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.[1] Although histologically considered to be a low-grade neoplasm, chordomas are highly recurrent, making their clinical progression very similar to that of malignant tumours.[2,3] Population-based studies using the Surveillance, Epidemiology, and End Results (SEER) database suggest an incidence of chordoma of 0·08 per 100 000, with predominance in men and peak incidence between 50–60 years of age.[4] Chordomas have very low incidence in patients younger than 40 years, and rarely affect children and adolescents (<5% of all chordoma cases).[4,5] The most comprehensive survival analysis, involving assessment of 400 cases from the SEER database, showed a median survival of 6·29 years with 5 year, 10 year, and 20 year survival dropping precipitously to 67·6%, 39·9%, and 13·1%, respectively, across all races and sex.[4]

Historically, it was presumed that chordomas present in the sacrum more so than the skull base; however, evidence suggests an almost equal distribution in the skull base (32%), mobile spine (32·8%), and sacrum (29·2%).[4] Disproportionately, chordomas constitute over 50% of primary tumours of the sacrum.[6] Unlike most malignant neoplasms, chordomas are generally slow-growing, radioresistant 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.[7] 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.[8] In fact, Ribbert first introduced the term chordoma in the 1890s,[9] in view of the notochord hypothesis. Examination of human embryos and fetuses[10–13] and cell-fate-tracking experiments in mice[14] showed that notochordal cell nests topo-graphically 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.[12,13]

Perhaps the most compelling evidence of the notochordal hypothesis was the discovery of a gene duplication in the transcription factor T gene (*brachyury*) in familial chordoma.[15] An important transcription factor in notochord development, *brachyury* is expressed in normal, undifferentiated embryonic notochord in the axial skeleton.[12,13] High-resolution array comparative genomic hybridisation showed unique duplications in the 6q27 region in tumour samples from patients with familial chordoma.[15] 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.[12,16] *Brachyury* regulates several compelling stem-cell genes and has recently been implicated in promoting epithelial–mesenchymal transition in other human carcinomas.[17] 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

Figure 1: CT and magnetic resonance images of lumbar chordoma
Preoperative axial magnetic resonance images of lumbar chordoma (A); preoperative sagital magnetic resonance images of lumbar chordoma (B); and postoperative lateral radiographs (C).

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 notochord 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.[10,12–14]

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.[18] 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.[2,21–23] 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.[2,21] 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.[24,25] 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.[26] 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.[23] 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.[27] Furthermore, chordomas show reduced or normal uptake of radioisotope on bone scanning when juxtaposed to other bone tumours.[28]

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.[25,29] 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).[2,6,30,31]

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.[32] 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[2]) has been suggested to be the most oncologically sound approach to establish a diagnosis before resection, with care to avoid tumour seeding.[23,33]

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.[34] 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).[34] Unlike classical chordoma, chondroid chordomas histologically show features of both chordoma and chondrosarcoma, a malignant cartilage-forming tumour.[34]

Classically, chordomas were pathologically identified by their physaliferous features and immunoreactivity for S-100 and epithelial markers such as epithelial membrane antigen (MUC1) and cytokeratins.[35–37] 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.[16,32] Several groups have postulated that the notochord developmental transcription factor, brachyury, could be a novel discriminating biomarker for chordomas.[3,12,13,16,32,38]

This hypothesis was validated with a tissue-microarray-based analysis that assessed 103 skull-base and head and neck chondroid tumours.[32] 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.[32] 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[39] 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,[40] spine,[41] and skull base.[42]

Early findings linked local recurrence to violations of tumour margin. Kaiser and colleagues[21] 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.[21] Although the implications of these findings are difficult to extrapolate to the management of clival chordomas, where en-bloc excision (or even gross total excision) 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;[43] 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,[40] mobile spine,[41] and skull base.[42]

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.[23,40,43,44] 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
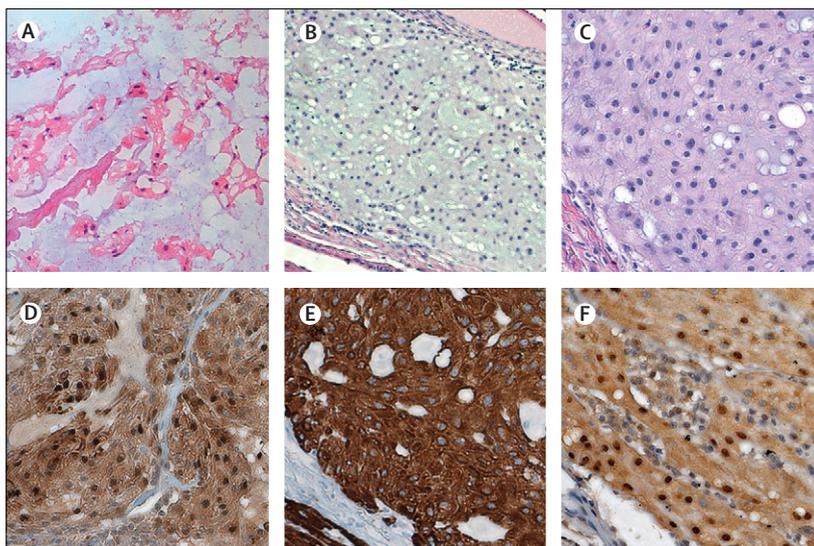

Figure 2: Immunohistochemical characterisation of human chordoma tissue
Intraoperatively obtained chordoma tissue with physaliferous phenotype; haematoxylin and eosin (H&E) stained, frozen tissue smear (A,B,C). Intraoperatively obtained chordoma tissue with physaliferous phenotype; H&E stained, formalin-fixed tissue (D,E,F). Chordoma tissue is positive for S-100β in A, for cytokeratin AE1/AE3 in B, and for brachyury in C; immunohistochemistry with diaminobenzidine chromogen.

an S3 nerve root is also preserved.[39,44] 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.[44]

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.[42] Transphenoidal, transmaxillary, transnasal, high anterior cervical retropharyngeal, and transoral approaches have been well documented in the literature, as have endoscopic techniques.[45,46] 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.[47]

Innovative endoscopic, endonasal techniques to access the clivus are minimally invasive and are also highly effective.[48] 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
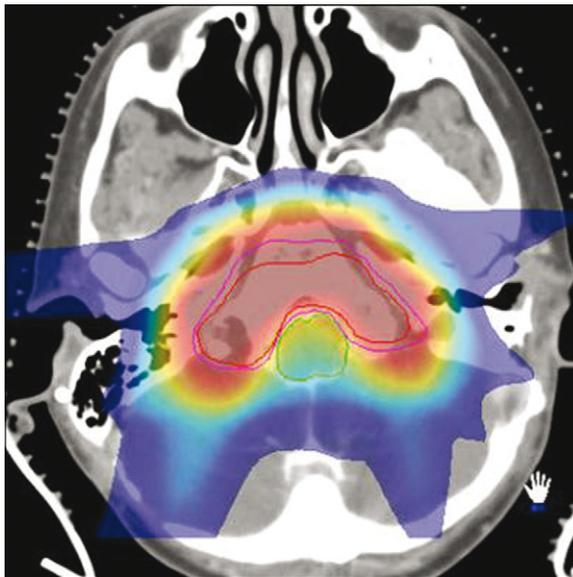
Figure 3: **Dosimetric treament plan for clival chordoma (proton therapy)**
Dosimetric treatment planning for clival chordoma aims to maximise dose to the target volume while minimising dose to surrounding critical structures.

the goal.[49] 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.[50] 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.[50]

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.[25,42,43,51] 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.[71] 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 colleagues[72] 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.[60,76] 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.[77] The cost of proton therapy is expected to decrease rapidly (it is roughly twice as expensive as IMRT at present), resulting in increased availability.[78]

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-irradiation[79] and reoperation.[80–82] 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 reoperation, 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 analogues[85] 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.[30,31]

Molecular profiling of chordomas has revealed that they overexpress platelet-derived growth factor receptor (PDGFR)B, PDGFRA, and KIT receptors, suggesting a role for new molecular-targeting agents.[87] 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.[88,89] 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.[88,89] 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.[90] In summary, these TKIs with known multitargeted activity against vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, PDGFRA, PDGFRB, KIT, FLT3, RET, and CSF-1 have shown activity against chordoma, probably 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.[91] This led to the report of a patient's response to cetuximab and gefitinib, two drugs designed to inhibit the EGFR pathway.[92] Another EGFR inhibitor, erlotinib, induced symptomatic and radiological response in a patient with disease refractory to imatinib.[93] 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.[94] The use of STAT3 inhibitors in chordoma cell lines in vitro showed strong inhibition of cell growth and proliferation.[95]

Current research and future directions

Despite aggressive surgical measures and high-dose radiation, local recurrence of chordoma is the marker of treatment failure.[96] Studies have identified a common gene duplication of the transcriptional regulator, *brachyury*, in patients with familial and sporadic chordoma.[15] 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.[87,88,91,94,95] 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 investigations are studying 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.

References
1. Healey JH, Lane JM. Chordoma: a critical review of diagnosis and treatment. *Orthop Clin North Am* 1989; **20:** 417–26.
2. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer* 2000; **88:** 2122–34.
3. Schwab JH, Boland PJ, Agaram NP, et al. Chordoma and chondrosarcoma gene profile: implications for immunotherapy. *Cancer Immunol Immunother* 2009; **58:** 339–49.
4. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973–1995. *Cancer Causes Control* 2001; **12:** 1–11.
5. Wold LE, Laws ER. Cranial chordomas in children and young adults. *J Neurosurg* 1983; **59:** 1043–47.
6. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC. Lumbosacral chordoma: prognostic factors and treatment. *Spine* 1999; **24:** 1639–45.
7. Virchow RL. Untersuchungen ueber die Entwicklung des Schaedelgrundes. Berlin: G Rimer, 1857.
8. Horten BC, Montague SR. In vitro characteristics of a sacrococcygeal chordoma maintained in tissue and organ culture systems. *Acta Neuropathol* 1976; **35:** 13–25.
9. Ribbert H. Uber die Ecchondosis physaliphora sphenooccipitalis. *Centralbl Allg Pathol Anat* 1894; **5:** 457–61.
10. Salisbury JR, Deverell MH, Cookson MJ, Whimster WF. Three-dimensional reconstruction of human embryonic notochords: clue to the pathogenesis of chordoma. *J Pathol* 1993; **171:** 59–62.
11. Salisbury JR. The pathology of the human notochord. *J Pathol* 1993; **171:** 253–55.
12. Vujovic S, Henderson S, Presneau N, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. *J Pathol* 2006; **209:** 157–65.
13. Shen J, Li C-D, Yang H-L, et al. Classic chordoma coexisting with benign notochordal cell rest demonstrating different immunohistological expression patterns of brachyury and galectin-3. *J Clin Neurosci* 2011; **18:** 96–99.
14. Choi K-S, Cohn MJ, Harfe BD. Identification of nucleus pulposus precursor cells and notochordal remnants in the mouse: implications for disk degeneration and chordoma formation. *Dev Dyn* 2008; **237:** 3953–58.
15. Yang XR, Ng D, Alcorta DA, et al. T (brachyury) gene duplication confers major susceptibility to familial chordoma. *Nat Genet* 2009; **41:** 1176–78.
16. Henderson SR, Guiliano D, Presneau N, et al. A molecular map of mesenchymal tumors. *Genome Biol* 2005; **6:** 76.
17. Fernando RI, Litzinger M, Trono P, Hamilton DH, Schlom J, Palena C. The T-box transcription factor Brachyury promotes epithelial-mesenchymal transition in human tumor cells. *J Clin Invest* 2010; **120:** 533–44.
18. Stark AM, Mehdorn HM. Images in clinical medicine. Chondroid clival chordoma. *N Engl J Med* 2003; **349:** 10.
19. Kitai R, Yoshida K, Kubota T, et al. Clival chordoma manifesting as nasal bleeding: a case report. *Neuroradiology* 2005; **47:** 368–71.
20. Levi AD, Kucharczyk W, Lang AP, Schutz H. Clival chordoma presenting with acute brain stem hemorrhage. *Can J Neurol Sci* 1991; **18:** 515–18.
21. Kaiser TE, Pritchard DJ, Unni KK. Clinicopathologic study of sacrococcygeal chordoma. *Cancer* 1984; **53:** 2574–78.
22. Gray SW, Singhabhandhu B, Smith RA, Skandalakis JE. Sacrococcygeal chordoma: report of a case and review of the literature. *Surgery* 1975; **78:** 573–82.
23. Fourney DR, Gokaslan ZL. Current management of sacral chordoma. *Neurosurg Focus* 2003; **15:** 9.
24. Boriani S, Chevalley F, Weinstein JN, et al. Chordoma of the spine above the sacrum. Treatment and outcome in 21 cases. *Spine* 1996; **21:** 1569–77.
25. Bjornsson J, Wold LE, Ebersold MJ, Laws ER. Chordoma of the mobile spine. A clinicopathologic analysis of 40 patients. *Cancer* 1993; **71:** 735–40.
26. Disler DG, Miklic D. Imaging findings in tumors of the sacrum. *AJR Am J Roentgenol* 1999; **173:** 1699–1706.
27. Llauger J, Palmer J, Amores S, Bagué S, Camins A. Primary tumors of the sacrum: diagnostic imaging. *AJR Am J Roentgenol* 2000; **174:** 417–24.
28. Rossleigh MA, Smith J, Yeh SD. Scintigraphic features of primary sacral tumors. *J Nucl Med* 1986; **27:** 627–30.
29. Chambers PW, Schwinn CP. Chordoma: a clinicopathologic study of metastasis. *Am J Clin Pathol* 1979; **72:** 765–76.
30. York JE, Kaczaraj A, Abi-Said D, et al. Sacral chordoma: 40-year experience at a major cancer center. *Neurosurgery* 1999; **44:** 74–79.
31. Azzarelli A, Quagliuolo V, Cerasoli S, et al. Chordoma: natural history and treatment results in 33 cases. *J Surg Oncol* 1988; **37:** 185–91.
32. Oakley GJ, Fuhrer K, Seethala RR. Brachyury, SOX-9, and podoplanin, new markers in the skull base chordoma vs chondrosarcoma differential: a tissue microarray-based comparative analysis. *Mod Pathol* 2008; **21:** 1461–69.
33. Arnautović KI, Al-Mefty O. Surgical seeding of chordomas. *Neurosurg Focus* 2001; **10:** 7.
34. Chugh R, Tawbi H, Lucas DR, Biermann JS, Schuetze SM, Baker LH. Chordoma: the nonsarcoma primary bone tumor. *Oncologist* 2007; **12:** 1344–50.
35. Crapanzano JP, Ali SZ, Ginsberg MS, Zakowski MF. Chordoma: a cytologic study with histologic and radiologic correlation. *Cancer* 2001; **93:** 40–51.

36   Mitchell A, Scheithauer BW, Unni KK, Forsyth PJ, Wold LE, McGivney DJ. Chordoma and chondroid neoplasms of the spheno-occiput. An immunohistochemical study of 41 cases with prognostic and nosologic implications. *Cancer* 1993; **72:** 2943–49.

37   Abenoza P, Sibley RK. Chordoma: an immunohistologic study. *Hum Pathol* 1986; **17:** 744–47.

38   Sangoi AR, Karamchandani J, Lane B, et al. Specificity of brachyury in the distinction of chordoma from clear cell renal cell carcinoma and germ cell tumors: a study of 305 cases. *Mod Pathol* 2011; **24:** 425–29.

39   Stener B, Gunterberg B. High amputation of the sacrum for extirpation of tumors. Principles and technique. *Spine* 1978; **3:** 351–66.

40   Hsieh PC, Xu R, Sciubba DM, et al. Long-term clinical outcomes following en bloc resections for sacral chordomas and chondrosarcomas: a series of twenty consecutive patients. *Spine* 2009; **34:** 2233–39.

41   Stacchiotti S, Casali PG, Lo Vullo S, et al. Chordoma of the mobile spine and sacrum: a retrospective analysis of a series of patients surgically treated at two referral centers. *Ann Surg Oncol* 2010; **17:** 211–19.

42   Tzortzidis F, Elahi F, Wright D, Natarajan SK, Sekhar LN. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. *Neurosurgery* 2006; **59:** 230–37.

43   Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. *J Bone Joint Surg Am* 2005; **87:** 2211–16.

44   Samson IR, Springfield DS, Suit HD, Mankin HJ. Operative treatment of sacrococcygeal chordoma. A review of twenty-one cases. *J Bone Joint Surg Am* 1993; **75:** 1476–84.

45   Holzmann D, Reisch R, Krayenbühl N, Hug E, Bernays RL. The transnasal transclival approach for clivus chordoma. *Minim Invasive Neurosurg* 2010; **53:** 211–17.

46   Singh H, Harrop J, Schiffmacher P, Rosen M, Evans J. Ventral surgical approaches to craniovertebral junction chordomas. *Neurosurgery* 2010; **66** (suppl 3): 96–103.

47   Potluri S, Jefferies SJ, Jena R, et al. Residual postoperative tumour volume predicts outcome after high-dose radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol (R Coll Radiol)* 2011; **23:** 199–208.

48   Dehdashti AR, Karabatsou K, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for treatment of clival chordomas: early results in 12 patients. *Neurosurgery* 2008; **63:** 299–307.

49   Fraser JF, Nyquist GG, Moore N, Anand VK, Schwartz TH. Endoscopic endonasal transclival resection of chordomas: operative technique, clinical outcome, and review of the literature. *J Neurosurg* 2010; **112:** 1061–69.

50   Stüer C, Schramm J, Schaller C. Skull base chordomas: management and results. *Neurol Med Chir (Tokyo)* 2006; **46:** 118–24.

51   Osaka S, Kodoh O, Sugita H, Osaka E, Yoshida Y, Ryu J. Clinical significance of a wide excision policy for sacrococcygeal chordoma. *J Cancer Res Clin Oncol* 2006; **132:** 213–18.

52   Casali PG, Stacchiotti S, Sangalli C, Olmi P, Gronchi A. Chordoma. *Curr Opin Oncol* 2007; **19:** 367–70.

53   Forsyth PA, Cascino TL, Shaw EG, et al. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. *J Neurosurg* 1993; **78:** 741–47.

54   Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol* 1996; **41:** 67–72.

55   Cummings BJ, Hodson DI, Bush RS. Chordoma: the results of megavoltage radiation therapy. *Int J Radiat Oncol Biol Phys* 1983; **9:** 633–42.

56   Suit HD, Goitein M, Munzenrider J, et al. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. *J Neurosurg* 1982; **56:** 377–85.

57   Austin-Seymour M, Munzenrider JE, Goitein M, et al. Progress in low-LET heavy particle therapy: intracranial and paracranial tumors and uveal melanomas. *Radiat Res Suppl* 1985; **8:** 219–26.

58   Austin-Seymour M, Munzenrider J, Linggood R, et al. Fractionated proton radiation therapy of cranial and intracranial tumors. *Am J Clin Oncol* 1990; **13:** 327–30.

59   Tobias CA, Blakely EA, Alpen EL, et al. Molecular and cellular radiobiology of heavy ions. *Int J Radiat Oncol Biol Phys* 1982; **8:** 2109–20.

60   Austin-Seymour M, Munzenrider J, Goitein M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 1989; **70:** 13–17.

61   Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. *Int J Radiat Oncol Biol Phys* 1995; **31:** 577–81.

62   Berson AM, Castro JR, Petti P, et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley Laboratory experience. *Int J Radiat Oncol Biol Phys* 1988; **15:** 559–65.

63   Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999; **91:** 432–39.

64   Noël G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol* 2005; **44:** 700–08.

65   Imai R, Kamada T, Tsuji H, et al. Carbon ion radiotherapy for unresectable sacral chordomas. *Clin Cancer Res* 2004; **10:** 5741–46.

66   Nishida Y, Kamada T, Imai R, et al. Clinical outcome of sacral chordoma with carbon ion radiotherapy compared with surgery. *Int J Radiat Oncol Biol Phys* 2011; **79:** 110–16.

67   Hasegawa T, Ishii D, Kida Y, Yoshimoto M, Koike J, Iizuka H. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg* 2007; **107:** 752–57.

68   Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium. *Neurosurgery* 2011; **68:** 379–89.

69   Marucci L, Niemierko A, Liebsch NJ, Aboubaker F, Liu MCC, Munzenrider JE. Spinal cord tolerance to high-dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2004; **59:** 551–55.

70   Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *Int J Radiat Oncol Biol Phys* 1999; **45:** 351–58.

71   Goitein M, Cox JD. Should randomized clinical trials be required for proton radiotherapy? *J Clin Oncol* 2008; **26:** 175–76.

72   Park L, Delaney TF, Liebsch NJ, et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. *Int J Radiat Oncol Biol Phys* 2006; **65:** 1514–21.

73   Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol* 2005; **44:** 850–61.

74   Levin WP, Kooy H, Loeffler JS, DeLaney TF. Proton beam therapy. *Br J Cancer* 2005; **93:** 849–54.

75   Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol* 2010; **7:** 37–43.

76   Rich TA, Schiller A, Suit HD, Mankin HJ. Clinical and pathologic review of 48 cases of chordoma. *Cancer* 1985; **56:** 182–87.

77   Suit H, Kooy H, Trofimov A, et al. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiother Oncol* 2008; **86:** 148–53.

78   Mohan R, Bortfeld T. Proton therapy: clinical gains through current and future treatment programs. *Front Radiat Ther Oncol* 2011; **43:** 440–64.

79   Jensen AD, Nikoghosyan A, Ellerbrock M, Ecker S, Debus J, Münter MW. Re-irradiation with scanned charged particle beams in recurrent tumours of the head and neck: acute toxicity and feasibility. *Radiother Oncol* 2011; published online June 1. DOI:10.1016/j.radonc.2011.05.017.

80   Heylen S, Michielsen J, Mahieu G, Somville J. Recurrent chordoma of the L2 vertebra: a case report. *Acta Orthop Belg* 2010; **76:** 416–19.

81   Matsumoto M, Watanabe K, Ishii K, et al. Complicated surgical resection of malignant tumors in the upper cervical spine after failed ion-beam radiation therapy. *Spine* 2010; **35:** 505–09.

82   Ito E, Saito K, Okada T, Nagatani T, Nagasaka T. Long-term control of clival chordoma with initial aggressive surgical resection and gamma knife radiosurgery for recurrence. *Acta Neurochir (Wien)* 2010; **152:** 57–67.

83 Tamaki M, Aoyagi M, Kuroiwa T, Yamamoto M, Kishimoto S, Ohno K. Clinical course and autopsy findings of a patient with clival chordoma who underwent multiple surgeries and radiation during a 10-year period. *Skull Base* 2007; **17:** 331–40.

84 Yang C, Hornicek FJ, Wood KB, et al. Characterization and analysis of human chordoma cell lines. *Spine* 2010; **35:** 1257–64.

85 Chugh R, Dunn R, Zalupski MM, et al. Phase II study of 9-nitro-camptothecin in patients with advanced chordoma or soft tissue sarcoma. *J Clin Oncol* 2005; **23:** 3597–604.

86 Fleming GF, Heimann PS, Stephens JK, et al. Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. *Cancer* 1993; **72:** 714–18.

87 Negri T, Casieri P, Miselli F, et al. Evidence for PDGFRA, PDGFRB and KIT deregulation in an NSCLC patient. *Br J Cancer* 2007; **96:** 180–81.

88 Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. *Cancer* 2004; **101:** 2086–97.

89 Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. *Ann Oncol* 2009; **20:** 1886–94.

90 George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol* 2009; **27:** 3154–60.

91 Weinberger PM, Yu Z, Kowalski D, et al. Differential expression of epidermal growth factor receptor, c-Met, and HER2/neu in chordoma compared with 17 other malignancies. *Arch Otolaryngol Head Neck Surg* 2005; **131:** 707–11.

92 Hof H, Welzel T, Debus J. Effectiveness of cetuximab/gefitinib in the therapy of a sacral chordoma. *Onkologie* 2006; **29:** 572–74.

93 Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. *Anticancer Drugs* 2009; **20:** 953–55.

94 Yang C, Schwab JH, Schoenfeld AJ, et al. A novel target for treatment of chordoma: signal transducers and activators of transcription 3. *Mol Cancer Ther* 2009; **8:** 2597–605.

95 Yang C, Hornicek FJ, Wood KB, et al. Blockage of Stat3 with CDDO-Me inhibits tumor cell growth in chordoma. *Spine* 2010; **35:** 1668–75.

96 Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. *Int J Radiat Oncol Biol Phys* 1995; **33:** 579–84.

97 Stacchiotti S, Casali PG. Systemic therapy options for unresectable and metastatic chordomas. *Curr Oncol Rep* 2011; **13:** 323–30.

98 Nikoghosyan AV, Karapanagiotou-Schenkel I, Münter MW, Jensen AD, Combs SE, Debus J. Randomised trial of proton vs carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study. *BMC Cancer* 2010; **10:** 607.

99 Hsu W, Mohyeldin A, Shah SR, et al. Generation of chordoma cell line JHC7 and the identification of Brachyury as a novel molecular target. *J Neurosurg* 2011; **115:** 760–69.