42 Fibroblastic/Myofibroblastic Tumors

Piero Picci, Angelo Paolo Dei Tos, Marco Gambarotti, and Alberto Righi

Fibroblastic/myofibroblastic sarcomas are mainly recognized and classified in the soft tissues while in the bone fewer entities were recognized.

It is now accepted that a broad variety of mesenchymal malignancies most often arising in the soft tissues may actually present as primary bone lesions. A more accurate morphologic partition is justified based on availability of distinct therapeutic options. An integrated diagnostic approach represents the only way to achieve a correct classification. In consideration of the significant complexity, primary bone sarcomas should ideally be handled in the context of expert centers.

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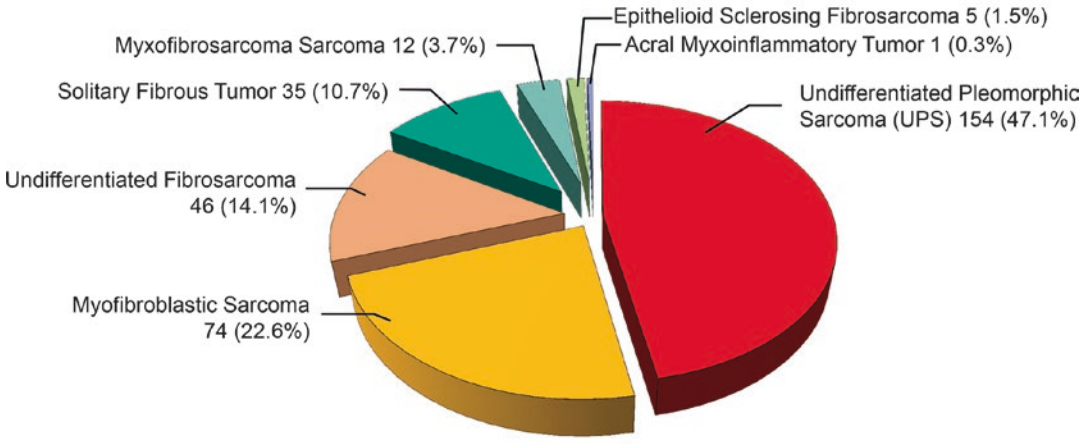
FIBROBLASTIC / MYOFIBROBLASTIC SARCOMA OF BONE
327 cases



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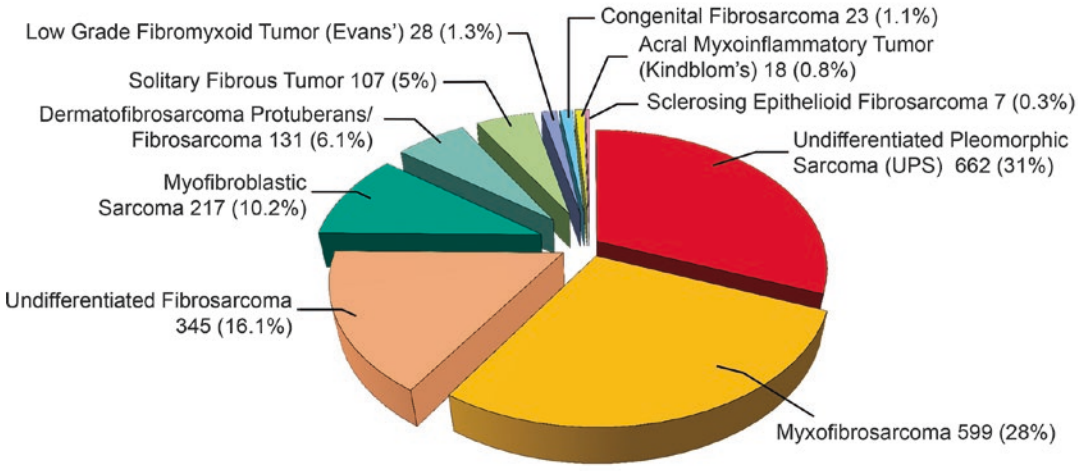
FIBROBLASTIC / MYOFIBROBLASTIC SARCOMA OF SOFT TISSUE
2.137 cases



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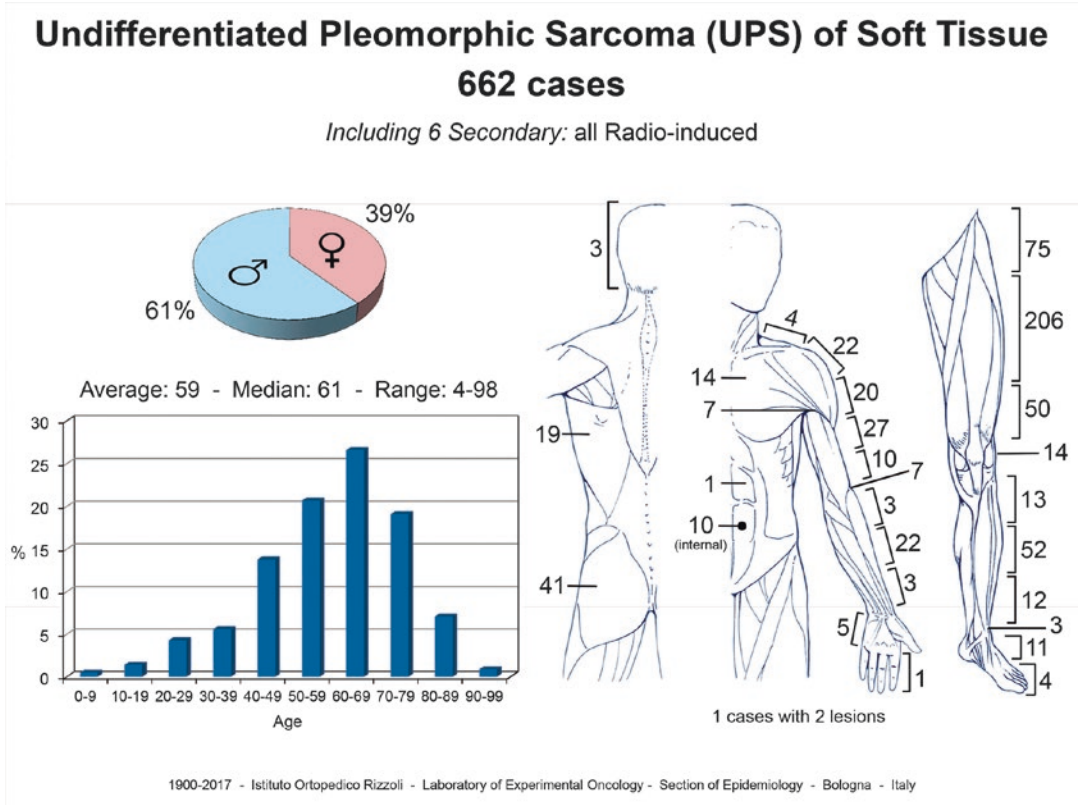
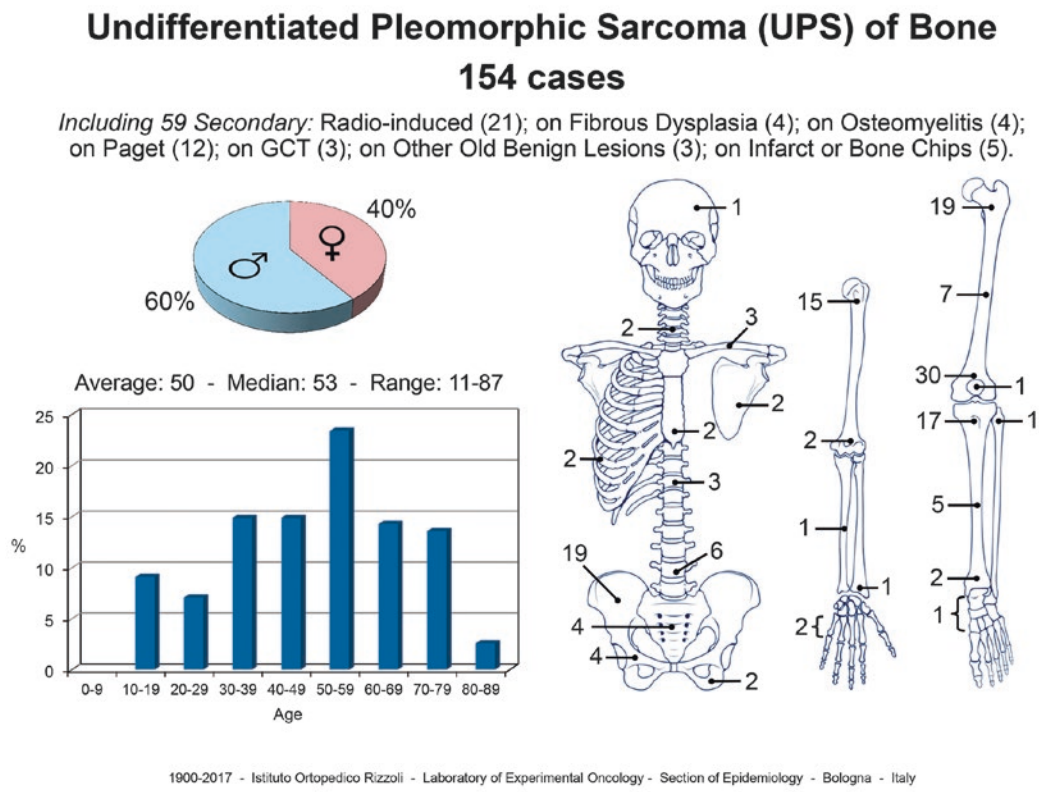
42.1 Undifferentiated Pleomorphic Sarcoma (UPS)

Definition: A sarcoma characterized by tumor cells with diffuse pleomorphism in the absence of a specific line of differentiation. The old term malignant fibrous histiocytoma (MFH) is obsolete as immunohistochemistry demonstrated that the phenotype of the neoplastic cells is closely aligned with a fibroblast than a histiocyte. In the 2013 WHO classification, UPS is classified in the group of undifferentiated/unclassified sarcomas that are divided into pleomorphic (UPS), round cell, spindle cells, and epithelioid subsets. Together they account for up to 20% of all soft tissue sarcomas.

Epidemiology: It is most frequent in soft tissues than in bone. It is the most frequent among secondary sarcomas of bone. More frequent in males, and in the adult age. Secondary UPS are observed in more advanced age groups.





Localization: In bone, it is most commonly localized in the long bones, femur, tibia, and humerus. It prevails in the metaphyses and metaepiphyses, although a purely diaphyseal location may be seen. There is prevalence for the distal femur and proximal tibia, but not as pronounced as it is in OS. In soft tissue, it affects skeletal muscles of extremities and retroperitoneum. Tumor is deep in 90% of cases.

Clinical: Globose and painless swelling with no characteristic clinical features other than a frequently rapid growth rate. In bone, pathologic fracture is common.

Imaging: In bone, it is a purely osteolytic tumor, centrally or eccentrically located. Osteolysis may be uniform with geographic ill-defined borders. Sometimes scattered or confluent radiolucent areas give a moth-eaten appearance. Infrequently some osteosclerosis is present at the margins of the tumor. The cortex is usually permeated or destroyed by the tumor. Periosteal reaction is not frequent. As in all purely osteolytic tumors, the real tumor extension in the bone and in the surrounding soft tissues is often more pronounced than what is indicated on radiographs. CT, MRI, isotope scan and angiography, as well as gross and microscopic study will show the real extension. In soft tissues, on X-ray: nonspecific STT displacing the adjacent fat. Peripheral calcifications are rare (9%). Florid periosteal reaction and smooth cortical erosion may be observed. In these cases, bone scan is always very hot. On angiography: typical changes occurring in sarcomas, with very large avascular areas of tumor due to necrosis or hemorrhage. Major vessels are almost never infiltrated. On CT: inhomogeneous, similar to or lower density than that of muscle, strong enhancement of the solid component, central hypodense area of necrosis, hemorrhage, myxomatous tis-

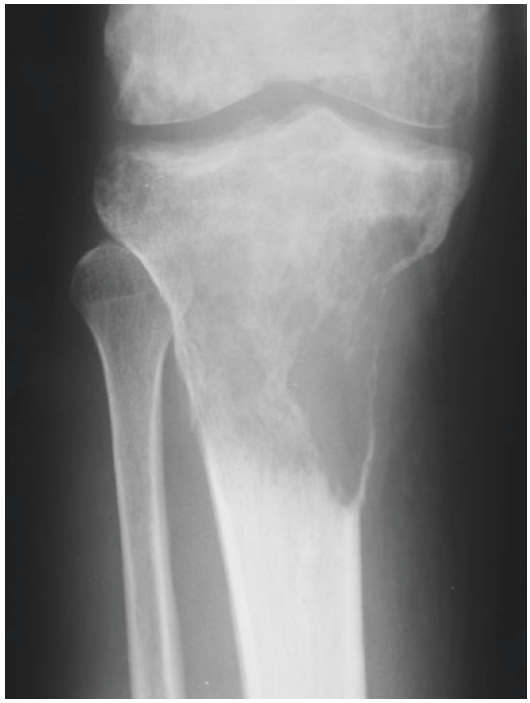
sue, with large cavities with fluid contents and a thick wall that are mistaken with a hematoma. On MRI: poorly defined margins, homogeneous, muscular intensity on T1 and heterogeneous high signal intensity on T2, dark central necrotic zones and strong enhancement at the periphery on contrast T1, internal low signal intensity septa of collagen bands on T1 and T2. In MFH, central myxoid area is black on T1 and white on T2. Hematoma is white on T1, fluid levels show low signal intensity for hemosiderin deposits and high for supernate on both sequences.

Histopathology: The tumor is a white-gray mass with no distinctive macroscopic features other than the frequent presence of necrosis. Histologically, it is composed of pleomorphic atypical cells with hyperchromic nuclei, coarse chromatin, large nucleoli; numerous typical and atypical mitotic figures are present. Histologically, UPS resembles other specific types of pleomorphic sarcoma, with frequent multinucleated giant cells and a frequent patternless pattern. In some areas, there is a distinctive orientation in whorl-like structures: "the storiform pattern". Collagen production may produce an accentuation of this feature. Clusters of histiocytes, foam cells, and inflammatory cells are sprinkled. In the 2013 WHO classification, UPS is classified in the group of undifferentiated/unclassified sarcomas that are divided into pleomorphic (UPS), round cell (similar to other specific types of round cell sarcoma, especially Ewing sarcoma), spindle cells, and epithelioid (similar to a metastatic carcinoma or melanoma) subsets. On immunohistochemistry, undifferentiated pleomorphic sarcomas are positive for vimentin and by definition no pattern of protein expression that would identify a specific line of differentiation can be identified. In bone, UPS frequently breaches the cortex and extends into the soft tissues. UPS of bone is frequently secondary (bone infarcts, old chondromas and chondrosarcomas, radiated bone, Paget, giant cell tumors, osteomyelitis).

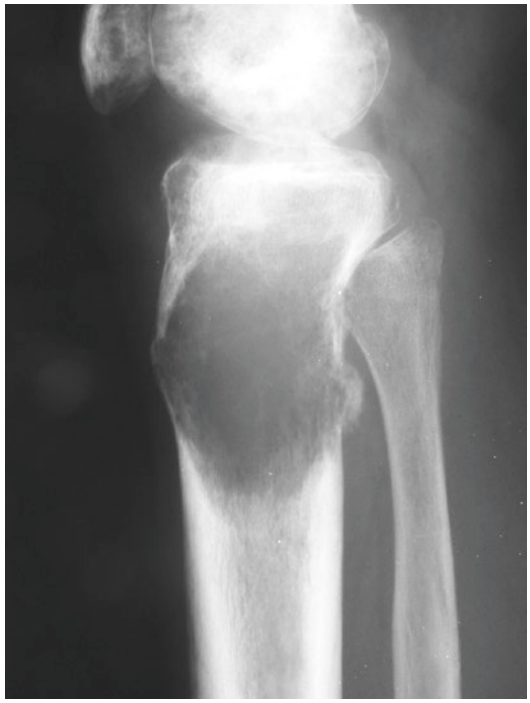
Course and Staging: The majority of UPS are high-grade sarcomas with a metastatic incidence that varies between 30 and 50%, with the common metastatic sites being lung, bone, and liver; regional lymph node metastases are decidedly uncommon. Usually, this tumor is stage IIB. IIIB presentation due to lymphatic or pulmonary metastases is not uncommon. UPS may be secondary to benign processes or radiation therapy. Several studies have suggested that pleomorphic sarcomas with myogenic differentiation are clinically more aggressive that those without myogenic differentiation.

Treatment and prognosis: UPS of bone moderately responds to chemotherapy. After preoperative chemotherapy, the same used for OS, the percentage of good responders (necrosis >90%) is less than in OS, but higher to that of fibrosarcoma. Postoperative chemotherapy is also indicated with the same schedules used for OS. With this aggressive treatment, the percentage of long-term survivors seems to be similar to that obtained in OS, around 60–70%. UPS is also relatively responsive to radiation therapy, which can be used rarely as adjuvant to surgery, or in inoperable cases. In soft tissues, wide excision or yet better radical surgery. Radiotherapy is effective in 50% of cases and is used as primary procedure to very well delimit the mass and to reduce the lesion making the operation possible and easier. Patients treated with adjuvant chemotherapy have a better survival.

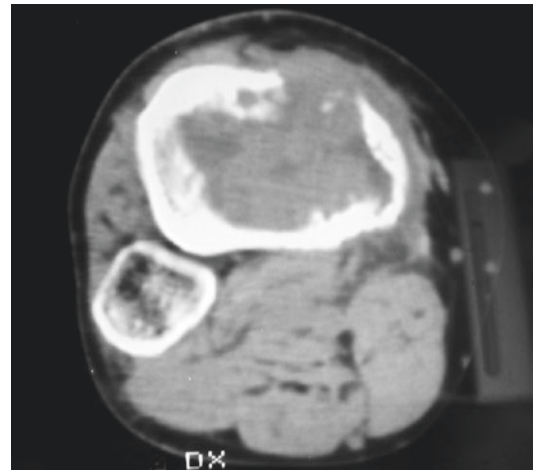
Key points	
• Clinical	Adults, pain and swelling
• Radiological	In bone pure lytic lesion; in ST no specificity
• Histological	High-grade spindle and pleomorphic cells
• Differential diagnosis	In bone, metastasis and all other primary purely osteolytic lesions of the adults. In ST, all other sarcomas



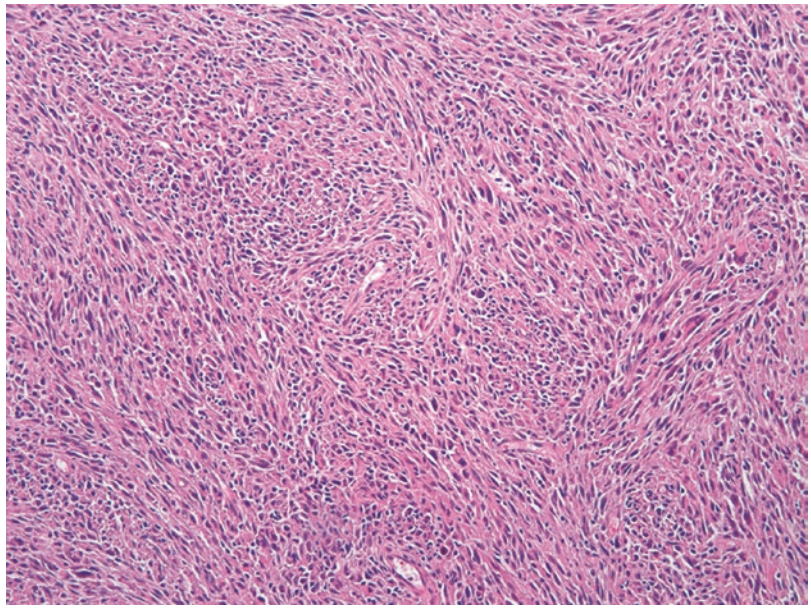
Radiographs and CT with contrast medium. Metaphyseal purely lytic, poorly limited lesion, destroying the cortex



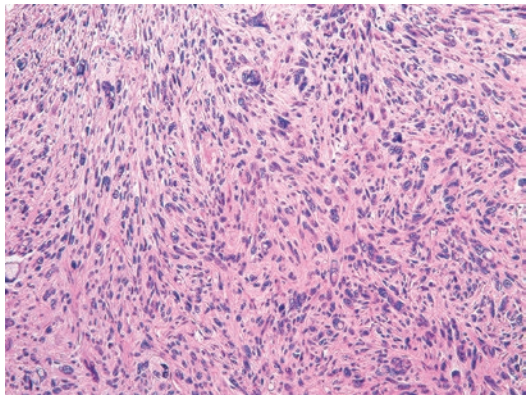
Radiographs and CT with contrast medium. Metaphyseal purely lytic, poorly limited lesion, destroying the cortex



Radiographs and CT with contrast medium. Metaphyseal purely lytic, poorly limited lesion, destroying the cortex



Cytologically high-grade malignant proliferation of spindle and pleomorphic cells arranged in a storiform growth pattern. Fine filamentous collagen is detected between tumor cells. Osteoid production must be absent



High-grade pleomorphic undifferentiated neoplasm with focal storiform pattern

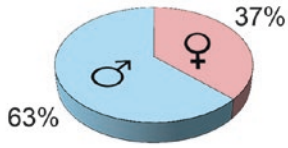
42.2 Undifferentiated Fibrosarcoma

Definition: Intermediated to high-grade spindle cells malignant neoplasm lacking any line of differentiation other than fibroblastic. It is a diagnosis of exclusion.

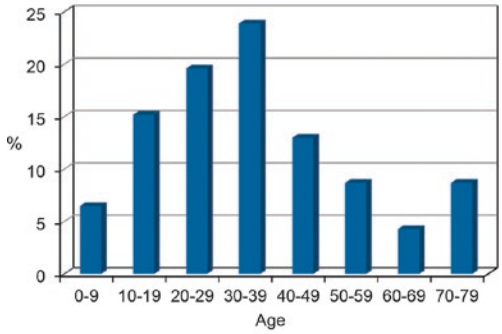
Epidemiology: <1% of adult soft tissue sarcomas. Medium age 40–45 years. No sex predilection.

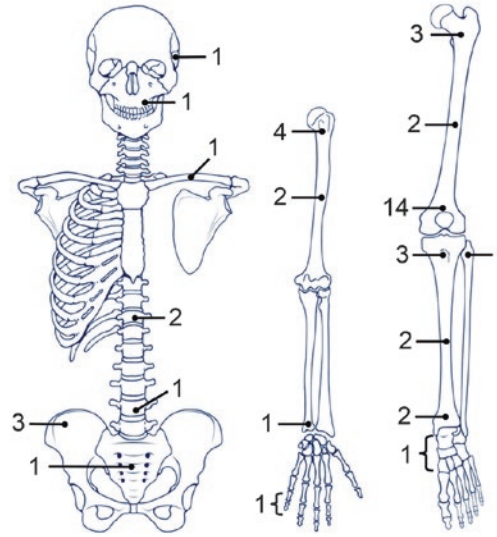
Undifferentiated Fibrosarcoma of Bone
46 cases

*Including*7 Secondary: after Radiation Therapy (4); on Infarct/bone Chips (2); on GCT (1).



Average: 37 - Median: 36 - Range: 1-78





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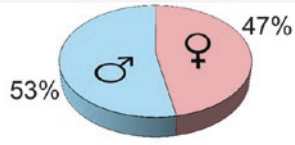
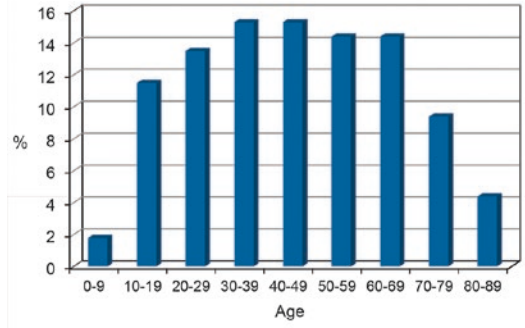
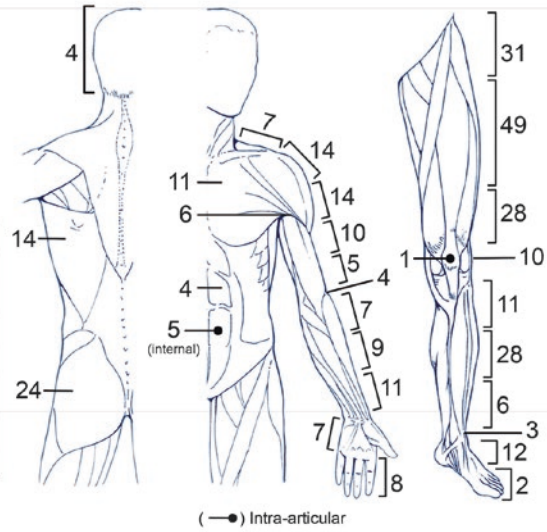
Undifferentiated Fibrosarcoma of Soft Tissue
345 cases

Including 4 Secondary: after Radiation Therapy (3); on Chronic Lymphedema (1)



Average: 45 - Median: 46 - Range: 5-89





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Localization: In bone, the most frequent locations are femur, tibia, humerus, and pelvis. Usually located in the meta-diaphysis, it may invade the epiphysis or be multicentric. In soft tissues, most are deep. Anywhere where fibrous tissue is found: thigh, knee, trunk, arm, forearm. Rare in the head and neck. Hand and foot are most frequent sites of fibrosarcoma in the child.

Clinical: In bone, in low-grade tumors, there is mild pain, no soft tissue mass, and a slow course. In high-grade fibrosarcoma, pain may be severe with a soft tissue mass, joint involvement, the course is rapidly progressive, and pathologic fracture is common. In soft tissues, palpable, globose, well-defined mass rarely >10 cm. It is slow growing (few weeks to 20 years). It is nearly or totally painless except when it compresses a nerve. In advanced forms, it may adhere to the bone and ulcerate the skin.

Imaging: In bone, it is a purely osteolytic tumor with ill-defined limits, interruption of the cortex, and soft tissue mass. Periosteal reaction is scarce or absent. Low-grade tumors may present better-defined borders. In soft tissues, on X-rays: a mass denser than muscles. Calcifications are exceptional. Bone may be eroded or saucerized with minimal periosteal reaction. On CT: homogeneous density, compact soft tissue mass with ill-defined margins and poor enhancement after contrast administration. On MRI: inhomogeneous, lower or isointense signal as those of muscle on T1, 90% marked, peripheral enhancement on gadolinium, dark areas on a background of intermediate or high intensity on T2.

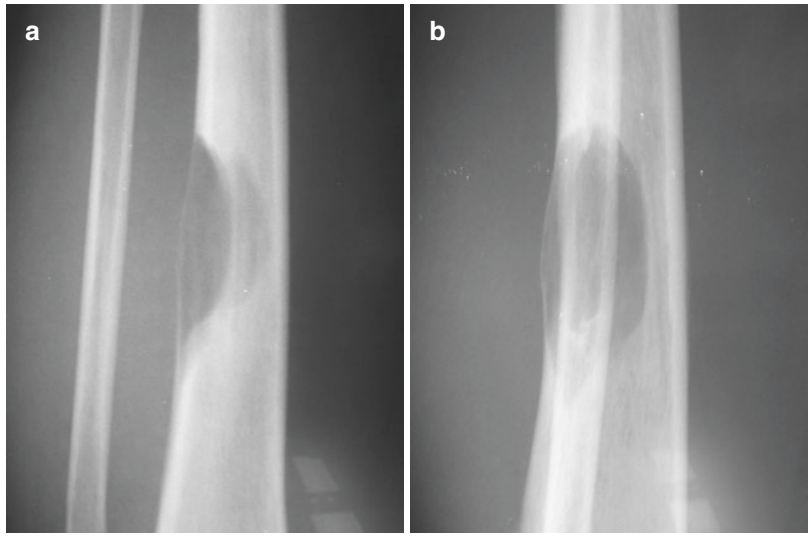
Histopathology: Fibrosarcoma tends to be firm and whitish when containing more collagen (low-grade); pink-gray and soft to encephaloid, when the cells prevail (high-grade). Low-grade well-differentiated tumor are firm and scar-like in consistency, white-yellow, with rounded limits, growing in an expansile fashion with a pseudocapsule of reactive tissue that sharply delimits it from surrounding normal tissues. High-grade poorly differentiated tumor are soft and fish-flesh in consistency, gray-white, with irregular margins, growing in an invasive fashion without a capsule and with multiple processes that infiltrate the surrounding tissues and satellite nodules isolated from the main tumor mass. Histologically, on low power view, it is characterized by a uniform proliferation of relatively monomorphic spindle cells, arranged in interlacing bundles, sweeping fascicles or in a herringbone pattern, with interwoven parallel arranged eosinophilic collagen fibers. The cells generally have tapered darkly stained nuclei. Lesions showing marked anaplasia and pleomorphism are better classified as undifferentiated pleomorphic sarcoma.

Course and Staging: Fibrosarcoma can come from transformation of pre-existing benign processes (neurofibromatosis, burn scars) and from radiation exposure. Any stage: more frequently stage IA and stage IIB. Low-grade and age <10 years are favorable prognostic factors. In children, metastases are rare (<10%). Lymph node metastases are rare (<5%).

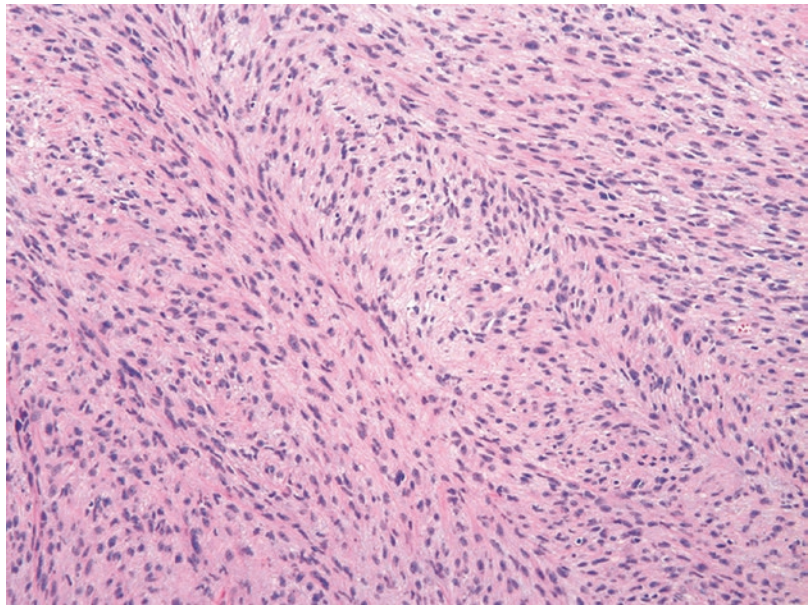
Treatment: Wide excision. In the adult and in a high-grade lesion, radical margins may be indicated. Radiotherapy is less effective and it is used as adjuvant in high-grade tumors in soft tissue lesions.

Prognosis: When surgical margins are inadequate, local recurrence occurs in 50% of cases. Lung metastases occur in 60% of cases. Ten-year survival rate is 60% for low-grade and 30% for high-grade tumors. Recent studies have demonstrated that adjuvant chemotherapy is useful for a better prognosis.

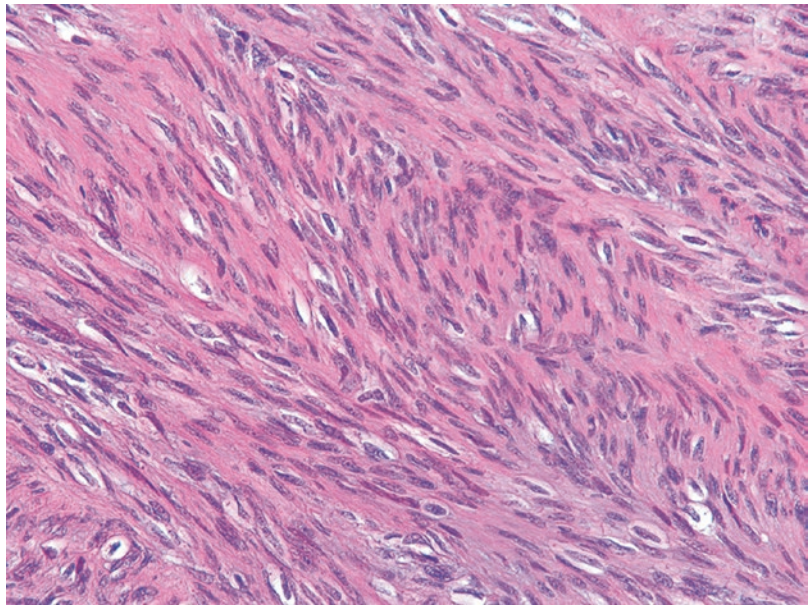
Key points	
• Clinical	Adults, pain and swelling
• Radiological	In bone pure lytic lesion; in ST no specificity
• Histological	High-grade spindle cells
• Differential diagnosis	In bone, metastasis and all other primary purely osteolytic lesions of the adults. In ST, all other sarcomas



Radiographs (AP (**a**) and lateral (**b**) views). Well-limited lytic lesion, with thin longitudinal periosteal formation



Proliferation of atypical spindle cells with slender and tapered nuclei, arranged in a herringbone growth pattern; slight to abundant collagen is present between cells

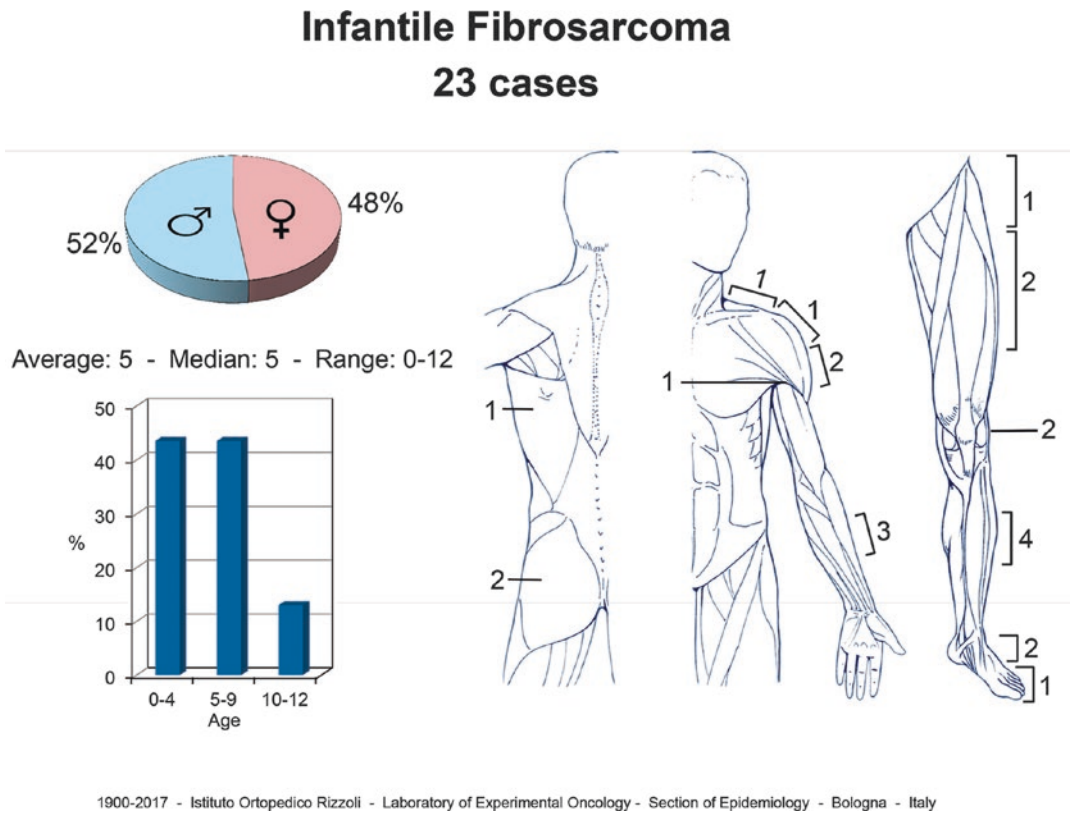


Spindle cell neoplasm with variable grade of atypia arranged in a herringbone pattern with intercellular fibrillary collagen

42.3 Infantile Fibrosarcoma

Definition: Congenital or infantile neoplasm resembling adult fibrosarcoma, characterized by the translocation t(12;15) with ETV6-NTRK3 gene fusion.

Epidemiology: Most cases occur in the first year of life, about 50% congenital. Slight male predominance.



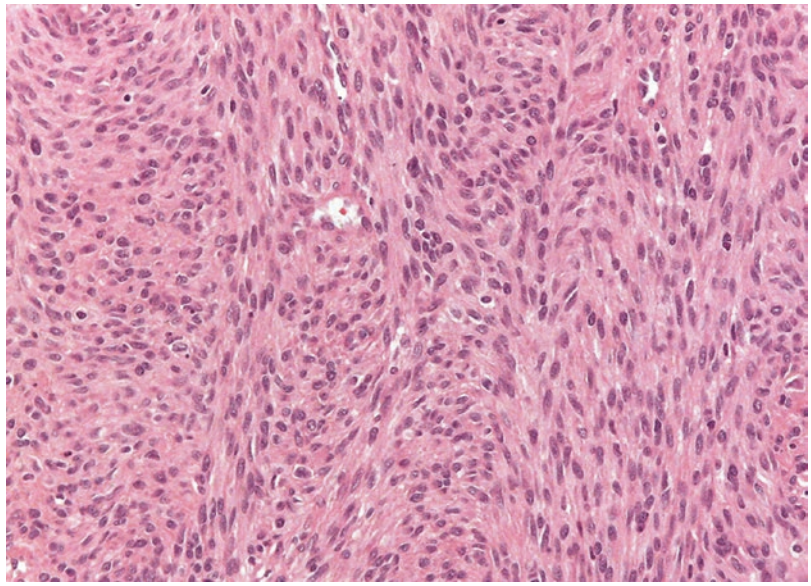
Location: Superficial or deep soft tissues of distal extremities, head and neck, trunk**.**

Clinical: Rapidly growing mass that can reach 30 cm in major dimension. Dark red to purple external surface, often with ulceration of the overlying skin.

Histopathology: Grossly, infantile fibrosarcoma is a poorly circumscribed lobulated mass, fleshy, tan-white, with areas of necrosis and hemorrhage. Histologically, it is characterized by a highly cellular proliferation of spindle, round, or plump polygonal cells, generally growing in intersecting fascicles, sometimes displaying a herringbone pattern. Pleomorphism is generally not prominent. Mitotic activity can be prominent. A hemangiopericytoma-like vascular pattern can be present. Histological variants include a predominantly round cell variant and a myxoid variant. Necrosis, hemorrhagic areas, dystrophic calcifications, and extramedullary hematopoiesis can occur. After chemotherapy, the tumor histologically resembles a fibrotic scar with vascular proliferation.

Course and Treatment: Recurrences occur in about 30% of cases and metastasis are rare (<5%). Overall survival at 5 years is >90%. Local excision is the treatment of choice. Occasional spontaneous regression after incomplete surgery can occur. Chemotherapy is effective, also as a substitute of the surgery.

Chromosomal translocations		
• t(12;15)(p13.2;q25.3)	ETV6-NTRK3	about 100%

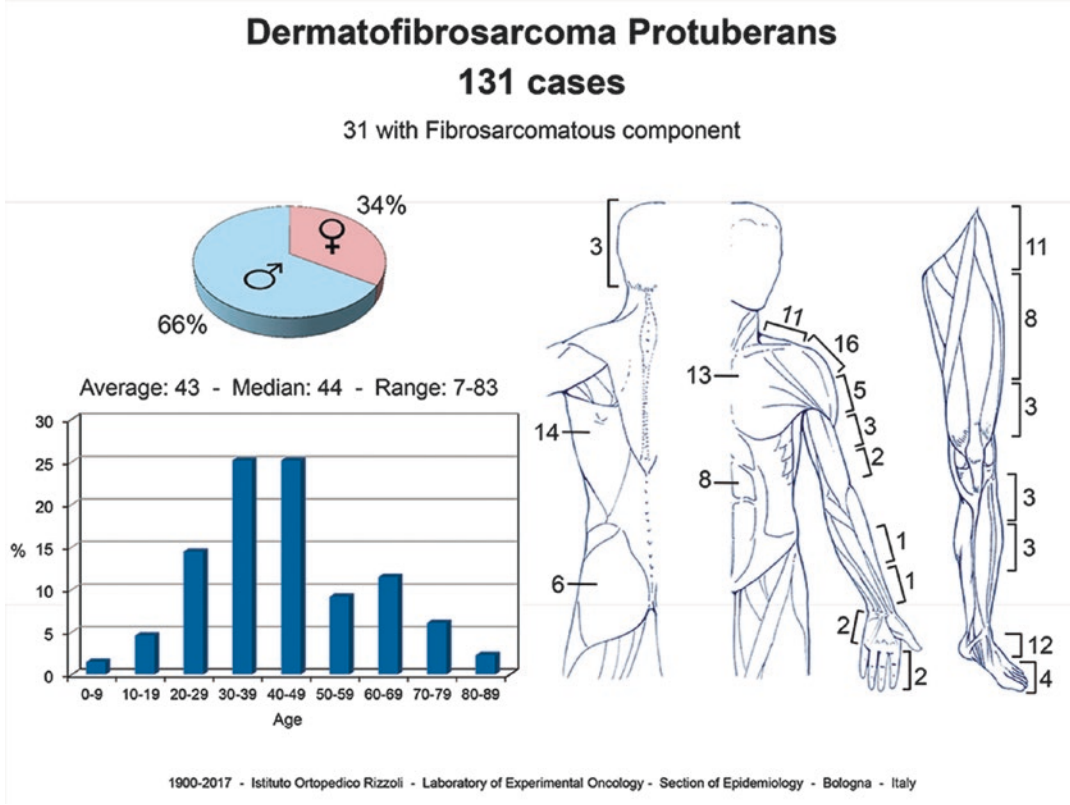


Spindle cell sarcoma with mild pleomorphism, growing in intersecting fascicles with a herringbone pattern

42.4 Dermatofibrosarcoma Protuberans

Definition: Low-grade fibroblastic tumor of the skin in adult patients. There is a juvenile form of DFSP, called giant cell fibroblastoma.

Epidemiology: Infrequent, males. DFSP: young to middle-aged adults, rare in children. Giant cell fibroblastoma: infants and children younger than 5 years, exceptional in adults.



Location: Trunk, groin, and proximal extremities.

Clinical: Nodular or plaque-like painless cutaneous tumor, slowly growing.

Diagnosis: A well-defined superficial tumor. On MRI, in T1 usually iso- or hypointense to skeletal muscle. In T2 intermediate or high signal intensity compared to fat. On STIR high signal, similar to water or blood vessels. Uniform enhancement of gadolinium.

Histopathology: Histologically, it is characterized by a monotonous spindle cell proliferation, diffusely infiltrating the dermis, subcutis, or both. Spindle cells show elongated wavy nuclei. Neoplastic cells are organized in a storiform pattern. There is minimal cellular atypia and mitoses are rare. Characteristically there is infiltration of the subcutaneous fat in a honeycomb pattern. Giant cell fibroblastoma is composed of spindle to pleomorphic cells, with variably collagenized matrix, and multinucleated-appearing giant cells bordering pseudovascular spaces. Mitoses are rare and necrosis is absent. Fibrosarcomatous DFSP is defined by a herring bone pattern, increased atypia, and mitoses. On immunohistochemistry, DFSP are positive for CD34. Apolipoprotein A1 has also been reported as a sensitive marker of DFSP. Giant cell fibroblastoma is positive for CD34, negative for S-100, CD31 and epithelial markers. DFSP and giant cell fibroblastoma share similar molecular abnormalities: the presence of supernumerary ring chromosomes consisting of amplified sequences from chromosomes 17 and 22, and/or the presence of t(17;22), a balanced reciprocal translocation that results in the fusion of COL1A1, a gene of collagen, and PDGFβ, a

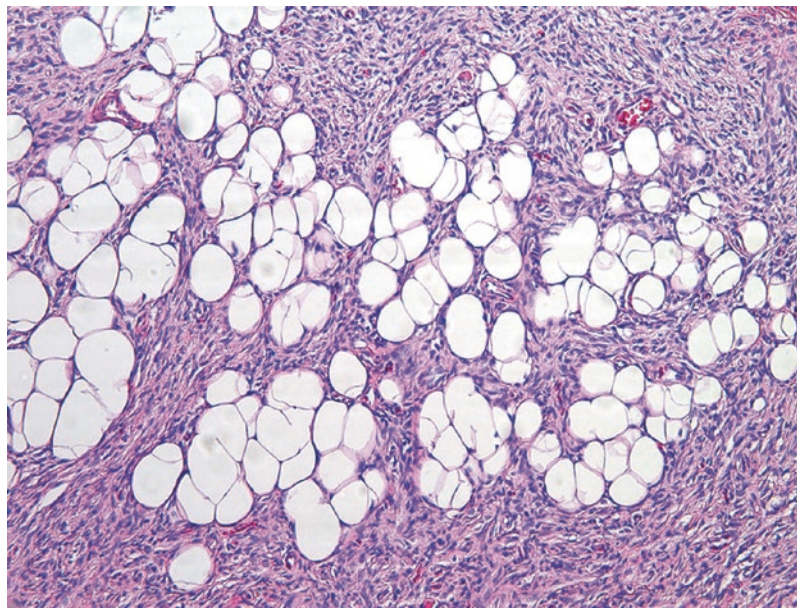
gene that encodes a growth factor. Ring chromosomes are predominantly observed in DFSP of adult patients, whereas the t(17;22) translocation is mostly seen in DFSP of children and in giant cell fibroblastoma.

Course and Staging: Conventional DFSP recurs locally in 10–50% of cases, often after incomplete excisions. Higher grade fibrosarcomatous chages can occur in about 10-15% of cases. Distant metastases are observed in about 15% of cases, all of which are associated with fibrosarcomatous changes. Giant cell fibroblastoma recurs in up to 50% but does not metastasize. Recurrence rates are closely related to surgical margins.

Treatment: Wide excision with tumor-free margins is curative. Radiotherapy has been proposed for unresectable tumors or after margin-positive resections. Imatinib mesylate (Gleevec), a tyrosine kinase inhibitor, may have potential value in the treatment of recurrent or metastatic DFSP.

Immunohistochemical panel	
• CD34	+

Chromosomal translocations		
• t(17;22) (q22;q13)	COL1A1-PDGFβ	>90%
• ring 17q, ring 22q, der(22)	COL1A1-PDGFβ	75%



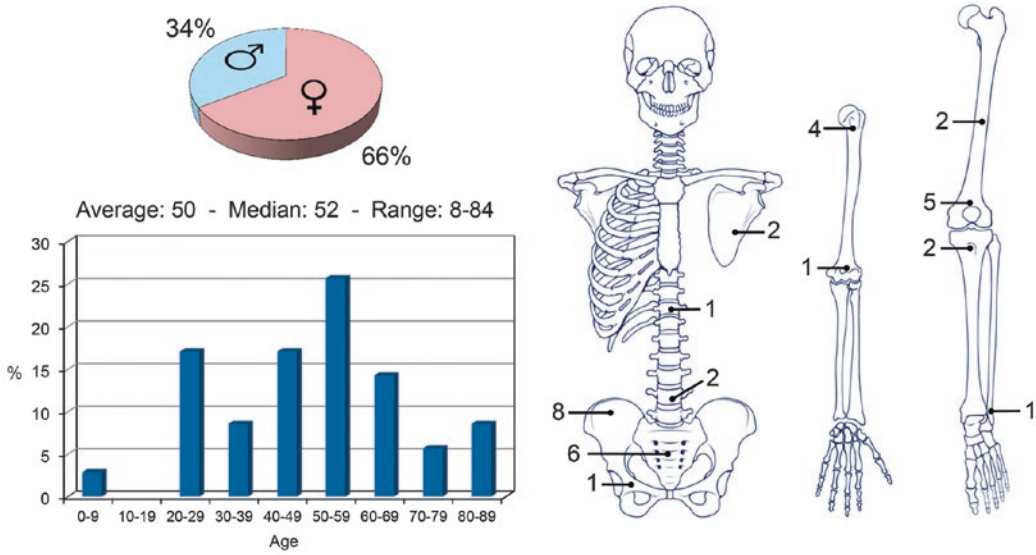
Bland-appearing spindle cells organized in a monotonous storiform pattern, with infiltrative margins that frequently surround lobules of fat

42.5 Solitary Fibrous Tumor

Definition: A mesenchymal neoplasm of fibroblastic type with collagen bands and branching, thin-walled, dilated "staghorn" vessels. According to WHO classification, hemangiopericytoma is currently considered identical to solitary fibrous tumor.

Epidemiology: Rare. No sex predilection. Adults.

Solitary Fibrous Tumor of Bone
35 cases



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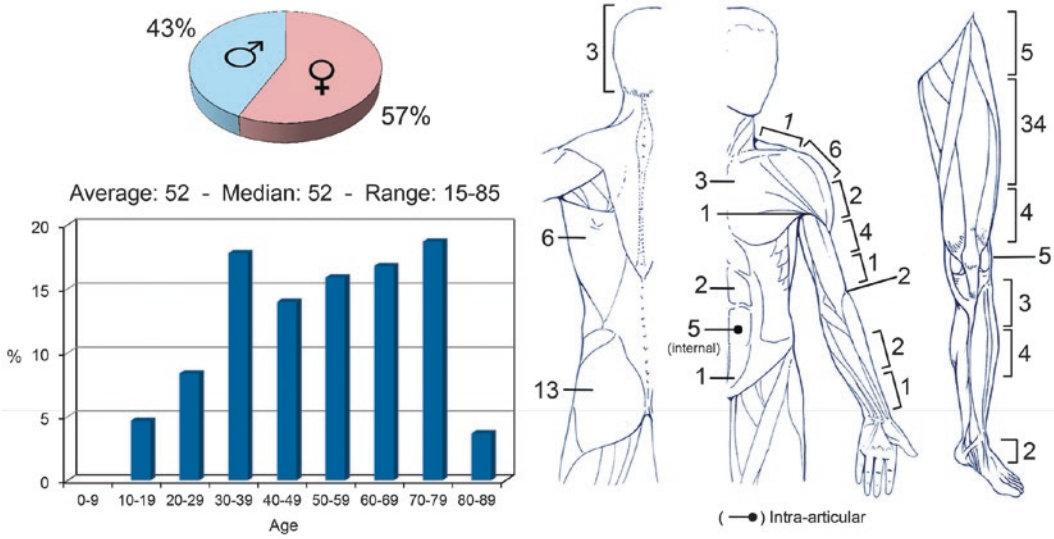
Solitary Fibrous Tumor of Soft Tissue
107 cases



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Location: Lower limb, retroperitoneum, pelvic region, upper limb, trunk, head and neck. Deeply located.

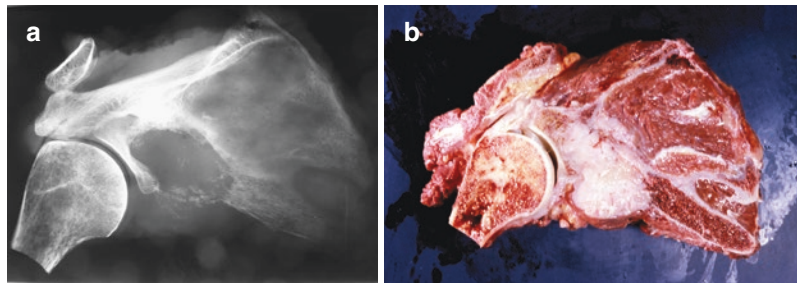
Clinical: Enlarging painless mass.

Imaging: In bone, it shows a solitary, centrally located, lytic lesion that may erode the cortex and extend into the soft tissues. On angiography: rich vascularity, encircled by tortuous vessels, arborizing from one pedicle, rapid arteriovenous flow. On CT: heterogeneous mass sharply enhanced after contrast. On MRI: homogeneous intermediate intensity with high signal hemorrhagic zones on T1, inhomogeneous bright lesion on T2, prominent serpentine vessels with signal intensity depending on the flow within them, strong enhancement with ill-defined necrotic areas that do not become enhanced.

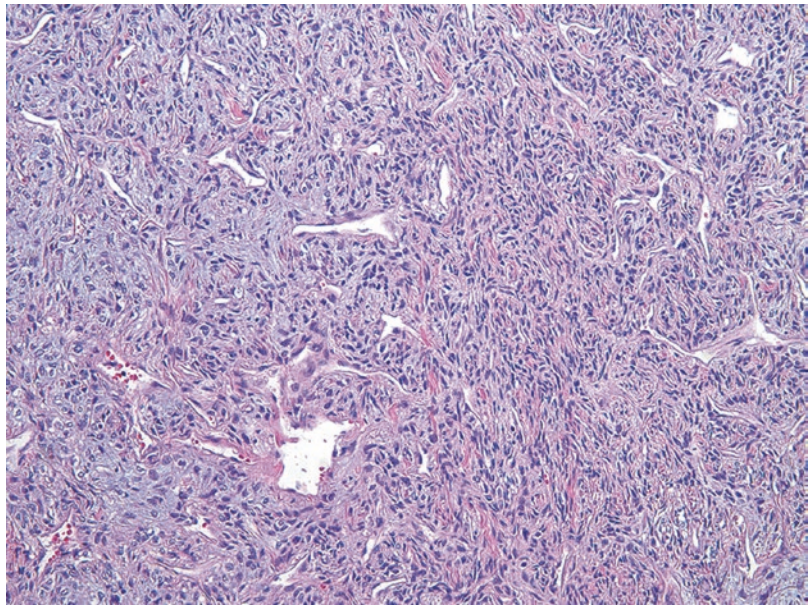
Histopathology: Soft, from pale to dull red or brownish red, heavily bleeding, thin pseudocapsule, cystic hemorrhagic necrotic areas. Thick, diffused network of capillaries, totally collapsed or wide-open sinusoids, surrounded by a compact proliferation of bland-appearing cells with oval nuclei, distinct nuclear membrane, granular chromatin, small nucleolus, ill-defined cytoplasm, thick reticular fibers all around. Cells are organized in a so-called "patternless" pattern or in the so-called hemangiopericytoma-like pattern around "staghorn-like" vessels. There is no strict correlation between morphology and behavior. However, histological aspects that could predict an aggressive and malignant behavior are: high cellularity, cellular atypia, extensive necrosis, infiltrative margins, and > or equal to 4/10 HPF mitotic figures. Demicco's risk stratification model (that consider age of the patient > or equal to 55 years, tumor size stratified by 5 cm tiers, number of mitotic figures, and presence and amount of necrosis) seems to accurately predict prognosis. Lesion in the high risk class can be considered malignant. Dedifferentiated solitary fibrous tumor represents the rarest variant and is characterized by an abrupt transition to an high-grade undifferentiated sarcoma.

Course and Staging: Slow growth, generally benign/low grade lesions. About 10-30% behave aggressively with local and distant recurrences. Malignant and dedifferetiated solitary fiboru tumor are high-grade malignant neoplasms, with frequent recurrences and distant metastases.

Treatment: As the biological behavior of SFT is unpredictable, wide excision is the treatment of choice. The role of radio- and chemotherapy is unclear.



Radiograph (**a**) evidences lytic lesion, destroying the scapulae, poorly limited, with cortical lysis and soft tissue involvement. The cut surface of the surgical specimen (**b**) is predominantly firm and white



Bland-appearing spindle cells organized around ramified staghorn vessels in the so-called hemangiopericytoma-like pattern or in a patternless pattern

Immunohistochemical panel	
• STAT6	+
• CD34	+

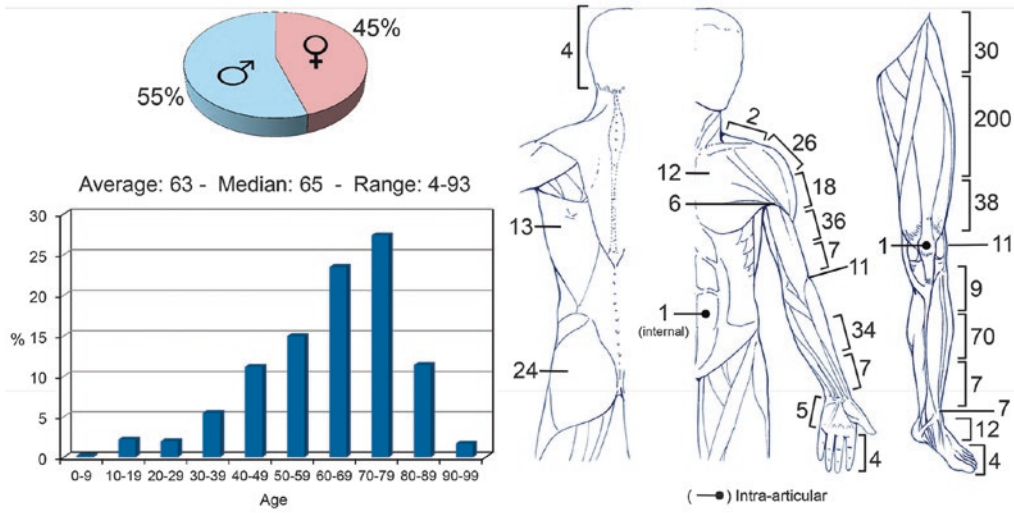
Genetic alteration		
• Intrachromosomal inversion	Inv12 (q13q13) NAB2-SATB6	90%

42.6 Myxofibrosarcoma

Definition: Malignant fibroblastic lesions with myxoid stroma, variable pleomorphism, and a distinctive curvilinear vascular pattern. The designation of myxofibrosarcomas and myxoid malignant fibrous histiocytoma have been considered almost synonymous in the 2013 WHO classification of soft tissue tumors. This classification does not mention a minimal amount of myxoid matrix for the definition of myxofibrosarcoma.

Epidemiology: Among the most common sarcomas in elderly patients. Very rare primarily in bone. Overall age range is wide, but they are more frequent in the sixth to eighth decade, whereas they are exceptional under 20 years of age. There is a slight male predominance.

Myxofibrosarcoma of Soft Tissue
599 cases



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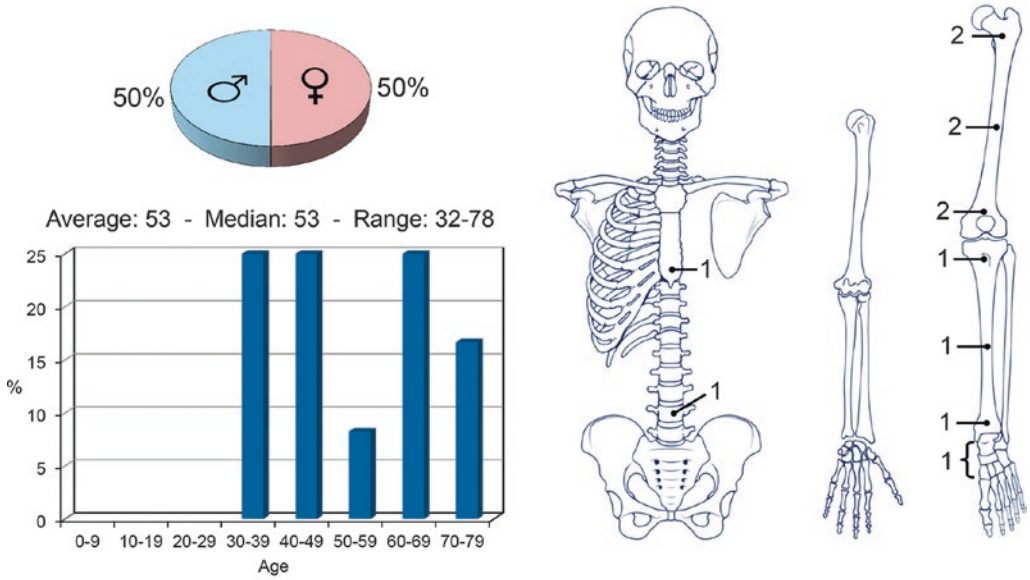
Myxofibrosarcoma of Bone
12 cases

Including 3 Secondary: Radio-induced (2); on Paget (1).



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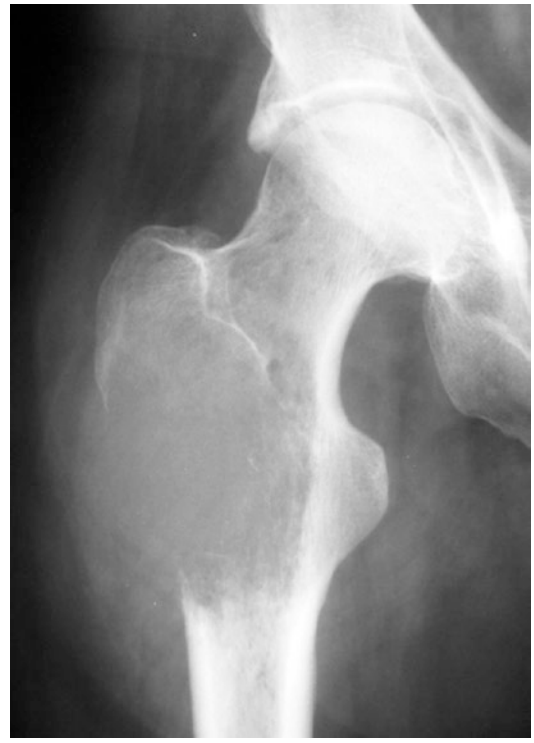
Location: The most frequent sites are the lower limbs, followed by upper limbs and limb girdles. Rare in trunk, head and neck, hands and feet. Most cases described in the retroperitoneum and in the abdominal cavity represent dedifferentiated liposarcomas. About half of cases arises in dermal/subcutaneous tissue, with the remaining arising in the underlying fascia and skeletal muscle.

Clinical and Imaging: Enlarging painless mass, with infiltrative margins. Very often heterogeneous at MRI.

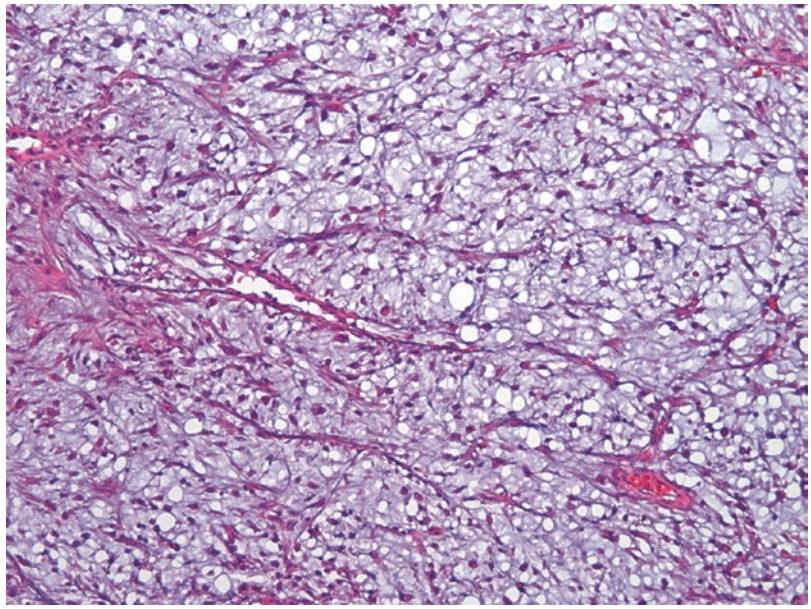
Histopathology: Grossly they appear as multiple gelatinous to firm nodules with infiltrative margins. Histologically all cases share distinct morphological features: multinodular growth with incomplete fibrous septa, a myxoid stroma composed of hyaluronic acid and prominent elongated, curvilinear, thin walled vessels with a perivascular condensation of tumor cells. Frequently, so-called pseudolipoblasts (vacuolated neoplastic fibroblastic cells with cytoplasmic acid mucin) are seen. Low-grade lesions are hypocellular, composed of few non-cohesive, plump spindled or stellate cells with ill-defined cytoplasm and hyperchromatic nuclei; mitosis are infrequent. High-grade lesions are composed in large part of solid sheets and cellular fascicles of spindle and pleomorphic tumor cells with numerous, often atypical mitosis, and areas of necrosis.

Course and Staging: In up to 50–60% of cases, local recurrences unrelated to histological grade repeatedly occur. In contrast, metastases and death from tumor are closely related to tumor grade: low-grade tumors do not metastasize, while metastases develop in 20–35% of intermediate and high-grade neoplasms. Metastases occur in lung, bone, and lymph nodes. Low-grade lesions that recur may subsequently increase in grade. The depth of the lesion does not influence the rate of local recurrence, while deep-seated neoplasms have a higher percentage of metastases and tumor-associated mortality. Overall 5-year survival rate is 60–70%.

Treatment: Excision with wide margins and adjuvant radiation therapy and/or systemic chemotherapy.



Radiograph: mainly lytic lesion, with peripheral sclerotic component, poorly limited, destroying the cortex and invading the soft tissues



Malignant spindle cells in a loose myxoid extracellular matrix. Cells are arranged in lobules, with elongated curvilinear blood vessels

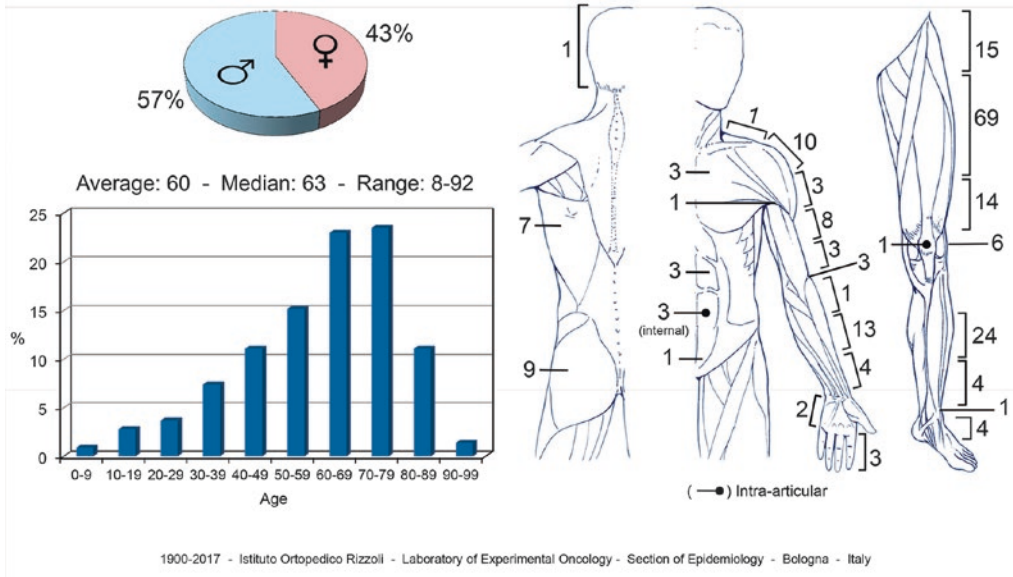
42.7 Myofibroblastic Sarcoma

Definition: Sarcomas composed of cells with myofibroblastic differentiation.

Myofibroblastic sarcomas display a range of differentiation. Low-grade myofibroblastic sarcoma is identified as a specific entity in the WHO 2013 classification, while the definition of high-grade myofibroblastic sarcoma is not well established. There is evidence that myofibroblastic differentiation in pleomorphic sarcomas is associated with a more aggressive behavior.

Epidemiology: Low-grade myofibroblastic sarcomas occur predominantly in adult patients (age range: 4–75 years, mean 38), while high-grade myofibroblastic sarcomas can also occur in children. There is a slight male predominance.

Myofibroblastic Sarcoma of Soft Tissue
217 cases



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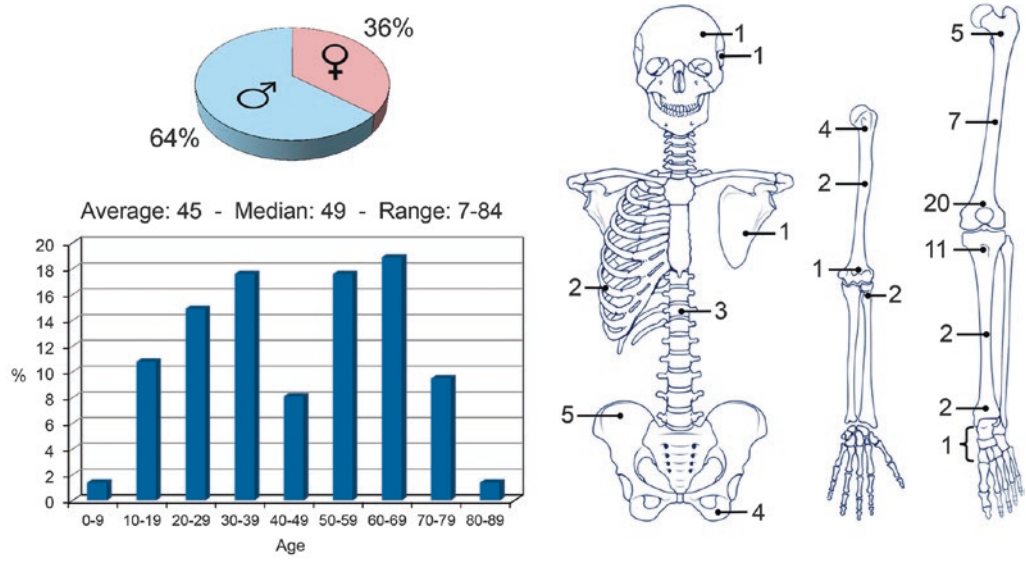
Myofibroblastic Sarcoma of Bone
74 cases

Including 11 Secondary: on Paget (4); on Bone Infarct (3); on Fibrous Dysplasia (2); after Radiation Therapy (2).



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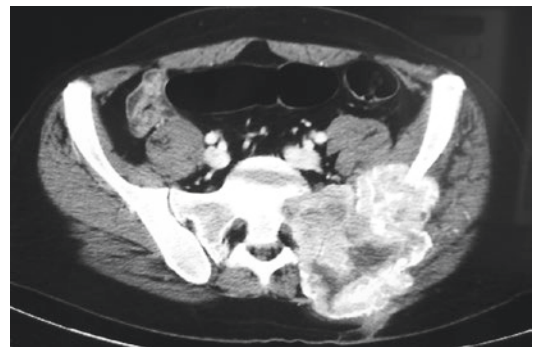
Location: Low-grade myofibroblastic sarcomas most commonly occur in the head and neck region, including the oral cavity, pharynx and parapharyngeal regions, proximal extremities and trunk; occasional cases can occur in the abdomen or pelvis. They usually arise in the deep soft tissues but cases have been seen in the subcutis and submucosa. Visceral lesions are rare. Cases have also been described in bone, including maxilla, mandible, femur, and ilium. High-grade myofibroblastic sarcomas arise in deep soft tissues, predominantly in lower limbs and trunk, with occasional cases in head and neck.

Clinical and Imaging: Enlarging painless mass, very often with infiltrative margins. High-grade sarcomas with hemorrhage and necrosis are heterogeneous at MRI.

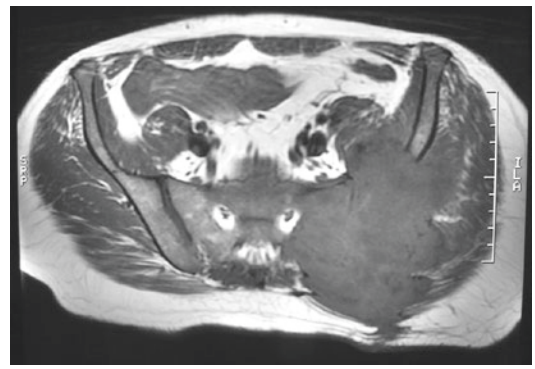
Histopathology: Grossly, low-grade myofibroblastic sarcomas are firm with a pale fibrous-appearing cut surface, ill-defined infiltrative margins, or sometimes with pushing margins. High-grade myofibroblastic sarcomas are large solid tumors with hemorrhage and necrosis. Histologically, low-grade myofibroblastic sarcomas are characterized by a proliferation of spindle cells arranged in a fascicular or in a storiform pattern. The neoplastic cells show tapered fusiform elongated to wavy nuclei, with discernible eosinophilic cytoplasm. Sometimes the nuclei are rounded and vesicular with small punctuated nucleoli. There is at least focally moderate nuclear atypia. The margins are predominantly infiltrative, with separation rather than destruction of skeletal muscle bundles. Mitotic activity is variable but atypical mitoses are rare. Stroma is often minimal and can be variably collagenous. High-grade myofibroblastic sarcomas are composed of pleomorphic, spindle or epithelioid cells arranged in a fascicular or in a storiform growth pattern, with scattered atypical mitotic figures. Both low- and high-grade myofibroblastic sarcomas show variable positivity for actins and/or desmin.

Course and Staging: About 33% of low-grade myofibroblastic sarcomas locally recur, especially after incomplete excision. Metastases have been reported in approximately 10% of cases. Progression to high-grade sarcoma has been documented. High-grade myofibroblastic sarcomas recur in 33% of cases with metastases in over 70%. These tumors, like the other pleomorphic sarcomas with myogenic differentiation, have a worse outcome than undifferentiated sarcomas.

Treatment: Low-grade myofibroblastic sarcomas are best managed by wide surgical excision and long-term follow-up to detect possible late metastases. High-grade myofibroblastic sarcomas should be managed by excision with wide margins and adjuvant radiation therapy and/or systemic chemotherapy.

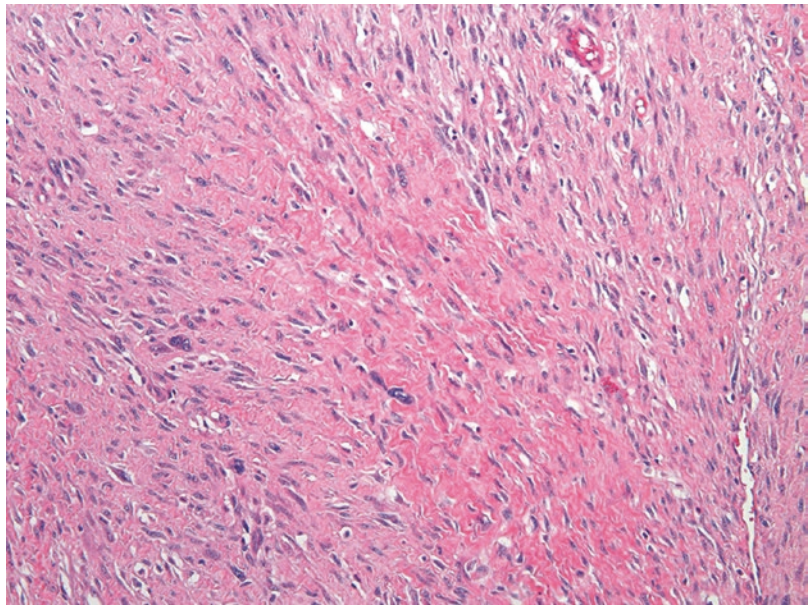


Axial CT with contrast medium and T1W MR. Purely lytic lesion of the left iliac wing and sacrum, with a strong heterogeneous uptake of contrast medium, destruction of the bone and soft tissue invasion



Axial CT with contrast medium and T1W MR. Purely lytic lesion of the left iliac wing and sacrum, with a strong heterogeneous uptake of contrast medium, destruction of the bone and soft tissue invasion

Immunohistochemical panel	
• Smooth M Act	±
• CD34	±
• Desmin	±
• Caldesmon	–



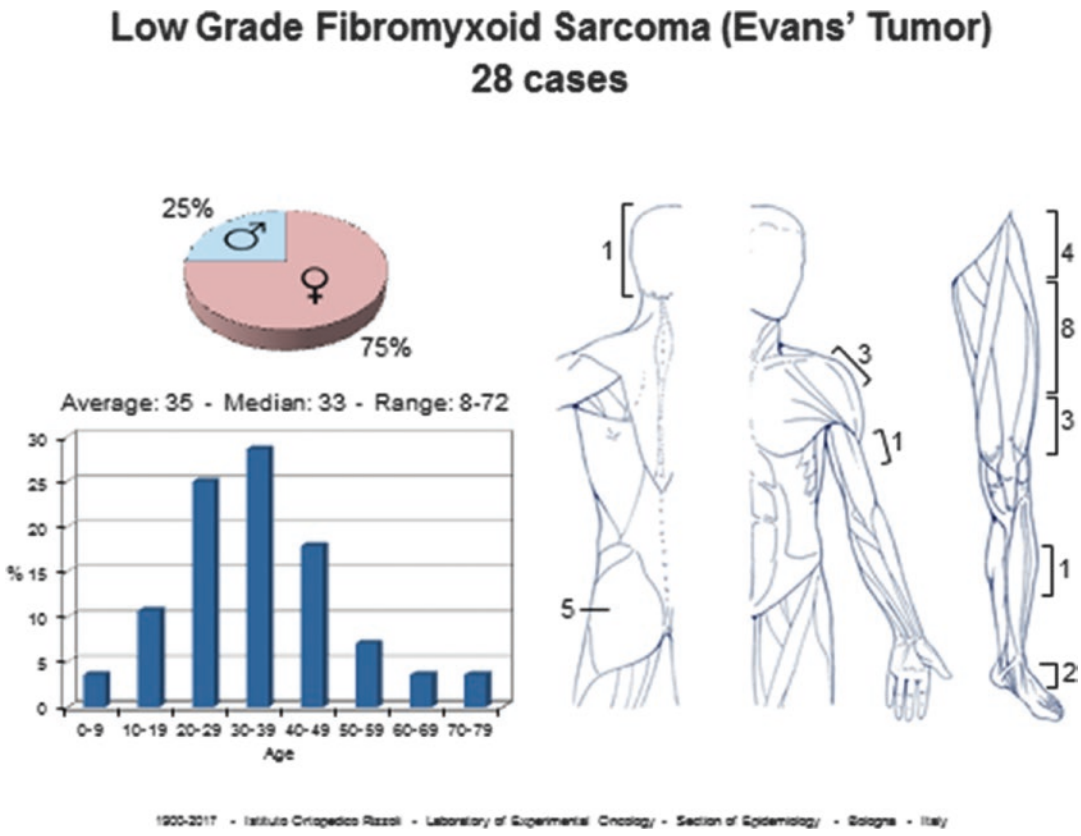
Fascicular to storiform arrangement of malignant spindle cells with short tapered wavy nuclei. Stroma is variably collagenous. Some tumors show a tissue culture-like growth pattern that resembles nodular fasciitis

42.8 Low-Grade Fibromyxoid Sarcoma (Evans' Tumor) and Sclerosing Epithelioid Fibrosarcoma

42.8.1 Low-Grade Fibromyxoid Sarcoma

Definition: Low-grade fibromyxoid sarcoma, also known as Evans' tumor or hyalinizing spindle cell tumor with giant rosettes, is an unusual and distinctive intermediate, rarely metastasizing, fibroblastic neoplasm.

Incidence: Rare tumors with a slight predilection for male individuals. Patients of any age may be affected, but it is more frequent in young adults (median age, 35 years). Up to 20% of cases occur in patients aged <18 years.

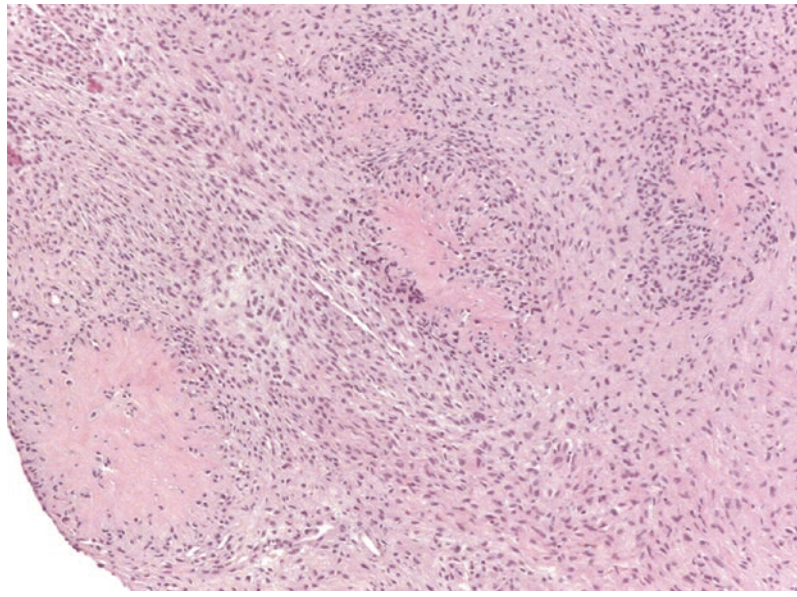


Location: The most frequent locations are the deep soft tissues of the limbs (thigh), limb girdles (shoulder), and trunk.

Clinical: The tumor usually presents as a long-standing, painless mass.

Histology: Macroscopically, low-grade fibromyxoid sarcoma is well circumscribed, sometimes lobulated, fibrous, and often focally mucoid, bearing some resemblance to a uterine leiomyoma. Morphologically, the tumor consists of slender spindle cells with long, narrow, delicate and mostly non-branching cell processes, embedded in a variable amount of collagenous and myxoid stroma. The cells have pale eosinophilic cytoplasm and deceptively bland, ovoid, or tapered nuclei with inconspicuous nucleoli and occasional nuclear inclusions. Mitotic figures are rare, and there is no necrosis. Some cases may contain clusters of large rosettes, consisting of cores of hyalinized collagen surrounded by rounded, epithelioid-looking tumor cells. Fifteen to 20% of low-grade fibromyxoid sarcoma contains high-grade, densely cellular areas of epithelioid sclerosing fibrosarcoma (hybrid tumor). Immunohistochemically, strong and diffuse granular cytoplasmic immunoreactivity for MUC4, an epithelial glycoprotein, is a peculiarity of this neoplasm with a very high specificity and sensibility among fibroblastic tumors. Cytogenetically, low-grade fibromyxoid sarcoma is characterized by the presence of a *FUS-CREB3L2* (t(7;16) (q33;p11) present in approximately 80–90% of cases) and a *FUS-CREB3L1* (t(11;16) (p11; p11) present in 5–10% of cases) gene fusion.

Course and Treatment: Wide excision with tumor-free margins is the optimal surgical treatment. Adjuvant radiotherapy and chemotherapy with trabectedin is suggested by some authors. The local recurrence rate is close to 10% and the metastatic rate is close to 15%. Metastases are mainly to lungs and pleura, also to bone, and can occur late in the course of the disease (15–25 years after initial excision).



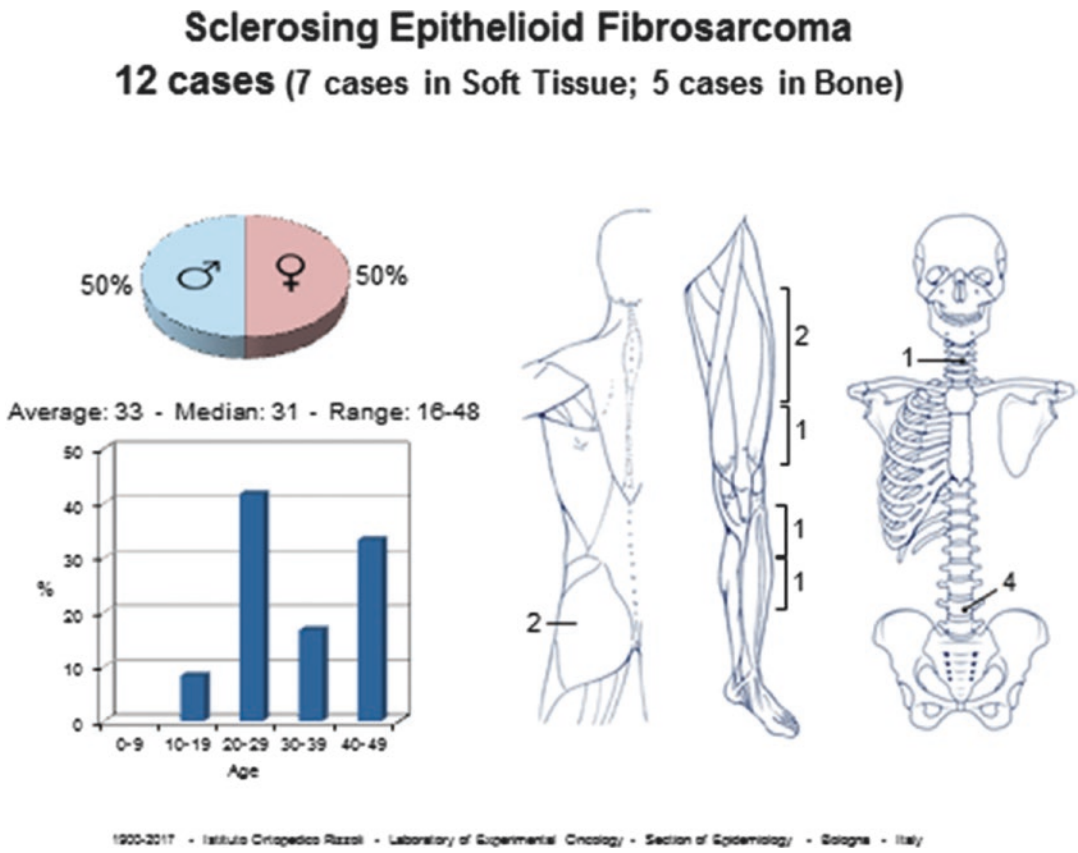
Slender spindle cells in a and myxo-collagenous stroma; large hyalinized collagen rosettes are present

Immunohistochemical panel	
• MUC4	+ (~100%)
• EMA	+ (80%)

42.8.2 Sclerosing Epithelioid Fibrosarcoma

Definition: Sclerosing epithelioid fibrosarcoma is considered a rare and distinctive variant of malignant fibroblastic tumor with peculiar morphological and immunohistochemical features. There are considerable morphological and genetic data to suggest a link between sclerosing epithelioid fibrosarcoma and low-grade fibromyxoid sarcoma.

Incidence: Since the first description, fewer than 200 cases have been published in literature.



Location: Most cases are located in the soft tissue of lower extremities and of limb girdles, with not more of 20 cases described as primary sclerosing epithelioid fibrosarcoma of bone.

Clinical: Most patients present with a mass of variable duration; one-third have a history of recent enlargement and pain.

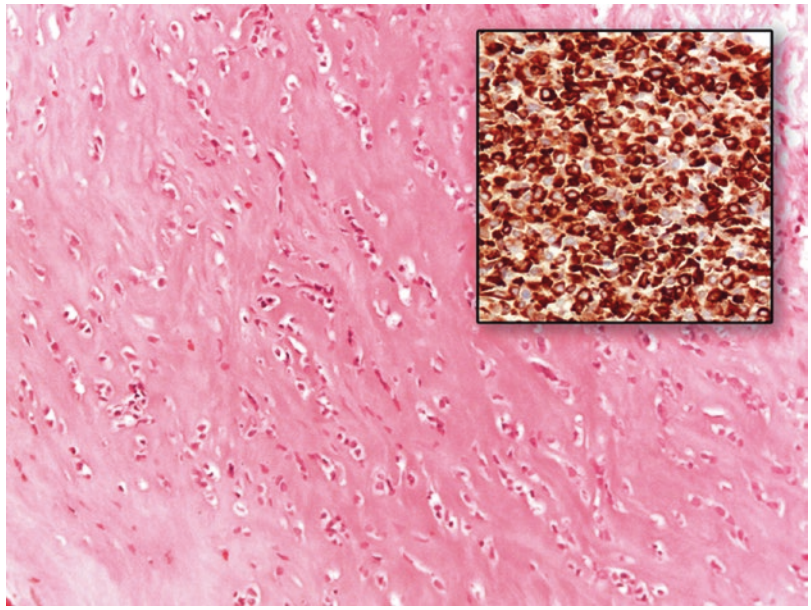
Imaging: On imaging, a mass, sometimes calcified, is evident showing on MRI low signal intensity on T1-weighted images and hypointense to intermediate signals on T2-weighted images

Histology: Macroscopically, sclerosing epithelioid fibrosarcoma is typically well circumscribed, lobulated or multinodular. The cut surface is predominantly firm and white. Areas of calcification are often seen.

Microscopically, at low magnification, the tumor appears well delineated without encapsulation with infiltration of soft tissue. At higher magnification, the tumor is composed of moderately pleomorphic epithelioid cells, sometimes with clear cytoplasm, arranged in cords and pseudoalveolar structures within a densely hyalinized stroma. The nuclei of the tumor cells range from ovoid to rectangular and have slightly irregular nuclear contours with bubbly chromatin, reminiscent of nuclear pseudo-inclusions. On immunohistochemistry, MUC4 positivity, a peculiar marker of sclerosing epithelioid fibrosarcoma found in more of 80% of cases, associated with negativity of both SATB2, a marker of osteoblastic differentiation, and pancytokeratin, allows the differential diagnosis with osteosarcoma or metastatic carcinoma. Genetically, subsets of sclerosing epithelioid fibrosarcoma, in particular those showing hybrid morphological features of low-grade fibromyxoid sarcoma, show identical findings as in low-grade fibromyxoid sarcoma, including t(7;16)(q32–34;p11)(*FUS–CREB3L2/L1*). Conversely, other studies have shown only a minority of "pure" sclerosing epithelioid fibro-

sarcoma to contain *FUS* rearrangements, with a relative predominance of EWSR1 gene rearrangements. Thus, the presence of the same gene rearrangement of the low-grade fibromyxoid sarcoma found in some cases of sclerosing epithelioid fibrosarcoma associated with similar morphological and immunohistochemical features leads some authors to postulate a strict relationship between low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma.

Course and Treatment: Wide excision with tumor-free margins is the optimal surgical treatment. Adjuvant radiotherapy and chemotherapy is suggested by some authors. About 50% of patients have local recurrence. Distant metastases develop in 40–80% of patients, mainly in the lungs and pleura, but also in bone and soft tissues. Five years survival is around 70%. Proximal location, large tumor size, and male sex are important adverse prognostic factors.



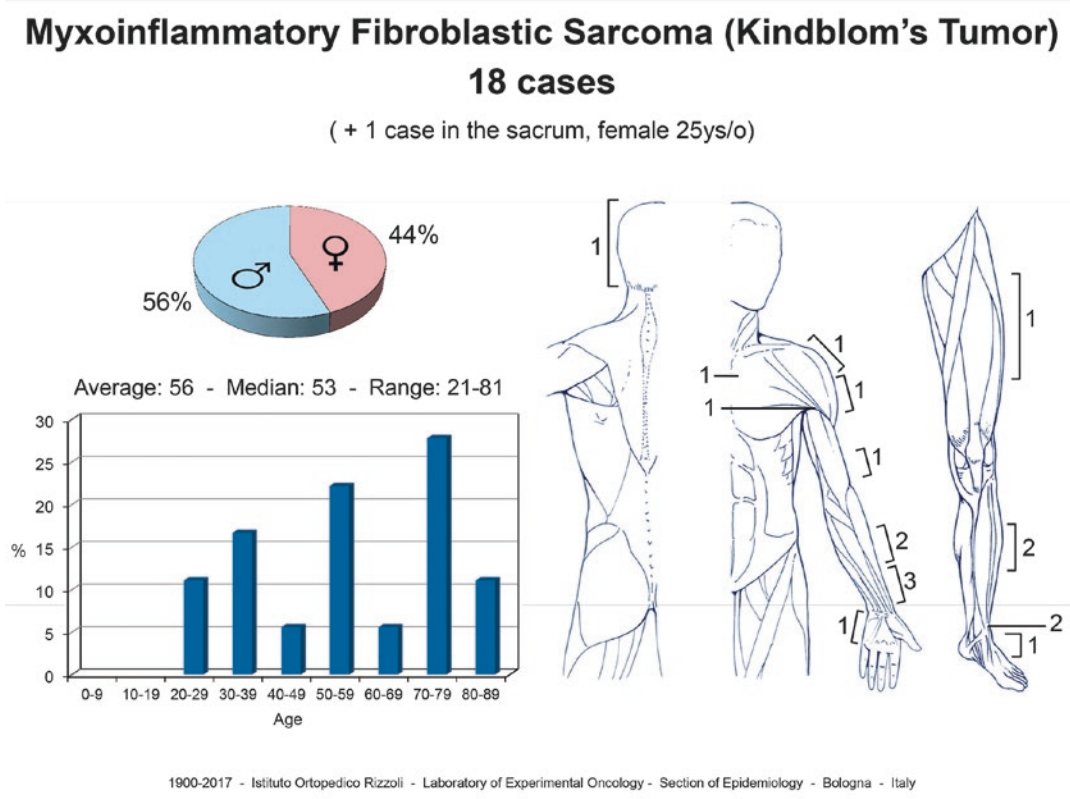
Moderately pleomorphic epithelioid cells arranged in cords within a densely hyalinized stroma. Immunohistochemical cytoplasmic positivity for MUC4 in the neoplastic cells (*inset*)

Immunohistochemical panel	
• MUC4	+ (~100%)
• EMA	+ (50%)

Epidemiology: Middle-aged patients; rare in children. Equally distributed between male and female.

42.9 Myxoinflammatory Fibroblastic Sarcoma (Kindblom's Tumor)

Definition: Low-grade tumor mostly occurring in the distal extremities. There is a morphologic continuum with hemosiderotic fibrolipomatous tumor and pleomorphic hyalinizing angiectatic tumor of soft parts.



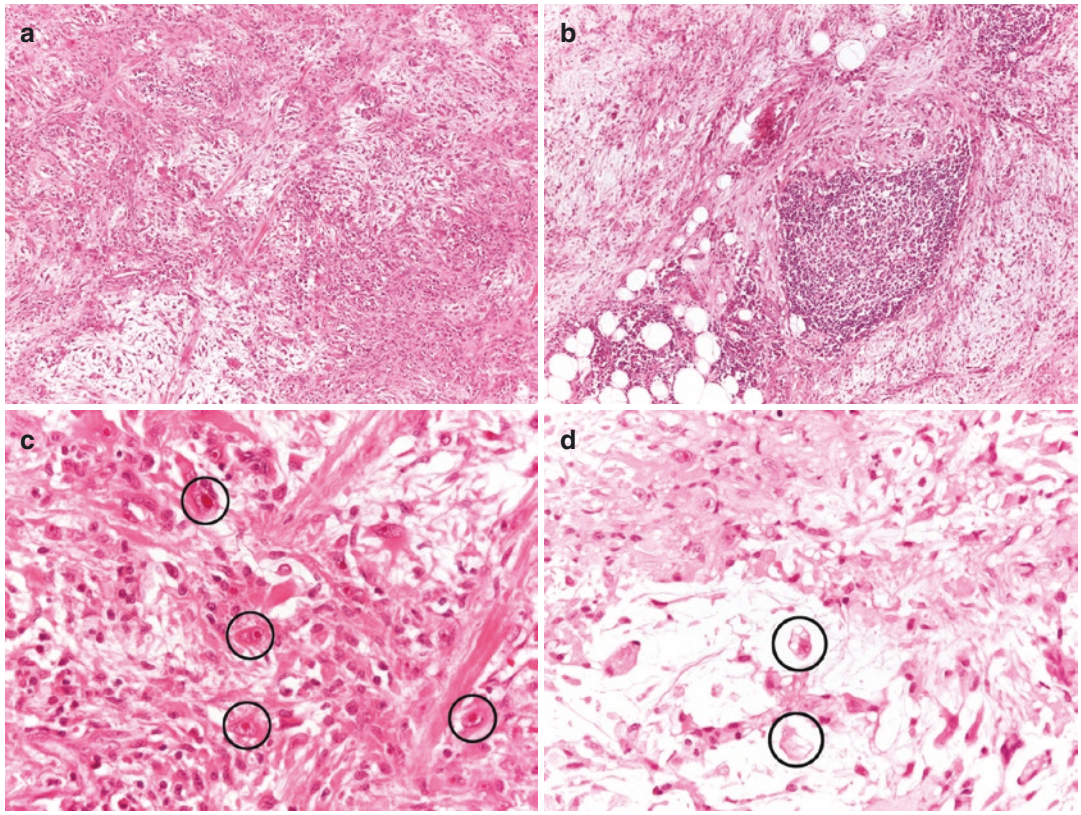
Location: The vast majority occurs in the subcutaneous tissues of the distal extremities, mostly in the upper limbs.

Clinical: Slow growing swelling.

Histopathology: Grossly, the tumor appears as a variably gelatinous multinodular mass with infiltrative margins, generally involving tenosynovial structures. Histologically, it appears as a lobulated lesion, with an alternation between fibrous and myxoid zones, containing a prominent mixed inflammatory infiltrate. Neoplastic cells show different morphology: epithelioid cells with mild to moderate nuclear atypia; large pleomorphic ganglion-like cells with large nuclei and viral inclusion-like nucleoli (resulting in a Reed–Sternberg-like appearance), and bubbly, multivacuolated cells of variable size with intracellular mucins resembling lipoblasts. Necrosis is uncommon and mitotic activity is low. Hemosiderin deposition can be abundant. Progression in a high-grade sarcoma has been reported.

Course and Treatment: Recurrences occur in 20–70% of cases; metastasis to lymph nodes and lung are rare. Wide excision is the treatment of choice.

Chromosomal translocations		
• t(1;10)(p22;q24)	TGFBR3-MGEA5	Frequent
• 3p11-12 (ring chromosome, amplification)	Deregulation of FGF8 and amplification of VGLL3, CHMP2B	Rare



Lobulated lesion with alternating fibrotic and myxoid zones **(a).** A mixed inflammatory infiltrate is characteristic **(b).** Virocyte-like cells (**c,** *circles*) and vacuolated cells (**d,** *circles*) are the hallmark of the lesion

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