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# Mesenchymal Chondrosarcoma

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## Abstract

**Purpose:** To review the treatment and outcomes of patients with mesenchymal chondrosarcomas (MC).

**Materials and Methods:** Review of the pertinent literature.

**Results:** MC is a rare aggressive small round blue cell malignancy that may arise in either bone or soft tissue. It usually presents in the 2nd or 3rd decade of life and exhibits an approximately equal gender predilection. Patients usually present with pain and swelling. The majority of MCs arise in either the trunk or extremities. Distant metastases are present at diagnosis in about 15% of patients. The most common sites for distant metastases are lung and bone. The optimal treatment is surgery. Although the role of adjuvant chemotherapy is unclear, an anthracycline-based chemotherapy regimen combined with ifosfamide or cisplatin, may be considered. Adjuvant radiation therapy (RT) is employed for patients with close (<5 mm) or positive margins as well as those with incompletely resectable tumors. The most common mechanism of recurrence is hematogenous dissemination. Although most recurrences are observed within 5 years of treatment, late recurrences are not unusual. The likelihood of successful salvage in the event of a recurrence is modest. The overall survival rates for all patients are approximately 50% at 5 years and 40% at 10 years. The overall survival rates for the subset of patients with localized disease that is resected are approximately 70% to 80% at 5 years and 60% at 10 years.

**Conclusion:** Patients with MCs are optimally treated with surgery. The role of adjuvant chemotherapy is uncertain. However, given the relatively high risk of recurrence, adjuvant chemotherapy should be considered in medically fit patients. Radiation therapy should be considered for those with incompletely resectable tumors and those with inadequate margins.

**Keywords:** mesenchymal chondrosarcoma; soft tissue sarcoma

## Introduction

Mesenchymal chondrosarcoma (MC) is a rare, aggressive small round blue cell malignancy that may arise in bone or soft tissue [1–10]. It exhibits a high propensity for hematogenous dissemination and is associated with significant morbidity and mortality. Because of its rarity, the optimal treatment is unclear. Most publications pertaining to MCs are small case series or epidemiologic studies where the details of treatment may be variable or unavailable [1, 3, 11–15]. The purpose of this paper is to discuss the treatment and outcomes of patients with this uncommon malignancy.

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## Materials and Methods

A PubMed search was conducted using the keywords "mesenchymal chondrosarcoma" and limited to publications from within the last 3 years. Approximately 166 peer-reviewed publications were identified. Those related to diagnosis, treatment, and outcomes were reviewed. The references of selected papers were also reviewed to select additional articles.

## Results

### Presentation

MCs are uncommon and comprise 3% to 10% of all chondrosarcomas [3]. They may arise in either bone or soft tissue, exhibit an approximately equal gender predilection, and most often present during the 2nd or 3rd decades of life. Schneiderman et al reported on 205 patients included in the Surveillance, Epidemiology, and End Results database between 1973 and 2011 [1]. The tumors were extraskeletal in 123 patients (60%), the mean age at diagnosis was 37 years, and 114 patients (56%) were male. Forty-four percent of patients presented during the 2$^{nd}$ or 3$^{rd}$ decade of life [1]. Patients usually present with pain and swelling at the primary site [3]. Frezza et al [3] reported on 113 patients treated at 17 centers and in one cooperative group under the auspices of the European Musculoskeletal Oncology Society. Age ranged from 11 to 80 years; 61 patients (54%) presented in the 2$^{nd}$ or 3$^{rd}$ decade of life. Seventy-two patients (64%) presented with skeletal primary lesions. Site distribution was: craniofacial, 15 patients (13%); trunk, 53 patients (47%); and extremities, 45 patients (40%). Seventeen patients (15%) presented with distant metastases that were located in the lung (7 patients, 42%), bone (2 patients, 11%), and in multiple sites (8 patients, 47%). Size at diagnosis is variable. Huvos et al [9] reported on 35 patients treated at the Memorial Sloan Kettering Cancer Center and observed a mean maximum diameter of 9.5 cm (range, 4 to 18 cm).

### Radiographic Findings

Skeletal primaries appear lytic and destructive on plain radiographs with a poorly defined periosteal reaction [3]. Cortical breakthrough and extraosseous extension are common [16]. Mottled calcifications are seen in about one third of cases; pathological fractures are uncommon [3]. Computed tomography (CT) findings are non-specific and consistent with a destructive bone malignancy often with subtle matrix mineralization [16]. MCs are isointense compared with muscle and exhibit decreased signal intensity compared with fat on T1-weighted magnetic resonance imaging [12]. They display increased intensity compared with muscle on T2-weighted magnetic resonance imaging [12]. Tumor margins are often well defined. They may appear heterogeneous with serpentine signal voids on T2-weighted images [16].

### Pathology

Histologically, MCs are composed of a mixture of immature cartilage and small round or spindled cells; the small round blue cell component mimics other round cell sarcomas, such as Ewing's sarcoma, and frequently contains a prominent "hemangiopericytoma-like" vascular proliferation [3, 17]. The small cell component stains positively for SOX9 and negatively for FLI-1, which may help distinguish the tumor from a Ewing's sarcoma [3]. A recurrent *HEY1-NCOA2* gene fusion has been identified in nearly 80% of MCs, and more recently a novel t(1;5)(a42;q32) tranlocation resulting in an *IRF2BP2-CDX1* has been described in an extraosseous MC [14]. Analysis of tumors for these alterations can be used in diagnostically challenging cases to aid in diagnosis.

### Treatment

The treatment of patients with MCs depends on the primary site, extent of disease, the presence of distant metastases at diagnosis, and the medical condition of the patient. Patients who have tumors that are amenable to a gross total resection are likely best treated with surgery [10, 18]. Patients who have tumors that have been inadequately resected with close ($<$5 mm) or positive margins, as well as those that are incompletely resectable, should be considered for radiation therapy (RT). MCs that arise in the skull base or spine are usually incompletely resectable and likely would benefit from proton beam or carbon ion RT to produce a more conformal dose distribution and reduce the RT dose to surrounding normal tissues including the brain, visual apparatus, and spinal cord [19]. Because data pertaining to RT for MCs are limited, it is necessary to extrapolate data from soft tissue sarcomas and other bone sarcomas [20–24]. The dose fractionation schedules are: negative (R0) margins, 60 Gy in 30 fractions over 6 weeks; positive margins (R1), 66 Gy in 33 fractions over 6.5 weeks; and gross disease (R2), 70 Gy in

35 fractions over 7 weeks. For the occasional patient suitable for preoperative RT, the schedule is approximately 50 Gy in 25 fractions over 5 weeks [20, 21].

The role of adjuvant chemotherapy is unclear because of the rarity of the disease and the understandable lack of prospective trials. Some have reported no apparent benefit from adjuvant chemotherapy while others have observed a survival benefit [10, 18]. In general, patients treated with adjuvant chemotherapy receive an anthracycline combined with ifosfamide or cisplatin.

The management of patients presenting with distant metastases is individualized. Those who are young with limited distant metastases may be considered for chemotherapy combined with aggressive local management with surgery and/or RT. Limited distant metastases may also be suitable for stereotactic body RT. Patients who are elderly, infirm, and/or with extensive disease may best be managed with palliative intent.

## Outcomes

There are two general sources of outcomes data: 1) large series of patients from multiple institutions where treatment details are lacking and overall survival is the primary endpoint; and 2) small single institution series where treatment details are available, albeit varied, but small patient numbers limit one's ability to determine the impact of various treatment variables on outcomes.

Schneiderman et al reported on 205 patients from the Surveillance, Epidemiology, and End Results database who were treated between 1973 and 2011 and had a mean followup of 129 months [1]. Treatment details were not available. The overall survival rates were 51% at 5 years and 43% at 10 years. The 5- and 10-year overall survival rates versus primary site were: appendicular, 50% and 39%; axial, 37% and 31%; and cranial, 74% and 64%, respectively ($p=0.002$). The 5- and 10-year survival rates for skeletal versus extraskeletal site were: skeletal, 49% and 41%; and extraskeletal, 52% and 44%, respectively ($p=0.82$). Multivariate analysis of overall survival revealed that this outcome was improved for patients who presented with localized disease ($p = 0.002$), decreasing lesion size ($p < 0.001$), and cranial tumors in young patients ($p<0.001$). In contrast, age ($p=0.81$), sex ($p=0.33$), and skeletal vs extraskeletal site ($p=0.06$) did not significantly impact this endpoint.

Frezza et al reported on 113 patients from 17 centers and 1 cooperative group who were treated between 1971 and 2012 [3]. The overall survival rates were 70% at 5 years and 54% at 10 years. The overall survival rates for 95 patients who presented with localized disease that was resected were 79% at 5 years and 60% at 10 years. Local recurrence was observed in 16 of 95 patients (17%); 5 patients had an isolated local recurrence and 11 also had distant metastases. Four of 5 patients with an isolated local recurrence underwent salvage surgery and were rendered disease-free. The remaining patient refused salvage surgery and died with disease. Distant metastases were observed in 45 of 95 patients (47%) with resected localized disease. Distant metastases were observed within 2 years in 25 of 45 patients (55%), during years 3 and 4 in 8 patients (18%), and during year 5 or later in 12 patients (27%). Six of 45 patients (13%) developed distant metastases after 10 years and 1 patient presented with distant metastases after 20 years. Sixteen of 45 patients (36%) presented with distant metastases to the lung alone, 12 patients had distant metastases to the bone only, and 17 patients (38%) had distant metastases in multiple sites. Tissue of origin, primary site, and resection margins did not significantly impact prognosis. However, for those in whom the data were available, patients with R1 resection margins had a higher local recurrence rate than those with R0 margins, 8 of 30 patients (27%) vs 1 of 46 patients (2%) [$p=0.002$]. Multivariate analysis revealed that the use of adjuvant chemotherapy was the only variable associated with a reduced risk of death ($p=0.004$). The overall survival rates after chemotherapy versus no chemotherapy were: 5 years, 84% vs 73%; and 10 years, 80% vs 46%, respectively. The progression free survival rates after chemotherapy vs no chemotherapy were: 5 years, 70% vs 35%; and 10 years, 67% vs 27%, respectively.

Cesari et al reported on 26 patients treated between 1959 and 2003 at the Instituti Ortopedici Rizzoli with surgery (24 patients), and/or RT (5 patients), and chemotherapy (12 patients) [18]. Patients were followed for a median 48 months (range, 7 to 237 months). Overall survival was better for those treated surgically ($p=0.0007$) and those who presented with localized disease at diagnosis ($p=0.02$). Of those who underwent complete resection, disease-free survival was improved for those who received adjuvant chemotherapy ($p=0.008$).

Kawaguchi et al reported on 37 patients treated at the M.D. Anderson Cancer Center between 1979 and 2010 with surgery alone (8 patients), surgery and chemotherapy (13 patients), surgery and RT (5 patients), surgery and chemotherapy and RT (8 patients), chemotherapy alone (1 patient), chemotherapy and RT (1 patient), and palliative care (1 patient) [10]. Thirty of 37 patients (81%) presented with localized disease. Mean followup was 6 years (range, 1 month to 17 years). The overall survival rates were 51% at 5 years and 37% at 10 years. Disease-free survival rates were 23% at 5 years and 5% at 10 years. The local control rates were 85% at 5 years and 68% at 10 years. Distant metastases-free survival rates were 37% at 5 years and

15% at 10 years. Age <30 years and male sex were associated with decreased overall survival and disease-free survival. The use of RT was associated with improved local control (p=0.037) in patients who presented with localized disease.

## Discussion

MC is a rare malignancy and the treatment is based on incomplete and sometimes conflicting information. Therefore, the level of evidence upon which treatment recommendations is based is relatively low. The optimal treatment is likely resection for those who present with tumors that are amenable to gross total resection. Although the potential benefit of adjuvant chemotherapy is unclear, because of the poor prognosis, patients who are medically fit should be considered for anthracycline-based adjuvant chemotherapy. Patients with inadequate margins and those with incompletely resectable lesions should be considered for adjuvant or definitive RT. Patients with skull base or spine tumors may benefit from proton or carbon ion RT to reduce the dose to the surrounding normal tissues such as the brain, visual apparatus, and spinal cord to decrease the probability of late complications. The management of patients presenting with distant metastases is individualized based on the extent of disease and the medical condition of the patient.

## ADDITIONAL INFORMATION AND DECLARATIONS

**Conflicts of interest:** The authors have no conflicts of interest to disclose.

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