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Tumor/Infection

CLINICAL, DIAGNOSTIC, AND THERAPEUTIC ASPECTS OF CHORDOMA: A NARRATIVE REVIEW

ASPECTOS CLÍNICOS, DIAGNÓSTICOS E TERAPÊUTICOS DO CORDOMA: UMA REVISÃO NARRATIVA

ASPECTOS CLÍNICOS, DIAGNÓSTICOS Y TERAPÉUTICOS DEL CORDOMA: UNA REVISIÓN NARRATIVA

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ABSTRACT

Objective: To review the main clinical, diagnostic, and therapeutic aspects of chordoma, a rare and locally aggressive neoplasm. Methods: A narrative literature review based on PubMed-indexed articles published between 2010 and 2025. Results: Currently, Chordoma are classified into three subtypes: 1- Conventional and/or chondroid; 2- dedifferentiated, 3- slightly differentiated. Each of these subtypes has different epidemiologies, treatments, and clinical course that must be individualized. En bloc surgical resection with negative margins remains the mainstay of treatment. In situations where complete resection is not possible, high-dose radiation therapy, especially with advanced technologies such as proton or carbon ion beam, plays an essential role as an adjuvant or definitive therapy. Although systemic therapy still has a limited role, advances in the molecular understanding of the disease have driven the development of promising targeted therapies. Conclusions: The management of chordoma requires a specialized multidisciplinary approach. En bloc resection combined with advanced radiotherapy improves prognosis, but local recurrence remains a challenge. Development of targeted and immunotherapeutic strategies is promising but lacks strong clinical validation. ***Level of Evidence V; Narrative Review.***

Keywords: Bone Neoplasms; Chordoma; Surgical Oncology; Radiotherapy; Targeted Therapy.

RESUMO

Objetivo: Revisar os principais aspectos clínicos, diagnósticos e terapêuticos do cordoma, uma neoplasia rara e de comportamento localmente agressivo. Métodos: Revisão narrativa da literatura baseada em artigos indexados no PubMed entre 2010 e 2025. Resultados: Atualmente, os cordomas são classificados em três subtipos: 1- Convencional e/ou condroide; 2- dediferenciado, 3- pouco diferenciado. Cada um desses subtipos tem diferentes epidemiologias, tratamentos e curso clínico que devem ser individualizados. A ressecção cirúrgica em bloco com margens negativas continua sendo o pilar do tratamento. Em situações em que a ressecção completa não é possível, a radioterapia de alta dose, especialmente com tecnologias avançadas como o feixe de prótons ou íons de carbono, desempenha um papel essencial como terapia adjuvante ou definitiva. Embora a terapia sistêmica ainda tenha um papel limitado, avanços na compreensão molecular da doença, têm impulsionado o desenvolvimento de terapias-alvo promissoras. Conclusões: O manejo do cordoma exige abordagem multidisciplinar e especializada. A ressecção em bloco associada à radioterapia avançada melhora o prognóstico, mas a recorrência local permanece um desafio. O desenvolvimento de terapias-alvo e imuno-oncológicas é promissor, mas ainda carece de validação clínica robusta. ***Nível de evidência V; Revisão narrativa.***

Descritores: *Neoplasias Ósseas; Cordoma; Cirurgia Oncológica; Radioterapia; Terapias Alvo.*

RESUMEN

Objetivo: Revisar los principales aspectos clínicos, diagnósticos y terapéuticos del cordoma, una neoplasia rara y localmente agresiva. Métodos: Revisión narrativa de la literatura basada en artículos indexados en PubMed entre 2010 y 2025. Resultados: Actualmente, se clasifican en tres subtipos: 1- Convencionales y/o condroides; 2- dediferenciado, 3- ligeramente diferenciado. Cada uno de estos subtipos tiene diferentes epidemiologías, tratamientos y curso clínico que deben individualizarse. La resección quirúrgica en bloque con márgenes negativos sigue siendo el pilar del tratamiento. En situaciones en las que no es posible la resección completa, la radioterapia de dosis altas, especialmente con tecnologías avanzadas como el haz de protones o iones de carbono, desempeña una función esencial como terapia adyuvante o definitiva. Aunque la terapia sistémica todavía tiene un papel limitado, los avances en la comprensión molecular de la enfermedad han impulsado el desarrollo de terapias dirigidas prometedoras Conclusiones: El manejo del cordoma requiere un enfoque multidisciplinario especializado. La resección en bloque combinada con radioterapia avanzada mejora el pronóstico, pero la recurrencia local sigue siendo un desafío. El desarrollo de terapias dirigidas e inmunológicas es prometedor, pero carece de validación clínica robusta. ***Nivel de evidencia V; Revisión narrativa.***

Descriptores: *Neoplasias Óseas; Cordoma; Cirugía Oncológica; Radioterapia; Terapias Dirigidas.*

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INTRODUCTION

Chordoma is an extremely rare neoplasm with an annual incidence of 1 per 1,000,000 inhabitants in the United States and Europe, representing approximately 350 new cases per year.[1,2] It is a tumor originating from residual embryonic notochord, most commonly affecting the sacral spine and the skull base, predominantly in middle-aged men. Currently, it is classified into three subtypes: 1 — conventional and/or chondroid; 2 — dedifferentiated; 3 — poorly differentiated.[1] Despite its slow growth, it exhibits locally aggressive features with local invasion and the potential for metastases, mainly to the lungs. This article aims to review the main diagnostic and therapeutic aspects of chordoma.

METHODS

This is a narrative literature review using the PubMed database, selecting articles available in English and published between 2010 and 2025. No patient data or animal experimentation were included in this study. Therefore, approval by an Ethics Committee or the obtainment of informed consent was not applicable.

RESULTS

Chordomas present with variable manifestations, ranging from indolent behavior to highly aggressive forms. They show recurrence rates of approximately 50% and metastatic disease in 30–40% of cases.

Currently, they are classified into three subtypes: 1 — conventional and/or chondroid; 2 — dedifferentiated; 3 — poorly differentiated[2] (Figure 1). Each of these subtypes has a distinct epidemiology, treatments, and clinical course, which must be individualized.[1]

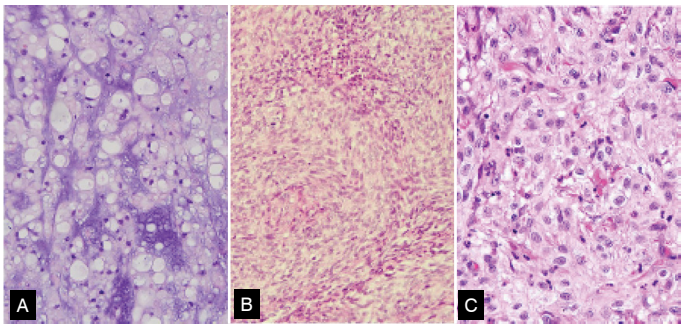
Diagnosis and Treatment of Chordoma Subtypes

1. Conventional and/or chondroid: These represent 95% of all chordoma cases.[3] They are more common in men and most frequently occur in the sacral region.

Histologically, conventional chordoma is characterized by nests and cords of physaliphorous cells, which show positivity for cytokeratins, S100 protein, and epithelial membrane antigen. Nuclear expression of the transcription factor brachyury represents a key diagnostic marker of this neoplasm. The chondroid subtype shares morphological features with conventional chordoma, differing mainly by the presence of a hyaline matrix.

The current standard treatment for both conventional and chondroid chordoma is based on surgical resection aimed at achieving negative microscopic margins. The surgical approach depends on tumor location, and several retrospective studies have demonstrated that complete resection with free margins is associated with better prognosis. However, achieving negative margins is a challenge in most cases, which is why radiotherapy is often recommended in neoadjuvant or adjuvant settings.

Radiotherapy may be a viable alternative in patients for whom surgery carries a high risk of morbidity or in those who refuse surgical procedures. Studies have indicated improvement in disease-free survival and local control rates in patients undergoing external radiotherapy. Current and future strategies related to the use of radiotherapy will be addressed in detail in subsequent sections. At present, systemic therapies are not indicated as first-line treatment in the management of conventional or chondroid chordoma.



Adapted from: Wedekind M, Widemann B, Cote G. Chordoma: Status, problems, and future directions. Current problems in cancer. 2021;45(4):100771.)

Figure 1. Chrodoma histologies: (A) Convencional; (B) Dedifferentiated; (C) Poorly differentiated.

2. Dedifferentiated: Dedifferentiated chordoma is a rare entity, accounting for approximately 2% to 8% of all chordoma cases. Epidemiological data are still limited; however, a recent study reported a mean age at diagnosis of 57 years (ranging from 15 to 81 years), with a slight male predominance and greater frequency in the sacral region. It was also observed that 57% of cases occurred primarily, whereas 43% arose as recurrence of a previously treated conventional chordoma.

Histologically, dedifferentiated chordomas frequently show areas with features of high-grade sarcoma, which may coexist with regions typical of conventional chordoma. These dedifferentiated areas demonstrate high mitotic activity, in addition to loss of brachyury and cytokeratin expression — markers usually present in the conventional component.

Currently, there is no standardized therapeutic approach for this subtype. In a comprehensive review of 87 patients, Hung et al.[4] observed that 92% underwent surgery, 41% received radiotherapy, and only 20% were treated with chemotherapy. Management is challenged by the aggressive behavior of the disease, as evidenced by the fact that 46% of patients already had metastases at the time of diagnosis, with an estimated median survival of 20 months.

3. Poorly differentiate: Poorly differentiated chordoma is a rare subtype that predominantly affects the pediatric population. The mean age at diagnosis is approximately 10 years (ranging from 3 months to 42 years), with a slight female predominance. The most common locations include the skull base and the cervical spine, accounting for about 91% of cases. Histologically, this subtype presents features overlapping with conventional chordoma, epithelioid sarcoma, and rhabdoid tumor, consisting of cohesive sheets of epithelioid cells with marked nuclear pleomorphism and scarce physaliphorous cells.

The main immunohistochemical characteristic that distinguishes it is the complete loss of SMARCB1/INI1 expression, while maintaining positivity for brachyury and cytokeratins. Currently, there is no standardized therapeutic protocol for managing poorly differentiated chordoma. With the recognition of this subtype as a distinct entity by the World Health Organization (WHO), it has become difficult to interpret historical survival and treatment response data, as poorly differentiated and dedifferentiated chordomas were often grouped together in previous analyses.

Given its biologically more aggressive nature, higher metastatic potential, and greater sensitivity to chemotherapy, there is consensus among experts that treatment should begin with chemotherapy regimens prior to surgery or radiotherapy. The regimens generally follow protocols used for Ewing sarcoma (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) or soft tissue sarcomas (doxorubicin/ifosfamide). Considering the loss of SMARCB1/INI1, there are case reports suggesting potential benefit from targeted therapies or immunotherapy, although these findings remain limited to isolated experiences without consolidated evidence for routine clinical application (Table 1).

Treatment

Therapeutic planning must be meticulous. This includes biopsy to confirm the lesion pathology, classification of the lesion, tumor staging with its subtype, and assessment of the patient's medical comorbidities to evaluate suitability for operative treatment.

The general recommendation is that biopsy should be performed using a core needle, whenever possible, due to higher diagnostic accuracy.[5,6] The procedure should be carried out by the same surgeon who will perform definitive treatment. The biopsy tract must be excised during the surgical approach following diagnostic confirmation. When diagnosis cannot be established by biopsy, repetition of the procedure is recommended to reduce false negatives.

After diagnostic confirmation by biopsy, tumor staging should

Table 1. Comparison among histological subtypes of chordoma.

Subtype	Conventional and/or chondroid	Dedifferentiated	Poorly differentiated
Prevalence	95%	2–8%	<1%
Epidemiology	Adult males	Adult males	Pediatric population, mean age of 10 years, slight female predominance
Region	Sacral	Sacral	Skull base and cervical spine
Histology	Cords of physaliphorous cells, positive for cytokeratin, S100 protein, and epithelial membrane antigen. The chondroid group presents a hyaline matrix.	High-grade sarcoma features with increased mitoses and loss of brachyury and cytokeratin within the dedifferentiated component.	Cohesive sheets of epithelioid cells with marked nuclear pleomorphism and minimal physaliphorous cells. Complete loss of SMARCB1/INI1, while still expressing brachyury and cytokeratin.
Treatment	Resection with negative margins; adjuvant radiotherapy if margins are not free. Chemotherapy not indicated.	Individualized, potentially including surgery, radiotherapy, and chemotherapy.	Neoadjuvant chemotherapy + surgery ± radiotherapy depending on margins. Chemotherapy regimens are generally based on Ewing sarcoma (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) or soft tissue sarcoma protocols (doxorubicin/ifosfamide).

be performed using the Enneking-Musculoskeletal Tumor Society (MSTS) system.[7] CT of the chest, abdomen, and pelvis is recommended for screening metastatic lesions (Table 2).

Following staging, the surgical plan is developed using the Weinstein-Boriani-Biagini (WBB) system (Figure 2), which guides the best surgical approach to the tumor.

Table 2. MSTS/Enneking Classification.

Stage	Grade	Extension	Metastasis
Stage IA	Low grade	Intracompartmental	No metastasis
Stage IB	Low grade	Extracompartmental	No metastasis
Stage IIA	High grade	Intracompartmental	No metastasis
Stage IIB	High grade	Extracompartmental	No metastasis
Stage III	Any grade	Any location	With metastasis

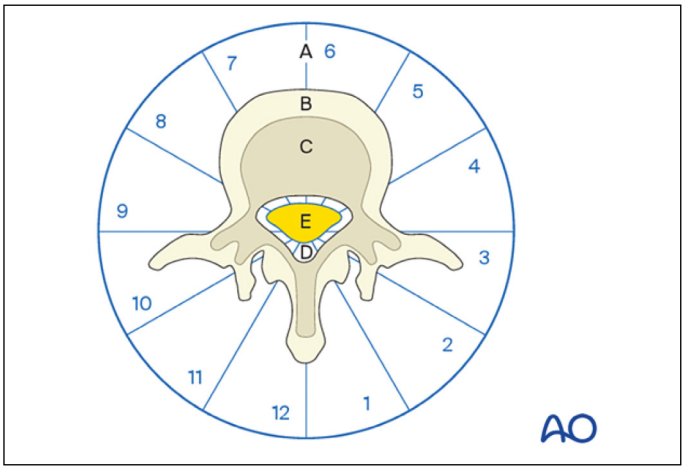


Figure 2. Weinstein-Boriani-Biagini (WBB) Surgical Staging System. The transverse extension of the vertebral tumor is described with references to 12 radiating zones (numbered 1 to 12) and five concentric layers (A to E, from the paravertebral extraosseous compartments to dural involvement). The longitudinal extension of the tumor is recorded according to the levels involved.

Surgery

The cornerstone of chordoma treatment is surgical resection with wide negative margins, as this is associated with better local control, recurrence-free survival, and overall survival across all anatomical sites.[7-11] (Figures 3) En bloc resection with negative margins is preferred whenever technically feasible, since intralesional or marginal excision is associated with significantly higher local recurrence rates and worse long-term outcomes.[12] Complete resection is often limited by the proximity of critical neurovascular structures.[9,10]

Radiotherapy

For chordoma, particularly of the skull base and spine, the comparative effectiveness of conventional photon radiotherapy, proton radiotherapy, and carbon-ion therapy has been the subject of several recent systematic reviews and meta-analyses.

Conventional photon radiotherapy (including fractionated and stereotactic techniques) is associated with lower local control (LC) and overall survival (OS) rates compared to particle therapies. Meta-analyses consistently report 5-year OS rates for photon-based modalities in the range of 65%–77%, with 5-year progression-free survival (PFS) and LC rates generally below 50% in most series. The main limitation of photon therapy is the inability to safely deliver the high doses required for optimal tumor control due to the proximity of critical structures, leading to suboptimal outcomes and increased toxicity.[13-15]

Proton radiotherapy offers dosimetric advantages, allowing higher, more conformal tumor doses while sparing adjacent normal tissues. Multiple meta-analyses and large series demonstrate superior OS rates (typically 78%–85%) and LC rates (75%–84%) at 5 years with protons compared to photons. Five-year PFS with protons is also higher, frequently exceeding 70% in modern series. Toxicity profiles are generally favorable, with severe toxicities (grade ≥3) occurring in fewer than 15% of patients. The superiority of protons over photons is supported by indirect comparisons and meta-analyses, although direct comparative data remain limited and of low certainty.[16-18]

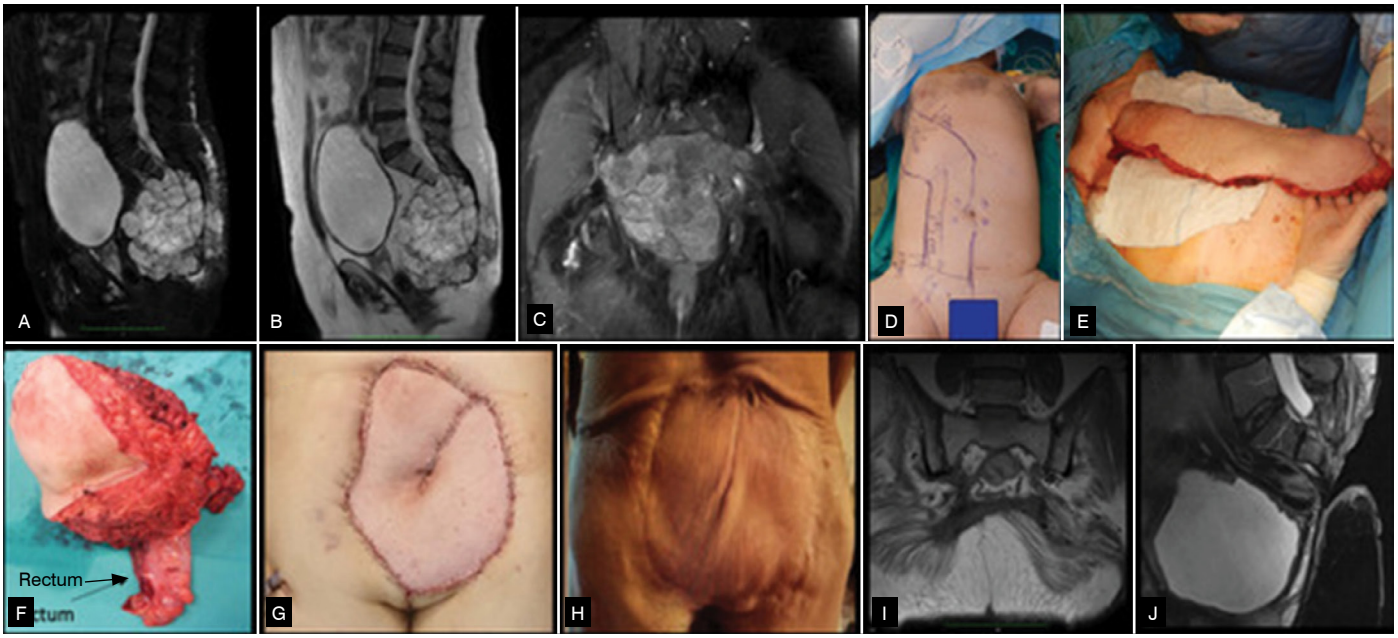
Carbon-ion therapy is another particle therapy modality with higher linear energy transfer and relative biological effectiveness than proton therapy, theoretically offering greater efficacy against radioresistant tumors such as chordoma. Clinical data indicate that carbon-ion therapy achieves 5-year OS and LC rates comparable to protons, with most series reporting 5-year OS of 75%–86% and LC of 71%–75%. Direct comparisons between protons and carbon ions in meta-analyses and institutional cohorts have not demonstrated significant differences in long-term OS or LC. Toxicity rates are similar between the two modalities, and both are generally well tolerated.[15-19]

Key clinical considerations:

- Both proton and carbon-ion therapy are superior to conventional photon radiotherapy for chordoma in terms of local control and survival.[13-15]
- There is no clear evidence of superiority between protons and carbon ions for most patients; both modalities achieve high tumor control rates with acceptable toxicity profiles.[15,19]
- Tumor volume, proximity to critical structures (e.g., brainstem, optic apparatus), and adequacy of dose coverage are important prognostic factors for local control regardless of particle type.[17,18]

Immunotherapy

Immunotherapy for chordoma is an active area of investigation, reflecting the limited efficacy of conventional chemotherapy



Adapted from: Goumenos S, Kakouratos G, Trikoupis I, Gavriil P, Gerasimidis P, Soultanis K, Patapis P, Kontogeorgakos V, Papagelopoulos P. Clinical outcome after surgical treatment of sacral chordomas: a single-center retrospective cohort of 27 patients. Cancers. 2024;16:973. https://doi.org/10.3390/cancers16050973.

Figure 3. (A, B) Sagittal T2-weighted fat-suppressed views and T2-weighted MRI showing an S2-level sacral chordoma (male, 62 years old); (C) Coronal post-contrast T1-weighted fat-suppressed view showing soft-tissue infiltration by the tumor; (D, E) Intraoperative photographs showing flap preparation and harvesting; (F) Photograph of the resected specimen demonstrating en bloc tumor resection with overlying skin and part of the rectum attached (combined approach); (G) Reconstruction of the soft-tissue defect with the flap; (H) Satisfactory wound healing outcome without complications 1 year after surgery; (I, J) Coronal T1-weighted and sagittal T2-weighted fat-suppressed MRI views, respectively, showing no local recurrence at 1-year postoperative follow-up.

and radiotherapy in this rare malignancy.[20] The most robust clinical evidence to date supports the use of immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 inhibitors such as pembrolizumab, in patients with advanced or recurrent disease. Retrospective and early-phase prospective studies have shown that ICIs may achieve clinical benefit — defined as stable disease, partial response, or complete response — in a substantial proportion of patients with recurrent chordoma, with median PFS of approximately 14 months and 1-year OS of 87% in one series. Toxicities are generally manageable, with grade 3/4 immune-related adverse events occurring in a minority of patients.[21,22]

The efficacy of ICIs does not appear to be strictly limited to patients with high PD-L1 expression, and some benefit has been observed even in PD-L1–negative tumors. However, overall response rates remain modest, and durable complete responses are rare. Combination immunotherapy has not shown superior efficacy to monotherapy and is associated with increased toxicity.[21]

Beyond ICIs, other immunotherapeutic strategies are under investigation. These include vaccines targeting brachyury, which have demonstrated favorable safety profiles but limited clinical efficacy to date. Monoclonal antibodies and tumor vaccines have shown promise in early-phase studies, but larger trials have produced heterogeneous results, and no immunotherapy other than ICIs can currently be considered standard of care.[23-25]

The tumor immune microenvironment in chordoma is complex and may influence immunotherapy response. While some studies suggest that chordomas exhibit an immunologically "hot" phenotype, others classify them as immune-excluded, with limited direct interaction between T cells and tumor cells. High immune infiltration scores and HLA-I expression have paradoxically been associated with poorer prognosis, raising questions about the optimal immunotherapeutic approach and the need for better predictive biomarkers.[26]

Chemotherapy / targeted therapy

The current landscape is characterized by the use of tyrosine kinase inhibitors (TKIs) and emerging approaches targeting specific molecular and epigenetic alterations. TKIs, particularly imatinib, have demonstrated modest clinical benefit in advanced or metastatic chordoma, with generally low objective response rates (1.7% by RECIST, 29% by Choi criteria), but a substantial proportion of patients achieve disease stabilization. Median PFS with TKIs is approximately 8–9 months, and median OS is around 36–39 months, with imatinib showing a more favorable toxicity profile compared with other TKIs such as sorafenib, dasatinib, and lapatinib. Adverse events are common, with severe events in more than half of patients, but combination regimens (e.g., TKI plus mTOR inhibitor) may reduce severe toxicity compared with monotherapy.[27-29]

Agents targeting EGFR and VEGFR, such as erlotinib and bevacizumab, have also been explored, with some patients achieving partial responses or stable disease. Selection of targeted therapy is increasingly guided by molecular profiling, including evaluation of PDGFR, EGFR, and other actionable mutations or amplifications.[27,28]

Epigenetic therapies, including inhibitors of KDM6, HDAC, and EZH2, are under preclinical and early clinical development, reflecting the growing recognition of epigenetic dysregulation in the pathogenesis and resistance of chordoma.[30-33]

Given the biologically more aggressive nature of poorly differentiated chordoma, there is some consensus among experts that treatment should begin with chemotherapy regimens prior to surgery or radiotherapy, based on protocols used for Ewing sarcoma (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) or soft tissue sarcomas (doxorubicin/ifosfamide).

Overall, although targeted therapies have not yet supplanted surgery and radiotherapy as the main pillars of chordoma treatment, they offer disease stabilization and potential survival benefit in advanced or refractory cases. The field is rapidly evolving, with ongoing clinical trials investigating biomarker-driven approaches to optimize patient selection and outcomes.[30,31,33]

DISCUSSION

The management of chordoma represents a significant clinical challenge due to its rarity, locally aggressive behavior, and relative resistance to conventional therapies. Clinical presentation is usually

insidious and nonspecific, varying according to the anatomical location of the tumor, which often results in delays in diagnosis. Although magnetic resonance imaging and computed tomography are essential for anatomical characterization and surgical planning, definitive diagnosis relies on histopathology and immunohistochemistry, with expression of the transcription factor brachyury (TBXT) serving as a key diagnostic marker to distinguish chordoma from other neoplasms of notochordal or chondroid origin. En bloc surgical resection with negative margins remains the most effective therapeutic strategy, associated with higher local control and overall survival rates, particularly in mobile spinal locations. However, the anatomical complexity of the skull base and sacrum often limits the achievement of wide margins, making adjuvant radiotherapy — preferably with proton or carbon-ion beams — an important component of multimodal treatment in such cases. Despite incremental advances with targeted therapies, such as PDGFR and EGFR inhibitors, the role of systemic therapy remains limited and non-curative. The high rate of local recurrence, even after aggressive treatment, underscores the need for prolonged and continuous follow-up. Ongoing clinical trials aim to validate molecular and immunotherapeutic approaches that may, in the future, shift the paradigm of chordoma management.

CONCLUSIONS

Chordoma is a rare and complex neoplasm whose management requires a specialized multidisciplinary approach. Currently, it is classified into three subtypes: 1 — conventional and/or chondroid; 2 — dedifferentiated; 3 — poorly differentiated. Each of these subtypes has distinct epidemiology, treatments, and clinical course, which must be individualized. En bloc surgical resection with negative margins remains the cornerstone of treatment, being directly correlated with local control and patient survival. In situations where complete resection is not feasible, high-dose radiotherapy — especially with advanced technologies such as proton or carbon-ion beams — plays an essential role as adjuvant or definitive therapy. Although systemic therapy still plays a limited role, advances in the molecular understanding of the disease, particularly involving the PDGFR pathway and the transcription factor brachyury, have driven the development of promising targeted therapies. However, these interventions remain largely experimental. The prognosis of chordoma is directly related to tumor location, extent of resection, and availability of specialized therapeutic resources. Investment in translational research, multicenter clinical trials, and the centralization of care in centers of excellence is essential to improve clinical outcomes and expand therapeutic options for these patients.

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CES: Substantial contribution to the conception or design of the work, acquisition, analysis, and interpretation of data for the work; drafting of the work or critical revision of its intellectual content; final approval of the version of the manuscript to be published. OVAP: Substantial contribution to the conception or design of the work, acquisition, analysis, and interpretation of data for the work; drafting of the work or critical revision of its intellectual content; final approval of the version of the manuscript to be published.

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