Chordoma: current concepts, management, and future directions

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Chordoma is a rare bone cancer that is aggressive, locally invasive, and has a poor prognosis. Chordomas are thought to arise from transformed remnants of notochord and have a predilection for the axial skeleton, with the most common sites being the sacrum, skull base, and spine. The gold standard treatment for chordomas of the mobile spine and sacrum is en-bloc excision with wide margins and postoperative external-beam radiation therapy. Treatment of clival chordomas is unique from other locations with an enhanced emphasis on preservation of neurological function, typified by a general paradigm of maximally safe cytoreductive surgery and advanced radiation delivery techniques. In this Review, we highlight current standards in diagnosis, clinical management, and molecular characterisation of chordomas, and discuss current research.

Historical overview and epidemiology
Chordoma is a rare cancer that accounts for 1–4% of all bone malignancies. Although histologically considered to be a low-grade neoplasm, chordomas are highly recurrent, making their clinical progression very similar to that of malignant tumours. Population-based studies using the Surveillance, Epidemiology, and End Results (SEER) database suggest an incidence of chordoma of 0·08 per million workers. Surveillance, Epidemiology, and End Results (SEER) data show a median survival of 6·29 years with 5 year, 10 year, and 50% of primary tumours of the sacrum. Unlike most bone malignancies, chordoma constitutes over 50% of primary tumours of the sacrum. Unlike most malignant neoplasms, chordomas are generally slow-growing, radioreistant tumours that are locally aggressive and invasive. The insidious course of the disease and spread along critical bony and neural structures makes clinical management of these patients difficult. Large tumour burden at the time of diagnosis, poor margination, and impingement on surrounding structures make gross total resection and radiation treatment challenging. Like most complex diseases, caring for patients with chordoma is best accomplished in a high-volume centre where specialised medical oncologists, neurosurgeons, nurses, orthopaedic surgeons, pathologists, plastic reconstructive surgeons, radiation oncologists, radiologists, and social workers have expertise with this rare cancer.

In this Review, we focus on the pathogenesis, diagnosis, and clinical management of chordoma. We also summarise recent investigations into molecular characterisation of chordomas in the context of diagnosis and management of this disease.

Pathogenesis
Chordomas were first characterised microscopically by Virchow in 1857. He described unique, intracellular, bubble-like vacuoles that he referred to as physaliferous, a term now synonymous with their histopathology. These physaliferous features of chordoma remain a distinguishing, if not pathognomonic, feature. Virchow hypothesised that chordomas were derived from cartilage; however, more contemporary evidence suggests that they are derived from undifferentiated notochordal remnants that reside within the vertebral bodies and throughout the axial skeleton. In fact, Ribbert first introduced the term chordoma in the 1890s, in view of the notochord hypothesis. Examination of human embryos and fetuses and cell-fate-tracking experiments in mice showed that notochordal cell nests topographically correspond and distribute to the sites of occurrence of chordoma. Although there is little direct evidence that cells transform to chordoma, molecular phenotyping of these primitive rests compared with neoplastic lesions suggests they are indeed the likely source for transformation.

Perhaps the most compelling evidence of the notochordal hypothesis was the discovery of a gene duplication in the transcription factor T (brachyury) gene in familial chordoma. An important transcription factor in notochord development, brachyury is expressed in normal, undifferentiated embryonic notochord in the axial skeleton. High-resolution array comparative genomic hybridisation showed unique duplications in the 6q27 region in tumour samples from patients with familial chordoma. This duplicated region contained only the brachyury gene, which was known to be uniquely overexpressed in almost all sporadic chordomas compared with other bone or cartilaginous lesions. Brachyury regulates several compelling stem-cell genes and has recently been implicated in promoting epithelial–mesenchymal transition in other human carcinomas. Although it is still unclear what role brachyury has in the pathogenesis of chordomas, identification of the duplication and the remarkable overexpression seen in samples suggests that it might...
be a crucial molecular driver in the initiation and propagation of this cancer.

In summary, three fundamental observations support the notochordal hypothesis: the site of notochordal vestiges corresponds closely to the distribution of chordomas; there is a morphological similarity between these remnants and the histopathology exhibited by chordomas; and both share a similar immunophenotype. 23–24

Clinical presentation
Chordomas are indolent and slow growing, therefore they are often clinically silent until the late stages of disease. The clinical manifestations vary and depend on location. Skull-base chordomas often grow in the clivus and present with cranial-nerve palsies. Depending on their size and involvement of the sella, endocrinopathy can also occur. Other rare presentations include epistaxis and intracranial haemorrhage. 19,20 Chordomas of the mobile spine and sacrum can present with localised deep pain or radiculopathies related to the spinal level at which they occur. 23–24 Unfortunately, the non-specific nature of these symptoms and insidious onset of pain often delays the diagnosis until late in the disease course, such that bowel or bladder function can be compromised. 22,23 Diagnosis is further complicated by the fact that lytic sacral lesions might be overlooked on plain radiographs, and CT and MRI studies often do not extend below the S2 level. 23 Studies show that neurological deficit is more often observed in chordomas of the mobile spine than in chordomas in the sacrococcygeal region. 23,24 Most sacrococcygeal chordomas involve the fourth and fifth sacral vertebrae, and although large tumours can protrude anteriorly into the pelvis, invasion into pelvic structures is often limited by presacral fascia. 23 Cervical chordomas can present with airway obstruction or dysphagia, and might even present as an oropharyngeal mass.

Chordomas are midline lesions and often appear radiographically as destructive bone lesions, with an epicentre in the vertebral body and a surrounding soft-tissue mass. Unlike osteosarcomas and chondrosarcomas of the vertebral column, chordomas locally invade the intervertebral disc space as they spread to adjacent vertebral bodies. 25 Calcification and bony expansion are features that appear isointense or hypointense on T1-weighted MRI images, hyperintense on T2-weighted MRI images, and enhance with gadolinium. Furthermore, chordomas show reduced or normal uptake of radioisotope on bone scanning when juxtaposed to other bone tumours. 26

Although chordomas are not typically metastatic on presentation, the often late-stage diagnosis of the disease makes distant metastasis more likely. 5% of chordomas show metastasis to the lungs, bone, skin, and brain at the time of initial presentation, and as high as 65% are metastatic in very advanced disease. 25,26 Patient survival seems to be less affected by distant metastasis than by local progression of the disease. 24 Local recurrence has emerged as the most important predictor of mortality in patients with chordoma, and the extent of initial resection has become the most compelling factor in affording an opportunity for a cure (figure 1). 2,3,30,31

Diagnosis and molecular characteristics
Accurate diagnosis of tumours of the spine and skull base is of valuable prognostic significance. Chordomas and chondrosarcomas represent two biologically distinct categories of mesenchymal neoplasms that share morphological similarity and often present in similar locations throughout the neuroaxis; however, they differ in response to treatment. 21 Advances in diagnostically differentiating between these two diseases have provided considerable insight into the surgical and postsurgical management of these patients. Fine-needle aspiration biopsy (or core-needle biopsy in the case of bony lesions) has been suggested to be the most oncologically sound approach to establish a diagnosis before resection, with care to avoid tumour seeding. 21,22

Chordomas exhibit various degrees of histological atypia, and the relationship between histopathological features and biological behaviour remains an active and controversial area of research. Chordomas manifest as one of three histological variants: classical (conventional), chondroid, or dedifferentiated. 21 Classical chordomas appear as soft, gray-white, lobulated tumours composed of groups of cells separated by fibrous septa. They have round nuclei and an abundant, vacuolated cytoplasm described as physaliferous (having bubbles or vacuoles). 27 Unlike classical chordoma, chondroid chordomas histologically show features of both chordoma and chondrosarcoma, a malignant cartilage-forming tumour. 26

Classically, chordomas were pathologically identified by their physiferous features and immunoreactivity for S-100 and epithelial markers such as epithelial membrane antigen (MUC1) and cytokeratins. 27–30 However, until recently, distinguishing between chondroid chordomas and chondrosarcomas was challenging because of their shared S-100 immunoreactivity, making it difficult to interpret cytokeratin expression on small biopsies. 27 Several groups have postulated that the notochord developmental transcription factor, brachyury, could be a novel discriminating biomarker for chordomas. 2,3,30,31,32,36

Figure 1: CT and magnetic resonance images of lumbar chordoma
Preoperative axial magnetic resonance images of lumbar chordoma (A); preoperative sagittal magnetic resonance images of lumbar chordoma (B); and postoperative lateral radiographs (C).
This hypothesis was validated with a tissue-microarray-based analysis that assessed 103 skull-base and head and neck chondroid tumours. The investigators identified brachyury as a discriminating biomarker of chordomas, and when combined with cytokeratin staining, sensitivity and specificity for detection of chordoma was 98% and 100%, respectively. Brachyury staining to discriminate chordomas from other chondroid lesions has become integral in the pathological work-up during diagnosis (figure 2).

Surgery
Chordomas of the mobile spine and sacrum
In the 1970s, Stener and Gunterberg first introduced the idea of wide en-bloc surgical resection for the treatment of sacral tumours. Since then, en-bloc excision has remained a central tenant in the surgical management of sacral chordoma. With the advent of more aggressive surgery and wider surgical margins, local control of disease recurrence has substantially improved for chordomas of the sacrum, spine, and skull base.

Early findings linked local recurrence to violations of tumour margin. Kaiser and colleagues showed that local recurrence was almost two-times higher in patients who received en-bloc resection where the tumour capsule was entered at the time of surgery than in those who had complete en-bloc excision of the tumour without violation of the capsule. This study provided the first compelling evidence that contamination of the surgical wound via cell seeding is responsible for recurrence, and therefore advocated complete excision of the tumour during initial surgery over any decompression.

Although the implications of these findings are difficult to extrapolate to the management of clival chordomas, where en-bloc excision (or even gross total resection) is rarely possible, they do emphasise the core biological characteristics of the disease.

One landmark study on the surgical management of chordomas showed a remarkable difference in recurrence between patients who underwent radical resection and those who had subtotal excision of sacral chordomas; the time from surgery to local recurrence was 2-27 years compared with 8 months, respectively. Several case series have corroborated this finding, supporting aggressive surgical resection upon initial surgery in chordomas of the sacrum, mobile spine, and skull base.

The surgical approach for many of these tumours depends on the extent of the lesion. For example, en-bloc resection of chordomas below the sacroiliac joint mainly involves a posterior–transperineal exposure, which can be achieved without elaborate reconstructive efforts. Chordomas that are caudal to the sacroiliac joint are more technically challenging, requiring both anterior and posterior exposures or a combined anterior–posterior approach.

Sacrectomies that spare the S2 nerve root are associated with up to a 50% chance of normal bladder and bowel control, a percentage that can be improved if an S3 nerve root is also preserved. Preservation of the bilateral S2 nerve root with the unilateral S3 nerve root is associated with normal bladder and bowel function, whereas sacrifice of any of the S2 nerve roots typically leads to at least loss of voluntary control.

Clival chordomas
Skull-base chordomas have a broad surgical approach strategy that is based on the location of the tumour and the surgeon’s preference. Transphenoidal, transmaxillary, transnasal, high anterior cervical retropharyngeal, and transoral approaches have been well documented in the literature, as have endoscopic techniques. Where en-bloc resection or gross total resection is not feasible, particularly for lesions in the clivus, radical or near total intralesional resection is advocated. Although subtotal resection is sometimes the goal of surgery, maximally safe aggressive resection on presentation with an emphasis on neurological preservation, followed by radiation therapy, is an optimum treatment paradigm. Tumour that remains after surgery, particularly when small in volume, can be managed effectively with radiotherapy. In a series of 19 patients who had surgery and postoperative stereotactic radiosurgery, a small residual tumour volume was controlled effectively with high-dose radiotherapy.

Innovative endoscopic, endonasal techniques to access the clivus are minimally invasive and are also highly effective. In a consecutive series of seven patients undergoing endonasal endoscopic resection of clival chordomas, greater than 95% resection was achieved in seven of eight procedures in which radical resection was
the goal. The challenge of preventing cerebrospinal fluid leakage after violation of the anterior skull-base dura is being addressed with novel, local flap repair techniques. This approach is part of the armamentarium of skull-base surgeons, complementing traditional surgical access techniques such as transoral and transmaxillary approaches. The surgical goals and approaches must be selected on a case-by-case basis and take into consideration the characteristics of the tumour and the patient’s expectations.

When local invasiveness into surrounding skull-base neurovascular structures is present, one management philosophy is to minimise neurological dysfunction, even at the price of postoperative residual tumour. A series instituting this management strategy along with universal adjuvant radiotherapy reported excellent outcomes. 11 patients underwent removal of skull-base chordomas, with resection being subtotal or partial in seven. Transient neurological deterioration (cranial-nerve deficits) occurred in seven patients, all of whom returned to neurological baseline. This result provides evidence that the operative strategy should not be excessively aggressive, but should take into account the options of radiotherapy and observation of residual tumour.20

Overall, it should be emphasised that complex removal of the tumour itself is not a satisfactory treatment goal; preservation of a patient’s neurological function and quality of life must also take priority when assessing surgical outcome.

Radiation therapy
Despite major advances in surgical interventions, total en-bloc resection is attainable in roughly 50% of sacral chordomas, with much lower rates for chordomas of the spine and skull base; therefore, recurrence is common without en-bloc resection.23,25 The use of radiotherapy as primary or adjuvant treatment for chordoma is debated. Unfortunately, stand-alone radiotherapy has proven to be ineffective when coupled with debulking or palliative therapy.24

Advances in radiation technology and treatment have led to more strategic targeting of neoplasms with higher doses of radiation. There is some consensus that radiation therapy in combination with surgery provides an added advantage. Since the tolerance dose of the spinal cord, brain stem, cranial nerves, and rectum is much lower than effective doses to treat chordomas, delivery of high doses is limited. For example, treatment of the sacrococcygeal region with high doses of photon radiation therapy (45–80 Gy) can be achieved because this region is less susceptible than the cervical spine, where myelopathy due to radiation injury is common.52 Treatment with conventional radiation therapy at doses of 40–60 Gy has led to 5-year local control of only 10–40%.53–55

Advances in radiation technology with the introduction of hadrons (ie, high-dose protons or charged particles, including carbon ions, helium, or neon) have led to higher doses of radiation being delivered to the target volume, with minimum injury to the surrounding tissue and improved radiobiological effect.56–58 Hadron-based therapy provides greater advantages than conventional photon-based therapy, and emerging evidence suggests that it might be more effective in the treatment of chordomas. Heavy ions provide biological, in addition to physical, advantages compared with photons, in terms of their high relative biological effectiveness and reduced oxygen-enhancement ratio in the tumour region.59

In fact, studies exploiting the use of hadron therapy in chordomas of the skull base, cervical spine, and sacrococcygeal region show local control at 5 years of 50–60%, and hadron therapy seems to be at least equally effective as photon therapy.60–64 Carbon-ion radiotherapy has been considered for treatment of unresectable chordoma.65 A retrospective analysis of 17 patients with primary sacral chordoma who received either surgery or carbon-ion radiation reported higher local control rates and better preservation of urinary–anorectal function for the carbon-ion radiotherapy group compared with surgery.66

Dosimetric planning for chordoma using radiotherapy aims to provide target coverage and lesion conformality while avoiding damage to surrounding critical structures—ie, brainstem, chiasm, spinal chord, retroperitoneal organs, or temporal lobes. Stereotactic doses typically administered by photon radiation are 15 000 rad,67,68 whereas proton therapy typically delivers 74 cobalt Gy equivalents to the treatment volume (figure 3).69,70

Although no head-to-head trials have compared photon and hadron therapy, preliminary evidence suggests that
the latter is a promising strategy when coupled with surgery.75 Proton-beam therapy with wide en-bloc excision is the accepted treatment standard in the management of chordomas at many quaternary-care cancer centres, especially in patients with a primary tumour as opposed to disease recurrence. Park and colleagues72 showed that treatment with proton or photon-beam radiation in combination with surgery resulted in higher local control in patients with primary sacral chordoma than in those with recurrence, underscoring the importance of radiation early in the treatment of the disease. Unfortunately, the availability of hadron-based therapy is limited because of the associated construction and operational expenses.73–75 Alternatives include intensity-modulated radiation therapy (IMRT) and stereotactic delivery techniques.74,75 Because of the relative rarity of chordoma and the difficulty randomising patients to treatment other than standard care at many facilities, it is unlikely that phase 3 trials will be done to compare different types of radiation, making differences in clinical effect difficult to determine. Compared with photons, proton therapy provides lower biologically effective doses to non-target tissue for a specified dose and dose distribution; without a trial the debate over clinical gain will persist, despite the known quantitative reduction in physical dose.76 The cost of proton therapy is expected to decrease rapidly (it is roughly twice as expensive as IMRT at present), resulting in increased availability.77

Retreatment

Despite best efforts at initial treatment, most chordomas will recur or progress. There are very few reports of treatment protocols and outcomes for recurrent lesions. Different treatment regimens have been described for recurrent disease, including re-irradiation79 and re-operation.80,81 Toxicities often limit the ability to safely deliver an effective radiation dose to a previously radiated field, and the dose delivered depends highly on lesion location, volume, and patient age and performance status. Surgical treatment for recurrent disease is fraught with the morbidity associated with re-operation, particularly if the field was previously irradiated. However, many patients elect to undergo complex reoperations, despite a high rate of morbidity for all lesion locations.83 Individualised care, with input from providers in all involved disciplines, is necessary to respect tolerances and achieve treatment goals.

Medical treatment

Anthracycline, cisplatin, alkylating agents,84 and camptothecin analogues85 have been reported to affect chordomas, and some case reports have suggested sensitivity of one of the histological variants—dedifferentiated chordoma.86 Unfortunately, systematic review of the literature found chordomas to be insensitive to conventional chemotherapies.86,87 Molecular profiling of chordomas has revealed that they overexpress platelet-derived growth factor receptor (PDGFR)B, PDGFRα, and KIT receptors, suggesting a role for new molecular-targeting agents.88 In fact, two studies in 2004 and a study in 2009 showed responsiveness of patients with chordoma to imatinib, a tyrosine-kinase inhibitor (TKI) with specificity for the kinase domain of PDGFR and KIT receptors.89,90 Patients with advanced disease showed non-dimensional tissue responses, marked by hypodensity and decreased contrast uptake on CT scan. There was also symptomatic improvement and a report of liquefaction of the tumour in some patients.90,91 Another TKI, sunitinib, has shown clinical efficacy. In a clinical trial, 44% of patients with chordoma who were given sunitinib achieved an outcome of stable disease for at least 16 weeks, and qualitative decreases in tumour density were noted.92 In summary, these TKIs with known multitargeted activity against vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, PDGFα, PDGFβ, KIT, FLT3, RET, and CSF-1 have shown activity against chordoma, probably as a result of targeted inhibition of several intersecting molecular pathways. Interpretation of efficacy in current clinical reports is limited by small patient numbers and short follow-up.

As tumour characteristics are further elucidated, additional molecular pathways have been targeted. In a series of 12 patients with chordoma, strong expression of epidermal growth factor receptor (EGFR) and c-MET was described.93 This led to the report of a patient’s response to cetuximab and gefitinib, two drugs designed to inhibit the EGFR pathway.94 Another EGFR inhibitor, erlotinib, induced symptomatic and radiological response in a patient with disease refractory to imatinib.95 A recent analysis of 70 chordoma samples showed activation of phosphorylated signal transducer and activator of transcription 3 (STAT3), a transcription factor known to be active in several human cancers and associated with poor prognosis.96 The use of STAT3 inhibitors in chordoma cell lines in vitro showed strong inhibition of cell growth and proliferation.97

Current research and future directions

Despite aggressive surgical measures and high-dose radiation, local recurrence of chordoma is the marker of treatment failure.98 Studies have identified a common gene duplication of the transcriptional regulator, brachyury, in patients with familial and sporadic chordoma.99 Furthermore, tyrosine kinases and transcriptional regulators have been shown to be overexpressed in chordoma. Studies targeting these kinase domains and their downstream effectors could provide translational therapies and will improve our understanding and treatment of patients with chordoma.100,101,102 A phase 1 trial of nilotinib therapy began enrolling patients in August, 2011 (NCT01407198), and a study involving dasatinib is finished enrolling patients with study
completion expected December, 2013 (NCT00464620). Additional molecular pathways are also being targeted in ongoing trials involving lapatinib and everolimus.97

The optimisation of radiation treatment is being investigated in a phase 3 study comparing the efficacy of proton versus carbon-ion radiation therapy in skull-base chordoma (NCT01182779).98 Other ongoing studies are investigating the efficacy of PET to affect delivery of intensity-modulated proton therapy (and the ability to detect relative tumour hypoxia) in an attempt to overcome radiation resistance (NCT00713037).

Pivotal to the preclinical study of this disease is the development of characterised cell lines. Several cultured human chordoma cell lines such as CH 8, GP 60, and U-CH1 have successfully been generated, with typified growth properties in a variety of media and response to chemotherapeutic agents.84 An additional line, JHC7, was recently generated and showed that brachyury silencing resulted in complete growth arrest and senescence of chordoma tumour cells in vitro.99 This exciting discovery highlights brachyury as an attractive potential therapeutic target, since it seems to be common and specific to all chordoma.32

Contributors
BPW and MJF conceived the Review. MJF was the senior author. J-VC provided oversight. AM provided the immunohistochemistry for figure 2. BPW formatted the manuscript, references, and figures. All authors participated in drafting and revising the manuscript, and approved the final version.

Conflicts of interest
The authors declared no conflicts of interest.

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