Primary Clivus Bone Lesions

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AIM: To address the diagnostic and therapeutic challenges posed by primary clival bone lesions, specifically chordoma, chondrosarcoma, giant cell tumor, and benign notochordal cell tumor, by providing a comprehensive review of their clinical, radiological, and biological characteristics.

METHODS: A systematic review was performed using the Cochrane Library, Scielo, and Medline databases. The search incorporated MeSH terms such as "chordomas", "chondrosarcoma", "giant cell tumor of bone", and "bone neoplasms". From 2630 initial results, 33 studies were selected and categorized by tumor type, histology, clinical presentation, imaging findings, diagnosis, treatment, and prognostic factors.

RESULTS: Despite extensive literature on individual aspects of these tumors, comprehensive reviews encompassing all four primary clival lesions are scarce. These tumors exhibit overlapping radiological features and complex anatomical locations, each with distinct biological behavior. The systematic review highlights the importance of differentiating among these lesions to inform diagnosis and management, as well as the current limitations in evidence-based treatment strategies due to the rarity and complexity of these entities.

CONCLUSIONS: Understanding the key characteristics of primary clival bone lesions is essential for clinicians and neurosurgeons to select optimal diagnostic and therapeutic approaches, ultimately aiming to improve patient outcomes.

Keywords: bone neoplasms; chordomas; chondrosarcomas; giant cell tumor of bone; benign notochordal cell tumor

Introduction

The clivus (Latin for "slope" or "hill") is a bony structure located at the central skull base, formed by the body of the sphenoid bone and the basal occipital bone, which are connected by the sphenoid-occipital synchondrosis. Anteriorly, it is in close proximity to the sphenoid sinus and pharynx; posteriorly, it is adjacent to the basilar artery, pons, and medulla oblongata; laterally, it borders the cavernous sinus, carotid arteries, cranial nerves V through XII, and the internal jugular vein; and in the anterosuperior direction, it is near the pituitary gland in the sella turcica [1–4].

Clival tumors are exceedingly rare, representing less than 1% of all intracranial neoplasms. Among them, chordomas are the most common primary tumors of the clivus, with an estimated annual incidence of 0.08 per 100,000 population [5]. Despite their low prevalence, these lesions are of substantial clinical importance due to their insidious growth, frequent involvement of adjacent cranial nerves and vasculature, and the high complexity of surgical management. Currently, there are limitations in surgical, radiotherapeutic, and systemic treatment options, compounded by the lack of large-scale, high-quality studies in this field, making comprehensive reviews of all clival lesions simultaneously scarce. Thus, the objective of this systematic review is to summarize the current knowledge regarding the diagnosis and treatment of the four primary clival tumors that clinicians and neurosurgeons should be familiar with.

Search Strategy and Selection Criteria

The literature search was conducted on the Cochrane Controlled Trials Register of the Cochrane Library, Scielo, and Medline databases using the MeSH terms "bone neoplasms", "chordomas", "chondrosarcoma", "giant cell tumor of bone" and Title or Abstract terms related to "benign notochordal cell tumor" and "bone neoplasms". ("Bone Neoplasms"[MeSH] OR "Neoplasms, Bone Tis-

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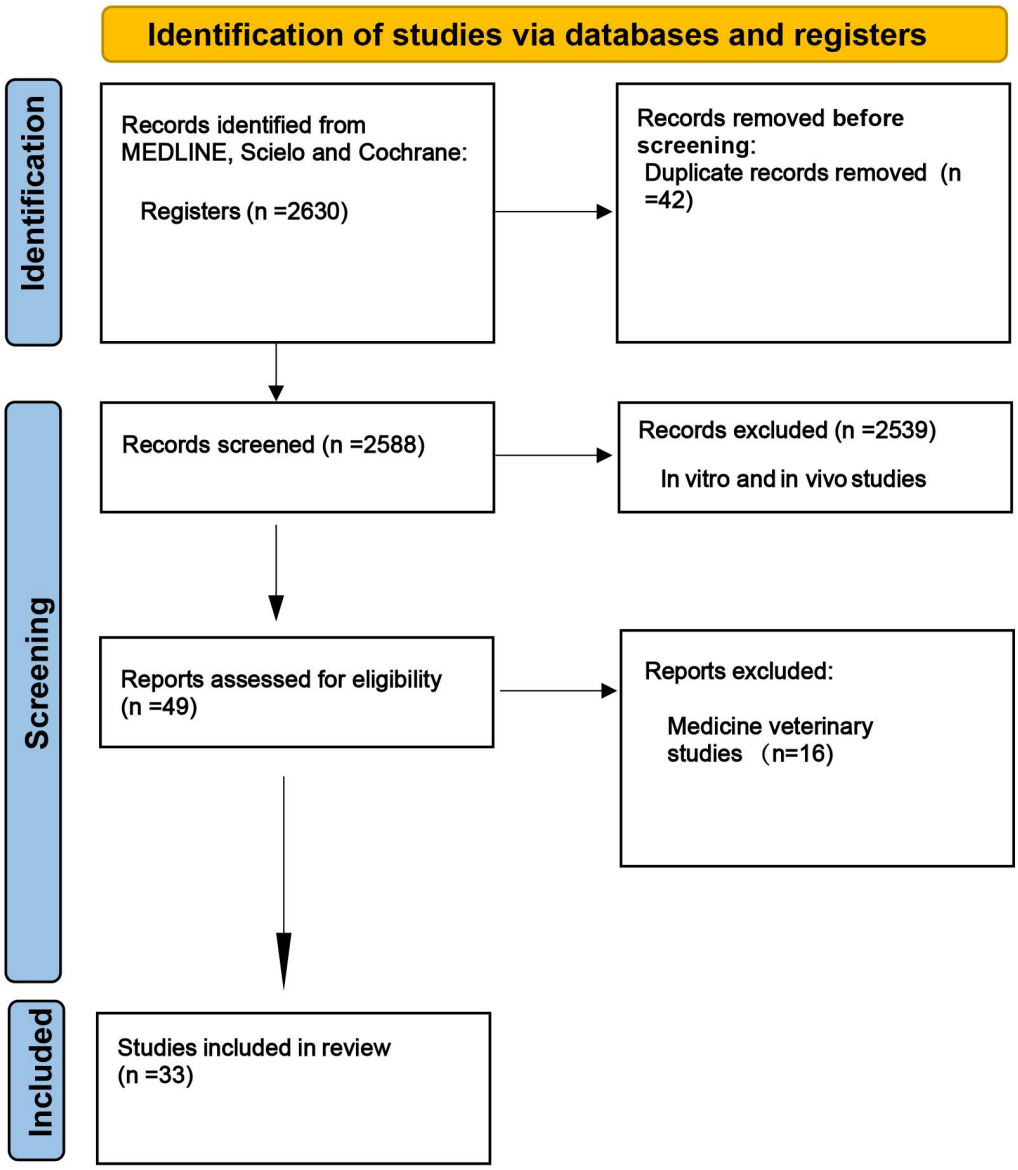

Fig. 1. PRISMA 2020 flow diagram for updated systematic reviews. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

sue"[MeSH]); ("Chordoma"[MeSH] OR "Chondrosarcoma"[MeSH] OR "Giant Cell Tumor of Bone"[MeSH]) AND ("Benign Notochordal Cell Tumor"[Title/Abstract] OR "Benign Notochordal Cell Tumors"[Title/Abstract] OR "Giant Notochordal Rest"[Title/Abstract] OR "Giant Notochordal Rests"[Title/Abstract]). The chronological parameter was publishing date from January 2006 to December 2022, English was the chosen language, and a review of the primary lesions of the clivus was determinant. Clinical trials, open-label studies, and case reports describing relevant patients treated with clivus bone lesions were included.

Titles and abstracts were reviewed by two independent reviewers. The eligibility criteria were experimental, clinical, or review studies on human patients with a primary clival bone lesion (chordoma, chondrosarcoma, giant cell of tumor bone, or benign notochordal cell tumor) aiming to report anatomical, clinical, radiological, immunological, and treatment characteristics of such lesions. Exclusion criteria included studies reporting therapeutic or immunological findings that were based on outdated methodologies or clinical practices no longer consistent with current standards. Screening first by title, abstract, and full text, studies that did not meet those criteria were excluded, and duplicates were removed in the first screening phase. The final eligibility phase included the full-text articles for analysis and collection of data. Table 1 (Ref. [6–38]) summarizes the search results with the main findings of the studies. Fig. 1 shows the step-by-step of a systematic review that was performed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [39]. The

Table 1. Summary of the main findings of studies included.

First author, year	Type of primary clival lesion	Study design	Summary	Citation
Chiarini, 2009	GCT*	Case report	A case report of GCT* involving the middle cranial fossa, originating from soft tissues of the temporomandibular joint.	[6]
Raparia, 2013	Chondrosarcoma	Case report	A 33-year-old man with a growing mass in the right parotid region of his face with an unusual presentation of a benign cartilaginous neoplasm.	[7]
Yin, 2019	Chordoma and GCT*	Retrospective study	A radiomic model based on CT ad multiparametric MRI to distinguish chordoma and GCT*.	[8]
Roy, 2013	GCT*	Case report	A case of clival GCT* presenting with an isolated trigeminal nerve involvement in a 19-year-old man was managed by surgery and adjuvant radiation.	[9]
Notarianni, 2008	GCT*	Case report	A 36-year-old healthy woman presented, reporting a “bump” over the left parietal area that had increased in size over the past six months. Cranial vault metastases can occur and should be considered in a differential diagnosis of bony lesions found in this location.	[10]
Gilani, 2019	GCT*	Case report	A 69-year-old man with a GCT* primary to the femur with metastasis to the occipital skull bone was treated with denosumab.	[11]
Huh, 2018	GCT*	Case report	The first report in the United States on the use of denosumab in treating GCT*.	[12]
Bardakhchyan, 2017	GCT*	Case report	The youngest patient ever reported a progressive skull base and cervical spine GCT* treated with denosumab.	[13]
Louis, 2014	Chordoma	Literature review	Reports the technical nuances, relative indications, and surgical approaches to the sella and parasellar region.	[14]
van der Heijden, 2017	GCT*	Case report	Two cases of pediatric patients underwent metastatic workup and biopsy before the resection of the tumor.	[15]
Company, 2009	GCT*	Case report	A 19-year-old man was seen for progressive visual loss and exophthalmia of the left eye, with a diagnosis of GCT* with sequelae of ophthalmoplegia of the left eye associated with palpebral ptosis and amaurosis.	[16]
Noël, 2006	GCT*	Case report and literature review	Two patients presented with aggressive GCT* that were irradiated by a combination of photons and protons.	[17]
Pelaz, 2008	GCT*	Case report and literature review	A 48-year-old man with hearing loss and facial pain with a tumor in the infratemporal fossa.	[18]
Tamura, 2016	GCT*	Case report and literature review	A 41-year-old man with headache and auditory disturbance with a temporal lesion into the middle cranial fossa.	[19]
Kaya, 2018	GCT*	Case report and literature review	A 56-year-old female with a case of temporal bone GCT* with a typical clinical presentation.	[20]
Jain, 2020	GCT*	Case report and literature review	A case of giant cell tumor of squamous portion in a 38-year-old male.	[21]
Chugh, 2022	GCT*	Case report	A 13-year-old man with a GCT of the occipital bone was treated with total excision surgery and adjuvant radiotherapy.	[22]

Table 1. Continued.

First author/s, year	Type of primary clival lesion	Study design	Summary	Citation
Lu, 2011	GCT*	Case report	A 19-year-old man with GCT* involving the left occipital bone and the petromastoid portion of the temporal bone.	[23]
Roeder, 2010	GCT	Retrospective study	Report of intensity-modulated radiotherapy in benign GCT*.	[24]
Niu, 2020	Bone neoplasms	Clinical practice guideline	The interpretation of core diagnostic and therapeutic approaches to bone cancers.	[25]
Freeman, 2016	GCT*	Literature review	A systematic review and meta-analysis of the effect of radiation and degree of resection on tumor recurrence.	[26]
Karamanakos, 2010	GCT*	Case report	A report of malignant giant cell tumor in the posterior fossa of a neonate.	[27]
McKinney, 2006	GCT*	Literature review	A review of histologic, CT, MRI, and positron-emission tomography/CT features of GCT*.	[28]
Lang, 2017	Chordoma and GCT*	Retrospective study	Characteristics of morphology and MRI features of 39 patients.	[29]
Kashiwagi, 2006	GCT*	Case series and literature review	CT and magnetic resonance findings of GCT* of the skull in 22 patients.	[30]
Yazdi, 2012	GCT*	Case report	Clinical and radiologic findings of a giant GCT* in a patient.	[31]
Aguiar Júnior, 2014	Chordoma	Retrospective study	A cohort of 42 patients with clinical-pathological variables described.	[32]
Mohyeldin, 2014	Clival Lesions	Literature review	Review of clinical presentation, diagnostic identification, and associated adjuvant therapies of this brain location.	[33]
Sekar, 2018	GCT*	Case report	A report of denosumab with neoadjuvant chemotherapy to the treatment of GCT*.	[34]
Gupta, 2018	GCT*	Case report	Four cases of GCT* highlighting the cytological examination.	[35]
Chatterjee, 2016	GCT*	Case report	GCT* of the sphenoid bone in a young woman.	[36]
Pionelli, 2022	GCT*	Case report and literature review	A 14-year girl with a clival GCT* was treated with denosumab after relapse.	[37]
Biermann, 2013	Bone neoplasms	Literature review	This review brings reports of new sections on giant cell tumor of bone (GCT*) and chordoma.	[38]

GCT*, giant cell tumor of bone; MRI, magnetic resonance imaging; CT, computed tomography.

Rayyan Qatar Computing Research Institute (QCRI) was used as a tool in the management of data and the exclusion, inclusion, and selection of the articles.

This systematic review followed the PRISMA 2020 guidelines, and the completed PRISMA 2020 Checklist is provided in the **Supplementary Material**.

Primary Clivus Bone Lesions

The following sections will present four clivus bone lesions: chordomas, chondrosarcomas, benign notochordal cell tumor (BNCT), and giant cell tumor of bone (GCT), along with the main aspects of each one regarding clinical presentation, diagnosis, treatment, and prognosis.

Chordomas

Chordomas are rare tumors that arise from remnants of the notochord throughout the neuroaxis, including the skull base, vertebral bodies, and sacrum. These tumors account for 1 to 4% of primary osseous tumors, with an estimated age-adjusted incidence rate of 0.08 per 100,000 individuals [40]. They are 1.6 times more common in males, with a mean age of diagnosis of 58 years. Historically, the distribution was described as 50% in the sacrococcygeal region, 35% in the skull base, and 15% in other vertebrae, with a higher frequency in the lumbar spine [40]. A recent study, however, has reported the following distribution: 32% in the skull base, 32.8% in the spine, and 29.2% in the sacrum [41].

Chordomas are classified into three histological variants [42]:

- Conventional: Characterized by osteolytic, multilobulated areas separated by fibrous septa. Each lobe consists of cords of clear cells (physaliphorous cells) with vacuolated cytoplasm and mucin deposits within a mucinous matrix. The nuclei are round or oval, dark in color, and display atypia and pleomorphism (Fig. 2).
- Chondroid: Less aggressive, with areas showing typical chordoma histological features and other regions resembling chondrosarcomas. Some areas exhibit cartilaginous tissue.
- Dedifferentiated: More aggressive, behaving as a high-grade tumor with increased atypia and a sarcomatous component (Fig. 2).

Genomic Alterations and Immunology

Chordoma cells are positive for cytokeratin, epithelial membrane antigen (*EMA*), and S-100 protein [43]. The *Brachyury* nuclear transcription factor, a known chordoma marker, when associated with cytokeratin, has a diagnostic sensitivity and specificity exceeding 90% [44]. *Brachyury* is expressed by the *T* or T-Box Transcription Factor T (*TBXT*) gene located on *chromosome 6* and plays a key role in notochord development. Overexpression of *Brachyury* is considered an oncogenic driver of the tumor and is associated with a poorer prognosis. As a result, *Brachyury* appears to be a potential therapeutic target, and vaccines targeting this factor are currently being investigated in phase II clinical trials.

The *CDKN2A* gene and the *PTEN* gene encode tumor suppressor proteins. Evidence suggests that mutations or loss of expression of these genes are involved in chordoma tumorigenesis and progression [45].

The immune microenvironment of chordomas, including the interaction between tumor cells and tumor-infiltrating lymphocytes, may provide insight into how the tumor evades immune responses, predict tumor aggressiveness, and help develop novel immunotherapeutic targets. A study has identified the presence of myeloid cells, cytotoxic T cells, and natural killer (NK) cells [46]. Tumor-associated macrophages produce tumor necrosis factor alpha (TNF-α), an inflammatory cytokine that can promote tumor growth and progression. TNF-α increases the expression of programmed death-ligand 1 (PD-L1) on tumor cells. PD-L1 is an immune checkpoint molecule that binds to the programmed death-1 (PD-1) receptor on T cells, inducing T cell anergy, preventing the apoptosis of regulatory T cells, and allowing immune evasion and tumor progression. PD-L1 expression has been identified in chordoma tissue and is associated with advanced stages of the disease. Other immune checkpoint molecules, such as cytotoxic T lymphocyte antigen 4 (CTLA4), which inhibits T cell-mediated immune responses, are also expressed in chordomas [46]. These molecules represent potential targets for immunotherapy, including the use of anti-PD-L1 monoclonal antibodies such as Avelumab [45].

Platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) bind to tyrosine kinase receptors, activating signaling cascades, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway, which regulates cellular proliferation and survival. High expression of *Brachyury* has been correlated with upregulation of PI3K in skull base chordomas. As such, PI3K/AKT/mTOR inhibitors are being explored as potential future therapies. The insulin-like growth factor 1 (IGF-1) pathway, which also activates the AKT/mTOR pathway, is another promising therapeutic target for chordomas [45].

Several studies are investigating immune-based therapies for chordomas, including *Brachyury*-targeted vaccines, nivolumab and pembrolizumab (anti-PD-1 antibodies), and ipilimumab (anti-CTLA4 antibodies). Table 2 (Ref. [47–52]) shows the genetic role and pathway in chordoma progression. However, evaluating the outcomes of these therapies remains challenging due to the tumor's rarity [53,54] (Table 3, Ref. [55–59]).

The molecular mechanisms underlying chordoma tumorigenesis and progression involve a complex interplay of oncogenes, tumor suppressors, and signaling pathways. Key players include Y-Box Binding Protein 1 (YBX1), CKLF-Like MARVEL Transmembrane Domain-

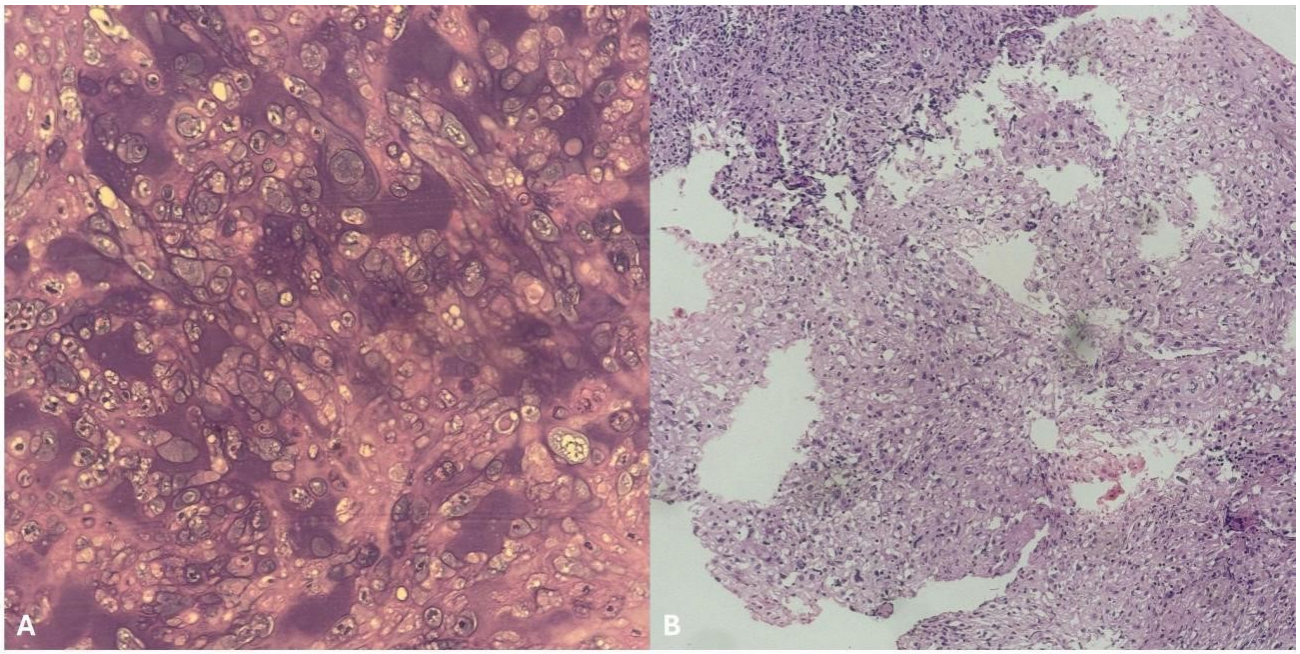

Fig. 2. Histological variants of chordomas. (A) Cells with abundant cytoplasm and well-defined cell borders are arranged in cords and clusters. The cytoplasm exhibits a characteristic vacuolated, "bubbly" appearance, known as the physaliphorous pattern. Scale bar: 40×. (B) Less differentiated chordoma, demonstrating reduced cellular organization and increased atypia compared to well-differentiated areas. Scale bar: 100×. (Personal archive; patient informed consent was obtained.)

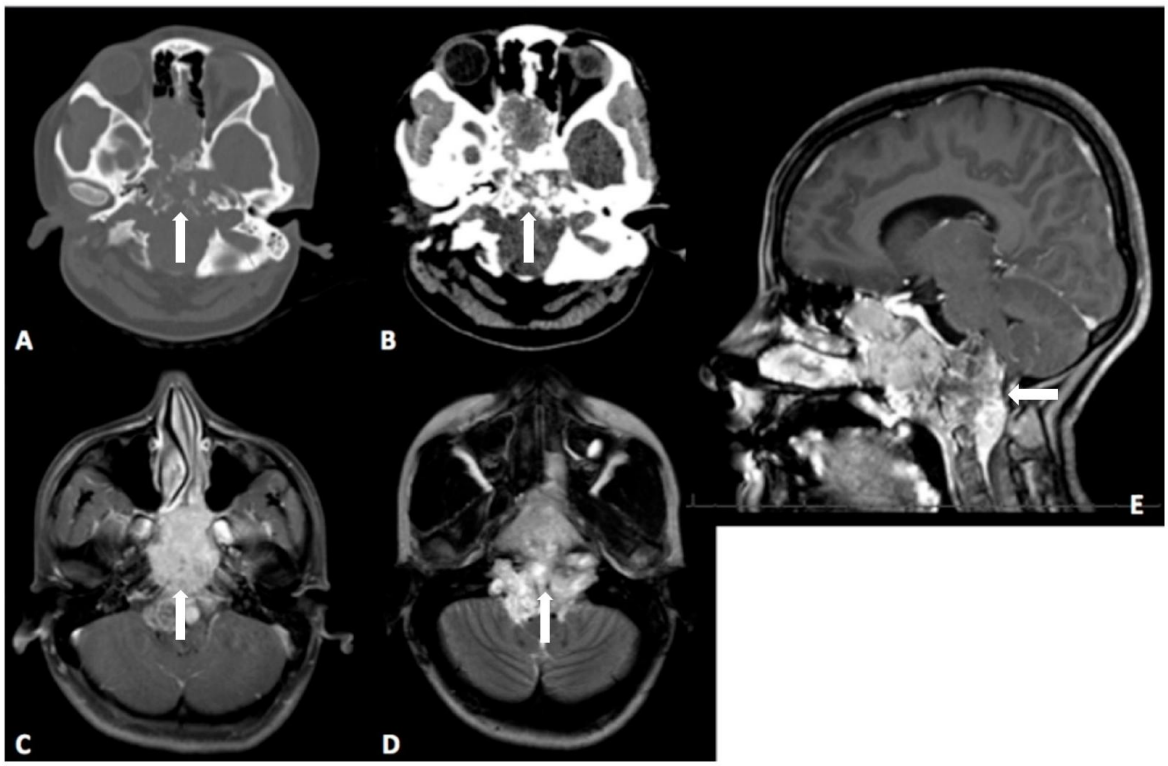

Fig. 3. Imaging features of a clival chordoma. (A,B) Osteolytic lesion in the clivus. (C) MRI shows intense tumoral enhancement. (D) The clival lesion is hyperintense in T2. (E) Sagittal view: extension to inferior clivus, C1, C2, odontoid process, and rhino pharynx. White arrows indicate the anatomical region of the tumor located in the clivus. (Personal archive; patient informed consent was obtained). MRI, magnetic resonance imaging.

Table 2. Summary of genetic role of chordoma progression.

Gene/pathway	Role in chordoma	Citation
YBX1	Promotes tumorigenesis via EGFR/AKT pathway	[47]
CMTM3	Suppresses tumorigenesis by inhibiting EGFR/STAT3 pathway	[48]
TBXT (Brachyury)	Drives chordoma development via TGF-β/SOX6/SOX9 pathway	[49]
EGFR/STAT3	Promotes cell proliferation, migration, and invasion	[48]
PI3K/AKT/mTOR	Activated in 65% of chordomas, potential target for mTOR inhibitors	[50]
FGFR/RAS/RAF/MEK/ERK	Activated in >90% of chordomas, drives tumor growth	[50]
Sonic Hedgehog	Upregulated in a subset of chordomas, associated with EMT	[51]
CA2	Novel target, inhibits cell growth and migration	[52]

YBX1, Y-Box Binding Protein 1; CMTM3, CKLF-Like MARVEL Transmembrane Domain-Containing Protein 3; *TBXT (Brachyury)*, T-Box Transcription Factor T; EGFR, Epidermal Growth Factor Receptor; STAT3, Signal Transducer and Activator of Transcription 3; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; FGFR, Fibroblast Growth Factor Receptor; RAS, Rat Sarcoma Small GTPase; RAF, Rapidly Accelerated Fibrosarcoma Kinase; MEK, Mitogen-Activated Protein Kinase Kinase; ERK, Extracellular Signal-Regulated Kinase; CA2, Carbonic Anhydrase II; TGF-β, Transforming Growth Factor Beta; SOX6, SRY-Box Transcription Factor 6; SOX9, SRY-Box Transcription Factor 9; EMT, Epithelial–Mesenchymal Transition.

Table 3. Summary of updated genetic engineering interventions for chordoma progression.

Therapy type	Mechanism	Efficacy
B7-H3 CAR-T cell therapy	Targets B7-H3 to kill chordoma cells, enhanced by IL-7 expression	Effective against bulk and radiation-resistant chordoma cells, improves CAR-T cell survival [55,56]
Oncolytic adenovirus (Delta-24-RGD)	Selectively infects and kills chordoma cells, modulates TME	Induces tumor shrinkage and improves survival in murine models [56]
CRISPR-Cas9 gene editing	Targets *TBXT (Brachyury)* for knockdown	Achieves 85% knockdown of *Brachyury*, inhibits chordoma cell proliferation [57]
LPD-shRNA Delivery	Delivers shRNA targeting *Brachyury*	Inhibits *Brachyury* expression, induces apoptosis, and suppresses cell growth [57]
CDK inhibition	Inhibits transcriptional CDKs to downregulate *Brachyury*	Reduces *Brachyury* expression and inhibits tumor growth *in vivo* [58]
DARPins	Binds to *Brachyury*, inhibits its transcriptional activity	Reduces cell cycle progression and tumor growth, induces senescence [59]

B7-H3, B7 Homolog 3 (also known as CD276); CAR-T, Chimeric Antigen Receptor T-Cell; IL-7, Interleukin-7; RGD, Arginine–Glycine–Aspartic Acid (integrin-binding motif); TME, Tumor Microenvironment; CRISPR-Cas9, Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated Protein 9; *TBXT (Brachyury)*, T-Box Transcription Factor T; LPD, Liposome–Polycation–DNA; shRNA, Short Hairpin RNA; CDK, Cyclin-Dependent Kinase; DARPins, Designed Ankyrin Repeat Proteins.

Containing Protein 3 (CMTM3), *TBXT*, Epidermal Growth Factor Receptor (EGFR)/Signal Transducer and Activator of Transcription 3 (STAT3), PI3K/AKT/mTOR, Fibroblast Growth Factor Receptor (FGFR)/Rat Sarcoma Small GTPase (RAS)/Rapidly Accelerated Fibrosarcoma Kinase (RAF)/Mitogen-Activated Protein Kinase Kinase (MEK)/Extracellular Signal-Regulated Kinase (ERK), and Sonic Hedgehog pathways. Epigenetic alterations and germline variants further contribute to chordoma development. Emerging therapeutic targets such as Carbonic Anhydrase II (CA2) and inhibitors of the EGFR and PI3K/AKT/mTOR pathways offer promising avenues for treatment, but their evidence is currently limited.

Genetic engineering interventions offer a promising avenue for the treatment of chordoma, a rare and challenging cancer. Strategies such as Chimeric Antigen Receptor T-Cell (CAR-T) cell therapy, oncolytic viral therapy, Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated Protein 9 (CRISPR-Cas9) gene editing, and transcriptional inhibition of *Brachyury* are being actively explored (Table 3). These approaches not only target the molecular drivers of chordoma but also modulate the tumor microenvironment to enhance anti-tumor immunity. As these therapies progress through preclinical and clinical testing, they hold the potential to revolutionize the treatment landscape for chordoma patients. Further research is needed to fully elucidate the molecular landscape of chordoma and to develop effective targeted therapies.

Clinical Presentation and Diagnosis

Cranial chordomas typically involve the clivus and cranial nerves, often resulting in compression of the brainstem. Rare manifestations can include epistaxis and intracranial hemorrhage. The diagnosis of chordomas is primarily based on head computed tomography (CT) scans, which reveal an osteolytic lesion centered in the clivus, with bone destruction and contrast enhancement (Fig. 3). Calcifications are observed in up to 70% of cases. Head magnetic resonance imaging (MRI) typically shows a tumor with cystic areas and calcifications, hypo or isointense in T1-weighted images, hyperintense in T2-weighted images, and that heterogeneously enhances with gadolinium contrast [54]. The lesion may extend to the cavernous sinus, suprasellar region, nasopharynx, cerebellopontine angle, and spine (mainly involving the first cervical vertebra (C1, atlas), as shown in Fig. 3, and the second cervical vertebra (C2, axis)). A biopsy is indicated whenever there is doubt about the diagnosis [60].

The differential diagnosis includes chondrosarcomas, metastases, plasmacytomas, lymphomas, invasive carcinomas, and benign lesions derived from notochord remnants [61]. Therefore, staging should be completed with imaging of the entire neuroaxis, as well as computed tomography (CT) scans of the thorax, abdomen, and pelvis.

Treatment

Based on the guidelines from the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the Spanish Group for Research on Sarcomas (GEIS) [62,63].

A preoperative biopsy is not recommended if there is a substantial risk of cell seeding and if the tumor can be reached safely. The first intervention should always be the surgical resection when feasible, considering the tumor's radioresistance. En bloc R0 resection is the recommended treatment, but it can rarely be done in skull base tumors, and adjuvant radiotherapy should always be considered. Conventional or chondroid chondrosarcomas should be treated with surgery, preferably a macroscopic resection (R0) or subtotal (R1 and R2 resections), followed by adjuvant radiotherapy [64,65]. The use of radiotherapy after complete resection is acceptable, given the poor prognosis associated with recurrences. When resection is not feasible or the surgical sequelae are unacceptable to the patient, radiotherapy alone should be considered as an alternative. The treatment modalities include mainly the fractionated radiotherapy high-energy photon irradiation, and proton beam therapy. The last one, due to the Bragg peak phenomenon, delivers the radiation dose more precisely, achieving better dosing escalation and reducing the risk to the normal tissue. High doses are recommended, at least 70 Gy, ideally more than 75 Gy, as shown in recent studies, preferably using proton beam therapy [66,67].

Dedifferentiated chordomas should be treated as soft tissue sarcoma for complete macroscopic resection, followed by adjuvant radiotherapy and chemotherapy [68]. In addition, neoadjuvant chemotherapy should be considered (Category 1, indicating the highest level of evidence and uniform expert consensus according to NCCN guidelines). The treatment is the same if metastasis is found, including the best palliative care.

Recurrent chordoma treatment – based on the Chordoma Global Consensus Group [69]: after localized recurrence, the first treatment choice is high-dose irradiation, with or without reassessment of the possibility of maximal tumor resection. If the patient has previously received irradiation, the radiotherapist should evaluate the possibility of reirradiation. Patients who are not candidates for surgery or high-dose radiotherapy should receive optimal palliative care. If the tumor is asymptomatic or stable/slow-growing, observation is the only feasible course of action. Medical therapy is recommended as a palliative treatment for tumors that are actively progressing and symptomatic. In cases of recurrent and advanced disease, classic cytotoxic chemotherapy is generally ineffective, but for high-grade dedifferentiated chordomas, doxorubicin and ifosfamide may be considered. Targeted agents such as imatinib and sorafenib are reasonable systemic palliative treatment options. For metastatic disease, treatment with resection, chemotherapy, radiotherapy, and palliative care are potential options and should be evaluated on a case-by-case basis [70].

Prognosis

The recurrence rate is 50%, with a 20% rate of distant metastasis. The overall survival rate is 7.7 years, with 72% survival at 5 years, 48% survival at 10 years, and 31% survival at 20 years [70].

Chondrosarcomas

Chondrosarcomas are non-meningothelial mesenchymal malignant tumors that originate in regions of endochondral ossification within the neuroaxis. Multiple areas of the skull base undergo endochondral ossification, including the petroclival, sphenopetrosal, petro-occipital, and sphenoid-occipital synchondroses. Chondrosarcomas represent 20% of osseous tumors, accounting for 0.1% to 0.2% of all intracranial tumors, with only 2% of these tumors located in the skull base [71].

The histological variants of chondrosarcoma are classified as conventional, mesenchymal, dedifferentiated, and clear cell [71].

The conventional variant comprises multinucleated cells within a cartilaginous matrix and accounts for 90% of chondrosarcomas. It is further divided into grades based on the degree of atypia, mitosis, the nucleus-cytoplasm ratio, and the amount of cartilaginous matrix present.

• Grade 1 (Low grade): Characterized by minimal atypia and a bulky cartilaginous matrix.

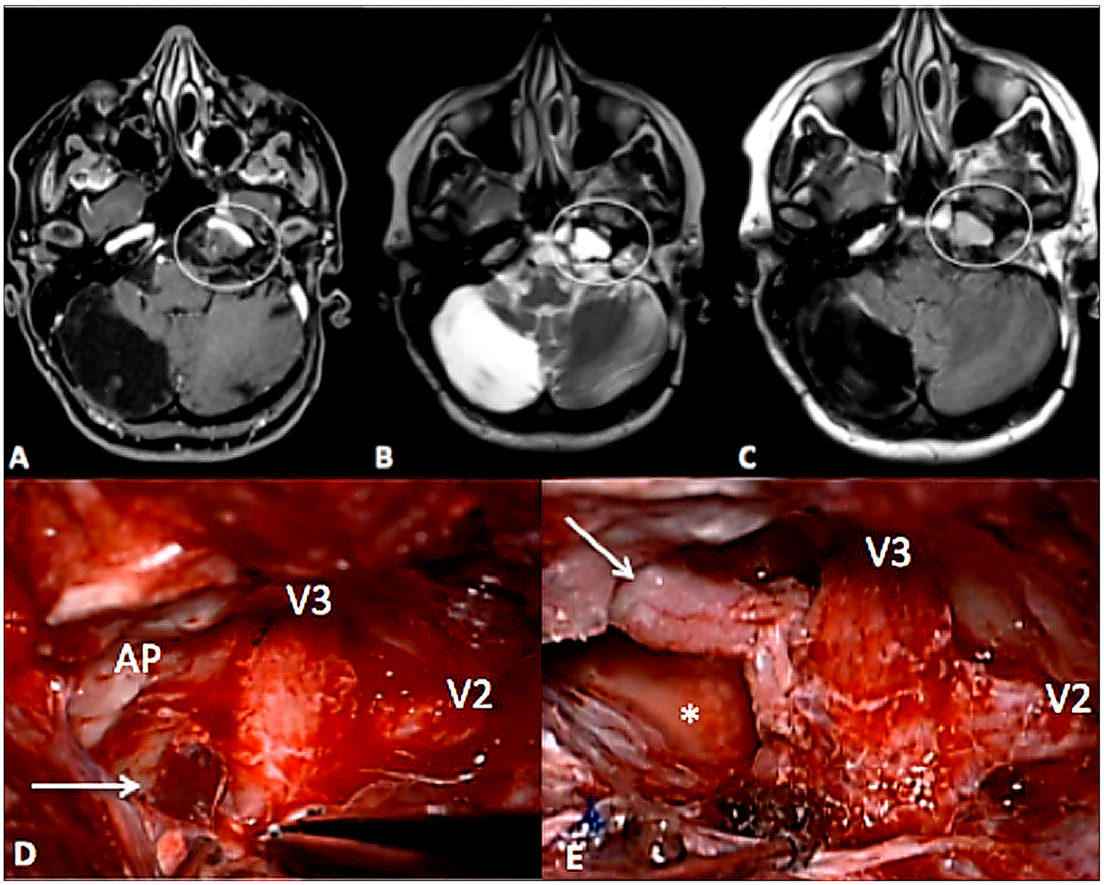

Fig. 4. Petroclival chondrosarcoma involving the petrous apex. (A) Axial contrast-enhanced T1-weighted MRI (T1+C) demonstrates a lobulated lesion centered in the left petrous apex (circle), with mild and heterogeneous contrast enhancement, suggesting a chondroid matrix. (B) Axial T2-weighted MRI shows the lesion as markedly hyperintense with a heterogeneous internal architecture (circle), consistent with high water content typical of cartilaginous tumors. There is expansion of the petrous apex with preservation of a relatively well-defined margin. (C) Axial FLAIR-weighted MRI confirms persistent hyperintensity of the lesion (circle), without significant surrounding edema. (D) Intraoperative view following anterior petrosectomy (Kawase approach) demonstrates exposure of the petrous apex (PA) and adjacent neurovascular structures. The tumor is visualized as a grayish, firm mass (arrow) within the drilled petrous apex. The mandibular division of the trigeminal nerve (V3) and the maxillary division (V2) are identified and preserved. (E) Final intraoperative aspect after tumor resection shows the drilled petrous apex (*). The arrow indicates the skeletonized intrapetrous segment of the internal carotid artery. (Personal archive; patient informed consent was obtained.)

• Grade 2: Displays increased cellularity and more atypia.
• Grade 3: Features high cellularity and less cartilaginous matrix. Grades 1 and 2 constitute 90% of conventional chondrosarcomas, with Grade 3 making up less than 10%.
The mesenchymal variant contains two types of cells: primitive mesenchymal cells and cells exhibiting a cartilaginous tissue pattern similar to the conventional variant.
A mixed pattern includes cells of cartilaginous origin along with fusiform cells, which are indicative of other types of sarcomas.
Finally, the clear cells variant consists of low-grade malignant tumors composed of glycogen-rich cells with abundant cytoplasm, which are organized into lobules.

Clinical Presentation and Diagnosis

Chondrosarcomas in the skull base typically involve the clivus and cranial nerves, often compressing the brainstem. Hormonal disorders are common in these patients and are frequently misdiagnosed as pituitary tumors. Headaches occur in approximately 75% of patients [71]. Nosebleeds and intracranial hemorrhage are rare manifestations [71, 72].

CT scans reveal a lytic lesion with bone destruction, and calcifications may be present. MRI typically shows a tumor that is hypo- or isointense on T1-weighted images, hyperintense on T2-weighted images, and demonstrates heterogeneous enhancement in the paramedian regions of the skull base, particularly at the synchondrosis regions. A biopsy should be performed when there is diagnostic uncertainty.

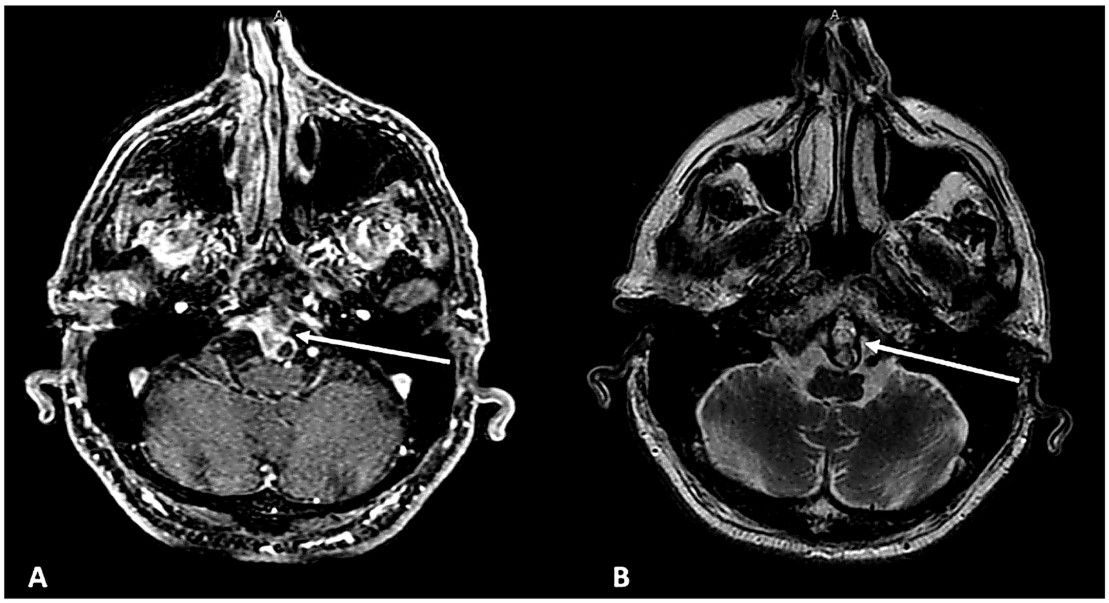

Fig. 5. Ecchordosis physaliphora involving the clival region. (A) Axial contrast-enhanced T1-weighted MRI (T1+C) demonstrates a small, well-defined retroclival lesion without significant contrast enhancement. The arrow indicates the retroclival lesion projecting into the prepontine cistern. (B) Axial T2-weighted MRI demonstrates a markedly hyperintense lesion with cystic-like signal similar to cerebrospinal fluid. The arrow indicates the lesion abutting the ventral surface of the pons without significant mass effect. (Personal archive; patient informed consent was obtained.)

Treatment

Based on the guidelines from the NCCN, the European Society for Medical Oncology (ESMO), and the Spanish Group for Research on Sarcomas (GEIS) [62,63].

The primary treatment for skull base chondrosarcomas is surgical excision with wide margins (Fig. 4). Radiotherapy is considered for unresectable tumors (either primary or recurrent), after incomplete resection, or for symptom palliation. High-dose radiotherapy (greater than 70 Gy) is recommended for skull base chondrosarcomas due to its high control rates (80–90%).

Localized mesenchymal and dedifferentiated chondrosarcomas are more responsive to chemotherapy and should be treated with neoadjuvant or adjuvant chemotherapy, typically combining anthracyclines and alkylating agents, along with adjuvant high-dose radiotherapy. Additionally, immunotherapy and IDH1 mutant inhibitors are being explored in clinical trials.

Prognosis

Chondrosarcomas are less aggressive than chordomas. The overall survival rate at 5 years is 50%, with a disease-free survival rate of 95% for the mesenchymal subtype at 5 years. In contrast, the overall survival for the dedifferentiated subtype ranges from 0% to 20% at 5 years.

Benign Notochordal Cell Tumor

Since 2013, the World Health Organization (WHO) has recognized the benign notochordal cell tumor as the precursor lesion to the chordoma [43].

Histopathology

It is characterized by adipocyte-like, eosinophilic, vacuolated cells lacking lobular architecture or a myxoid matrix. The presence of mitosis is rare. Immunohistochemically, the tumor is positive for *Brachyury*, vimentin, and S-100 protein [73].

Clinical Presentation and Diagnosis

The diagnosis is image based. CT scans show sclerotic areas without lytic areas or extraosseous extension. MRI reveals homogeneous lesion hypointense in T1-weighted images and hyperintense in T2-weighted images without contrast enhancement (Fig. 5). The *Ecchordosis physaliphora* (EP) is a subtype of the BNCTs with intradural lesions that have marked limits and usually occupy the pre-pontine cistern in the region of the Dorello canal. Biopsy should be limited to doubts about the diagnosis [74] (Fig. 5; Fig. 6, Ref. [61]).

Treatment and Prognosis

There is no need for surgical treatment, and the prognosis is excellent. However, patients should be followed with serial MRIs because of the risk of transformation into a chordoma.

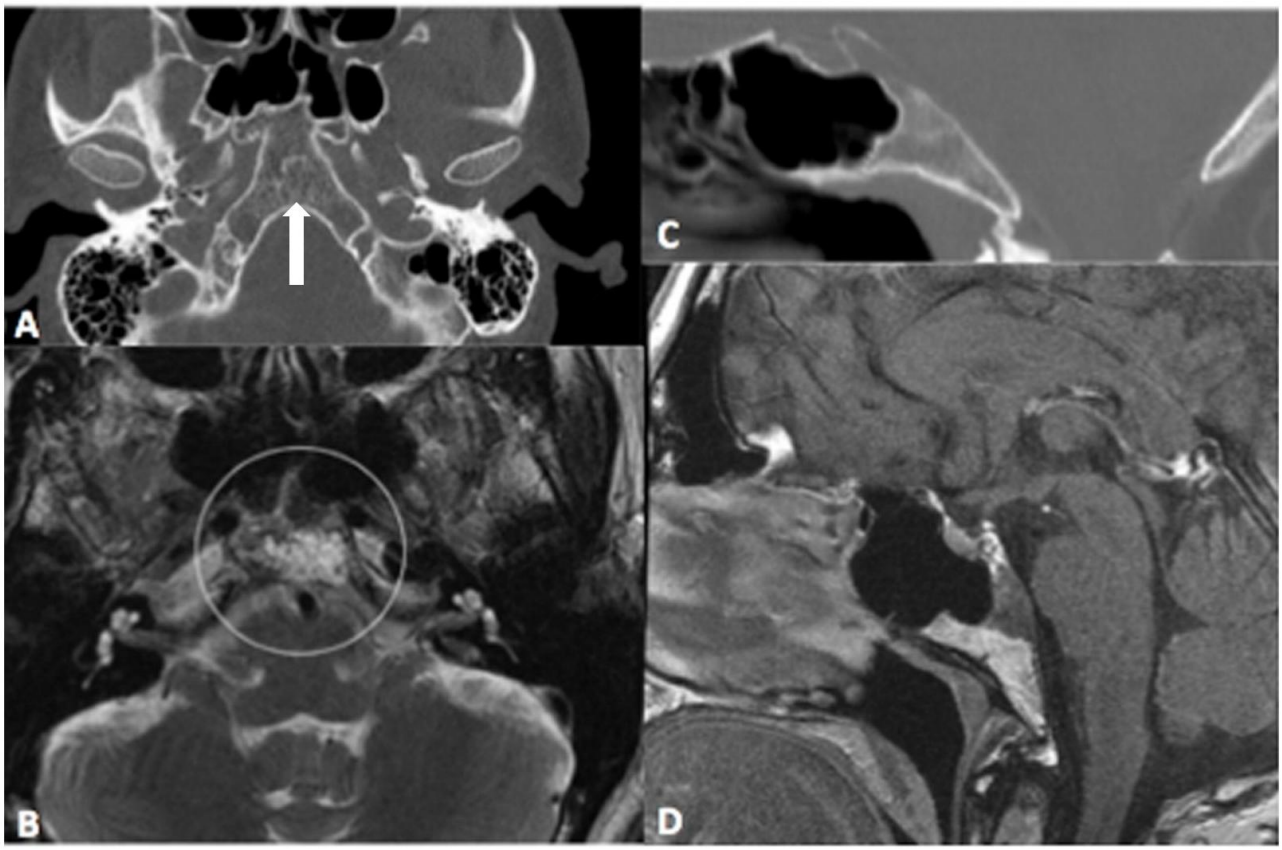

Fig. 6. Benign notochordal cell tumor (BNCT) of the clivus. (A) Axial computed tomography (CT) in bone window demonstrates preservation of the normal clival architecture, with intact cortical bone and maintained trabecular pattern, without evidence of osteolysis, cortical breach, or expansile remodeling. (B) Axial T2-weighted MRI shows a subtle, ill-defined lesion within the clivus, with mildly heterogeneous signal and preservation of the surrounding bony contours (circle), without associated soft tissue mass or extension into the prepontine cistern. (C) Sagittal CT reconstruction confirms preservation of the clival cortex and normal osseous alignment, without bone destruction or deformity. (D) Sagittal T1-weighted MRI demonstrates a lesion that is iso- to mildly hypointense relative to normal marrow, without contrast enhancement, and without evidence of extraosseous extension. The adjacent anatomical structures, including the dorsum sellae, basiocciput, and ventral brainstem, remain preserved, with no mass effect or displacement. The arrow and circle highlight the region of interest in the clivus, emphasizing preserved trabecular bone and lack of aggressive imaging features. These findings are characteristic of a benign notochordal cell tumor, particularly the absence of osteolysis, cortical disruption, or enhancement, helping to distinguish it from chordoma. Reprinted from Santegoeds RGC *et al.* [61], available under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Giant Cell Tumor of Bone

The GCT is a neoplasm that primarily affects the metaphyseal region of long bones but is exceedingly rare in the skull. Its bone-destructive properties and high local recurrence rate pose significant challenges for management [20]. GCTs account for 5% of all bone neoplasms, with only 0.51% arising from the skull bones. The most common sites in the skull are the sphenoid (superior clivus) and temporal bone [75].

Histopathology

This mesenchymal neoplasm is characterized by scattered multinucleated giant cells surrounded by ovoid or spindle-shaped mononuclear stromal cells. The osteoclast-like giant cells are responsible for bone resorption, leading to localized bone destruction within the tumor region, despite its benign nature. The stromal cells represent the neoplastic component of the tumor and exhibit mutations in the H3F3A gene [73]. These stromal cells recruit osteoclast-like giant cells through overexpression of RANK-ligand, a potential therapeutic target [14].

Clinical Presentation and Diagnosis

The symptoms depend on the tumor's location. Common presentations include headache, visual disturbances, ophthalmoparesis, and other cranial nerve deficits.

Neuroimaging aids in distinguishing GCTs from other lesions, but a biopsy with immunohistochemistry is necessary for definitive diagnosis. A head CT scan typically reveals a bone-destructive lesion centered in the sphenoid body. MRI

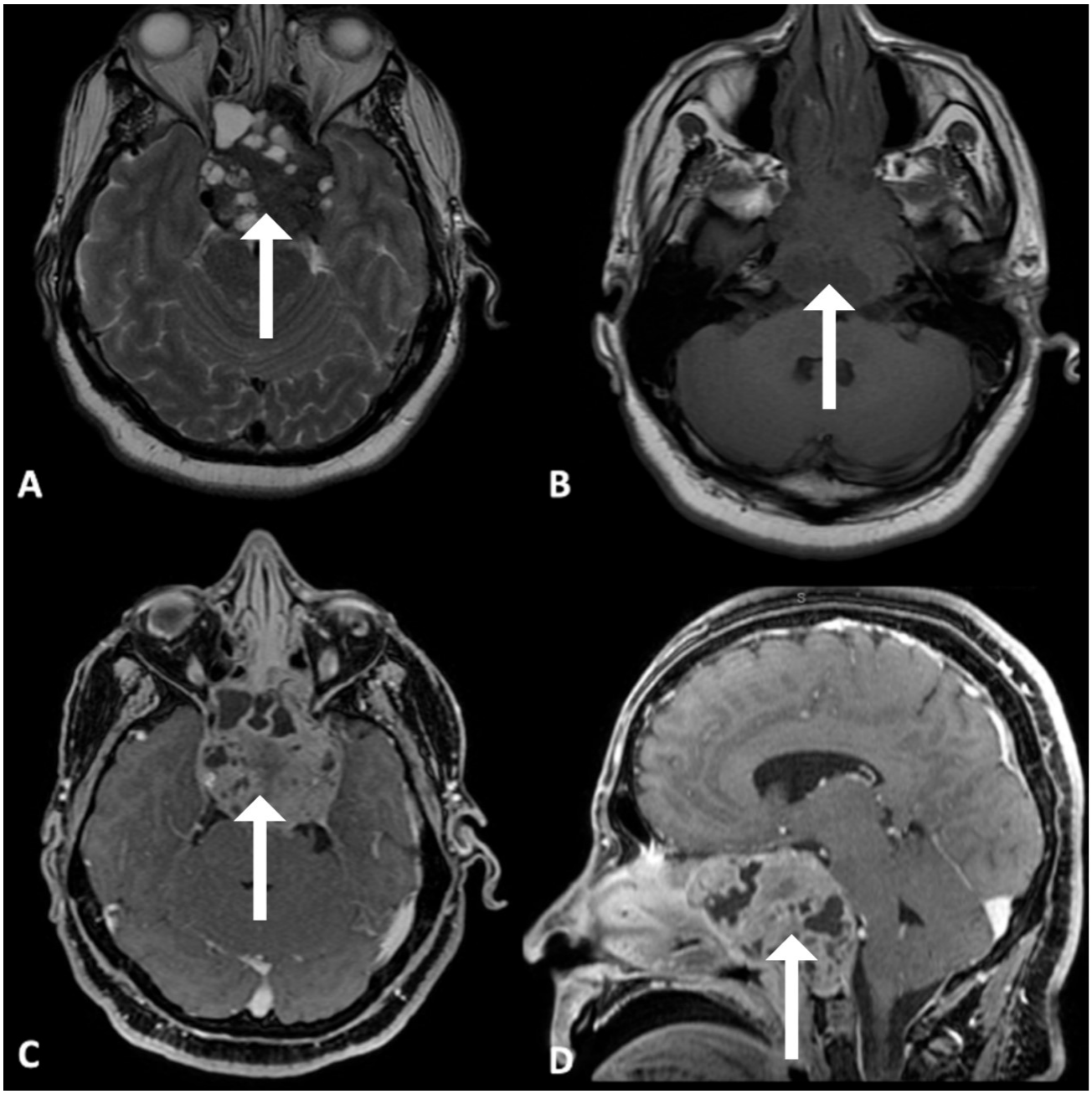

Fig. 7. Contrast-enhanced MRI of a giant cell tumor of bone (GCT) of the clivus. (A) Axial T2-weighted MRI demonstrates a lobulated expansile lesion centered in the clivus. The arrow indicates posterior extension into the prepontine cistern with mass effect on the ventral surface of the pons. (B) Axial T1-weighted MRI shows the lesion as predominantly isointense to brain parenchyma. The arrow highlights the region of clival cortical involvement and marrow replacement. (C) Axial contrast-enhanced T1-weighted MRI (T1+C) reveals marked heterogeneous enhancement with probable extension into adjacent skull base compartments. The arrow indicates the petroclival extension adjacent to the cavernous carotid region. (D) Sagittal contrast-enhanced T1-weighted MRI (T1+C) demonstrates extensive clival destruction with superior extension toward the dorsum sellae and inferior extension toward the basiocciput. The arrow indicates posterior displacement and compression of the brainstem. (Personal archive; patient informed consent was obtained.)

shows a hypo- to isointense tumor on T1 and T2-weighted images, with slight homogeneous contrast enhancement. Secondary aneurysmal bone cysts may form within the tumor, appearing as areas of high-intensity fluid levels on T2 images, along with peripheral contrast enhancement of the cyst [29] (Fig. 7).

Treatment

A preoperative biopsy is a valuable tool for guiding the therapeutic strategy. Whenever possible, complete surgical resection of the tumor should be performed to minimize the risk of local recurrence. However, due to the rarity of this tumor, evidence-based recommendations for the treatment

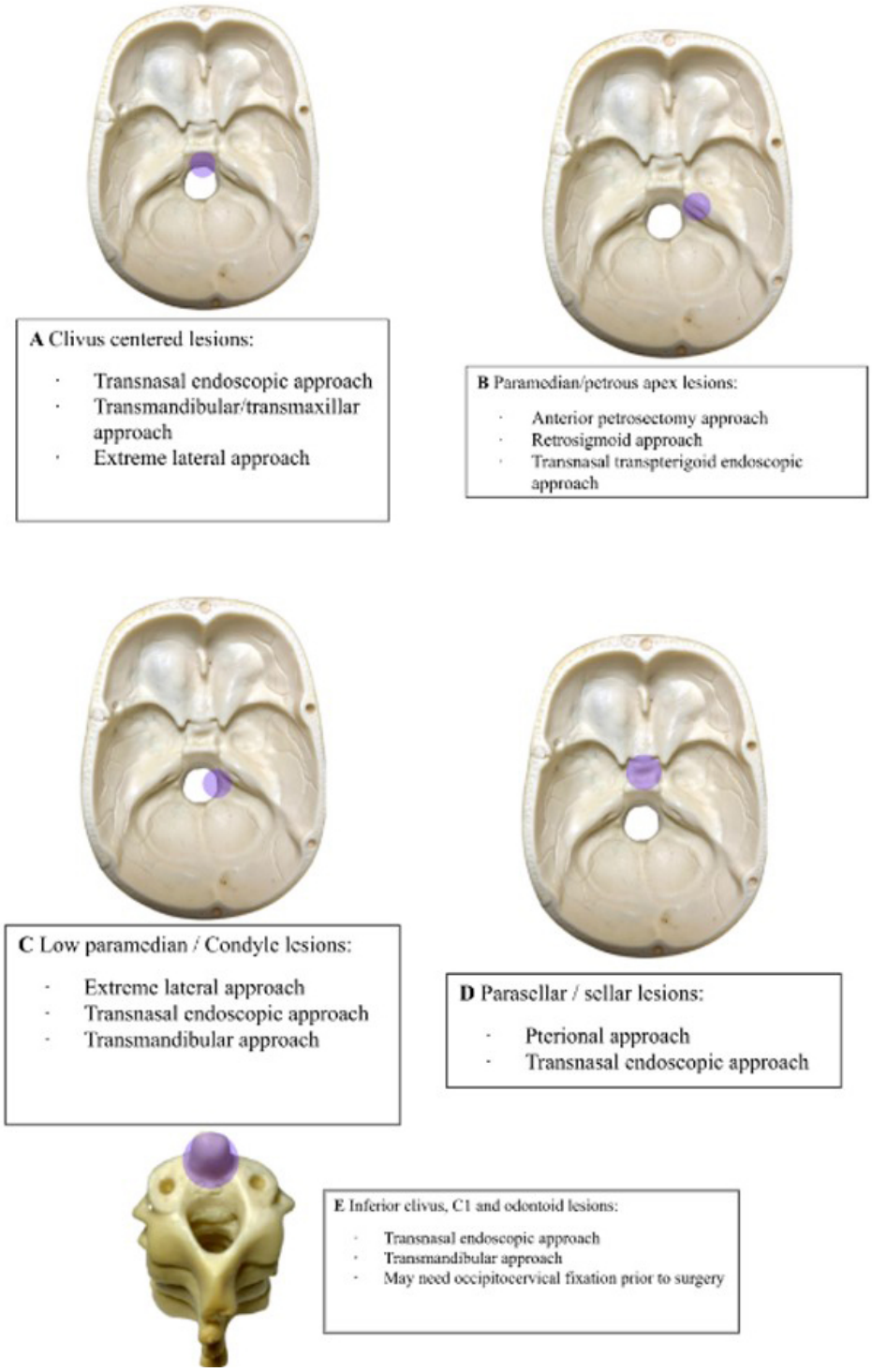

Fig. 8. Surgical strategies of clivus lesions. (A) Clivus-centered lesions. (B) Paramedian/petrous apex lesions. (C) Low paramedian/condyle lesions. (D) Parasellar/sellar lesions. (E) Inferior clivus, C1, and odontoid lesions. Macroscopic anatomical image obtained by direct photography of synthetic vertebrae specimens, illustrating vertebral morphology and structural features, and it was subsequently edited using Adobe Photoshop CS6 (Adobe Systems Incorporated, San Jose, CA, USA).

of skull GCTs are limited. The use of adjuvant radiotherapy remains controversial due to concerns about potential malignant transformation. Nevertheless, a study has suggested that the absence of radiotherapy may be an independent risk factor for poor survival [74].

The subcutaneous administration of denosumab (a human monoclonal antibody that inhibits RANK-ligand) is currently recommended as targeted therapy for recurrent and unresectable long bone GCTs. The recommended dosing regimen is 120 mg monthly (every 28 days), with ini-

tial loading doses of 120 mg on days 1, 8, and 15 of the first month. The most significant adverse events are bone-related, including fractures and osteonecrosis of the jaw [11,12,14,76–80].

Despite its generally favorable safety profile, the prolonged use of denosumab raises concerns due to its high cost and the potential risks of bone-related adverse events. In a large phase 2 study, Osteonecrosis of the Jaw (ONJ) was reported in 3% of patients, with 28 cases positively adjudicated as ONJ [78]. The same study reported 1% incidence of atypical femur fractures. Hypocalcemia and pain in extremities has been described as a potential adverse event, with a very low incidence reported in a clinical study [79]. Prevention strategies to minimize these complications are dental and oral care, dose optimization, regular monitoring for adverse events and a lower postoperative time to introduce denosumab [81]. There is a risk of tumor progression after discontinuation of denosumab treatment. One potential strategy to mitigate the duration of treatment is to use it as a neoadjuvant therapy to reduce tumor size, thus enabling complete resection of clival tumors with better local control, particularly in cases where the tumor involves the cavernous sinus, cranial nerves, and carotid arteries, making it otherwise unresectable. This approach, originally derived from the treatment of long bone GCTs, was successfully described in a report by Sekar *et al*. [34], but it still requires further evaluation in larger studies.

Prognosis

Weng *et al*. [80] evaluated 128 patients from the literature, reporting an overall survival rate of 98.4% at 1 year and 89.2% at 5 years, with a recurrence rate of 22.7%. The surgical strategies for treating clivus lesions are summarized in Fig. 8.

Conclusions

Identifying a clivus lesion in imaging studies presents a diagnostic challenge due to the wide array of possible clinical conditions. This can lead to incorrect diagnoses and inappropriate treatment. While there is a wealth of literature on the histopathology, imaging findings, diagnosis, clinical presentation, and treatment of each type of lesion, comprehensive reviews comparing all lesions are lacking and are urgently needed.

Understanding the distinct characteristics of each lesion helps clinicians and neurosurgeons to establish the most likely diagnosis and determine the appropriate course of investigation and treatment. Accurately deciding whether a clival lesion warrants serial imaging follow-up, a biopsy, or immediate surgery is an essential clinical skill that minimizes patient suffering in the case of benign lesions and ensures better outcomes for patients requiring aggressive treatment strategies for their tumors.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

VTGdS: conceptualization, methodology, investigation, writing — original draft, writing — review and editing. TBN: data curation, formal analysis, visualization, writing — review and editing. RPdSS: investigation, data curation, writing — review and editing. CM, EGF: conceptualization, supervision, writing — review and editing. WSP: conceptualization, supervision, writing — review and editing. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4056.

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