

Factors associated with distant metastasis in chondrosarcoma

A comprehensive review of current research

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Abstract: Chondrosarcoma is the second most common primary malignant bone tumor, predominantly affecting individuals over 50 years of age. While low-grade tumors rarely metastasize, high-grade and dedifferentiated subtypes exhibit significant metastatic potential, with the lung being the most frequent site of dissemination. Current research identifies older age (> 60 years), high histological grade, axial tumor location (pelvis or spine), large tumor size (> 10 cm), and local recurrence as independent risk factors for distant metastasis. Metastasis represents a critical determinant of poor prognosis, with 5-year survival rates significantly falling to 23% upon the development of distant secondary lesions. Although surgical resection remains the primary treatment and can improve survival even in metastatic cases, chondrosarcoma is generally resistant to standard chemotherapy and radiotherapy. Despite established knowledge regarding distant metastasis, specific risk factors and prognostic markers for pulmonary metastasis remain underresearched, highlighting a critical gap for future investigation.

Keywords: chondrosarcoma, metastasis, prognosis, pulmonary, risk factors

1. Overview of chondrosarcoma

1.1. Overview

Chondrosarcoma is a malignant neoplasm of cartilaginous lineage. It represents the second most prevalent primary malignant bone tumor, accounting for approximately 30% of cases, surpassed only by osteosarcoma (about 35%).^[1] Global epidemiological data indicate that while osteosarcoma exhibits the highest annual incidence (2–3.5 cases per million), chondrosarcoma follows closely with an incidence of approximately 1 to 3 cases per million.^[2] Studies have demonstrated no statistically significant gender predilection. The pathology predominantly affects middle-aged and elderly cohorts, constituting

the most frequent primary bone malignancy within this demographic.^[3] The incidence increases with age, with the majority of patients being over 50 years old.^[4] Anatomically, lesions most frequently involve the proximal long bones (femur and humerus), pelvis, and scapula, followed by the spine; involvement of the sacral skeleton and skull base remains rare.^[3,4] Representative imaging includes an anteroposterior (AP) radiograph of a proximal femoral lesion (Fig. 1) and a computed tomography (CT) scan showing a lesion at the T12 level (Fig. 2).

1.2. Classification

Chondrosarcomas are generally classified into central and peripheral types based on their anatomical location. Histologically, the malignancy encompasses several distinct subtypes—including conventional, juxtacortical, myxoid, mesenchymal, clear cell, and dedifferentiated variants—with conventional chondrosarcoma constituting the vast majority (85%–90%) and nonconventional subtypes comprising the remaining 10% to 15%.^[5,6] Furthermore, tumors are stratified into three histological grades (I, II, and III) based on cellularity, degree of nuclear atypia, and mitotic activity, with higher grades directly correlating with an increased risk of distant metastasis. The differentiation of grade I chondrosarcoma from benign enchondroma presents a significant diagnostic challenge across both imaging and histopathology^[7–10]; consequently, the 2003 World Health Organization Classification of Tumors of Soft Tissue and Bone designated grade I lesions as borderline tumors. While grade I chondrosarcomas exhibit negligible metastatic potential,

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Figure 1. Anteroposterior (AP) radiograph demonstrating a lesion involving the proximal femur.

Andreou et al.^[11] suggested that metastasis in grade I cases may be due to the tumor having progressed to grade II. Conversely, grade III tumors demonstrate aggressive behavior, with metastasis occurring in approximately 70% of cases.^[12]

1.3. Clinical symptoms

Pain constitutes the cardinal presenting symptom, which may present with or without an associated soft tissue mass or localized swelling. Notably, the presence of worsening nocturnal pain often correlates with high-grade malignancy, necessitating urgent diagnostic evaluation. Conversely, clinicians must remain vigilant for cases exhibiting an insidious onset, where the malignancy remains clinically silent until the occurrence of a pathological fracture.



Figure 2. Computed tomography (CT) scan demonstrating a lesion involving the T12 vertebra.

1.4. Diagnostic methods

Current diagnostic imaging modalities for chondrosarcoma encompass plain radiography, CT, magnetic resonance imaging, and positron emission tomography–CT. Two-plane X-rays are performed first based on symptoms such as pain and swelling. A significant diagnostic challenge lies in differentiating grade I chondrosarcoma from benign enchondroma due to overlapping radiographic and histological features. In instances where plain radiography is inconclusive, magnetic resonance imaging serves as a critical adjunctive tool for differentiating low-grade malignancies from benign lesions.^[13] Characteristically, chondrosarcoma exhibits hypointensity on T1-weighted sequences and hyperintensity on T2-weighted sequences. Furthermore, CT imaging is instrumental for assessing cortical integrity and intralesional calcification, particularly within pelvic or long bone tumors.^[14] Additionally, comprehensive clinical staging mandates chest radiography and positron emission tomography–CT to exclude systemic disease.^[15]

Adherence to National Comprehensive Cancer Network (NCCN) guidelines necessitates histological confirmation via biopsy for all suspected cases of chondrosarcoma before the initiation of therapeutic intervention. Current clinical practice predominantly utilizes either open biopsy

or percutaneous needle biopsy for tissue acquisition.^[16] While open biopsy affords the retrieval of substantial tissue volume facilitating ancillary analyses—including flow cytometry, cytogenetics, and immunohistochemistry—it is associated with significant morbidity, encompassing the requirement for anesthesia, extended operative duration, heightened infection risk, and increased hospitalization costs.^[17,18] Conversely, percutaneous CT-guided needle biopsy—encompassing both fine-needle aspiration and core needle variants—offers a minimally invasive alternative performed under local anesthesia, demonstrating a diagnostic accuracy exceeding 85%.^[19–21] Figure 3 depicts the procedural precision of CT-guided percutaneous core needle biopsy; the axial view highlights the needle trajectory toward a lesion localized within the T12 vertebra. This modality secures adequate tissue sampling while mitigating soft tissue contamination and reducing healthcare resource utilization. Although both approaches carry an inherent risk of tumor seeding along the biopsy tract, the incidence of local recurrence is demonstrably lower with needle biopsy compared with open techniques.^[22]

Furthermore, comprehensive pretreatment evaluation should include serological markers such as complete blood count, lactate dehydrogenase, and alkaline phosphatase.^[23]

1.5. Treatment methods

According to current NCCN guidelines, surgical resection serves as the cornerstone of therapy for chondrosarcoma.^[1] The selection of the specific surgical strategy is strictly dictated by the tumor's anatomical site and malignancy

grade. Regarding resectable low-grade (grade I) tumors, prior investigations have proposed intralesional resection as a viable option to balance tumor eradication with the reduction of local recurrence and functional preservation.^[24,25] However, NCCN guidelines maintain a recommendation for wide resection in cases of resectable grade I or intracompartmental tumors. A meta-analysis by Chen et al.^[26] encompassing 394 patients (214 intralesional vs. 180 wide resection), revealed no statistical difference in therapeutic efficacy between these modalities for low-grade chondrosarcoma. In contrast, for high-grade (grade II/III) and extracompartmental lesions, wide resection with negative margins is the mandatory standard of care.^[27,28] To optimize oncologic outcomes, a surgical margin exceeding 4mm is recommended to significantly mitigate the risk of local recurrence and subsequent metastatic progression.^[29]

Due to the indolent growth kinetics and low mitotic index characteristic of chondrosarcoma, the therapeutic efficacy of conventional radiotherapy—which targets the cell division cycle—is inherently limited. Nevertheless, radiotherapy remains a viable modality for the management of unresectable or subtotally resected lesions, serving to restrain local tumor expansion and provide palliative analgesia, thereby enhancing quality of life.^[5] This utility is corroborated by McNaney et al.^[30] and Krochak et al.^[31] While conventional radiotherapy typically necessitates doses exceeding 60 gray (Gy) to achieve adequate local control, such high-dose regimens are frequently contraindicated for lesions involving the spine or skull base due to the proximity of critical neural structures. Conversely, proton beam therapy leverages



Figure 3. Axial computed tomography (CT) image demonstrating the percutaneous core needle biopsy technique for a lesion at the T12 vertebral level.

high-energy particle physics to deliver precise dosimetry to deep-seated tumors. Compared with traditional photon-based methods, proton beam therapy demonstrates superior local control rates (exceeding 90%)^[32] while minimizing collateral damage to surrounding tissues, rendering it particularly suitable for the treatment of chondrosarcomas located in the axial skeleton and skull base.^[33,34]

Analogous to radiotherapy, systemic chemotherapy demonstrates limited efficacy in the management of chondrosarcoma, particularly within the conventional and clear cell subtypes. This inherent chemoresistance is significantly attributed to the expression of the *multidrug resistance gene 1* (*MDR1*) p-glycoprotein (P-gp). P-gp serves as a negative predictor of chemosensitivity, with positive expression correlating with refractoriness to cytotoxic agents.^[35] Furthermore, chemoin sensitivity in chondrosarcoma is associated with the overexpression of antiapoptotic proteins. Previous investigations have established that the upregulation of B-cell lymphoma 2 (*Bcl-2*) family members constitutes a critical mechanism of drug resistance; consequently, the inhibition of these proteins may sensitize chondrosarcoma cells to chemotherapeutic agents.^[36–38] Notably, B-cell lymphoma-extra large (*Bcl-xl*) exhibits the highest expression profile within this family, and its inhibition has been shown to potentiate sensitivity to doxorubicin and cisplatin regimens while concurrently suppressing tumor proliferation.^[39] Limited evidence suggests that doxorubicin-based regimens may provide therapeutic benefit in dedifferentiated and mesenchymal subtypes.^[40–45] Additionally, emerging modalities such as anti-PDGFR (platelet-derived growth factor receptor) antibodies, targeted therapies, and phytomedicine are currently under investigation, although clinical validation remains requisite.^[46]

1.6. Prognosis

Prognostic outcomes in chondrosarcoma are strictly stratified by histological malignancy, where increasing tumor grade correlates with a progressively deleterious prognosis. A comprehensive Dutch cohort study comprising 2,186 cases quantified this grade-dependent survival divergence: grade I tumors exhibited 3-, 5-, and 10-year survival rates of 96%, 93%, and 88%, respectively; grade II lesions showed rates of 82%, 74%, and 62%; whereas grade III tumors demonstrated significantly poorer outcomes, with rates of 38%, 31%, and 26%, respectively. Furthermore, Song et al.^[47] constructed a predictive model based on independent prognostic factors to estimate 3-year and 5-year survival probabilities. The clinical application of this model facilitates precise risk stratification, allowing for tailored therapeutic surveillance and optimized management strategies for high-risk patient cohorts.

2. Distant metastasis in chondrosarcoma

2.1. Epidemiology of chondrosarcoma metastasis

Utilizing the SEER (Surveillance, Epidemiology, and End Results) database—encompassing 34.6% of the US population—Song et al.^[48] analyzed a cohort of 2,349 patients, reporting a metastatic rate of 8% ($n = 180$). A recent epidemiological study spanning 2000–2014 documented an annual chondrosarcoma incidence of 1.5 cases per million, with a metastasis rate of 10%.^[49] Notably, other investigations have cited significantly higher metastatic rates, reaching up to 38%^[50–52]; this divergence may be attributed to the SEER database's lack of data regarding asymptomatic chondrosarcomas, thereby potentially underestimating the true metastatic incidence. Analogous to osteosarcoma, the lung serves as the predominant site of distant dissemination,^[53] followed in frequency by soft tissue, lymph nodes, and the



Figure 4. Pulmonary computed tomography (CT) scan depicting a metastatic lesion in a patient with chondrosarcoma confirmed via percutaneous needle biopsy.

brain. A representative case of such pulmonary spread is illustrated in Figure 4, depicting a metastatic nodule identified on CT imaging in a patient with biopsy-proven disease. Andreou et al.^[11] noted that within a series of 225 patients, 14 exhibited distant metastasis, with 12 cases involving the lung (5.3% incidence). Similarly, Ozaki et al.^[54] identified pulmonary metastasis as the primary mode of spread, reporting a rate of approximately 26.4%.

2.2. Risk factors for chondrosarcoma metastasis

Contemporary investigations into the metastatic potential of chondrosarcoma have extensively analyzed clinical determinants, including age at diagnosis, gender, race, primary anatomic site, histological subtype, malignancy grade, tumor diameter, and local recurrence status. The prevailing consensus identifies advanced age, high histological grade, dedifferentiated subtype, axial skeletal involvement, large tumor diameter, and local recurrence as independent risk factors for distant dissemination. Advanced age, in particular, exerts a deleterious effect on overall prognosis, a correlation partially mediated by its association with increased metastatic risk. In a population-based study utilizing the SEER database ($n = 2,349$), Song et al. stratified patients into four age cohorts (< 40, 40–49, 50–59, and > 60 years). Both univariate and multivariate logistic regression analyses established age > 60 years as an independent predictor of distant metastasis, demonstrating an approximate 2-fold increase in risk compared with younger cohorts.^[48]

In a retrospective analysis of 227 chondrosarcoma cases, Lee et al.^[55] stratified the cohort based on pathological grading into high-grade ($n = 141$) and low-grade ($n = 86$) groups. The study observed metastasis in 47 cases (33%) within the high-grade group, compared with only 3 cases (3%) in the low-grade group; chi-square analysis confirmed this disparity as statistically significant ($p < 0.0001$), indicating that high-grade malignancy significantly predisposes patients to metastatic progression. Validating these findings, Thorkildsen et al.^[56] identified high tumor grade as an independent risk factor for metastasis. Furthermore, they noted that dedifferentiated chondrosarcoma, a high-grade subtype, exhibits the highest metastatic rate among all variants at approximately 65%. This is consistent with findings by Amer et al.^[57] who demonstrated that the dedifferentiated subtype is associated with a statistically significant elevation in metastatic rate compared with other histological forms.

Regarding the primary anatomical site, the intricate architecture of the pelvis and spine—coupled with the immediate proximity of critical neurovascular and visceral structures—frequently precludes the attainment of wide, tumor-free margins, particularly in high-grade chondrosarcomas. Consequently, tumors of the axial skeleton demonstrate a statistically significant increase in metastatic incidence compared with appendicular lesions.^[56,58] Corroborating this, Lee et al.^[55] identified

pelvic location as a distinct risk factor for metastatic progression. Mechanistically, the proximity of axial tumors to Batson's venous plexus facilitates hematogenous dissemination to distant sites, predominantly the lungs. Furthermore, spinal and pelvic lesions frequently exhibit an insidious clinical onset; at the time of diagnosis, cortical breach and invasion into adjacent soft tissues, venous sinuses, or regional lymphatics are often established. Andreou et al.^[11] demonstrated that in spinal chondrosarcoma, the risk of distant metastasis is significantly elevated following intralesional resection compared with wide excision. Moreover, pelvic location and inadequate surgical margins are established risk factors for local recurrence,^[29,59] which acts as a driver for metastasis in high-grade malignancy.^[12,54] Stevenson et al.^[29] advocate for a minimum surgical margin of 4 mm across all grades to mitigate the risk of local recurrence and subsequent metastatic dissemination.

To elucidate the relationship between tumor burden and metastatic progression, Song et al.^[48] stratified tumor diameters into three cohorts (< 5, 5–10, and > 10 cm), demonstrating a positive correlation between increasing tumor size and the risk of metastasis. Notably, a tumor diameter exceeding 10 cm was identified as an independent risk factor for dissemination. Given the indolent growth kinetics of chondrosarcoma, diagnostic delays frequently result in substantial tumor expansion, thereby facilitating the invasion of surrounding tissues and vascular structures—specifically venous sinuses—which promotes hematogenous and lymphatic spread.

Furthermore, an analysis of therapeutic modalities indicated significant disparities in metastatic outcomes.^[60] Patients with unresectable, axially located, or advanced-stage tumors who were selected for palliative radiotherapy exhibited the highest metastatic rate (41.4%), whereas those managed solely with surgical resection demonstrated the lowest incidence (4.4%). In the aggregate cohort, metastasis occurred in 22% of patients receiving radiotherapy compared with only 6.5% of those who did not. Surgical intervention was associated with a marked reduction in metastatic prevalence, lowering the rate from 30.7% to 5.6%.

2.3. Prognostic factors for chondrosarcoma metastasis

The occurrence of distant metastasis is consistently identified in the literature as an independent negative prognostic determinant for chondrosarcoma. Relative to nonmetastatic cohorts, patients presenting with metastatic disease demonstrate significantly inferior outcomes, exhibiting a mortality risk more than 4-fold higher.^[49,60] Epidemiological data indicate that while the 5-year survival rate for localized chondrosarcoma is approximately 89%, this figure precipitates to 23% in the presence of metastasis.^[61] Furthermore, advanced age—specifically > 50 years—is well-established as an independent adverse prognostic factor,^[50,52,60] associated with a 2-fold elevation in mortality compared with younger counterparts.

Similarly, age remains a critical determinant of survival within the metastatic cohort; using 60 years as a baseline, each incremental year of age correlates with a progressive increase in mortality risk.^[62] Regarding histological subtypes, dedifferentiated chondrosarcoma is characterized by high metastatic potential, translating to diminished survival outcomes.^[51] In univariate analysis of metastatic cases, dedifferentiated histology was associated with a mortality risk twice that of conventional chondrosarcoma ($p = 0.002$); however, this significance was not maintained in multivariate analysis.^[62]

Several studies identify tumor location within the axial skeleton—specifically the pelvis and spine—as an independent negative prognostic factor for chondrosarcoma.^[12,61,63] Notably, patients with pelvic tumors demonstrate significantly inferior survival rates compared with those with appendicular lesions.^[11] However, in the specific context of metastatic disease, the prognostic significance of the primary tumor site remains controversial.^[64] Given the paucity of data elucidating the relationship between the primary anatomical site and outcomes in metastatic chondrosarcoma, further investigation is warranted to validate these findings.

Histological grade is universally recognized as a critical independent prognostic determinant. A Norwegian cohort study substantiated that higher malignancy grade correlates with worse outcomes in metastatic patients. Wang et al.^[64] corroborated this, reporting a 2.5-fold increase in the risk of poor prognosis for high-grade tumors compared with low-grade variants; this attrition is likely attributable to the heightened propensity for metastasis and local recurrence inherent to high-grade lesions. Furthermore, Nakamura et al.^[65] in a study of 179 patients (including 20 with pulmonary metastasis), identified tumor grade as an independent risk factor for both overall survival and cancer-specific survival. Thus, regardless of the timing of metastatic diagnosis, histological grade remains a robust prognosticator.

Regarding therapeutic management, current clinical practice guidelines emphasize wide resection with negative margins as the mainstay of treatment, given the tumor's characteristic refractoriness to radiotherapy and chemotherapy.^[1] Resection of the primary tumor has been demonstrated to improve survival rates and prolong survival duration.^[62] Nie et al. analyzed the impact of surgical intervention across different stages, revealing that within the distant metastasis cohort, patients undergoing surgical resection exhibited the most favorable prognosis. Conversely, no statistical difference in survival was observed between patients undergoing amputation and those managed nonsurgically.^[60]

3. Conclusions

The dismal prognosis associated with distant metastasis in chondrosarcoma is well-established, with pulmonary metastasis representing the predominant pattern of dissemination. While extant literature has extensively

characterized the risk and prognostic profile for distant metastasis in general, there remains a paucity of data specifically delineating the determinants of pulmonary involvement. Consequently, it is imperative to elucidate the specific risk factors governing the incidence and prognostic outcomes of pulmonary metastasis in chondrosarcoma.

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Written informed consent was obtained from the patient for the publication of accompanying images.

Conflicts of interest

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The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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