Skull Base Chordomas
Clinical Features, Prognostic Factors, and Therapeutics

Arman Jahangiri, BS[a,b], Brian Jian, MD, PhD[a,b,1], Liane Miller, BS[a,b,1], Ivan H. El-Sayed, MD[b,c], Manish K. Aghi, MD, PhD[a,b,d,*]

KEYWORDS

• Chordoma • Skull base • Clivus • Radiation therapy • Radiosurgery

KEY POINTS

By the end of this article, physicians should be able to

- Easily identify the clinical presentation as well as the radiologic findings witnessed in patients with skull base chordomas.
- Identify the most appropriate surgical approach based on the location of the skull base chordoma and the advantages and disadvantages associated with each surgical technique.
- Have a better understanding for the role of radiation therapy in the postoperative adjuvant management of chordomas.
- Develop an understanding for some of the current chemotherapies used to treat refractory chordoma and the direction in which future research in chordoma chemotherapy is headed.

Video of 'Endoscopic endonasal resection of a chordoma' accompanies this article at http://www.neurosurgery.theclinics.com/

INTRODUCTION

Primary bone tumors are uncommon in the skull base. When they do occur, they are typically aggressive even if histologically benign, and most are chondrosarcoma or chordoma. The phenotypes of chondrosarcoma and chordoma may reflect the embryologic development of the skull base because persistent rests of fetal cartilage typically located more laterally and the notochord located medially are believed to give rise to chondrosarcoma and chordoma, respectively, with the former located more laterally and the latter located more medially.

Chordomas, the focus of this review, are rare tumors that arise from the remnant of undifferentiated notochord tissue residing within the vertebral bodies and extra-axial skeleton.[1] Accounting for greater than half of primary tumors of the sacrum, chordomas were originally believed to be found more commonly in the sacrum than the skull base; however, recent evidence suggests an

Disclaimer: AJ is a Howard Hughes Medical Institute Advanced Research Fellow.

[a] Department of Neurological Surgery, University of California, San Francisco, CA 94143, USA; [b] Department of Neurological Surgery at UCSF, Center for Minimally Invasive Skull Base Surgery, University of California San Francisco, CA 94143, USA; [c] Department of Otolaryngology - Head and Neck Surgery, University of California, San Francisco, CA 94115, USA; [d] University of California at San Francisco (UCSF), 505 Parnassus Avenue, Room M779, San Francisco, CA 94143-0112, USA

[1] B Jian and L Miller are contributed equally to work.

* Corresponding author. The University of California at San Francisco (UCSF), 505 Parnassus Avenue, Room M779, San Francisco, CA 94143-0112.

E-mail address: AghiM@neurosurg.ucsf.edu

Neurosurg Clin N Am 24 (2013) 79–88
http://dx.doi.org/10.1016/j.nec.2012.08.007
1042-3680/13/$ – see front matter

even distribution amongst the sacrum, mobile spine, and the skull base.[2,3] Of all intracranial tumors, skull base chordomas account for only 0.1% to 0.2%. Skull base chordomas are challenging to manage surgically because of their proximity to the brainstem and other vital neurovascular structures, in addition to an aggressive and locally invasive cellular characteristic.[4,5] Within the skull base, chordomas most often arise extradurally in the clivus, with frequent tendency for intradural invasion; although rare, primary intradural lesions have been reported.[6–9] Although chordomas are considered to be histologically low-grade malignancies,[10] they carry a poor prognosis even after surgery and radiation therapy.[11] This article discusses the pathogenesis, diagnosis, and clinical management of skull base chordomas and presents newly discovered biomarkers, prognostic factors, and benefits of novel chemotherapeutics for this rare aggressive intracranial tumor.

EPIDEMIOLOGY

Chordomas are rare, accounting for only 0.1% to 0.2% of all skull base tumors.[12–14] Analysis of the SEER (Surveillance Epidemiology and End Results) database indicates that chordomas have an overall incidence of 0.08 per 100,000, with peaking incidence between 50 and 60 years of age with a 2:1 male/female ratio.[3,15] They have a low incidence in patients younger than 40 years and are extremely rare in children and adolescents, with these younger patients making up less than 5% of all chordoma cases.[3,16] Chordomas occur in 3 locations (skull base, mobile spine, and sacrum), and evidence suggests an approximately equal distribution (32%, 32.8%, and 29.2% of reported cases, respectively).[3] Chordomas have a poor prognosis because of their insidious nature when an en bloc excision cannot be performed. If untreated, estimated patient survival is 6 to 24 months.[17] However, if treated, median survival is 6 to 8 years, with a 5-year survival rate of 67% to 87%.[3,18,19] In the largest single series to date of patients treated over 25 years, the 5-year and 10-year survival rates are 55% and 36%.[20] Because these tumors are prone to seeding during surgery, it is believed that an en bloc resection is necessary to achieve cure. Patients with lesions of the thoracolumbar spine and appendicular musculoskeletal system have increased survival when an en bloc resection with wide margins is achieved.[21] En bloc resection of lesions involving the C2 vertebra has been reported in only 6 cases, with only 1 of these including the C1 vertbra.[22] Higher lesions involving the clivus are resected in a piecemeal fashion because of the complex anatomy of the surrounding brainstem, cranial nerves (CNs), basilar, vertebral, and carotid arteries.

HISTOPATHOLOGY

Chordomas grossly appear as encapsulated lobular lesions that infiltrate surrounding bone and tissue and can be gray-white to reddish in color.[23] Histologically, they show 3 variants: classic, chondroid, and dedifferentiated.[24] Classic chordoma tumor cells show a lobular arrangement, with intervening fibrous septa. The cells are large, with round nuclei and vacuolated or bubble-containing cytoplasm, often described as physaliferous.[23] Alternatively, chondroid chordomas show features of both chordomas and chondrosarcomas, with chordoma foci surrounded by an extensive cartilaginous matrix.[25] Chordomas were historically identified pathologically based on their physaliferous features and positive immunohistochemical staining for S-100, epithelial membrane antigen, and cytokeratins, but distinction between chondroid chordoma and chondrosarcoma was suboptimal and challenging.[10,26,27] Recently, a nuclear transcription factor, brachyury, was identified as a distinguishing biomarker for chordomas, and in combination with cytokeratin staining, has a sensitivity and specificity greater than 90% for diagnosing chordoma.[28,29]

NEURORADIOLOGIC FINDINGS

Magnetic resonance imaging (MRI) is the main diagnostic modality for skull base chordomas, with chordomas characteristically appearing isointense or hypointense on T1-weighted MRI images and hyperintense on T2-weighted images.[30] Gadolinium enhancement has also been shown but can be variable.[31] Intradural extension can be difficult to predict on preoperative MRI (**Fig. 1**). On computed tomography (CT) scan, chordomas appear as expansive, lytic lesions with bone destruction and soft tissue mass, with varying degrees of enhancement compared with surrounding brain tissue.[32] In addition, on [18F]fluorodeoxyglucose (FDG) positron emission tomography/CT imaging, chordomas show a large, destructive mass with heterogeneous increased uptake of FDG, indicating hypermetabolism.[33]

CLINICAL PRESENTATION

Because of their slow-growing nature, chordomas are often asymptomatic until the late stages of disease, when compression of vital structures may lead to neurologic deficits and pain secondary to mass effect. It is reported that the most common