SCIENTIFIC CULTURE

www.sci-cult.com

SCIENTIFIC CULTURE, Vol. 11, No. 3, (2025), pp. 1918-1938
Open Access. Online & Print

DOI: 10.5281/zenodo. 21687024

CLIVAL CHORDOMA MANAGEMENT: LATEST UPDATES AND BEST PRACTICES

Hany Ibrahim Mohamed Zahy[1*], Mostafa Mahmoud Aboelkhir[2], Ahmed Ibrahim Rewehy[3], Ahmed Adel Ayad[4], Abdullah Hamdan Alsayed Abdelrahman[5], Ezz eldin Elsayed Mohammed[6], Ahmed M. Mohammed Qushisha[7], Alazzazi Rabei[8], Mahmoud Kamel Elawady[9], Mohammed El Shazly Ghaneim[10]

[1]Assistant Professor of Neurosurgery, Faculty of Medicine, Al-Azhar University, Assiut, Egypt. Email: Zahyhany@gmail.com
[2]Assistant Professor of Neurosurgery, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: mostafaaboelkhir81@gmail.com
[3]Assistant Professor of Neurosurgery, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: Dr.rewehy@gmail.com
[4]Assistant Professor of Neurosurgery, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: Ahmedayadneuro1985@gmail.com
[5]Lecturer of Neurosurgery, Faculty of Medicine, Al-Azhar University, Assiut, Egypt. Email: Abdullahneuro7@gmail.com
[6]Lecturer of Neurosurgery, Faculty of Medicine, Al-Azhar University, Assiut, Egypt. Email: ezzmansor54@gmail.com
[7]Lecturer of Neurosurgery, Faculty of Medicine, Al-Azhar University, Assiut, Egypt. Email: drqushisha@gmail.com
[8]Assistant Professor, Department of Neurosurgery, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: elazzazirabei@yahoo.com
[9]Assistant Professor of Neurosurgery, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: drmkawady@yahoo.com
[10]Lecturer of Neurosurgery, Faculty of Medicine, Cairo University, Cairo, Egypt. Email: drshazly.ns@gmail.com

Received: 27/05/2025
Accepted: 27/08/2025

Corresponding Author: Hany Ibrahim Mohamed Zahy (Zahyhany@gmail.com)

ABSTRACT

Clival chordomas are rare, locally aggressive tumors originating from the skull base. Although they are histologically benign, they are locally infiltrative, located adjacent to important neurovascular structures, and have high rates of recurrence that hinder management. To conduct a review on the surgical, radiotherapeutic, and systemic treatments for clival chordomas with practical synthetic algorithms since the last review in 2020 and future directions. A systematic search was conducted using PubMed/Embase/Scopus (2019-2025). There was a strong emphasis on articles utilizing surgical management, particle therapy, stereotactic radiosurgery (SRS), re-irradiation, and systemic or novel therapies during the age range for articles. Expanded endoscopic endonasal surgery, proton and carbon-ion therapy, and systemic targeted agents including EGFR inhibitors,

Copyright: © 2025. This is an open-access article distributed under the terms of the Creative Commons Attribution License. (https://cre-ativecommons.org/licenses/by/4.0/).

VEGFR blockade, and immune checkpoint inhibitors provided opportunities to improve both disease control and functional status. Many systemic targeted agents are still investigational therapies. Maximal safe surgical resection and reconstruction to offer timely particle therapy remains the standard of care; particle therapy offers improved local control over photons. Systemic therapy can be used for salvage; afatinib and immunotherapy provided signals of activity for previously treated patients with chordomas. Future directions for the treatment of chordomas; linac- and LET-guided RT, combined immunotherapies, and biomarker-led systemic reprogramming based on the individual.

KEYWORDS: Clival Chordoma Management, Best Practices.

1. INTRODUCTION

Clival chordomas are rare, slow-growing tumors that originate from embryonic notochordal remnants. They represent only 1–4% of all primary bone tumors and 0.1–0.2% of all intracranial neoplasms, they also represent a substantial portion of the skull base malignant lesions. Although chordomas often exhibit low-grade histology, they possess clinically aggressive characteristics due to their infiltrative nature, and their proximity to critical structures such as the brain stem, basilar artery, and cranial nerves. Due to their rarity, aggressive characteristics, and technical complexity, clival chordomas represent some of the greatest obstacles in skull base neurosurgery.

The clinical presentation is usually subtle, with patients reporting cranial neuropathies, diplopia, or headache once they develop local extension of the tumor. Surgery is the foundation of treatment, and complete surgical resection is the goal, but gross total resection (GTR) is often not possible because of involvement of critical neurovascular structures. Subtotal resection remains an option, but increased risk and high recurrence rates (historically over 50% at 5 years) follow subtotal resection.[1] Conventional chemotherapy yields little to no benefit and although radiotherapy has proven effective at prolonging progression free survival, it is limited by dose-limiting toxicity of adjacent neural tissue.

In the past ten years, there have been significant changes in how surgical management of clival, or skull base lesions are managed. The classical surgical approach, transcranial surgery, allowed exposure of a large field but led to increased morbidity. In contrast, endoscopic endonasal approaches (EEA) have become the surgical approach of choice for midline clival lesions and resulted in a direct surgical corridor that minimized morbidity and lead to improved visualization. Recently, with the evolution in endoscopic surgical technique and development of multidisciplinary surgical teams, combined approaches and staged approaches, incorporating extended EEA and patient specific transcranial or far-lateral approaches, have been developed for giant tumors or tumors that extend laterally.[2] This has demonstrated another paradigm shift toward radicality and increased emphasis on function preservation. The application of intraoperative navigation, Doppler ultrasonography and neurophysiological monitoring has also enhanced safety.[3]

In parallel, advancements in radiation oncology have changed the management of residual or recurrent disease. Proton beam therapy and carbon ion therapy are now the standard of care following maximal safe resection, with increasing evidence supporting improved local control when compared to conventional photon techniques, while considerable effort in molecular biology of chordomas, with focus on brachyury (T gene) expression and the PI3K/AKT/mTOR pathway, has also prompted targeted therapies and immunotherapy to enter early phase clinical trials. Taken together, this represents the transition from a purely surgical paradigm towards a more multimodal precision-based strategy.

Although there has been substantial advancement, the development of recurrence and treatment-related morbidity continues to be significant clinical challenges to a definitive cure. Nonetheless, we do not have one approach that yields guaranteed durable cure. The last five years have seen a rapid evolution of new technologies and concepts in therapeutic approaches. As such, there is an urgent need for an updated synthesis of surgical, radiotherapeutic, and molecular therapeutic approaches. This review will serve as an overview of clival chordoma management with an emphasis on recently published literature in 2024-2025. We aim to highlight developing surgical approaches, developments in the use of advanced radiotherapy, and the emergence of targeted and immune based therapies to help bolster clinical practice and inform future research.

2. EPIDEMOILOGY

Clival chordoma is an infrequent yet clinically important diagnosis. A large genomic-clinical study from several centers in North America (U.S. and Canada) noted an average age of diagnosis for clival chordoma of 45.5 years; clival chordomas accounted for 49.2% of the group, followed by spinal (26.2%), and sacral locations (24.0%) [1]. Interestingly, when

[1] Lee, Sarah et al. "Surgical management of skull base and spinal chordomas: A case series with comprehensive review of the literature." *North American Spine Society journal* vol. 20 100569. 4 Nov. 2024, doi:10.1016/j.xnsj.2024.100569

[2] Munuzuri-Camacho, Marco Antonio et al. "Combined microscopic transoral and endoscopic endonasal approach for a clival chordoma: A case report and literature review." Surgical neurology international vol. 15 383. 25 Oct. 2024, doi:10.25259/SNI_323_2024

[3] Soffer, Justin M et al. "A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis." *Neurosurgical focus* vol. 56,5 (2024): E5. doi:10.3171/2024.2.FOCUS23933

compared with patients with tumors from sacral origin the patients with clival chordomata were younger (mean: 41.8, vs mean 52.3) [4]. The data thus suggests that the clival type generally affects the mid-40s person, since it includes patient demographics for pediatric/adolescent and middle aged patients alike.

The clinical presentation is typically one of masses either effecting neurovascular structures. A national Danish series of 22 clival chordoma patients (2010-2023) reported a mean age at first surgery of 51 years, with the most common clinical manifestations being diplopia (present in 19 of 32 patients evaluated), headache (11), and dizziness (9).[5] Objective neurologic findings of cranial nerve palsy of cranial nerve VI (8 patients), trigeminal deficit (6), and extremity weakness (4) were present . These clinical findings generally exhibit a pattern for clival chordomas with early cranial neurological deficits particularly cranial nerve VI (abducens) palsy often being the harbinger of the diagnosis.

Clival chordoma remains at a high risk of recurrence despite maximal resection and multimodal therapy. In a large meta-analysis of skull base chordomas that included 3,871 patients (4,127 surgeries), the pooled 5-year overall survival (OS) was 73%, with a pooled 5-year progression-free survival (PFS) of 52%. When categorized by grade of resection, those with complete resection (GTR) had a considerably higher 5-year OS (84%) and PFS (74%) than those with incomplete resection (IPR) (OS 52%, PFS 34%).[6] These findings support the clinical tenet that the extent of resection matters, and more aggressive resection is an indication of improved outcomes.

Recurrence is still a significant challenge, even after gross or near-total resection. In their single-centered cohort of 100 primary clival chordoma patients, Liu et al. demonstrated GTR or near-total resection (NTR) and adjuvant radiation therapy: 0 patients experienced recurrence after 48 months post therapy, whereas patients with subtotal resection (STR) plus radiotherapy or biopsy with radiotherapy had recurrence occur in 29% of patients after 48 months.[4] Their 5-year PFS was 51%, and 5-year OS was 84% which reinforces the value of early aggressive intervention and ongoing observation.[7]

Longitudinal data on recurrence outcomes made it clear that patients can live longer with multimodal retreatment options. One retrospective study of 40 patients with recurrent clival chordoma (95 recurrences total) showed that 48% of patients still lived 5 years or longer following the first recurrence with median OS after recurrence of 68 months. Of note, the recurrence management approach times that involved surgery and radiation provided the longest progression-free survival time (median PFS of 120 months) and thus highlights the importance of a multimodal retreatment strategy as the most aggressive and effective option.[8]

3. ANATOMY AND CLASSIFICATION

3.1 Anatomical Segmentation of the Clivus

The clivus is a sloping midline bony surface formed by the sphenoid and occipital bones, and it lies between the dorsum sellae and foramen magnum. To maximize descriptive clarity, and to facilitate surgical planning, the clivus is divided into three anatomical regions (commonly referred to as upper, middle, and lower clivus).

Upper clivus: Extends from the superior aspect of the sella turcica to Dorello's canal. The upper clivus is bordered anteriorly by the dorsum sellae and posterior clinoid processes; the basilar artery and midbrain are posterior to this area.

Middle clivus: Extends from the floor of the sella to the choana. Laterally, the middle clivus is bordered by the paraclival internal carotid arteries, the foramen lacerum, and the petroclival fissure. The anterior border of the prepontine cistern is formed by the middle clivus which includes the basilar trunk,

[4] Koka, H., Zhou, W., McMaster, M.L. et al. Genomic profiles and clinical presentation of chordoma. acta neuropathol commun 12, 129 (2024). https://doi.org/10.1186/s40478-024-01833-9

[5] Skotting, Mikkel Bundgaard et al. "Clival chordomas and chondrosarcomas in Denmark-Outcomes in 33 patients following the national centralization of treatment in 2010." Acta neurochirurgica vol. 166,1 354. 29 Aug. 2024, doi:10.1007/s00701-024-06241-5

[6] Fiore, G., Porto, E., Bertani, G. A., Marcus, H. J., Saladino, A., Pradilla, G., DiMeco, F., & Locatelli, M. (2024). The burden of skull base chordomas: insights from a meta-analysis of observational studies. Neurosurgical Focus, 56(5), E13. https://doi.org/10.3171/2024.3.FOCUS23922

[7] Hong, S., Shinya, Y., Mahajan, A., Laack, N. N., O'Brien, E. K., Stokken, J. K., Janus, J. R., Raghunathan, A., Link, M. J., & Van Gompel, J. J. (2024). Long-term outcome of primary clival chordomas: a single-center retrospective study with an emphasis on the timing of recurrences based on the primary treatment. Neurosurgical Focus, 56(5), E4. https://doi.org/10.3171/2024.2.FOCUS23924

[8] Hong, S., Mahajan, A., Shinya, Y., Laack, N. N., Link, M. J., O'Brien, E. K., Stokken, J. K., Janus, J. R., Ho, T. P., Choby, G., & Van Gompel, J. J. (2024). Longitudinal treatment outcomes of recurrent clival chordomas: a single-center retrospective study. Journal of Neurosurgery, 140(4), 920-928. https://doi.org/10.3171/2023.7.JNS231196

abducens nerve, and pons.

Lower clivus (nasopharyngeal clivus): Extends from the choana (or jugular foramen, depending on the classification) to the foramen magnum. The lower clivus is located next to the medulla, surrounded by cranial nerves IX-XII, the jugular bulb, occipital condyles, and atlanto-occipital joint.

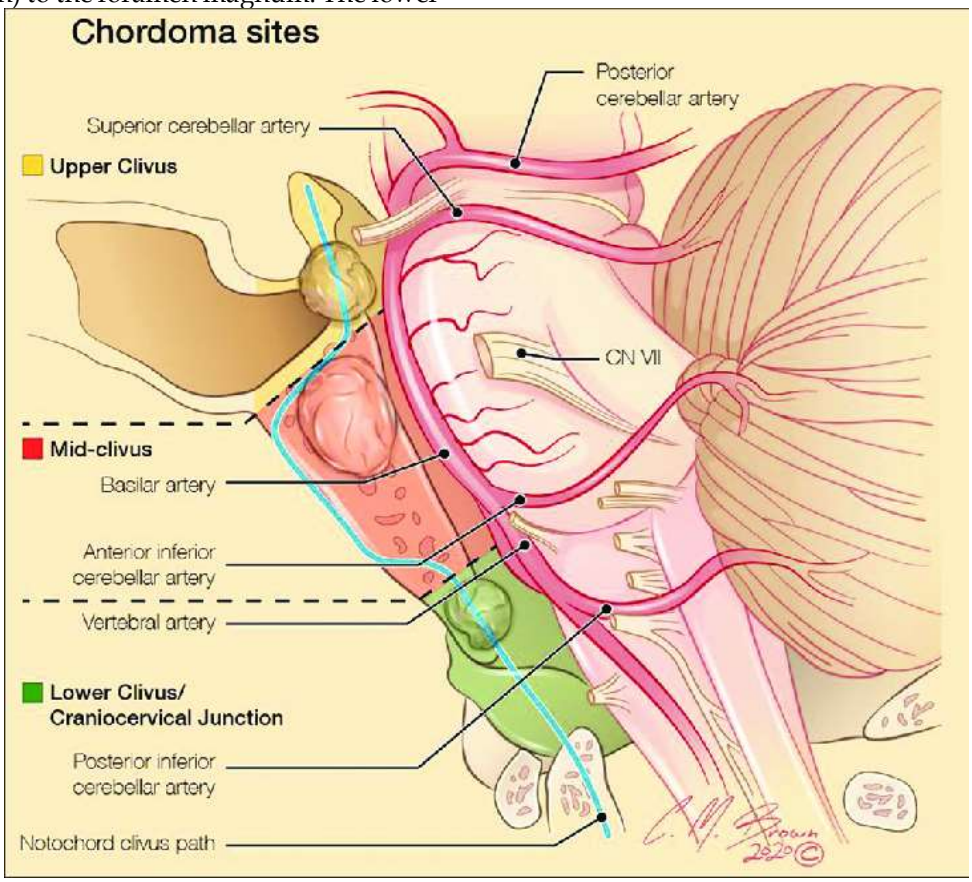

Figure 1: Anatomical segmentation of the clivus into upper (sellar), middle (petrous), and inferior (nasopharyngeal) thirds, with adjacent neurovascular landmarks. Adapted under CC BY-NC-SA 4.0 from Soule et al., 2021.

3.2 Clinical Classification: Types of Clival Chordoma

Using Wang's classification system, clival chordomas can be classified based on their origin relative to two axial planes (sellar floor and sphenoid floor) to create a virtual "Wang's line":

Type I: (dorsal middle & superior clivus): tumors originating above Wang's line; frequently allowing for an Endoscopic Endonasal Approach (EEA).

Type II (ventral middle & superior clivus): tumors ventrally located, but still in the upper or middle zones; access with EEA is still possible.

Type III (inferior clivus): tumors located below Wang's line; these tumors often extend out toward the craniovertebral junction; these cases are aggressive and usually take instability into consideration. The surgical approach for these tumors often has to be an extended approach (combined or staged).[9]

[9] Wang, Quancai et al. "Clinical classification of clival chordomas for transnasal approaches." Neurosurgical review vol. 43,4 (2020): 1201-1210. doi:10.1007/s10143-019-01153-w

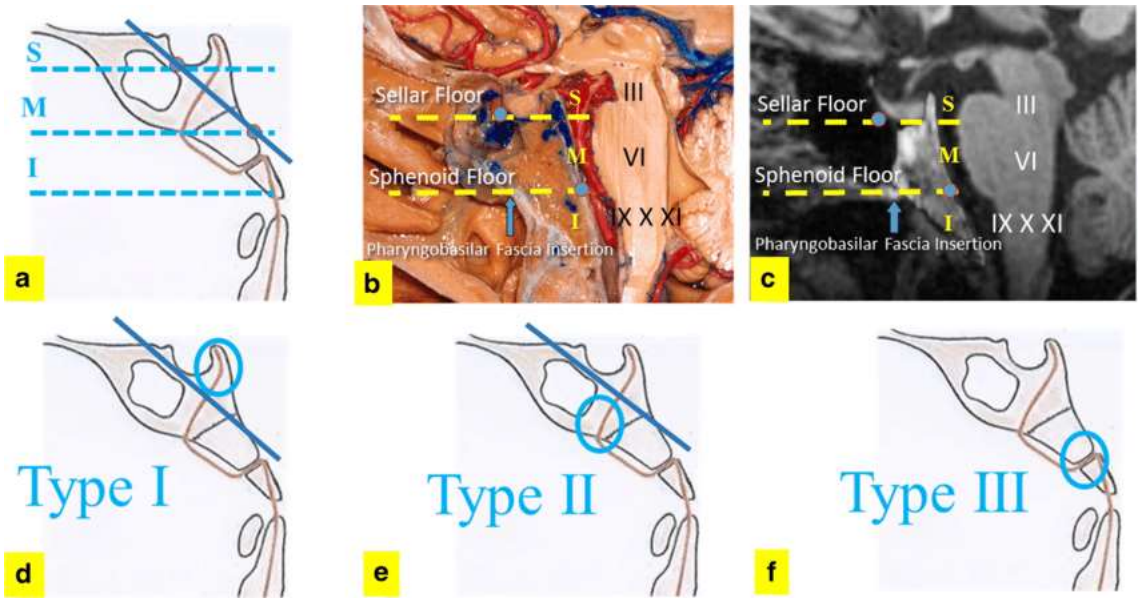

Figure 2: Illustration of clival segmentation (upper/middle/lower) and Wang classification for clival chordomas.

3.3 Classification systems

Various classification systems exist to categorize chordomas based on their extension and complexity. Historically, they were classified based on anatomic zones, tumor invasion, and radiologic characteristics. More recently, grading systems have started to be employed, which have enhanced assessments for surgical feasibility and outcomes.

The Sekhar Chordoma Grading System introduced and validated in recent updates is one of the most widely used. This system considers:

Tumor volume

Location (upper, middle, lower clivus)

Vascular encasement (ICA, basilar artery)

Extent of intradural extension (brain stem compression/invasion)

Prior treatment history

Tumors are then classified into low-, intermediate-, and high-risk categories, with higher scores associating with lower rates of gross total resection (GTR), greater surgical morbidity, and worse long-term control.[10]

4. MOLECULAR AND GENETIC INSIGHTS

In 2024, a pivotal study examined 184 sporadic cases of chordoma in the In the United States and Canada, and reported an average age of diagnosis of 45.5 years. The clival subtype accounted for 49.2% of cases which dominance is notable when cohort studies typically consist of all forms of chordoma. Genomic profiling of their tumor specimens showed that 6q27 as a region was amplified - especially the highly characterized TBXT (brachyury) gene - occurred in 16.3% of clival cases, further demonstrating its role as a molecular driver. Recurrent somatic mutations were reported in PIK3CA (12%), and chromatin remodeling genes such as PBRM1 and SETD2 in non-clival sites. The brachyury transcription factor produced by TBXT still represents a significant diagnostic and oncogenic hallmark in chordoma. Brachyury upregulation and expression is associated with increased EMT expression and invasiveness, and the transcriptional programs associated with EMT. Brachyury overexpression can occur through superenhancer amplification, or without multiplicative focal gene duplication - potentially influenced by regulatory epigenetic events as a result of CDKN2A deletions.[11]

Translational advances have begun indicate brachyury as a therapeutic target. A 2025 published research article utilized advanced structural biology to further identify drug binding sites upon brachyury surface in the field of drug design - enabling an avenue to develop targeted protein degraders (TPD) as a potential treatment approach to precisely eradicate chordoma cells that are sensitive to

[10] Brito da Silva, Harley et al. "Cranial Chordoma: A New Preoperative Grading System." Neurosurgery vol. 83,3 (2018): 403-415. doi:10.1093/neuros/nyx423

[11] Koka, Hela et al. "Genomic profiles and clinical presentation of chordoma." Acta neuropathologica communications vol. 12,1 129. 12 Aug. 2024, doi:10.1186/s40478-024-01833-9

brachyury.[12]

Newer clinical studies have also examined immunotherapeutic strategies directed against brachyury as well, including peptide vaccines. While early stage studies did not demonstrate any meaningful clinical benefits with these studies, newer immune modalities—such as checkpoint inhibition in the context of brachyury-antigen presentation— are in active study.[13]

Overall, these observations together tell a story which is changing: while chordoma was typically thought of as a surgical/ radiation opportunity— there is an increased understanding— and targeting— from a molecular ontogenesis standpoint, with the brachyury process at the center of both biology and emerging therapies.

5. RADIOLOGICAL EVALUATION

Magnetic resonance imaging (MRI) remains the gold standard for the workup of clival chordomas. Clival chordomas typically appear hypo- to isointense on T1-weighted images and hyperintense on T2-weighted images due to the myxoid and vacuolated matrix composition[14],. Clival chordomas have been shown to be heterogeneously enhancing; however, 2022 institutional data (n=28) revealed as many as 64% of cases showed mild to no enhancement at all, challenging the previously held assumptions that non-enhancing lesions were benign.

Computed tomography (CT) provides valuable complementary information, revealing expansile, lytic bone destruction from the clivus and calcific foci, particularly in chondroid variants, or occasionally sequestra [5,7]. The classic "thumb sign", in which a clival chordoma indents the anterior pons on sagittal imaging, can also serve as helpful locational features.[15]Novel MRI techniques and classification systems allow for improved surgical planning and differential diagnosis. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient values (ADC), can assist in differentiating chordoma from chondrosarcoma, which are preliminary but valuable data indicating the ADC values for chordomas is typically lower, indicating higher cellularity. Radiological classification systems that differentiate zones of the clivus, i.e., superior, middle, and inferior zones, can help neurosurgeons determine surgical approaches and estimate resectability, although there are some likely due to advances in technology that will be updated in the 2024-2025 classification systems to differentiate chordomas.[16]

6. SURGICAL MANAGEMENT

Surgical management of clival chordoma involves the principal goal to perform maximal safe cytoreduction so that the adjuvant therapy can get to the site of disease, while also improving long-term outcomes. The most recent data reemphasizes that the only true prognostic factor is "how much is taken out" - gross total or near total excision greatly correlates with prolonged progression free survival and complex vascular and adjacent brainstem involvement paralleled poor outcomes.[17],[18]

The endoscopic endonasal approach (EEA) has established itself as the preferred surgical corridor for midline upper and middle clival chordoma. A National Cancer Database report on the treatment of clival chordoma, published in 2024, demonstrated that the EEA provided equivalent outcomes to an open approach with a comparative reduction in

[12] Jin, Michael C et al. "Unraveling molecular advancements in chordoma tumorigenesis and treatment response: a review of scientific discoveries and clinical implications." Neurosurgical focus vol. 56,5 (2024): E18. doi:10.3171/2024.2.FOCUS2417

[13] Palsetia, Delnaz R et al. "Clival and Paraclival Lesions: A Pictorial Review." The Indian journal of radiology & imaging vol. 33,2 201-217. 11 Feb. 2023, doi:10.1055/s-0043-1761183

[14] Miladinovic, Vesna et al. "Combining morphological and functional imaging parameters to diagnose primary bone neoplasms in the skull base, spine and sacrum." Skeletal radiology vol. 54,2 (2025): 287-302. doi:10.1007/s00256-024-04742-z

[15] Bozer, Ahmet, and Yeliz Pekçevik. "Clival and paraclival pathologies: imaging features and differential diagnosis." Diagnostic and interventional radiology (Ankara, Turkey), 10.4274/dir.2025.243148. 27 Mar. 2025, doi:10.4274/dir.2025.243148

[16] Skotting, M.B., Poulsgaard, L., Springborg, J.B. et al. Clival chordomas and chondrosarcomas in Denmark—Outcomes in 33 patients following the national centralization of treatment in 2010. Acta Neurochir 166, 354 (2024). https://doi.org/10.1007/s00701-024-06241-5

[17] Fiore, Giorgio et al. "The burden of skull base chordomas: insights from a meta-analysis of observational studies." Neurosurgical focus vol. 56,5 (2024): E13. doi:10.3171/2024.3.FOCUS23922

[18] Soffer, Justin M et al. "A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis." Neurosurgical focus vol. 56,5 (2024): E5. doi:10.3171/2024.2.FOCUS23933

hospital stay.[19],[20] Technical contributions, including but not limited to designation and conceptualization of allowable anatomic considerations (i.e., vidian canal, foramen lacerum, and Dorello's canal), neuronavigation, angled endoscopes, intraoperative MRI, and neuromonitoring, have increased the safety and the extent of excision particularly where cranial nerve VI or carotid artery was in ancillary proximity.[21],, In institutional series published in 2024, gross-total resection rates were around 70% as appropriately selected for patients, with manageable cerebrospinal fluid (CSF) leak rates of about 14%, suggesting that the EEA is a now a well-established and reliable midline strategy.

Tumors involving the inferior clivus, extending to the craniovertebral junction (CVJ), or with significant lateral extension beyond the paracival internal carotid artery, are treated in a combined (or staged) fashion frequently. In a 2024 case report and literature review, a successful combined microscopic transoral and EEA resection with occipito-cervical stabilization was described.[22] The early adoption of endoscopic far-lateral infratentorial approaches (e.g. EF-SCITA) has also shown promise for selected complex lesions [8]. Farlateral, transcondylar, or transpetrosal approaches, while more invasive, are nonetheless critical alternatives and adjuncts for larger tumors extending laterally or posteriorly, especially after achieving superior midline control using EEA.[23]

Skull-base reconstruction is a critical component of management, particularly when surgery for clival chordoma typically results in high-flow defects. Modern staged protocols, which involve an inlay collagen matrix, fascia lata graft, and vascularized nasoseptal flap (NSF), sometimes use balloons or lumbar drainage, have reduced reported rates of CSF leaks to less than 10% in many reports. Advances in reconstruction may also mitigate morbidity from CSF leaks, allowing for the earlier initiation of adjuvant radiation therapy[24],[25].

[19] Youssef, A., Morsi, H., Bazak, R. et al. Endoscopic endonasal approach for skull base chordoma. Egypt J Otolaryngol 40, 32 (2024). https://doi.org/10.1186/s43163-024-00594-5

[20] Banu, M. A., Raza, S. M., Amini, M., Seaman, S., Rubino, F., Snyder, R., Patel, S., DeMonte, F., & Conley, A. P. (2024). The role of systemic therapy in advanced skull base chordomas: overview of the current state and the MD Anderson protocol. Neurosurgical Focus, 56(5), E15. https://doi.org/10.3171/2024.2.FOCUS2416

[21] Soffer, J. M., Ulloa, R., Chen, S., Ziltzer, R. S., Patel, V. A., & Polster, S. P. (2024). A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis. Neurosurgical Focus, 56(5), E5. https://doi.org/10.3171/2024.2.FOCUS23933

[22] Valencia-Sanchez BA, Kim JD, Zhou S, Chen S, Levy ML, Roxbury C, Patel VA, Polster SP. Special Considerations in Pediatric Endoscopic Skull Base Surgery. Journal of Clinical Medicine. 2024; 13(7):1924. https://doi.org/10.3390/jcm13071924

[23] Hong, Sukwoo et al. "Long-term outcome of primary clival chordomas: a single-center retrospective study with an emphasis on the timing of recurrences based on the primary treatment." Neurosurgical focus vol. 56,5 (2024): E4. doi:10.3171/2024.2.FOCUS23924

[24] Maroufi, S. F., Fallahi, M. S., Sabahi, M., Maroufi, S. P., & Sheehan, J. P. (2024). Stereotactic radiosurgery in the management of skull base chordomas: a comprehensive systematic review and meta-analysis. Neurosurgical Focus, 56(5), E10. https://doi.org/10.3171/2024.2.FOCUS249

[25] Palavani, Lucca B et al. "Optimizing radiotherapy strategies for skull base chordoma: a comprehensive meta-analysis and systematic review of treatment modalities and outcomes." Neurosurgical focus vol. 56,5 (2024): E11. doi:10.3171/2024.2.FOCUS2413

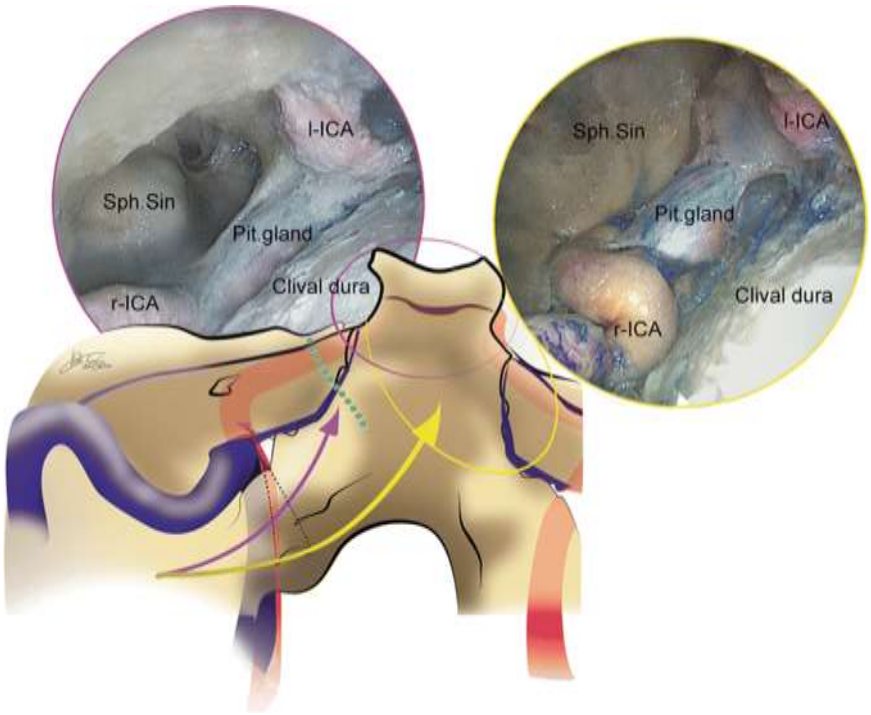

Figure 3: Schematic of EEA corridors: yellow arrow = infra-hypoglossal route toward the clivus and petrous apex; violet arrow = trans-tuberculum jugular corridor. Structures: ICA, cranial nerve VI. Reproduced with permission from Di Carlo et al. in Acta Neurochirurgica.

Vascular injury—especially to the internal carotid artery—is extremely rare but catastrophic. Standard of care has progressed to require intra-op Doppler intra-op confirmation of carotid and vertebral artery status, neuronavigation with angiographic fusion, along with contingencies in case of vascular injury, including packing with hemostatic agents and endovascular backup.[26],[27]

The most recent evidence can be synthesized and expressed as a modular surgical decision-making algorithm. (1) For midline lesions on the upper/middle clivus, use endoscopic endonasal approach (EEA); (2) if the lesion extends inferiorly to the craniovertebral junction (CVJ), use the transoral or posterior approaches; (3) if the tumor crosses borders laterally around vascular structures, add lateral skull-base corridors; (4) if there is vascular encasement, safely debulk the tumor, while preserving neurologic function, so high-dose particle therapy can be given post-operatively; (5) have good reconstruction techniques to prevent cerebrospinal fluid (CSF) leaks [1–11].

This section maps the research landscape of the literature on current advancements in surgical techniques for Clival Chordoma management, encompassing a diverse range of retrospective cohort studies, case series, and systematic reviews. The studies primarily focus on evaluating endoscopic endonasal approaches (EEA) versus traditional open or lateral approaches, assessing surgical outcomes such as extent of resection, morbidity, and progression-free survival. Many investigations also explore the integration of adjunctive technologies like intraoperative imaging and radiosurgery, reflecting a multidisciplinary and evolving surgical paradigm. This comparative analysis is crucial to address the challenges posed by the tumor's complex anatomy and to inform optimal surgical decision-making and patient management. (Table 1).

Table 1: Comparative analysis is crucial to address the challenges posed by the tumor's complex anatomy and to inform optimal surgical decision-making and patient management.

[26] Baig Mirza, Asfand et al. "Systematic Review Comparing Open versus Endoscopic Surgery in Clival Chordomas and a 10-Year Single-Center Experience." Journal of neurological surgery. Part B, Skull base vol. 83,Suppl 2 e113-e125. 22 Feb. 2021, doi:10.1055/s-0041-1722933

Study	Extent of Resection	Surgical Morbidity Rate	Progression-Free Survival	Functional Outcome Scores	Adjunctive Technologies Use
(Alsayed et al., 2023)	Maximal removal via expanded EEA; GTR not always achieved	Low severe toxicity; no grade 3+ radiation toxicity; mortality 17.6%	2-year PFS 76.5%	Not explicitly quantified; survival focus	CyberKnife radiosurgery post-op adjunct
(Butenschoen et al., 2023)	Complete resection in 74% with transnasal endoscopic approach	Low complication rate; CSF leak 3.4%; cranial nerve palsy improved in 75%	Not directly reported; neurological improvement emphasized	Median KPSS 90% post-op	Neuronavigation and classification system for tumor extension
(Zoli et al., 2023)	GTR in 64.7% elderly patients via EEA	Morbidity includes CSF leak 5.9%, meningitis 2.9%, cranial nerve palsy 2.9%	Recurrence in 38.2% at ~38 months follow-up	Ophthalmoplegia improved in 39.1%	Radiation therapy used in 79.4% post-op
(Yoo et al., 2023)	GTR 35.3%, NTR 52.9% via ETCA; combined approaches for lateral extension	Low CSF leak; no leaks reported; fewer cranial neuropathies than combined approaches	10-year PFS 67.4%; 5-year PFS 53% with GTR	Functional outcomes improved with ETCA; cranial nerve recovery noted	Early adjuvant radiation therapy; neuronavigation
(Schnurman et al., 2022)	Radical resection associated with better outcomes; GTR rate not specified	Post-op new cranial nerve deficits reduced with EEA	5-year PFS 55.9%; OS 76.3%	Better pre-op function reduces risk of death and progression	Mostly EEA; adjunct radiation therapy
(Chen et al., 2022)	GTR in 41%, STR 41%, PR 18% via EEA	CSF leak 12%, meningitis 18%; no perioperative deaths	Follow-up showed tumor progression mainly in STR/PR groups	No new neurological deficits post-op	Radiotherapy used in STR group
(Bai et al., 2021)	GTR 40.1%, near-total 34.5% in 284 cases	Post-op complications 14.3%; CSF leak 4.9%	5-year PFS and CSS improved with pre-recurrence RT	Not detailed	Pre-recurrence radiation therapy improves outcomes
(Zacharias et al., 2020)	Wide clearance margins with endoscopic approach; GTR rate not specified	No major complications; safe and reliable	No evidence of disease at 24-32 months	Not quantified	High energy photon radiotherapy adjunct
(McDowell et al., 2021)	GTR in 14/20 pediatric patients; combined approaches for larger tumors	CSF leaks requiring reoperation; cranial nerve palsies reported	20% recurrence during follow-up	Functional outcomes variable; some permanent deficits	Combined EEA and open approaches
(Potter et al., 2024)	Maximal safe resection via expanded EEA standard	Multilayer skull base repair reduces CSF leak risk	Not specified	Imaging guides surgical planning	Proton beam therapy post-op standard

(Lekatompessy et al., 2024)	Successful EEA in two cases; GTR details limited	Not reported	Not reported	Emphasis on interdisciplinary teamwork	Collaborative neurosurgeon-ENT approach
(Maugeri et al., 2024)	Surgical approaches tailored to tumor location; GTR rates variable	Morbidity reduced by tailored approaches	Not specified	Preservation of neurological function emphasized	Advances in imaging and adjuvant therapies
(Youssef et al., 2024)	GTR in 33-43.5% cases; subtotal and partial resections common	Low morbidity; CSF leaks repaired multilayered	Recurrence correlated with residual tumor	Cranial nerve dysfunction mostly unchanged post-op	Intraoperative navigation used
(Schnurman et al., 2022)	Higher radical resection rates with EEA (82.9%) vs open (64.3%)	Similar morbidity rates between EEA and open	No difference in OS or PFS between approaches	Fewer staged surgeries with EEA	EEA increasingly preferred
(Hong et al., 2022)	Gross to near total resection increased to 64% post-2013	Post-op new cranial nerve deficits reduced from 32% to 2.6%	5-year PFS 58%, OS 87%	Improved functional outcomes with multidisciplinary team	Proton beam therapy introduced
(Bai et al., 2021)	GTR 60.8%-75% with growth pattern-based surgical strategy	Not explicitly reported	Not specified	Not detailed	Use of pituitary transposition, clinoidectomy
(Spiessberger et al., 2022)	Endoscopic refinements increase resection rates	Reduced morbidity compared to open	Not specified	Anatomical considerations guide approach	Advanced endoscopic techniques
(Cavallo et al., 2020)	GTR 51.1% with increased EETA use over time	Post-op complication rate 14.3%; CSF leak 4.9%	5-year PFS 62.3%, OS 73.5%	Quality of life preserved	Proton beam therapy increasingly used
(Snyderman & Gardner, 2020)	GTR remains primary goal; EEA improves resection rates	Morbidity minimized with endoscopic techniques	Not specified	Molecular markers may predict prognosis	Proton beam and IMRT standard adjuncts
(Shahein et al., 2020)	GTR achieved via endoscopic transclival approach	No CSF leak; improved cranial nerve function	Not specified	Functional improvement post-op	Endoscopic approach avoids brain retraction
(Passer et al., 2021)	GTR often not feasible; EEA mainstay for skull base	High morbidity with open; EEA reduces morbidity	Not specified	Multidisciplinary approach emphasized	Intraoperative navigation and radiotherapy
(Rychen et al., 2024)	Supramarginal resection feasible; GTR in 23%	Low CSF leak; cranial nerve palsy rates low	Early data suggest reduced recurrence	Functional outcomes comparable	Individualized post-op radiation decisions

(Soffer et al., 2024)	GTR 32.5% overall; no difference between EEA and open	Similar morbidity; EEA reduced hospital stay by 2.1 days	No OS difference between approaches	Not specified	Multivariate analysis supports EEA safety
(Han et al., 2024)	GTR achieved with endoscopic far-lateral supracerebellar approach	No post-op CSF leak or morbidity reported	Not specified	Cranial nerve function recovered	Endoscopic far-lateral approach novel
(Muñuzuri-Camacho et al., 2024)	Combined microscopic transoral and endoscopic approach successful	Not reported	Not reported	Good clinical outcomes	Combined approach tailored to anatomy
(Golub et al., 2024)	OC fusion often needed after extensive resection	Fusion associated with morbidity; predictors identified	Not specified	Stability outcomes important	Surgical planning based on anatomy
(Fava et al., 2021)	EA-FLTA safe and effective; GTR in 55.6%	No approach-related complications	One recurrence at 12 months	Functional outcomes favorable	Endoscope-assisted lateral approach
(Hong et al., 2024)	OCF needed based on condyle integrity; EEA common	Wound issues higher post-OCF	Survival rates similar with/without OCF	Neck pain and ligament status influence	Imaging guides fusion decisions
("Management strategies in clival and cran...", 2022)	GTR and Ki-67 <6% predict longer PFS and OS	CSF leak rate 14.8% after EEA	5-year PFS 52.1%, OS 75.1%	EEA better for upper/middle clival tumors	EEA preferred for suitable lesions
(Passeri et al., 2022)	Similar to ("Management strategies in clival and cran...", 2022); EEA better EOR and lower deficits	CSF leak 14.8% post-EEA	5-year PFS 52.1%, OS 75.1%	Multidisciplinary approach emphasized	EEA gold standard for midline lesions
(Shin, 2023)	Neuroendoscopic surgery improves visualization and resection	Morbidity reduced with endoscopic techniques	Not specified	Radical resection emphasized	Neuroendoscopy advances surgical strategy
(Kadri et al., 2021)	Anterior clivectomy with endoscopic assistance effective	No major complications; low morbidity	Not specified	Microsurgical and endoscopic combination	Neuronavigation aids resection
(Ngu et al., 2021)	Endoscopic endonasal resection safe with low morbidity	Hospital stay 9-23 days; no major complications	Not specified	Post-op recovery good	Combined ENT and neurosurgical team

(Joyce et al., 2020)	Extreme lateral transodontoid approach allows GTR	Post-op cranial nerve deficits improved	Not specified	Functional recovery noted	Open lateral approach for CVJ lesions
(Wu et al., 2024)	Extreme lateral transcondylar approach with fusion	Vertebral artery pseudoaneurysm complication	Not specified	Hypoglossal palsy post-coiling	Complex vascular management required
(Caixeta et al., 2024)	Endonasal endoscopic technique challenging but effective	Morbidity not detailed	Not specified	Aggressive tumor behavior noted	Surgical challenges emphasized
(Glancz et al., 2024)	Higher volume centers achieve better GTR and clearance	Use of intraoperative MRI improves outcomes	Not specified	Multidisciplinary care improves results	Intraoperative imaging critical
(Hong et al., 2024)	GTR/NTR and radiation therapy improve PFS and OS	Low CSF leak (4%) and cranial nerve deficits (7%)	5-year PFS 51%, OS 84%	Younger age and extent of resection important	Radiation therapy standard adjunct
(Baker et al., 2023)	Side-firing intraoperative ultrasound aids resection	Safe, fast, reduces operative time	Not specified	Improved surgical orientation	IOUS adjunct to EEA
(Чернов et al., 2024)	Transoral approach used selectively for CVJ chordomas	Morbidity not detailed	Not specified	Surgical access to CVJ emphasized	Transoral approach specialized
(Mugnier, 2023)	Proton radiotherapy effective post-surgery in pediatrics	Mild/moderate acute toxicities common	5-, 10-, 20-year OS 84%, 78%, 64%	Functional outcomes favorable	Proton therapy well tolerated
(Dallan et al., 2020)	Personalized multiportal approaches for recurrent CCJ chordomas	Morbidity varies with approach	Not specified	Tailored surgical strategies	Versatile approach selection
(Imai et al., 2024)	Reconstructive surgery after recurrence post-carbon ion therapy	Complications include wound dehiscence	Not specified	Salvage surgery improves lifespan	Multimodal treatment needed
(Maroufi et al., 2024)	Stereotactic radiosurgery effective for skull base chordomas	Low adverse event rate (~12%)	55% no progression at follow-up	Symptom improvement in 28%	Gamma Knife predominant

(Reyes-Soto et al., 2024)	Transoral clivus-cervical stabilization effective	Neurological recovery and pain reduction	Not specified	Improved Karnofsky and ECOG scores	PMMA-filled cervical mesh used
(Ogawa et al., 2021)	Extended transsphenoidal approach with GK radiosurgery	Low morbidity; 5-year survival 94.7%	Mean PFS 57.2 months	Early detection improves outcomes	Radiosurgery dose important
(Wang et al., 2022)	EEA improved GTR rate (27.8%-38.9%) vs transcranial	CSF leak common in EEA (36.1%)	OS and recurrence-free survival better in EEA	Karnofsky scores better with EEA	Surgical approach tailored to tumor

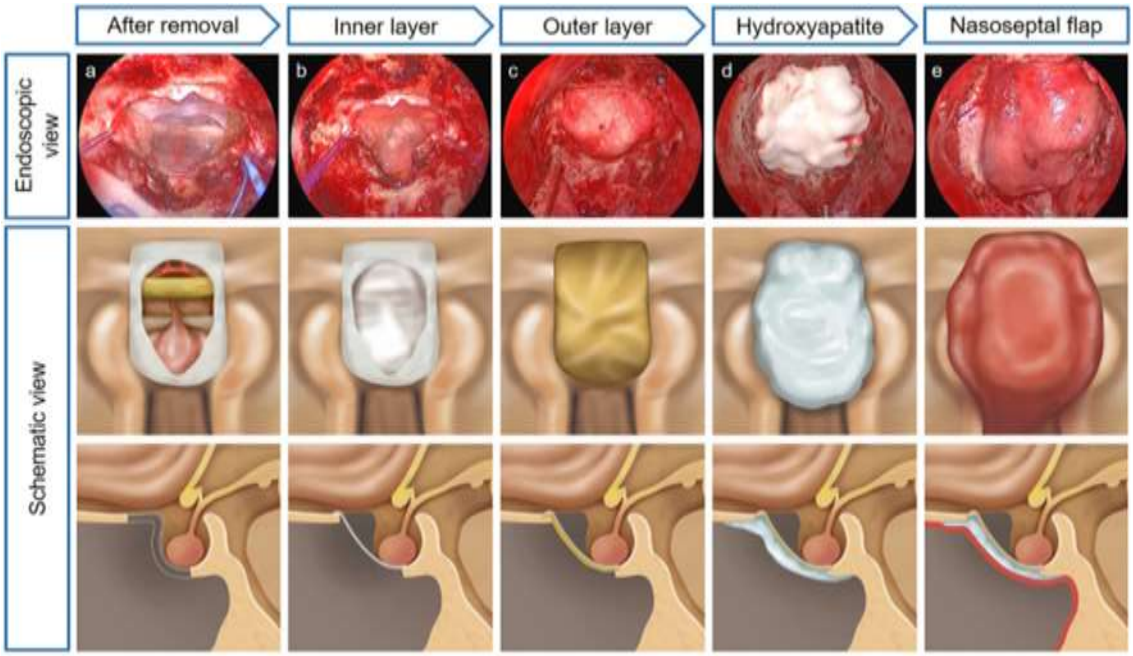

Figure 4; Illustrative sequence of multilayer skull-base reconstruction after clival chordoma resection: (a) collagen matrix inlay over the dura, (b) acellular dermal outlay reinforced with fibrin sealant, (c) injectable hydroxyapatite to seal the bony defect, (d) vascularized nasoseptal flap coverage. Reproduced under CC BY 4.0 from Scientific Reports.

6.1. Reconstruction Techniques for Clival Chordoma Resection

Reconstruction of the skull base after a large clivus chordoma resection is crucial in minimizing complications such as cerebrospinal fluid (CSF) leaks and intracranial infections. A systematic review of 396 endoscopic endonasal approaches for clival chordoma demonstrated that a multilayer reconstruction approach was employed in approximately 75% of cases and included an NSF and grafting in 72% demonstrating an overall postoperative CSF leak rate of 10.1% overall; the use of NSF showed a trend toward lower CSF leak rates (9.4%) but was not statistically significant ($p = 0.273$).[28]

Advancements in technique have yielded even further improvements in outcomes. In a single surgeon high-volume series of patients with high-flow intraoperative CSF leaks, a multilayer closure without nasal packing and lumbar drains, reduced the postoperative leak rate from 19% to 4% (p =

[28] Gupta, Keshav Kumar et al. "Reconstruction and Cerebrospinal Fluid Leaks in Endoscopic Endonasal Approach for the Management of Clival Chordomas-A Systematic Review." Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India vol. 74,Suppl 3 (2022): 4807-4815. doi:10.1007/s12070-022-03114-0

0.006).[29]

A novel technique we have employed for unexpected or large dural defects such as diaphragma sellae tears is termed, the "Fishing method", which uses an artificial dura plug and free mucosal flap, and has shown fantastic results. In this cohort of 15 patients, 14 avoided a postoperative CSF leak and in the one recurrent piece of chordoma, it subsequently needed a multilayer repair after the plug had prolapsed, but ultimately the defect was successfully managed with usage of fascia and balloon support.[30]

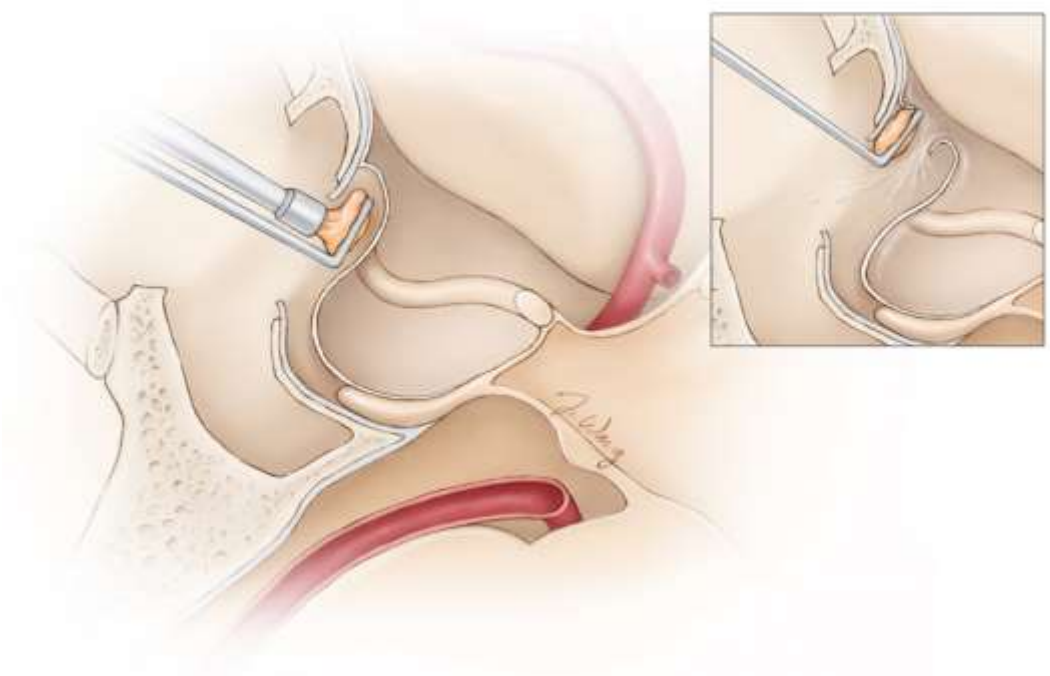

Figure 5; Diagram of endoscopic NSF harvest and placement over clival defect illustrating orientation and coverage. Adapted from Neurosurgical Atlas resources.

6.2. Adjuvant Radiotherapy: Proton and Carbon Ion Therapy

Due to the inherent radioresistance of chordomas and their proximity to critical neurovascular structures, adjuvant particle therapy—either proton beam therapy (PBT) or carbon ion radiotherapy (CIRT)—has emerged as a superior alternative to photons, enabling delivery of high-dose, conformal treatment with reduced toxicity.[31]

As to a large mono-institutional study between 2017-2021 of 44 skull base chordoma patients treated with PBT or CIRT, the 2-year local control (LC) was 95.5%, the 3-year LC was 90.9%, with excellent overall survival (OS) and progression-free survival (PFS) (~93-97). Importantly, no grade ≥3 toxicities occurred, and those with tumor volumes below 49 cc experienced 100% LC.[32]

In a quality-of-life retrospective cohort trial at the Hyogo Ion Beam Medical Center, 24 patients treated with PBT or CIRT had a 5-year LC of 85%, PFS of 81%, and OS of 86%, suggesting improved outcomes for patients with previous surgeries; betweens PBT and CIRT treated patients, toxicity profiles were similar.

[29] Hannan, Cathal John et al. "Multi-layered repair of high-flow CSF fistulae following endoscopic skull base surgery without nasal packing or lumbar drains: technical refinements to optimise outcome." Acta neurochirurgica vol. 165,8 (2023): 2299-2307. doi:10.1007/s00701-023-05581-y

[30] Zhang, Hengsen et al. "Repair of high-flow cerebrospinal fluid leak by combined artificial dura plug and free mucosal flap in 15 cases." Frontiers in surgery vol. 12 1422524. 22 Apr. 2025, doi:10.3389/fsurg.2025.1422524

[31] Rodrigues, A.C.L.F., Tos, S.M., Shaaban, A. et al. Proton beam and carbon ion radiotherapy in skull base chordoma: a systematic review, meta-analysis and meta-regression with trial sequential analysis. Neurosurg Rev 47, 893 (2024). https://doi.org/10.1007/s10143-024-03117-1

[32] Tubin, Slavisa et al. "Proton or Carbon Ion Therapy for Skull Base Chordoma: Rationale and First Analysis of a Mono-Institutional Experience." Cancers vol. 15,7 2093. 31 Mar. 2023, doi:10.3390/cancers15072093

[33]

A meta-analysis evaluating particle therapy versus photon-based therapies consistently reported a 5-year PFS of 76% (95% CI 67-86%) with the baseline modality being PBT, 5-year local controls of 76% (95% CI 59-92%) with the baseline being CIRT, none of the analyses reported a statistically significant difference in 5-year OS; however, important heterogeneity existed (I^2 up to 75–90%) so there was variability among studies.[34]

Technique (Dosage, Delivery) and Toxicity

Particle therapy commonly uses RBE adjusted doses greater than 74 Gy(RBE) to minimize radioresistance inherent in tumors and spare adjacent structures (the brainstem and optic pathways). The Bragg peak allows for rapid dose fall-off and collateral organ sparing, which would not be feasible to the same degree using photons. [35]

The best effect on local control and survival, combining surgery, is recognized as optimal. Still, there are also late toxicities (for example, low-grade radionecrosis) that require careful monthly monitoring long-term, and also, although the number of grade ≥3 toxicities is comparatively rare (less than 4% in some series), all toxicities should be noted carefully.

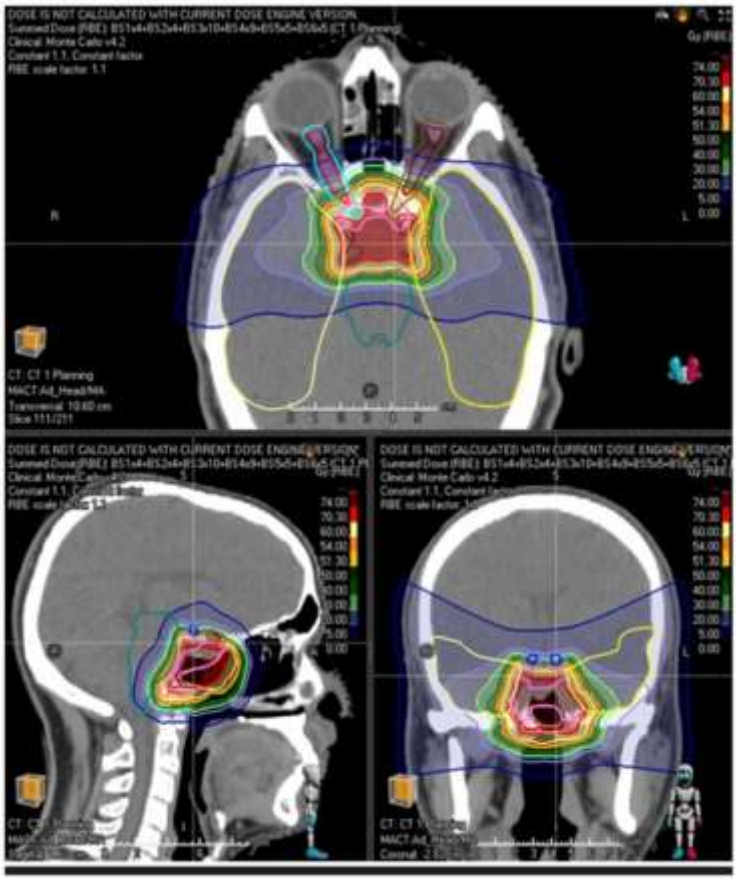

Figure 6: Proton beam therapy plan demonstrating sharp dose fall-off near the brainstem and optic pathways—ideal for skull-base chordoma. Reproduced under CC BY from Cancers.

[33] Takagi, Masaru et al. "Treatment outcomes of proton or carbon ion therapy for skull base chordoma: a retrospective study." Radiation oncology (London, England) vol. 13,1 232. 26 Nov. 2018, doi:10.1186/s13014-018-1173-0

[34] Palavani, L. B., Borges, P., Andreão, F. F., Borges, J., Batista, S., Brenner, L. B. O., Ferreira, M. Y., Reis, P. C. A., Pontes, J., Negri, H., Beer-Furlan, A., Krishna, C., Bertani, R., & Rassi, M. S. (2024). Optimizing radiotherapy strategies for skull base chordoma: a comprehensive meta-analysis and systematic review of treatment modalities and outcomes. Neurosurgical Focus, 56(5), E11. https://doi.org/10.3171/2024.2.FOCUS2413

[35] Rodrigues, A.C.L.F., Tos, S.M., Shaaban, A. et al. Proton beam and carbon ion radiotherapy in skull base chordoma: a systematic review, meta-analysis and meta-regression with trial sequential analysis. Neurosurg Rev 47, 893 (2024). https://doi.org/10.1007/s10143-024-03117-1

6.3. Emerging & Targeted Therapies in Clival Chordoma

The therapeutic landscape for clival chordoma is changing rapidly. A large part of this ongoing research focuses on the brachyury (TBXT) transcription factor, which mediates tumor cell proliferation and survival. Indeed, recent molecular studies (2025) demonstrate that brachyury is able to oncogenic pathways such as the WNT/PCP signaling pathway, TGF-β pathway, and NF-κB, establishing it as an attractive target for therapy. Receptor tyrosine kinases (e.g., EGFR and PDGFR) are implicated in tumor progression by upregulation of brachyury signaling, both of which are also candidates for targeting/ inhibition.[36]

Using targeted agents such as imatinib (PDGFR-β inhibitor) has shown disease stabilization in a large number of patients with advanced chordomas. Individuals treated with EGFR inhibitors (e.g., erlotinib and gefitinib), mTOR pathway blockers, and multi-kinase inhibitors (sunitinib and pazopanib) have had fair success in very small studies - there are not many responses; however, a few individuals experience durable stabilizations in disease progression, suggesting further evaluation of targeted agents are warranted.[37]

Immunotherapy is rapidly becoming a very popular subject in clinical and academic discussions. The preliminary phases of clinical trials with brachyury-targeted therapeutic vaccines (i.e., yeast-based GI-6301 and MVA–brachyury) have shown safe administration and immunogenicity with partial responses in ~5–10 % of patients and stable disease in ~40–50% of patients with a median progression-free survival (PFS) of 8–20 months. While these results so far have not changed clinical delivery, it is reassuring to know that, given the lack of systemic therapies with meaningful efficacy, we have treatments that previously have not been sanctioned by regulatory approval were consistent with what we have seen so far. Other immunotherapeutic instrument - checkpoints inhibitors (anti–PD-1, anti-PD-L1, with or without CTLA-4 blockade) - have induced very rare responses and challenge our current encounter with stability. These responses have been particularly notable in tumors with inflamed microenvironments, greater mutational burden, or studies of combination treatment with radiation or with vaccines have rekindled interest.[38],[39]

Moreover, we are seeing continuing evolution with antibody–drug conjugates (ADCs), CAR T-cell therapies targeting brachyury and newer protein degraders (e.g., PROTACs) designed against TBXT-binding sites emerging from structural studies completed in 2025 will also provide a new frontier in precision medicine to treat chordoma. While preliminary data is severely limited for the immunotherapeutic strategy we will discuss, there is an opportunity here for molecularly informed strategies to explore expanding the treatment of chordoma from merely local control, to systemic control, particularly for persistent unresectable or recurrent disease.[40]

6.4. Prognosis & Future Directions in Clival Chordoma

Clival chordomas remain difficult to treat, and long-term outcomes have demonstrated late recurrences despite aggressive multimodal treatment. A large retrospective cohort study from 2024 (n= 100) reported 5-, 10-, 15-, and 20-year progression-free survival (PFS) rates of approximately 51%, 25%, 17%, and 7%, respectively and overall survival (OS) rates of 84%, 60%, 42%, and 34%, respectively. Importantly, there was significantly improved PFS amongst patients that had gross or near-total resection (GTR/NTR) with timely adjuvant particle therapy (41 months median vs 18 months median, $p < 0.001$) which again emphasizes the enduring role of surgery in a curative-striving context.

A subsequent meta-analysis published in 2025, including nearly 4,000 cases of chordoma in the skull base, similarly affirmed: patients with complete resection report the best 5-year OS (84%) and PFS

[36] Mark, Ian T et al. "MRI enhancement patterns in 28 cases of clival chordomas." Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia vol. 99 (2022): 117-122. doi:10.1016/j.jocn.2022.02.037

[37] Saito, Takashi et al. "Systematic Review and Meta-Analysis of Particle Beam Therapy versus Photon Radiotherapy for Skull Base Chordoma: TRP-Chordoma 2024." Cancers vol. 16,14 2569. 17 Jul. 2024, doi:10.3390/cancers16142569

[38] Chen, Yujia, and Hongwei Zhang. "Immune microenvironment and immunotherapy for chordoma." Frontiers in oncology vol. 14 1374249. 24 Jun. 2024, doi:10.3389/fonc.2024.1374249

[39] Wang, Xiang et al. "Immunotherapy as a Promising Option for the Treatment of Advanced Chordoma: A Systemic Review." Cancers vol. 15,1 264. 30 Dec. 2022, doi:10.3390/cancers15010264

[40] Freed, Daniel M et al. "Emerging target discovery and drug repurposing opportunities in chordoma." Frontiers in oncology vol. 12 1009193. 27 Oct. 2022, doi:10.3389/fonc.2022.1009193

(74%) as compared to subtotal resection (OS 52%, PFS 34% continued follow in order to avoid error). Additional recent data from tertiary centers have suggested similar 5-year OS and PFS rates from 70-86% (OS) and 55-65% (PFS) predominantly when surgical resection is combined with trajectory, high-dose proton or carbon-ion therapy.

The future holds several potential areas for improvement in prognosis:

Molecular prognostic indicators- including brachyury expression, RTK mutation status, and immune microenvironment profiling may open the door for individualized risk-adapted treatment.

Combined modality trials- there are current trials pairing immunotherapies (e.g., vaccines, checkpoint inhibitors) with particle radiotherapy inferring some synergistic immune–radiation effect, particularly in the adjuvant setting.

Increased availability of particle therapy- The more proton and carbon-ion facilities that open around the globe, the more patients will receive definitive high dose radiation, which improves advancement.

Adaptive and multi-institutional clinical trials. The rarity of chordoma promotes collaborative registries and innovative clinical trial designs (e.g., basket/adaptive trials) to increase evidence generation for the developing systemic therapies.

Surviving the long game will necessitate synergistic surgical expertise, systemic approaches guided by molecular insights, and precision radiation that is supported by clinical research infrastructure that adequately manages this rare disease.

7. CONCLUSION

Clival chordomas represent a challenging problem in neurosurgery and oncology due to their challenging anatomy, locally aggressive nature, and high rates of recurrence. Recent technical advances in skull base surgery, particularly advances in microsurgery and endoscopic techniques, have facilitated a safe and more radical approach to resection. Importantly, adjuvant radiotherapy (specifically proton and carbon-ion therapy) have begun to improve long-term local control. Recent advances in molecular characterization (brachyury and alterations of the PI3K/AKT/mTOR signaling pathway) have led to new avenues of targeted therapy and immunotherapy to add to the treatment paradigm.

Despite these advances, prognosis for clival chordomas remain limited due to gross-total resection, treatment resistance (some advanced chordomas show no response to treatment), and lack of systemic therapies (quasi-systemic therapies have not been formally studied yet). Key areas for future research should include the implementation of multi-modality treatment protocols, better prognostic biomarkers for treatment and prognosis, and increased clinical trials for targeted agents. Due to the rarity of the disease, case reports and small case series are difficult to measure scientific rigor, and multi-centered studies and international registries will be imperative to achieving robust evidence.

In summary, the management of clival chordomas is transitioning from a purely surgical and radiotherapeutical approach ultimately toward personalized (biology-informed) treatment paradigms. The combination of new imaging modalities, minimally-invasive surgical avenues, precision radiotherapy, and systemic targeted treatment approaches may improve survival and quality of life for this complex and rare tumor type.

REFERENCES

1. Lee, Sarah et al. “Surgical management of skull base and spinal chordomas: A case series with comprehensive review of the literature.” North American Spine Society journal vol. 20 100569. 4 Nov. 2024, doi:10.1016/j.xnsj.2024.100569
2. Munuzuri-Camacho, Marco Antonio et al. “Combined microscopic transoral and endoscopic endonasal approach for a clival chordoma: A case report and literature review.” Surgical neurology international vol. 15 383. 25 Oct. 2024, doi:10.25259/SNI_323_2024
3. Soffer, Justin M et al. “A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis.” Neurosurgical focus vol. 56,5 (2024): E5. doi:10.3171/2024.2.FOCUS23933
4. Koka, H., Zhou, W., McMaster, M.L. et al. Genomic profiles and clinical presentation of chordoma. acta neuropathol commun 12, 129 (2024). https://doi.org/10.1186/s40478-024-01833-9
5. Skotting, Mikkel Bundgaard et al. “Clival chordomas and chondrosarcomas in Denmark-Outcomes in 33 patients following the national centralization of treatment in 2010.” Acta neurochirurgica vol. 166,1 354. 29 Aug. 2024, doi:10.1007/s00701-024-06241-5
6. Fiore, G., Porto, E., Bertani, G. A., Marcus, H. J., Saladino, A., Pradilla, G., DiMeco, F., & Locatelli, M.

(2024). The burden of skull base chordomas: insights from a meta-analysis of observational studies. Neurosurgical Focus, 56(5), E13. https://doi.org/10.3171/2024.3.FOCUS23922

7. Hong, S., Shinya, Y., Mahajan, A., Laack, N. N., O'Brien, E. K., Stokken, J. K., Janus, J. R., Raghunathan, A., Link, M. J., & Van Gompel, J. J. (2024). Long-term outcome of primary clival chordomas: a single-center retrospective study with an emphasis on the timing of recurrences based on the primary treatment. Neurosurgical Focus, 56(5), E4. https://doi.org/10.3171/2024.2.FOCUS23924
8. Hong, S., Mahajan, A., Shinya, Y., Laack, N. N., Link, M. J., O'Brien, E. K., Stokken, J. K., Janus, J. R., Ho, T. P., Choby, G., & Van Gompel, J. J. (2024). Longitudinal treatment outcomes of recurrent clival chordomas: a single-center retrospective study. Journal of Neurosurgery, 140(4), 920-928. https://doi.org/10.3171/2023.7.JNS231196
9. Wang, Quancai et al. "Clinical classification of clival chordomas for transnasal approaches." Neurosurgical review vol. 43,4 (2020): 1201-1210. doi:10.1007/s10143-019-01153-w
10. Brito da Silva, Harley et al. "Cranial Chordoma: A New Preoperative Grading System." Neurosurgery vol. 83,3 (2018): 403-415. doi:10.1093/neuros/nyx423
11. Koka, Hela et al. "Genomic profiles and clinical presentation of chordoma." Acta neuropathologica communications vol. 12,1 129. 12 Aug. 2024, doi:10.1186/s40478-024-01833-9
12. Jin, Michael C et al. "Unraveling molecular advancements in chordoma tumorigenesis and treatment response: a review of scientific discoveries and clinical implications." Neurosurgical focus vol. 56,5 (2024): E18. doi:10.3171/2024.2.FOCUS2417
13. Palsetia, Delnaz R et al. "Clival and Paraclival Lesions: A Pictorial Review." The Indian journal of radiology & imaging vol. 33,2 201-217. 11 Feb. 2023, doi:10.1055/s-0043-1761183
14. Miladinovic, Vesna et al. "Combining morphological and functional imaging parameters to diagnose primary bone neoplasms in the skull base, spine and sacrum." Skeletal radiology vol. 54,2 (2025): 287-302. doi:10.1007/s00256-024-04742-z
15. Bozer, Ahmet, and Yeliz Pekçevik. "Clival and paraclival pathologies: imaging features and differential diagnosis." Diagnostic and interventional radiology (Ankara, Turkey), 10.4274/dir.2025.243148. 27 Mar. 2025, doi:10.4274/dir.2025.243148
16. Skotting, M.B., Poulsgaard, L., Springborg, J.B. et al. Clival chordomas and chondrosarcomas in Denmark—Outcomes in 33 patients following the national centralization of treatment in 2010. Acta Neurochir 166, 354 (2024). https://doi.org/10.1007/s00701-024-06241-5
17. Fiore, Giorgio et al. "The burden of skull base chordomas: insights from a meta-analysis of observational studies." Neurosurgical focus vol. 56,5 (2024): E13. doi:10.3171/2024.3.FOCUS23922
18. Soffer, Justin M et al. "A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis." Neurosurgical focus vol. 56,5 (2024): E5. doi:10.3171/2024.2.FOCUS23933
19. Youssef, A., Morsi, H., Bazak, R. et al. Endoscopic endonasal approach for skull base chordoma. Egypt J Otolaryngol 40, 32 (2024). https://doi.org/10.1186/s43163-024-00594-5
20. Banu, M. A., Raza, S. M., Amini, M., Seaman, S., Rubino, F., Snyder, R., Patel, S., DeMonte, F., & Conley, A. P. (2024). The role of systemic therapy in advanced skull base chordomas: overview of the current state and the MD Anderson protocol. Neurosurgical Focus, 56(5), E15. https://doi.org/10.3171/2024.2.FOCUS2416
21. Soffer, J. M., Ulloa, R., Chen, S., Ziltzer, R. S., Patel, V. A., & Polster, S. P. (2024). A comparison of endoscopic endonasal versus open approaches for skull base chordoma: a comprehensive National Cancer Database analysis. Neurosurgical Focus, 56(5), E5. https://doi.org/10.3171/2024.2.FOCUS23933
22. Valencia-Sanchez BA, Kim JD, Zhou S, Chen S, Levy ML, Roxbury C, Patel VA, Polster SP. Special Considerations in Pediatric Endoscopic Skull Base Surgery. Journal of Clinical Medicine. 2024; 13(7):1924. https://doi.org/10.3390/jcm13071924
23. Hong, Sukwoo et al. "Long-term outcome of primary clival chordomas: a single-center retrospective study with an emphasis on the timing of recurrences based on the primary treatment." Neurosurgical focus vol. 56,5 (2024): E4. doi:10.3171/2024.2.FOCUS23924
24. Maroufi, S. F., Fallahi, M. S., Sabahi, M., Maroufi, S. P., & Sheehan, J. P. (2024). Stereotactic radiosurgery in the management of skull base chordomas: a comprehensive systematic review and meta-analysis. Neurosurgical Focus, 56(5), E10. https://doi.org/10.3171/2024.2.FOCUS249

25. Palavani, Lucca B et al. "Optimizing radiotherapy strategies for skull base chordoma: a comprehensive meta-analysis and systematic review of treatment modalities and outcomes." Neurosurgical focus vol. 56,5 (2024): E11. doi:10.3171/2024.2.FOCUS2413
26. Baig Mirza, Asfand et al. "Systematic Review Comparing Open versus Endoscopic Surgery in Clival Chordomas and a 10-Year Single-Center Experience." Journal of neurological surgery. Part B, Skull base vol. 83,Suppl 2 e113-e125. 22 Feb. 2021, doi:10.1055/s-0041-1722933
27. Gupta, Keshav Kumar et al. "Reconstruction and Cerebrospinal Fluid Leaks in Endoscopic Endonasal Approach for the Management of Clival Chordomas-A Systematic Review." Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India vol. 74,Suppl 3 (2022): 4807-4815. doi:10.1007/s12070-022-03114-0
28. Hannan, Cathal John et al. "Multi-layered repair of high-flow CSF fistulae following endoscopic skull base surgery without nasal packing or lumbar drains: technical refinements to optimise outcome." Acta neurochirurgica vol. 165,8 (2023): 2299-2307. doi:10.1007/s00701-023-05581-y
29. Zhang, Hengsen et al. "Repair of high-flow cerebrospinal fluid leak by combined artificial dura plug and free mucosal flap in 15 cases." Frontiers in surgery vol. 12 1422524. 22 Apr. 2025, doi:10.3389/fsurg.2025.1422524
30. Rodrigues, A.C.L.F., Tos, S.M., Shaaban, A. et al. Proton beam and carbon ion radiotherapy in skull base chordoma: a systematic review, meta-analysis and meta-regression with trial sequential analysis. Neurosurg Rev 47, 893 (2024). https://doi.org/10.1007/s10143-024-03117-1
31. Tubin, Slavisa et al. "Proton or Carbon Ion Therapy for Skull Base Chordoma: Rationale and First Analysis of a Mono-Institutional Experience." Cancers vol. 15,7 2093. 31 Mar. 2023, doi:10.3390/cancers15072093
32. Takagi, Masaru et al. "Treatment outcomes of proton or carbon ion therapy for skull base chordoma: a retrospective study." Radiation oncology (London, England) vol. 13,1 232. 26 Nov. 2018, doi:10.1186/s13014-018-1173-0
33. Palavani, L. B., Borges, P., Andreão, F. F., Borges, J., Batista, S., Brenner, L. B. O., Ferreira, M. Y., Reis, P. C. A., Pontes, J., Negri, H., Beer-Furlan, A., Krishna, C., Bertani, R., & Rassi, M. S. (2024). Optimizing radiotherapy strategies for skull base chordoma: a comprehensive meta-analysis and systematic review of treatment modalities and outcomes. Neurosurgical Focus, 56(5), E11. https://doi.org/10.3171/2024.2.FOCUS2413
34. Rodrigues, A.C.L.F., Tos, S.M., Shaaban, A. et al. Proton beam and carbon ion radiotherapy in skull base chordoma: a systematic review, meta-analysis and meta-regression with trial sequential analysis. Neurosurg Rev 47, 893 (2024). https://doi.org/10.1007/s10143-024-03117-1
35. Mark, Ian T et al. "MRI enhancement patterns in 28 cases of clival chordomas." Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia vol. 99 (2022): 117-122. doi:10.1016/j.jocn.2022.02.037
36. Saito, Takashi et al. "Systematic Review and Meta-Analysis of Particle Beam Therapy versus Photon Radiotherapy for Skull Base Chordoma: TRP-Chordoma 2024." Cancers vol. 16,14 2569. 17 Jul. 2024, doi:10.3390/cancers16142569
37. Chen, Yujia, and Hongwei Zhang. "Immune microenvironment and immunotherapy for chordoma." Frontiers in oncology vol. 14 1374249. 24 Jun. 2024, doi:10.3389/fonc.2024.1374249
38. Wang, Xiang et al. "Immunotherapy as a Promising Option for the Treatment of Advanced Chordoma: A Systemic Review." Cancers vol. 15,1 264. 30 Dec. 2022, doi:10.3390/cancers15010264
39. Freed, Daniel M et al. "Emerging target discovery and drug repurposing opportunities in chordoma." Frontiers in oncology vol. 12 1009193. 27 Oct. 2022, doi:10.3389/fonc.2022.1009193
40. Brown, N.J., Gendreau, J., Kuo, C.C. et al. Assessing survival outcomes and complication profiles following surgical excision and radiotherapy as interventions for skull base chordoma: a systematic review of operative margins and surgical approaches. J Neurooncol 165, 41–51 (2023). https://doi.org/10.1007/s11060-023-04477-2