Liddy Shriver Sarcoma Initiative

FIBROSARCOMA OF BONE:

REVIEW OF A RARE PRIMARY MALIGNANCY OF BONE

An ESUN Article

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Abstract

Fibrosarcoma of bone is a rare primary malignancy. It shares imaging and clinical features with several other bone pathologies. Fibrosarcoma shares histological features with other bone tumors and often cannot be distinguished from such lesions other than by an experienced musculoskeletal pathologist. Similarly, it is histologically indistinguishable from its soft tissue counterpart but has a significantly different incidence pattern and clinical profile. Treatment and prognosis are similar to other sarcomas of bone. Surgical extirpation is central to control of local disease. Given the rarity of fibrosarcoma of bone, large trials of chemotherapeutic regimens have not been possible. There have been promising results reported though. The following review will discuss this rare malignancy.

Introduction

The goal of the following essay is to provide a concise, accurate review of fibrosarcoma of bone to patients and healthcare professionals for whom this disease is new or unfamiliar. In the following pages, there will be a discussion of normal and pathologic (cancerous) fibrous tissue. From there, patient demographics, typical bones affected, classification, and survival expectations in fibrosarcoma of bone will be reviewed. A description of a typical patient course from the first symptoms through post-operative rehabilitation will ensue, including important expectations for both the patient and treating providers. Last, this passage will close with a glance at what the future looks to bring in terms of fibrosarcoma diagnosis and treatment.

What is fibrous tissue?

Fibrous tissue is a normal component of the human body and an important part of many physiologic processes. It is found in all organ systems in varying quantity and quality. Fibrous tissue is largely composed of collagen, glycoaminoglycan, and glycoprotein. The quantity and physical arrangement of collagen fibers determines the properties of the tissue. Dense, tightly

arranged collagen fibers running in parallel give tendon its ability to transmit large forces from muscles to bones and, similarly, give scar its firm, durable character. There is immeasurable diversity of function in fibrous tissue through these variations of content and arrangement.

Derivatives of mesenchymal cells, fibroblasts are found throughout the body and are the cells primarily responsible for collagen production. The fibroblast also synthesizes glycoaminoglycan, glycoprotein, and reticular and elastic fibers. Fibroblasts have experienced a renewed interest by investigators as their potential in tissue engineering and regeneration continues to be explored.(Ref. 1)

> *–blast* implies a cell that produces a given material. An osteoblast produces osteoid (organic bone matrix); a chondroblast produces cartilage matrix. Similarly, *–clast* is used to describe cells that breakdown tissue.

What is fibrosarcoma?

Fibrosarcoma is a malignant neoplasm (cancer) of mesenchymal cell origin in which histologically the predominant cells are fibroblasts that divide excessively without cellular control; they can invade local tissues and travel to distant body sites (metastasize). Fibrosarcoma is part of a larger collection of cancers known as sarcomas. Sarcomas are spindle cell malignancies of mesenchymal cell origin and are named and classified after the predominant cell line that is present. For example, in bone (osteosarcoma), cartilage (chondrosarcoma), smooth muscle (leiomyosarcoma), and skeletal muscle (rhabdomyosarcoma). Though all are sarcomas, specific diseases vary considerably in presentation, treatment, and prognosis. At the same time, there are characteristics shared by many sarcomas. Since all are connective tissue in origin, they form solid tumors, as opposed to a disease such as leukemia in which abnormal cells are circulating in the blood stream, or certain gastrointestinal tract cancers that may develop within the wall of a hollow organ.

Only approximately 5% of all primary bone sarcomas are fibrosarcoma.(Ref. 2) According to data compiled by the NCI in the SEER database between the years 2000 – 2004, the age-adjusted incidence of all bone and joint sarcoma was 0.9 per 100,000 men and women per year. Applying the previously published incidence, approximately 1 case of fibrosarcoma of bone is diagnosed annually for every two million people.

> Fiber-forming tumors and tumor-like lesions of bone fall into one of two categories: benign or malignant. Benign conditions include: periosteal desmoids, non-ossifying fibroma (fibrous cortical defect, benign fibrous histiocytoma), fibrous dysplasia, osteofibrous dysplasia, myofibromatosis, and intraosseous desmoplastic fibroma. Malignant lesions include fibrosarcoma, fibroblastic osteosarcoma, myofibroblastic sarcoma, malignant fibrous histiocytoma (fibromyxosarcoma, spindle cell sarcoma), and adamantinoma.

How is fibrosarcoma similar or different from other bone sarcomas?

As the name implies, fibrosarcoma results from abnormal fibroblast cell division. Osteosarcoma and chondrosarcoma are distinguished by the extracellular matrix (material) the malignant cells produce. Osteosarcoma is characterized by production of osteoid (the organic matrix of bone) whereas chondrosarcoma neoplasms make abundant cartilage. In contrast, fibrosarcomas produces neither bone nor cartilage. Collagen is the predominant product produced by the malignant cells in

fibrosarcoma. The amount of collagen production is inversely proportional to the histological grade (grade to be reviewed later) (i.e., high grade tumors produce less collagen and vice versa). It is the rapidly dividing and spreading cells in sarcoma (not the matrix produced) that can threaten life and limb.

Distinguishing between different bone tumors can be challenging. The differential diagnosis for any given bone lesion often includes both benign and malignant processes. Lesions that may appear similar to fibrosarcoma on radiographs include malignant solitary fibrous tumor, leiomyosarcoma, myofibromatosis, myeloma, osteosarcoma, lymphoma, metastatic disease, malignant fibrous histiocytoma of bone, and desmoplastic fibroma.(Ref. 3)

Fibrosarcoma can be confused with osteosarcoma because both can affect young patients, including patients in the second decade of life (ages 10 – 19). Both have a predilection for the distal femur and radiographically can appear as aggressive lesions. The telangiectatic variant of osteosarcoma may be particularly confusing, radiographically, since it forms a rapidly destructive, lytic lesion.

Fibrosarcoma is a distinct entity from fibroblastic osteosarcoma. A fibrosarcoma will produce no osteoid. Osteoid production may be scant in fibroblastic osteosarcoma, but will always be present. In the latter, the traditional herringbone pattern of fibrosarcoma is often absent. Immunohistochemical evaluation can further help delineate between the two.(Ref. 4)

When comparing osteosarcoma to fibrosarcoma, the latter has a broader age distribution and is even less common than osteosarcoma. Radiographically, bone lesions of fibrosarcoma are generally osteolytic (bone destroying). Osteosarcoma can be osteolytic, osteoblastic (bone forming), or have a mixed lytic and blastic appearance.

Malignant fibrous histiocytoma (MFH) of bone is a distinct entity from fibrosarcoma and was first described in the 1970's.(Ref. 5) Like fibrosarcoma, MFH more commonly arises in soft tissue (soft tissue sarcoma). Histologically, these lesions are composed of a heterogeneous population of cells. MFH often contain areas of swirling (storiform) spindle-shaped cells and giant cells. This, too, can resemble fibroblastic osteosarcoma and it takes an experienced pathologist to distinguish between these lesions.

MFH can share genetic abnormalities with other bone sarcomas, such as deletion of the retinoblastoma tumor suppressor gene.(Ref. 6) Advances in genetic research have allowed more detailed study. In particular, genomic hybridization has allowed identification of genetic variations that help distinguished MFH from other bone and soft tissue sarcomas.(Ref. 7)

After the original descriptions of MFH of bone, many lesions previously diagnosed as other bone sarcomas (including fibrosarcoma) were re-classified and described in subsequent publications.(Ref. 8) MFH is thought to more commonly occur as a secondary tumor from a pre-existing bone lesion than is fibrosarcoma. Otherwise, age distribution, location, treatment, and prognosis are similar to that of fibrosarcoma of bone.(Ref. 9, 10) Immunohistochemical and ultrastructural differences can help differentiate the two.(Ref. 11)

The term MFH has come under significant scrutiny and may soon be removed from the medical lexicon. Histiocytosis infers the presence of histiocytes – cells of the immune system located within connective tissue that engulf cellular debris and pathogens. Evidence supports the claim

that MFH does not contain histiocytes and these lesions are often referred to as a member of the spindle cell sarcoma family (e.g. fibromyxosarcoma).

Immunohistochemistry adds to the pathologist's diagnostic techniques when trying to distinguish morphologically similar tumors. (Ref. 4) Fibrosarcoma stains strongly positive for the intermediate filament vimentin.(Ref. 11) Markers for muscle (desmin, smooth muscle actin, HHF-35), human osteoblasts (osteocalcin), macrophages (CD-68), leukocyte common antigen (LCA), neural tissue (s100, neuron specific enolase), melanoma (HMB-45), neutrophils (CD-31), hematopoietic cells (CD-34), epithelial tissue (cytokeratin, epithelial membrane antigen), and CD-99 will be absent.(Ref. 12, 13)

Immunohistochemistry is a technique that labels proteins on the cell surface. A (primary) antibody designed to recognize and bind to a specific cell surface protein is added to the specimen. A second antibody, designed to recognize and bind to the primary antibody is added. This secondary antibody contains a marker that allows identification by the pathologist. The absence of this specific marker or tag indicates that the specimen does not contain the targeted protein on its cell surface. Different surface proteins are unique to certain tissue types.

Advances in specimen evaluation, such as identification and analysis of chromosomal translocations, are allowing tumors to be identified based on more than histological appearance and may provide important insight to pathogenesis, prognosis, and treatment.(Ref. 4, 13) Fibrosarcoma, like many sarcomas, can have a complex chromosomal pattern and no one finding allows it to be definitively distinguished from similar lesions.(Ref. 13)

Despite the continually improving imaging, immunologic staining, and genetic techniques, differentiating fibrosarcoma of bone from other bony lesions remains challenging; it often requires the input of specialists in several fields of medicine. Errors in diagnosis can delay treatment or expose patients to suboptimal, harmful, or unnecessary therapies.

Who gets fibrosarcoma? Are there known risk factors?

Fibrosarcoma affects men and women with equal frequency. Tumors can occur in patients of any age but are most common between the third and sixth decades of life. In older patients, fibrosarcoma is often thought to be secondary to transformation of a preexisting benign lesion such as an enchondroma (benign cartilage tumor), bizarre parosteal osteochondromatous proliferation, chronic osteomyelitis, giant cell tumor, or fibrous dysplasia.(Ref. 14, 15, 16, 17, 18) Transformation is more common in fibrous dysplasia lesions that are isolated (monostotic), as opposed to when multiple bones are involved.(Ref. 14, 17, 18) Jaw, femur and rib lesions more commonly undergo malignant degeneration. New pain and/or swelling at a sight of known fibrous dysplasia are the most common symptom in cases of malignant transformation. Unfortunately, prognosis is poor in these cases.(Ref. 18) Cases have also been described in the literature of fibrosarcoma arising in areas of radiation treatment, Paget's disease, bone infarct, or surgically treated fracture.(Ref. 19, 20) Known malignant lesions, such as low grade chondrosarcoma, may also give rise to a secondary fibrosarcoma.(Ref. 21)

Fibrous dysplasia is a disorder of bone in which normal bone is replaced by immature fibro-osseous tissue. This condition most commonly affects only one bone (monostotic) but can also be polyostotic. Fibrous dysplasia can be present as an isolated bone lesion or be part of a larger

syndrome (i.e. McCune Albright or Mazebraud syndrome) often with associated endocrine disorders. Isolated lesions are commonly identified incidentally.

Though genetic studies have identified specific gene alterations in fibrosarcoma(Ref. 4), no screening test has been developed to stratify who may be at increased risk of developing the disease. Similarly, though a multitude of pre-existing lesions can pre-date a secondary fibrosarcoma, little is available to help predict what small fraction of these benign lesions will transform into a malignancy.

Where does fibrosarcoma occur?

The location of bone tumors can be divided by any of several methods. One method is to look at the bone in cross-section and classify lesions as being on the surface, within the compact cortical bone, or in the less dense (intramedullary) marrow space. Fibrosarcoma of bone is most commonly located within the intramedullary cavity. Periosteal and parosteal (surface) lesions have been described and offer a better prognosis.(Ref. 22) Rare cases of tumors arising within the cortex have also been described.

Parosteal lesions occur on the external surface of the bone and can often surround the bone before invading. Periosteal lesions are believed to arise from within the periosteum of the bone. The initial description of periosteal osteosarcoma excluded any cases in which there was medullary invasion. This exclusion has been challenged by several authors.

Another useful method is to classify lesions based on their location along the bone's long axis. The end of a long bone is referred to as an epiphysis. The bone transitions to the shaft (diaphysis) through zone referred to as the metaphysis. Long bone involvement comprises approximately 70% of cases, with metaphyseal lesions being most common. Extension into the epiphysis or diaphysis is common. Isolated epiphyseal and diaphyseal lesions are exceedingly rare. The distal femur (thigh bone) is the most commonly involved bone. The proximal tibia (shin bone) is another common site, making the area around the knee most commonly affected.

Though less common than long bone lesions, fibrosarcoma can affect bones of the head and neck.(Ref. 23) Lesions can cause pain, swelling, and paresthesias. Intra-osseous fibrosar¬coma affecting the jaw must be distinguished from odontogenic sarcomas (ameloblastic fibrosarcoma, ameloblastic fibrodentinosar¬coma, ameloblastic fibro-odontosarcoma and odontogenic carcinosarcoma).(Ref. 24) Again, the various techniques described above are instrumental in making a correct (and timely) diagnosis.

Ameloblastic fibrosarcoma is a rare odontogenic malignancy distinct from fibrosarcoma of bone. The former is characterized by areas of a benign odontogenic epithelium interspersed with areas of fibrosarcoma. It has been described both as de novo lesion and secondary to ameloblastic fibroma.

Multifocal (occurring in multiple bones) disease has been described in the literature and is exceedingly rare. Multifocal disease will present similar to (the far more common) metastatic bone disease with multiple non-contiguous sites involved.(Ref. 25, 26, 27, 28, 29, 30) The work-up often finds no known other primary malignancy and biopsy findings consistent with fibrosarcoma of bone. There are seven cases reported in the literature and the longest reported

survival is 18 months from time of diagnosis.

Are all cases of fibrosarcoma the same? How are they different? What do those differences mean?

The **grade** of a cancer refers to the appearances of the tumor under the microscope. Based on established standards, a cancer may be given one of several grades. In a 'low' grade, the cancer cells may look very similar to normal cells, with only slightly abnormal changes. A 'high' grade is where the cells look very abnormal and show little or no resemblance to normal tissue. The grade of a cancer is a guide to how aggressive the tumor is.

The **stage** of a cancer is a measure of how far it has progressed. A cancer that is small and at a single site is in an early stage; one that has spread to different parts of the body is at an advanced stage. Specific grading and staging systems are in place for all malignancies. In many cases, multiple systems exist for the same tumor. These systems are used to guide treatment, predict prognosis, facilitate communication among medical professionals, and steer research efforts. Learn more at Understanding Cancer Types and Staging.

Several grading systems are in use for sarcomas of bone and most contain two to four grades. Higher grades describe more cellular, less organized, highly active tumors that are more concerning for a lesion that will act aggressively. The specific qualifications needed for a lesion to fall into a particular grade in any particular grading system are beyond the scope of this essay.

Sarcomas of bone are staged according to the system first described by Dr. Enneking and adopted by the Musculoskeletal Tumor Society (MSTS). Stage I lesions are low grade (<25% rate of metastasis); stage II are high grade (>25% rate of metastasis). From there, lesions are further described with a letter, A representing a tumor that remains within its anatomic compartment (in this case, bone); B representing lesions that have extended outside of their compartment. Stage III lesions are any grade or anatomic site that have metastasized.(Ref. 31) The majority of fibrosarcomas of bone present in Stage IIB.(Ref. 32, 33) Though the lung is the most common site of metastasis, when compared to osteosarcoma, fibrosarcoma is more likely to spread to non-pulmonary sites, including other bones, lymph nodes, brain, subcutaneous tissue, muscle, and visceral organs. Fibrosarcoma also tends to have a longer time from presentation to metastasis than does osteosarcoma.(Ref. 22) The relative sparing of pulmonary sites and later metastasis may explain the slightly improved survival reported for fibrosarcoma in some series.(Ref. 33, 34)

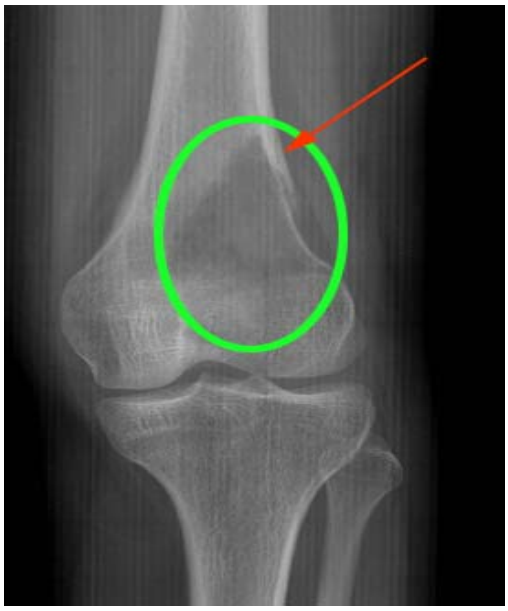
Fibrosarcoma can be divided into the following categories (Ref. 4):

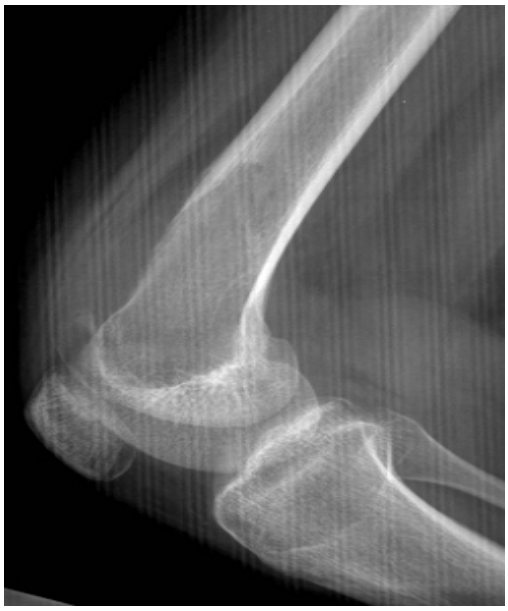
1. Primary medullary fibrosarcoma
2. Primary surface fibrosarcoma
3. Secondary fibrosarcoma
4. Multi-centric fibrosarcoma
5. Congenital fibrosarcoma

The last two are exceptionally rare. There are two reported cases in the medical literature of congenital fibrosarcoma of bone.(Ref. 35)

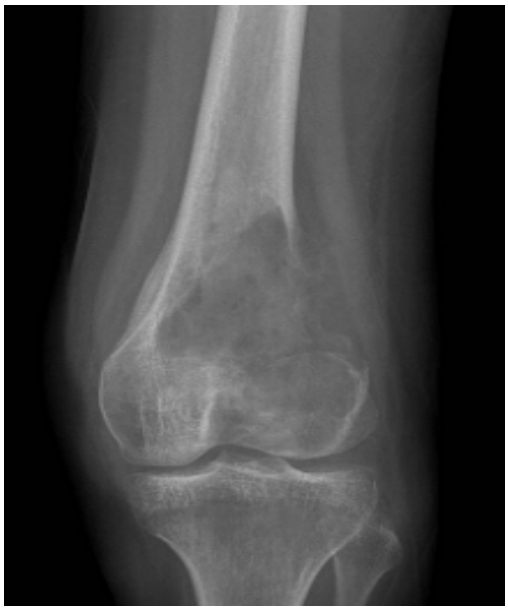
Most cases of primary medullary fibrosarcoma of bone are intermediate to high grade, often moderately to poorly differentiated, and with abundant cellularity. Only a small percentage of medullary lesions are low grade.

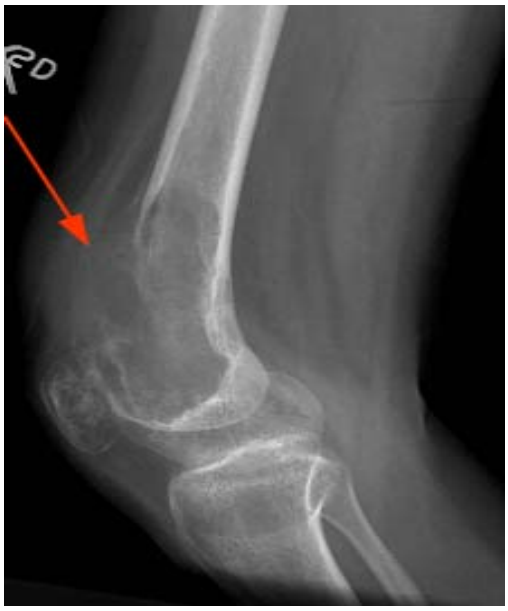
Primary medullary fibrosarcoma has a predilection for the metaphysic of long bones about the knee (Figure 1). Isolated diaphyseal or epiphyseal lesions are rare (Figure 2). Most lesions demonstrate a lytic, destructive lesion on radiograph.(Ref. 32) Prognosis is worse in the intermediate to high grade medullary lesions compared to low grade medullary and surface lesions.



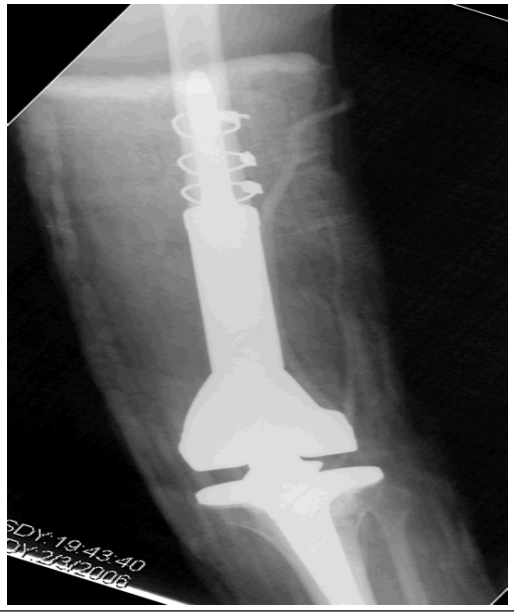


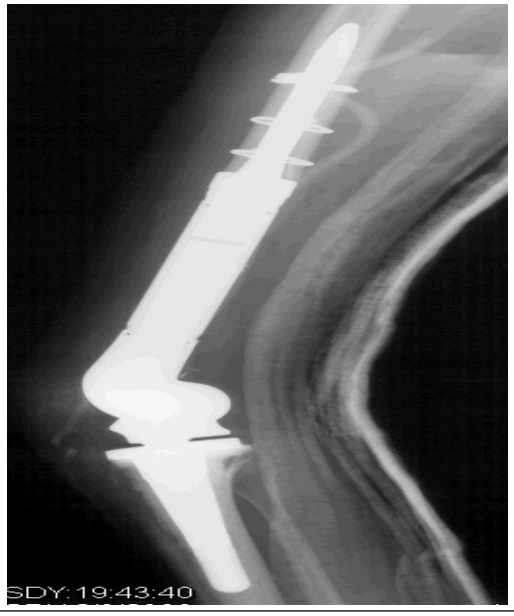
FIGURES 1A & 1B: AP and lateral knee radiographs of a 15 yr old female with progressive knee pain. The green oval encircles a lytic, eccentric lesion involving the metaphysis of the distal femur with extension into the epiphysis. The arrow points to an incomplete periosteal reaction generated by the host bone in response to the destructive tumor. The lesion extends into the soft tissue with violation of the lateral femoral cortex. Biopsy was consistent with fibrosarcoma of bone.





FIGURES 1C & 1D: AP and lateral knee radiographs 5 months later after completion of neo-adjuvant chemotherapy demonstrate progressive bone destruction by the tumor. The arrow in image D marks the extent of the soft tissue mass that is visible on the plain radiograph.





FIGURES 1E & 1F: AP and lateral knee radiographs following resection and reconstruction with an endoprosthetic distal femur and hinged knee joint.

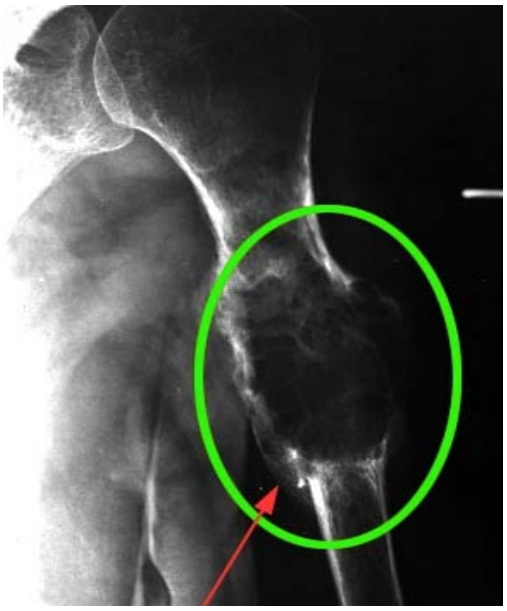


FIGURE 2: AP radiograph of a rare diaphyseal fibrosarcoma involving the left humerus (green oval). Extensive cortical destruction is seen laterally. Tumor expansion of bone and periosteal reaction (arrow) are more pronounced medially. At the inferior border of the tumor, the increased radiodensity represents the body's attempt to control tumor growth by laying down new bone below it.

Debate exists as to whether fibrosarcoma can arise from the surface of bone or if these lesions are soft tissue tumors that grow onto bone. Regardless, these lesions occur less frequently than the medullary form of fibrosarcoma and have a better prognosis.(Ref. 15, 36, 37) Most surface lesions are low grade.

Secondary fibrosarcoma comprises approximately 25 – 30% of fibrosarcomas of bone.(Ref.

36) The anatomic distribution is variable as the location is largely dependent on the natural distribution of the primary lesion. Due to the small number of cases, it is difficult to ascertain an accurate prognosis, but the studies available suggest a survival similar to that of primary, medullary fibrosarcoma.(Ref. 36)

What might someone with fibrosarcoma first notice?

No symptom is indicative that an underlying bone tumor is a fibrosarcoma. Pain, swelling, and loss of range of motion are the most common symptoms but can be experienced in any sarcoma of the bone. A common source of diagnostic delay is the presumption that the pain is a result of trauma or arthritis. (Ref. 66) Unfortunately, this assumption is often made in the absence of a recent injury. Commonly, a minor trauma brings the already present swelling to the patient's attention. Since most knee and other joint pains are not associated with a tumor, the key is to identify symptoms that warrant further evaluation. Persistent pain or swelling without antecedent trauma warrants evaluation. Night pain and pain with weight-bearing that is relieved by rest is also concerning. Many sarcoma patients do not feel "sick" and classic symptoms of cancer such as fatigue and weight loss are often absent.

A tumor may not come to attention until the weakened bone breaks (pathologic fracture). The underlying lesion may be overlooked by an inexperienced observer. Similar to pain, pathologic fracture is not specific for any particular tumor type. Fracture of a long bone following a trivial injury should alert the patient and healthcare provider that this may be a pathologic fracture. Even in older patients, long bone fractures following trivial trauma warrant a high suspicion for an underlying cause and should not automatically be attributed to normal aging.

> A pathologic fracture does not necessarily indicate that the underlying lesion is malignant. Benign lesions often weaken bones enough that they fracture with minimal trauma, even in healthy patients. Regardless, all pathologic fractures warrant a work-up to identify the underlying lesion.

What clues do healthcare providers have that there may be a fibrosarcoma?

Pain with fibrosarcoma is often rapidly progressive with most patients having fewer than six months of symptoms before diagnosis. This course is somewhat more rapid than that seen in osteosarcoma.(Ref. 15) Regardless of type of bone sarcoma, there is often a delay to diagnosis from the time symptoms first arise. This is not surprising as healthcare providers can evaluate countless patients with extremity pains over their careers without encountering one of these exceptionally rare conditions.

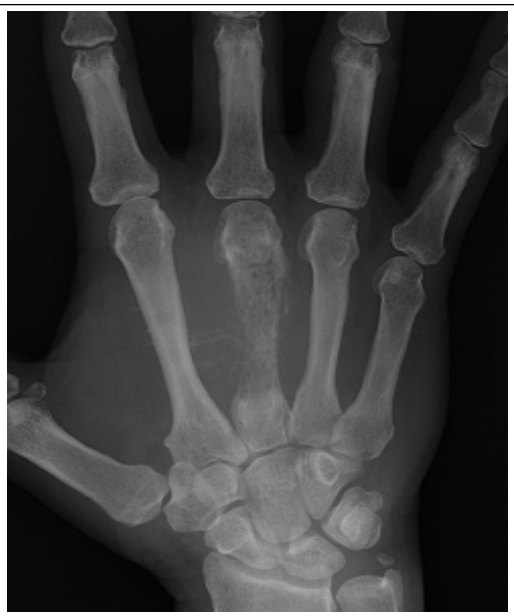
Like patient symptoms, physical exam signs are also non specific. The best tact for healthcare providers is to be more vigilant with a patient whose musculoskeletal complaint and exam findings persist or do not have any logical cause. A sign such as significant thigh swelling after minimal or no trauma is not likely to be a hematoma.(Ref. 38) Similarly, ligament strains should follow some force across a joint and tenderness should be focused to the anatomic location of the ligament.(Ref. 39) Lesions are often missed when a diagnosis of tear or strain is made in patients with bone pain and whose history makes ligament or cartilage injury less likely.

What studies are needed? What information do they provide? Once there is an MRI, why is anything else needed?

The first study most commonly ordered is a plain radiograph (x-ray). This easily accessible and

inexpensive study can provide a lot of useful information. Radiographs will likely be taken of both the affected area and the entire bone in which the tumor is located (i.e. both the knee and femur for a distal femoral lesion). Radiographs are also performed in multiple places (i.e. frontal (AP) and side (lateral) planes) since bone destruction anywhere around the bone and multiple views are needed to assess the bone adequately. Imaging the entire bone is essential as sarcomas of bone can have "skip lesions" where tumor is present within the same bone, but not contiguous with the primary lesion. Though there can be significant variance, fibrosarcomas of bone commonly display several radiographic features.

Tumor location can greatly assist the physician who is compiling a differential diagnosis for a bone tumor. Most fibrosarcoma lesions are intramedullary and located within the metaphysis of long bones. Medullary lesions can be central or eccentrically located within the medullary space.(Ref. 40) In both groups, the tumor may be well-defined (geographic), make the bone appear "moth eaten", or diffusely permeate the bone (FIGURE 3A). Well-defined lesions are found in low grade fibrosarcoma and can have a "halo-like" rim of bone around them, a result of the body trying to repair the damage the tumor caused. This may confuse these tumors with cystic lesions of bone.(Ref. 15, 22) The cortex may be expanded as a low grade tumor grows within the medullary space. Absent cortices are more indicative of aggressive lesions that rapidly destroy cortical bone. Poorly defined lesions have been associated with more histologically aggressive, high grade tumors, and poorer patient survival.(Ref. 15, 40)



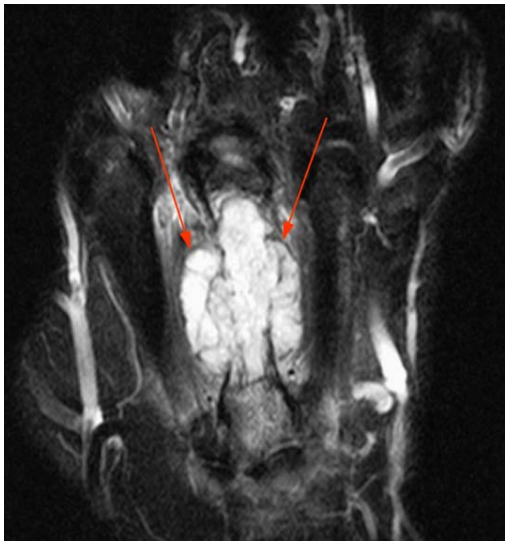


FIGURE 3A– AP radiograph of the hand demonstrates a permeative, lytic lesion of the metacarpal of the middle finger. Though a rare location, the biopsy confirmed the diagnosis of fibrosarcoma of bone. FIGURE 3B - MRI of the same hand. The white areas represent tumor and this image show the extent that the lesion invades the soft tissue on the hand (arrows). This information about the soft tissue cannot be ascertained from the radiograph.

As a tumor infiltrates out of the bone, adjacent healthy bone often tries to contain the process by forming new bone on its surface (periosteal reaction).(Ref. 3, 40) This normal body reaction to the growing tumor is often incomplete and is usually absent in fibrosarcoma, as the tumor growth destroys the bone faster than the bone lays down reinforcement. When there is a periosteal reaction, it is often present later in the course of disease or in more slowly growing tumors (low grade fibrosarcoma). The lesion can break through bone and expand into the soft tissue. These soft tissue masses are often radiolucent and necessitate advanced imaging to be visualized (FIGURE 3B).

Secondary fibrosarcoma commonly displays areas of lucency at the site of a previously imaged or otherwise well described, benign appearing lesion.(Ref. 14, 41, 42, 43, 44) Serial radiographs of benign lesions can help identify transforming lesions early in their course. Lesions, such as in fibrous dysplasia, often show radiographic signs of an process that is well controlled by the surrounding bone, such as a well corticated rim of bone around the tumor, preserved cortical bone, and no soft tissue mass. Benign lesions can alter the bone structure, such as a myofibroma which will often expand the bone. Though the lesion remains surrounded by remodeled host cortical bone, an expansive lesions can impinge adjacent structures such as nerves.

Less common variants (diaphyseal, cortical, and surface types) will show similar destructive and reparative features as described above. The complex bony anatomy of the pelvis can obscure the findings described above and advanced imaging is often helpful in describing the extent of bone involvement.

Similar to extremity lesions, jaw tumors will show radiolucency, irregular borders, and cortical infiltration.(Ref. 45) Conventional AP radiographs can miss these lesions, particularly if in an area of overlapping structures and panoramic imaging may be more beneficial.(Ref. 46)

Magnetic Resonance Imaging (MRI) (FIGURE 3B) helps determine the extent of bone marrow and soft tissue involvement. MRI can delineate the relationship between the tumor and the nerves and blood vessels. This is essential for operative planning. The use of contrast dye is standard when solid tumors are being examined. The contrast helps identify blood vessels and post contrast enhancement helps differentiate normal tissue from tumor. Imaging of the entire bone is necessary as bone marrow involvement can extend beyond the area delineated by radiographs. Non-contiguous "skip" lesions can arise within the same bone and can be detected with MRI.

A whole body bone scan is a nuclear medicine study used for identifying lesions in other bones without performing radiographs of the entire skeletal. Positive findings on the bone scan should lead to further studies to further examine the involved area. There are many processes (including benign conditions) that can give positive findings on a bone scan. Tumors, such as fibrosarcoma of bone, uptake of the tracer material and are often referred to as "hot" areas.

Chest radiograph or computed tomography (CT) of the chest is performed at initial diagnosis to determine if there is metastasis (Stage III disease) of the tumor to the lungs – the most common site of sarcoma metastasis. Imaging is repeated periodically, even if negative initially, to continually survey for pulmonary dissemination of disease.

Though not always performed, a CT scan of the affected extremity can define the amount of bony destruction and the amount and quality of intact bone remaining. CT may substitute for an MRI if a patient cannot have an MRI for medical reasons (implanted medical devices). CT can also be helpful in areas of complex bony anatomy such as the pelvis and shoulder girdle.

Angiography has largely been replaced in the evaluation of bone sarcomas. It was previously used to delineate location of the blood vessel in relation to the tumor and to assess tumor response to treatment; however, this information can now often be obtained from the MRI.

Positron Emission Tomography (PET) scanning is a newer method that can provide information about the biologic activity of the tumor by quantifying its glucose metabolism. Its efficacy as a tool for staging, monitoring response to therapy, and surveillance in sarcomas of bone continues to be elucidated by research. The value of PET in evaluating treatment response has been demonstrated in Ewing's sarcoma and osteosarcoma.(Ref. 47) No specific study of fibrosarcoma of bone has been published. PET scanning for sarcoma is not reimbursed by insurance providers in many areas of the country.

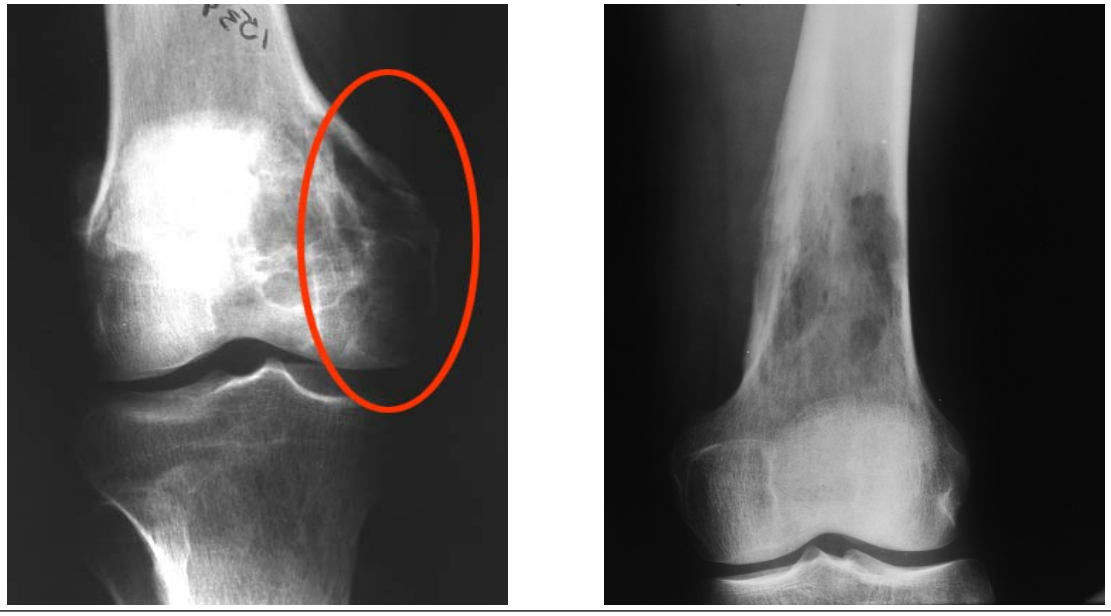
A specialist in orthopaedic oncology should be involved early in any case concerning for a bone sarcoma. A familiarity with the work-up of such lesions can minimize unnecessary tests and ensure that needed studies are performed in the most efficacious manner (i.e. specific MRI sequences, use of contrast, and evaluation of the entire bone). The MSTS (Musculoskeletal Tumor Society) maintains an online database to help locate members. Alternatively, an orthopaedic surgeon at your hospital or to whom you refer patients, will likely be able to direct you to someone he or she refers tumor cases to.

The above studies are often repeated throughout the treatment course. Correlating imaging changes with response to therapy is the aim of considerable research. Ideally, imaging can be used to determine if a particular chemotherapy regimen is effective. In cases that demonstrate tumor progression or lack of efficacy, treatment regimens can be changed early. However, microscopic examination of the specimen after resection is considered the most reliable means of determining response. By that point though, the patient will likely have already received several rounds of chemotherapy and all the side effects that follow.

How is treatment initiated? Will there be surgery?

The most important step before initiating treatment is a **correct diagnosis**. The rarity of malignant bone tumors has led to most cases being reviewed and treated at university hospitals and other tertiary referral centers. Although this often requires significant patient expense and inconvenience, referral to such a center is the best opportunity a patient has to have access to all the services needed to treat this rare condition. A multi-disciplinary approach has become the standard of care in sarcoma. Cases are often collectively reviewed by a sarcoma tumor board consisting of a medical oncologist, pediatric oncologist, radiologist, pathologist, radiation oncologist, and surgical oncologist to thoroughly examine all treatment options. Such a collection of medical professionals with an expertise in sarcoma is rarely encountered outside of a large referral center.

The work-up often begins after plain radiographs reveal the bone lesion. (FIGURE 4) Advanced imaging, often CT, MRI, and/or bone scan will follow. These studies can be performed adequately at any facility, though the ultimate treating physicians may prefer the studies be performed with certain parameters that help guide treatment (i.e., use of contrast dye, computer reconstructions of images). Staging, imaging, and laboratory tests should be complete prior to biopsy.



FIGURES 4A & 4B display radiographs of more "traditional" fibrosarcoma of bone. Image A demonstrates an eccentric lesion in the distal femoral metaphysis, extending into the epiphysis. The lytic lesion has significantly thinned the femoral cortex (oval). Image B demonstrates a central lesion in the metadiaphyseal region. This permeative lesion has incited a periosteal reaction over the medial femoral cortex. That reaction is "incomplete" as the central area of the newly formed bone is not contiguous, but interrupted.

A biopsy is a procedure for sampling the tumor and obtaining a specimen for diagnostic evaluation. Biopsies can be incisional (a piece is taken from the tumor) or excisional (the entire tumor is removed). In bone tumor evaluation, an incisional biopsy is often preferred because the type of tumor will determine the treatment, including the manner in which the tumor is ultimately removed.

The next step is biopsy. As a rule, an open surgical biopsy should be performed or directed by the physician who will be performing the definitive surgery(Ref. 48). A surgical biopsy is often misconstrued as a fool-proof procedure. In reality, an inappropriately performed biopsy can jeopardize the patient's chance to undergo limb salvage. This has been demonstrated in several studies.(Ref. 49, 50)

Advances in imaging and methods of evaluating biopsy specimens have allowed many bone tumors to be sampled by needle biopsy. These techniques are often performed by a musculoskeletal radiologist in consultation with an orthopaedic oncologist. Though the techniques are user-dependent, studies support needle biopsy (often with advanced imaging guidance) as safe and reliable.(Ref. 51, 52) In some case, an open biopsy may still be required to get a definitive diagnosis. A correct diagnosis is rarely reached in a vacuum. Radiologic and clinical correlation is essential to correctly achieve an accurate diagnosis.

A needle biopsy often entails the use of advanced imaging (CT, MRI, or ultrasound) to help the person performing the biopsy aim the needle in the portion of the tumor expected to give the highest yield for the pathologist who will review the specimen. Needle biopsies are being performed more often as research has shown them to be effective and they can be performed without making an incision.

The biopsy should be reviewed by a pathologist experienced with tumors of the musculoskeletal system. Light microscopy features mimic those of the soft tissue counterpart.(Ref. 37) The tumor will consist of spindle shaped malignant cells often interdigitating in a "herringbone" pattern. (FIGURE 5) The nuclei are often plump and hyperchromatic but can also be elongated or "cigar-shaped". High grade lesions often show more atypical cells and disruption of the herringbone pattern.(Ref. 15) Bone tissue may be present, but as remnants of host bone or reactive bone, not osteoid synthesized by malignant cells.(Ref. 15) Immunohistochemical stains and translocation analysis can be employed to help distinguish this from other malignancies of bone.

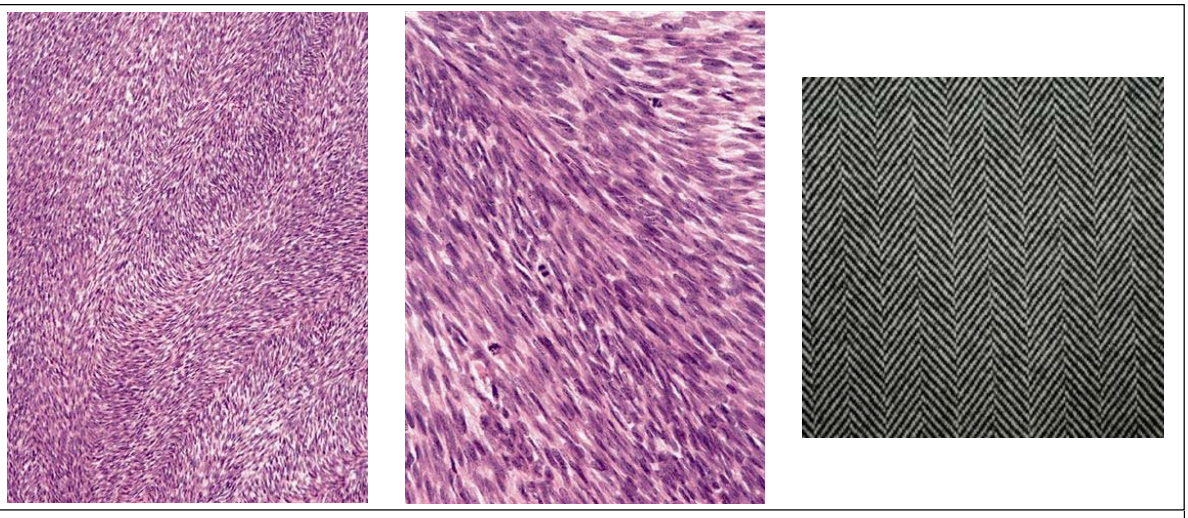


FIGURE 5A & 5B – Low and high power histology specimen images of a fibrosarcoma. This lesion is composed of homogenous spindle shaped cells arranged in the "herringbone" pattern classically described in this lesion. It shows little pleomorphism and is a well differentiated fibrosarcoma. FIGURE 5C is a photograph of a "herringbone" patterned garment.

As described above, genetic and immunohistochemical testing help delineate fibrosarcoma of bone from similar lesions.

Surgical resection is the standard treatment for fibrosarcoma of bone. Some patients are candidates for chemotherapy in either the pre-operatively (neoadjuvant), post-operatively (adjuvant), or both. The goal of chemotherapy is to kill both the large tumor mass(es) and any circulating cancer cells that are not detectable on imaging.

Though no large chemotherapy studies of fibrosarcoma of bone are published, it is often administered to patients with stage IIB or III disease. Drug regimens are formulated at the discretion of the medical or pediatric oncologist but likely will contain some combination of Adriamycin and cisplatin. The specific agents and scheduling is in part based on patient tolerance of the side effects that accompany each agent. Not surprising, young patients often tolerate larger doses and longer duration of treatment. Older patients, particularly those with significant medical co-morbidities, may only tolerate small dose, if any, chemotherapy.

Reports of chemotherapy have not been encouraging.(Ref. 34) However, successes in the treatment of osteosarcoma have led investigators to continue to look for efficacious drug regimens in fibrosarcoma of bone.(Ref. 53) Again, the inability to collect a large number of patients, makes performing well-controlled treatment trials difficult.

Radiation treatment has similarly been shown to have little effect on overall disease course, but may play a role in palliation.(Ref. 8, 22)

Limb salvage surgery has revolutionized musculoskeletal surgical oncology. Advanced imaging, adjuvant therapy, surgical technique, and implant development have allowed limb sparing surgery to be performed safely in cases that previously would have required an amputation. A discussion of the pro's and con's of limb salvage surgery and how one comes to a final decision on the type of surgery is out of the scope of this review other than to say the field continues to evolve.

Despite advances in limb salvage, amputation remains a valuable technique in disease management. Indications include unresectable lesions, local recurrence, failure of previous reconstruction, and certain tumor locations (in particular, areas in which a functional reconstruction is not possible). Amputations avoid the complications associated with limb salvage such as non-union, implant infection, and implant failure. This results in fewer subsequent surgeries for patients undergoing amputation. Amputation has been shown to have lower local recurrence rate, but no clear survival benefit, when compared to limb salvage surgery.

Regardless of the type of surgery, several goals remain constant. Complete removal of the tumor surrounded by a margin of healthy tissue has been shown to give patients the best chance at survival without a local recurrence.(Ref. 33, 34) Since even microscopic amounts of remaining tumor can be of clinical significance, a wide volume of tissue around the tumor is excised and the actual tumor is rarely even visualized during its extirpation.

Surgery to address metastatic lesions to the lungs has also been investigated and its indications are based on the size, number, and locations of the lesions. General patient condition and length of disease-free interval are also considered.(Ref. 54) No definitive statements about survival benefit can be made as relates to metastatectomy in metastatic fibrosarcoma of bone.

The type of surgery will largely dictate the rehabilitation that follows. The type and duration of rehabilitation is almost exclusively dependent on the treating surgeon and the specific procedure performed.

> Treatment of any sarcoma often involves many doctors and medical professionals. Specialists in radiology, surgery, pediatric/medical oncology, pathology, radiation oncology, internal medicine, and rehabilitation will often all be involved in any given case. This multi-disciplinary approach is the standard of care in sarcoma management.

Comparing the functional and psychosocial differences between limb salvage and amputation patients is a area of great interest.(Ref. 55) There is variability in the results, but studies trend toward greater disability in the amputation patients.(Ref. 56, 57) This is frequently counter balanced by the increased complication risk and need for repeat operations in the limb salvage group. As a result, there has been the hypothesis that there is an improved quality of life in patients who undergo amputation since they rarely require revision surgery, have a lower risk of infection, and fewer hospital re-admissions. This theory has not been *reproducibly* supported.(Ref. 58, 59, 60) Though reported differences exist, functional and psychosocial outcomes are comparable and patients in both categories frequently live well-adjusted, mobile, productive lives.

How long should patients be followed after treatment?

Most treating physicians use a surveillance protocol similar to what they use for surveillance of other bone sarcomas. National Comprehensive Cancer Network (NCCN) guidelines recommend that for the first two years, physical exam and radiographic follow-up occur every 3 months. The interval can be increased to every 4 months for the next 2 years, to every 6 months for years four

and five, and then annually. Radiographs of the effected extremity may be performed more frequently to evaluate the status of the reconstruction. Data suggests later appearance of metastasis and an increased incidence of extra-pulmonary sites of metastasis in fibrosarcoma of bone. This may warrant longer or more frequent surveillance.(Ref. 61) The incidence of bony metastases may prompt the treating physician to include bone scan in his or her follow-up routine. Regardless of formal follow-up, the patient must remain aware that new lumps, masses, or pains may represent recurrent or metastatic disease.

What is the prognosis?

Prognosis in fibrosarcoma is largely dependent on the histological grade.(Ref. 8) Historically reported 5-year survival rates with high grade medullary lesions are approximately 30%.(Ref. 8, 22, 33, 36, 40, 62) Survival rates from 50 – 80% have been reported in low grade and surface fibrosarcomas.(Ref. 22, 36)

Other factors associated with a poor survival include age over 40 years, primary tumor in the axial skeleton, eccentric permeative lesions, and stage of disease at presentation.(Ref. 33, 40) There is no conclusive data that suggests a different prognosis between primary and secondary tumors.

Local recurrence is largely dependent on the ability to obtain wide surgical margins. Local control rates of 93% and 100% have been described at five years for patients following wide and radical resection, respectively.(Ref. 33) Though early studies support the use of ablative surgery, more recent studies demonstrate a comparable rate of disease control with radical resection and limb salvage surgery.

Are there new tests or treatments on the horizon?

Classifying tumors beyond their gross and microscopic appearance will hopefully allow investigators to subdivide (or reclassify) known diseases. Identifying subclasses of tumors that vary in treatment response and prognosis will help direct treatment and future research. Chromosomal translocations are an example of how sarcomas are being classified.(Ref. 13) The gene products of these translocations may help elucidate the pathogenesis of these diseases while also providing targets for novel drug therapy.

Much of cancer research focuses on identifying and targeting specific genes and their products that are unique to a given malignancy. Ideally, a drug will disrupt a pathway unique to tumor development and progression without disrupting normal physiologic processes. Unfortunately, overlap is common and altering shared pathways results in some of the toxicities associated with cancer treatment. Studies are being performed in fibrosarcoma and commonly altered pathways are being identified.(Ref. 4) How these findings can be translated into clinical therapies is still unknown.

The rarity of fibrosarcoma (and all bone sarcomas) makes collecting enough cases to perform outcome studies difficult. Large referral centers and collaborations between centers offer the best opportunities to amass large patient series. The heterogeneity of patient populations, treating physicians, and observers collecting data can make it difficult to draw conclusions though. Differences in diagnostic criterion may result in patients being included or excluded differently between studies. Medical oncologists may also vary in their preference of drug regimens, particularly in older patients where side effects may be less well tolerated. An increased tolerance and willingness to treat side effects may lead some physicians to continue chemotherapy longer than others. Differences in surgical technique and skill also factor into varying patient outcomes.

Recent Published Reports

Over the past ten years, there have been 70 published reports in the English literature that included a description of fibrosarcoma of bone. Most have been descriptions of surgical techniques or case reports of unusual presentations of the disease. Given the heterogeneity of published reports, it is difficult to draw definitive conclusions about trends or treatment approaches from them. Tables 1 and 2 summarize.

Conclusion

Fibrosarcoma is a rare malignancy of bone. Though it shares features with other sarcomas, fibrosarcoma of bone is a distinct clinical entity that has several unique features. The improvement of outcomes for fibrosarcoma of bone has lagged behind that of other sarcomas. Large randomized trials cannot be performed since even large cancer centers see few cases, if any, of primary fibrosarcoma of bone a year.

Surgery remains the standard treatment but advances in translational research may help identify novel targets for systemic treatment. Five year survival remains poor and variations in reported survival between different studies may be attributed to differing inclusion and exclusion criterion. The trend toward these rare cases being treated at centers with a collection of medical professionals specializing in sarcoma offers the best opportunity to maximize care delivered and to compile data to guide treatment of future generations.

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