondrosarcomas typically present in adults during the fifth to seventh decades and are rare in young patients. The biological behaviour and oncological outcomes may be different in children and adolescents.
Methods: We retrospectively evaluated the outcomes of all patients with chondrosarcoma of bone who were younger than 18 years of age at the time of diagnosis and were treated at our centre between 1995 and 2018.
Results: The 15 consecutive patients studied included nine male and six female cases, with a mean age at diagnosis of 13 years (7 to 17). The median follow-up was 117 months (30 to 277). The tumours were primary and secondary in ten and five patients, respectively. The tumours were central in 13 and surface in

two patients. The tumour locations were the humerus in five, digits in five, femur in three, radius in one and pelvis in one patient. The histological grades were grade I in seven, grade II in seven and grade III in one patient. The surgical treatments were limb salvage in ten patients and ray amputation in five patients. The surgical margins were wide in eight, marginal in two and intralesional in five patients. All the patients were alive and continuously free of disease at the time of the last follow-up. No patient developed metastases or local recurrence.
Conclusion: Chondrosarcoma of bone in children and adolescent patients has a very good prognosis and is less aggressive compared with published outcomes in older patients.

Tumour Grade and Tumour Stage
Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

What are the cancer stages?
Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging
Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.

- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.
Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Chondrosarcoma in South Africa

The National Cancer Registry (2017) does not provide any information regarding Chondrosarcoma.

Signs and Symptoms of Chondrosarcoma

The signs and symptoms of Chondrosarcoma may include:

- Sharp or dull pain where the tumour is located - the pain is usually worse at night, and may become more constant as the bone cancer grows
- Swelling or redness at the tumour site
- A large lump at the site
- Limping or decreased use of the affected limb.

Amer, K.M., Munn, M., Congiusta, D., Abraham, J.A. & Mallick, A.B. 2020.

"Chondrosarcomas are rare tumors and, historically, investigation of these tumors has been limited to small series and single-institution studies. There have been no studies that evaluated the identification or comparison of differences in prognostic factors between the five known non-conventional chondrosarcoma subtypes (myxoid, juxtacortical, clear-cell, mesenchymal, and dedifferentiated). The purpose of this paper

was to determine the demographic, clinical, incidence, and tumor characteristics of all five known non-conventional chondrosarcoma subtypes, determine the 1-, 5-year, and median survival differences between these subtypes, and to determine the demographic and clinical variables that are significant prognostic indicators for each chondrosarcoma subtypes. We retrospectively reviewed the SEER database for all patients with non-conventional chondrosarcoma. χ^2 testing was used for correlations between clinical variables. Kaplan-Meier and Cox proportional hazard analysis were used to compare survival of the subtypes, and to assess the prognostic value of age group, race, sex, grade, anatomic location, and metastatic involvement. Several demographic characteristics including gender, race, age, and grade varied between chondrosarcoma subtypes. The tumor characteristics showed marked differences in presence of metastasis on presentation between the subtypes with increasing order of rate of metastasis with juxtacortical (2.1%), clear cell (5.7%), myxoid (7.6%), mesenchymal (10.6%), and the highest in dedifferentiated (19.8%). One-, 5-year, and median survival differed significantly between chondrosarcomas subtypes. The highest median survival was found in the juxtacortical subtype (97 months), followed by clear cell (79 months), myxoid (60 months), mesenchymal (33.5 months), and lowest in dedifferentiated (11 months). The only prognostic variable that was shown to significantly impact the survival of each non-conventional chondrosarcoma subtype was a metastatic disease at diagnosis ($p = 0.03$ to $p < 0.001$). Subtyping classification of chondrosarcoma should be made whenever possible, given differences in survival and prognostic factors between chondrosarcoma subtypes. J Orthop Res 38:311-319, 2020."

Types of Chondrosarcoma

Chondrosarcoma can be divided into various subtypes:

Limaiem, F., Davis, D.D. & Sticco, K.L. 2020.

"Chondrosarcomas are malignant cartilaginous neoplasms with diverse morphological features and clinical behavior. They account for about 20% of all primary malignant tumors of the bone . They usually arise in the pelvis or long bones . Primary or conventional chondrosarcoma arises in preexisting normal bone and is distinguished from the rarer secondary tumors, which occur in a preexisting enchondroma or osteochondroma . Conventional chondrosarcoma, which accounts for 85%–90% of chondrosarcomas is subdivided into the central, periosteal, and peripheral subgroups . Non-conventional chondrosarcoma variants include clear cell chondrosarcoma, mesenchymal chondrosarcoma, and dedifferentiated chondrosarcoma . The radiographic features of chondrosarcoma are often very characteristic, and a definitive diagnosis can usually be made by imaging examination alone."

Risk Factors for Chondrosarcoma

Chondrosarcoma begins with a single abnormal cartilage cell that starts dividing out of control. No one is certain what exactly prompts chondrosarcoma, although it is suspected that genetic abnormalities or damaged chromosomes might have something to do with it.

People with certain medical conditions may have an increased risk for developing chondrosarcoma. These conditions include:

- Ollier's Disease
- Maffucci Syndrome
- Multiple Hereditary Exostoses (MHE or osteochondromatoses)
- Wilms' Tumour
- Paget's disease

- Diseases in children that required previous treatment with chemotherapy or radiation therapy

Diagnosis of Chondrosarcoma

The following may be used to make the diagnosis of Chondrosarcoma:

- A bone tumour is often first discovered on X-ray after a physical examination. It can be difficult to tell the difference between a benign bone tumour and chondrosarcoma by merely looking at an X-ray.

Additional tests may be done, including:

- a bone scan
- Computerised Tomography (CT scan)
- Magnetic resonance imaging (MRI scan) and/or
- Positron-emission tomography (PET scan)
- A biopsy of the tumour is the only way to make a definite diagnosis of chondrosarcoma.

After the biopsy procedure, a pathologist looks at the tumour's cells under the microscope to confirm the diagnosis.

Limaiem, F., Davis, D.D. & Sticco, K.L. 2020.

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Treatment of Chondrosarcoma

Doctors use the results of the biopsy and imaging studies to develop a patient's treatment plan. The treatment of Chondrosarcoma may include the following:

- Enrolment in a clinical trial should be considered when available
- Patients should be referred to a tertiary care centre with expertise in sarcoma, for treatment by a multidisciplinary team
- Wide excision or intra-lesional excision with or without adjuvant therapy for resectable low-grade and intra-compartmental lesions
- Wide excision for pelvic low-grade tumours
- If resectable, high-grade (grade II, III), clear cell, or extra-compartmental lesions, should be treated with wide excision
- Wide excision should provide negative surgical margins and may be achieved by either limb-sparing surgery or amputation
- Postoperative treatment with proton and/or photon beam radiation for tumours in unfavourable location
- Possible radiation therapy for unresectable tumours
- There is no established chemotherapy regimens for grade I-III tumours

- Treatment of patients with dedifferentiated chondrosarcoma should follow osteosarcoma guidelines
- Treatment of patients with mesenchymal tumour should follow Ewing sarcoma guidelines

Monga, V., Mani, H., Hirbe, A. & Milhem, M. 2020.
"Chondrosarcomas are the most common malignant tumors of the cartilage, are seen predominantly in adults, and have varied clinical behavior. The majority of them affect the medullary canal of long bones and pelvic bones. The prognosis of chondrosarcoma is closely related to histological grading; however, the grading is subject to interobserver variability. Conventional chondrosarcomas are overall considered to be chemotherapy- and radiation-resistant, resulting in limited treatment options. The majority of advanced conventional chondrosarcomas are treated with chemotherapy without any survival benefit. Recent studies have evaluated molecular genetic findings which have improved the understanding of chondrosarcoma biology. Newer therapeutic targets are desperately needed. In this review article, we explore ongoing clinical trials evaluating novel ways of treating advanced conventional chondrosarcoma."

Zhu, J.X. & Xiao, J.R. 2019.
Developing novel therapeutic agents against chondrosarcoma is important. SF2523 is a PI3K-Akt-mTOR and bromodomain-containing protein 4 (BRD4) dual inhibitor. Its activity in human chondrosarcoma cells is tested. Our results show that SF2523 potently inhibited survival, proliferation and migration, and induced apoptosis activation in SW1353 cells and primary human chondrosarcoma cells. The dual inhibitor was yet non-cytotoxic to the primary human osteoblasts and OB-6 osteoblastic cells. SF2523 blocked Akt-mTOR activation and downregulated BRD4-regulated genes (Bcl-2 and c-Myc) in chondrosarcoma cells. It was more efficient in killing chondrosarcoma cells than other established PI3K-Akt-mTOR and BRD4 inhibitors, including JQ1, perifosine and OSI-027. In vivo, intraperitoneal injection of SF2523 (30 mg/kg) potently inhibited subcutaneous SW1353 xenograft tumor growth in severe combined immunodeficient mice. Akt-mTOR inhibition as well as Bcl-2 and c-Myc downregulation were detected in SF2523-treated SW1353 tumor tissues. In conclusion, targeting PI3K-Akt-mTOR and BRD4 by SF2523 potently inhibited chondrosarcoma cell growth in vitro and in vivo.

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."
Song, K., Song, J., Chen, F., Lin, K., Ma, X. & Jiang, J. 2019.
BACKGROUND: Although surgical resection or amputation has been the mainstay of localized chondrosarcoma management for many decades, its efficacy in patients with metastatic chondrosarcoma remains unknown, and likewise we do not know whether there are any tumor- or patient-related factors associated with better survival after surgery for metastatic chondrosarcoma.
QUESTIONS/PURPOSES: (1) Is resection of the primary tumor associated with improved survival in patients with metastatic chondrosarcoma? (2) Which subgroups of patients with chondrosarcoma benefit more from resection in terms of survival?
METHODS: We identified 200 of 222 patients with metastatic chondrosarcoma in the Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2014 based on the exclusion criteria.

Among those patients, 107 (53.5%) underwent primary tumor resection or amputation. Patient information, including demographics (patient age, gender, race, year of diagnosis), tumor characteristics (primary site, histologic subtype, tumor grade, tumor size), and treatment (record of operation and radiation), was collected and included in the study. Kaplan-Meier analyses, log-rank tests, competing risks framework, multivariable Cox regression modeling, and interaction tests were conducted to assess the association of primary tumor resection and survival in the overall cohort and subgroups.
RESULTS: Resection of the primary tumor was associated with improved overall survival (hazard ratio [HR], 0.481; 95% confidence interval [CI], 0.340-0.680; $p < 0.001$) and cancer-specific survival (HR, 0.493; 95% CI, 0.343-0.709; $p < 0.001$) after controlling for confounding variables. After controlling further for age, histologic subtype, and grade, primary tumor resection was associated with a survival advantage in patients with conventional subtype and Grade II chondrosarcoma (conventional subtype: HR, 0.403; 95% CI, 0.260-0.623 for overall survival and HR, 0.396; 95% CI, 0.250-0.627 for cancer-specific survival). However, primary tumor resection was not associated with increased survival in patients with metastatic chondrosarcoma who had the dedifferentiated subtype and Grade III malignancy.
CONCLUSIONS: The present study demonstrates a possible favorable association between primary tumor resection and survival in some patients with metastatic chondrosarcoma at initial diagnosis. Specifically, patients with conventional subtypes and Grade II malignancies who underwent primary tumor resection had better survival compared with those patients who did not have primary tumor resection. Thus, there might be a benefit from primary tumor resection in these patients, but given the limitations of this database, further prospective studies or randomized trials are needed to confirm our findings. In the meantime, this information might be helpful to consider when discussing surgical options with patients who have conventional, Grade 2 metastatic chondrosarcoma at diagnosis.

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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Sources and References Consulted or Utilised

Amer, K.M., Munn, M., Congiusta, D., Abraham, J.A. & Mallick, A.B. 2020. Survival and prognosis of chondrosarcoma subtypes: *SEER database analysis. J Orthop Res*. 2020 Feb;38(2):311-319. doi: 10.1002/jor.24463. Epub 2019 Sep 22.

Chondrosarcoma
https://www.mayoclinic.org/diseases-conditions/chondrosarcoma/symptoms-causes/syc-20354196
https://www.everydayhealth.com/bone-cancer/bone-cancer-and-cartilage-chondrosarcoma.aspx
http://sarcomahelp.org/chondrosarcoma.html
https://emedicine.medscape.com/article/1258236-guidelines
https://clinicalsarcomaresearch.biomedcentral.com/articles/10.1186/s13569-016-0047-1
https://orthoinfo.aaos.org/en/diseases--conditions/chondrosarcoma/
http://theoncologist.alphamedpress.org/content/13/3/320.full
https://www.drugs.com/health-guide/chondrosarcoma.html
http://www.cancer.ca/en/cancer-information/cancer-type/bone/treatment/chondrosarcoma/?region=on

Chondrosarcoma of the Radius
http://www.webmedcentral.com/article_view/1274

Ene, R., Panti, Z.A., Nica, M., Popa, M.G., Cîrstoiu, M.M., Munteanu, O., Vasilescu, S.L., Simion, G., Vasilescu, A., Daviţoiu, D.V. & Cîrstoiu, F.C. 2018. Chondrosarcoma of the pelvis – case report. *Rom J Morphol Embryol*. 2018;59(3):927-931. PMID: 30534835.

Kaneuchi, Y., Fujiwara, T., Tsuda, Y., Yoshida, S., Stevenson, J.D., Abudu, A.J. 2020. Chondrosarcoma of bone in children and adolescents. *Child Orthop*. 2020 Aug 1;14(4):330-334.

Leddy, L.R. & Holmes, R.E. 2014. Chondrosarcoma of bone. *Cancer Treat Res*. 2014;162:117-30. doi: 10.1007/978-3-319-07323-1_6.

Limaiem, F., Davis, D.D. & Sticco, K.L. 2020. Cancer, Chondrosarcoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Aug 10.

Monga, V., Mani, H., Hirbe, A. & Milhem, M. 2020. Non-convenstional treatments for conventional chondrosarcoma. *Cancers (Basel)*. 2020 Jul 19;12(7):1962.

Song, K., Song, J., Chen, F., Lin, K., Ma, X. & Jiang, J. 2019. Does resection of the primary tumor improve survival in patients with metastatic Chondrosarcoma? *Clin Orthop Relat Res*. 2019 Mar;477(3):573-583. doi: 10.1097/CORR.0000000000000632.

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.

Tumour Grade and Tumour Stage
https://www.medicinenet.com/cancer_101_pictures_slideshow/article.htm

Zhu, J.X. & Xiao, J.R. 2019. SF2523 inhibits human chondrosarcoma cell growth in vitro and in vivo. Biochem Biophys Res Commun. 2019 Feb 26. pii: S0006-291X(19)30277-3. doi: 10.1016/j.bbrc.2019.02.080. [Epub ahead of print]