Chordoma Management: A Review of the Literature

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Abstract

Chordoma is an uncommon bone neoplasm. Despite being considered a low-grade or benign bone tumor because of its histology, it is aggressive and locally invasive. It has a poor prognosis because it has a high rate of recurrence and is likely to be malignant. Chordoma is usually recurrent. Although its histology is considered a low-grade tumor or benign tumor, its behaviour of recurrence leads to a poor prognosis and higher likelihood of malignant tumors occurring. Chordoma is believed to emerge from transformed remnants of notochord and appears to favor the axial bone. The most commonly affected parts of chordoma are at the sacrum, vertebra, and skull base. The present gold standard for management of chordoma is a wide surgical resection. This article highlights recent practices and future directions for treatment.

Keywords : chordoma, recurrent chordoma, treatment of chordoma

Chordoma is considered to be a rare low-grade malignant tumor of the spine occurring in only 1-4% of all malignant skeletal tumors.[1] The reported incidence of chordoma is quite low (only 0.08 per 100,000 pop). More males than females are affected as are more Caucasians and Hispanics than African-Americans.[2] The peak incidence of chordoma occurs in the fifth decade of life (50-59 years), and the incidence is very low in patients under the age of 40.[2-4] A total of only three hundred patients are newly diagnosed annually world-wide.[2,5] The median survival time is about 6 years, and the survival rate drops each year.[2] The 10-year survival rate of chordoma patients is about 40%.[2]

While the distribution is almost equal in the sacrum, skull base, and vertebra,[2] Chordoma is involved in most of the primary bone tumors of the sacrum.[6] Chordoma generally differs from others malignant tumors in that it is a slow growing neoplasm, although it is locally invasive and aggressive. At the time of diagnosis, the tumor is generally in an advanced stage, i.e., usually large, impinging on surrounding structures, and with poor margination, which makes Chordoma difficult to treat with gross total resection and radiation. The rate of local recurrence is usually high despite the best initial management efforts.

In this article, emphasis is on recent choices of recently developed options for treatment and management of chordoma including radiation therapy and molecular-targeting agents.

Clinical features

Chordomas are slow-growing tumors with no or very mild symptoms until the late stage. The clinical presentations of chordomas are different depending on their location.[7] Skull-based chordomas often grow in the clivus, so initial symptoms are headache and diplopia. If the disease progresses without treatment, the clinical symptoms can include cranial nerve palsy, visual disturbance, or weakness. If the chordoma involves the sella, endocrinopathy may be present. For chordomas of the sacrum and spine, initially, patients usually present

with deep local pain, radiculopathy, bowel or bladder dysfunction, or even sexual dysfunction. When the disease progress, the tumors are sometimes palpable externally or during per rectal or vaginal examination.[8, 9] Chordomas of the sacrum generally involve the 4th and 5th level of sacral vertebrae. When the neoplasm progresses, and becomes large, it can sometimes extend into the pelvic cavity, although the presacral fascia protects the pelvis from tumor invasion. Chordomas of the cervical spine, however, can initially present with upper airway obstruction or dysphagia; sometimes the patient will seek medical attention for a mass around the cervical or oropharyngeal area, depending on the tumor location.

In radiographic studies, chordomas typically appear as a destructive lesion that affects the axial skeleton and are associated with a large soft tissue mass at the epicenter of the tumors within the vertebral body. Chordomas are unlike osteosarcoma and chondrosarcomas of the vertebral body as these are more often found in the appendicular skeleton. Chordomas usually extend locally into the intervertebral disc space, and finally spread to adjacent vertebra[8] (Figure 1). In computed tomography (CT) scans, chordomas commonly appear as an osteolytic, or mixed osteolytic and osteosclerotic bone lesion which usually has a myxoid component. The view of chordomas can be enhanced with intravenous contrast injection. With magnetic resonance imaging images (MRI), chordomas appear to be hyperintense on T2- weighted images, but range from isointense to hypointense on T1-weighted images. Chordoma can also be enhanced with gadolinium contrast (Figure 2-3).

Distant metastases generally present in the late stage of chordomas and usually are not presented at the time of initial diagnosis for the reasons described earlier. The incidence of chordomas which show distant metastatic at the time of initial presentation has been reported to be only 5%. The most common sites of distant metastases are lung, bone, skin, and brain. In the very late stage, the metastasis rate is as high as 65%.[10,11]

Case Example

A 45-year-old female presented with chronic low back pain for 5 years. Magnetic resonance imaging (MRI scan) shows a large mass located at the sacrum with T1-hypointensity and T2-hyperintensity with wall enhancement (internal septa) (Figure 2-3)

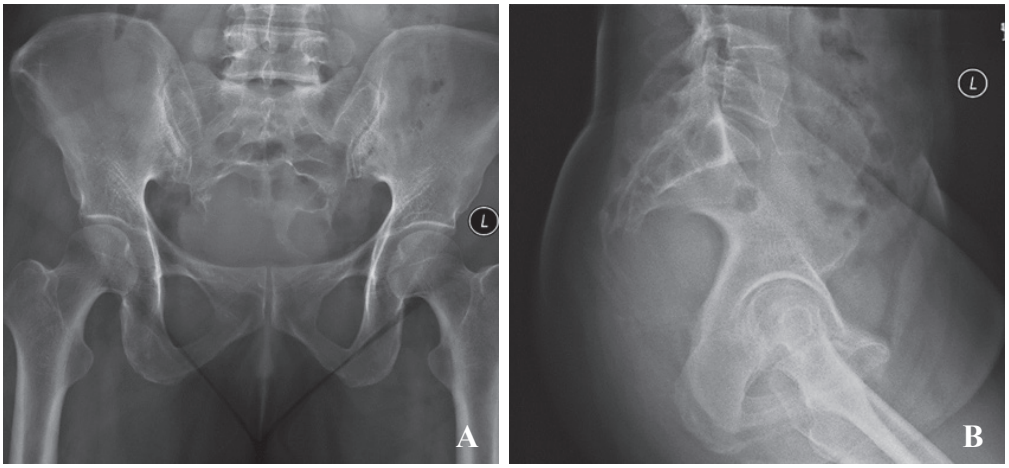

Figure 1: A: Film sacrum AP, **B:** Film lateral, the mass was accidentally palpated during an annual gynecological examination. From plain radiographs showing a large soft tissue mass with extensive osteolytic lesion with its epicenter at the sacrum.

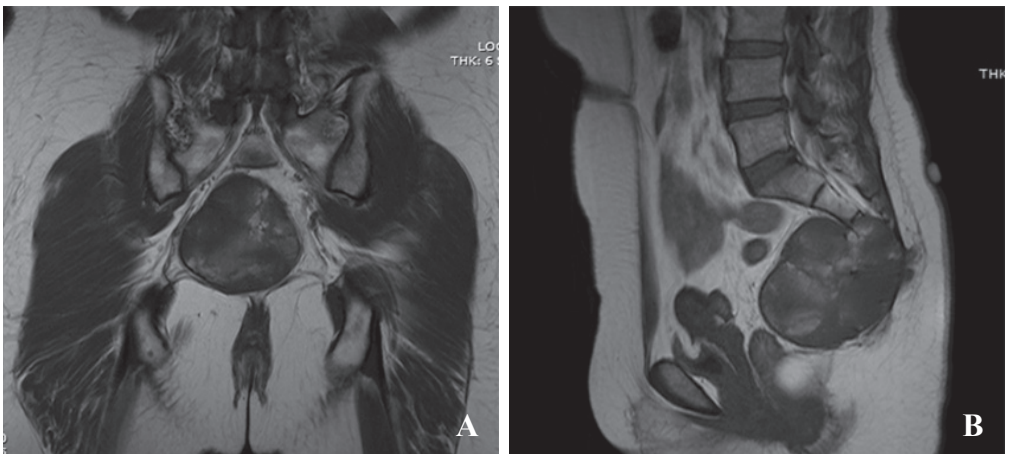

Figure 2: Show T-1 weight MRI, **A:** coronal view, **B:** saggital view

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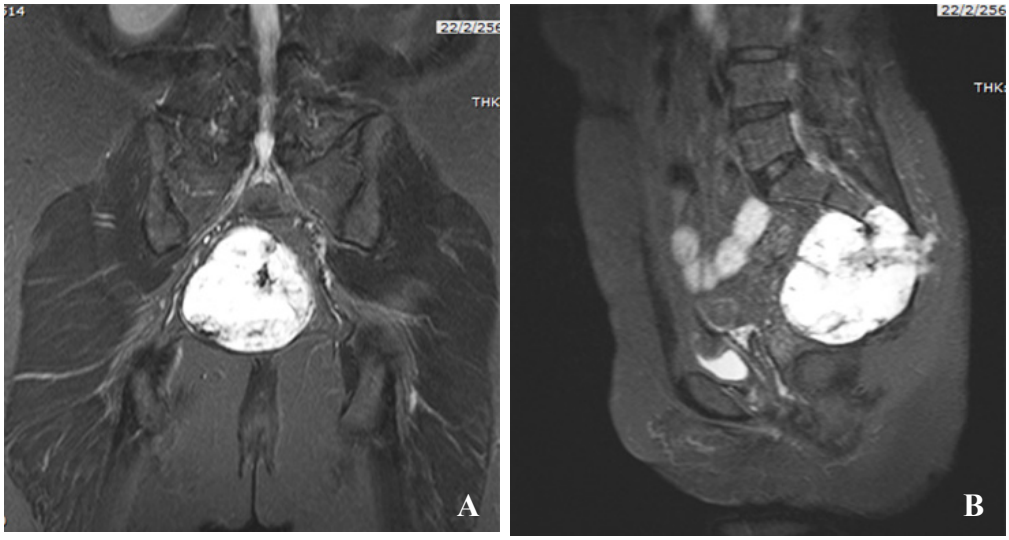

Figure 3: Show T-2 weight MRI, **A:** coronal view, **B:** saggital view

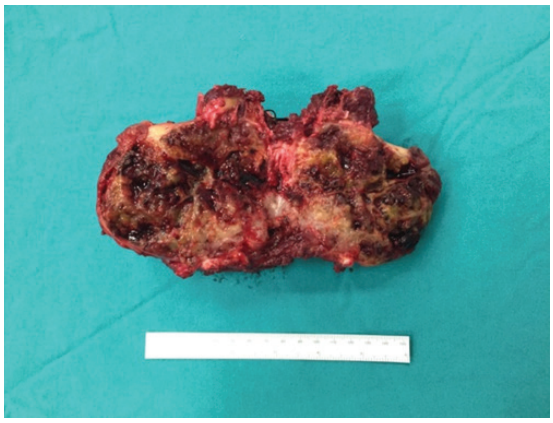

Figure 4: Specimen of chordoma from en bloc removal.

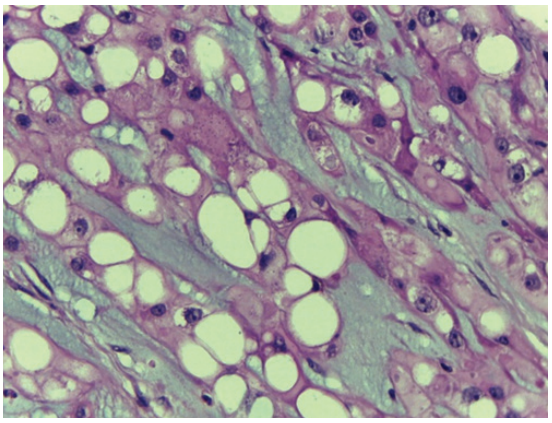

Figure 5: Chordoma histology showing large lobulated tumor cell nests including sheets and elongated cords of clear cells with intracytoplasmic vacuoles, called physaliphorus or "soap bubble" cells in the area of the myxoid matrix

Pathogenesis

Reports have indicated that chordomas may arise from notochordal remnants which remain in the vertebra. They can occur along the midline of the spine through the axial skeletal bone from the skull base to the sacrum.[12] Histological studies of chordomas are very similar to studies in the notochord in that both consist of large lobulated tumor cell nests and include sheets or elongated cords of clear cells with intracytoplasmic vacuoles, called physaliphorus or "soap bubble" cells in the area of the myxoid matrix[13] (Figure-5).

A recent study of chordomas showed the evidence of similarities between chordomas and notochord which both have including a strong genetic relationship.[14] The Brachyury protein, which is encoded by the T gene, is located on chromosome 6q27. Duplications or amplifications of the T gene have been found to be closely associated with familial and almost all sporadic chordomas when compared with other bone neoplasm. The relationship between the T gene, Brachyury protein, and chordomas is still unclear and needs more research, although, it is believed that the Brachyury gene might be an important initiator of this type of tumor.

A recent study of chordomas showed that there is a significant connection between notochord gene and chordomas. The T gene, located on chromosome 6q27, encodes the Brachyury protein.[14] A study of familial chordomas reported that duplications of the T gene in family members will increase susceptibility to chordomas. Furthermore, in the most sporadic cases, an over-expression and amplification of this gene when compared with other bone or cartilaginous lesions has been reported.[15-17] Although the role of the Brachyury protein in the pathogenesis of chordomas is still unclear, identification of the duplication and amplification of the T gene and its significant overexpression have been seen in these studies.

Many studies have tried to demonstrate prognosis markers and one of the recent studies show SNF5 which is observed in cytoplasm. The study investigated the relationship between SNF5 and clinical features in skull base chordoma and found that low SNF5 expression is correlated with poor prognosis including progression free survival (PFS) and overall survival (OS).[18] Platelet-derived growth factor receptor–b (PDGFR-b) is one of the prognostic markers that has been recently reported. Higher expression level of PDGFR-b in chordoma also correlated with poorer prognosis for clival chordoma patients. PDGFR-b could regulate invasion through the mTOR pathway in clival chordoma cells.19

Treatment

The treatment of chordomas is complicated and is still continuously evolving. The need for comprehensive multimodality treatment has been increasing in recent years including; 1) Expert surgeons, 2) Radiotherapy team. Recent retrospective cohort studies show the initial treatment in a multidisciplinary center resulted in a significant improvement in patients-free-survival (PFS) and reduction in the risk of recurrence.[20] Although chordoma is classified histologically as a benign neoplasm, chordomas are locally invasive and have a high recurrence rate. These factors make prognosis as a benign neoplasm unlikely.[9,21] Additionally, radiation therapy is still limited due to the lower tolerance of the spinal cord and brain stem to the dose needed for clinically effective treatment of the tumors.[22] The use of radiotherapy as a primary treatment has proven to be not as effective as debulking surgery.[23] A systematic review reported that chordomas are insensitive to conventional chemotherapies because of their slow rate of growth and their low cellular turnover rate.[24] For all of these reasons, the gold standard for chordomas management is usually extended resection with wide tumor-free margins.[24] However, en bloc surgical resection, introduced by Stener and Gunterberg[25] in 1987, has become a standard treatment for sacral chordomas. That operation can be challenging because almost all patients are diagnosed at the late stage and because of the invasion of surrounding tissue including vital neural structures with poor margination.[25] As a result, partial resection is often the only option, although it can lead to significant residual tumor, tumor seeding, and finally recurrence of the tumors, although more aggressive and wider surgical margins have proved to significantly decrease local recurrence of chordomas.[26,27] A study of surgical management of chordomas showed a significant difference in outcomes between radical and subtotal resection. The average time to local recurrence in patients who underwent subtotal resection was 8 months compared with 2.27 years for those who had radical resection of chordomas.[28] The complications seen after surgery vary depending on the area of the tumor involvement. Sacrectomies that resect the S2 nerve root are associated with abnormal bowel and bladder function (up to 50%). The percentage of bowel and bladder involvement increases if the S3 nerve root is also resected.[29] Even though the best option for treatment of recurrent chordoma is en bloc resection with negative surgical margin, it is often difficult to perform in cases of multifocal disease. In those cases, limited resection should be considered to prevent disease progression as well as to preserve function and avoid additional morbidity. For palliative treatment, there are many options other than resection, e.g., radiofrequency ablation (RFA), cryotherapy, low-dose RT and just continued observation. Good candidates for complete re-resection are patients with a single recurrent tumor, a long disease free interval, and otherwise in overall good health. Patients who have not received radiation therapy either before or after primary surgery should be considered for radiation therapy.[30]

Some studies suggest that radiation therapy in combination with surgical treatment can provide additional advantages. However, conventional radiation therapy with a high dose of radiation can cause a variety of side effects. Common side effects such as myelopathy can occur due to radiation overdose because the spinal cord and the brain stem are more sensitive to radiation than the tumor. It is not possible to provide appropriately administered clinically effective doses of radiation without causing radiation side effects. Newer methods of radiation using hadrons i.e., high-dose of protons or charged particles, including carbon ions, helium, and neon, have been introduced. With these new technologies, it is possible to give higher doses of radiation and to achieve more effective tumor radiation therapy with less severe side effects on surrounding structures.[31-33] The heavy ions such as those in hadron-based therapy provide more benefit compared with photon radiation, their biological effectiveness is relatively higher, and they can reduce the oxygen enhancement ratio in the tumor area. Carbon-ion radiation therapy has been recently introduced for management of advanced chordomas which are unresectable.[34] A retrospective study showed that carbon-ion radiation can lower local tumor recurrence rates and has better outcomes in term of preservation of bowel and bladder function when compared with surgery.[35] Other studies reported that Intensity Modulated Proton Therapy (IMPT) show greater local control rates, improved tolerance to treatment and overall survival rates with a reduced toxicity profile compared with traditional photon RT.[36] Despite the better outcomes of particle beam radiation in management of chordomas, the radiation machines used in these treatments are not commonly available worldwide as they are still very costly especially for countries like Thailand.[37]

Molecular profiles of chordomas have revealed that chordomas overexpress the platelet-derived growth factor receptors (PDGFR)B, PDGFRA, and KIT receptors. This suggests that there is a role for new molecular-targeting agents such as imatinib a tyrosine-kinase inhibitor (TKI).[38] Some studies have shown a good responsiveness to imatinib, a TKI with specificity for the kinase domain of PDGFR and KIT receptors, in patients with chordoma.[39,40] Imatinib has shown the greatest promise for palliative treatment of advanced chordoma. It can slow down the tumor progression and alleviate patients' symptoms. Unfortunately, evaluation of its

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efficacy in current clinical reports is still limited due to small sample sizes and a relatively long follow-up period. Afatinib is a new drug in recent preclinical studies which is one of the epidermal growth factor receptor (EGFR) inhibitors. Multiple reports in the literature show the activity of different EGFR inhibitors in chordoma cell lines.[41] Afatinib might have an immediate therapeutic application for chordoma patients but it is still at the in vivo models stage and needs further investigation in the upcoming phase II study.[42]

There is as yet no consensus regarding the frequency and duration of follow-ups for patients with recurrent chordoma. Many experts agree that all patients should receive an magnetic resonance image (MRI) at least every 3-6 months for the first 3 years following treatment. The follow-up period should be extended because chordoma can relapse after several years due to its slow growing nature.[30]

Conclusion

Chordoma is relatively rare. Despite a histology which makes it appear to be a benign tumor, chordoma is still considered to be malignant due to its aggressive behavior. It is usually invasive to the nearby structures and also has a poor prognosis. The treatment of chordomas is challenging because they often recur or progress even with the best possible initial treatment. Recent studies have introduced many treatment choices, but there is a paucity of literature on tumor management. Chordoma of the spine is a rare disease and there is very limited discussion in the literature involving only small samples. For these reasons, recurrent chordomas remain extremely difficult to manage, although management options continue to evolve.

Conflicts of interest: The authors declare no conflicts of interest.

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