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Chordoma: The Nonsarcoma Primary Bone Tumor

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ABSTRACT

Chordomas are rare, slowly growing, locally aggressive neoplasms of bone that arise from embryonic remnants of the notochord. These tumors typically occur in the axial skeleton and have a proclivity for the spheno-occipital region of the skull base and sacral regions. In adults, 50% of chordomas involve the sacrococcygeal region, 35% occur at the base of the skull near the spheno-occipital area, and 15% are found in the vertebral column. Craniocervical chordomas most often involve the dorsum sella, clivus, and nasopharynx. Chordomas are divided into conventional, chondroid, and dedifferentiated types. Conventional chordomas are the most common. They are characterized by the absence of cartilaginous or additional mesenchymal components. Chondroid chordomas contain both chordomatous and chondromatous features, and have a predilection for the spheno-occipital region of the skull base. This variant accounts for 5%–15% of all chordomas and up to 33% of cranial chordomas. Dedifferentiation or sarcomatous transformation occurs in 2%–8% of chordomas. This can develop at the onset of the disease or later. Aggressive initial therapy improves overall outcome. Patients who relapse locally have a poor prognosis but both radiation and surgery can be used as salvage therapy. Subtotal resection can result in a stable or improved status in as many as 50% of patients who relapse after primary therapy. Radiation therapy may also salvage some patients with local recurrence. One series reported a 2-year actuarial local control rate of 33% for patients treated with proton beam irradiation. *The Oncologist* 2007;12:1344–1350

INTRODUCTION

Chordoma is a rare primary bone tumor (Table 1) with an incidence rate of <0.1 per 100,000 per year, with around 25 afflicted persons diagnosed in the U.S. annually [1]. It accounts for 1%– 4% of all primary malignant bone tumors [2, 3]. Chordomas arise from embryonic remnants of notochord and show a dual epithelial-mesenchymal differentiation. Reaching maturity in the embryo at 11

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Table 1. Classification of primary malignant bone tumors

I. Osteosarcoma
A. Intramedullary high grade (conventional)
1. Osteoblastic
2. Chondroblastic
3. Fibroblastic
4. Mixed
5. Small cell
6. Other (telangiectatic, epithelioid, chondromyxoid fibroma–like, chondroblastoma-like, osteoblastoma-like, giant cell rich)
B. Intramedullary low grade
C. Juxtacortical high grade (high-grade surface osteosarcoma)
D. Juxtacortical intermediate-grade chondroblastic (periosteal osteosarcoma)
E. Juxtacortical low grade (pariosteal osteosarcoma)
II. Chondrosarcoma
A. Intramedullary
1. Conventional (hyaline/myxoid)
2. Clear cell
3. Dedifferentiated
4. Mesenchymal
B. Juxtacortical
III. Primitive neuroectodermal tumor/Ewing's sarcoma
IV. Angiosarcoma
A. Conventional
B. Epithelioid hemangioendothelioma
V. Fibrosarcoma/malignant fibrous histiocytoma
VI. Chordoma
A. Conventional
B. Dedifferentiated
VII. Adamantinoma
A. Conventional
B. Well-differentiated-osteofibrosis dysplasia-like
VIII. Other
A. Liposarcoma
B. Leiomyosarcoma
C. Malignant peripheral nerve sheath tumor
D. Rhabdomyosarcoma
E. Malignant mesenchymoma
F. Malignant hemagiopericytoma
G. Sarcoma, NOS; primary malignant lymphoma; multiple myelomas are not included

Abbreviation: NOS, not otherwise specified.

mm, the notochord obliterates and is displaced from the central to the cranial and caudal positions. Microscopic foci remain in the vertebral bodies at the cranial and caudal ends of the embryo. Malignant transformation typically occurs in the third to fourth decades of life for spheno-occipital lesions and in the fifth to sixth decades for the sacrococcygeal type [4]. Histologically, they display lobules and vacuolated (physaliphorous), moderately atypical, neoplastic cells across a myxoid stroma separated by fibrous bands [5]. Given that they have an ectodermal origin, chordomas are technically not sarcomas; however, they are traditionally classified and approached as sarcomas on the basis of being a primary bone tumor [6].

Chordomas are usually relatively slow-growing, low-grade malignancies. They arise from the sacrum in approximately 50%–60% of cases, from the skull base region (spheno-occipital/nasal) in approximately 25%–35% of cases, from the cervical vertebrae in approximately 10% of cases, and from the thoracolumbar vertebrae in approximately 5% of cases [3]. The median age at presentation is around 60 years; however, presentation with skull base tumors may occur at a younger age and has been reported in children and adolescents [3]. Clinical presentation is usually with pain as the cardinal symptom, whereas neurologic deficits tend to vary based on the location of the lesion. Chordoma has been considered of low metastatic potential; however, distant metastasis to lung, bone, soft tissue, lymph node, liver, and skin has been reported in up to 43% of patients [7–9]. Metastatic sites, however, usually occur late in the course of the disease. In most instances, control of primary disease remains the major therapeutic challenge. Nonetheless, metastatic disease may be considered of adverse prognostic significance because the median survival time was reported to be <12 months in a series of 28 chordoma patients after the development of distant metastasis [6]. The overall median survival time with chordoma has been estimated to be approximately 6 years, with a survival rate of 70% at 5 years, falling to 40% at 10 years. Of prognostic value is a chondroid histology, which exhibits low-grade behavior and a favorable long-term outcome. Conversely, dedifferentiated chordoma is observed in $<5\%$ of cases, has features of high-grade spindle cell sarcoma, and demonstrates an aggressive clinical course [10] (Figs. 1 and 2).

The therapeutic approach to chordoma has traditionally relied heavily on surgical control. More recently, radiation therapy has been demonstrated to be a valuable modality for local control, particularly with the advent of charged particle radiotherapy. Medical therapy continues to be suboptimal in this tumor, which is relatively refractory to cytotoxic chemotherapy; however, newer targeted agents may offer therapeutic alternatives.

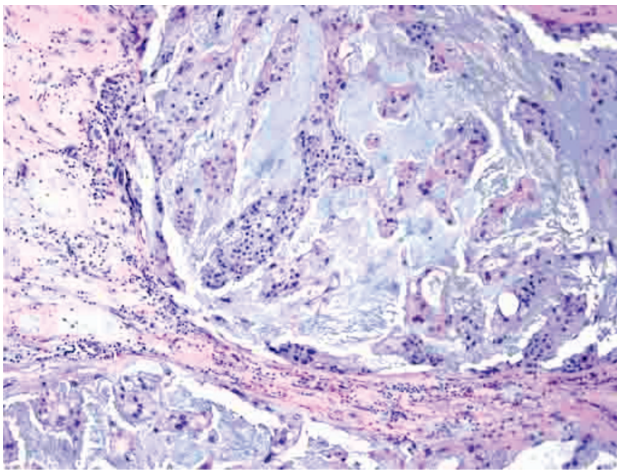

Figure 1. Classic lobular architecture of chordoma. Fibrous bands divide it into lobules containing cords of cohesive epithelioid cells with abundant eosinophilic cytoplasm and round nuclei within a myxoid matrix.

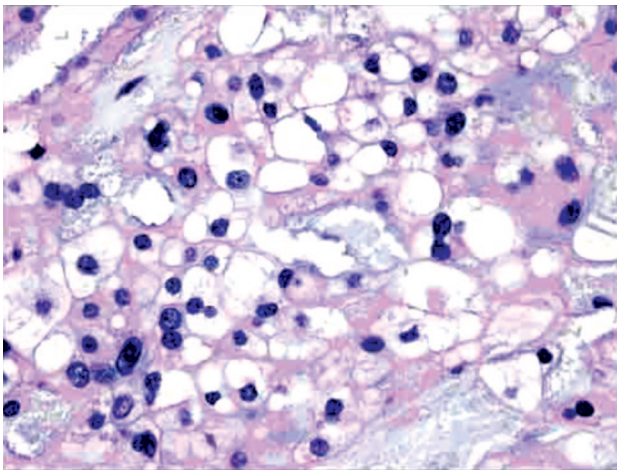

Figure 2. Physiliforous cells are characteristic of chordoma. These cells have large, sharply delimited, clear vacuoles imparting a bubbly appearance.

Genetics

Genetic studies performed on chordomas include chromosome analysis, telomere reduction and telomere activity, DNA microsatellite, loss of heterozygosity (LOH), and clonality studies. Unfortunately, given the rarity of the tumor, studies of molecular abnormalities are generally small and often unvalidated. Various cytogenetic and molecular findings indicate 1p36 loss as a consistent change in sporadic and inherited chordomas [11]. In addition, microsatellite instability (MSI) and LOH studies performed on 12 chordomas detected MSI in 50% of patients at one or more loci, and LOH was identified in two chordomas, one of which had corresponding MSI [12].

Numerical and structural alterations in chromosomes 3 and 21 have also been observed. Many cases showed a hypodiploid or near diploid chromosome number [13]. Sandberg and Bridge [14] noted that about half of all chordomas show chromosome aberrations of diverse nature, suggesting that these alterations occur as late events in tumor progression. The retinoblastoma (*RB*) gene is a well-characterized tumor-suppressor gene whose protein binds nuclear DNA and plays a key role in cell-cycle regulation. Inactivation of the *RB* gene has been associated with a number of malignant neoplasms. Chordomas have demonstrated LOH at intron 17 of the *RB* gene in two of seven samples studied [15].

A limited analysis of chromosome telomeres from chordomas has revealed lengthening in all four of four samples. In marked contrast, telomere length reduction has been observed during in vitro senescence of human fibroblasts and most cancers [16]. Telomerase, the enzyme responsible for maintenance of telomere length, has been identified in about one half of the chordomas studied to date [17]. Clonality studies on eight cases of sacral chordomas indicated a polyclonal origin of the tumor [4].

Surgery

Surgery continues to be the primary modality in the management of chordomas. Rates of local recurrence, as well as survival, appear to be dependent on the achievement of negative surgical margins, with recurrence rates on the order of 70% in cases where negative margins are not achieved. In a series of 52 patients, Boriani et al. [18] reported that 100% of patients treated with radiation alone, palliative therapy, or intralesional intracapsular excision had local recurrence within 17–20 months. In contrast, only 20% of patients had local recurrence at 56–94 months after en bloc resection with appropriate margins [18]. Similarly, Tzortzidis et al. [19] used aggressive surgical approaches to achieve total resection in up to 70% of patients, resulting in long-term control in >50% of cases.

The surgical techniques for margin-free, en bloc tumor resection have been proven to be effective in terms of local control and long-term prognosis for chordomas occurring in the thoracic and lumbar spine [20–25]. Thus, efforts to perform en bloc resections are warranted, even in the cervical spine [26]. Surgical outcomes are dependent on location and tumor size at diagnosis. Bulky tumors adjacent to critical structures frequently preclude margin-negative resections [27]. In the past, often the only surgery possible was decompression or debulking of the tumor [28, 29]. Recent advances in imaging techniques play an important role in improving the prognosis of chordoma by discovering small intraosseous tumors, which can be submitted more easily to en bloc resection [30–33].

Recurrent tumors are generally more challenging for

surgical interventions and clearly have worse overall outcomes. This could be related, in part, to the more aggressive biological behavior of a recurrent tumor [19]. The combination of palliative and/or debulking surgery with high-energy radiation seems promising in recurrent tumors or in tumors not suitable for en bloc surgery [34–37]. It is noteworthy that outcome results show a large difference in the local failure rate between patients treated for primary and those treated for recurrent chordomas. In a series of 21 patients, local control of sacral chordomas treated with surgery and radiation was achieved in 86% for primary lesions, as opposed to 14% for recurrent lesions [38].

In addition to the technical difficulties obtaining negative margins, the surgical management of chordomas may result in poor functional outcomes. For instance, resections of sacral chordomas above the level of S2 are marked by significant perioperative morbidity and long-term sequelae [39, 40]. In fact, resections of both S2 roots result in urinary and bowel incontinence, while the loss of both S3 roots may result in substantial problems in a significant proportion of patients.

Radiation Therapy

Chordomas are considered radioresistant tumors and require doses in excess of 60 Gy. However, these dose levels cannot be safely delivered because they exceed the tolerance of most neurologic structures, especially the brain stem and optic pathway [41–44]. Conventional radiotherapy (RT) with high-energy photons up to a dose of 50–55 Gy does not provide a high local control rate [8, 45, 46]. Between 60 and 65 Gy is considered a minimum useful dose, but higher doses have been favored in some series, particularly when using particle radiation [47–51], although a dose–response relationship has not been consistently reported across all series [45, 52].

Surgery for skull base and upper cervical spine tumors poses a risk of damage to normal structures, including the spinal cord and cranial nerves. These same normal tissue structures also impose a limitation on the external-beam RT dose, which adds additional difficulty. The combination of surgery and RT appears to be the best treatment for these tumors [53–55]. The use of razoxane as a radiosensitizing agent along with conventional RT was explored in a small series and showed a trend for superior local control [56].

The advent of advanced imaging, planning, and delivery of photon RT over the past one to two decades has provided opportunities for delivering high doses of radiation safely to patients with skull base and cervical spine tumors [57, 58]. However, an additional method for improving the physical dose distribution of radiation treatment for chordomas is the use of charged particles, especially protons. These approaches offer better tumor control and/or fewer side effects, such as contralateral hearing loss/brain atrophy and radiation-induced second malignancies.

The best results in the treatment of chordomas of the skull base are reported when using surgery and adjuvant high-dose proton RT. The actuarial 5-year local control rate was 73% using tumor doses of 66–83 cobalt Gray equivalents (CGE) for 519 patients with skull base chordomas treated with protons at the Massachusetts General Hospital [53]. Hug et al. [59] reported an actuarial 3-year local control rate of 67% for 58 chordoma patients treated at the Loma Linda University Medical Center with proton RT. Tumor doses were in the range of 64.8–79.2 CGE. Noel et al. [60] reported the results of combined photon and proton RT in 45 patients with chordomas and chondrosarcomas of the skull base treated with a median total tumor dose of 67 CGE (range, 60–70 CGE). Photons represented two thirds of the total dose and protons represented one third. At 3 years, the local control rates for chordomas and chondrosarcomas were 83.1% and 90% [60].

Experience using particle therapy with particles heavier than protons, such as helium and carbon ions, is limited. Between 1977 and 1992, Castro et al. [61] treated 223 patients with helium ions (target dose, 65 CGE) at the Lawrence Berkeley Laboratory; the actuarial 5-year local control rates were 63% for chordomas and 78% for chondrosarcomas.

Compared with helium ions, carbon ions offer potential biologic advantages and appear to be highly effective in the treatment of chordomas. Schulz-Ertner et al. [49] reported on a series of 54 chordoma patients treated with carbon ion therapy, achieving a 3-year local control rate of 81%. Local control rates at 3 years were at least comparable to those of proton RT, while severe radiation-induced side effects were minimized, allowing a target dose of 60 CGE to be delivered with a low risk for severe sequelae.

Extracranial chordomas are more difficult to treat than tumors of the skull base. Radiosensitive structures as well as larger setup errors limit the prescription dose. As a consequence of suboptimal RT doses, local control rates have been poor. The best results were obtained with heavy charged particles. Schoenthaler et al. [62] treated 14 patients with helium or neon ions at the Lawrence Berkeley Laboratory. Four of 14 patients were treated after gross tumor resection. They reported a 5-year local control rate of 55%, with a trend for better local control in patients treated with neon ions, compared with helium ions, and for four patients who received RT after gross tumor resection [62].

Berson et al. [63] reported a 5-year local control rate of 54% for 10 patients with chordomas and chondrosarcomas of the cervical spine treated with charged particles at the Lawrence Berkeley Laboratory. Similar results were ob-

tained with protons in 14 patients with spinal and sacral chordomas at the Massachusetts General Hospital, with a 5-year local control rate of 53% [59].

Medical Therapy

Chordomas are not reported to be sensitive to chemotherapy, similar to many other low-grade malignancies. Accordingly, chemotherapy response has been reported in patients with high-grade dedifferentiated chordomas, which represent <5% of all chordomas [64].

Anecdotal reports of responses to chemotherapy such as vinca alkaloids and alkylating agents have been limited to case reports [65–68]. The only prospective phase II clinical trial using conventional chemotherapy in the treatment of chordomas was conducted at the University of Michigan. A topoisomerase I inhibitor, 9-nitro-camptothecin (9-NC), was used to treat 15 patients with chordomas. Although only one (7%) objective response rate was observed, 9-NC appeared to delay progression of disease, with a median 3-month progression-free survival rate of 47%, and a 6-month progression-free survival rate of 33% [69].

The advent of molecularly targeted therapies has raised interest for their use, particularly in low-grade malignancies with poor response to chemotherapy. Casali et al. [70] treated six chordoma patients with imatinib mesylate at 800 mg daily and observed nondimensional tissue responses, marked by hypodensity and decreased contrast uptake on computed tomography scan (and concordant changes on magnetic resonance imaging). It was subsequently shown that chordomas express platelet-derived growth factor receptor (PDGFR)-β and its phosphorylated form, denoting constitutive activation. That series was expanded to a multicenter phase II trial in Italy and Switzerland that enrolled 55 patients. In 44 patients evaluable for antitumor response, 37 (84%) had stable disease as their best response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (maintained for >6 months in most patients), for a clinical benefit rate (complete response plus partial response plus stable disease for >6 months) of 73%. In seven of the patients noted to have stable disease (16%), some degree of objective tumor shrinkage was reported. In 39 patients who were symptomatic at baseline, subjective improvement in symptoms was reported by 25 patients (64%). In an intention-to-treat analysis, the median progression-free survival time was 32 weeks, with 38% of patients free from progression at 1 year, and 16% on treatment at 18 months [71]. A series of 31 chordoma samples was then analyzed, showing that PDGFR-β was overexpressed and activated in all cases, while PDGFR-α and Kit were expressed less but activated [72]. Activating point mutations were not found, confirming previous findings [73]. Casali et al. [74] also reported that the addition of low-dose cisplatin to the treatment of patients with chordoma who progressed on imatinib restored sensitivity of the tumor, suggesting synergism between imatinib and cisplatin.

Other signal transduction pathways that may provide therapeutic targets include the epidermal growth factor receptor (EGFR) pathway, because strong expression of EGFR and c-Met has been reported in 12 chordomas [75]. This was targeted in one patient treated with the combination of cetuximab and gefitinib with a good response [76]. Another anecdotal report involved the possibly antiangiogenic therapy thalidomide in one patient achieving long-term disease control [77].

Conclusion

Chordomas are rare primary bone tumors with a high risk for local recurrence and modest propensity for distant metastasis. Surgery is the primary modality to achieve the best long-term control. However, the location of these tumors makes en bloc excision to achieve adequate negative margins technically challenging. Conventional RT has a proven role; however, the high doses required for these radioresistant tumors lead to significant toxicity to surrounding normal tissues and limit its therapeutic value. Newer techniques and charged particle radiotherapy allow for better dose delivery, and hence better disease control. Cytotoxic chemotherapy has virtually no role in this disease; however, molecularly targeted therapy is showing significant promise and is an area of great potential.

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