Chondrosarcoma of the Bone

An ESUN Article

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WHAT IS CHONDROSARCOMA?
Chondrosarcoma is a malignant cancer whose tumor cells produce a pure hyaline cartilage that results in abnormal bone and/or cartilage growth. People who have chondrosarcoma have a tumor growth, or abnormal bony type of bump, which can vary in size and location. The term chondrosarcoma is used to define a heterogeneous group of lesions with diverse morphologic features and clinical behavior. Primary chondrosarcoma (or conventional chondrosarcoma) usually develops centrally in a previously normal bone. Secondary chondrosarcoma is a chondrosarcoma arising from a benign precursor such as enchondromas or osteochondromas.

Cartilage is a type of dense connective tissue. It is composed of cells called chondrocytes which are dispersed in a firm gel-like substance, called the matrix. Cartilage is normally found in the joints, the rib cage, the ear, the nose, in the throat and between intervertebral disks. There are three main types of cartilage: hyaline, elastic and fibrocartilage.

Chondrosarcoma is the second most common primary bone cancer. The malignant cartilage cells begin growing within or on the bone (central chondrosarcoma) or, rarely, secondarily within the cartilaginous cap of a pre-existing osteochondroma (peripheral chondrosarcoma). There are several different types of chondrosarcoma, with names based on the type of cells identified when they are examined under a microscope (see next section for detailed descriptions).

It is important to understand the difference between a benign and malignant cartilage tumor. Chondrosarcoma is a sarcoma, or malignant tumor of connective tissue. A chondroma, also called exostosis or osteochondroma, is a benign bone tumor. Benign bone tumors are not sarcomas. Benign bone tumors do not spread to other tissues and organs, and are not life threatening. They are generally left alone or cured by surgical removal if they cause symptoms such as tenderness via pressure on surrounding muscles, tendons or nerves.

Other types of benign bone tumors include osteoma, osteoid osteoma, osteoblastoma, osteochondroma, (also known as exostoses), hemangioma, and chondromyxoid fibroma. These also are not malignant. Of these, only osteochondroma has the possibility of becoming a chondrosarcoma.

Malignant tumors arising from the skeletal system are rare, representing only about half of one percent of all new cancers. Approximately 2100 new cases of malignant bone cancers (sarcomas) occur in the United States each year (Unni, 1996). The most common type of bone cancer is osteosarcoma, which develops in new tissue inside growing bones. About one fourth of malignant bone cancers are chondrosarcomas.
Not all malignant cartilage tumors of bone are chondrosarcomas. For example, **chondroblastic osteosarcoma** is a bone-forming tumor (osteosarcoma) where production of cartilage (or chondroid) matrix is predominant.

Chondrosarcoma should not be confused with **osteosarcoma**, also called osteogenic sarcoma. Osteosarcoma is a malignant tumor arising from bone cells, (not from cartilage) and is the most common primary bone cancer. Although osteosarcoma most often occurs in young people between age 10 and 30, about 10% of cases develop in people in their 60’s and 70’s. Osteosarcoma is rare during middle age. These tumors develop most often in bones of the arms, legs and pelvis. Conventional chondrosarcoma has a better outcome than osteosarcoma. The treatment options for both these cancers are different; see the section below, “What are the current treatments for chondrosarcoma?”

**WHAT ARE THE DIFFERENT KINDS OF CHONDROSARCOMA?**

The single most important factor to consider when evaluating the malignant potential of a chondrosarcoma is its “histologic grade”, determined by the appearance of tumor material under the microscope (Donati et al., 2005; Lee et al., 1999; Marcove et al., 1977; Reith et al., 2003; Springfield et al., 1996; Wang et al., 2001). In addition to histologic grade (I-III, dedifferentiated, and mesenchymal, see Table 1), chondrosarcomas can be classified by their location within the bone (i.e., central, peripheral, periosteal) and body (i.e., axial skeleton versus appendicular skeleton), whether they are primary or secondary (i.e., arising de novo versus secondary to a premalignant but benign lesion such as an osteochondroma), or whether it fits into a specific histologic variant (i.e., clear cell, myxoid, mesenchymal, dedifferentiated). The lower grade variants of chondrosarcoma can often be quite difficult to differentiate from benign lesions because they have similar appearances on radiographic studies. Benign cartilage tumors, called enchondromas do not usually cause symptoms and never metastasize.

The axial skeleton and the appendicular skeleton together form the complete skeleton. The axial skeleton consists of the bones in the head and trunk of a vertebrate body. It is composed of three major parts; the skull, the bony thorax (i.e. the ribs and sternum), and the vertebral column. The appendicular skeleton is the part of the skeleton that includes the pectoral girdle, the upper limbs, the pelvic girdle, and the lower limbs.

Molecular techniques to classify tumors, such as cDNA expression arrays may prove useful in the future but have yet to be substantiated in the clinical arena.

Conventional chondrosarcomas are divided into four histologic grades based upon their appearance under a microscope (Table 1). The grading is based primarily on nuclear size of tumor cells, nuclear staining (hyperchromasia, or darker staining of nuclear material) and cellularity (Evans et al., 1977).
Bone structure can be either woven or lamellar. **Woven bone** is put down rapidly during growth or repair. It is called woven because its fibers are aligned at random, and as a result has low strength. In contrast, **lamellar bone** has parallel fibers and is much stronger. Woven bone is often replaced by lamellar bone as growth continues.

Bone is composed of both compact (cortical) and cancellous (spongy) material. **Cortical bone** (outer layer, or cortex) is synonymous with compact bone. Cortical bone makes up a large portion of skeletal mass. It is dense and has a low surface area. **Cancellous bone** is trabecular (honeycomb structure); it has a relatively high surface area, but forms a smaller portion of the skeleton. The **medullary canal** is the central cavity of the bone shaft where marrow is stored. The medullary cavity has walls composed of compact bone referred to as endosteum. **Endosteal scalloping** refers to erosion of endosteal bone, caused by a tumor, compared to adjacent cortex.

Grade I (or “low grade”) tumors most resemble normal cartilage, but may surround areas of lamellar bone (which is not seen in benign lesions), or show atypical cells including binucleate forms (cells with two nuclei instead of one), see Figure 1.

Grade II (or “intermediate grade”) are more cellular with a greater degree of nuclear atypia, hyperchromasia and nuclear size (Schiller, 1985).

Grade III (or “high grade”) tumors have significant areas of marked pleomorphism, large cells with more hyperchromatic nuclei than grade II, occasional giant cells and abundant necrosis. Mitoses are frequently detected.

**Hyperchromatic** (hyperchromasia) refers to nuclear material staining more intensely than usual. **Pleomorphic** means varying shapes between cells of the same type. **Necrosis** refers to unprogrammed cell death resulting from acute cellular injury. This is in contrast to apoptosis, which refers to programmed cell death.

Myxoid changes or chondroid matrix liquefaction is a common feature of chondrosarcomas particularly in Grade II and Grade III lesions. The vast majority of chondrosarcoma are Grade I or Grade II. Grade III is rare (Bjornsson et al., 1998).

The variant known as differentiated is less common. It is typically thought of as arising from one of the other three histologic subtypes or from a benign precursor. De-differentiated chondrosarcomas, along with mesenchymal chondrosarcomas, are highly malignant, particularly aggressive (i.e., rapidly growing and disturbing surrounding tissues) and carry with them a poor prognosis.
### TABLE 1: Chondrosarcoma Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptoms</th>
<th>Prognosis</th>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enchondroma</td>
<td>Usually no symptoms</td>
<td>Excellent</td>
<td>Surveillance, intralesional excision if symptomatic</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Low grade)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grade I Chondrosarcoma</td>
<td>60% are painful</td>
<td>Good</td>
<td>Controversial: Extended intralesional excision vs. Wide resection</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Intermediate grade)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II Chondrosarcoma</td>
<td>Up to 80% are painful</td>
<td>Fair</td>
<td>Wide resection</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
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<tr>
<td>(High grade)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grade III Chondrosarcoma</td>
<td>Up to 80% are painful</td>
<td>Poor</td>
<td>Wide resection. Chemotherapy and radiation therapy in select cases</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
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<tr>
<td>(High grade)</td>
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<tr>
<td>Dedifferentiated Chondrosarcoma</td>
<td>Most are painful</td>
<td>Poor</td>
<td>Wide resection. Chemotherapy and radiation therapy in select cases</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
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<tr>
<td>(High grade)</td>
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<tr>
<td>Mesenchymal Chondrosarcoma</td>
<td>Pain and swelling</td>
<td>Poor</td>
<td>Wide resection. Chemotherapy and radiation therapy in select cases</td>
</tr>
</tbody>
</table>

Enchondromas, which are benign cartilage tumors, are usually found incidentally, most commonly in the bones of the hand and feet (Enneking, 1983). Radiographically they appear as small cartilage nests (usually <5cm in diameter) with multiple intralesional calcifications. Occasionally, very mild endosteal scalloping will occur, however true cortical invasion and the involvement of adjacent soft tissues is rare (Enneking, 1983). Histologically, islands of normal hyaline cartilage are found surrounded by lamellar bone. On rare occasion, enchondromas will become symptomatic, or lead to pathologic fracture, and will require surgical treatment.

The juxtacortical chondrosarcoma arises on the surface of bone and is histologically identical to conventional intramedullary chondrosarcoma.

Chondrosarcomas may also be classified by their histologic sub-type. These sub-types include Clear cell, mesenchymal, and de-differentiated. Clear cell chondrosarcomas are low-grade tumors with significant amounts of glycogen. They typically involve the proximal portion of femur, tibia or humerus. Histologically, cells have abundant clear cytoplasm embedded in a loose hyaline cartilaginous matrix and an infiltrative growth pattern. Radiographs show a lytic defect at epiphyseal end of long bones that is sharply demarcated with sclerotic margins. They carry a low recurrence rate and a good prognosis with wide resection.
Figure 1: Grade I chondrosarcoma demonstrates increased cellularity, perhaps some hyperchromatism but not necessarily atypical cells.

Clear cell chondrosarcoma is different from clear cell sarcoma, which is an aggressive, rare soft-tissue sarcoma that primarily affects the tendons and aponeuroses. Clear cell sarcoma histologically resembles malignant melanoma and rarely affects bones.

Clear cell chondrosarcomas produce lytic defects at the ends of long bones and can have the radiographic appearance of chondroblastoma, a rare benign cartilage tumor arising in the epiphysis of a long bone in young patients. Clear cell chondrosarcomas frequently extend to joint surfaces.

Mesenchymal chondrosarcomas are highly aggressive tumors that are radiographically and histologically distinct from conventional and dedifferentiated types. They are eccentrically located in bone and commonly extend into soft tissues. This variant of chondrosarcoma is characterized by a bimorphic pattern that is composed of highly undifferentiated small round cells (similar to Ewing’s Sarcoma) and islands of well-differentiated hyaline cartilage. This tumor usually affects young adults and teenagers and shows a widespread distribution in skeleton. The craniofacial bones, the ribs, the ilium and the vertebrae are the most common site (Bertoni et al., 1983). The treatment is radical surgery combined with chemotherapy.

De-differentiated chondrosarcomas represent about 10% of all chondrosarcomas. The most common sites of involvement are pelvis bones, femur and humerus. This tumor is a distinct variety of chondrosarcoma containing two clearly defined components: a well-differentiated cartilage tumor (enchondroma or chondrosarcoma grade I and II) juxtaposed to a high grade non-cartilaginous sarcoma. They are most often found in the femur, pelvis, or humerus bones, although they may also occur in the head, spine, breast, and prostate. Histologically there is a typical abrupt transition between the two components, cartilaginous and non-cartilaginous; both tumor components are evident in varying proportions. The malignant non-cartilaginous component is most frequently malignant fibrous histiocytoma, osteosarcoma or fibrosarcoma, although other malignant tumors have been reported as the differentiated component. The cartilaginous and non-cartilaginous components are often adjacent, and the term “collision of two tumors” has been applied to this lesion. Radiographically the tumor produces an ill defined, lytic, intraosseous lesion associated with cortical disruption and extension into the soft tissues.
WHO GETS CHONDROSARCOMA?
Most chondrosarcomas are low-grade lesions. They are typically seen in adults in their late 20s to 60s. They occur more commonly in men than women. Chondrosarcoma is not contagious. It cannot be passed on to another person by exposure to a chondrosarcoma patient. Although specialists are not yet certain what causes chondrosarcoma, there are several factors that put people at a higher risk; see the section below, “What is known about the genetics of chondrosarcoma?” for details.

Certain hereditary conditions may make people more susceptible to chondrosarcomas. These include Ollier's Disease, Maffucci Syndrome, Multiple Hereditary Exostoses (MHE, a.k.a., osteochondromatoses), and Wilms Tumor. People affected by these conditions are at a higher risk because they usually develop several benign bone tumors (sometimes called bone spurs in the case of MHE), which have a higher chance of becoming malignant. People with these hereditary conditions who experience sudden growth spurts or increases in hormone production, such as pregnancy, have a slight increased risk of a benign bone tumor changing into a chondrosarcoma. These patients should be followed by a bone tumor specialist for all of their lives.

Ollier's Disease (a.k.a multiple enchondromatosis) is a disease of multiple benign bone tumors (enchondromas) within the bones which cause affected bones to swell. The disease often primarily affects one side of the body. It may affect the hands or feet, or be generalized. It is not an inherited disease. Patients have bony swellings, limb shortening and mechanical difficulties, associated with joint disruption and short stature. The condition usually presents before age 10. These typically occur in the bone metaphyses and can lead to secondary deformity of the growth plates. A secondary Madelung deformity may occur at the wrists. There is a small increased risk of malignant transformation to chondrosarcoma, particularly in flat bones, during adult life. Ollier's is often diagnosed at the time chondrosarcoma is diagnosed.

Maffucci Syndrome is a rare genetic disorder characterized by benign enlargements of cartilage (enchondromas), bone deformities, and dark, irregularly shaped hemangiomas within the body or on the skin. The disease manifests early in life, usually around the age of 4 or 5 years, with 25% of cases being congenital. There is relatively high risk of malignant transformation to chondrosarcoma in adult life (reportedly 20-30%). Relatively few cases have been published in the English literature.

Multiple Hereditary Exostoses (MHE, a.k.a., osteochondromatoses) is a hereditary skeletal disorder in which there are numerous cartilage-capped excrescences (sp) in areas of actively growing bone (osteochondromas). The condition is genetically heterogeneous, and at least three genes (ext1 and ext2) have been demonstrated to be involved. The reported risk for malignant transformation to chondrosarcoma has been from 0.6% to 2.8% The lesions most at risk for malignant transformation are those occurring near the pelvis, scapula, proximal humerus, proximal femur, and spine. Change in size of the exostosis or onset of pain in an affected adult is cause for further investigation.

Wilms Tumor is a neoplasm of the kidneys that typically occurs in children. It is also known as a nephroblastoma. Although rare, chondrosarcoma of bone has been described as secondary tumor after diffuse anaplastic Wilms' tumor.

However, most patients with chondrosarcoma do not have any of these genetic conditions. Adults with Paget's disease, a non-cancerous condition characterized by abnormal development of new bone cells, may be at increased risk for chondrosarcoma. When chondrosarcoma occurs in
children and young adults, it is often in patients who have had radiation or chemotherapy treatments for other conditions.

Recently, genetic studies have shown that there are specific locations on chromosomes where the genetic information for chondrosarcoma resides (Bovee et al., 2005; Sandberg, 2004). Continuing research of the genes and how the proteins encode for them will offer tremendous insight into the growth of these cancerous cells. This information is important since chondrosarcoma is a problem with the growth of cells. An understanding of the involved gene and the function of its protein may eventually lead to better treatment. It is feasible that, in the future, genetic manipulations may aid in the detection, treatment and/or prevention of chondrosarcoma.

WHERE IN THE BODY ARE CHONDROSARCOMAS USUALLY FOUND?
Chondrosarcomas may develop in any part of the body, but most are commonly found in the pelvis, rib cage, arms (humerus), shoulder blades (scapula) and legs (proximal femur, tibia). Although any bone can be affected, the long bones (legs, arms, fingers, toes,) pelvis and shoulder blades are most commonly involved. Occasionally chondrosarcoma has been found in the spine or skull bones. It is extremely rare to find chondrosarcoma in any internal organs, but this has been described. If chondrosarcoma spreads from its primary site (i.e., metastasizes), it usually spreads to the lungs. Metastasis is rare with low-grade tumors, but has been seen, even up to 10 years after diagnosis (Lee et al., 1999). About half of grade III and nearly all de-differentiated chondrosarcomas will metastasize; see Table 2.

HOW DOES SOMEONE WITH CHONDROSARCOMA FEEL?
People with benign cartilage tumors (i.e., enchondroma or osteochondroma) rarely have pain that is caused by the tumor (Marco et al., 2000b). Most patients with a chondrosarcoma will have pain (Bjornsson et al., 1998; Marco et al., 2000a; Mirra et al., 1985; Murphey et al., 1996) and many will have swelling. It has been reported that in patients with grade I chondrosarcoma, 60% have night pain or rest pain, 21% have vague regional pain, and only 19% have painless tumors (Marco et al., 2000a). People with benign cartilage tumors (i.e., enchondroma or osteochondroma) rarely have pain that is caused by the tumor (Marco et al., 2000b). People with higher grade tumors (grade II or III chondrosarcoma) have pain up to 80% of the time (Pritchard et al., 1980). Rarely, people will discover they have a chondrosarcoma when they develop a fracture through the tumor (Bjornsson et al., 1998).

Pain associated with chondrosarcoma is usually in the location of the lesion or adjacent joints, muscles, tendons, nerves, blood vessels, or other soft tissues. In addition to pain, patients with chondrosarcoma may notice an enlargement of a bone or limb, changes in their ability to walk normally, or decreased range of motion in joints near the affected bone. Sometimes patients with benign cartilage tumors can have pain caused by something other than the tumor. For example, a rotator cuff injury can be painful at night and an x-ray might show a cartilage tumor in the shoulder. It is very important to determine whether pain is being caused by the tumor or by another process. This difference is vital in the diagnosis and treatment of chondrosarcomas.

Distinguishing between low-grade chondrosarcoma and benign enchondroma is perhaps one of the most challenging endeavors in the field of musculoskeletal oncology because they are difficult to differentiate. Even with diligent clinical practice and advanced radiographic and histologic technologies, the diagnosis may still prove elusive.
WHAT TESTS ARE NEEDED TO DETERMINE IF SOMEONE HAS CHONDROSARCOMA?

After a doctor asks questions (a history) and performs a physical examination, he/she may order plain x-rays to evaluate the area of concern. It can be very difficult for doctors to tell the difference between benign cartilaginous lesions and low-grade chondrosarcomas on x-rays. Both can demonstrate the classic stippled calcified appearance of cartilaginous bony lesions (Figure 2). If the hard outside covering of the bone (cortex) appears to be getting chewed away (endosteal scalloping) there is an increased likelihood that the tumor has malignant potential, but is not necessarily confirmatory. One helpful analysis of chondrosarcoma had endosteal scalloping of more than 2/3rd of the cortical thickness, whereas only 9% of enchondromas had similar findings (Murphey et al., 1996).

More aggressive (malignant) tumors may show more telling signs of malignancy on x-ray. This includes adaptive changes such as expansion and/or thickening of the cortex and expansion of the surrounding soft tissues (Murphey et al., 1996; Unni, 1996). Features typical of lower grade 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 change in radiographic appearance over time. In particular, there may be more endosteal scalloping and destruction of the cortex or a decrease in the calcifications with more malignant tumors. If there is no change in the appearance of a benign cartilage tumor on radiographs over time, it is appropriate for the doctor to continue to recommend watchful waiting and repeat x-rays at a later visit.

A bone scan of the entire body can also be helpful in differentiating between benign and malignant tumors, and in identifying whether more than one bone is involved (although multiple bone involvement is rare with chondrosarcomas). This test works by injecting a small amount of radioactive material into the blood stream and taking images using a gamma camera to detect uptake of radioactive material. Lesions demonstrated on bone scan can be compared to internal controls (Murphey et al., 1996). Those lesions demonstrating a higher degree of uptake are more likely to be of higher histologic grade. However, most enchondromas exhibit some radioisotope
uptake, and some will erroneously appear as malignancy. Great caution should therefore be used in drawing conclusions from bone scan results, but these results can add to the overall picture, and better inform the decision making process.

![Bone scan of patient with left distal femoral chondrosarcoma](image)

**Figure 3:** Bone scan of patient with left distal femoral chondrosarcoma

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 intralesional calcifications. As with plain radiographs, disappearance or change in the nature of calcifications with repeat scanning can be suggestive of malignancy.

Magnetic Resonance Imaging (MRI) can be helpful in differentiating between benign and malignant lesions in several ways. First, the degree to which the tumor fills the medullary canal can be helpful (Figure 4). Greater than 90% medullary involvement can be suggestive of chondrosarcoma, while the absence of 90% medullary involvement of non-contiguous areas of cartilage within the bone can suggest the presence of an enchondroma (Colyer et al., 1993). In addition, the timing and progression of gadolinium contrast enhancement patterns may help direct a clinician toward or away from a diagnosis of malignancy (Geirnaerd et al., 2000). Early enhancement (within 10 seconds of arterial enhancement) may be seen in chondrosarcoma but not in enchondroma. Many surgeons consider MRI critical for surgical planning because it can illustrate the extent of tumor involvement in bone and soft tissues.
Recently, there has been some research into the use of a specialized radiographic test called fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) for grading of tumors in patients with chondrosarcoma (Aoki et al., 1999; Brenner et al., 2004). This test is not yet available at all centers, but may become a useful tool for tumor grading and prediction of outcome in chondrosarcoma patients. This may hence allow for identification of patients at high risk for local relapse or metastatic disease.

**WHAT IF A CHONDROSARCOMA IS SUSPECTED?**

If chondrosarcoma is suspected, two additional (staging) tests will usually be done to determine whether the tumor has spread. These include: 1) a computerized tomography (CT) scan of the lungs; and, 2) a total body bone scan. The results of these staging studies help physicians determine treatments and outcomes (prognosis). Blood tests are generally not helpful in making the diagnosis, although they can be used to make sure that there is not another process going on, such as infection or a different malignant process. After all of these tests are performed, a sample of the tumor (biopsy) is sometimes necessary to figure out if the problem is truly chondrosarcoma. Most biopsies for chondrosarcoma are achieved by surgical excision (i.e., complete removal of the tumor) of the lesion rather than through incisional biopsy (i.e., surgery to remove only part of the tumor for diagnostic evaluation).

**WHAT WILL A BIOPSY TELL THE PATIENT AND THE DOCTOR?**

When fresh tissue from a chondrosarcomas is viewed under a microscope after a biopsy, it is generally not difficult to identify a clear distinction between normal host tissue and the malignant tissue. However, with higher-grade tumors, more aggressive margins may have more malignant tissue, and have infiltrating satellite components. They will exhibit heterogeneous gross properties including lobulated areas of chalky calcific admixture, regions of firm translucent unmineralized gray cartilage and relatively low vascularity. Higher-grade tumors tend to have areas of necrosis and degenerative material as well (Enneking, 1983).
On microscopic analysis, 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 5). There may sometimes 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.

Figure 5: Grade II chondrosarcoma: Increased cellularity and atypical cells

As both benign and malignant cartilage lesions can share certain clinical and histological characteristics, pathologists will often consider the patient’s history when interpreting specimens. Permeation of cortical and/or medullary bone is an important characteristic of conventional chondrosarcoma that the pathologist can use to separate it from enchondroma. The decision by the orthopaedic oncologist for definitive treatment is based upon the areas of highest concern for malignancy. Lesions appearing more aggressive clinically and radiographically must be widely resected without biopsy to avoid contamination of healthy tissue, which would likely necessitate an additional surgery. However, this remains controversial.

WHAT IS KNOWN ABOUT THE GENETICS OF CHONDROSARCOMA?

As evolving molecular techniques are available, several genotypic and phenotypic markers for chondrosarcoma have been tested to see if they assist in determining tumor grade prognosis. There is considerable complexity and heterogeneity in the pathologic and clinical behavior of chondrosarcomas. This is reflected in the diversity of cytogenetic and molecular genetic characteristics that have been described in these tumors. Please see Sandberg and Bridge (2003), Sandberg (2004), and Bovee et al. (2005) for a thorough review.

The genetic changes specific to chondrosarcoma continue to be investigated extensively. Although studies have not yet established a specific or recurrent karyotypic feature for any of these tumors, different chondrosarcomas have demonstrated anomalies in several tumor suppressor genes, oncogenes, and transcription factors, including TP53, RAS, EXT1, EXT2, and Sox9. Available cytogenetic and comparative genomic hybridization (CGH) studies reveal
changes in some chondrosarcomas, but fail to do so in others. These studies are thus far difficult to interpret.

An impressive number of chromosomes have been demonstrated to be affected in chondrosarcomas, by either loss or gain of genetic information, many with implications on prognosis or clinical significance. For example, 6q13–q21 changes in chondrosarcoma appear to be associated with locally aggressive behavior (Sawyer et al., 1998), loss of 13q may be a predictor of metastases (Mandahl et al., 2002), c-MYC amplification and polysomy 8 can be used for prognostic purposes (Morrison et al., 2005), and overexpression of the STK15 gene may play a role in tumor progression, particularly in dedifferentiated chondrosarcoma, and can be used as a prognostic factor for identifying patients who are at high risk for the development of local recurrence or distant metastases (Vakar-López et al., 2001). However, these assays are not routinely performed.

Based on the available studies, it is likely that chondrosarcomas are generated by a coordinated, multi-step process involving primarily tumor suppressor genes. In fact, the complexity and variety of genetic changes seen in chondrosarcomas may indicate several distinct genetic pathways. Some of the same genes may be involved in each, but the order and manner in which they are affected may differ among chondrosarcomas. Establishing the genes that initiate the neoplastic processes, and that are subsequently involved along the pathways leading to chondrosarcoma may lead to therapies addressing these molecular changes, as has been accomplished for several other sarcomas.

**WHAT ARE THE CURRENT TREATMENTS FOR CHONDROSARCOMA?**

For benign-appearing, asymptomatic cartilage tumors (i.e., enchondroma), patients are usually followed with clinical evaluation and sequential x-rays 3, 6 and then 12 months apart. This is continued unless there is a change in clinical examination findings or the radiographic appearance of the lesion at different points in time. Symptomatic enchondromas (i.e., those that cause pain, discomfort, or are disfiguring but do not show indications of malignancy) can be treated with a relatively non-invasive procedure, involving curettage of the lesion within the bone with placement of a bone graft. Fractures through the tumor (called a *pathologic fracture*) can be treated with either concurrent or staged treatment of both the fracture and the lesion if there is concern over the risk of recurrent pathologic fracture.

*Surgical resection* remains the primary and most successful means of treating chondrosarcomas. The decision regarding the extent of surgical resection and adjuvant therapy is dependent upon the clinical and histologic characteristics of the lesion. Optimal treatment for low-grade chondrosarcoma remains a dilemma for surgical oncologists, but no chemotherapy or radiation is indicated. For higher-grade tumors, with a worse prognosis for recurrence and metastasis, adjuvant therapies may be considered. Unfortunately, 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. Proton beam radiation is generally reserved for refractory tumors in high risk anatomic areas such as the skull base and axial skeleton. As these adjunctive modalities are of no proven benefit, the burden of a cure still falls upon adequate initial surgical resection.
Irradiation may be useful in younger patients or those with metastatic disease, where surgery would cause major unacceptable morbidity or be technically impossible (Krochak et al., 1983). This remains controversial. Cytotoxic chemotherapy is ineffective against traditional chondrosarcomas, but may have a role in the dedifferentiated subtype or in stage IV disease (Dickey et al., 2004). There are no established regiments for such cases. For patients who have developed pulmonary metastatic disease, treatment in a clinical trial at a Sarcoma center, or with conventional chemotherapy, if appropriate for the patient, may be indicated.

In the past, wide resection was considered the method 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 limb function. Thus, less aggressive approaches such as marginal excision and extended intralesional excision with margin expansion using adjuncts such as phenol or cryotherapy have received increasing attention with a national study underway to investigate efficacy. Most surgical oncologists prefer limb salvage techniques with bone graft and prosthetics, preserving the function of the limb. Amputation is still used in advanced disease or as a last option.

Phenol is an organic compound sometimes used as an adjunct to surgical excision of chondrosarcoma to destroy any remaining diseased tissue. Cryotherapy, using liquid nitrogen, is often used as an adjunct to surgical excision of chondrosarcoma to destroy remaining diseased tissue.

While rigorous evidence-based criteria are presently lacking, individual centers may have their own criteria and algorithms for surgical decision-making. In general, benign lesions should be treated conservatively, while high-grade malignancies should be treated aggressively with complete resection. If surgical margins are not clear on histologic evaluation of the tissue after resection of an intermediate- or high-grade lesion, wider surgical resection and possibly bone and/or joint prosthesis may be necessary.

Clinical Trials: Optimal treatment for low-grade chondrosarcoma remains a dilemma for surgical oncologists. For patients who have developed pulmonary metastatic disease, treatment in a clinical trial at a Sarcoma Center, or with conventional chemotherapy, if appropriate for the patient, may be indicated. At the time of this writing, there is a multi-center, international trial evaluating the diagnosis and treatment of low-grade chondrosarcoma and a trial dealing with advanced chondrosarcomas sponsored by the National Institutes of Health, the Southwest Oncology Group, and The American College of Surgeons Oncology Group.

ARE THERE ANY EMERGING THERAPIES IN THE TREATMENT OF CHONDROSARCOMA? During the past several years, substantial new insights have been gained about molecular cell biology, molecular cytogenetics, and immunopathology (Terek, 2006). These have led to a better understanding of chondrosarcoma development at the molecular level and will ultimately lead to the development of targeted treatments. Though they are at present highly experimental, researchers are investigating several new treatments for chondrosarcoma. Examples include agents targeting estrogen receptors (Cleton-Jansen et al., 2005), new chemotherapeutic agents, such as ET-743 (Marchini et al., 2005), and agents effecting cytogenetic pathways (Bovee et al., 2005).
WHERE IS THE BEST PLACE TO GO TO RECEIVE APPROPRIATE TREATMENT?
Patients with chondrosarcoma are best treated at major Sarcoma Centers with specialized diagnostic and treatment facilities and the availability of Musculoskeletal Tumor Specialists or Orthopedic Oncologists. Because this, like many other bone cancers, are not common, it is often a good idea to seek an opinion from a major cancer center that has a wide experience in treating bone cancers. A major sarcoma center will offer an organized group of doctors and other health care professionals who work together to provide the best treatment options and recovery. If your primary care physician suspects chondrosarcoma, a simple referral to an orthopedic doctor may not be adequate. Be sure that you are referred to an orthopaedic oncologist or “bone cancer specialist.”

WHAT ARE THE CHANCES FOR CURE AND SURVIVAL FROM CHONDROSARCOMA?
In general, the prognosis for chondrosarcoma depends on the grade of the tumor and the attainment of complete excision of the tumor and other conditions the patient has such as diabetes, lupus, and clotting and coagulation problems (Table 2). For lower grade chondrosarcomas, prognosis is very good after adequate excision. There is a low incidence of pulmonary metastasis if the primary lesion is widely resected. Metastasis to other bones can occur, but is much less common. Dedifferentiated chondrosarcoma have a uniformly poor prognosis.

**TABLE 2: PROGNOSIS BY TUMOR GRADE**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Five-Year Survival</th>
<th>Metastatic Potential</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>90%</td>
<td>0%</td>
<td>Low</td>
</tr>
<tr>
<td>Grade II</td>
<td>81%</td>
<td>10-15%</td>
<td>Fair</td>
</tr>
<tr>
<td>Grade III</td>
<td>29%</td>
<td>&gt;50%</td>
<td>High</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>&lt;10% (1 year)</td>
<td>Most</td>
<td>High</td>
</tr>
</tbody>
</table>

SUMMARY
Cartilaginous lesions of the human skeleton exist on a continuum spanning from the completely benign embryonic inclusion, to the dangerously aggressive neoplastic process. In order to determine the appropriate treatment for each individual lesion, musculoskeletal oncologists must take into account the clinical, radiographic, histologic and soon the microbiologic characteristics of the tumor. It is important for patients to seek treatment for these tumors at a Sarcoma center with availability of specialists possessing a sound understanding of these lesions and a firm grasp of the evolving treatment options. The health care team at these centers will keep patients informed about the details of the treatment course in both the short and long term. Understanding and recognizing the spectrum of appearances of the various types of chondrosarcoma allow improved patient assessment and are vital for optimal clinical management including diagnosis, biopsy, staging, treatment and prognosis. As more advanced molecular tools for predicting tumor behavior are developed, more sophisticated means of diagnosing and treating these tumors will be developed and put into use.
REFERENCES


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