Original Article

Craniovertebral junction chordomas: Case series and strategies to overcome the surgical challenge

ABSTRACT

Introduction: Chordomas are rare and malignant primary bone tumors. Different strategies have been proposed for chordomas involving the craniovertebral junction (CVJ) compared to other locations. The impossibility to achieve *en bloc* excision, the impact on stability and the need for proper reconstruction make their surgical management challenging.

Objective: The objective is to discuss surgical strategies in CVJ chordomas operated in a single-center during a 7 years' experience (2013-2019).

Methods: Adult patients with CVJ chordoma were retrospectively analyzed. The clinical, radiological, pathological, and surgical data were discussed.

Results: A total number of 8 patients was included (among a total number of 32 patients suffering from skull base chordoma). Seven patients underwent endoscopic endonasal approach (EEA), and posterior instrumentation was needed in three cases. Three explicative cases were reported: EEA for midline tumor involving lower clivus and upper cervical spine (case 1), EEA and complemental posterior approach for occurred occipitocervical instability (case 2), C2 chordoma which required aggressive bone removal and consequent implant positioning, focusing on surgical planning (timing and type of surgical stages, materials and customization of fixation system) (case 3).

Conclusion: EEA could represent a safe route to avoid injuries to neurovascular structure in clival locations, while a combined approach could be considered when tumor spreads laterally. Tumor involvement or surgical procedures could give raise to CVJ instability with the need of complementary posterior instrumentation. Thus, a tailored preoperative planning should play a key role, especially when aggressive bone removal and implant positioning are needed.

Keywords: Chordoma, craniovertebral junction, endoscopic endonasal approach, skull base, tailored reconstruction

INTRODUCTION

Chordomas are rare aggressive bone tumors which arise from the primary notochord remnants. Mostly they present at the proximal or distal end of the spine are mostly represented at the sacrum (50%) and the clivus (30%), respectively.[1-5] The mobile spine is less likely to be involved. Generally, surgery is considered the most crucial step of the treatment strategy. When feasible, en bloc excision in the sacral or mobile spine locations showed to improve disease-free survival rate, especially if wide or marginal margins could be obtained.[6-8] On the other hand, the craniovertebral junction (CVJ) areas of the anatomy, considering the juxtaposition of neural structures and vessels, are of paramount importance that make the en bloc

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resection attempt nearly impossible and are feasible only in very few selected cases.[9]

Thus, surgical approach to CVJ chordomas still remains challenging. The impairment of junctional stability represents a main issue that needs to be faced oftentimes, resulting in complex anterior/posterior fixation solutions. The aim of this article is to discuss surgical strategies and various approaches in CVJ chordomas operated in a single-center during a 7-year experience.

METHODS

This study is a retrospective case series of patients treated at the author's institution. Inclusion criteria were: (a) a diagnosis of CVJ chordoma involving lower clivus and/or C1 and/or C2 vertebrae (upper cervical spine) (b) availability of all clinical and radiological data (c) at least 6 months' follow-up. Patient data, clinical and surgical reports, radiological studies (pre- and post-operative magnetic resonance imaging [MRI], computerized tomography [CT], angio-CT) and pathology results were retrospectively analyzed by two different surgeons. Preoperative complete neurological examination was assessed. Type of surgical procedures performed, outcomes, and postoperative complications were evaluated by comparing to the literature. In order to report surgical oncological outcomes in a standard manner, the evaluation has been conducted according to the Boriani-Weinstein-Biagini terminology which focused on the strategy of removal (intralesional vs. *en bloc* with characterization of margins) even for clival lesions.[10-13]

RESULTS

A total of 32 patients suffering from chordoma were treated at the author's institution between December 2013 and December 2019. Among these, 8 patients had lower clivus, CVJ, and upper cervical spine involvement.

Results are summarized in Table 1. Of the 8 patients, 2 were female and 6 were male. Ages ranged from 14 to 77 with a mean age of 37.75. Seven patients had primary chordoma, while in 1 case there was a recurrence of the disease. In two cases, the entire clivus was involved, while in 4 cases only the lower clivus had been attacked by the tumor. C1 and C2 vertebrae were found to be the tumor site in 4 and 2 cases, respectively. Condyle involvement was reported in 3 cases. Moreover, there was an intradural extension in 1 case.

In most cases, the initial symptom was mechanical occipito-cervical pain which was recorded in 5 patients.

Cranial nerve impairment was detected in 4 patients, while other presenting symptoms were dysphagia (1 patient), rhinolalia (1 patient), and recurrent otitis (1 patient) [Table 2].

A three-dimensional (3D) endoscopic endonasal approach (EEA) was performed in 7 cases. Among them, 2 patients required a subsequent posterior approach. A single case was treated with a two-step cervical approach (anterolateral and posterior). According to the extent of resection, in 6 cases, total intralesional removal was achieved, while partial intra-lesional removal (<90%) resulted in 2 patients. Three patients required an occipitocervical fixation due to tumoral involvement of CVJ complex and/or instability surgery-related [Table 3].

The postoperative course was characterized by complications in 3 cases: a pulmonary infection (case 3), a XII cranial nerve disfunction (case 3), hydrocephalus, (case 4), and cerebrospinal fluid (CSF) leak (case 6) were detected. Hydrocephalus and CSF leak required surgical management. Histological examination revealed classic chordoma in 6 cases, chondroid chordoma in 1 case, low differentiated chordoma in 1 case. All patients received adjuvant radiation therapy [Table 4].

Case series
Three explicative cases were reported with the aim to highlight three fundamental aspects of CVJ chordomas: The feasibility of EEA for midline tumors involving lower clivus ad upper cervical spine (case 1), the need of complemental posterior approach when tumor involvement or surgical procedures provoked occipito-cervical joint instability (case 2) and the importance of surgical planning (timing and type of surgical stages, materials, and customization of fixation system) in patients with cervical chordomas, that require aggressive bone removal and consequent adequate fixation to allow subsequent radiation therapy (case 3).

Case 1
A 16-year-old male patient with a 5-month history of severe headache and neck pain, not responsive to medical therapy and an episode of drowsiness and diffuse tremors. CT scan and MRI revealed a 20 mm × 10 mm mass, delimited anteriorly by the C1 anterior arch and posteriorly by the atlas cruciate ligament. There was no involvement of critical anatomical boundaries, such as anterior longitudinal ligament or condyles. The tumor was localized in extradural space with epidural compression [Figure 1a-c]. The neurological examination was unremarkable. The patient solely underwent endoscopic-assisted endonasal transclivus surgery. The parapharyngeal carotid course was studied with a preoperative angiography CT scan. Somatosensory evoked potentials and motor evoked potentials (MEPs)

Table 1: Patient characteristics and surgical results

Case number	Sex, years	Disease status	Tumor location	Intradural extension	Clinical features	Surgical approach	Extent of resection	CVJ fixation	Complications	Management of complications	Adjuvant radiation	Histological features	Follow-up (months)
1	Male, 16	Primary	Lower clivus, C1	No	Mechanical occipito-cervical pain	EEA	Intralesional total removal	No	None	-	Yes	Classic chordoma	24
2	Male, 14	Primary	Lower clivus, right condyle, C1	No	Mechanical occipito-cervical pain, recurrent otitis	EEA + posterior approach	Intralesional total removal	Yes	None	-	Yes	Low differentiated chordoma	4
3	Male, 45	Primary	C2	No	Dysphagia, rhinolalia	Posterior approach + anterior lateral cervical approach	Intralesional total removal	Yes	Pulmonary aspergillosis, acute pancreatitis, right XII cranial nerve palsy	Antifungal therapy	Yes	Chondroid chordoma	14
4	Female, 22	Recurrence	Holoclivus, right condyle, C1	Yes	Right VI cranial nerve palsy	EEA + posterior approach	Intralesional subtotal removal	Yes	Hydrocephalus, right hemiparesis (4+/5 MRC)	External ventricular drainage	Yes	Classic chordoma	7
5	Male, 77	Primary	Holoclivus, right cavernous sinus, sellar region	No	Right VI cranial nerve palsy	EEA	Intralesional total removal	No	None	-	Yes	Classic chordoma	11
6	Male, 53	Primary	Middle clivus, lower clivus	No	Mechanical occipito-cervical pain, dyplopia	EEA	Intralesional total removal	No	CSF leakage	EEA repair	Yes	Classic chordoma	77
7	Female, 42	Primary	Lower clivus	No	Mechanical occipito-cervical pain, left XII cranial nerve palsy	EEA	Intralesional subtotal removal	No	None	-	Yes	Classic chordoma	40
8	Male, 33	Primary	Right condyle, C1, C2	No	Mechanical occipito-cervical pain	EEA	Intralesional total removal	No	None	-	Yes	Classic chordoma	24

CVJ - Cranio-vertebral junction; EEA - Endoscopic endonasal approach; MRC - Medical research council; CSF - Cerebrospinal fluid

Table 2: Preoperative patient and tumor characteristics

	n (%)
n (patients)	8 (100.0)
Male	6 (75.0)
Female	2 (25.0)
Age at onset	37.75
Disease status	
Primary	7 (87.5)
Recurrence	1 (12.5)
Symptoms at onset	
Mechanical occipito-cervical pain	5 (62.5)
Cranial nerve disfunctions	4 (50.0)
Others	2 (25.0)
Tumor location	
Holoclivus	2 (25.0)
Lower clivus	4 (50.0)
C1 vertebra	4 (50.0)
C2 vertebra	2 (25.0)
Condyle involvement	3 (37.5)
Intradural extension	
Yes	1 (12.5)
No	7 (87.5)

Table 3: Surgical treatment

	n (%)
Surgical approach	
EEA	5 (62.5)
EEA+posterior approach	2 (25.0)
Posterior approach + anterior lateral cervical approach	1 (12.5)
Extent of resection	
Intralesional total removal	6 (75.0)
Intralesional subtotal removal	2 (25.0)
CVJ fixation	
Yes	3 (37.5)
No	5 (62.5)

CVJ - Cranio-vertebral junction; EEA - Endoscopic endonasal approach

Table 4: Operative and histological outcomes

	n (%)
Complications	
None	5 (62.5)
Cranial nerve palsy	1 (12.5)
Infectious disease	1 (12.5)
Hemiparesis	1 (12.5)
Hydrocephalus*	1 (12.5)
CSF leakage*	1 (12.5)
Histological features	
Classic chordoma	6 (75.0)
Chondroid chordoma	1 (12.5)
Low differentiated chordoma	1 (12.5)
Dedifferentiated chordoma	0
Mean follow-up (months)	22.78
Adjuvant radiation therapy	8 (100.0)

Complications required surgical treatment. CSF - Cerebrospinal fluid

data were collected. The surgical team was composed of a senior neurosurgeon and an ear-nose-throat (ENT) surgeon.

The patient was positioned supine, with his head fixed by a three-pin head holder slightly tilted to the left on the coronal plane and moderately flexed. Optic neuronavigation was acquired. The nasal cavities were preoperatively decongested with naphazoline, applied topically with patties to reduce perioperative bleeding and reduce mucosal damage. All surgical procedures were performed with a 3DHD endoscope. A four hands-two nostrils technique was applied. Middle and inferior turbinates were gently displaced laterally to consent a wide-open view of the surgical corridor. The inferior margin of the middle turbinate, the nasopharynx and the eustachian tubes were the surgical landmarks that guided the surgical approach toward CVJ, always after neuronavigation confirmation since anatomy was displaced by the tumor. An inverted U-shaped rhino-pharyngeal mucosal e muscular flap was harvested with a laser. The rostrum was removed to identify the superior anatomical boundary. The surgical field was defined superiorly by the sphenoid floor, laterally by the eustachian tubes, and inferiorly by the upper part of the oropharynx. Once the pharyngeal tuberculum was drilled, and the pharyngobasilar fascia was opened, the lower third of the clivus was drilled with a 3-mm coarse diamond burr, and the underlying lesion involving the anterior arch of C1, was completely removed. There was no intradural invasion nor intraoperative CSF leak. Then, the nasopharyngeal flap was repositioned and fixed with fibrine glue. Pressure was applied inflating a 14-F Foley catheter to keep the reconstruction in place until the scar began to form. It was removed 4 days after surgery. A progressive improvement in headaches was observed. The postoperative contrast MRI revealed that intralesional total removal was successfully achieved [Figure 1d-f]. Brainstem and upper spinal cord resulted decompressed. At discharge, no neurological impairments were observed. Histopathological examination confirmed the hypothesis of classic chordoma, and the patient was scheduled for proton beam radiation therapy. At a 2-year follow-up, patient was free from tumor recurrence.

Case 2

A 14-year-old male patient with 6-month history of headaches, recurrent otitis and sleep apnea episodes, presented for an ENT evaluation due to an expanding left palatal mass. No focal neurological symptoms were complained. Contrast MRI showed an extensive skull base neoplasm with polylobate margins, located in the left paramedian paravertebral space, extending from the clivus toward the left anterior portion of C1 arch, involving the left occipital condyle and both C0-C1 and C1-C2 left joints [Figure 2a-c]. CT scan revealed that there was gross asymmetry between the two joints on a coronal view <50% unilateral destruction of left occipital condyle. An endoscopic endonasal transclival procedure
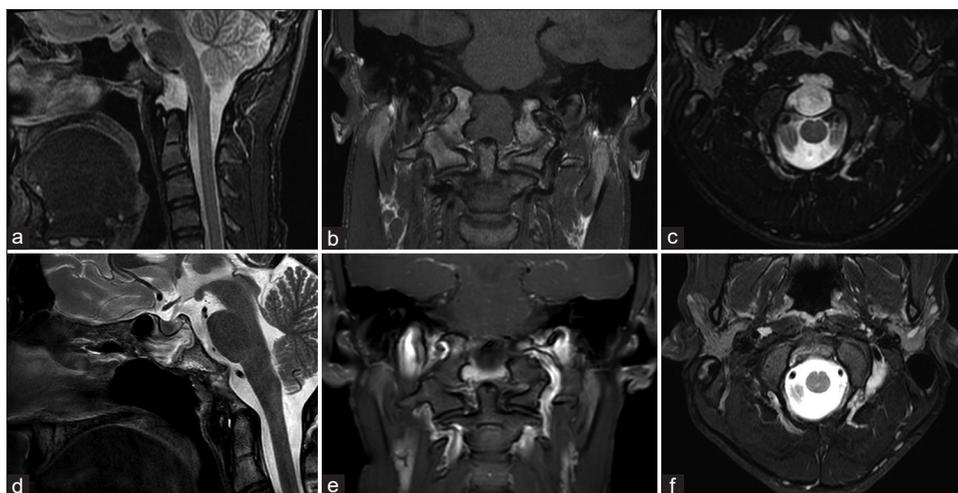
Figure 1: Case 1, preoperative sagittal (a), coronal (b), and axial (c) magnetic resonance imaging views of a C1 chordoma delimited anteriorly by C1 anterior arch and posteriorly by the atlas cruciate ligament. Postoperative sagittal (d), coronal (e), and axial (f) magnetic resonance imaging views showed tumor GTR and brainstem decompression
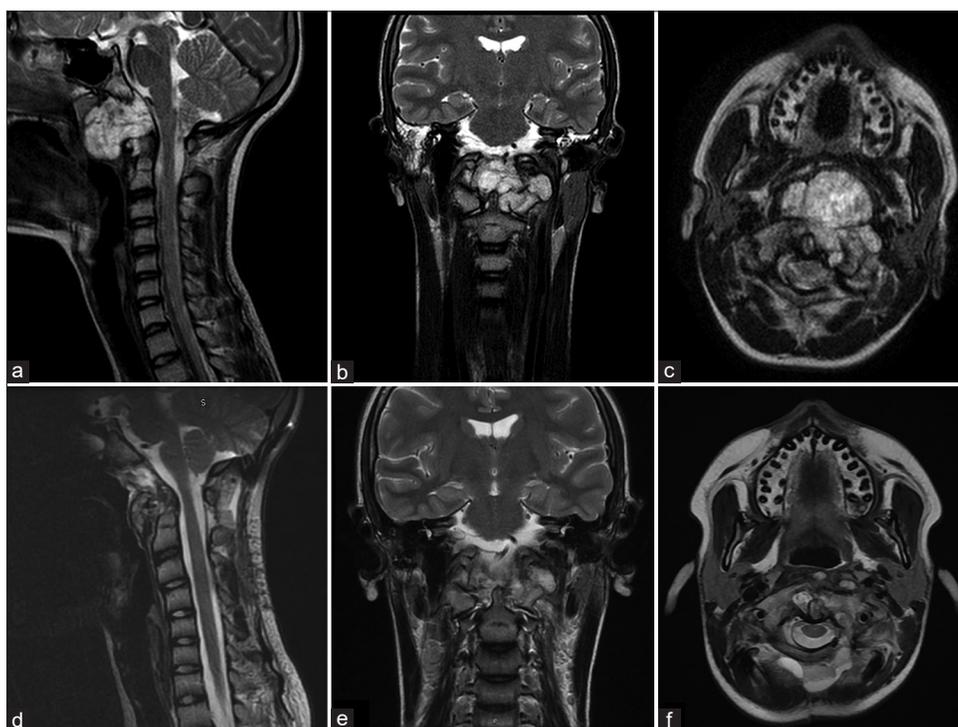

Figure 2: Case 2, preoperative sagittal (a), coronal, (b) and axial, (c) magnetic resonance imaging views of a low differentiated chordoma with polylobulated margins, located in the left paramedian paravertebral space, extending from the lower clivus to the left anterior portion of C1 arch with left occipital condyle and left C1 articular mass involvement. Postoperative sagittal (d), coronal (e), and axial (f) magnetic resonance imaging showing tumor GTR

followed by a posterior approach with a C0-C3 fixation was planned. A 3D preoperative reconstruction was obtained from cervical CT scans, from which individualized 3D-printed guides were developed for the placement of C2 pedicle screws[14,15] [Figure 3a].

First surgical step

The operating room setting and patient positioning for endoscopic step was previously described (case 1).

All procedures were performed with intraoperative neuromonitoring (IONM). After nasal cavity decongestion, middle and inferior turbinates were lateralized, the posterior aspect of nasal septum was removed, and the rostrum was drilled. A right Haddad nasoseptal flap (NSF) was harvested with a laser. The rhino-pharyngeal mucosa was incised and reflected to consent the tumor visualization. Tumor margins were checked with neuronavigation system, and partial circumferential dissection of the mass was performed. The

extreme lateral part of the tumor was tightly attached to the pharyngeal muscles. Therefore, only internal debulking of the mass was performed followed by centripetal dissection of tumor margins. Left condylectomy and C1 anterior arch drilling were performed because of the involvement of the left occipital condyle and the left anterior C1 hemiarch. At the end of the procedure, the dura was preserved, and no CSF leakage was observed. The NSF was placed to cover the occipito-cervical junction and then secured with fibrin glue. The rhino-pharyngeal mucosa was reflected back in its original position and held tight by a 14-F Foley catheter.

Second surgical step

The patient was positioned prone, and his head was fixed with a three-pin head holder. No modification of IONM was detected after patient re-positioning. A midline skin incision from the inion to C3 spinous process was performed. Dissection was carried out in a subperiosteal fashion to expose occiput, C1, C2, and C3 posterior elements. A rigid plate was fixed to the occiput with bicortical screws. C1 vertebra was excluded from the fusion due to its disease involvement. The patient-matched targeting guides were docked on the C2 vertebra, and pedicle screws were inserted, while C3 lateral mass screws were positioned with a fluoro-assisted technique. The left posterior arch of C1, infiltrated by tumor, was removed. A pair of precontoured rods were placed along the screw heads. Cancellous bone was laid on the midline between the occiput and the C2 to promote fusion.

Postoperative course was uneventful. Postoperative cervical CT scan confirmed the extent of tumor removal and assessed the accuracy of screw placement [Figures 3b and 4a-c].

Figure 3: Case 2, cranio-vertebral junction fixation preoperative model (a) composed by a rigid plate fixed to the occiput, C2 patient-matched pedicle screws, C3 lateral mass screws and preoperative-contoured rods placed along the screw heads. Postoperative three-dimensional computerized tomography reconstruction (b) of cranio-vertebral junction fixation complex matching the preoperative three-dimensional model

Subsequently, the Foley catheter was removed 3 days after surgery, and no CSF leakage was detected during ENT evaluation. The patient was discharged without further neurological disfunctions. Pathology returned as low differentiated chordoma. Postoperative enhanced MRI did not show any tumor residual [Figure 2c-f], and proton-beam radiation therapy was then performed.

Case 3

A 45-year-old patient presented with an 8-month history of rhinolalia and dysphagia, and cervical spine MRI revealed a retropharyngeal prevertebral mass. A biopsy was performed which carried out diagnosis of chondroid chordoma. Contrast MRI better defined the destroying polylobate mass which was 50 mm × 22 mm large and located into the prevertebral space, involving the C1 and C2. Laterally, it reached and included the two vertebral arteries, with a greater extension on the right side. No spinal cord compression was detected [Figure 5a and b].

After neurosurgical evaluation, a preoperative vertebral arteries occlusion test showed good unilateral compensation for both vessels. Given the location and vascular involvement, the lesion was considered high risk for en bloc excision. Hence, after a careful multidisciplinary evaluation, an intralesional removal of the lesion followed by proton beam radiation therapy was preferred. In this case, a proper reconstructive strategy was considered crucial, in order to provide adequate support after the removal of the entire C2 vertebra. In order to better replace the C2 anterior support and ensure a proper fixation, a 3D printed custom-made implant was projected. Thus, using high-resolution cervical CT images as guide, an accurate full-scale 3D printed prosthesis made of trabecular titanium was obtained.

Then, two-staged surgical strategy was planned: First, a posterior cervical approach, in order to achieve C2 decompression and C0-C4 fixation, followed by an anterior approach to remove the tumor and to place the 3D custom made prosthesis. Even in this case, all the surgical steps were performed with IONM.
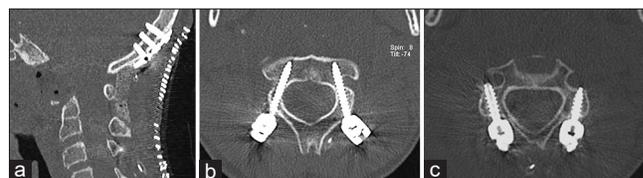

Figure 4: Case 2, postoperative sagittal computerized tomography (a) demonstrating cranio-vertebral junction fixation with a rigid plate fixed to the occiput with bicortical screws. Computerized tomography axial views of C2 patient-matched pedicle screws (b), and C3 lateral mass screws (c)

First surgical step

the patient was placed in a prone position, with head fixed in neutral position by a three-pin head-holder. After baseline CT intraoperative acquisition, the posterior elements of the spine were exposed through a midline incision, from the inion to C4 spinous process. C3 and C4 lateral mass screws were inserted with the aid of neuronavigation system. The C2 spinous process was removed, and bilateral laminectomy was performed, followed by partial bilateral pediculectomy. The posterior component of tumor bulk, located on the right side of the dural sac, was removed. Vertebral arteries were carefully freed in an inferior toward superior fashion. Tumor removal was performed until C3 upper endplate was displayed. Intra-operative CT control confirmed the effective size of the resection and showed adequate screws positioning. Then, the occipital plate was positioned and was connected to the screw with precontoured rods of appropriate length. The system was tightened, supplemented with autologous bone. IONM remained unchanged throughout the entire operation.

Thus, an anterior approach with resection of the remaining tumor was carried out the day after.

Second surgical time

The patient was placed supine with head fixed. Before surgery, a tracheostomy was performed. A right oblique submandibular incision was marked. The sternocleidomastoid muscle, the internal jugular vein, and the common carotid artery up to its bifurcation were exposed. The accessory nerve and the hypoglossal nerve were identified and preserved. Laterocervical lymph nodes were dissected and sent to pathology. The parapharyngeal space was then smoothly opened, and a bulky polylobate mass was spotted and removed, trying to avoid locoregional dissemination. C2-C3 and C3-C4 complete discectomies were performed, and C2 body with its articular masses was removed in an intralesional fashion with a high-speed drill, until the anterior arch of C1 was clearly defined. The 3D printed custom-made titanium prosthesis was positioned, firmly matching superiorly with the anterior arch of the C1 and inferiorly with the superior endplate of C3. Then, the prothesis was secured with three screws placed within C3 body. Cancellous bone was added to promote fusion inside the space obtained by the previous discectomies.

The postoperative course was complicated by pulmonary aspergillosis and an episode of acute pancreatitis, but both were completely solved at discharge. Postoperative radiograms revealed a stable circumferential construction that were anatomically well aligned, while no evidence of tumor residual was observed at the MRI [Figures 5c, d and 6a-c]. The histopathology examination confirmed the diagnosis of chondroid chordoma, and no lymph node involvement was reported.

The patient presented severe dysphagia, which required a nasogastric tube first and a gastrostomy later. Moreover, although a complete bilateral XII nerve palsy was observed in the immediate postoperative period, it slowly improved in the weeks after surgery until complete remission at discharge. The tracheostomy was weaned and removed by postoperative day 35.

The patient received proton-beam radiation therapy and at a 12-month follow-up, and there were minimal residual neurological deficits with no observable tumor regrowth.
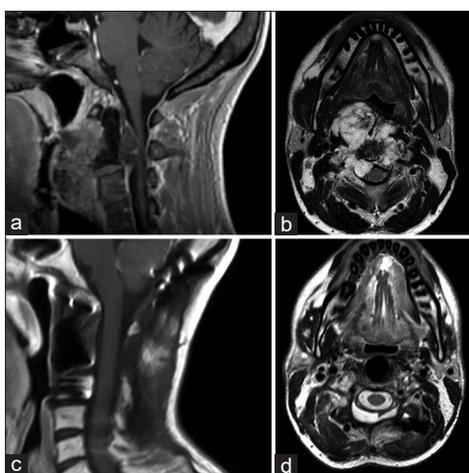

Figure 5: Case 3, preoperative sagittal (a) and axial (b) magnetic resonance imaging views of a retropharyngeal prevertebral chondroid chordoma, involving C1 and C2 vertebral body, extending in the retropharyngeal space from C2 to C7, and involving both vertebral arteries. Postoperative sagittal (c) and axial (d) magnetic resonance imaging views demonstrating no evidence of tumor residual, pharynx decompression and vertebral arteries patency
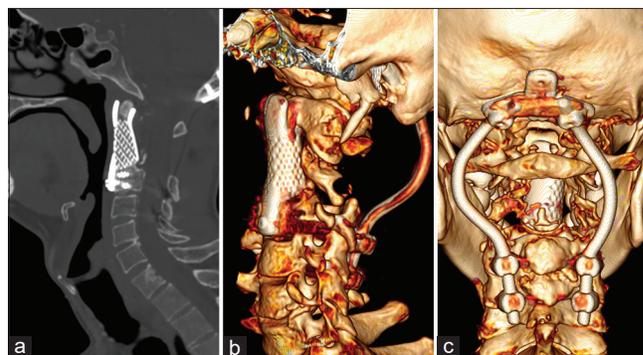

Figure 6: Case 3, postoperative computerized tomography sagittal view (a) and three-dimensional computerized tomography reconstruction (b and c) showing the three-dimensional printed custom-made titanium C2 prosthesis (a and b), firmly matching superiorly with the anterior arch of C1 and inferiorly with the superior endplate of C3. The prothesis was then secured with three screws placed within C3 body, and the occipital plate connected to the screws with appropriate length and precontoured rods (c)

DISCUSSION

Chordomas are rare primary bone tumors which arise from embryonic remnants of the notochord. Although they can originate anywhere along the skeletal neuroaxis, they most commonly occur at the spine extremities, being the clivus, the sacrum, and spine the most frequent locations. Upper cervical spine involvement was described with an incidence of 3%–7% in different series.[1,16,17] Given these critical locations and the high rate of loco-regional recurrences with consequent related morbidity, identifying the best surgical and oncological management of chordomas is a real challenge.[3,18-21]

The optimal management of chordomas is still debatable and controversial. Notably, different strategies have been proposed for chordomas involving skull base and CVJ compared to other locations since *en bloc* resection is not considered feasible in these regions. The anatomical location and the proximity to critical neurovascular structures, indeed, represent the major constraint in achieving complete tumor removal.[17,22] A meta-analysis of 23 retrospective studies by Di Maio at al., reported that the best outcomes in terms of progression-free survival and overall survival were observed in gross total resection group.[12] However, in a recent international survey regarding the management of mobile spine chordomas, Dea *et al*. underlined an existing variability across different centers worldwide.[23]

Currently, given the impossibility to perform *en bloc* resection for CVJ chordomas, the treatment of choice lies in surgical intralesional removal, with the aim to ensure maximal exposure and to perform maximal safe tumor resection, followed by a focused radiation therapy, being in this more similar to the treatment of metastatic spine tumor.[24,25] However, *en bloc* resection, when feasible, and pre-or post-operative radiotherapy should be considered mostly for mobile spinal chordomas.[1,4,22,26-28] Surgical planning should be made according to location, size, and tumor extension to enable postoperative radiotherapy, and it should be tailored to each patient.[1,28] The extent of resection is the most important factor in choosing the surgical strategy: the approach should allow maximum removal of the tumor, if not total removal with the lowest possible morbidity rate.[6-9,12,17,19,23]

Thus, while EEA has represented one of the most important novelties, able to improve the extent of resection of CVJ chordomas, the choice of adequate reconstruction strategy, being both able to guarantee CVJ stability and to allow further radiation therapy, is still a matter of debate.[29-32]

Endoscopic endonasal advantages

In the reported series, the majority of cases underwent surgery through a 3D EEA. In the last decades, endoscopy proved to reduce traditional surgical invasiveness in skull base tumor surgery and potentially in spine surgery,[33,34] while 3D technology has improved hand-eye coordination and the ability to identify anatomic structures.[35,36]

In the last years, EEA has been increasingly adopted to treat midline tumors with no significant lateral extension; EEA, indeed, is not suitable when anatomical compartments harboring chordomas are too lateral or too inferior.[17,22,37-39] In the reported series, EEA allowed direct surgical access, with no extensive destruction of anatomic structures and, besides, it provided a wider operative view, with minimal access corridor, allowing to reach the whole clival region until C2 vertebra, above the boundary defined by the rhino-palatine line.[40,41]

As Fernandez-Miranda *et al*. reported in their algorithm, for tumors located in the midline, EEA offers a safer and more direct anatomic route in terms of avoiding injuries to the neurovascular structure. As the lesion starts to spread laterally or inferiorly, an open approach or a combination of endoscopic and open approaches in stages should be taken into account.[17,42]

An anterior-lateral submandibular approach should be considered when chordomas involve primarily the anterior-lateral cervical spine and the CVJ with a prevalent extradural extension. It gives access to anterior arch and lateral mass of C1, C0-C1 joint, ipsilateral occipital condyle, body and articular mass of C2, and other inferior cervical segments.[43]

For chordomas involving the craniocervical junction, a gross total resection was not always feasible due to the necessity to preserve cranial nerves and cervical nerve roots as well as to protect the carotid and vertebral arteries. Additionally, it could only be carried out with the risk of endangering spinal stability.[4,30,32,44]

Cranio-vertebral junction instability and need for reconstruction

Chordomas were considered particularly high risky to require occipito-cervical fusion because of their aggressive behavior and tendency to arise from or in close proximity to the occipital condyles, C1 and C2 vertebrae.[32] Kooshkabadi *et al*. showed that EEA resection greater than 75% of the occipital condyle significantly increases the risk of CVJ instability, requiring subsequent fixation.[32,45]

Even the atlanto-axial complex involvement could lead to CVJ instability. The main function of C1 vertebra is to support and cradle the base of the occiput at the atlanto-occipital joint, contributing to approximately fifty percent of neck flexion-extension while limiting lateral displacement of the occiput. The C2 vertebra, instead, is the primary weight-bearing bone of the upper cervical region. The hallmark feature is its odontoid process, representing the principal attachment point for the soft tissues that stabilize the atlanto-axial junction. The C1-C2 joint is responsible for about 50% of the rotational motion of the cervical spine. Hence, tumor involvement of these bone structures or their surgical removal could compromise CVJ stability.[46-49]

Moreover, the tumor could involve surrounding soft tissue, like the alar ligament, the apical ligament, the cruciate ligament, and the tectorial membrane. Moreover, surgical procedures could also damage the occipito-cervical ligamentous complex, indeed, if the ligaments become dysfunctional, instability ensues, because ligaments play an integral role in maintaining CVJ stability.[50,51]

Therefore, CVJ instability should be suspected if a CVJ chordoma extends beyond the limits of an EEA; if the foramen magnum is removed, the medial corridor of an EEA will lead to tectorial membrane disruption and apical ligament, increasing the risk to jeopardize cranio-cervical stability.[32]

Necessarily, when CVJ instability ensues, the surgical strategy should be complemented by a direct secondary approach and, the choice of appropriate surgical timing for occipito-cervical fusion is essential to prevent instability-and fusion-related morbidity.[32]

In this series, 3 patients required CVJ fixation due to tumoral involvement of critical structures which could lead to surgically related instability.

Although the need for CVJ fixation could represent the major issue when facing these tumors, the need to define the correct time of fixation (i.e., before or after tumor removal) and the choice of the type of reconstruction (i.e., materials) represent debatable arguments.

While performing CVJ fusion after the first surgical step of tumor removal could allow to limit instability induced after extensive tumor resection, it increases the risk for spinal cord damage in the window period between tumor removal and fixation. Therefore, in these cases, patient positioning for fixation needs to be achieved with extreme caution (e.g. by using IONM) after tumor resection, in order to avoid instability-related neurogenic shock and spinal cord injury.[43,52,53] In this series IONM was always used and allowed surgeons to safely re-positioning the patient when a subsequent posterior approach was required.

On the other hand, when occipito-cervical fixation is performed before tumor removal, more undisrupted bone is available for fusion, and anatomical landmarks and bone implants interface for fixation– if not destroyed by the chordoma– result intact. Also, since the CVJ is already fixed, there is no risk of spinal cord injury during patient positioning and if one surgical approach is not adequate for complete tumor removal, an additional surgical approach can be performed.[52]

In this series, occipito-cervical fusion was performed after tumor removal in two cases; no positioning-related complications were detected [cases 2 and 4, Table 1]. One case required occipito-cervical fixation before the main surgical step: the custom made anterior vertebral prosthesis in fact was projected with the final amount of cervical lordosis [case 3, Table 1].

Moreover, when tumor removal required subsequent occipito-cervical fixation, the radiation scatter, due to the implants should be considered for postoperative radiation therapy, especially when anterior column reconstruction is performed. Many manufactured metals used for prostheses could absorb radiation, consequently decreasing radiotherapy effectiveness.[54-57] Carbon fiber implants have been developed and used in spinal oncology with the aim to reduce artifacts and scattering effects while maintaining adequate mechanical properties.[58,59] However, carbon fiber instrumentation is available mostly for thoracolumbar spine, while surgical experiences for CVJ complex reconstruction are far from being sufficiently described. Boriani *et al*. recently described an interesting technique for subaxial cervical spine posterior fixation after tumor removal by using a hybrid combination of titanium sublaminar bands and carbon fiber/PEEK rods.[60]

Furthermore, when anterior column reconstruction was required, the use of trabecular titanium represented a viable option: Compared to standard titanium which shows a more favorable profile in reducing metal artifacts and absorption than being more suitable for a proper postoperative radiation therapy with particles. Furthermore, evidence reported satisfactory biomechanical properties and an adequate elastic modulus closer resembling the bone.[61] The use of a 3D-printed technology was preferred to ensure a proper fixation closer to the physiological anatomy of C1-C2 complex.[62]

Moreover, even the titanium rods used in cases 2 and 3, were countered in a laterally convex fashion to reduce artifacts and scatter subsequent radiations.[63]

In this series, the patient who required an anterior cervical implant due to tumor involvement was chosen to use a full-scale 3D-printed vertebral prosthesis made of porous titanium to allow following radiation treatment [case 3, Table 1].

The role of radiation
In order to achieve stabilization of the residual disease and to prevent further recurrence, surgical removal of the chordoma should be followed by adjuvant radiation therapy.[3,12,18,19,23,64] In this series, all patients underwent radiation after surgery.

Postoperative radiation can decrease local recurrence, but a longer interval between surgery and radiation, as well as gross disease present at the time of radiation, could be adverse prognostic factors.[58] Therefore, patients should undergo radiation therapy in the early postoperative stage, prior to disease recurrence or progression.[65] The role for radiation therapy for chordomas remains incompletely described, and there is no full agreement between centers.[23,66] Adjuvant treatment with radiation therapy may improve local control and potential overall survival. However, the proximity of the operative bed to critical structures, such as the spinal cord and the exiting nerve roots, has the potential to add considerable toxicity.[6,67] Moreover, higher doses are needed to achieve local control, considering the relative resistance of chordomas to radiation.

Jin *et al.* have recently investigated the effectiveness of high-dose stereotactic radio surgery in order to reduce the need for *en bloc* removal and its related surgical toxicity, showing durable radiological control and effective symptom relief with an acceptable toxicity in patients with primary chordomas as either a definitive or adjuvant therapy.[28]

Particle therapy, including proton beam radiation, have unique physical properties that may spare normal tissues from unnecessary exposure.[58,61] Proton beam therapy could be advocated for chordomas for its ability to deliver high doses while sparing adjacent neural structures.[26,68,69]

No valid chemotherapeutic agents for chordoma treatment have been described, but many recent studies focused on target therapy for spine tumor, with the aim to try to inhibit specific molecules and their pathways, which are known to be implicated in chordoma development and progression, such as EGFR, PDGFR, mTOR, and VEGF.[38,70-75]

Limitations
Principal limitations of this study are due to its retrospective nature. Moreover, this is a small case series with the aim of highlighting only the role that endonasal endoscopy could play in the treatment of CVJ chordoma, and the relevant role of surgical reconstructive planning, especially when a complex location (i.e., the CVJ) is involved.

The follow-up, although acceptable, is still too short to reach any definite conclusion about overall tumor control and hardware failure. Nevertheless, the extent of removal and the safety profile of endoscopic approach resulted to be comparable to those reported in previous literature, and this was the substantially the aim of the paper. At the same manner, the small size of the series did not allow to provide absolute indications regarding the best reconstruction technique, but it shows the safety and the effective of the reported ones.

CONCLUSIONS

The treatment of CVJ chordomas remains challenging. EEA could be a valuable option as it offers a safer and more direct anatomic route allow to avoid injuries to the neurovascular structure, although when chordomas spread laterally or inferiorly, an open approach or a combined approach should be taken into account. Moreover, when CVJ stability is jeopardized by tumor involvement or surgical procedures, a complementary posterior approach needs to be considered. Tailored preoperative plan should play a key role to achieve maximal resection and allowing safe and effective postoperative radiation therapy.

Informed consent
We obtained patient consent and parents' consent for patients ages below 16 years for scientific use of their personal data. Furthermore, as we used nonexperimental data and accordant to common literature clinical methods, no specific authorizations were required for this study by our Ethics Committee.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

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