Grade 1 Chondrosarcoma of Bone: A Diagnostic and Treatment Dilemma

R. Lor Randall, MD, and William Gowski, MD, Salt Lake City, Utah

Abstract
Cartilaginous lesions of bone are relatively common and cover a large spectrum from latent enchondroma to aggressive dedifferentiated chondrosarcoma. Differentiating among these lesions, particularly benign enchondroma and low-grade chondrosarcoma, can be challenging. Differentiating involves assimilation and interpretation of clinical, radiographic, and histologic criteria. Molecular techniques to assist in distinguishing among the various subtypes are being developed, but these techniques have not yielded any clinically significant contribution. As a result of an imperfect diagnostic schema, a consensus on treatment algorithms has been elusive. This review highlights the specific clinical, radiographic, and histologic criteria currently used clinically to differentiate between benign enchondroma and low-grade chondrosarcoma. We discuss the promise of emerging molecular technologies. Finally, we provide a review of the available literature on treatment outcomes, along with a discussion of our own particular preferences. (JNCCN 2005;3:149–156)

Cartilaginous tumors can be found in any bone in the human body and cover a spectrum of lesions that range from completely benign to dangerously aggressive.1 Although the radiographic characteristics that are typical of cartilaginous bone lesions can be consistent, specialists are often challenged when differentiating among the different varieties. Though difficult, making these distinctions is crucial in determining appropriate treatment. Enchondromas, by definition, are benign intramedullary cartilage tumors that do not metastasize. They are typically found incidentally. Most commonly, they are found in the metacarpals and their adjacent phalanges, but they may occur in the long bones also. Radiographically, they appear as small cartilage nests (usually less than 5 cm in diameter) with multiple intrallesional calcifications. Occasionally, very mild endosteal scalloping will occur; however, true cortical invasion and the involvement of adjacent soft tissues are rare.1 Histologically, islands of normal hyaline cartilage (Figure 1) are found surrounded by lamellar bone. On rare occasions, enchondromas will become symptomatic or lead to pathologic fracture and will require surgical treatment.

More concerning are the malignant cartilaginous lesions, or chondrosarcomas, the lower grade variants of which can often be quite difficult to differentiate from benign lesions. These are classified in several ways, including histologic grade (I–III plus dedifferentiated); location within the bone and body (peripheral vs. central, axial skeleton vs. appendicular skeleton); whether the lesion is primary or secondary (arising de novo vs. secondary to a premalignant lesion such as an osteochondroma); or whether it fits into a specific histologic subtype (clear cell, mesenchymal, base of skull, soft parts).

To date, the single most important factor in evaluating the malignant potential of a chondrosarcoma is its histologic grade.2–4 These tumors are divided into three histologic grades based on microscopic appearance. Grade I (“low-grade”) tumors most resemble normal hyaline cartilage, but may surround areas of lamellar bone (a feature not seen in benign lesions) or show mild cellular atypia including binucleate forms. Grade III (“high-grade”) tumors have significant areas of marked pleomorphism, large cells with hyperchromatic nuclei, occasional giant cells, and abundant necrosis. Grade II (“intermediate-grade”) tumors lie somewhere in the middle and may have...
The fourth histologic subtype, known as dedifferentiated, is less common. It is typically thought of as arising from one of the other three histologic subtypes or from a benign precursor. Dedifferentiated chondrosarcomas have malignant spindle cells (with no identifiable cartilage origin) adjacent to areas of neoplastic chondrocytes.

Chondrosarcomas are then staged using either the method of Enneking et al. or the AJCC method. The majority of chondrosarcomas are low-grade lesions. They are typically seen in adults between the third and sixth decades of life and are more common in men than in women. The most common locations are (in order of decreasing frequency) the pelvis, femur, ribs, humerus, scapula, and tibia. Chondrosarcomas are found most commonly in the metaphysis, but diaphyseal tumors can occur as well. In general, the prognosis for low-grade lesions is very good, with a very low rate of local recurrence and pulmonary metastasis if adequate resection is performed. Metastases as late as 9.8 years, although rare, have been reported.

Distinguishing between low-grade chondrosarcoma and benign enchondroma is perhaps one of the most challenging endeavors in the field of musculoskeletal oncology. Even with diligent clinical practice and advanced radiographic and histologic technologies, the diagnosis may still prove elusive. It is the purpose of this review is to highlight some of the difficulties in making this distinction, with a particular focus on the significant clinical, radiographic, and histologic features that can assist. A review of management options and the salient points of the decision tree will be presented.

**History and Physical**
Most patients with a chondrosarcoma will have pain. Marco et al. reported on 58 cases of grade I chondrosarcoma and found that 60% had night pain or rest pain, 21% had vague regional pain, and only 19% had lesions that were encountered incidentally in the absence of pain. This is in contrast to individuals with benign cartilaginous lesions (who rarely have pain that can be attributed to the lesion) and patients with grade II or III chondrosarcoma (who will have pain in up to 80% of cases). Patients will present with pathologic fracture in a relatively small number of cases (3%–8%) of low-grade chondrosarcoma.

Subtle clinical findings to be cognizant of include antalgic gait, decreased range of motion at adjacent joints, and mild atrophy of the affected extremity. Rarely, a mild increase in the Westergren erythrocyte sedimentation rate will be seen, but the remainder of laboratory findings will be normal.

When the lesion arises in the proximal humeral metaphysis, a very common site, the clinician must very carefully differentiate between signs and symptoms arising from the lesion and those arising from rotator cuff arthropathy. Both can potentially cause pain at night. The patient’s presenting interview and examination must be meticulously documented, because symptoms may change with invasive procedures such as biopsy and may obscure both the patient and physician’s understanding of the disease.

**Radiologic Findings**
Differentiating between the radiographic findings of benign cartilaginous lesions and grade I chondrosarcoma can be challenging. Both can show the classic stippled calcified appearance of cartilaginous bony lesions (Figure 2). Endosteal scalloping can be a hint toward the increasing likelihood that the lesion has malignant potential, but it is not necessarily confirmatory. Murphey et al. published on 95 cases of chondrosarcoma, in which 75% had endosteal scalloping of more than two thirds of cortical thickness versus 92% of benign enchondroma in which 9% had similar findings.
Telling signs of malignancy include a variety of adaptive and aggressive radiographic features. Adaptive changes often cited include cortical expansion or thickening, whereas aggressive features include cortical disruption and soft tissue expansion. Features typical of grade I lesions include dense calcifications appearing in rings or spicules, uniformly distributed calcifications, and eccentric lobular growth of a soft tissue mass. Findings suggestive of higher grade include faint amorphous calcifications, large areas lacking calcifications, and a concentrically growing soft tissue mass.

Perhaps the most reliable radiographic finding when differentiating between benign and malignant lesions is the recognition of radiographic change with time. In particular, increases in endosteal scalloping and cortical destruction or decreases in intralesional calcifications can be telling of malignant potential.

A technetium-99m diphosphonate bone scan of the entire body can be helpful in differentiating between benign and malignant lesions and in identifying polyostotic disease. Using the method of Murphey et al., lesions seen on bone scan can be compared with internal controls. Those lesions showing a higher degree of uptake are more likely to be of higher histologic grade. However, most enchondromas exhibit some amount of uptake, and some will uptake sufficient label to erroneously appear as malignancy. Great caution therefore should be used in drawing conclusions from bone scan results, but these results can add to the overall clinical picture and better inform the decision making process.

Axial computed tomography (CT) can assist in determining the extent of bony destruction and in better delineating bony architecture. CT will also help in better understanding intrallesional calcifications. As with plain radiographs, disappearance or change in the nature of calcifications with repeat scanning can suggest malignancy.

Magnetic resonance imaging (MRI) can be helpful in differentiating between benign and malignant lesions in several ways. First, the degree of medullary fill that is exhibited can be helpful (Figure 3). Greater
than 90% medullary involvement can be suggestive of chondrosarcoma, whereas in the absence of 90% medullary involvement, non-contiguous foci of cartilage can be suggestive of enchondroma. Secondly, the presence of septal enhancements on MRI can elucidate the presence of intraläsional fibrotic bands, a histologic finding often associated with grade I and II chondrosarcomas. Finally, the timing and progression of gadolinium enhancement patterns can help steer a clinician toward or away from a diagnosis of malignancy. Early enhancement (within 10 seconds of arterial enhancement) was seen in chondrosarcoma but not in enchondroma.

Furthermore, many surgeons consider MRI critical for surgical planning. Its contributions can include identifying marrow replacement, showing proximity to important neurovascular or parosteous structures, and delineating the non-mineralized extent of the tumor.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) may have a role in tumor grading in chondrosarcoma. The standard uptake value (SUV) may prove to be a useful parameter for tumor grading and prediction of outcome in chondrosarcoma patients, allowing identification of patients at high risk for local relapse or metastatic disease.

Biopsy

Macroscopically, chondrosarcomas tend to reveal a clear distinction between normal host tissue and the malignancy, though with increasing grade, more aggressive margins may be fleshier and have infiltrating satellite components. Chondrosarcomas will exhibit heterogeneous gross properties, including lobulated areas of chalky calcific admixture, regions of firm translucent unmineralized gray cartilage, and relatively low vascularity. They tend to have areas of necrosis and degenerative material as well.

Lower grade chondrosarcomas will exhibit increasing amounts of relatively acellular heavily calcified areas as well as regions of increased activity exhibiting immature cartilage cells with multiple nuclei. By contrast, higher-grade lesions tend to harbor regions of densely packed hyperchromatic malignant looking cells (Figure 4). Sometimes there may be difficulty in determining that these cells are truly of cartilaginous origin. In some regions, myxomatous changes and highly degenerative areas may make identification impossible.

Sanerkin showed that the diagnosis and grading of chondrosarcoma of bone is best established by a complementary study of its cytology and of its tissue structure and relationship to the host bone. Mirra et al. refined the methods of Sanerkin. Collectively, their work introduces the notion that islands of hyaline cartilage surrounded by plates of lamellar bone and bone marrow, called an “enchondroma encasement pattern,” can be distinguished from the chondrosarcomatous pattern of hyaline or myxoid cartilage permeating lamellar bone, replacing marrow fat, and infiltrating the Haversian system. This latter appearance has been referred to as a “chondrosarcomatous permeative pattern.”

Ranty et al. showed that low-grade chondrosarcomas tend to exhibit regions of hyaline cartilage surrounding by plates of lamellar bone and bone marrow, called an “enchondroma encasement pattern,” can be distinguished from the chondrosarcomatous pattern of hyaline or myxoid cartilage permeating lamellar bone, replacing marrow fat, and infiltrating the Haversian system. Intracytoplasmic hyalin globules were more likely to be seen in malignant lesions, whereas tenascin matrix immunoreactivity was more likely to be found in benign neoplasms.

Fine needle biopsy may be attempted in easily accessible lesions with soft tissue components, whereas core needle techniques may be required to access intramedullary lesions requiring bony penetration. Given the great heterogeneity in both higher and lower grade lesions, sampling error inherent in limited biopsy techniques may make differentiating between

Figure 4 High power photomicrograph shows malignant chondrocytes of intermediate grade chondrosarcoma.
benign and malignant lesions improbable. Therefore, biopsy of suspected low-grade chondrosarcoma remains controversial. Lesions that are clinically and radiographically of a higher grade can often, however, be confirmed using these less invasive techniques.1

Because both benign and malignant cartilage lesions share certain clinical and histologic characteristics, pathologists often consider the patient’s history when interpreting specimens. Definitive treatment should be rendered based on the areas of highest histologic concern. Resection methods should adhere to sound surgical oncologic principles. Surrounding tissues should be protected from exposure to tumor material, and meticulous hemostasis should be gained to prevent local contamination with remaining microscopic disease. Postoperative evacuation with intraoperatively placed drains is recommended when feasible. Lesions appearing more aggressive clinically and radiographically can be widely resected without biopsy to avoid contamination of healthy tissue, but this choice remains a matter of surgeon preference.

Molecular Biology

With the advent of improved molecular techniques, several genotypic and phenotypic markers have been tested to see if they assist in determining tumor grade and therefore better predict patient prognosis. Unfortunately, most are not independent of histologic grade. Additional independent markers, therefore, would be highly valuable for selecting treatment algorithms.

Bridge24 cytogenetically analyzed 120 non-neoplastic, benign, and malignant cartilaginous lesions from 103 patients using fluorescent in situ hybridization (FISH) techniques. Trisomy of chromosome 7 was seen only in malignant tumors. The correlation of chromosome aberrations and increasing histologic grade was seen, and complex aberrations were noted nearly exclusively in high-grade tumors.

Aigner25 evaluated biologic markers for various chondrocytic phenotypes by histochemical and immunohistochemical techniques in a large series of enchondromas and chondrosarcomas. Collagen types II and X and the proteoglycan aggrecan suggested a low-grade neoplastic phenotype and better prognosis. The presence of collagen type I, together with cell spindling, indicated a transition to a higher-grade phenotype. The data indicated, however, that these markers are to a large extent the biologic basis of the conventional grading, rather than representing independent prognostic indicators.

Soderstrom et al.25 analyzed 12 chondrosarcomas for expression of various connective tissue components and SOX9, an important regulator of normal chondrocyte differentiation. As well, they screened for additional changes in gene expression using cDNA array analysis. Grade 3 chondrosarcomas exhibited the highest levels of SOX9 mRNA and pro-alpha 1(I)A collagen. Results of the cDNA array analyses confirmed the heterogeneous nature of chondrosarcoma, because no individual transcript was up- or downregulated in all tumors analyzed. Interestingly, upregulation of decorin mRNA was noted in 7 of the 10 tumors analyzed, suggesting that decorin may play a role in pathogenesis.

Sjogren et al.26 used a combination of chromosome banding, spectral karyotyping, and FISH to characterize the chromosomal pattern in 18 benign and malignant cartilage tumors. The karyotypic findings in the chondrosarcomas were more complex than those in the benign tumors, but they were unable to identify any consistent abnormalities.

Immunohistochemical detection of telomerase has indicated increased expression during malignant transformation in Ewing family tumors.27 A cooperative trial that opened December 1, 2004 (Combined SWOG S0344/ACOSOG Z9041: A Phase II Surgical Trial of Intralesional Resection of Low-Grade Intracompartmental Chondrosarcoma of Bone) performs a similar analysis of chondrosarcoma specimens to determine the presence or absence of a similar transformation associated with recurrence and metastasis. The same study will analyze cDNA microarrays of those same specimens to better understand chondrosarcoma biology as well as look at telomerase expression.

Treatment

Suggested treatment of an enchondroma involves clinical reassessment and sequential radiographs 3, 6, and then 12 months apart, assuming no progressive changes either clinically or radiographically at any point in time. Symptomatic lesions can be treated with intralesional curettage and bone grafting. Pathologic fracture can be treated with either concurrent or staged treatment of both the fracture and

© Journal of the National Comprehensive Cancer Network | Volume 3 Number 2 | March 2005
the lesion if there is concern over the risk of recurrent pathologic fracture. Treatment of chondrosarcomas depends on determining both the clinical and histologic characteristics of the lesion, and, despite much attention in the literature, remains somewhat controversial.

Chemotherapy may offer some benefit in a very small subset of patients with high-grade chondrosarcoma\(^1\) (healthy patients under the age of 60 with a dedifferentiated subtype). However, no conclusive data exist to suggest that this should be standard of care.\(^2\) In metastatic disease, chemotherapy may assist in slowing the growth of lesions, but a cure is not likely.\(^3\)

High-dose irradiation may be of some benefit in cases in which wide surgical margins are not possible. Spinal lesions in particular, though very rare, can be quite challenging to resect. Marginal resection can be augmented with doses of radiation greater the 60 Gy and may be helpful in treating microscopic disease.\(^29,30\)

To date, studies have not shown adjuvant treatments such as chemotherapy or radiation to have any significant impact on patient morbidity or mortality in the majority of isolated primary lesions.\(^1,4\) Because these adjunctive modalities are of benefit in only a small minority of cases, the burden of a cure falls on the surgeon.

Historically, wide resection was considered the methods of choice for all chondrosarcomas. Unfortunately, these tumors are frequently found in regions such as the pelvis or proximal long bones, where aggressive surgical management may endanger adjacent vital organs and structures or compromise the limb significantly.\(^14\) As a result, less aggressive approaches such as marginal excision and intralesional excision with margin expansion using adjuncts such as phenol or cryotherapy have received increasing attention.

In 1977, Marcove et al.\(^4\) sought to determine whether cryosurgery techniques could be successfully implemented in cases of low and moderate grade chondrosarcomas in surgically inaccessible areas. The study followed up 18 patients for an average period of 5 years, and showed no recurrence or metastasis in 17 individuals. The last patient had a presumed but not yet confirmed metastasis. More recent studies, however, have called into question whether a 5-year follow-up is adequate to draw conclusions from these data.\(^5\)

In 1999, Lee et al.\(^2\) compiled data on 86 grade I and 141 combined grade II and III chondrosarcomas treated over a 25-year period at a single institution. All patients received wide, marginal, or intralesional resection without local margin expansion techniques. They showed remarkably improved survivorship in patients who had a wide resection, versus those who had either a marginal or intralesional resection. All 19 patients with a marginal resection of a high-grade lesion died of their disease. They did not have large enough numbers, however, to comment on the survivorship or rates of metastasis in those individuals with grade I disease treated in the same manner, nor did they describe the manner in which these procedures were performed. Further confounding interpretation of the results was the inclusion of histologic grade II tumors within the “high grade” classification, a distinction that has more recently been called into question.\(^3\)

Intralesional curettage can be effective.\(^31\) Bauer et al.\(^31\) studied 40 patients with enchondroma and 40 with low-grade chondrosarcoma of the extremities for an average of 7 years. Twenty-three patients from each group were treated by intralesional curettage. The calculated 10-year local recurrence rate was 0.04 in the enchondroma group and 0.09 in the chondrosarcoma group, and metastases were non-existent.

Schreuder et al.\(^32\) managed 3 chondroblastomas, 14 enchondromas, and 9 grade I chondrosarcomas with curettage, cryosurgery, and bone grafting. No recurrences were seen, although, regrettably, short follow-up (average 26 months) and the small number of included cases of malignancy hamper the interpretation of this study. However, the results lend a modicum of credibility to intralesional curettage with margin expansion techniques for low-grade disease.

Ozaki et al.\(^33\) treated 26 chondrosarcoma (14 grade I, 8 grade II, 4 grade III) with intralesional excision, and followed them for a mean of over 12 years. The 20-year overall survival rate for grade I disease was 68% despite 93% recurrence over that same time period. The overall survival rates for the patients with tumors of histologic grade I was 85% compared with 44% for those of grade II or III. This study highlighted the fact that local relapse does not always result in metastases and death. This group, however, did not employ margin expansion techniques and showed clear bias toward marginal or wide excision for all cases in which either was technically feasible.

One ongoing prospective multi-institutional trial (SWOG S0344/ACOSOG Z9041) seeks to determine
whether low-grade lesions can be treated exclusively with intralesional resection and local adjuvant therapies, thereby improving patient functionality and decreasing overall morbidity without compromising overall survivorship.

Chondrosarcomas arising in the pelvis deserve special mention here. Because pelvic tumors can be particularly difficult to access and even harder to ensure adequate surgical margins for, they tend to be associated with significantly increased rates of local recurrence compared with lesions of similar grade arising in the axial skeleton. Most authors therefore recommend wide resection of all cartilaginous lesions of the pelvis.10,14,33,34

Although specific centers may have their own individualized criteria and algorithms for the surgical decision making process when treating cartilaginous lesions, strict evidence-based criteria are elusive. In general, there is consensus that benign lesions should be conservatively addressed, while aggressive malignancies should be respected and completely resected. Optimal treatment for low-grade chondrosarcoma remains, however, a surgical dilemma.

**Summary**

Cartilaginous lesions of the human skeleton exist on a continuum spanning from the completely benign embryonic inclusion to the dangerously aggressive neoplastic process. To determine the appropriate treatment for each unique lesion, the practitioner must take into account the clinical, radiographic, histologic, and soon the microbiologic personality of the tumor (Table 1). Even then, the lack of a consensus can make choosing optimum surgical management a challenge. The musculoskeletal specialist must develop a strong understanding of each lesion while maintaining a firm grasp of the evolving treatment options. As more advanced molecular tools for predicting tumor behavior are developed and more conclusive evidence regarding treatment outcomes revealed, it is likely that more definitive treatment recommendations will be agreed upon.

**Table 1 Schema to Differentiate and Outline Treatment for Benign and Malignant Cartilage Lesions**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical</th>
<th>Radiology</th>
<th>Histopathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enchondroma</td>
<td>Mostly asymptomatic, incidentally recognized</td>
<td>9% will have endosteal scalloping</td>
<td>Enchondroma encasement pattern</td>
<td>Surveillance, intralesional excision if symptomatic</td>
</tr>
<tr>
<td>Grade I</td>
<td>Chondrosarcoma 60% are painful (Marco 9,10,12,14)</td>
<td>Up to 75% with endosteal scalloping, calcifications in rings or spicules, uniform calcifications, eccentric lobular growth</td>
<td>Chondrosarcomatous permeative pattern</td>
<td>Controversial: Intralesional excision with margin expansion vs. wide resection</td>
</tr>
<tr>
<td>Grade II</td>
<td>Chondrosarcoma 80% painful (Marco 6)</td>
<td>Up to 75% with endosteal scalloping, potentially more aggressive and adaptive changes</td>
<td>Mixture of grade I and grade III characteristics</td>
<td>Marginal vs. wide resection</td>
</tr>
<tr>
<td>Grade III</td>
<td>Chondrosarcoma 80% painful (Marco 6)</td>
<td>Up to 75% with endosteal scalloping, faint amorphous calcifications, large areas without calcifications, concentrically growing soft tissue mass</td>
<td>Densely packed hyperchromatic malignant looking cells, cells of questionable cartilaginous origin, myxomatous changes, highly degenerative areas</td>
<td>Wide resection. Possible adjunct XRT and CTX with selected cases</td>
</tr>
</tbody>
</table>

References


5. Reith JD, Horodyski MB, Scarborough MT, et al. Grade 2


