Cancer Association of South Africa (CANSA)

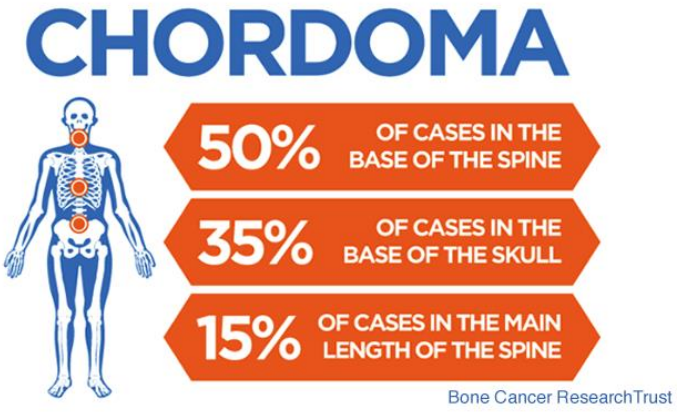
Research • Educate • Support

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

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]

Tenny, S. & Varacallo, M. 2020.
"A chordoma is a low-grade, slow-growing, but locally invasive and locally aggressive tumor. Chordomas belong to the sarcoma family of tumors. They arise from the remnants of the notochord and occur in the midline along the spinal axis from the clivus to the sacrum, anterior to the spinal cord. The location distribution of chordomas is 50% sacral, 35% skull base, and 15% occur in the vertebral bodies of the mobile spine (most commonly the C2 vertebrae followed by the lumbar then thoracic spine). Overall 5-year survival is approximately 50%, and treatment is *en bloc* surgical resection followed by high-dose conformal radiation therapy such as proton beam radiation."

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.
Shih, A.R., Chebib, I., Deshpande, V., Dickson, B.C., Iafrate, A.J. & Nielsen, G.P. 2019.

"Pediatric poorly differentiated chordoma is a subtype of chordoma with a much more aggressive clinical course and has been characterized by loss of SMARCB1. This study characterizes the molecular features of these tumors in comparison to conventional chordoma. A search of records between 1990 and 2017 at Massachusetts General Hospital identified two patients with sufficient excess tissue for molecular analysis and a third patient diagnosed with a highly cellular conventional chordoma. The three tumors were sent for array comparative genomic hybridization for genome-wide copy number variants; multiplex PCR for single-nucleotide variants; and RNA-sequencing for fusions. Poorly differentiated chordoma showed chromosome 22q loss, including SMARCB1, with no identifiable mutations on multiplex PCR. The cellular conventional chordoma showed a complex pattern of chromosomal gains and losses involving 12 chromosomes, and an RB1 mutation at low allelic frequency. RNA-Seq identified no disease-defining gene fusion events. Poorly differentiated chordoma appears to represent a distinct type of tumor that is genetically unrelated to conventional chordoma. Recognition of this subtype is important because these malignancies should be treated aggressively with multimodality therapy, and possibly targeted therapy."

Incidence of Chordoma in South Africa

The National Cancer Registry (2017) 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.

Scheipl, S., Igrec, J., Leithner, A., Smolle, M., Haybäck, J. & Liegl, B. 2020.

"Chordomas are malignant bone tumours with a reported annual incidence of 0.08 per 100,000 cases. They show a notochordal differentiation and are characterised by their nuclear expression of brachyury (TBXT). Chordomas are localised in the axial skeleton, where they occur from the clivus to the sacrococcygeal region. They are slow growing, locally destructive tumours, and are often not diagnosed until they have reached an advanced stage. Putative precursor-lesions are benign notochordal cell lesions, which are microscopically small and intraosseous. Different histological chordoma subtypes exist, which differ in their prognosis. To date, there are no known recurrent genetic drivers for this disease. Brachyury seems to play a key role in the pathogenesis of chordoma, though the detailed mechanism still needs to be elucidated. Surgical en bloc resection with negative margins is the only curative treatment for this disease. High-dose irradiation, particularly with protons and carbon ions, is a therapeutic alternative in cases of inoperable tumours. Currently, there is no approved medical treatment for chordoma. Clinical trials exploring additional therapeutic modalities are ongoing."

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.

Gulluoglu S, Tuysuz EC, Sahin M, Yaltirik CK, Kuskucu A, Ozkan F, Dalan AB, Sahin F, Ture U, Bayrak OF. 2019.
Purpose: Chordomas are highly therapy-resistant primary bone tumors that exhibit high relapse rates and may induce local destruction. Here, we evaluated the effects of tumor necrosis factor-alpha (TNF-α) on chordoma progression and clinical outcome.
Methods: Chordoma cells were treated with TNF-α after which its short- and long-term effects were evaluated. Functional assays, qRT-PCR and microarray-based expression analyses were carried out to assess the effect of TNF-α on chemo-resistance, epithelial to mesenchymal transition (EMT), migration, invasion and cancer stem cell-like properties. Finally, relationships between TNF-α expression and clinicopathological features were assessed in a chordoma patient cohort.
Results: We found that TNF-α treatment increased the migration and invasion of chordoma cells. Also, NF-κB activation was observed along with increased EMT marker expression. In addition, enhanced tumor sphere formation and soft agar colony formation were observed, concomitantly with increased chemo-resistance and CD338 marker expression. The TNF-α and TNFR1 expression levels were found to be significantly correlated with LIF, PD-L1 and Ki67 expression levels, tumor volume and a short survival time in patients. In addition, a high neutrophil to lymphocyte ratio was found to be associated with recurrence and a decreased overall survival.
Conclusions: From our data we conclude that TNF-α may serve as a prognostic marker for chordoma progression and that tumor-promoting inflammation may be a major factor in chordoma tumor progression.

Bongers, M.E.R., Dea, N., Ames, C.P. & Schwab, J.H. 2020.
"Chordomas are rare tumors of the axial skeleton whose slow growth belies a relentless tumor with a propensity for recurrence and late metastasis. Local control remains an issue with chordoma in spite of aggressive operative management. High local failure rates have led to the exploration of alternative methods of treatment. Radiation continues to gain acceptance as an adjuvant to surgery and, in some cases, as a standalone treatment. However, the use of radiation remains controversial, and operative management remains the standard of care in spite of relatively high morbidity."

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

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Akhavan-Sigari, R., Schulz-Schaeffer, W., Angelika Harcej, A. & Rohde, V. 2019, The importance of the Hedgehog Signaling Pathway in taumorigenesis of spinal and cranial chordoma. *J Clin Med*. 2019 Feb 15;8(2). pii: E248. doi: 10.3390/jcm8020248.

AOSpine Knowledge Forum Tumor. 2018. Current treatment strategy for newly diagnosed chordoma of the mobile spine and sacrum: results of an international survey. *J Neurosurg Spine***,** 2018 Oct 1:1-7. doi: 10.3171/2018.6.SPINE18362. [Epub ahead of print]

Bongers, M.E.R., Dea, N., Ames, C.P. & Schwab, J.H. 2020. Surgical Strategies for Chordoma. *Neurosurg Clin N Am*. 2020 Apr;31(2):251-261. doi: 10.1016/j.nec.2019.11.007. Epub 2020 Jan 16.

Chordoma
https://www.chordomafoundation.org/understanding-chordoma/
https://ghr.nlm.nih.gov/condition/chordoma
https://www.urmc.rochester.edu/neurosurgery/specialties/neurooncology/conditions/chordoma.aspx
https://rarediseases.org/rare-diseases/chordoma/
https://emedicine.medscape.com/article/250902-overview
https://theoncologist.alphamedpress.org/content/12/11/1344.full
https://www.mdanderson.org/publications/cancerwise/understanding-chordoma-bone-cancer-skull-base-tumor-spine-sacrum.h00-159149190.html
https://www.macmillan.org.uk/information-and-support/bone-cancer/understanding-cancer/types-of-bone-cancer/chordoma.html
https://www.pacificneuroscienceinstitute.org/blog/brain-tumor/chordoma-a-rare-bone-cancer-of-the-skull-base-and-spine/

Chordoma Picture
https://www.pacificneuroscienceinstitute.org/blog/brain-tumor/chordoma-a-rare-bone-cancer-of-the-skull-base-and-spine/

Chugh, R., Tawbi, H., Lucas, D.R., Biermann, J.S., Schuetze, S.M. & Baker, L.H. 2017. **Chordoma: the nonsarcomas primary bone tumor. *The Oncologist*. doi: 10.1634/theoncologist.12-11-1344The Oncologist November 2007 vol. 12no. 11 1344-1350.**

Frezza, A.M., Botta, L., Trama, A., Dei Tos, A.P. & Stacchiotti, S. 2019. Chordoma: update on disease, epidemiology, biology and medical therapies. *Curr Opin Oncol*. 2019 Mar;31(2):114-120. doi: 10.1097/CCO.0000000000000502.

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. Low dose radiotherapy is associated with local complicastions but not disese control in sacral chordoma. *J Surg Oncol*. 2019 Feb 7. doi: 10.1002/jso.25399. [Epub ahead of print]
Gulluoglu S, Tuysuz EC, Sahin M, Yaltirik CK, Kuskucu A, Ozkan F, Dalan AB, Sahin F, Ture U, Bayrak OF. 2019. The role of TNF-α in chordoma progression and inflammatory pathways. *Cell Oncol (Dordr)*. 2019 Oct;42(5):663-677. doi: 10.1007/s13402-019-00454-y. Epub 2019 Jun 7.

Meng, T., Jin, J., Jiang, C., Huang, R., Yin, H., Song, D. & Cheng, L. 2019. Molecular targeted therapy in the treatment of chordoma: a systematic review. *Front Oncol*. 2019 Feb 1;9:30. doi: 10.3389/fonc.2019.00030. eCollection 2019.

Scheipl, S., Igrec, J., Leithner, A., Smolle, M., Haybäck, J. & Liegl, B. 2020. Chordoma: is there a molecular basis for diagnosis and treatment? *Pathologe*. 2020 Mar;41(2):153-162. doi: 10.1007/s00292-020-00761-4.

Shih, A.R., Chebib, I., Deshpande, V., Dickson, B.C., Iafrate, A.J. & Nielsen, G.P. 2019. Molecular characteristics of poorly differentiated chordoma. *Genes Chromosomes Cancer*. 2019 Nov;58(11):804-808. doi: 10.1002/gcc.22782. Epub 2019 Jun 13.

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. Treatment coutcomes of proton or carbon ion therapy for skull base chordoma: a retrospective study. *Radiat Oncol*. 2018 Nov 26;13(1):232. doi: 10.1186/s13014-018-1173-0.

Tenny, S. & Varacallo, M. 2020. Chordoma. ***In***: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2020 Jan. 2020 Aug 10.