Skull Base Chordomas and Chondrosarcomas

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Keywords

Skull base · Chordoma · Chondrosarcoma · Diagnosis · Therapy

Abstract

Skull base chordomas account for less than 0.2% and chondrosarcomas for less than 0.15% of all intracranial tumors. Although their clinical and imaging presentations are similar, they derive from different origins. Chordomas arise from embryonic remnants of the primitive notochord and chondrosarcomas from primitive mesenchymal cells or from the embryonic rest of the cranial cartilaginous matrix. Both entities are characterized by infiltration and destruction of the surrounding bone and soft tissue and a high locoregional recurrence rate. Chondrosarcomas, when treated with similar complex strategies, display a much better prognosis than chordomas. The overall survival is approximately 65% for chordomas and 80% for chondrosarcomas at 5 years and 30 and 50%, respectively, at 10 years. Chordomas are divided into the following 3 histological types: classical (conventional), chondroid, and dedifferentiated. Chondrosarcomas have conventional, mesenchymal, clear cell, and dedifferentiated subgroups. Both tumor entities often present with nonspe-

cific symptoms, and headaches are the most reported initial symptom. Computed tomography and magnetic resonance imaging are required to determine the tumor localization and the extent of tumor growth. The treatment philosophy is to maximize tumor resection, minimize morbidity, and preserve function. Neurosurgical approaches commonly used for the resection of intracranial chordomas and chondrosarcomas are transsphenoidal, transbasal, cranio-orbitozygomatic, transzygomatic extended middle fossa, transcondylar, and transmaxillary approaches. Chordomas and chondrosarcomas are not sensitive to chemotherapy and there are no approved drugs for their treatment. The present treatment concept is a combination of surgical resection with a maximal excision and preserving patients' quality of life by adjuvant radiotherapy for both chordomas and chondrosarcomas.

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Introduction

Chordomas and chondrosarcomas are a heterogeneous group of primary malignancies that develop within and invade the skull base region. They represent patholo-

gies that exhibit a wide diversity of oncologic behavior. A standard classification is difficult to apply. It appears appropriate to divide the lesions according to their clinical presentation and radiologic characteristics. For this reason, chordomas and chondrosarcomas have been historically grouped together. However, these tumors are distinct clinicopathological entities and vary significantly in terms of their clinical outcome. Chordomas and chondrosarcomas are rare malignant tumors characterized by slow, destructive, and locally invasive growth. Chordomas arise from embryonic remnants of the primitive notochord with a molecular alteration preceding their malignant transformation. On the other hand, chondrosarcomas are considered to originate from primitive mesenchymal cells or from embryonic remnants of the cartilaginous matrix in the cranium. Furthermore, chordomas and chondrosarcomas share a high propensity for locoregional recurrence with infiltration and destruction of the surrounding bone and soft tissue. Although the metastatic potential of these malignancies is considered to be relatively low, distant metastases has been reported in patients with advanced disease. This is associated with a poor prognosis and a median survival of less than 12 months. Both of these tumors usually display slow growth patterns and cause gradual displacement of neurovascular structures, in turn leading to the manifestation of clinical signs and subsequent diagnosis. The complex structure of the cranial base, together with the close proximity to cranial nerves and vessels, represents a significant challenge in the management of these tumors. It ought to be noted that aggressive surgery is associated with a considerable risk of high morbidity and mortality. Herein, we present a review of the literature summarizing the epidemiology, histopathology, clinical signs, diagnosis and differential diagnosis, imaging characteristics, and various multimodal treatments with related clinical outcomes of skull base chordomas and chondrosarcomas.

Epidemiology

Skull base chordomas are rare malignancies and account for less than 0.2% of all intracranial neoplasms [1, 2]. Several large population-based studies have estimated the overall incidence rate of chordomas to be 0.08 per 100,000 persons per year [3–5]. They may occur in all age groups (although most cases are diagnosed during adulthood, with the mean age of affected person being in the fifth and sixth decades of life) [3], rarely affecting children and adolescents (<5% of all chordomas) [6]. The gender

distribution has been reported to be nearly equal in skull base lesions. Chordomas have no known causative association with irradiation or other environmental factors. However, there is a very small percentage of cases displaying a familial pattern of inheritance.

Interestingly, chondrosarcomas also represent approximately 0.15% of all intracranial neoplasms [7] and constitute 6% of all skull base tumors [8, 9]. The peak incidence occurs in the fourth and sixth decades of life with no gender predilection. In a study by Bloch et al. [10], 32% of chondrosarcomas involved the clivus and 27% arose at the temporo-occipital junction. It ought to be noted that distant metastases are very rare for both of these intracranial tumors. The outcome is quite different between chordomas and chondrosarcomas, with the latter displaying a much better prognosis when treated with similar complex strategies.

Histopathology

Chordomas

The first macro- and microscopical description of chordomas was provided by the German physician and pathologist Rudolf Virchow [11]. He described on autopsy an incidental, small, slimy growth on the surface of the clivus. Since that time the intracellular, bubble-like vacuole cells referred to by Virchow [11] as “physaliferous” remain a distinguishing, if not pathognomonic, feature of chordomas. Another German pathologist, i.e., Hugo Ribbert, later proposed the term chordoma [12].

The following 3 histopathological types of chordomas have been identified: classic (conventional), chondroid, and dedifferentiated types [13–15]. The histopathological type of a chordoma predicts the prognosis of this tumor. The first 2 forms have a favorable long-term prognosis, with a 3-year overall survival rate of 90% [13]. The dedifferentiated subtype displays aggressive behavior and only a 60% 3-year overall survival rate [13, 16].

A conventional (classic) chordoma consists of cords and islands of eosinophilic and clear vacuolated cells, also called “physaliphorous cells,” suspended in a myxoid-mucous matrix (Fig. 1a, b). The nuclei are round and uniform, although some exhibit considerable pleomorphism. A thin fibrous septum divides groups of these cells into lobules. This classic pattern of chordoma should not show evidence of chondroid or other mesenchymal tissue differentiation. The second type of chordoma or chondroid chordoma shows regions where the stroma resembles hyaline cartilage and neoplastic, sometimes phys-

Fig. 1. Characteristic histologic features of chordomas (**a–f**) and chondrosarcomas (**g–k**). **a, b** HE staining of a chordoma showing epithelioid cells arranged in cords (arrow in **a**) and detectable extracellular mucin (asterisk in **a**). In other areas a lobular arrangement can be observed (arrows in **b**). Chordomas show a characteristic immunohistochemical expression of S100 (**c**), pan-cytokeratins (**d**), and vimentin (**e**). Moderate proliferation activity (Ki67

immunostaining in **f**). **g** HE staining showing a well-differentiated chondrosarcoma (G1) with moderate cellularity without mitoses or necrosis. Chondrosarcomas show a characteristic immunohistochemical expression of S100 (**h**) and vimentin (**j**), while pan-cytokeratins (**i**) are not expressed. Low proliferation activity (Ki67 immunostaining in **k**).

aliphorous, cells grow in lacunae. The rare dedifferentiated chordomas are characterized by a frankly malignant, mesenchymal component and have a sarcomatoid appearance. They carry a very poor prognosis. Finally, on immunohistochemistry (Fig. 1c–e), chordomas stain positively for S100, vimentin, epithelial membrane antigen, and pan-cytokeratins [6, 17–20]. “Brachyury” is a new, recently discovered specific diagnostic marker for chordomas [21]. A high brachyury expression was found in chordoma tissue samples [22]. There is no correlation between brachyury expression and clinicopathological parameters in chordoma patients [23]. Other tumors do not show expression of this protein [21, 24]. The determination of brachyury can therefore be used to differentiate

tumors with a similar histology and geographical location [25]. However, some poorly differentiated and dedifferentiated areas of chordomas may display a loss of brachyury immunoreactivity [21, 24, 26, 27].

Chondrosarcomas

The first histological report of an intracranial chondrosarcoma was published in 1899 by the British biochemist and neuropathologist Sir Frederick Walker Mott [28]. Histologically, chondrosarcomas are characterized by an abundant hyaline type of cartilaginous stroma and the presence of a neoplastic chondrocyte population. The chondrocytes have an inconspicuous cytoplasm and a small, dark nucleus with fine chromatin (Fig. 1g). Infiltration

tion of the bony trabeculae is a histological feature of malignancy. Moreover, extension into the surrounding soft tissue may be observed [29, 30]. Chondrosarcomas can be classified into the following 4 histological subgroups: conventional chondrosarcoma, mesenchymal chondrosarcoma, clear cell chondrosarcoma, and dedifferentiated chondrosarcoma [31, 32]. It is well known that chondrosarcomas demonstrate recognizable histological grades of differentiation. Based on cellularity, mitotic activity, atypia, and nuclear size, the WHO introduced the following 3 classes: grade I (well differentiated), grade II (intermediately differentiated), and grade III (poorly differentiated) [33]. Grade I and II chondrosarcomas show a better outcome, whereas grade III chondrosarcomas are associated with a high recurrence rate and even metastases [34]. Chondrosarcomas stain positive for S-100 and vimentin but fail to express epithelial markers such as cytokeratin and epithelial membrane antigen (Fig. 1h, I, j), [35].

Clinical Signs and Symptoms

Patients with chordomas and chondrosarcomas usually present with nonspecific and sometimes confusing symptoms, which markedly delays the diagnosis until later stages of the disease [36–39]. The initial presentation of the tumors can significantly vary depending on the location, extension, and proximity of the lesion to critical structures. Besides headaches typically located in the occipital or retro-orbital region, the most commonly reported signs are neuro-ophthalmological [37–42]. The visual symptoms may include blurred vision or loss of vision, ptosis, and visual field defects related to cranial nerve palsies which could be explained by the location and growth pattern of the tumors [43–47]. It is not unusual for this kind of tumor to invade structures such as the cavernous sinus, the petroclival region, the cerebellopontine angle, the infratemporal fossa, the parapharyngeal space, and the temporal bone [42, 44, 46]. Other signs and symptoms that may present with clival lesions include hearing loss, facial paralysis or hypoesthesia, dysphonia, dysarthria, dysphagia, dyspnea, anosmia, and vertigo [44, 48, 49]. Involvement of the suprasellar space may lead to hypopituitarism and diabetes insipidus through damage of the pituitary gland or the stalk and visual impairment through damage to the optic apparatus, respectively [50, 51]. Larger tumors may also compress the brainstem and cerebellum, causing gait disturbances, ataxia, dysmetria, and motor weakness (e.g., hemiparesis or tetraparesis) [44, 51, 52]. The nature of the tumor cannot be distinguished on the basis of the clinical presentation alone.

Endocrine Dysfunction

Chordomas and chondrosarcomas can arise within the sellar/parasellar region but also extend into this region. In a large transsphenoidal surgical series about 10% of nonpituitary sellar lesions were found to be cartilaginous tumors. Chordomas were diagnosed more frequently than chondrosarcomas [53, 54]. It is well known, that neither tumor entity secretes any bioactive compounds or hormones. Although there are a few published cases about endocrine abnormalities in patients presenting with these tumors, a significant endocrinopathy is highly unusual [53–59]. The most reported complaints were amenorrhea, galactorrhea, and male sexual dysfunction [56, 58–60]. The severity of these symptoms was correlated with the level of hyperprolactinemia secondary to compression of the pituitary stalk. In rare cases, aggressive tumor growth may lead to partial or complete destruction of the pituitary gland, resulting in correspondingly variable degrees of hormonal deficiency [57, 61, 62]. Depending on the imaging peculiarities and presenting symptoms, a lack of systematic measurement of the preoperative hormonal status as part of the diagnostic work-up could lead to the failed diagnosis of not clinically apparent hormonal deficiencies.

Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred diagnostic tools for the initial evaluation of patients with suspicion of skull base neoplasms [63–65]. Preoperative sagittal and coronal multiplanar reconstructions are essential for evaluation of the detailed tumor's relationship to adjacent brain structures and hence planning of the optimal surgical treatment. In the follow-up, these planes are needed to detect treatment-related complications and tumor recurrences [66]. Since both tumors display an equally wide diversity in terms of their localization as well as the pattern and extent of invasive growth within the skull base, neither MRI nor CT can be useful for differentiating chordomas from chondrosarcomas preoperatively [63–66].

High-Resolution CT

A high-resolution CT scan is sensitive enough to detect lesions of the skull base and should be performed with intravenous contrast and reviewed in bone and soft-tissue windows. Intracranial chordomas and chondrosar-

Fig. 2. MRI and CT scans of intracranial chordoma. Axial (a–c), sagittal (e), and coronal (g) T1-weighted and axial T2-weighted (c) MR images show a tumor with clival/retroclival extension. b, e, g Contrast-enhanced images. Axial (d) and sagittal (f) CT scans demonstrate involvement of the clivus.

comas are both delineated in CT scans, as are well-defined expansive tissue masses that arise from the clivus with associated osteolytic transformation with frequent expansion to the adjacent soft tissue [67, 68]. The tumors are seen on noncontrast CT as isodense or slightly hypodense in comparison to normal brain tissue. Intratumoral calcifications are mostly found in chondrosarcomas and are hence suggestive of this diagnosis.

Magnetic Resonance Imaging

MRI provides optimal resolution and soft tissue contrast with exquisite anatomic details in the evaluation of intracranial lesions in comparison to CT scans [69, 70]. The sagittal planar images are indispensable for identification of the posterior tumor margins, as well as their relation to the brainstem, and the coronal planar images are essential for identification of the lateral tumor margins and the tumor extension into the cavernous sinus. Intracranial chordomas and chondrosarcomas are characterized by an intermediate-to-low signal intensity on spin-echo T1-weighted MR sequences and they are recognized within the high signal intensity of the clivus fat tissue. Small foci of hyperintensity recognized in T1-weighted sequences, appearing as bright spots and dark areas on gradient-weight-

ed sequences, represent intratumoral hemorrhage or a mucus pool. Furthermore, the tumors show a high signal intensity on T2-weighted images. The sagittal and axial T1-weighted, postcontrast, fat-suppressed images also help to distinguish tumor from fat in the adjacent bone marrow spaces, since normal bone marrow in adults is characterized by a bright signal intensity on both T1-weighted images and fast spin echo T2-weighted images [71, 72]. Clival chordomas and chondrosarcomas may exhibit similar growth patterns by extending anteriorly, laterally, posteriorly, inferiorly, and superiorly with affection of the sellar/parasellar area, the middle cranial fossa, the prepontine cistern, and the foramen magnum (Fig. 2, 3). Nevertheless, a slight difference in predilection in terms of origin with chordomas tending to arise from the midline as opposed to more laterally for chondrosarcomas may be of use in the initial differential diagnosis on MRI.

Treatment

Surgery

Treatment of intracranial chordomas and chondrosarcomas still represents a big challenge despite advances in

Fig. 3. MRI scans of intracranial chondrosarcoma. Coronal (**a**, **b**), sagittal (**d**), and axial (**e**, **f**) T1-weighted and coronal (**c**) and axial (**g**) T2-weighted MR images demonstrate a tumor with extension into the posterior fossa. **b**, **e**, **g** Contrast-enhanced images.

neurosurgical techniques [73–77]. The surgery philosophy is to remove as much tumor as possible and to preserve or improve the patient's status. Macroscopic complete resection with a negative surgical margin is usually impossible due to aggressive and infiltrative tumor growth pattern with involvement of the surrounding neurological structures [51, 73, 78–83]. Many surgical approaches have been described for the resection of skull base chordomas and chondrosarcomas. Taking into consideration the aggressive nature of these tumors and especially the patient's expectations, the best approaches or even multiple approaches must be selected on an individual basis. It is important to consider the common and serious complications that may occur following the resection of skull base lesions. Many authors report new cranial nerve deficits in up to 80% of the patients, which were frequently transient in the majority of cases. Other complications include cerebrospinal fluid leaks, meningitis, hearing loss, visual decline, and consequences of vascular injury [34, 84]. Neurosurgical approaches often used in the resection of intracranial chordomas and chondrosarcomas include the transsphenoidal, transbasal, cranio-orbitozygomatic, transzygomatic extended middle fossa,

transcondylar, and transmaxillary approaches [34, 79–92]. Their applications are summarized as follows.

Transsphenoidal Approach. The transsphenoidal approach is a well-established method for the treatment of tumors limited to the upper clivus, the sellar and suprasellar regions, or the medial aspect of the cavernous sinus. This approach provides visualization to many intracranial anatomical structures (the internal carotid arteries, the pituitary gland, the infundibulum, the optic nerve and chiasm, the mammillary bodies, the basilar artery bifurcation, the hypothalamus etc.). This approach, mostly in an extended fashion, permits tumor resection with minimal displacement or distortion of surrounding tissue. The neurosurgeon can work effectively either above or below the optic chiasm, depending on its situation relative to the lesion. The transsphenoidal approach is the one most often used for the treatment of chordomas and chondrosarcomas in our institute.

Transbasal Approach. There are a number of modifications of the transbasal approach (e.g., uni- or bilateral orbital-cranial subfrontal transbasal, nasofrontal transbasal). It creates the possibility to reach the midline clivus, the medial cavernous sinus, the petrous apex, the occipital

condyles, and the foramen magnum. However, this approach is a midline approach between the 2 optic nerves and cannot expose tumors located laterally to the internal carotid artery (ICA). The main disadvantage is the narrow and deep corridor between the optic nerves and the ICA.

Cranio-Orbitozygomatic Approach. This approach provides the shortest route with full exposure of lesions displacing the brain structures superiorly and laterally in the parasellar region. It gives a multidirectional view of the tumor and allows surgical dissection via multiple routes (subfrontal-transbasal, transsylvian, subtemporal, and infratemporal). Many authors have reported using this approach for tumors in the region of the upper clivus with extension lateral to the ICA and into the middle fossa, the petrous apex, and the infratemporal fossa.

Transzygomatic Extended Middle Fossa Approach. This approach has become useful in the treatment of lesions located in the infratemporal, sphenopalatine, and temporal fossae, the orbit, the petrous apex, the upper petroclival region, and the cavernous sinus. It creates a wider surgical corridor offering a direct view of the clivus and brainstem. Tumors extended in the sphenoid sinus can be removed through the Parkinson triangle between the first and second divisions of the fifth cranial nerve.

Transcondylar Approach. Many indications have been reported for the transcondylar approach. In selected cases, it allows approach to chordomas/chondrosarcoma in the region of the inferior clivus with lateral extension to the craniocervical junction or the upper cervical vertebrae. It requires extraperiosteal management of the vertebral artery. This approach can be combined with a transtemporal approach superiorly and a transcervical approach inferiorly. However, the surgery can cause cerebellar damage, vertebral artery injury, or occipito-cervical instability, where extensive condyle resection may even require future occipito-cervical fusion.

Transmaxillary Approach. This technique enables tumor resection located in the clivus area with extension into the nasopharynx or craniocervical junction, inferior to the anterior cranial fossa, superior to the C2-C3 interspace, and medial to the pterygoid plate. The maxillary osteotomy provides a direct view of the clivus region, the posterior nasooropharynx, and the cervical spine. This approach is associated in appropriately selected patients with limited morbidity and mortality. Procedurally related complications include damage to neurovascular structures along the paramedian skull base, including maxillary, mandibular, and vidian neurovascular bundles. The risk of aseptic bone necrosis is increased with multisegmented osteotomies and intraoperative hypotension.

Radiotherapy

The recent literature supports the concept of a combination treatment for chordomas and chondrosarcomas consisting of surgical resection with maximal excision followed by adjuvant radiotherapy [84, 93–97]. It is believed that radiation therapy leads to clearance of the tumor bed from invisible, microscopic tumor nests. The most common adjuvant treatment methods for chordomas and chondrosarcomas include high-dose radiotherapy with proton beam radiation and radiosurgery using a gamma knife and a CyberKnife [98–102]. However, there are no published studies directly comparing these forms of radiation therapy [103]. Retrospective studies have shown a longer local progression-free time following adjuvant radiotherapy. Conventional radiotherapy does not appear to increase the survival duration. The 5-year recurrence-free survival for cranial base chordomas after proton-based therapy ranges between 59 and 73% [94, 100, 104]. In contrast, skull base chondrosarcomas after the same proton-based therapy are characterized by a disease-specific 5-year survival rate of about 99% [102]. Adjuvant radiotherapy is not indicated for chondrosarcomas of WHO grade I and II in case of complete resection, as opposed to chordomas where this is universally advocated.

Chemotherapy

Traditionally, chordomas and chondrosarcomas are not sensitive to chemotherapy [105, 106] and there are no drugs approved for their treatment [106–108]. Dysregulation of different signaling pathways has been found in the development of chordomas and chondrosarcomas [109–119]. Agents that interrupt these signaling pathways could become attractive targets for anticancer therapy. Tyrosine kinase inhibitors (TKI) showed activity against chordomas as a result of targeted inhibition of several intersecting molecular pathways [120]. In a small number of patients treated with the TKI sunitinib, stable disease for at least 16 weeks was achieved [121]. Other studies have demonstrated that TKI, such as imatinib mesylate and erlonitib, and epidermal growth factor receptor inhibitors such as cetuximab and gefitinib, have a beneficial effect on the treatment of advanced or metastatic chordomas [122–124]. TKI, mTOR, hedgehog, and AKT inhibitors have also been tested in clinical studies for chondrosarcoma patients [115–119]. Unfortunately, most of them have failed to demonstrate a clinical benefit in terms of disease progression or outcomes. However, all clinical reports have been limited by a small patient numbers and short fol-

low-ups. Finally, the published studies are clinical phase I/II studies, rendering it difficult to arrive at any conclusions.

It is of interest to note that immunotherapy based on enhancement of the immune system to eliminate cancer cells has developed into a promising modality in cancer therapy [125–127]. As in the case of other human cancers, it has recently been demonstrated that some fractions of chordoma cells escape immune modulated destruction by upregulating the programmed death-1 receptor (PD-1) and programmed cell death ligand 1 (PD-L1) [128–130]. Many checkpoint inhibitor (ICI) antibodies blocking the PD-1/PD-L1 pathways have been developed and introduced into clinical practice [131, 132]. Migliorini et al. [133] have published anecdotal cases of clinical responses to immunotherapy with ICI in relapsing chordomas. Although there are currently several clinical studies on chordomas and ICI (for details, please see <https://clinicaltrials.gov>), it remains too early to speculate on whether adding ICI antibodies to existing treatment protocols of chordomas could improve the outcome.

Prognosis and Outcome

There are no reliable markers for the prognosis of skull base chondrosarcomas and chordomas known to date. However, Weber et al. [134] identified histology, gross tumor volume, and brain compression as independent prognostic factors for local control and overall survival (OS) based on multivariate analysis. On the other hand, several authors have considered the prognosis to be based on multiple factors [3–5, 8, 42, 78, 79, 82, 84, 92–94]. Dedifferentiated chordomas exhibit a particularly poor prognosis with an aggressive clinical course. This subtype has a 60% 3-year OS compared to an 89.4% 3-year OS for classical chordomas [10, 15, 16, 79]. Poorly differentiated or grade III chondrosarcomas show aggressive behavior and are associated with the lowest survival rates [10]. Tumor volume has been incorporated in the TNM staging system and can be considered as a potential prognostic factor. Kamrin et al. [135] reported a mean survival time for untreated chordoma patients ranging from 6 to 24 months. According to published data, the median OS of patients with chordomas after surgery and radiation was 6.29 years [3], the 5-year progression-free survival varied from 45 to 56% [3, 8, 9] and 10-year OS rates ranged from 32 to 60% [16]. Metastases from chordomas from all anatomic sites have been estimated to vary from 9 to 41% [78,

136–139]. In a systematic review of 560 patients with intracranial chondrosarcomas, the calculated 5-year mortality was 11.5%, with a median survival time of 24 months [10]. The Surveillance, Epidemiology, and End Results program of the National Cancer Institute shows an OS of 65% for chordomas and 82% for chondrosarcomas at 5 years, as well as rates of 32 and 50% at 10 years, respectively [140].

Conclusion

Skull base chordomas and chondrosarcomas are local invasive and destructive growing tumors with a high locoregional recurrence rate and rare distant metastases. The patients often have nonspecific and confusing symptoms independently of the tumor subtype. CT and MRI still represent equally valuable diagnostic tools for the initial evaluation of patients with a suspected brain disease. Preoperative differentiation between chordomas and chondrosarcomas based on the clinical presentation and clinical and instrument-based diagnostics alone is impossible. The treatment philosophy for both intracranial tumor entities is to maximize tumor resection, minimize morbidity, and preserve function. The appropriate approaches or even multiple approaches must be determined on a case-by-case basis. Surgery should be followed by adjuvant radiotherapy to improve the local progression-free time, where proton-beam therapy has been shown to be more profitable than conventional radiotherapy. To date, there are no drug agents approved for the treatment of chordomas and chondrosarcomas. In recapitulation, from our personal point of view, intracranial skull base chordomas and chondrosarcomas should be subjected to the maximum possible cytoreduction via an appropriate approach without deterioration of the general condition and without incurring in neurological deficits followed by radiotherapy in the form of proton beam therapy.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflict of interests to declare

Funding Sources

There was no funding support for this article.

Author Contributions

Conception, design, and writing of this paper: N.K. and M.B. Redaction: S.-M.S., R.C., T.G., and T.M.K. All of the authors approved the final submitted version of this work.

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