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

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[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

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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

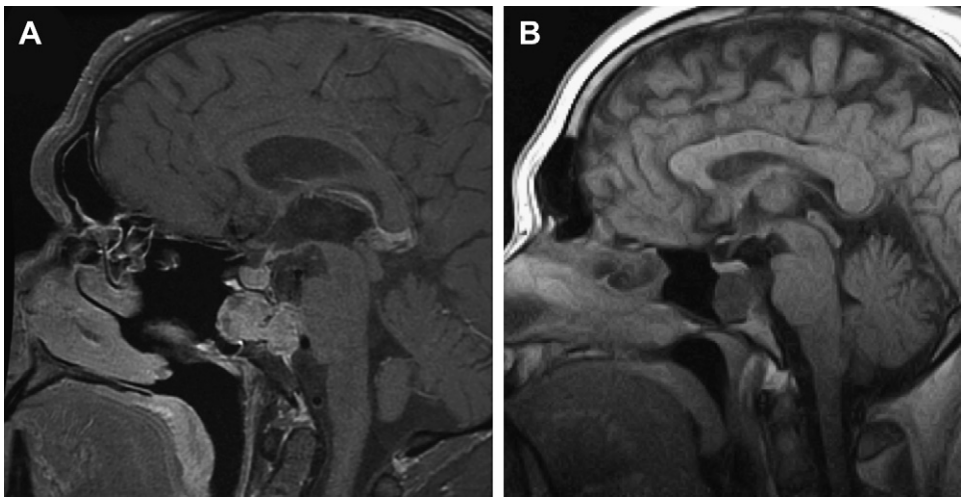

Fig. 1. MRI of chordoma. Preoperative sagittal images of (*A*) a chordoma that showed intradural invasion at surgery, and (*B*) a chordoma that proved to be entirely extradural at surgery.

physical findings at the primary clinical evaluation include in order: sixth nerve palsy, visual field deficits, decreased visual acuity, extraocular motility disorders, and lower CN palsy.[7,14,23,34–36] Dividing the clivus into an upper, mid, and lower section allows for the correlation of tumor location to the ensuing CN deficits. Clival chordomas within the lower clivus present with lower nerve palsies (CN IX, X, XII), whereas tumors in the midclivus often result in diplopia (CNVI) (the most common finding), and chordomas in the upper clivus present with visual acuity deterioration (CNII) and CNIII palsy.[8,23,37–39] Endocrinologic deficits can also occur if chordomas invade superiorly into the sella, but this is rare.[40] Also reported in the literature, but in rare instances, are skull base chordomas presenting with epistaxis and intracranial hemorrhage.[41,42] Although nonspecific, headaches are also common complaints as a result of direct invasion of the dura, compression of trigeminal nerves, diplopia, or increased intracranial pressure.[43]

MANAGEMENT

The therapeutic approach to managing skull base chordomas entails an aggressive surgical procedure with attempts at gross total resection (GTR), followed by focal radiation therapy.[8,44–46]

Surgical Approaches to the Skull Base

Several different approaches have been well documented in the literature for skull base chordomas.[47,48] When a GTR or en bloc resection is not practical, as is often the case for lesions of the clivus, a near total intralesional resection is recommended. Remnant lesions that are small have been shown to respond well to high-dose radiation therapy, as shown by Potluri and colleagues[49] in a series of 19 patients receiving stereotactic radiosurgery after subtotal resection (STR), with effective control of the small residual tumor volume. Recently, the endoscopic endonasal approach has become increasingly used for clival chordomas. When there is extensive involvement of local neurovascular structures, the operative approach should not be aggressive, and use of radiotherapy and observation of residual tumor should be taken into account, because a patient's quality of life and neurologic function must be of priority when evaluating surgical outcomes.[50,51] The following sections describe 4 of the most common transcranial approaches as well as the endoscopic endonasal approach, which are used solely or in combination with one another for resection of skull base chordomas. Each technique is summarized briefly with a discussion of its benefits and shortcomings. Furthermore, the minimally invasive endonasal endoscopic approach is contrasted with the more invasive cranial procedures, with a focus on the future direction for treatment and neurosurgical approach to the skull base chordoma.

Frontotemporal transcavernous approach

This technique uses an orbitozygomatic osteomy and clinoidal resection to allow the surgeon to reach skull base chordomas invading into the cavernous sinus (CS) and grants exceptional intradural access.[52] This approach is beneficial in that it decreases the amount of brain retraction required for sufficient exposure.[53] Structures such as the supraorbital nerves and vessels, the frontotemporal branch of CNVII, the optic nerve,

CNIII as well as CNIV are at risk for injury with this approach during the resection of clinoid.[43]

Extended frontal transbasal approach

The transbasal approach was first described by Derome,[54] and its use has been modified by the removal of the central segment of the supraorbital bar to become the extended transbasal approach, in which lesions that have superior and inferior extensions can be resected with minimal brain retraction. Midline tumors of the lower to upper clivus that extend into the occipital condyles, foramen magnum, medial CS, or the sphenoethmodial region can be accessed with this approach.[55] This approach fails to gain direct access to the dorsum sella, and chordomas with widespread lateral elements are unreachable. The lateral limits for this approach are CNXII, CNVI, the carotid arteries, and the optic nerve, which places these structures at high risk for operative injury.[43] By further removing the entire supraorbital bar (extensive frontal transbasal approach), one can gain better exposure, specifically for visualization of the contralateral clivus.[56]

Subtemporal and subtemporal-infratemporal approach

The subtemporal approach can be used for gaining access to the posterior CS, upper clivus, middle fossa, petrous apex, and horizontal petrous internal carotid artery. For additional exposure, the subtemporal-infratemporal approach is used, which further aids in visualization of the CS, the clivus all the way to the foramen magnum, the ethmoid, maxillary, and sphenoid sinuses, the orbit, parapharyngeal and retropharyngeal spaces, infratemporal fossa, as well as the orbit.[43] This extensive approach is reserved for instances in which there is involvement of the petroclival bone inferior to the level of the horizontal segment of the petrous internal carotid artery.[57] The most frequent complications of this approach include associated meningitis and cerebrospinal fluid (CSF) leak. Because of the extensive nature of this approach, all CNs are exposed and are put at great risk for injury, whereas the internal carotid artery may be injured during drilling.[43]

Extreme lateral transcondylar approach

Chordomas involving the ventral upper cervical spine, occipital condyles, foramen magnum, and lower clivus can be accessed with this approach.[58] For chordomas located extradurally, the complete transcondylar approach is most often used, but must be conducted in combination with an occipitocervical fusion to guarantee occipitocervical junction stability. Vascular injury to vertebral arteries can lead to cerebellar or brainstem infarction, and lower CN dysfunction and CSF leak are other common complications with this approach.[43]

Endoscopic endonasal approach

The endoscopic endonasal approach is a minimally invasive approach to the clivus as well as the anterior brainstem, serving as the most direct path to the clival chordoma, and has been described in detail by many groups (Video 1).[56,59–61] Reviewing the combined 66 cases published of skull base chordomas undergoing the endoscopic endonasal approach, Fraser and colleagues[56] found the combined GTR rate to be 55%, with a near total resection of more than 95% of the tumor achieved in 7 of 8 patients in their follow-up case series. Other studies have also suggested that this approach to resection of chordomas is equally successful compared with open approaches at achieving total resection.[39,56,61,62] CSF fluid leak occurred in 17% of the patients in the review analysis of Fraser and colleagues.[56] This potential complication is often avoided with the use of the vascularized nasoseptal flap.[63–65] Although all CNs are at risk of injury during this approach, CNVI is at an increased risk because it exits the Dorello canal, coursing toward the CS, a complication for which the risk can be reduced by opening the dura at or below the location of the vertebrobasilar junction identified by neuronavigation. The internal carotid arteries may also be injured during drilling. A contraindication to this approach is when the tumor extends to the lateral edge of the optic nerve, when a different approach should be taken into consideration.[65] For lesions that involve the clivus and extend inferiorly into the upper spine, a combined endonasal endo-oral approach can be performed to limit the need for a palate split or more invasive transoral approach.[66]

POSTOPERATIVE COMPLICATIONS, SURVIVAL, AND RECURRENCE

Postoperative Complications

The Karnofsky performance status (KPS) can be used to assess preoperative and postoperative functional disabilities, and is an appropriate tool for surgeons to determine whether the patient has worsened as a result of surgical treatment, and also an aid to monitor for recurrence, or residual tumor regrowth.[23] In a series of 60 patients, Gay and colleagues[8] found 40% of their patients to show permanent postoperative functional deterioration of about 10 points using the KPS scoring system. A reduction of greater than 10 points was a sign of disease progression as reported by Sen and colleagues,[67] and every

patient with this score died as a result of disease progression. In 1 study,[35] GTR was achieved in more than 40% of patients undergoing their first operation, with an overall mortality of only about 5%, a fifth of which were attributed to CSF leaks. The same study reported the risk for CSF leaks to be nearly tripled at 51% for patients undergoing reoperation. Other surgical complications include new CN deficits, nasal speech, and dysphonia, as well as meningitis, all of which are reported to be less common than CSF leaks.[8,35,68,69]

Survival

Chordomas are fatal in many patients, although some patients become long-term survivors, particularly after GTR and appropriate use of adjuvant therapy. A recent study reports their overall 5-year survival rate to be 75%.[38] A review of all cranial chordomas from 1973 to 1995 using the SEER database found relative survival of skull base chordomas to be 65% and 47%, respectively, for 5-year and 10-year survival.[3] Furthermore, the literature[6,23,35,38] reports that when GTR of a tumor is accomplished, the 5-year overall survival increases to 80% or more. Repeat surgery has been shown to correlate with worsened overall survival compared with patients who receive only a single surgery for tumor resection, and the general consensus in the literature is that the best prognosis is achieved via the greatest extent of surgical resection of tumor during the initial operation.[20,35,38]

Recurrence

The literature emphasizes extent of tumor resection as the variable that best correlates with lowering the risk for skull base chordoma recurrence.[70] The progression-free survival (PFS) rate from several studies at 5 years after GTR ranges from 55% to 84%, whereas the corresponding range for patients with a partial or STR is between 36% and 64%.[8,23,35,38,67,71]

RADIATION

Radiation plays a crucial role in the management of chordomas and can be used as an excellent tool for controlling tumor growth.[68,72,73] Chordomas do not generally respond to conventional radiotherapy and their radiosensitivity is limited to high doses, usually in the 70-Gy to 80-Gy dose range.[70] Because skull base chordomas are often located near critical structures such as the optic apparatus, cervical spinal cord, and the brainstem, exposure to high doses of radiation must be limited to prevent permanent damage.[74,75] As a result of these challenges, radiation must be delivered to chordomas in a high dose but focal fashion. The most common radiation modalities used in chordoma management include photon-based radiosurgery methods like Cyber Knife and Gamma Knife and proton beam radiation.[6,69,72,76–78] Proton beam radiation therapy is useful because of its ability to deliver higher doses of radiation to the tumor mass and spare critical nearby structures.[76,79] In a systematic review of 47 articles, Amichetti and colleagues[45] reviewed the data of skull base chordomas treated with proton therapy, and compared it with other irradiation techniques (conventional radiation therapy, ion therapy, radiation therapy, fractionated stereotactic radiation therapy, and radiosurgery). This study showed that the use of protons results in better outcomes compared with the use of conventional photon irradiation, resulting in superior 10-year outcomes.[45] Although the role of proton therapy in patients with residual tumors is well established because it has achieved superior disease control and extended survival, the impact of this treatment has yet to be defined for patients who have undergone GTR after the primary operation.[38] Furthermore, there are only a few centers that offer proton beam therapy, limiting access of many patients to this treatment modality. The likelihood of treatment success is increased for both proton therapy as well as photon-based radiosurgery when the tumor has a smaller volume and is located further from the optic apparatus as well as the brain stem.[68,80] Some of the major complications associated as a result of radiation therapy are pituitary insufficiency (13.2%) as well as involvement of the optic apparatus (4.4%), as described by Austin-Seymour and colleagues[81] in their experience with fractionated proton radiation therapy for chordomas.

CHEMOTHERAPY

Systemic review of the literature[82,83] has found chordoma to be unresponsive to conventional chemotherapies, once again adding to the challenge of managing these tumors. Recent molecular analysis of chordomas has shown an overexpression of several factors that could be targeted by chemotherapy. The tyrosine kinases KIT and BCR-ABL as well as platelet-derived growth factor receptor A (PDGFRA), and PDGFRB are found to be overexpressed in some patients with chordoma, all of which are inhibited via imatinib mesylate (IM), a chemotherapy that inhibits receptor tyrosine kinases.[70] In particular, patients with skull base chordomas are found to have

increased expression of PDGFRB, which is likely the primary antitumor target for IM.[84,85] Sunitinib is yet another tyrosine kinase inhibitor that has shown efficacy against chordomas. In a multicenter phase II trial of sunitinib, George and colleagues[86] found that 44% of their patients with chordoma showed stable disease at 16 weeks when treated with sunitinib.

The epidermal growth factor receptor (EGFR) is another marker that has received investigational attention as a possible therapeutic target in chordomas. To determine the EGFR expression of chordomas, Shalaby and colleagues[87] characterized chordomas of 160 patients and found 60% of cases to show EGFR mutations. Using the chordoma cell line U-CH1, as well as patient chordomas from different locations, EGFR overactivation in several chordomas was shown via phosphoreceptor tyrosine kinase array membranes. Tyrphostin, an EGFR inhibitor, showed substantial inhibition of proliferation in the chordoma cell line U-CH1 in vitro and decreased the phosphorylation of EGFR in a manner that was dose-dependent. This study showed that chordomas have abnormal EGFR signaling and suggested that molecular analysis of the EGFR activation status of tumors could be used to select patients who are good candidates for treatment using EGFR antagonists. Furthermore, a case report by Singhal and colleagues[88] reported treatment response with erlotinib, an EGFR tyrosine kinase inhibitor, in a patient unresponsive to a vascular disrupting agent and IM. Other agents shown to be effective in the setting of disease progression after IM treatment include sirolimus and cisplatin.[89,90]

In addition to PDGFR and EGFR, chordomas express receptors and signaling molecules to which currently available molecular-targeted therapies exist, such as c-Met (hepatocyte growth factor receptor) and downstream effectors Phosphatidylinositol 3-kinases (PI3K)/Protein Kinase B (AKT) and mammalian target of rapamycin (mTOR).[84,85,91–97] Therapies targeting several of these molecules have already shown initial success in patients with chordoma and in in vitro models, and combinational therapy is being explored.[89,98,99]

PROGNOSTIC FACTORS AND NOVEL BIOMARKERS

Many factors have been examined and subsequently implicated in the prognosis of chordomas, including extent of surgical resection, previous treatments, and adjuvant therapies.[23] However, many studies have conflicting results. It was initially believed that a younger age at diagnosis was prognostic of a poorer outcome, because previous studies have pointed to the aggressive behavior of chordomas in children, highlighting the hypercellularity, pleomorphism, and high levels of mitotic activity seen in this age group.[100] Moreover, Borda and colleagues[101] reported that the prognosis is worse in these younger patients because of the extremely diverse and malignant pathologic appearance of these tumors observed in children and adolescents. However, more recent studies have indicated that the recurrence rate is lower in patients younger than 40 years and points to a better prognosis.[7,46] Other factors believed to influence prognosis include the classic and chondroid histology (better prognosis compared with dedifferentiated variant), the presence of necrosis and mitotic figures (poor prognosis), metastases (poor prognosis), larger tumor volume at diagnosis (prognostic factor for tumor recurrence and poor prognosis), and Ki67-positive staining (poor prognosis).[5,7,102]

Additional molecular expression marker studies have identified MIB-I, p53, and cyclin D1 as potential predictors of recurrence and prognosis, citing that the proliferative potential of chordomas may be correlated with the combination of p53 overexpression, anaplasia, and high-grade atypia.[103,104]

SUMMARY

Skull base chordomas are exceptionally rare tumors that grow in the clivus, often presenting with CN palsies, headache, and visual field cuts. The management of these tumors entails surgical resection as well as radiation treatment, although many different treatment preferences are presented in the literature. Both extent of resection as well as adjuvant therapy have been shown to affect PFS as well as overall survival. Nonetheless, there is a wide range of variability within the literature of skull base chordomas treated with similar therapeutic options, which may point to a spectrum of heterogeneity amongst these tumors going beyond the extent of resection and radiation therapy. Biomarker profiling has identified several factors that are upregulated in chordomas as prognostic factors, although this literature is by no means complete. The future of skull base chordoma management lies in the increasing recognition of the need for these cases to be referred to surgical centers of excellence, followed by judicious use of high-dose focal radiation techniques like proton beam therapy, and expanding our understanding of the molecular markers responsible for the aggressive behavior of these tumors so that chemotherapies targeting these markers can be incorporated into treatment paradigms in a patient-specific manner.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.nec.2012.08.007.

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