Cancer Association of South Africa (CANSA)

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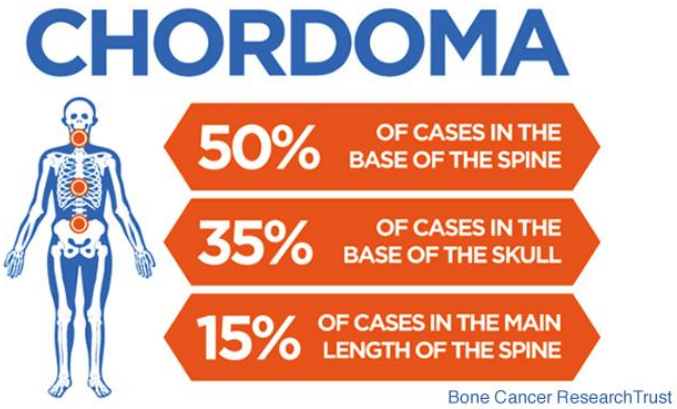
Fact Sheet
on
Chordoma

Introduction

A chordoma is a rare type of cancerous tumour that can occur anywhere along the spine, from the base of the skull to the tailbone. Chordomas grow slowly, gradually extending into the bone and soft tissue around them.

It is part of a group of malignant bone and soft tissue tumours called sarcomas. Chordomas account for about 3 percent of all bone tumours and about 20 percent of primary spinal tumours. They are the most common tumour of the sacrum and cervical spine.



[Picture Credit: Chordoma Picture]

A Chordoma tumour usually grows slowly, often without symptoms at first, and then might cause symptoms for years before doctors find it. Approximately half of all Chordomas occur at the base of the spine (sacrum), about one third occur in the base of the skull (occiput), and the rest occur in the cervical (neck), thoracic (upper back), or lumbar (lower back) vertebrae of the spine.

Chordoma is diagnosed in just one in one million people per year. It is diagnosed most often in people in their 50s and 60s, but it can occur at any age. Skull base Chordomas occur more frequently in younger patients, while spinal Chordomas are more common later in life. About twice as many men are diagnosed with Chordoma as women. While Chordoma can run in families, however, this is very rare.

Synonyms of Chordoma include:

- clival Chordoma
- familial Chordoma
- intracranial Chordoma
- sacrococcygeal Chordoma
- skull base Chordoma
- spinal Chordoma

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Chugh, R., Tawbi, H., Lucas, D.R., Biermann, J.S., Schuetze, S.M. & Baker, L.H. 2017.
"Chordomas are rare, slowly growing, locally aggressive neoplasms of bone that arise from embryonic remnants of the notochord. These tumors typically occur in the axial skeleton and have a proclivity for the spheno-occipital region of the skull base and sacral regions. In adults, 50% of chordomas involve the sacrococcygeal region, 35% occur at the base of the skull near the spheno-occipital area, and 15% are found in the vertebral column. Craniocervical chordomas most often involve the dorsum sella, clivus, and nasopharynx. Chordomas are divided into conventional, chondroid, and dedifferentiated types. Conventional chordomas are the most common. They are characterized by the absence of cartilaginous or additional mesenchymal components. Chondroid chordomas contain both chordomatous and chondromatous features, and have a predilection for the spheno-occipital region of the skull base. This variant accounts for 5%–15% of all chordomas and up to 33% of cranial chordomas. Dedifferentiation or sarcomatous transformation occurs in 2%–8% of chordomas. This can develop at the onset of the disease or later. Aggressive initial therapy improves overall outcome. Patients who relapse locally have a poor prognosis but both radiation and surgery can be used as salvage therapy. Subtotal resection can result in a stable or improved status in as many as 50% of patients who relapse after primary therapy. Radiation therapy may also salvage some patients with local recurrence. One series reported a 2-year actuarial local control rate of 33% for patients treated with proton beam irradiation."

Chordoma
There are four subtypes of chordoma, which are classified based on how they look under a microscope:

Conventional (or classic) Chordoma - is the most common form of Chordoma. It is composed of a unique cell type that resembles notochordal cells and can have areas of Chondroid appearance
.
Poorly differentiated Chordoma - is a recently identified subtype. It can be more aggressive and faster growing than conventional Chordoma, and is more common in paediatric and young adult patients, as well as in skull base and cervical patients. Pathologists can diagnose poorly differentiated Chordoma by testing a tumour sample for deletion of a gene called INI-1. All poorly differentiated Chordomas have loss of the INI-1 gene.

Dedifferentiated Chordoma - is more aggressive and generally grows faster than the other types of Chordoma, and is more likely to metastasize than conventional Chordoma. It can also have loss of the INI-1 gene, but this is not common. This type of chordoma is rare, occurring in only about 5 percent of patients, and is more common in pediatric patients.

Chondroid chordoma - is a term more commonly used in the past when it was difficult to distinguish conventional chordoma from chondrosarcoma. This is no longer a problem because brachyury is expressed in nearly all conventional chordomas, making them easier to distinguish from cartilaginous tumors like chondrosarcoma that do not express brachyury. There is no evidence that chordomas with a chondroid appearance behave differently than conventional types that do not have this appearance.

Frezza, A.M., Botta, L., Trama, A., Dei Tos, A.P. & Stacchiotti, S. 2019.
PURPOSE OF REVIEW: Chordoma is an exceedingly rare subtype of bone sarcoma. This review aims to provide a comprehensive insight into chordoma epidemiology, and an update on the recent advances in disease, biology and medical therapies.

RECENT FINDINGS: The incidence of chordoma is approximately 0.08/100 000 and the 5-year overall age-adjusted relative survival is 72% in the United States and 61% in Europe. Over the last years, significant steps forwards have been done in the comprehension of chordoma complexity, with insights gained into the biology and morphology of this disease. New entities have been described and potentially druggable molecular targets identified. This is becoming all the more relevant today, as new potentially active agents are under development.
SUMMARY: Chordoma is a complex disease because of its rarity, biological heterogeneity and peculiar clinical behaviour. Despite the progress done, the outcome in this disease remains unsatisfactory and the identification of active systemic treatments remains an urgent, unmet medical need.

Incidence of Chordoma in South Africa
The National Cancer Registry (2015) does not provide any information on the incidence of Chordoma in South Africa

Signs and Symptoms of Chordoma
Symptoms depend on exactly where the tumour is in the spine or skull.
If the Chordoma starts in the spine, symptoms may include:

- pain
- numbness
- changes in bowel habits, such as constipation
- problems passing urine or poor bladder control
- problems walking
- feeling weak or unsteady.

Men may also have problems getting an erection.

If the Chordoma starts in the base of the skull, symptoms may include:

- headache
- double vision
- facial pain or numbness
- changes in hearing
- problems swallowing
- feeling dizzy or unsteady.

Causes and Risk Factors for Chordoma
There are currently no known environmental risk factors for Chordoma.

Changes in the TBXT gene have been associated with Chordoma. An inherited duplication of the *TBXT* gene identified in a few families is associated with an increased risk of developing a Chordoma. Duplications or increases in activity (expression) of the *TBXT* gene have also been identified in people with Chordoma who have no history of the disorder in their family. In these individuals, the changes occur only in the tumour cells and are not inherited.

The *TBXT* gene provides instructions for making a protein called brachyury. Brachyury is a member of a protein family called T-box proteins, which play critical roles during embryonic development. T-box proteins regulate the activity of other genes by attaching (binding) to specific regions of DNA. On the basis of this action, T-box proteins are called transcription factors.

The brachyury protein is especially important for the early development of the spine. In human embryos, a structure called the notochord is the precursor of the spinal column. The notochord disappears before birth, but in a small percentage of individuals, some of its cells remain in the base of the skull or in the spine. In rare cases these cells begin to grow and divide uncontrollably, invading the nearby bone and soft tissue and resulting in the development of a Chordoma.

Duplications and increases in expression of the *TBXT* gene both result in the production of excess brachyury protein. The specific mechanism by which excess brachyury protein contributes to the development of Chordomas is unclear. Some people with Chordoma do not have changes in the *TBXT* gene, and the cause of the disorder in these individuals is unknown.

Diagnosis of Chordoma

An MRI scan can help rule out other tumour types, but a tissue sample is needed for a definitive Chordoma diagnosis. If the tumour is in the spine, an interventional radiologist will typically perform a CT-guided core biopsy to obtain a tissue sample. Most skull base Chordomas grow in a bone called the clivus. This area is difficult to access for biopsy, so a skull base Chordoma diagnosis cannot be confirmed until after the neurosurgeon accesses the tumour during surgery, which is also the first step for treatment.

Treatment of Chordoma

Chordomas are complicated tumours to treat due to the involvement of critical structures such as the brainstem, spinal cord, and important nerves and arteries.

In most cases, aggressive surgical removal followed by radiation therapy to remaining tumour offers the best chance of long-term control. Because Chordomas invade the bone, complete removal is often impossible. Additionally, Chordomas are relatively resistant to radiation therapy and are located adjacent to important and delicate brain structures, such as the brain stem and cranial nerves, which limits the dose of radiation that can be given. For these reasons, highly-focused radiation must be used to treat these tumours. Stereotactic radiosurgery and proton beam are the two most effective methods.

There are no chemotherapy drugs that are particularly effective in the treatment of Chordomas.

Chordomas are malignant and potentially life threatening tumours. Currently the median survival in the United States is about 7 years. The overall survival rates are 68% at 5 years and 40% at 10 years. Complete surgical resection offers the best chance for long-term survival. In many cases, radiation therapy can also increase local control rates and prolong survival. Even after surgery and/or radiation, Chordomas tend to return locally - in the same location or in the areas around the original tumour. Many patients undergo multiple surgeries over several years to treat local recurrences. After a local recurrence the chances of achieving a cure are significantly diminished. Distant metastasis (spreading to other body parts) occurs in 20-40% of patients with Chordomas of the spine and less than 10% of patients with skull-base tumours. The most common sites of distant metastasis are the lungs, liver, bones, and skin.

Akhavan-Sigari, R., Schulz-Schaeffer, W., Angelika Harcej, A. & Rohde, V. 2019,
"Chordomas is rare malignant bone tumors thought to arise from remnants of embryonic notochord along the spine, frequently at the skull base and sacrum. Although chordoma is slow growing tumors, while are extremely recurrent, and aggressive, as well as the rate of prognosis remains poorly. Radical surgery and high-dose radiation are the most used treatments. Currently, there is no effective chemotherapeutic standard for chordomas. The Hedgehog (HH) pathway adjusts various processes included in expansion and differentiation of tissues and organs throughout the fetus's life, furthermore cell growth and differentiation in the adult organism, of the cell in an adult organism, in which acute anesthesia is involved in multiple cancers. To study the role of signaling the hedgehog in the base of the skull and sacrum chordomas, the expression of SHH and GLI-1 levels were detected immuno histochemically, Additionally, PTCH-1 and GLI-1 expressions were distinguished by in- Situ- hybridization. Based on the findings presented herein, it is likely that the HH signal cascade was revealed even in cranial, where consecoently spinal chordoma and their recurrences play an important role. Our staining exhibited a canonical, ligand- dependent and autocrine Hedgehog signaling in skull base and sacrum chordomas including relapse. Due to the high levels of SHH and GLI-1 expression in all investigated chordoma samples, the study suggests a possible autocrine ligand-dependent activation of the canonical HH signaling cascade. A paracrine or non-canonical pathway cannot be excluded. Our results suggest that Hedgehog-inhibitors, like SHH-, GLI- and SMO- inhibitors, might serve as a potential and effective target for the treatment of chordomas."

Houdek, M.T., Rose, P.S., Hevesi, M., Schwab, J.H., Griffin, A.M., Healey, J.H., Petersen, I.A., DeLaney, T.F., Chung, P.W., Yaszemski, M.J., Wunder, J.S., Hornicek, F.J., Boland, P.J., Sim, F.H., Ferguson, P.C. & Other Members of the Sacral Tumor Society. 2019.
BACKGROUND: We reviewed the disease control and complications of the treatment of sacrococcygeal chordoma from four tertiary cancer centers with emphasis on the effects of radiotherapy in surgically treated patients.
METHODS: A total of 193 patients with primary sacrococcygeal chordoma from 1990 to 2015 were reviewed. There were 124 males, with a mean age of 59 ± 15 years and a mean follow-up of 7 ± 4 years. Eighty-nine patients received radiotherapy with a mean total dose of 61.8 ± 10.9 Gy.
RESULTS: The 10-year disease-free and disease-specific survival was 58% and 72%, respectively. Radiation was not associated with local recurrence (hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.59-2.17; P = 0.71), metastases (HR, 0.93; 95% CI, 0.45-1.91; P = 0.85) or disease-specific survival (HR, 0.96; 95% CI, 0.46-2.00; P = 0.91). Higher doses (≥70 Gy; HR, 0.52; 95% CI, 0.20-1.32; P = 0.17) may be associated with reduced local recurrence. Radiotherapy was associated with wound complications (HR, 2.76; 95% CI, 1.64-4.82;, P < 0.001) and sacral stress fractures (HR, 4.73; 95% CI, 1.88-14.38; P < 0.001).
CONCLUSIONS: In this multicenter review, radiotherapy was not associated with tumor outcome but associated with complications. The routine use of radiotherapy with en-bloc resection of sacrococcygeal chordomas should be reconsidered in favor of a selective, individualized approach with a radiation dose of ≥70 Gy.

AOSpine Knowledge Forum Tumor. 2018.
OBJECTIVE: The purpose of this study was to investigate the spectrum of current treatment protocols for managing newly diagnosed chordoma of the mobile spine and sacrum.
METHODS: A survey on the treatment of spinal chordoma was distributed electronically to members of the AOSpine Knowledge Forum Tumor, including neurosurgeons, orthopedic surgeons, and radiation oncologists from North America, South America, Europe, Asia, and Australia. Survey participants were pre-identified clinicians from centers with expertise in the treatment of spinal tumors. The suvey responses were analyzed using descriptive statistics.

RESULTS: Thirty-nine of 43 (91%) participants completed the survey. Most (80%) indicated that they favor en bloc resection without preoperative neoadjuvant radiation therapy (RT) when en bloc resection is feasible with acceptable morbidity. The main area of disagreement was with the role of postoperative RT, where 41% preferred giving RT only if positive margins were achieved and 38% preferred giving RT irrespective of margin status. When en bloc resection would result in significant morbidity, 33% preferred planned intralesional resection followed by RT, and 33% preferred giving neoadjuvant RT prior to surgery. In total, 8 treatment protocols were identified: 3 in which en bloc resection is feasible with acceptable morbidity and 5 in which en bloc resection would result in significant morbidity.
CONCLUSIONS: The results confirm that there is treatment variability across centers worldwide for managing newly diagnosed chordoma of the mobile spine and sacrum. This information will be used to design an international prospective cohort study to determine the most appropriate treatment strategy for patients with spinal chordoma.

Takagi, M., Demizu, Y., Nagano, F., Terashima, K., Fujii, O., Jin, D., Mima, M., Niwa, Y., Katsui, K., Suga, M., Yamashita, T., Akagi, T., Sakata, K.I., Fuwa, N. & Okimoto, T. 2018.
BACKGROUND: The usefulness of particle therapy for skull base chordoma has not been established. The aim of this retrospective study was to analyse the treatment outcomes of proton therapy (PT) and carbon ion therapy (CIT) in patients with skull base chordoma at a single institution.
METHODS: All patients who underwent PT or CIT with curative intent between 2003 and 2014 at Hyogo Ion Beam Medical Center were included in this study. Twenty-four patients were enrolled. Eleven (46%) received PT and 13 (54%) received CIT. Overall survival (OS), progression-free survival (PFS) and local control (LC) were calculated using the Kaplan-Meier method. Late toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.
RESULTS: The median follow-up was 71.5 months (range, 14-175 months). The five-year LC, PFS and OS rates were 85, 81, and 86%, respectively. The LC (P = 0.048), PFS (P = 0.028) and OS (P = 0.012) were significantly improved in patients who had undergone surgery before particle therapy. No significant differences were observed in the LC rate and the incidence of grade 2 or higher late toxicities between patients who received PT and CIT.
CONCLUSIONS: Both PT and CIT appear to be effective and safe treatments and show potential to become the standard treatments for skull base chordoma. To increase the local control, surgery before particle therapy is preferable.

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/

Meng, T., Jin, J., Jiang, C., Huang, R., Yin, H., Song, D. & Cheng, L. 2019.
Objectives: Chordoma is a rare bone malignancy that affects the spine and skull base. Treatment dilemma leads to a high rate of local relapse and distant metastases. Molecular targeted therapy (MTT) is an option for advanced chordoma, but its therapeutic efficacy and safety have not been investigated systematically. Therefore, a systematic review was conducted on studies reporting MTT regimens for chordoma.
Methods: Clinical trials, case series and case reports on chordoma MTT were identified using MEDLINE, Cochrane library and EMBASE, and systematically reviewed. Data on clinical outcomes, such as median overall survival, progression-free survival, response rate and adverse events (AEs) were extracted and analyzed.
Results: Thirty-three eligible studies were selected for the systematic review, which indicated that imatinib and erlotinib were the most frequently used molecular targeted inhibitors (MTIs) for chordoma. For PDGFR-positive and/or EGFR-positive chordoma, clinical benefits were achieved with acceptable AEs. Monotherapy is preferred as the first-line of treatment, and combined drug therapy as the second-line treatment. In addition, the brachyury vaccine has shown promising results.
Conclusions: The selection of MTIs for patients with advanced or relapsed chordoma should be based on gene mutation screening and immunohistochemistry (IHC). Monotherapy of TKIs is recommended as the first-line management, and combination therapy (two TKIs or TKI plus mTOR inhibitor) may be the choice for drug-resistant chordoma. Brachyury vaccine is a promising therapeutic strategy and requires more clinical trials to evaluate its safety and efficacy.

Medical Disclaimer

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Chordoma Picture
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