Chordoma

Ossama Al-Mefty¹

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The accompanying reports on chordoma are very welcomed and informative. This extremely rare but behaviorally malignant tumor continues to lack biologic understanding, recognition of the effective treatment and improved outcome. Two aspects in the treatment of chordoma are emphasized in these articles: the paramount importance of radical surgical resection even beyond gross total removal and the role of adjuvant high-dose radiation therapy that requires advanced technical methodology because of the proximity of the brain stem and vital neural structures. Missing in these articles is the histochemical staining confirmation of these cases showing that they were indeed all chordomas.

Chordoma is not a benign tumor. It grows invasively, has a high rate of local recurrence, metastasizes, implants surgically, demonstrates “tumor progression” as it becomes more malignant by accumulating genetic mutations and has a dismal prognosis following recurrence [1–3]. For these reasons, chordoma needs to be treated aggressively. Prior to embarking on this treatment, an accurate diagnosis is essential. Because of the clinical and radiologic features, location, means of treatment and sometimes even the histologically masquerading appearance, skull base chordoma is confused with low-grade chondrosarcoma, and to date the two are frequently lumped together. However, they are totally different disease entities with disparate outcomes [4]. I believe that the diagnosis of chordoma should only be accepted with positive immunohistochemical markers demonstrating its epithelial origin (cytokeratin, EMA and Brachyury) [2]. Once there is positive

immunohistochemical staining, the histologic subtype of chondroid chordoma does not have any better prognosis.

Despite the surge in studies and advancements in imaging techniques, chordoma is still plagued by unpredictability and misconceptions. The opinions and methods regarding treatment today are still diversified, conflicting, and subject to advocacy and promotion. Unfortunately, this leaves the patient anxious, confused, torn and stricken not only with their grave disease, but also with the outcome of their presumed “choice” [5]. Owing to their rarity, studies and experience in chordoma are very limited. The landmark article of Heffelfinger et al. lists only 55 patients with clival chordomas over a 60-year period drawn to their world referral center [3]. This extreme rarity and the time passed between the different eras of management make it difficult but extremely critical to have a true long-term follow-up.

Once the diagnosis has been confirmed, aggressive treatment is needed. This often requires multiple surgical approaches that are necessary to manage these patients. Following recurrence, chordoma has a dismal prognosis, with 3- and 5-year survival rates of 43% and 7%. The management of chordoma, once it occurs, is palliative and doomed to repeated interventions and continuous progression associated with additional deficits, risks and complications from both the tumor and the repeated interventions. Hence, chordoma should be treated at the onset with the most radical approach to aim for longer disease-free survival [6, 7].

Chordoma is frequently described as a benign, slow-growing disease, totally contradicting its natural history and outcome. The deceptive impression might lead to a course of observation in small, incidental, asymptomatic lesions that I believe should be radically excised like any other malignancy at the time of their detection [5].

The extent of surgical removal’s relation to recurrence-free survival has been well established. The advancements

✉ Ossama Al-Mefty
almeftyossama@bwh.harvard.edu

¹ Brigham and Women’s Hospital, Harvard School of Medicine, 75 Francis Street, Boston, MA 02115, USA

in skull base and microsurgery have made radical removal of skull base chordomas safe. Several considerations must be made when discussing the surgical removal of chordomas. Key among them is the fact that chordoma exists as islands in the surrounding bone and not just the clearly visible soft tissue mass. Therefore, to achieve radical resection, extensive resection by drilling or ultrasound aspirator removal of the surrounding bone should be performed in addition to complete removal of the soft tissue mass. Preoperative computed tomography (CT) imaging must be thoroughly reviewed to understand the bony involvement and plan surgery accordingly, as chordoma has a tendency to spread throughout the skull base. Multidirectional extension must be anticipated, studied and planned for the operative approach or approaches. Indeed, often multiple skull base approaches are needed to achieve radical removal of chordomas and provide the best chance of long-term control [6, 8]. Contrary to the purported concern there were no differences in morbidity between patients who had radical or subtotal surgical resection. The extent of resection was shown to be an important factor in improving disease-free survival, and a significantly more extensive resection was achieved in those without a previous history of surgery [6]. Wu et al. [9] reviewed 106 cases treated by their group with similar findings. To my dismay, one could still see advocacy for the routine use of one certain approach in preference over others—although certainly a team that wants to take on chordomas should master all the approaches and apply them as needed for each individual patient.

Considering that chordoma begins as an extradural tumor, tends to spread through the cerebrospinal fluid (CSF) and implants surgically [13], extradural approaches to avoid CSF spread and a surgical field precaution to prevent implantation should be used. If the tumor has not yet spread intradurally, then every effort should be made to keep the operation extradural. If the tumor has extended intradurally, then it can be followed from an extradural approach. Given the frequent involvement of the cavernous sinus, radical resection of chordomas includes removal of the cavernous sinus component.

All modern advancements and technology are employed in chordoma surgery as needed, and this certainly involves navigation, endoscopic techniques, microscopic techniques and endovascular rescue if needed.

Given the paramount importance of radical resection, we take every step possible to ensure the maximal possible resection has been achieved. As a part of this strategy, we feel intraoperative imaging is essential. We prefer to perform all chordoma resections in the state-of-the-art Advanced Multimodality Image-Guided Operating (AMIGO) suite. This suite is equipped with intraoperative magnetic resonance imaging (MRI), CT, positron emission tomography

(PET)/CT, ultrasound and angiography, allowing one to leave the operating room knowing all of the tumor possible has been resected.

Chordomas are relatively radiation-resistant tumors; however, high-dose radiation such as is possible with particle-based therapy has been shown to offer improved local control and survival [10, 11]. The goal of radiation is to sterilize the bed of the tumor from invisible, microscopic tumor nests. Hence, radiosurgery will not be the primary optimal radiation modality because it is directed to a small, visible target; however, it may have a palliative role in repeated recurrences. It needs to be clear that the addition of radiation comes, however, with a heavy price, and despite the advanced techniques available today, there is still a high complication rate.

Chordoma frequently follows a different growth pattern. Tumor biology and genetic studies are scarce, but there has been a surge in interest in the subject. However, the simple question of what makes a benign remnant of the notochord accelerate in aggressiveness is not easily answered: Chordoma is a fine example of the oncologic doctrine of tumor progression in which tumors become more aggressive as they accumulate added genetic aberrations. Chordoma with a normal karyotype has been demonstrated to have a better prognosis and disease-free survival [1]. It has further been demonstrated that chordoma is exposed to ever-changing genetic aberrations that involve many chromosomes, and this chaotic instability is associated with increased clinical recurrence within a shorter period of time and with faster growth. Furthermore, the end result of this progression can be dedifferentiation to a highly malignant sarcoma. These findings lead again to designing initial management that eliminates the original tumor cells so that they will not be allowed to go through the progression with recurrences of a more aggressive tumor. Like other highly malignant tumors with continuous added mutations, finding an effective targeted drug therapy may be elusive.

Pediatric chordoma is extremely rare and was initially thought of as a poor prognosis. The management of chordoma in children involves special consideration. The small size and developing skull represent additional challenges. The potential adverse effects that neurologic deficits or cosmetic defects can have on physical and psychologic development mandate maintaining the use of exquisite technique. Nevertheless, safe, radical resection of chordomas in children can be frequently accomplished and with adjuvant high-dose radiation offers the best chance for long-term disease-free survival despite the known risks and long-term complications of radiation in the young, including cognitive, endocrinologic and radiation-induced tumors. We recently reported that long survival in children conforms to Wilson's rule for embryonic tumors. Hence, there is hope that chordoma can be amenable to cure [12].

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