Cancer Association of South Africa (CANSA)

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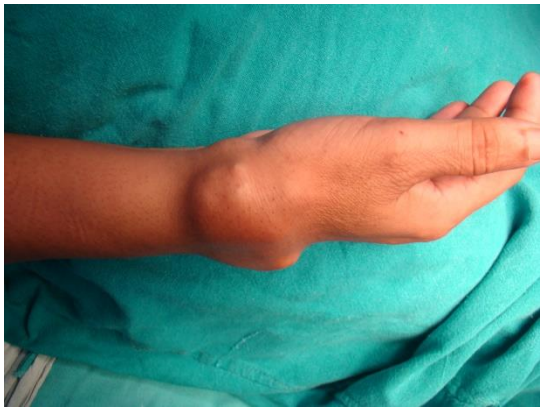
Fact Sheet
on
Chondrosarcoma

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

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 (CHS) is the third most common primary bone tumor after myeloma and osteosarcoma. Histologically, it is made of pure hyaline cartilage differentiation. The tumor itself may have myxoid modification and calcification. It occurs especially after 50 years, with an equal gender distribution. Most CHS are solitary, the etiology is still unclear and most of them are discovered accidentally. Early diagnosis is crucial for a good prognosis. In this paper, we would like to present a case of a female patient with an accidentally discovered CHS of the iliopubic and ischiopubic ramus of the pelvis. The purpose of this report is to highlight the importance of multidisciplinary management of tumor pathology, especially when the site of

the tumor is surgically hardly accessible and to underline possible common genetic aspects of benign and malignant tumors."

Leddy, L.R. & Holmes, R.E. 2014.
"Chondrosarcoma is a cartilage forming neoplasm, which is the second most common primary malignancy of bone. Clinicians who treat chondrosarcoma patients must determine the grade of the tumor, and must ascertain the likelihood of metastasis. Acral lesions are unlikely to metastasize, regardless of grade, whereas axial, or more proximal lesions are much more likely to metastasize than tumors found in the distal extremities with equivalent histology. Chondrosarcoma is resistant to both chemotherapy and radiation, making wide local excision the only treatment. Local recurrence is frequently seen after intralesional excision, thus wide local excision is sometimes employed despite significant morbidity, even in low-grade lesions. Chondrosarcoma is difficult to treat. The surgeon must balance the risk of significant morbidity with the ability to minimize the chance of local recurrence and maximize the likelihood of long-term survival."

Incidence of Chondrosarcoma in South Africa
The National Cancer Registry (2016) 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. © 2019 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. 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.

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

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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