Skull base chordomas - emphasis on surgical strategy and recurrence-free survival

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Abstract

Background and aim. Chordomas arise from remnants of the notochord. The aim of this study is to report a series of cases with operated skull base chordomas, with reviewing clinical data, assessing surgical strategy and outcome.

Methods. We performed a 13-year retrospective study, between 2009 and 2022, in which we included patients operated for skull base chordomas.

Results. There were 6 males and 9 women, mean age 52.8 ± 16.55 years. Tumor site was clivus (13 patients), left cavernous sinus (one case) and sphenoidal sinus (one case). We performed endoscopic endonasal approach (18 times), transcranial subtemporal approach and combined approach. We achieved GTR in 8 patients, NTR in 4 patients, STR in 7 patients and biopsy in 1 patient. Grade of resection was associated with recurrence incidence (p=0.002).

Histological exam revealed conventional chordoma in 14 cases, chondroid chordoma in 5 cases and dedifferentiated (chondrosarcoma) in 1 case. Patients' neurological status improved following surgery (p=0.000). Five patients underwent adjuvant conventional radiotherapy.

Five patients presented local recurrence. All recurrences were reoperated using endoscopic endonasal approach. Survival analysis identified grade of resection and adjuvant radiotherapy as predictive factors for recurrence-free survival.

Conclusions. Surgery is the treatment of choice in skull base chordomas. Surgical approach should be tailored according to tumor original site and extensions. Midline chordomas are proper candidates for endoscopic endonasal approach, while lateral lesions require transcranial surgery. Combined approaches should be used in extensive tumors. GTR and radiotherapy prolong recurrence-free survival. Further studies on larger samples of patients are needed.

Keywords: chordoma, notochord, skull base neoplasms, endoscopic endonasal approach

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Background and aim

Notochord, a rod-like structure, placed anterior to the neural tube, is the first organ to arise in the process of differentiation during human embryogenesis [1]. In spite of its important role in inducting neural plate development, notochord arises from mesoderm. It pays a key role in the formation of the longitudinal axis of the embryo and during the embryonal development it transforms into nucleus pulposus of the intervertebral disk [2]. Apoptosis is involved in notochord regression, but in chordomas this mechanism is altered [3]. Chordomas arise from remnants of the notochord, according to a theory proposed by Müller in 1858 [4]. Due to their origin from the embryonal neuraxis, they develop mainly on the edges of the central nervous system, basically in the skull base or sacral bone. Rarely, they can extend caudally to the axial vertebra or rostrally to the lumbar spine.

Virchow described skull base chordomas for the first time in 1846 [4].

Chordomas are rare tumors, usually occurring in the 5th and 6th decades of life. They have an incidence of 0.18-1/1.000.000 persons/year, with slight male predominance [5]. Although they are slow-growing and histologically benign tumors, they have a malignant behavior due to invasion of the surrounding tissue, difficulty of achieving gross total resection (GTR), high tendency of recurrence and possibility to generate metastases [6]. In the WHO 2021 Central Nervous System Tumor Classification, chordomas, including poorly differentiated chordomas, are presented as a single entity of notochordal tumors [7]. In practice, they are generally divided into three histopathological types: conventional, chondroid and dedifferentiated (sarcomatous) [8]. Macroscopically, they present as soft, gelatinous tissue, with a tendency to invade and compress nearby structures, such as bone and soft tissues [9]. Microscopically, they contain pathognomonic vacuolated cells filled with mucin (physaliphorous cells) [10].

Clinical presentation is dominated by cranial nerves deficits, the most common symptom being 6th nerve palsy and symptoms secondary to brainstem compression or cavernous sinus invasion. Radiologically, chordomas are osteolytic lesions, rarely osteosclerotic. The CT-scan reveals an extradural, centrally located, well-circumscribed osteolytic lesion, sometimes with marginal sclerosis. It can contain areas of necrosis, hemorrhage, or rarely calcifications representing sequestration of normal bone. The MRI shows a T1 usually low-intense and a T2 hyper-intense lesion. Contrast enhancement is inhomogeneous, sometimes resembling a honeycomb aspect [11]. Other authors reported lack of enhancement after contrast administration [12].

Differential diagnosis is made with skull base sarcomas, carcinomas, metastases, meningiomas, plasmacytomas, ecchordosis physaliphora, pituitary macroadenoma, epidermoid and dermoid cysts [8,11].

Surgery is the treatment of choice in skull base chordomas. Neurosurgeons can use various approaches, based on the location and tumor size. The extent of resection can alleviate symptoms, but it does not provide a recurrence-free survival. Prognosis is poor, due to the chordomas propensity to recur [5].

The aim of this study is to report a series of cases of operated skull base chordomas, review clinical data, assess surgical strategy and outcome, emphasizing on recurrence-free survival. Due to paucity of intracranial chordomas, large cohorts are lacking. The present study aims to improve knowledge on the outcome of skull base chordomas.

Methods

We performed 13-years retrospective study, between 2009 and 2022, in which we included consecutive patients admitted and operated for skull base chordomas in a single neurosurgery department. Positive histopathological diagnosis was done using WHO 2016 and 2021 Central Nervous System Tumor Classifications. Patients who did not undergo surgery or carrying sacral chordomas were excluded. We recorded demographic, clinical and paraclinical data, surgical protocols, outcome and survival. All patients included in the study gave their informed consent to be part of medical research activity. The study was approved by the hospital's ethic board. Statistical analysis was performed using SPSS IBM®.

Results

We found 15 consecutive patients operated for skull base chordomas. (Figure 1 and Figure 2).

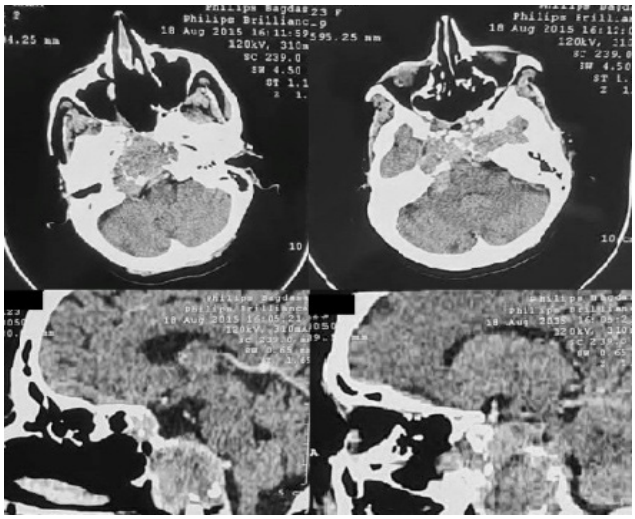

Figure 1. CT axial and sagittal planes. Skull base midline extraaxial tumor, growing from the upper and middle thirds of the clivus, well-defined, osteolytic, extending to the right petrous apex, inhomogeneous, soft mass containing calcifications, highly suggestive for chordoma.

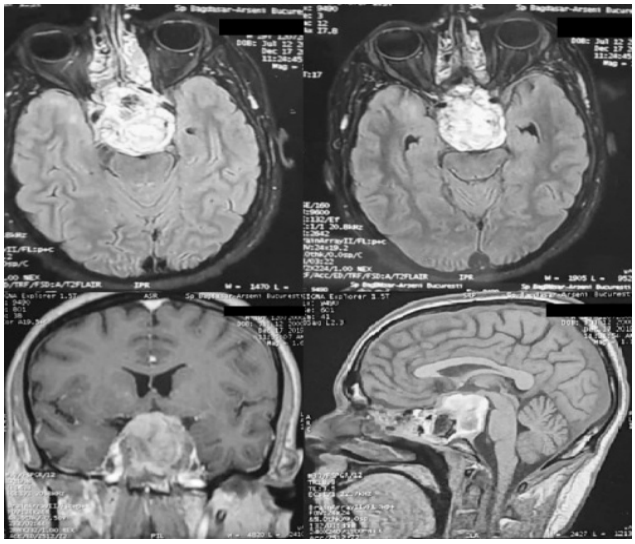

Figure 2. MRI FLAIR-weighted axial, coronal and sagittal planes. Skull base midline extraaxial tumor, also originating from the upper and middle thirds of the clivus, well-circumscribed, heterogeneous, mostly high-signal, growing cranial and dorsal, compressing prepontine cistern and brainstem, highly suggestive for chordoma.

There were 6 men and 9 women, mean age 52.8±16.55 years (median age 54±16.55 years), range 19 to 79 years. Male mean age was 45.83±18.9 years, while female mean age was 57.44±13.98 years. Main symptoms were diplopia (73.33%), 6th nerve palsy (66.67%), vision loss (53.33%), headache (60%), nausea (13.33%), vomiting (6.67%), 3rd nerve palsy (40%), 4th nerve palsy (20%), facial hypoesthesia (6.67%), optic atrophy (6.67%), vertigo (13.33%), hearing loss (6.67%), dysphagia (13.33%) and motor weakness (6.67%).

Thirteen patients had de novo lesions and 2 patients, first operated in a different service, were admitted in our department with recurrences. Original tumor site was clivus (13 patients), left cavernous sinus (one case) and sphenoidal sinus (one case). Both recurrences were located in the clivus. According to Al-Mefty and Borba classification, tumor extension was type I in 5 cases, type II in 9 cases and type III in one case. Sites of tumor extension were sphenoid sinus (53.33%), cavernous sinus (40%), prepontine cistern (40%), perimesencephalic cisterns (20%), sellar (40%), suprasellar (13.33%), third ventricle (6.67%), petrous bone (6.67%), ethmoid sinus (6.67%) and orbit (6.67%).

We performed 13 initial surgeries and 7 operations for recurrences (2 cases first operated in another hospital and reoperated in our department). We preferred mostly endoscopic endonasal approach (18 times), because it is fast, less invasive, extradural and allows direct access for skull base midline lesions, providing a very good view on upper and lower thirds of the clivus.

Resection of a de novo cavernous sinus chordoma was done using transcranial left subtemporal approach. One patient with clival chordoma extending sellar and suprasellar into the third ventricle, cavernous sinuses, sphenoid sinus, posterior ethmoid cells and right orbit underwent a combined approach – transcranial right frontotemporal and endoscopic endonasal approach. We achieved gross total resection (GTR complete resection of the entire tumor as detected on postoperative MRI) in 8 patients, near total resection (NTR resection of >90% of the tumor) in 4 patients, subtotal resection (STR) in 7 patients and biopsy in 1 patient. We achieved GTR in patients with transcranial and combined approaches. From all patients with GTR, two had only clival lesions, four had extensions into the adjacent soft-tissues and two had primary chordomas limited only to soft-tissue (left cavernous sinus and sphenoidal sinus, respectively). All patients with NTR and STR had clival chordomas extending into surrounding soft-tissues. Biopsy was performed in the oldest patient (79 years old woman), with significant comorbidities, with de novo clival chordoma extending into the sella, right cavernous sinus and petrous apex. After biopsy she was referred to adjuvant radiotherapy. Using univariate Mann-Whitney U test, we found a strong correlation between the grade of resection and recurrence incidence (p=0.002).

Histological exam revealed conventional chordoma in 14 cases, chondroid chordoma in 5 cases and dedifferentiated (chondrosarcoma) in 1 case. We had no 30-days mortality. Postoperative course was uneventful, except for two patients with endoscopic endonasal approach who presented postoperative cerebrospinal fluid (CSF) leaks. We performed daily lumbar taps, with CSF leak closure within a few days. Postoperative outcome was assessed using Wilcoxon signed-rank test for preoperative versus postoperative modified Rankin score and Karnofsky performance status scale. Patients' neurological status and quality of life improved following surgery, for both scores (p=0.000 and p=0.001, respectively).

Five patients underwent adjuvant conventional radiotherapy.

Follow-up ranged between 7 to 156 months, with a mean follow-up of 85.03±49.315 months. Ten patients were recurrence-free at follow-up, but 5 of them presented local recurrence. Time to recurrence varied between 7 and 54 months, mean time to recurrence being 32±21.201. Malignant behavior, with large, wide-spread recurrence was encountered in 3 patients. Two patients had only local recurrence, with no tumor extension. All of them were reoperated using endoscopic endonasal approach, alleviating symptoms. Recurrence-free survival was assessed through Kaplan-Meier log-rank (Mantel-Cox) test and Cox proportional hazard regression. Survival analysis identified grade of resection and adjuvant radiotherapy as predictive factors for recurrence-free survival (Table I).

Table I. Recurrence / progression-free survival.

Variables	Log Rank (Mantel-Cox)	Cox regression		
	p-value	HR	95% CI	p-value
Age*	0.647	1.662	0.185-14.904	0.650
Sex	0.172	0.305	0.050-1.848	0.196
Preop. mRS	0.870	1.352	0.438-4.172	0.599
Preop. Karnofsky score†	**0.014**	0.012	0.000-17.461	0.234
Tumor extension	0.132	36.749	0.013-106279.576	0.375
Al-Mefty and Borba classification	0.642	1.105	0.243-5.021	0.897
Grade of resection	**0.019**	2.895	1.267-6.613	**0.012**
Radiotherapy	**0.003**	13.561	1.486-123.767	**0.021**

* (< 50 years vs. > 50 years); † (< 70 vs. > 70); HR hazard ratio, CI confidence interval, mRS modified Rankin score.

Even if preoperative Karnofsky scores seem to influence recurrence-free survival through Kaplan-Maier method, multivariate Cox regression invalided it. There were no metastases at follow-up.

Discussion

Chordomas are rare tumors of the skull base. Considering the scarcity of skull base chordomas, few and far between large studies have been published so far in the literature [3,13-16]. Our study joins the ranks of the select group of surgical studies including at least 15 patients with skull base chordomas reported in the literature [3].

Even if considered slow-growing tumors, and still meeting benign criteria, chordomas behave like malignant lesions, independent of the histological result. Boari et al. support the idea that there are two growing patterns: one with a benign course and one with an aggressive, fast-growing course [3]. However, tumor behavior is the most relevant factor for predicting the benign or malignant feature and guide therapeutic decision. Tumor size, smaller than 35 mm, together with well-defined bony margins, lack of contrast enhancement, no soft tissue extension, absence of dural penetration and low rate of development are factors involved in accepting the benign feature [17]. Malignant lesions were found mostly in the midline location, while benign lesions were associated with lateral locations [18]. Imaging shows more extensive growth and less probability of calcification as higher the malignancy [18]. Age, tumor size and metastasis were associated with low survival rate, while surgery and radiotherapy were associated with higher survival rate [19].

Chondrosarcomas are dedifferentiated chordomas, carrying a sarcomatous compound. Although chondrosarcomas have high grade of malignancy and has been associated with other neoplasia, such as Ewing sarcoma or osteosarcoma, some authors state that chordomas have a higher grade of malignancy and even poorer prognosis than low-grade chondrosarcomas [3].

In theory, chordomas are extradural tumors, usually involving bones, without dural invasion. However, giving the malignant growth pattern, they often destroy bone, infiltrate surrounding structures, penetrate dura mater and grow into the intradural space [20,21]. Intradural growth increases surgical difficulty and morbidity rate. In our study tumor extension went in all skull-base directions; from the clivus the tumor mainly extended posterior (in the prepontine cistern), superior (sellar, retrosellar, suprasellar, into third ventricle), anterior (sphenoidal sinus and ethmoid cells) and lateral (cavernous sinus, orbit, petrous apex).

Dural breach and intradural growth are associated with the difficulty to achieve complete resection, resulting in high recurrence rates, poorer prognosis and higher rate of postoperative complications [14]. Platelet-derived growth factor receptor β (PDGFRβ) expression may predict tumor tendency of invading and penetrate dura mater [14]. Pure intradural chordomas are rare [12,20-22]. One of our patients presented clivus chordoma with large extension into sellar and suprasellar areas, third ventricle, cavernous sinuses, sphenoid sinus, posterior ethmoidal cells and right orbit. The tumor extended high up into the third ventricle. Intraventricular extension of a skull base tumor is an uncommon finding. Smith et al. reported a intraventricular recurrence of a clival chordoma [23]. Such cases with large tumor extension cannot be addressed using a single approach. We recommend combined approaches in order to achieve complete resection in extensive tumors. In recurrences, dural invasion and intradural tumor growth are more frequent.

Tumor resection, as complete as possible, is the gold standard treatment of chordomas. Skull base chordomas pose a great challenge for surgery due to their midline and profound location and vicinity to critical neurovascular structures, such as brainstem, cranial nerves, cavernous sinus, basilar and carotid arteries. An unanimous surgical principle pronounces that surgeons should aim for complete resection, but it is almost impossible to achieve en-bloc resection in skull base lesions. However, GTR is still possible. En-bloc resection has been associated with better outcome compared to piece-meal resection [5]. Surgery must be aggressive the first time because at the initial operation the tumor is soft and there are no adherences.

Surgery of skull base chordomas can be either open transcranial or endoscopic endonasal [24,25]. Each one of these two main routes has its advantages, but also its drawbacks. Proper approach must be tailored according to location and extensions of the tumor. As a rule of thumb, endoscopic endonasal approach offers a large movement range for the surgeon in the sagittal plane, but the transcranial approach shows a wider exposure for cranial base structures, especially for the supratentorial extension.

Subfrontal, frontotemporal and subtemporal approaches are suitable for chordomas of the middle fossa. Lateral and anterior extensions of clival chordomas are also proper candidates. These classical transcranial approaches alone usually do not provide sufficient access to achieve complete resection of clivus chordomas, being used for lateral lesions or to complete resection of lateral and anterior extensions [9,10].

Most skull base chordomas usually arise from the upper and middle third of the clivus [26,27]. Good exposure of upper and middle clivus is provided through anterior transpetrosal, retrosigmoid transpetrosal or combined supra-intratentorial approach. Extended approaches provide extra space for surgery. Sanna et al. extended the transcochlear approach, in order to widen surgical field. Posterior (basilar), anterior, superior (supratentorial) and inferior extensions of the transcochlear approach provide supplementary access to basilar retropharyngeal spaces and foramen lacerum (anterior), 3rd nerve, posterior cerebral arteries (superior) and vertebrobasilar junction and

vertebral arteries (inferior) [28].

For lower clivus we recommend approaches of the craniocervical junction, such as far-lateral transcondylar approach, transoral or submandibular.

Advantages of transcranial approaches are represented by good lateral view, vessels control, good visualization of cranial nerves, and lower risk of postoperative CSF leak. Disadvantages are dural opening, significant brain retraction, encountering cranial nerves and vessels in the surgical field, and higher rate of postoperative cranial nerve palsy. Neuromonitoring is needed for resection of the tumor in front of the brainstem [29].

We used transcranial surgery only in two patients, a subtemporal approach to the middle fossa for a chordoma growing into the cavernous sinus and for a second patient with a highly extensive chordoma with intradural extension, as part of the combined approach. We used transcranial approach in these cases because we needed access laterally, anterior and superior.

Our favorite surgical approach was endoscopic endonasal approach, which we performed 18 times, as de novo surgery or for recurrences. Access to the clival area is best achieved through extended posterior endoscopic endonasal (transclival) approach. It takes advantage of the natural cavities and it preserves anatomy. Extended endonasal endoscopic approach for clival and paraclival chordomas was made, in the sagittal plane, through sphenoid (middle) and infrasphenoid (inferior) corridors [30]. In patients with presellar or conchal sphenoid sinus, bone removal was orientated by neuronavigation. Clivus bone was removed from a cranial to caudal fashion depending on the extent of the tumor. In the coronal plane, lateral extend of the approach is limited by ICA (internal carotid artery). A key point is identifying the vidian nerve, with points to the junction of C2 and C3 segments of the ICA, at the level of the foramen lacerum. Skeletonization of ICA avoids its accidental injuries. Encasement of ICA is a cut-off for complete resection. Angled endoscopes improve visualization of the controlateral tumor.

We favored endoscopic endonasal approach, because, in our experience, it poses important advantages compared to transcranial surgery. It is faster, less invasive and provides a direct surgical corridor to deep midline skull base. Being a completely extradural approach, dissection field is free of vital brain tissue and neurovascular structures, thus avoiding parenchyma or cranial nerves accidental injuries during tumor resection. It has better cosmetic results by avoiding craniotomy and less morbidity. Disadvantages are poor access to lateral tumors, higher rate of postoperative CSF leaks and risk of accidental ICA injuries.

Endoscopic approaches increase the rate of GTR by 10% compared to open surgery [16,24]. Some authors disagree and consider that the rate of resection is similar [13,25]. In our experience, we consider that grade of tumor resection was influenced by tumor extension and consistency.

Skull base reconstruction is a major surgical key step. It is absolutely mandatory and very challenging. Multilayer closure of the skull base, using synthetic materials, fat, muscle, fascia lata or nasal flap, reduces the incidence of postoperative CSF leaks.

Nevertheless, a great challenge in therapy management of chordomas is recurrence. Giving the malignant behavior of chordomas, not even complete resection can guarantee cure. In spite of compete resection, about 50% of them relapse within ten years from initial surgery [13,25,31], making recurrence an expected event. Mean time to recurrence according to the literature [32] was similar to our findings. We recommend redo surgery in recurrences.

In our study, short- and long-term follow-up showed improvement after surgery. Morbidity rate was low, and complications were light. Surgery improves outcome and quality of life.

In these types of tumors, with high tendency of recurrence, association of adjuvant therapies can prolong survival. In our study grade of resections and adjuvant radiotherapy increased recurrence / progression-free survival.

Chordomas are radioresistant lesions, requiring doses higher than 70 Gy. Care must be taken to deliver high dose to the tumor and not to overdose brainstem or optic nerves. Radiotherapy is effective when there is still a tumor remnant, but there are no clues that it can be effective where there is no tumor remnant. Al-Mefty suggests radiotherapy should be done postoperatively in all cases, but Sekhar and Crockard suggest keeping this only where there is a tumor remnant [33]. Other authors suggest radiotherapy should be done before surgery [34]. Overall survival rate is higher for advanced radiotherapy methods (stereotactic, proton-beam and carbon-ion therapy) than for conventional radiotherapy [35]. We recommend radiotherapy in all cases where complete resection was not achieved. Even if they are radioresistant lesions, the only way to prolong survival is to associate adjuvant radiotherapy with as large as possible resection. Chemotherapy is not effective.

Molecular analysis begins to play an increasingly important role in chordomas pathology. Duplication of TBXT gene, which encodes brachyury is the most common genetic abnormality found in both familial and sporadic chordomas [15]. In fact, nonsynonymous SNP rs2305089, a common genetic variant of the TBXT gene, was associated with a significantly higher risk of developing chordomas [36]. Besides this well-established fact, a plethora of other pleomorphic genomic events were reported in sporadic chordomas, such as: mutation in SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin modeling genes (PBRM1, SMARCB1, SETD2, ARID1A) [15,37], mutation of PI3K signaling genes pathway (PIK3CA, PIK3R1,

PTEN) [15,37], gains of chromosome 7p [38], homozygous deletions of chromosome 9p21.3 and 9p21.11 regions harboring epidermal growth factor receptor (EGFR) and CDKN2A/2B gene loci [15,38], deletions of chromosome 22q [15] and inactivation of LYST genes [37]. Genetic abnormalities may predict outcome. Tumor aggressiveness and propensity to recur is higher in cases with deletions of chromosome 9p21 and 22q and alterations of SWI/SNF chromatin modeling genes [15].

Molecular studies are useful not only to understand the pathogenesis, but also to develop novel targeted therapies. Many of these drugs are currently in phase II studies and show promising results. These therapies can be divided according to their mechanisms of action. Inhibitors of EGFR, including EGFR wild-type, are afatinib, erlotinib and lapatinib [39,40] Sorafenib is an inhibitor of vascular endothelial growth factor receptor (VEGFR3) [39]. Drugs intervening with the PDGFR α/β pathway are imatinib, nilotinib, dasatinib and sorafenib [39,41] Therapies targeting PI3K signaling genes, at the level of mTOR, everolimus and sirolimus also show promising results in advanced chordomas [40,41]. Other molecular target medication is palbociclib, an inhibitor of the CDK4/6 cell-cycle pathway [38]. Nivolumab and pembrolizumab intervene with PD-L 1/2 pathway [39].

Association of targeted therapies is more effective than monotherapy [39]. Adjuvant radiotherapy and molecular targeted therapy may be helpful in the treatment of advanced chordoma [39].

Limitation of this study is the small patient sample size without a comparison group, making it prone to bias. Our study is level IV evidence. However, paucity of skull base chordomas limits the possibility of conducting large studies. Molecular panel of the tumors were not available. Further studies on larger samples are needed.

Conclusions

Surgery is the treatment of choice in skull base chordomas. Surgical approach should be tailored according to the tumor original site and extensions, in order to achieve as complete as possible resections. Midline chordomas are proper candidates for endoscopic endonasal approach, while lateral lesions require transcranial surgery. Combined approaches should be used in extensive tumors. Surgery improves the outcome in skull base chordomas. Gross total resection and radiotherapy prolong recurrence-free survival. Age, sex, preoperative status, tumor extension had no impact on recurrence-free survival. However, further studies on larger samples of patients are needed.

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