Diagnosis and Treatment of Chordoma

Brian J. Williams, MD; Daniel M.S. Raper, MBBS; Erin Godbout; T. David Bourne, MD; Daniel M. Prevedello, MD; Amin B. Kassam, MD; and Deric M. Park, MD

Abstract
Chordoma is a primary bone cancer arising on the midline from the skull base to the sacrum. Diagnosis is often delayed because of insidious onset and nonspecific symptoms. Chordomas appear histologically low-grade but are highly invasive and often recur locally. Management centers primarily on radical en bloc surgical resection when possible. Radiation therapy using protons and/or photons is often necessary because complete resection is seldom possible due to critical location and invasion of the cancer cells into surrounding structures. No approved medical therapy exists. The high rate of recurrence is reflected by a median survival of 6 to 7 years. This article reviews the clinical management of chordoma and discusses ongoing research in the field. (JNCCN 2013;11:726–731)

Chordoma is a rare, slow-growing primary bone malignancy. It is believed to arise from transformed notochordal remnants and occurs along the spinal axis from the clivus in the skull base to the sacrum. Chordomas are typically diagnosed at a locally advanced stage due to insidious onset and nonspecific symptoms. Although histologically low-grade, chordomas are highly invasive and often recur locally. The gold standard treatment is radical en bloc resection with wide margins. If this is not feasible, then external-beam radiation therapy or radiosurgery is often used. No effective medical therapy is available, although several promising targets are currently under investigation. The prognosis for chordoma is poor and depends primarily on the extent of surgical resection and surgical margins. This article reviews the epidemiology, pathogenesis, presentation, diagnosis, and management of chordoma, and highlights future directions for potential therapy.

Epidemiology
Chordoma is a rare tumor that constitutes 1% to 4% of primary bone malignancies. Chordoma has an incidence of approximately 1 per 1,000,000; displays a male predominance (≈2:1 male-to-female ratio); and has a peak age of presentation between 50 and 60 years. Chordomas are uncommon in the pediatric population. Consistent with their presumed notochordal origin, chordomas form along the midline near the neuraxis. The anatomic distribution is roughly even across the sacrum, skull base (clivus), and mobile spine. Younger patients and women are more likely to be afflicted by skull base disease. Chordomas are the most common primary bone tumors of the sacrum, accounting for greater than 50% of all sacral tumors.

Pathogenesis
Virchow first described a probable chordoma in 1857. He noted vacuolated cells on microscopic inspection, and coined the term *physaliphorous*, derived from the Greek word for bubbles. The term *chordoma* was not introduced until the 1890s after the notochord hypothesis had been postulated. Evidence from human fetuses and cell-fate tracking experiments support the notochord hypothesis. Moreover, brachyury, a transcription factor necessary for mesoderm formation expressed by the notochord, is also
present in chordoma.\(^8,9\) High-resolution comparative genomic hybridization (CGH) on samples from a group with familial chordoma showed duplications of the 6q27 region, which contains brachury.\(^10\) In addition, other areas of genomic abnormality have been identified, including polysomy of chromosome 7 and homozygous or heterozygous loss of loci 9p21.\(^11\) The area 9p21 contains CDKN2A (p14 ARF, p16 INK4a) and CDKN2B (p15 INK4b), which are known to be critical regulators of G1 phase arrest and are often lost in other cancers.

Molecular signaling pathways involved in the pathogenesis of chordoma include the platelet-derived growth factor (PDGF) receptor tyrosine kinase (RTK) pathway mediated by PI3K/Akt and mTORC1, transforming growth factor \(\alpha\) (TGF-\(\alpha\)), and basic fibroblast growth factor (bFGF). In a series of 31 chordomas, molecular profiling showed high expression and activation of PDGF receptor B (PDGFRB) and activation of PDGF receptor A (PDGFA) and KIT.\(^12\) Building on this work, Han et al\(^13\) demonstrated hyperactivation of mTORC1 signaling from complete or partial loss of PTEN in 10 sporadic sacral chordomas. They further demonstrated that chordoma cell lines are sensitive to rapamycin and PI3K/Akt inhibitor but not an ERK/MAPK inhibitor. Finally, in a series of 14 skull base chordomas, immunohistochemical analysis showed significantly higher expression of TGF-\(\alpha\), bFGF, and fibronectin in a cohort of early-recurrent compared with late-recurrent chordomas.\(^14\) Overall, this evidence suggests that RTK signaling through PI3K/Akt and mTORC1 may serve as a critical mitogenic pathway for chordoma.

**Presentation**

Presentation depends primarily on location; however, the symptoms can be categorized into local pain from invasion, and compression of adjacent structures (eg, rectum, esophagus, trachea), including neural tissues (eg, nerve root, cauda equina, abducens nerve). Because early symptoms are typically nonspecific, patients are often diagnosed after a significant delay.\(^3,15\) Additionally, because of their late presentation, approximately 5% of chordomas show metastasis to the lungs, bone, skin, or brain at initial presentation. This increases up to 65% with more advanced cases of the disease.\(^16\)

Patients with skull base chordomas most often present with headache and diplopia.\(^17\) The most common findings on physical examination are extracranial motility deficits, typically caused by abducens nerve involvement. Additionally, lower cranial nerve findings also occur frequently.\(^17\)

Chordomas of the mobile spine and sacrum typically present with local deep pain and a pattern of neurologic compromise according to the involved level.\(^15,18,19\) Sacral chordomas often originate from the S4 or S5 segments and may be missed on typical spine imaging, because plain radiographs often fail to diagnose chordoma and CT and MRI often end at S2.\(^15,18,19\) Invasion and compression of adjacent neurologic structures can result in myriad symptoms, including weakness, numbness, bowel and bladder incontinence, and sexual dysfunction.\(^18\) Presacral extension may cause obstipation, constipation, tenesmus, or hemorrhoids. These masses can often be palpated on rectal examination, but tissue invasion is limited by the dense presacral fascia.\(^18\) Cervical chordomas may obstruct the airway, present as an oropharyngeal mass, or cause dysphonia, dysphagia, and Horner syndrome (ipsilateral ptosis, miosis, and anhydrosis).

Radiographically, chordoma classically appears as an osteolytic lesion centered in the midline (clivus, vertebral body, or sacrum) associated with a soft tissue mass.\(^20\) Chordomas are well-defined extradural masses that compress or encase adjacent neurovascular structures.\(^21\) They also often invade adjacent vertebrae through the basivertebral veins, usually sparing the intervertebral disk space, which is in contrast to chondrosarcomas and osteosarcomas of the vertebral column.\(^18\) CT imaging may show areas of osteolytic and osteosclerotic bone destruction.\(^20\) Intratumoral calcification is present in 30% to 90% of cases.\(^17,18,20\) On MRI they appear isointense to hypointense on T1-weighted sequences, with areas of internal hypointensity from calcifications, cystic changes, and hemorrhage.\(^17,18,20\) On T2-weighted sequences they appear hyperintense with some small areas of heterogeneity. Finally, they exhibit heterogeneous contrast enhancement (Figure 1).

Chordomas demonstrate diminished or normal uptake of radioisotope on bone scanning compared with other bone tumors.\(^22\) On metabolic imaging with FDG-PET, chordomas show heterogeneously increased uptake of tracer. When combined with CT imaging, the findings of osteolytic bone destruction and hypermetabolism on FDG-PET are highly suggestive of chordoma.\(^23\)
Diagnosis

Fine-needle aspiration or core needle biopsy is the preferred method of diagnosis before surgical resection. Tumor seeding is a significant concern after biopsy, thus the tract of the biopsy needle should be marked and excised with the tumor.\textsuperscript{24,25}

Chordomas grossly appear reddish with a soft gelatinous-to-firm cartilage-like consistency. Microscopically, 3 recognized variants exist: classical, chondroid, or dedifferentiated.\textsuperscript{26} The classical subtype is composed of sheets of cells separated by fibrous septae. The cells display varying degrees of atypia and pleomorphism but typically have small, round, darkly staining nuclei with a heavily vacuolated cytoplasm, dubbed \textit{physaliphorous}, and few mitotic figures\textsuperscript{21,26} (Figure 2). Necrosis is infrequent, whereas calcification, hemorrhage, and hemosiderin deposition are more frequent.\textsuperscript{21} Chondroid chordoma displays areas of hyaline cartilage resembling chondrosarcoma. Finally, dedifferentiated chordoma is characterized by areas of sarcomatous change resembling malignant fibrous histiocytoma, fibrosarcoma, or osteosarcoma.

Previously, chordomas were diagnosed by their histopathologic features and immunoreactivity for S-100 and epithelial markers (eg, cytokeratins).\textsuperscript{27} Based on these criteria, discriminating between chondroid chordoma and chondrosarcoma remained a challenge because of their common immunoreactivity for S-100 and the difficulty in interpreting cytokeratin profiles from small biopsies.\textsuperscript{9} Brachyury has emerged as an integral distinguishing biomarker for chordoma from other chondroid lesions.\textsuperscript{9} Tissue microarray analysis of 103 chondroid tumors from the skull base and head and neck demonstrated that brachyury combined with cytokeratin staining had a sensitivity and specificity for detecting chordoma approaching 100\%.\textsuperscript{9} Histologic characteristics predictive of recurrence include number of mitotic figures and Ki-67 labeling index greater than 6%.\textsuperscript{28}

Management

Surgical resection is the most effective treatment modality, and the goal is radical en bloc resection with wide surgical margins. Radical en bloc resection was first proposed for sacral tumors in the 1970s.\textsuperscript{29} Kaiser et al\textsuperscript{30} then showed that maintaining the integrity of the tumor capsule reduced the
Radical en bloc resection is possible for approximately half of sacral chordomas, and fewer for skull base chordomas.17,18,31,33 This results in a high incidence of local recurrence and residual disease. The utility of conventional ionizing radiation is limited, with control of only 10% to 40% at 5 years with doses of 40 to 60 Gy.19 This is primarily because chordomas require high doses (>70 Gy) of radiation and reside close to radiation sensitive structures (eg, spinal cord, brainstem, cranial nerves, rectum), limiting the ability to deliver biologically effective doses without significant toxicity. The advent of high-dose focused radiation delivery technology with particles (protons, carbon ions, helium, or neon) or photons (radiosurgery, intensity-modulated radiotherapy, or fractionated stereotactic radiotherapy) has allowed treatment with higher doses of radiation to the tumor while sparing the surrounding normal structures. Each technology uses various methods to target and spare structures. For example, proton radiotherapy uses the Bragg peak phenomenon, whereas others use multiple fixed sources and shielding or a single source with multiple arcs. Overall, from all locations, local control with particle-based radiotherapy is 50% to 60% at 5 years.35

In a report on the results of surgery with postoperative radiotherapy (proton and photon) for sacral chordoma, Park et al16 showed an encouraging 91% local control rate for the initial resection (n=14).36 Treatment with other delivery modalities can also achieve an acceptable rate of tumor control, and hypofractionated proton or photon radiation has been proposed as an effective alternative to traditional schedules.17,38 The role of preoperative radiation for spinal and sacral chordomas is also being explored to reduce the incidence of local recurrence believed to be caused by tumor seeding during surgery.39 The results from this trial are promising. No patients with primary chordoma (0 of 23) experienced local recurrence compared with half of those with recurrent chordoma (3 of 6). Because local treatment results are significantly better at initial presentation than when patients experience a local recurrence, at which stage even aggressive surgery and radiation therapy are often unsuccessful salvage treatments, optimizing local therapy at initial presentation is critical to avoid local recurrence and the associated morbidity.36

In general, no effective medical therapy exists for chordoma, although some reports suggest that
Future Directions

Molecular characterization has shown that PDGFRA, PDGFRB, and KIT receptors are overexpressed in chordoma specimens.43 These data support previous observations that imatinib, a tyrosine-kinase inhibitor, can occasionally exhibit activity against chordoma.42 However, variability is seen in the frequency and magnitude of responses. This may be partly due to observations from the authors’ group and others regarding downstream activation of the PDGFR pathway.13 When evaluating the potential culprits, the authors found that 25% of 23 consecutive chordoma specimens had loss of heterozygosity at the 10q23 locus that contains the phosphatase and tensin homolog gene (PTEN) (unpublished data, 2013). Based on observation of downstream pathway activation, a report of imatinib and sirolimus in chordoma specimens showed activation of signal transducer and activator of transcription 3 (STAT3).45 These data corroborate other reports that STAT3 inhibitors have in vitro activity against chordoma.46

Finally, brachyury, a histologic marker for chordoma, may also drive chordoma pathology. Transient genetic knockdown of brachyury in chordoma cells was found to induce differentiation and senescence.47 Furthermore, brachyury has been shown in experimental models of human carcinomas to contribute to epithelial-mesenchymal transition, control metastatic potential, and regulate expression of several stem cell markers.48 Based on these observations, researchers at NCI are currently evaluating the safety of a brachyury-based immune therapy for patients with cancers, including chordoma.

Performing research in the chordoma field has been challenging because of the lack of available cell lines and a faithful model system. Partly because of the efforts of dedicated researchers and the support of not-for-profit organizations such as the Chordoma Foundation, additional cell lines are currently under development. Additionally, in vivo xenograft models of chordoma have been reported. Initially, a standard xenograft model using the U-CH1 cell line was reported, using a severely immunosuppressed background (nonobese diabetic/severe combined immunodeficiency/interleukin-2 receptor gamma null).49 Two additional options have recently been reported: one using a novel primary chordoma cell line and standard orthotopic xenograft strategy, and the other a primary orthotopic xenograft model.50,51 In addition, transgenic mouse and zebrafish models of chordoma are also under development. Increasing availability of cell lines and model systems should allow development of more-effective medical therapies for chordoma.

References

9. Oakley GJ, Fuhrer K, Seethala RR. Brachyury, SOX-9, and podoplanin, new markers in the skull base chordoma vs...
Chordoma Diagnosis and Management


