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What is chondrosarcoma?

The term chondrosarcoma is used to define an heterogeneous group of lesions with diverse features and clinical behavior. Chondrosarcoma is a malignant cancer that results in abnormal bone and cartilage growth. People who have chondrosarcoma have a tumor growth starting from the medullary canal of a long and flat bone. However, in some cases the lesion can occur as an abnormal bony type of bump, which can vary in size and location. 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 Exostoses, Osteochondromas or Enchondromas. Although rare, 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 Exostoses (peripheral chondrosarcoma).

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.

It is important to understand the difference between a benign and malignant cartilage tumor. Chondrosarcoma is a sarcoma, (i.e.) a malignant tumor of connective tissue. A chondroma, , is the benign counterpart. 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.

Exostoses / Osteochondromas

It is a relatively common lesion and can be solitary or multiple. Multiple osteochondromas occur in multiple hereditary exostosis, usually arise from the metaphysis near the growth plate of long tubular bones. The outer layer of the head of the osteochondroma is composed of benign hyaline cartilage varying in thickness and is delineated peripherally by perichondrium.
The cartilage has the appearance of disorganized growth plate and undergoes enchondral ossification with the newly made bone forming the inner portion of the head
Exostoses usually present as slow growing masses, which can be painful if they impinge on a nerve or if the stalk is fractured.

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 chondrosarcomas can be classified by their specific histologic variant (clear cell, 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.

Conventional chondrosarcomas are divided into four histologic grades based upon their appearance under a microscope. 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).

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).

Grade II (or "intermediate grade") is 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.

The vast majority of chondrosarcoma are Grade I or Grade II. Grade III is rare (Bjornsson et al., 1998).

Grade IV. Belong to this group the subtype variant called mesenchymal and de-differentiated chondrosarcomas. 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.

Hyperchromatic (hyperchromasia) refers to nuclear material staining more intensely than usual, meaning a more intense cell activity

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.

Mitoses indicate cells in the act of replicating

Chondrosarcomas may also be classified by their histologic sub-type. These sub-types include Clear cell, mesenchymal, and de-differentiated.

a) 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.

Clear cell chondrosarcoma is different from ***clear cell sarcoma,*** which is and aggressive, rare soft-tissue sarcoma that primarily affects of 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.**

b) 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.

c) 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. 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. Radiographically the tumor produces an ill defined, lytic, intraosseous lesion associated with cortical disruption and extension into the soft tissues. It is more common in adult aged patients and when possible antiblastic chemotherapy is advised. Surgical treatment has to be radical.

Who gets chondrosarcoma?

Most chondrosarcomas are low-grade lesions. Low grade means very low attitude to spread out in other organs and tissues. 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. Certain conditions may make people more susceptible to chondrosarcomas:

a) Enchondromas are benign tumors of hyaline cartilage, they arise within the medullary cavity, or on the surface of bone, where they are called subperiosteal or juxtacortical chondromas. Enchondromas are the most common of the intraosseous cartilage tumors, they are usually solitary, located in the metaphyseal region of tubular bones.

b) 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 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. There is a small increased risk of malignant transformation to chondrosarcoma, particularly in flat bones, during adult life.

c) 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.

d) Multiple Hereditary Exostoses (MHE / MO / HME 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 2% to 5%. 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.

People affected by these conditions are at a higher risk because they usually develop several benign bone tumors, 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

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.
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.

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.

How does someone with chondrosarcoma feel

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. 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). Rarely, people will discover they have a chondrosarcoma when they develop a fracture through the tumor (Bjornsson et al., 1998).

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.

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. Features typical of lower grade lesions include dense calcifications appearing in rings or spicules, uniformly distributed calcifications and eccentric lobular growth of an intramedullary soft tissue mass.
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).

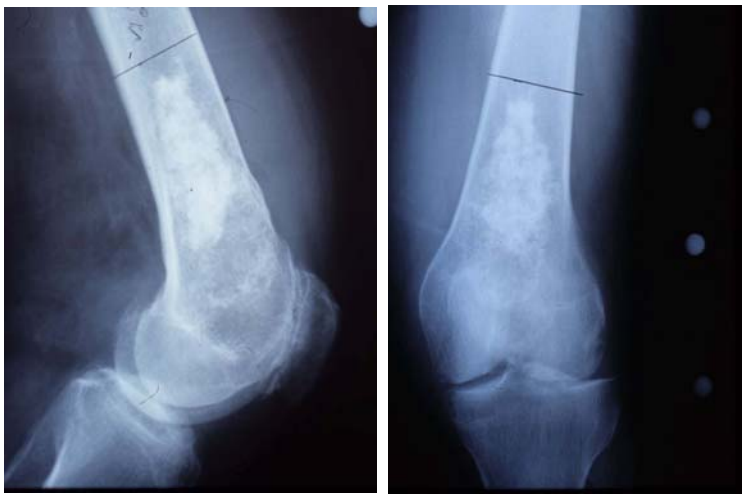

Figure 2: Plain radiographs of a low-grade cartilage lesion in a distal femur bone.

CHONDROSARCOMA, PROXIMAL RADIUS (Fig.1:-6:

History: 33 y/o male with pain and swelling about elbow.

Findings: Plain films show an expansile lesion. The MR shows cortical destruction and soft tissue extension.

Diagnosis: Chondrosarcoma, proximal radius.

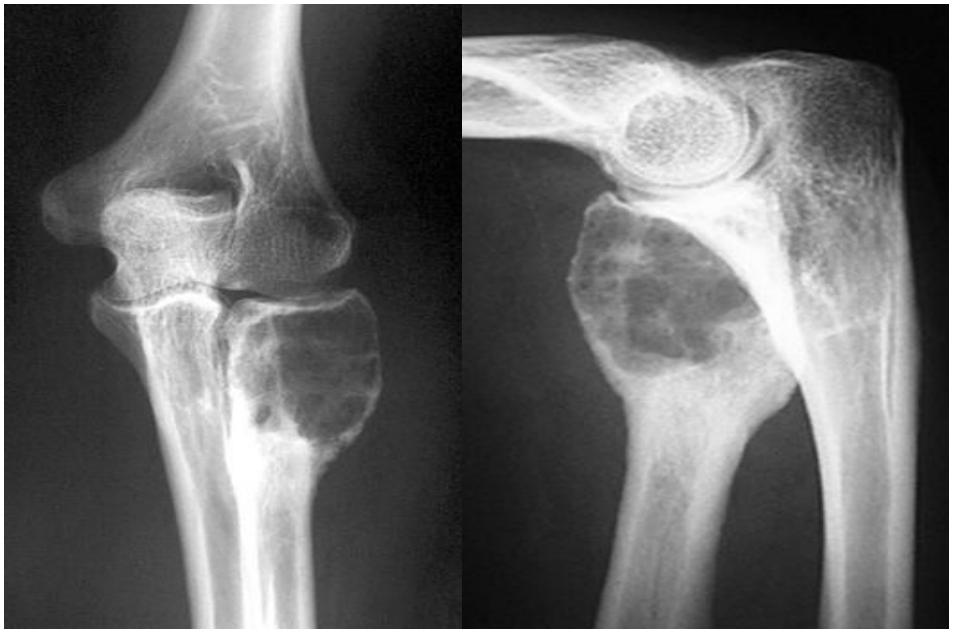

Fig. 1: AP

Fig. 2: LAT80B

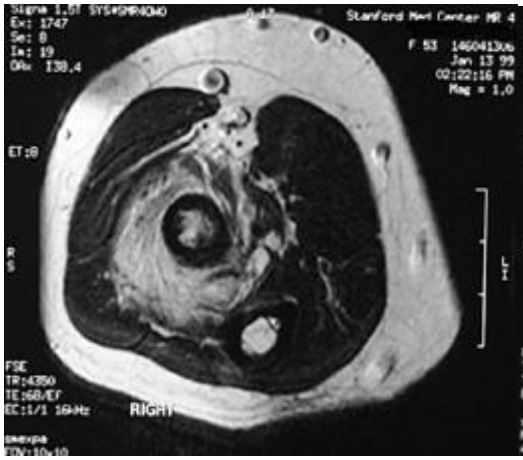

Fig. 3: MR imaging: Axial FSE T2

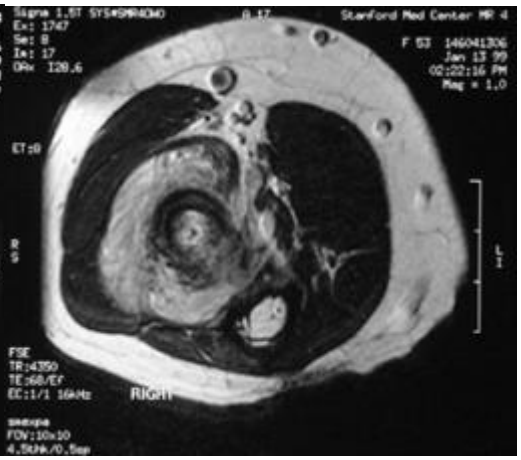

Fig. 4: MR imaging: Axial FSE T2

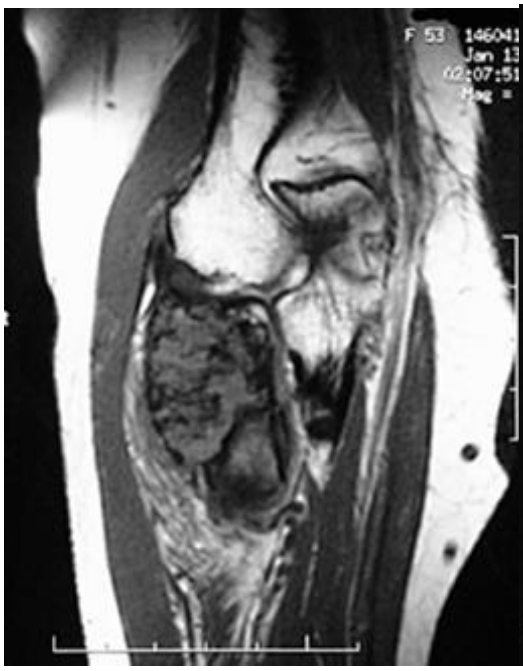

Fig. 5: MR imaging: Coronal T1

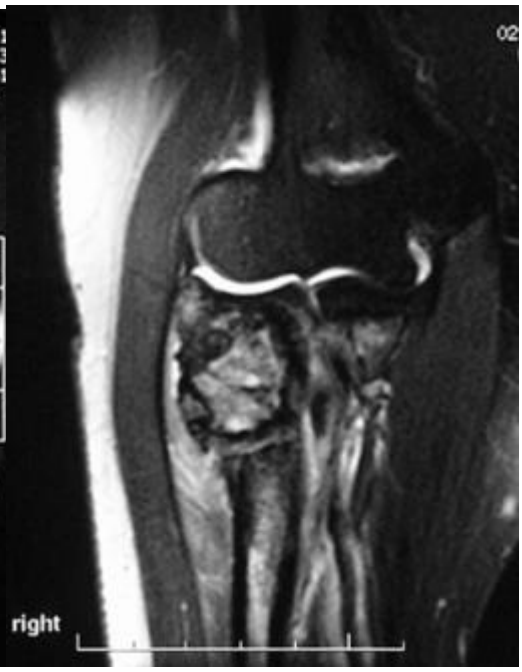

Fig. 6: MR imaging: FSE T2

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). 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** and **Exostoses / Osteochondroma** 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. **Figure 3:**

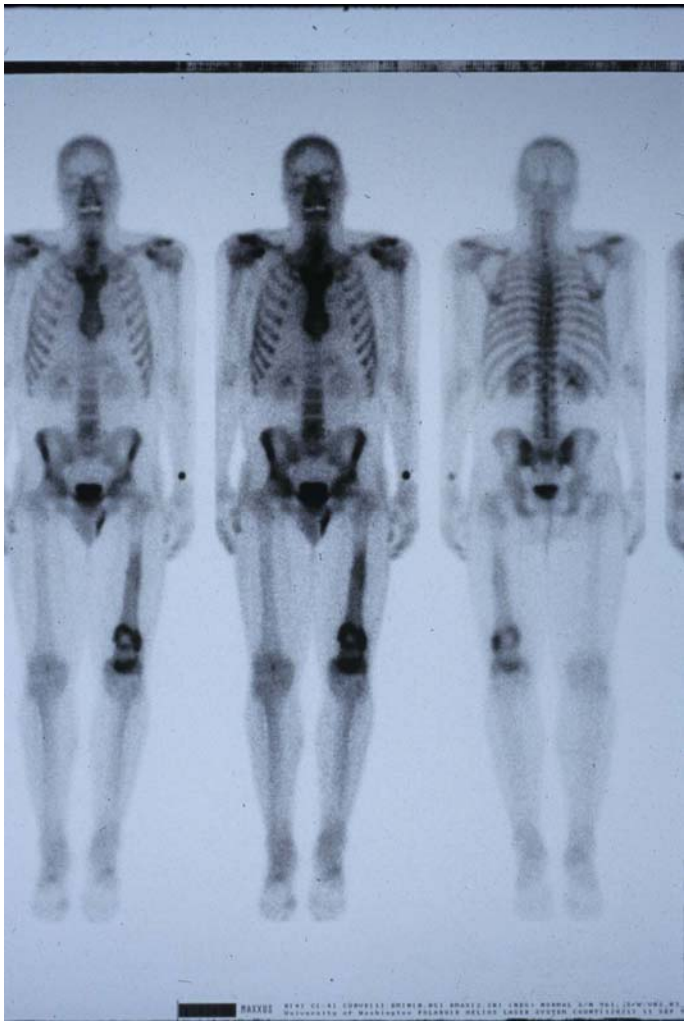

Figure 3: Bone scan of patient with left distal femoral chondrosarcoma.

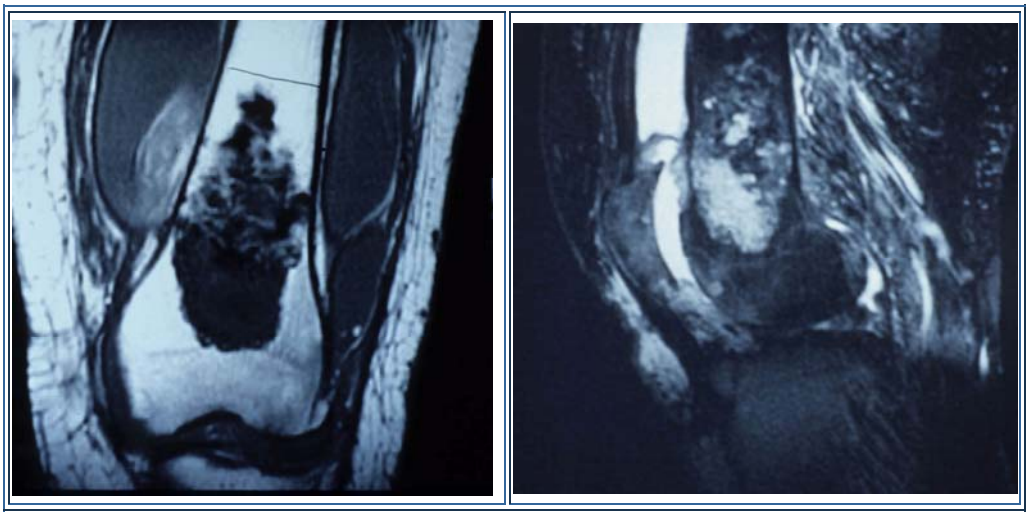

Figure 4: MRI images of distal femoral chondrosarcoma.

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.

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 (Geirnaerdt 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.

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.

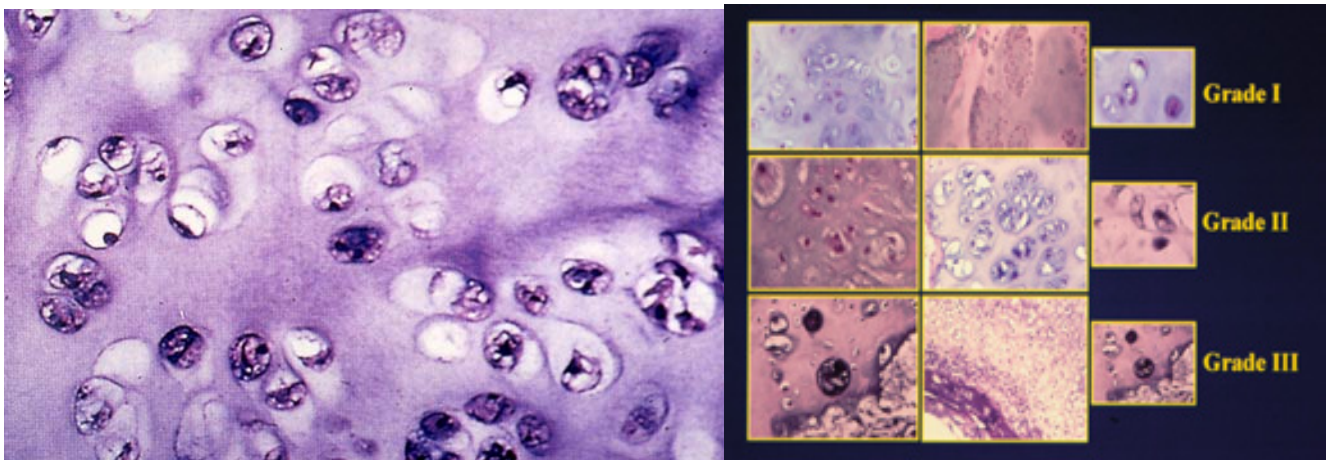

Figure 5: Grade II chondrosarcoma: Increased cellularity and atypical cells.

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 / Osteochondroma.** 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. The surgeon decision is based on history and progression of the lesion referred by the patients and confirmed by the previous examinations. The histological grade is sometimes necessary to plan a preoperative chemotheraphy in IV grade chondrosarcomas. Or on the other hand to plan a more conservative surgery in border line lesions (benign, low-grade)

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 as well as exostoses /osteochondroma (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. Enchondromas can be curetted out from inside the medullary canal of the bone with placement of a bone graft, while exostoses can be excised from the bone surface.
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 (table1). 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.

Table 1	TUMOR	SYMPTOMS	PROGNOSIS	TREATMENT
BENIGN	**Enchondroma Osteochondroma**	Usually no symptoms	Excellent	Surveillance, intralesional excision if symptomatic
MALIGNANT (Low grade)	**Grade I Chondrosarcoma**	60% are painful	Excellent	Controversial: Extended intralesional excision vs. Wide resection
MALIGNANT (low grade)	**Grade II Chondrosarcoma**	Up to 80% painful	Good	Wide resection
MALIGNANT (Intermediate grade)	**Grade III Chondrosarcoma**	Up to 80% painful	Fair	Wide resection. Chemotherapy and radiation therapy in select cases
MALIGNANT (High grade)	**De-differentiated Chondrosarcoma**	Most are painful	Poor	Wide resection. Chemotherapy when possible in all cases Radiation therapy in selected
MALIGNANT (High grade)	**Mesenchymal Chondrosarcoma**	Pain and swelling	Fair-Poor	Wide resection. Chemotherapy in all cases

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. 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.

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**

Intralesional Resection in Treating Patients With Chondrosarcoma of the Bone

This Phase II trial is currently recruiting patients. Intralesional resection is a less invasive type of surgery for **chondrosarcoma** of the bone and may have fewer side effects and improve recovery. The purpose of this trial is to study how well intralesional resection works in treating patients with low-grade

chondrosarcoma of the bone. Patients undergo intralesional resection (curettage with high-speed burr). Patients then receive local adjuvant treatment comprising of liquid nitrogen, phenol, alcohol, or argon beam to the excision site. The bone cavity is then filled with either polymethyacrylate cement or a bone graft (allograft or homograft). Patients may also have a metal plate installed at the wound site. Patients are followed every 3 months for 1 year and then every 6 months for 4 years. A total of 60 patients will be accrued for this study within 30-60 months. Patients 18 years of age and older are eligible. This trial is taking place at centers in **Arkansas**, **Colorado**, **Florida**, **Michigan**, **Minnesota**, **Missouri**, **New Mexico**, **Oregon**, **Utah**, and **Washington**.

Pemetrexed Disodium in Treating Patients With Recurrent and Unresectable or Metastatic Chondrosarcoma

This Phase II trial is currently recruiting patients. **Pemetrexed disodium** (Alimta) is a potent new antifolate which inhibits many folate-dependent reactions that are essential for cell proliferation. Its primary target is thymidylate synthase but it also inhibits folate-dependent enzymes involved in purine synthesis. Cells that are resistant to antifolates are generally less resistant to pemetrexed, irrespective of the mechanism of resistance. Pemetrexed has shown good activity in preclinical models with human tumor cells and xenografts. In the majority of clinical trials of pemetrexed, the dose-limiting toxic effect is neutropenia; other side-effects are mostly gastrointestinal. Preclinical studies indicate that the toxic effects of pemetrexed can be reduced by dietary folate, resulting in an improved therapeutic index. Low folate status is also associated with higher levels of toxicity in patients. As a single agent pemetrexed has shown good activity against non-small-cell lung cancer, squamous-cell carcinoma of head and neck, colon cancer, and breast cancer, and it appears to be particularly active in combination with cisplatin against non-small-cell lung cancer and mesothelioma. The purpose of this trial is to study how well pemetrexed disodium works in treating patients with recurrent and unresectable or metastatic **chondrosarcoma**. Patients are stratified according to prior chemotherapy (yes vs. no). The treatment outline is as follows. Patients receive pemetrexed disodium IV over 10 minutes on day 1. Courses repeat every 21 days* in the absence of disease progression or unacceptable toxicity (NOTE: *The duration of course 1 is 28 days; the duration of all subsequent courses is 21 days). Beginning 7 days before the first dose of pemetrexed disodium and continuing until 21 days after the completion of pemetrexed disodium, patients receive cyanocobalamin (vitamin B-12) intramuscularly once every 63 days and oral folic acid once daily. Patients achieving a complete response (CR) receive 2 additional courses beyond CR. Patients achieving a confirmed partial response (PR) that is resectable, proceed to surgical resection and then receive 2 additional courses of therapy after recovering from surgery. Patients achieving a confirmed PR that is not resectable continue treatment in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients are followed every 3 months until disease progression and then every 6 months for up to 5 years. A total of 40-75 patients (20-40 in the previously treated stratum and 20-35 in the previously untreated stratum) will be accrued for this study within 20-37.5 months. Patients 18 years of age and older are eligible. This trial is taking place at centers in **California**, **Illinois**, **Kansas**, **Missouri**, **Montana**, **North Carolina**, **South Carolina**, and **Wyoming**.

Gemcitabine and Docetaxel to Treat Bone and Soft Tissue Cancers

This Phase II trial is currently recruiting patients. This study will examine the side effects and possible benefits of the anti-cancer drugs gemcitabine (Gemzar) and docetaxel (Taxere) in patients with bone or soft tissue cancer (sarcoma); determine how the body absorbs and eliminates the drugs; and perform genetic studies on the tumor and try to grow the tumor in the laboratory or in animals. Patients 10 years of age and older with recurrent **osteosarcoma**, **Ewing's sarcoma**, and inoperable or recurrent inoperable **chondrosarcoma** may be eligible for this study. Participants receive gemcitabine and docetaxel in 21-day cycles as follows: Gemcitabine is given as a 90-minute infusion on days 1 and 8 of each cycle. Docetaxel

is given as a 60-minute infusion following the gemcitabine infusion on day 8 of each cycle. Filgrastim is given as an injection under the skin either: 1) daily, beginning the day after each docetaxel infusion and continuing until the bone marrow is recovered from chemotherapy (usually 7 to 10 days); or 2) in a long-acting form on the day after the docetaxel infusion. Filgrastim boosts production of blood cells that have been depleted as a result of chemotherapy. Patients are taught to self-administer the injections. Treatment will continue for a total of 14 cycles or until the patient's tumor gets larger, side effects are unacceptable, the patient decides to stop treatment, or further treatment would not be in the patient's best interest. At the end of chemotherapy, patients will be monitored for treatment side effects and disease progress, initially every 3 months and then every 6 months until 2 years from finishing treatment. The total expected enrollment is 20 patients. This trial is taking place at the National Cancer Institute, Bethesda, Maryland.

Gemcitabine and Docetaxel in Treating Patients With Recurrent Osteosarcoma or Ewing's Sarcoma or Unresectable or Locally Recurrent Chondrosarcoma

Drugs used in chemotherapy, such as gemcitabine and docetaxel, work in different ways to stop tumor cells from dividing so they stop growing or die. Combining gemcitabine with docetaxel may kill more tumor cells. The purpose of this trial is to study the effectiveness of combining gemcitabine with docetaxel in treating patients who have recurrent **osteosarcoma**, recurrent **Ewing's sarcoma**, or unresectable or locally recurrent **chondrosarcoma**. Patients are stratified according to diagnosis (recurrent osteosarcoma vs. recurrent Ewing’s sarcoma vs. unresectable or locally recurrent chondrosarcoma). Patients receive gemcitabine IV over 90 minutes on days 1 and 8 and docetaxel IV over 1 hour on day 8. Patients also receive filgrastim (G-CSF) subcutaneously (SC) beginning on day 9 and continuing until blood counts recover. Patients may receive pegfilgrastim SC on day 9 (once per course) as an alternative to G-CSF. Treatment repeats every 21 days for up to 14 courses in the absence of disease progression or unacceptable toxicity. Patients are followed every 3 months for 1 year and then every 6 months for 1 year. A maximum of 120 patients (40 per stratum) will be accrued for this study within 17-24 months. Patients 4 years of age and older are eligible. This trial is taking place at centers in **California**, the **District of Columbia**, **Georgia**, **Illinois**, **Maryland**, **Massachusetts**, **Michigan**, **Minnesota**, **New York**, and **Texas**.

The effects of ciprofloxacin and paclitaxel on metastatic and recurrent chondrosarcoma

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Currently, the only treatment available for recurrent/metastatic chondrosarcoma is further surgical resection. Fluoroquinolones have shown toxicity in immature cartilage, inducing apoptosis and inhibiting the proliferation of human chondrosarcoma cells. Since previous studies suggested that ciprofloxacin and paclitaxel act synergistically in slowing the growth of chondrosarcoma in vitro, we investigated their effects on human recurrent/metastatic chondrosarcoma. Four patients received oral ciprofloxacin (750 mg twice daily) and intravenous paclitaxel (90 mg/m^2) for 6–8 weeks of each cycle. Patient 1 remained stable 32.8 weeks after initiation of treatment. Patient 2 showed a 60% decrease in tumor growth but progressed by 10.3 weeks. Patient 3 progressed over 9 weeks, remained stable for 16 months, and then progressed after treatment with paclitaxel was discontinued. Patient 4 had three lesions: the recurrent lesion progressed despite treatment, showing an 8% increase in growth; one metastatic lesion remained stable (18 weeks), and the second metastatic lesion progressed. Gene expression profiling of normal articular cartilage and human chondrosarcoma cells exposed to ciprofloxacin showed differential expression of the genes DDX5, MYST2, ISGF3, APC, RPL3, EIF4G2, and ERH, all of which are involved in cell proliferation, cell-cycle regulation, or apoptosis.

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: Survival Features of Chondrosarcoma

(Table 2).	**Five-year Survival**	**Metastatic Potential**	**Recurrence rate**
Grade I	90%	0%	Low
Grade II	81%	10-15%	Fair
Grade III	29%	>50%	High
Dedifferentiated	<10% (1-year)	Most	High

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 and histologic 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.

Where else can one learn about Chondrosarcoma?

Steve Dunn's **CancerGuide** provides a very useful starting point for undertaking investigations into cancer and cancer-related issues on the Internet. Among other things discussed is how to research the medical literature and how to use and access medical databases and online resources, explains the medical research cycle, where to get medical references and describes the various types of papers in the medical literature, and how to find and use a medical library.

Interested readers are encouraged to continue their investigations into chondrosarcoma by examining the resources at the websites listed below:

Chondrosarcoma by Dr. Geoff Hide on the eMedicine.com website
The Doctor's Doctor chondrosarcoma webpage