Review Article

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# Evaluation of different treatment and management options for chondrosarcoma; the prognostic factors determining the outcome of the disease

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**Importance:** This review provides an in-depth discussion of the different treatment and management strategies adopted for chondrosarcoma, the various outcomes and the prognostic factors of the disease. Chondrosarcoma is the third most common malignant bone tumor after myeloma and osteosarcoma. It is characterized by the production of a cartilaginous matrix by malignant cells. It can be classified according to the source of its origin, histopathologic grade, site of occurrence, and rarity. Chondrosarcomas that are de novo in nature are classified as primary chondrosarcomas, while those derived from pre-existing enchondromas or osteochondromas are regarded as secondary chondrosarcomas. Other rare forms of chondrosarcoma include dedifferentiated, mesenchymal, and clear cell chondrosarcomas.

**Observations/Findings:** Early diagnosis, accurate interpretation of histopathology, precise grading, and careful localization are crucial in the management of chondrosarcoma. Surgery is the treatment of choice. Three forms of surgical interventions are present; curettage, radical resection, and amputation. The choice of procedure depends on the size and site of the lesion and degree of malignancy. Radical procedures give the most promising outcomes with wider margins yielding better prognosis. Recurrence is usually seen with delayed surgery, high histopathologic grading, inadequate surgical procedures, marginal excision or curettage, tumor present in inaccessible sites such as sacrum and metastasis.

**Conclusion:** Chondrosarcoma is responsible for placing a significant burden on pediatric as well as adult orthopedic oncology. Optimum diagnosis, accurate interpretation of histopathology, precise grading, careful localization, and timely as well as adequate management is crucial to successfully manage and prevent recurrence of the disease. Surgery is the most effective form of treatment. The main goal of treatment and management is to keep well ahead of the growth of the neoplasm and to prevent recurrences.

**Keywords:** Chondrosarcoma, Osteosarcoma, Curettage, Radical resection, Phenolization, Cryosurgery

Chondrosarcoma is a term used for a group of cartilaginous bone tumors that lack histologic and morphologic consistency. Chondrosarcoma is considered to be the most common primary malignant bone tumor after myeloma and osteosarcoma[1]. Chondrosarcoma is characterized by the production of a cartilaginous matrix by malignant cells. Chondrosarcomas may develop at any age with a predilection toward femur and pelvis[2]. Henderson and Dahlin[3] reported the age range of 8–80 years with peak in between 30 and 60 years. In another study, majority of primary chondrosarcoma were seen in fifth to seventh decades of life[4,5]. It has been well-established that secondary chondrosarcoma more frequently occur 10 years earlier than primary chondrosarcoma. Irrespective of the age at which chondrosarcoma develops, it has been observed that patients who have received adequate and prompt surgical treatment were cured while those patients who did not receive adequate surgical intervention died within 10 years or so[3]. After selection of appropriate management option, the second most challenging aspect of chondrosarcoma is to reduce the chances of its recurrence. Although these tumors are slow growing and rarely metastasize, local recurrence is high especially after inadequate excision[4].

This review will analyze the different treatment and management options adopted by the surgeons globally and will assess the outcomes and prognostic factors. It will also assess the frequency of local recurrence and treatment measures taken by the surgeons to reduce the risk of recurrence in patients.

## Discussion

### *Definition of chondrosarcoma*

Chondrosarcoma is one of the sarcomas, which is defined as a malignant neoplasm that produces pure cartilage giving rise to abnormal bone or cartilage growth[5]. According to epidemiological studies, even though the occurrence of bone cancers is rare,

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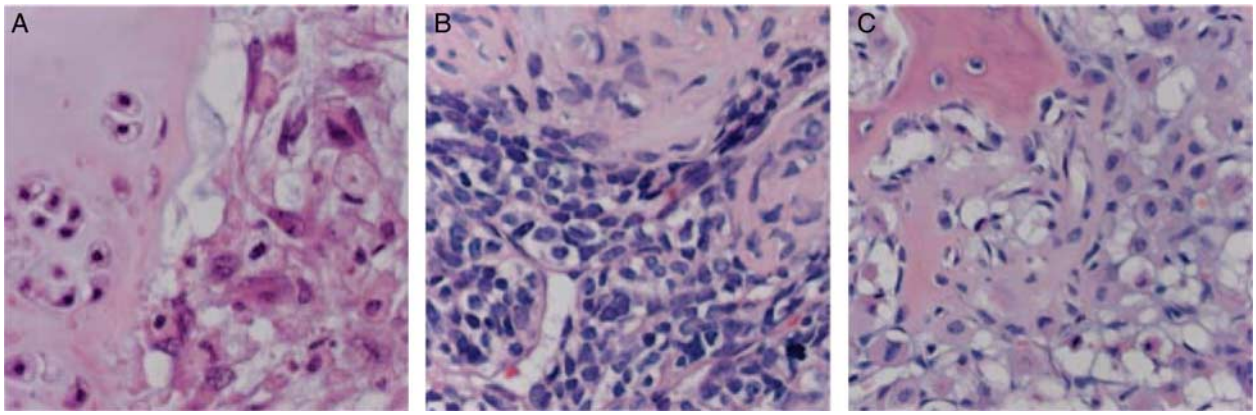


**Figure 1.** Histology of rare chondrosarcoma subtypes. A, Dedifferentiated chondrosarcoma with a sharp interface between conventional chondrosarcoma (left) and anaplastic sarcoma (right). B, Mesenchymal chondrosarcoma with undifferentiated small blue round cells (below) and cartilage differentiation (top). C, Clear cell chondrosarcoma demonstrating chondrocytes with abundant clear cytoplasm, cartilaginous matrix, and deposition of osteoid (hematoxylin and eosin staining, ×500). Courtesy of Gelderblom et al[1]. Reproduced with the permission of The Oncologist and Wiley Publishers.

chondrosarcoma is the second most common primary malignant bone tumor after osteosarcoma constituting of about 30% of all bone tumors[6]. Most common sites for a chondrosarcoma to occur are the pelvis, proximal femoral shaft, ribs, and shoulder girdle with slight male dominance[7].

### *Classification of chondrosarcoma*

Chondrosarcoma is divided into 2 broad categories (**Fig. 1**):

(i) Primary chondrosarcoma: it arises from the center or the periphery of the bone without a benign precursor.
(ii) Secondary chondrosarcoma: it arises from a pre-existing enchondroma or some other benign tumor such as osteochondroma, Ollier's, Paget's or Chondroblastoma, etc.

Primary chondrosarcoma is further classified into central and peripheral primary tumors. Primary central chondrosarcoma comprises of the following types (**Figs. 1**, **2**):

(a) Conventional primary central chondrosarcoma: conventional chondrosarcoma also known as central chondrosarcoma is the most common subtype of chondrosarcoma and may further be divided according to their grades. It may be low, intermediate or of high-grade chondrosarcoma. They classically occur in the fourth and fifth decades of life with a slight predilection toward male sex with a 2:1 prevalence ratio[8,9].
(b) Dedifferentiated primary central chondrosarcoma: they are composed of islands of well-differentiated chondrosarcoma juxtaposed to an additional nonchondroid mesenchymal component. They make up 10% of all reported chondrosarcomas with a poor prognosis and survival rate of 2 or more years[5,10].
(c) Mesenchymal primary central chondrosarcoma: they are characterized by a bimorphic pattern, with undifferentiated small round cells and islands of well-differentiated hyaline cartilage. They make up 3%–10% of all primary chondrosarcomas, with frequency in second till fourth decade of life[11].

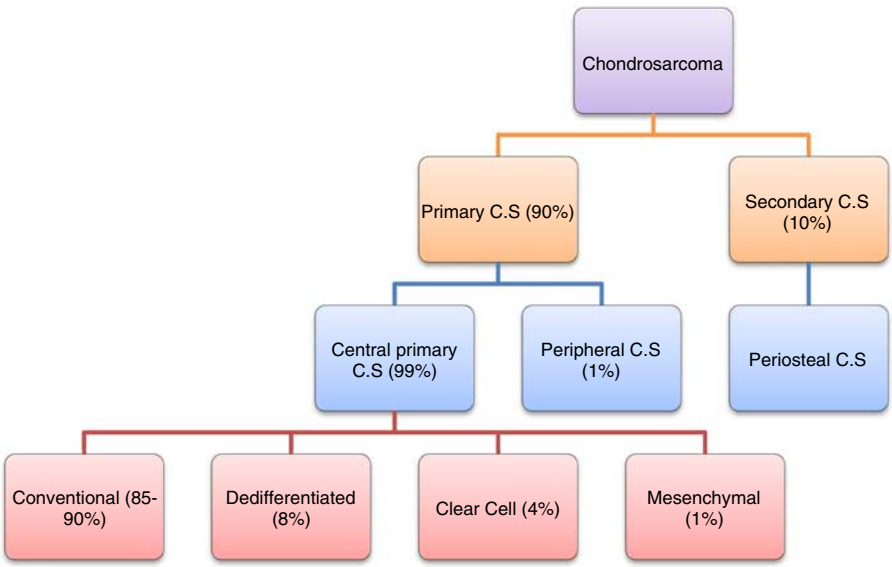


**Figure 2.** Classification of chondrosarcoma (CS).

(d) Clear cell primary central chondrosarcoma: they are low grade chondrosarcomas, which has a predilection toward the epiphyseal ends of long bones. They are characterized, histologically, by bland clear cells in addition to hyaline cartilage and make up 2% of all chondrosarcomas[12]. More common in men; they are reported in age range of 12–84 years[13,14].

### *Difference between a chondroma and central chondrosarcoma*

There are 3 general differentiating points between a chondroma, which is benign, and a chondrosarcoma, which is malignant[7]:
(i) a benign tumor is always well demarcated,
(ii) fusiform thickening of the shaft is highly suggestive of malignancy,
(iii) perforation of the cortex confirms malignancy.

### *Difference between a chondroma and a peripheral chondrosarcoma*

A chondroma can be differentiated from a peripheral chondrosarcoma by observing the widespread blotchy calcification and disappearance of the sharp boundary between the core of cancellous bone and its cartilage cap[15].

### *Difference between osteosarcoma and chondrosarcoma*

Anatomically, chondrosarcoma is the malignancy of the chondroblast cells while osteosarcoma is the malignancy of osteoblasts. High-grade chondrosarcomas are very hard to differentiate on the basis of cytomorphology or histology, from chondroblastic osteosarcoma in which tumor osteoid is absent[16]. The tumor cells in osteosarcoma contain plethora of alkaline phosphatase which is very scarce in chondrosarcoma[17]. Most of the osteosarcomas occur in children while chondrosarcoma target the age of 40[18].

### *Difference between enchondroma and chondrosarcoma*

Enchondroma is a benign hyaline cartilage neoplasm of medullary bone, while chondrosarcoma is a malignant tumor of the cartilage. Enchondroma are hypocellular and painless whereas chondrosarcoma is hypercellular and painful[19].

Primary chondrosarcoma is the one which arises without a benign precursor. It is most often centrally located, originates within the bone and is confined by the cortex or burst forth through the cortex of the bone resulting in a formation of a malignant mass in soft tissues[5,7]. More than 90% of all chondrosarcomas are primary (conventional) type[5].

Secondary chondrosarcoma arises from a previously benign chondroma. Its incidence is rare and is located peripherally with bulk of the chondrosarcoma outside the bone, extending outwards through the cortex[6,7]. Two percent of chondrosarcomas are associated with solitary osteochondroma and its risk is 5%–25% from osteochondromatosis[20]. Patients with Ollier disease and Maffucci syndrome have a 25%–30% risk of developing chondrosarcoma[21,22].

### *Localizing chondrosarcoma*

Because of under/misdiagnosis, it is very difficult to localize the commonly effected sites. However, according to the literature, the most commonly involved sites are long tubular bones, innominate bones, and ribs[18]. A case series of 288 cases observed that innominate bones are the most commonly involved bones, followed by ribs, femur, humerus, spine, etc[3].

### *Clinical findings of chondrosarcoma*

Chondrosarcomatous lesions are high-grade, yet mostly slow growing tumors with few mitotic figures. Patients can present with pain and/or swollen region with or without functional disability.

Central chondrosarcoma presents with a shorter history. Patient may complain of a dull, aching pain at the site of the tumor which exacerbates periodically. Some functional disability may be associated with it[18].

Peripheral chondrosarcoma presents with a long history of mass. The mass appears to be painless, slow growing, firm or bone-hard, not very tender without any erythema of the skin. When the area involved is near a joint, the mass might be swollen with associated restriction of motion of the joint.

### *Morphology of chondrosarcoma*

#### Gross and histologic features

According to literature morphology of chondrosarcoma is described as "viable areas of noncalcification that shows 3 main characteristics findings:
(i) many cells with plump nuclei;
(ii) more than an occasional cell with 2 such nuclei; and especially
(iii) giant cartilage cells with large single or multiple nuclei or with clumps of chromatin."

Two cases of central/primary chondrosarcoma in the femur were reported as chondrosarcomas, with localized spontaneous cortical perforations as an ominous gross feature. One of them showed stump of the marrow cavity filled with cartilage. After disarticulation of the femur, medullary cavity of the tumor was seen to be filled with cellular neoplastic tissue, which extended up into the spongiosa of the metaphysis and part of the neck. Cortex of the shaft was permeated everywhere by the tumor and that there were large pockets, bordered by modified and eroded cortex and distended periosteum and filled with soft, gelatinous neoplastic cartilage.

In contrast, a peripheral/secondary chondrosarcoma may be composed of large facets of cartilage with some calcification and ossification, especially centrally at the site of the original benign chondroma[18].

A case of peripheral chondrosarcoma with multiple exostosis showed heavy sprinkling of bone and foci of calcification among islands of cartilage[7]. Externally, there was an irregular zone of cartilage several centimeters thick in some places and dearly delimited here and there from the interior of the tumor by a line of endochondral ossification[18].

#### Radiologic features

Radiologic findings can confirm one's suspicion of a chondrosarcoma. Irregularly mottled with calcified patches is usually a general appearance of but may vary with the site of the tumor. There is a chance that any mottling or calcification will not be found. In such cases, the only thing that helped differentiate a

chondrosarcoma from a benign tumor is the invasion of cortex from the medulla that appeared as fuzzy regions on scans[18,19].

In case of a central chondrosarcoma following findings could help in diagnosis:

(a) Presence of mottled and clacified regions.
(b) Extensive destruction of the cortex.
(c) Presence of large extraosseous mass.

In case of a peripheral chondrosarcoma, look for a densely and blotchy appearing mass usually associated with ragged, irregular radiopaque streaks extending away from the main part of the lesion.

### Metastasis of chondrosarcoma

Metastasis is uncommon in chondrosarcoma and there is very slight chance of early metastasis. This gives the surgeon ample time for careful assessment of all aspects of each case before the definitive style of management is decided upon[3].

Myxoid and mesenchymal chondrosarcoma were found to metastasize to the lungs, liver, and bone and involved supraclavicular lymph nodes[23,24].

### Grading systems for chondrosarcoma

Grading is very important in chondrosarcoma with respect to its management. Three-grade system is by far the best predictor of clinical behavior of chondrosarcoma. The grading is based primarily on nuclear size, nuclear staining (hyperchromasia) and cellularity[25].

*Grade 1*. Tumors are moderately cellular and contain hyperchromatic plump nuclei of uniform size. Occasionally binucleated cells are present. The cytology is very similar to enchondroma.

*Grade 2*. Tumors are more cellular and contain a greater degree of nuclear atypia, hyperchromasia and nuclear size.

*Grade 3*. Lesions are more cellular and pleomorphic and atypical than grade 2. Mitosis is easily detected. Most primary chondrosarcoma are grades 1 or 2. Rarely, grade 3 tumors are reported. Bjornsson et al reviewing 338 patients with chondrosarcoma of pelvis, shoulder and tubular bones found that 61% were grade 1, 36% were grade 2, and 3% were grade 3[26].

## *Different management options for chondrosarcoma*

### Diagnosis

Before diving into various treatment options, we must analyze how to diagnose a chondrosarcoma. In most cases, the diagnosis is made through biopsy but clinical and radiologic features may also help. Hence, for diagnosis a pathologist, radiologist and an orthopedic surgeon must all come together.

Histologically, it is essential to not only detect malignancy but also determine the grade of the tumor. Presence of myxoid quality in a tumor weighs heavily toward a diagnosis of malignancy and is an ominous sign[3].

There are 3 main problems that occur while differentiating a low-grade chondrosarcoma from a benign tumor. First, histologic features specific to malignant tumors lie in only a few scattered fields which makes it hard to detect via small biopsies. Second, the criteria of malignancy are poorly defined even when the lesion is adequately sampled. The characteristic features such as "plump nuclei" are often subjective when it comes to interpretation. This lack of precision may be justified: it is said that the cytologic features of benign and low-grade malignant tumors overlap in a quarter of cases[27]. Lastly, the criteria vary depending on the anatomic site. Thus one must rely on clinical and radiologic presentation in such cases. Misdiagnosis can have disastrous consequences[7].

There are other new and exciting methods to diagnose a malignant tumor but their efficiency is still questionable and more thorough assessment is required before they can be brought into clinical use. Of these, the most promising approach is the assessment of ploidy, which may be used as an alternative to distinguish between a benign tumor and a malignant one[28].

### Treatment options

The team of doctors should look at the following factors before coming up with an efficient plan of action for their patient:

(i) Type of tumor—is it benign or malignant?
(ii) If malignant, is it chondrosarcoma or osteosarcoma?
(iii) If it is chondrosarcoma, which grade is it?

Management of chondrosarcoma depends on the type, the grade and the location of the tumor. The best predictor of clinical behavior of chondrosarcoma is the grading system form 1 to 3 as discussed previously.

It has been well established that surgical treatment is the best, and the only, treatment for chondrosarcoma as other treatments, such as radiotherapy and chemotherapy, have been rendered unresponsive and refractory[4,24–29].

The surgical options are curettage, radical resection, and amputation. The choice between these procedures often requires considerable judgment and is based on factors, such as the size and site of the lesion and its degree of malignancy[7].

Radical procedures give the most promising outcomes, especially when taken as the initial form of intervention. It is advisable to give the lesion wider margins for the best prognosis. Sometimes, surgeons might have to disarticulate the joint region which he thought would be cancer free, but it is essential to take that step of disarticulation otherwise a recurrence is inevitable and by that time it will be too late to save the patient[18]. Same rule applies for any other site as well. The main idea is to keep well ahead of the growth of the neoplasm and to prevent recurrences. In order to ensure an en bloc removal of the lesion, the surgeon must be aware of the size and extent of the tumor when curative surgery is planned[24].

For intermediate to high-grade chondrosarcoma, the preferred treatment option available is the wide en bloc excision of the lesion or amputation[7].

For low-grade chondrosarcoma, extensive intralesional curettage followed by local adjuvant treatment, for example, phenolization or cryosurgery (liquid nitrogen), and filling the cavity with bone graft has promising long-term clinical results and satisfactory local control[29,30]. Some studies say that en bloc excision with clear margins usually results in cure, but marginal excision or curettage provides unacceptable results with an 86% recurrence rate. In these incompletely excised cases, metastases, usually to the lungs and other skeletal sites, may develop, and the overall mortality rate in these cases is 15%[5,23].

If the lesion is accessible and metastasis has not occurred yet, one must proceed to perform adequate surgery as the initial intervention which can lead to cure and a good prognosis.

### Treatment for extra-skeletal chondrosarcoma

In a comparative case study, myxoid tumors were treated by surgically excising the tumors both marginally and widely. The

latter approach provided a better prognosis. The risk of local recurrence is high with marginal excision[24].

In the case of mesenchymal tumors, treatment was varied depending on the site, size, and grade of the tumor. It was also kept in mind whether the tumor has metastasized or not.

### Prognosis/outcome of treatment and recurrence rate

The outcome and the prognosis depend on the adequate and prompt treatment. For example, in one of the cases in the series observed by R. Barnes and Mary Catto, a woman of 68 years old, presented with a lesion that was diagnosed as malignant and probably chondrosarcomatous, thus the surgeons decided to perform disarticulation of the hip. A follow-up after 5 years showed that the patient was well with no evidence of local recurrence or pulmonary metastasis[7]. Hence, malignant lesions should be excised or amputated as soon as possible to achieve the best prognosis.

According to WHO, survival rate for patients with grade 1 chondrosarcoma is 89%. The combined group of patients with grade 2 and 3 has a 5-year survival of 53%. Approximately 10% of tumors that recur have an increase in the degree of malignancy. Occasionally in chondrosarcomas there is the coexistence of various histologic grades in the same tumor[5].

Several histologic parameters are associated with increased risk of recurrence and metastasis including grade, tumor necrosis, mitotic count, and myxoid tumour matrix. Histologic grading is the single most important predictor of local recurrence, metastasis and prognosis[24]. Patients who had undergone inadequate surgical procedures presented with local recurrences[3]. Marginal excision or curettage provides unacceptable results with an 86% recurrence rate. In these incompletely excised cases, metastases, usually to the lungs and other skeletal sites, may develop[31]. Neoplasms of the spinal column, including the sacrum, had the poorest prognosis because of their inaccessibility. Patients who develop multiple recurrences along with metastasis have a poor prognosis. One case study observed that patients with metastatic lesions in lungs, liver and other regions died within years of the last surgical intervention[24].

## Conclusions

Chondrosarcomas places a significant burden on pediatric as well as adult orthopedic oncology. Optimum diagnosis, accurate interpretation of histopathology, precise grading, careful localization and timely as well as adequate management is crucial to successfully manage and prevent recurrence in these forms of malignancies. Surgery forms the mainstay of treatment. Three forms of surgical managements include curettage, radical resection, and amputation. The choice of procedure depends on the size and site of the lesion and degree of malignancy. Radical procedures give the most promising outcomes with wider margins yielding better prognosis. The goal should be to keep well ahead of the growth of the neoplasm and to prevent recurrences. Recurrence is usually seen with delayed surgery, high histopathologic grading, and inadequate surgical procedures.

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## Author contribution

A.K.: conception of the topic, literature review, drafting of the manuscript.

S.A.T.: critical revision of the article, final approval of the version to be published.

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