Vascular Tumors

46

Alberto Righi

The common denominator of vascular tumors consists of their endothelial differentiation with a variable capability of forming mature or immature vessels. Although tumors with this morphology have been recognized for many years, there is a considerable degree of confusion regarding their nomenclature and classification. It is proposed that the osseous vascular tumors should be classified in a similar manner to their soft tissue counterparts and it is suggested that this approach should help to clarify the confusion surrounding this topic. The last classification of vascular tumors as proposed in the 2013 WHO is supported by the rapid elucidation of novel, characteristic translocations in the different vascular tumor entities. In the last 5 years, there have been further several important refinements in the classification of vascular neoplasms, along with the identification of novel and recurrent molecular genetic findings broadening the spectrum of available ancillary tests for the surgical pathologist, that better define epithelioid hemangioma, pseudomyogenic hemangioendothelioma, and epithelioid hemangioendothelioma.

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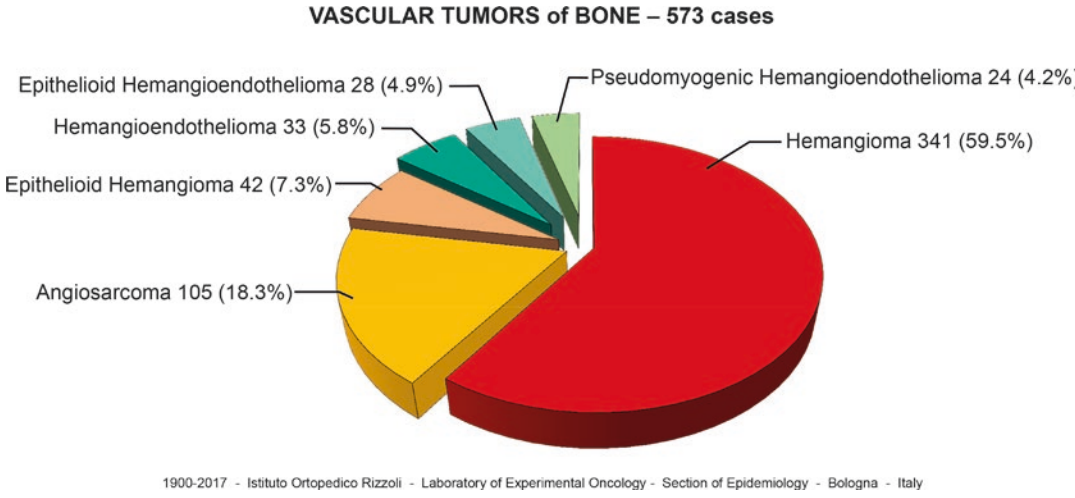
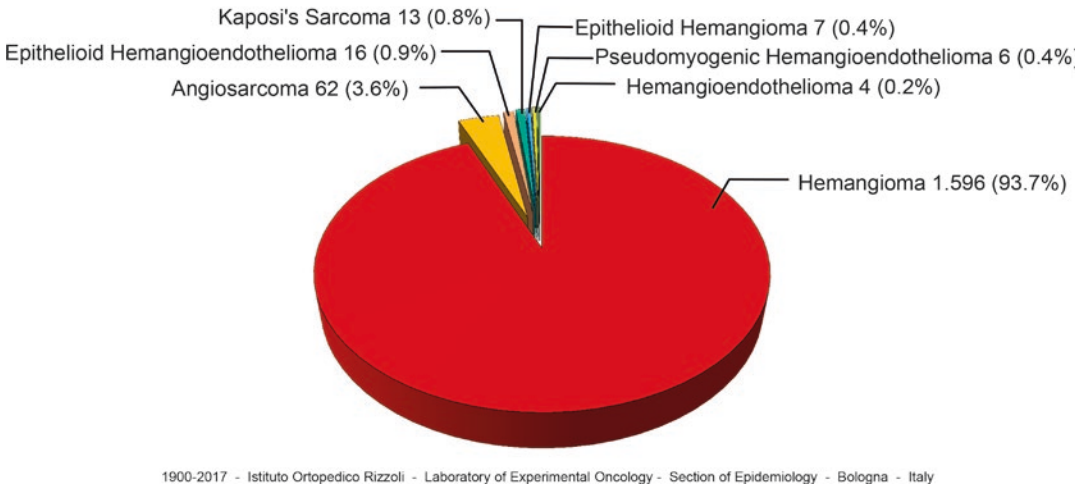




Key points	
• Clinical	Adults, pain and swelling
• Radiological	Frequently multifocal, pure lytic lesion
• Histological	Proliferation of endothelial cells at various grade of differentiation
• Differential diagnosis	Bone metastasis, myeloma, and all other primary purely osteolytic lesions of adults

Immunohistochemical panel	
• CD31, ERG	+
• CD34	±
• CK	± (+ in pseudomyogenic hemangioendothelioma)
• CAMTA1 or TFE3	+ in epithelioid hemangioendothelioma
• FOSB	+ in epithelioid hemangioma (20–25% of cases) and in pseudomyogenic hemangioendothelioma

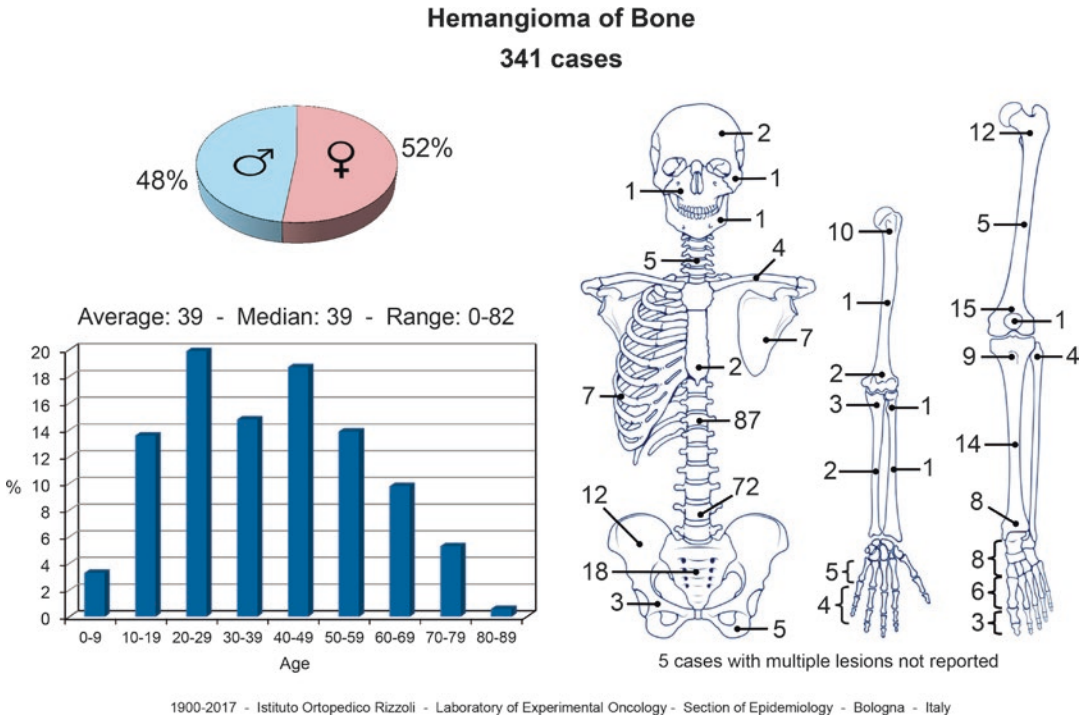
Prognosis
Hemangiomas (with epithelioid variant) → benign lesions
Hemangioendothelioma → good prognosis
Angiosarcoma → poor prognosis

46.1 Hemangioma of Bone

Definition: Benign tumor composed of capillary-like blood vessels of small or large caliber.

Incidence: Rare tumors (<1% of primary bone tumors), even throw at least 10% of patients from autopsy series shows vertebral hemangiomas as occasional finding. About 70% of the cases are diagnosed in patients between 30 and 60 years.

Location: The most frequent location is the vertebral bodies, followed by the cranio-facial bones, the ribs and the diaphysis or metadiaphysis of the long bones. Medullary origin is most frequent, but 45% of cases are either periosteal (33%) or intracortical (12%).



Clinical: Frequently asymptomatic sometimes pain when pathologic fracture occurs.

Imaging: A well-demarcated, lucent mass that frequently contains coarse trabeculations or striations. In flat bones, the tumor is expansile and lytic and produces a sunburst pattern of reactive bone formation. Indolent lesions frequently contain fat and sclerotic trabeculae on CT and MRI.

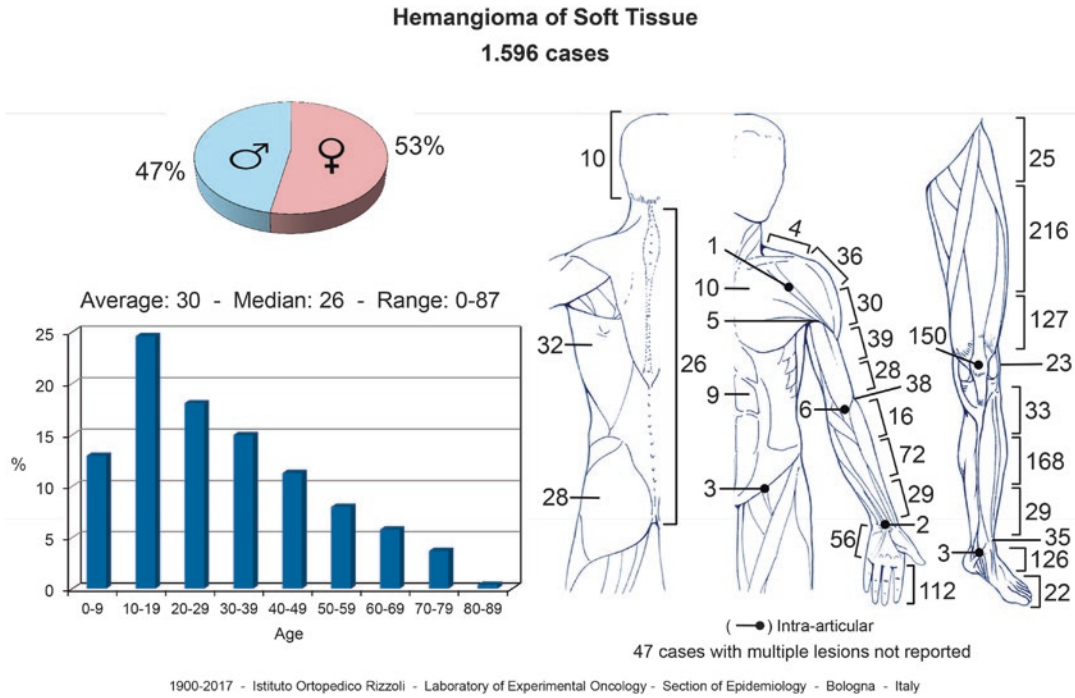
Histopathology: Hemangiomas of bone have variable histological features. Capillary and cavernous hemangiomas, that represent the vast majority of hemangiomas, show numerous blood-filled spaces, lined by a thin layer of flat endothelial cells, without atypia. The vascular spaces are surrounded by loose connective tissue and grow in-between the bone trabeculae that are often thickened. When hemangiomas involve a large localized region, or are widespread throughout the skeleton, it is known as angiomatosis.

Course and Treatment: Excellent prognosis and low rate of local recurrence. Most patients with hemangiomas need no treatment. Lesions causing symptoms are treated with intralesional excision.

46.2 Hemangioma of Soft Tissues

Definition: Hemangiomas are benign tumors that closely resemble normal vessels.

Incidence: Benign hemangiomas represent 7% of all benign soft tissue tumors, the most frequent in infancy and childhood. In this age group, they are generally cutaneous or subcutaneous capillary hemangiomas. They grow until body growth has ended. Intramuscular hemangioma, although relatively uncommon, is one of the most frequent deep-seated soft tissue tumors. Adolescents and young adults are most commonly affected, with an equal sex incidence.



Location: Intramuscular hemangioma most commonly affects the lower limb, particularly the thigh. Hemangiomas can also arise in a synovium-lined surface, particularly in the knee (synovial hemangiomas) or can affect a large segment of the body (angiomatosis) in a contiguous fashion, either by vertical extension, to involve multiple tissue planes or by crossing muscle compartments to involve similar tissue types.

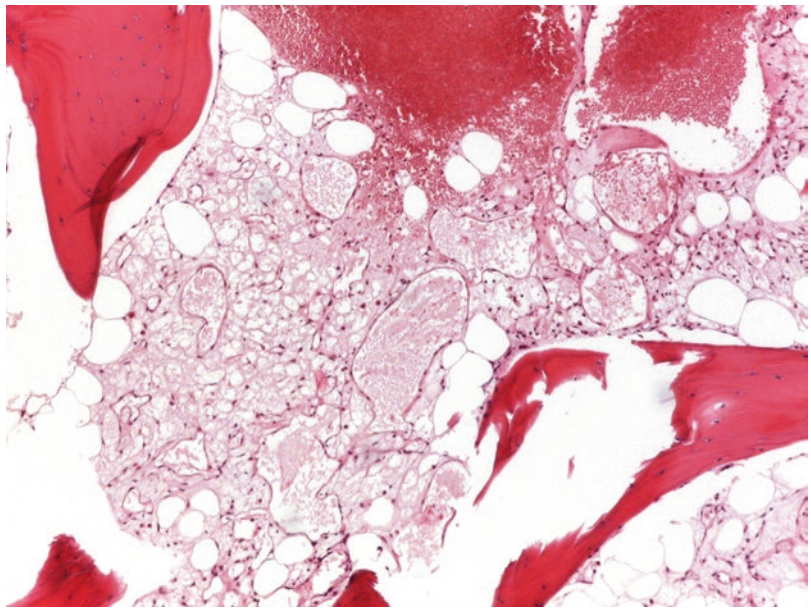
Clinical: Superficial (cutaneous/subcutaneous) hemangiomas are reddish-wine colored, painless lesions, generally present at birth. Intramuscular hemangioma arises within the belly of a single muscle; only in the hand and foot it may expand between the fascia, muscles, and tendons. Pain is sharp and becomes more intense with tension of the muscle. Shortening of muscles causes first joint dysfunction and then joint deformity. In the hand and foot, an increase of skin temperature, and of the superficial venous reticulum, telangiectasia, cyanosis, and hyperhidrosis are observed.

Imaging: X-rays are usually negative although small round granular calcifications with a smooth surface and concentric stratifications (phleboliths) can be seen.

Histopathology: Hemangiomas can be divided in synovial, intramuscular, venous, and arteriovenous malformation. Synovial hemangioma is often a cavernous type with multiple dilated thin-walled vascular channels, surrounded by myxoid or fibrotic stroma. Intramuscular hem-

angioma has been traditionally classified according to vessel size into small (capillary) and large (cavernous), although most are mixed, also including lymphatics. It usually consists of large thick-walled veins, a mixture of cavernous-like vascular spaces and capillaries or a prominent arteriovenous component associated with variable amounts of mature adipose tissue. Venous hemangioma consists of large thick-walled muscular vessels, which are variably dilated and commonly display thrombosis with occasional formation of phleboliths. Elastic stains reveal the absence of an internal elastic lamina that helps in the distinction from an arteriovenous hemangioma. Arteriovenous malformation is characterized by large numbers of vessels of different sizes, including veins and arteries, with the former largely outnumbering the latter.

Course and Treatment: Complete local excision and eventually follow-up are the optimal management for symptomatic benign hemangiomas.

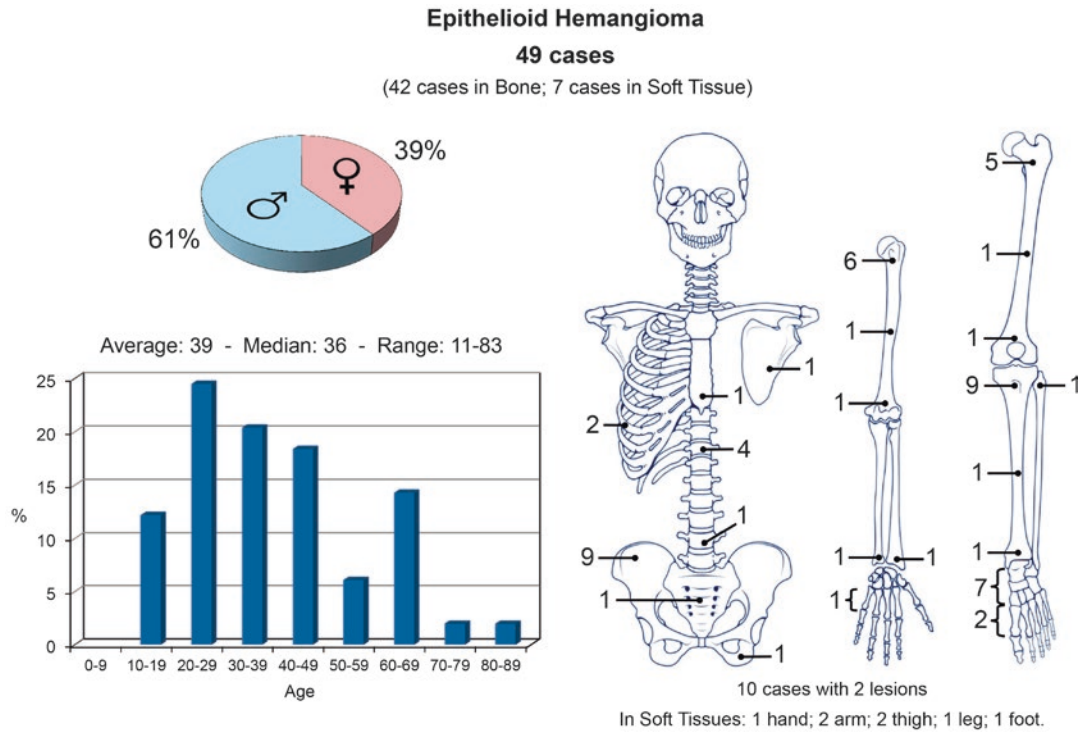


On histology, hemangioma shows thin-walled blood vessels lined by a single layer of endothelial cells with the marrow and between bony trabeculae.

46.3 Epithelioid Hemangioma of Bone and Soft Tissues

Definition: Epithelioid hemangioma of soft tissue is a unique benign vasoformative tumor composed of epithelioid endothelial cells. Epithelioid hemangioma of bone is classified as an intermediate and locally aggressive but rarely metastasizing vascular tumor.

Incidence: Because epithelioid hemangioma is a rare entity, exact prevalence is difficult to determine. In our series and in the cases reported in literature, the age of occurrence as varying from 11 to 83 years with a median of 37 years and a slight preference for boys and men.



Location: Epithelioid hemangioma has been described as occurring in many different locations, showing a slight preference for the long tubular bones, but the spine and the small tubular bones of the extremities are also often affected. Multifocal bone involvement occurs in approximately 20% of cases.

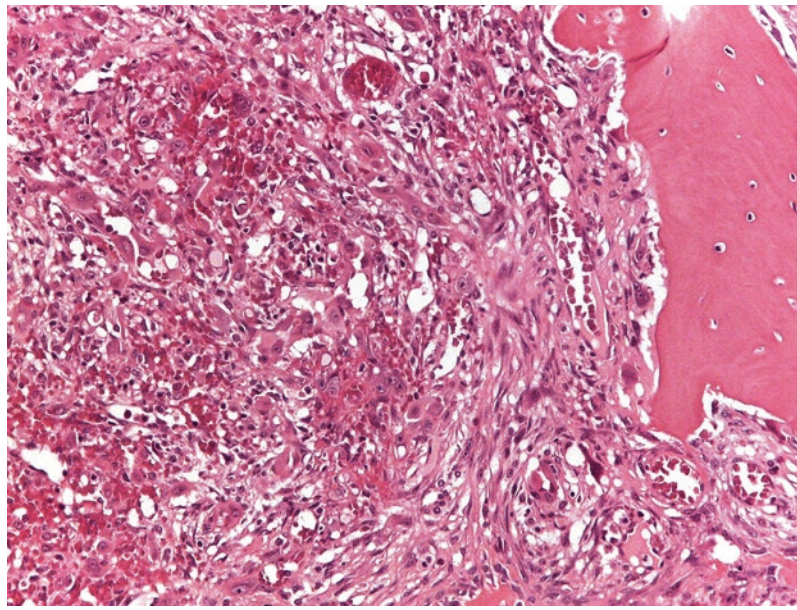
Clinical: Patients usually present with pain localized to the involved anatomical site. In soft tissues, the majority of epithelioid hemangioma presents as subcutaneous masses of a year or less in duration. The process is usually uninodular, but multinodularity, generally in contiguous areas, can be present. Dermal examples are less frequent, and deep-seated cases are rare.

Imaging: In bone, a well-defined lytic, sometimes expansile, septated mass that may erode the cortex and extended into the soft tissue. On CT scans, a honeycomb pattern can be visible. On MRI, they are hypo- or isointense to muscle on T1-weighted images, and hyperintense on T2-weighted images. In soft tissues, epithelioid hemangiomas present an inhomogeneous pattern on MRI. The lesion often appears as a "bunch of grapes," occasionally with a serpentine or tubular pattern. On T1 angiomatous tissue has an intermediate intensity between that of muscle and fat, but areas of stagnant blood and hemorrhage can cause high signal intensity. On T2, vascular spaces seen are hyperintense but fibrous septa and calcified foci are hypointense. Fluid-fluid levels can be appreciated.

Histopathology: Epithelioid hemangioma is usually 0.5–2.0 cm in size, generally with a rather nonspecific nodular appearance. Subcutaneous examples of epithelioid hemangioma are characterized by a prominent proliferation of small, capillary-sized vessels, sometimes lacking a well-defined lumen. These vessels are rimmed by a single cell endothelium layer with an intact myopericytic/smooth muscle layer. Numerous eosinophils and lymphocytes are generally present in most cases. Dermal examples of epithelioid hemangioma generally show a more mature appearance with a well-canalized lumen, and endothelial cells are somewhat less plump, frequently more

cobblestone or hobnail-like in appearance. The neoplastic cells are immunoreactive for ERG and CD31. Focal expression of keratin may be seen. A novel and recurrent *FOS* gene rearrangements in nearly one-third of epithelioid hemangioma across a variety of locations. The *FOS* rearrangements are also much more common in the epithelioid hemangioma of extremities, trunk, and penis, being seen in 40–50% of cases. In contrast, head and neck epithelioid hemangiomas are rarely affected by this genetic abnormality. Recently, a recurrent *ZFP36-FOSB* fusion in a small subset of epithelioid hemangioma with atypical features has been reported.

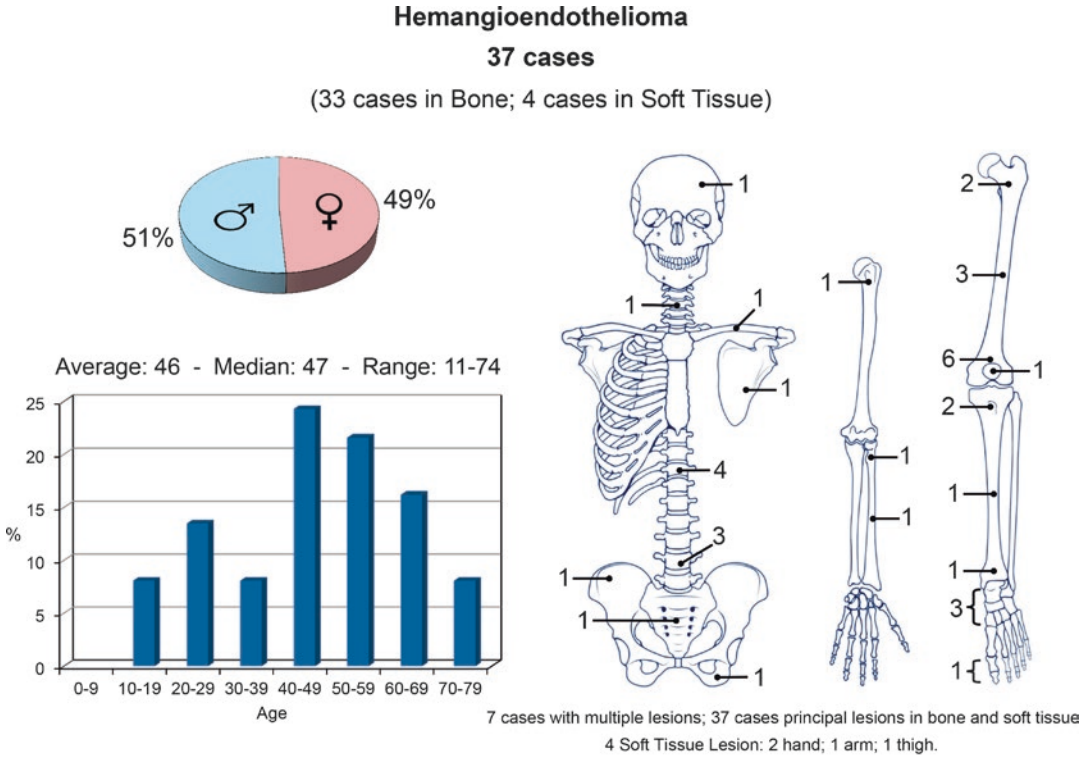
Course and Treatment: Epithelioid hemangioma of bone is a locally aggressive lesion and treatment usually consists of curettage and less frequently, marginal en-bloc excision of the tumor. Radiotherapy could be used for tumors in inaccessible locations. Local recurrence is reported to occur in 1/3 of epithelioid hemangiomas. There are no reports of distant metastases. The vast majority of recurrences are indolent and cured by re-excision, but very rarely recurrences can be locally aggressive. Recurrences may appear to be anatomically separate, perhaps reflecting multicentricity of this tumor.

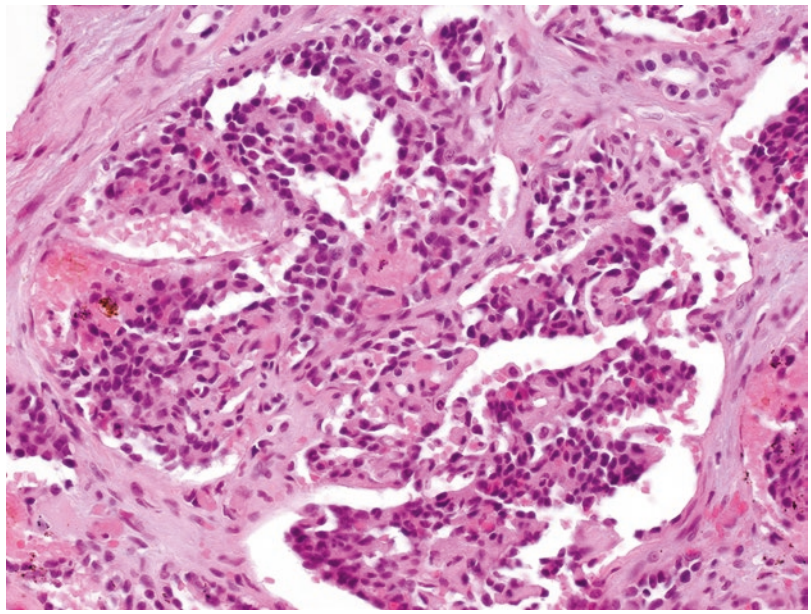


Large epithelioid cells line well-formed vascular spaces associated with isolated prevalent epithelioid or slightly spindled cells adjacent to a well-formed neoplastic vessel

46.4 Hemangioendothelioma

The term hemangioendothelioma has been used historically in a variety of contexts but is now applied exclusively to vascular tumors in the intermediate group. The latter category includes two groups of tumors, mainly reported in the soft tissue: (1) those that may be locally aggressive but have no metastatic potential (kaposiform hemangioendothelioma) and (2) those that have a low and histologically unpredictable risk of metastasis (retiform hemangioendothelioma, papillary intralymphatic angioendothelioma, composite hemangioendothelioma, pseudomyogenic hemangioendothelioma). Epithelioid hemangioendothelioma is now classified as a low-grade malignant tumor capable of aggressive local growth, recurrence or both, and of distant metastases.



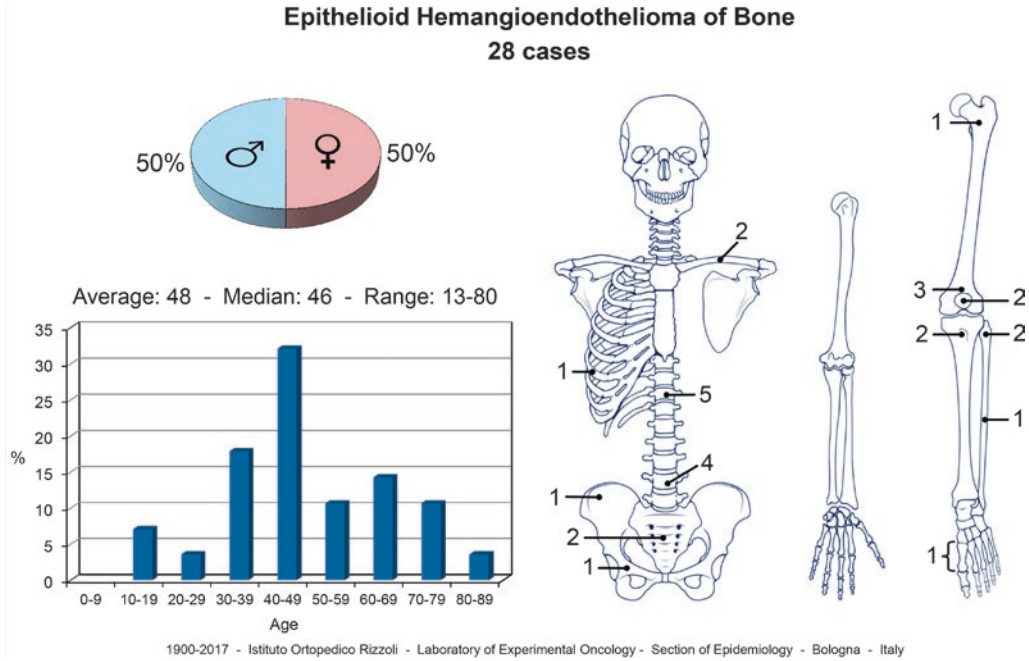


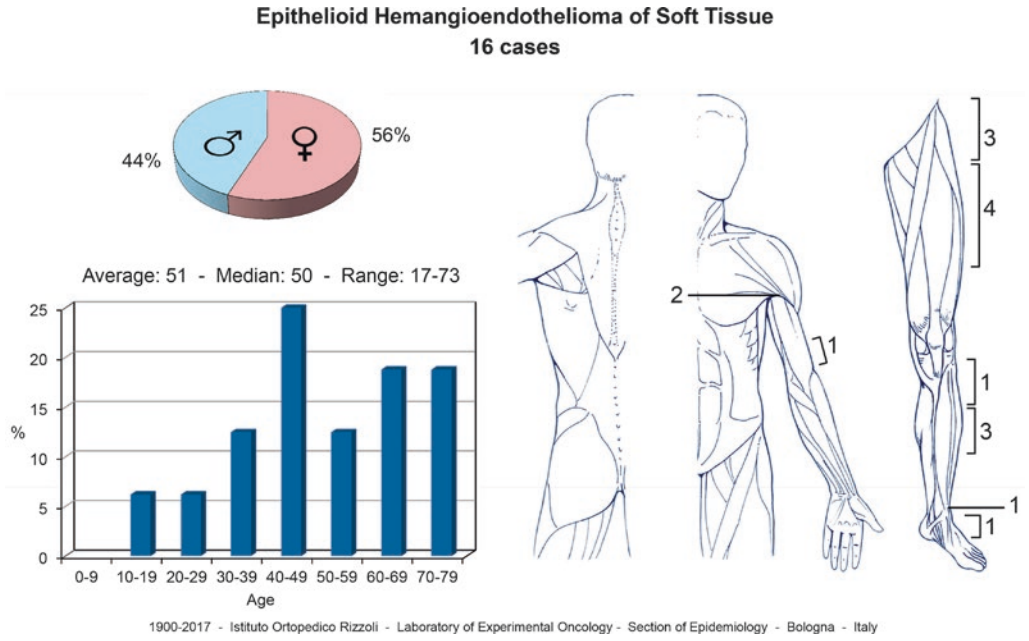
Histological features of papillary intralymphatic angioendothelioma, composed of glomerulus-like structures with papillary structures projecting into the lumen, covered by plump “hobnail” endothelial cells

46.5 Epithelioid Hemangioendothelioma of Bone and of Soft Tissue

Definition: Epithelioid hemangioendothelioma is a malignant tumor that shows endothelial differentiation and can occur in a variety of anatomical sites, including soft tissue and bone.

Incidence: Epithelioid hemangioendothelioma is rare and the true incidence is unknown. The age of occurrence is regularly distributed between 10 and 80 years with most patients diagnosed during the second and third decades of life. The sexes are equally affected although some series have reported a male predominance in bone tumor and a female predominance in soft tissue tumor.





Location: The most frequent location of bone and soft tissue epithelioid hemangioendothelioma are the lower extremities. About bone tumor, the spine, pelvis, and ribs are other sites of involvement. Separated synchronous foci are present in different anatomic locations in more than 50% of the cases.

Clinical: Epithelioid hemangioendothelioma of soft tissue develops often as a painful nodule in either superficial or deep soft tissue. Deeply situated tumors may be associated with focal ossification that can be detected on plain films. Localized pain and swelling are the most frequent symptoms of bone tumors.

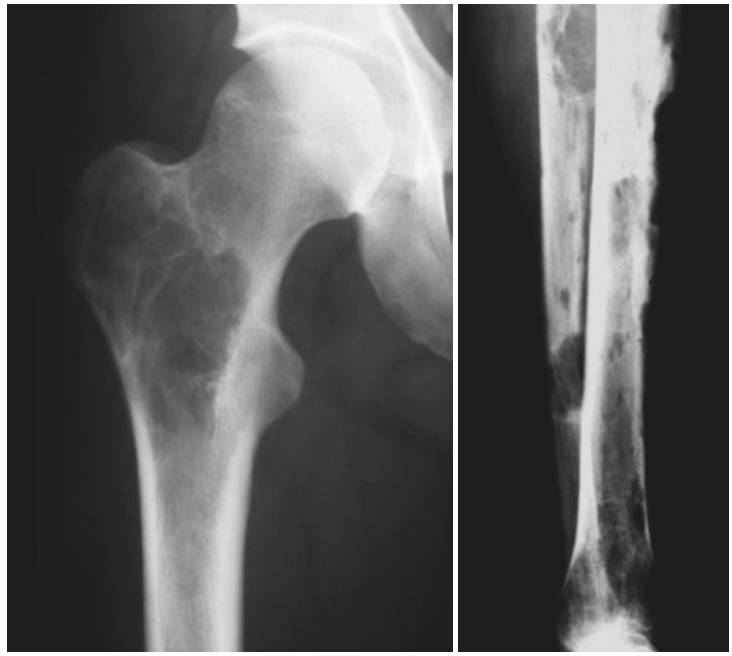
Imaging: Radiologically epithelioid hemangioendothelioma of bone, like the other vascular tumors in bone, presents as a lytic lesion, without a sharp demarcation and they may be expansile and erode the cortex.

Histopathology: Epithelioid hemangioendothelioma typically consists of epithelioid cells, with abundant eosinophilic cytoplasm, sometimes with intracytoplasmic vacuolization (so-called blister cells). The cells are organized in short cords or strands and characteristically are embedded in hyalinized or myxoid stroma. The tumor has an infiltrative growth pattern. Although epithelioid hemangioendothelioma usually shows low-grade morphology, a small subset of cases is of cytologically higher grade and may show a significant solid growth pattern mimicking angiosarcoma, and it is called "aggressive" or "malignant" variant of epithelioid hemangioendothelioma. Immunohistochemically, epithelioid hemangioendothelioma expresses the endothelial markers CD31, CD34, and ERG and in a different percentage can express cytokeratin AE1/AE3 representing a diagnostic pitfall. In 2001, a t(1;3)(p36;q25) translocation was identified, involving *WWTR1* and *CAMTA1* genes. This *WWTR1–CAMTA1* fusion gene has been identified in 80–90% of epithelioid hemangioendothelioma with classic morphology and is not found in morphological mimics. Immunohistochemical nuclear expression of CAMTA1 has very recently been shown to be a sensitive and specific surrogate marker for the fusion gene. The remaining subset of epithelioid hemangioendotheliomas, which were negative for WWTR1-CAMTA1, has a t(x;11)(p11;q22) translocation, resulting in a *YAP1-TFE3* fusion. This specific subset has a distinct morphology, with vasoformative and vasoinvasive growth, combined with solid areas. The cytoplasm is voluminous, deeply eosinophilic or histiocytoid, and sometimes feathery. The nuclei can be mild to moderately atypical. The immunohistochemical nuclear expression of TFE3 and *TFE3* gene rearrangement using FISH analysis can be used to confirm the diagnosis.

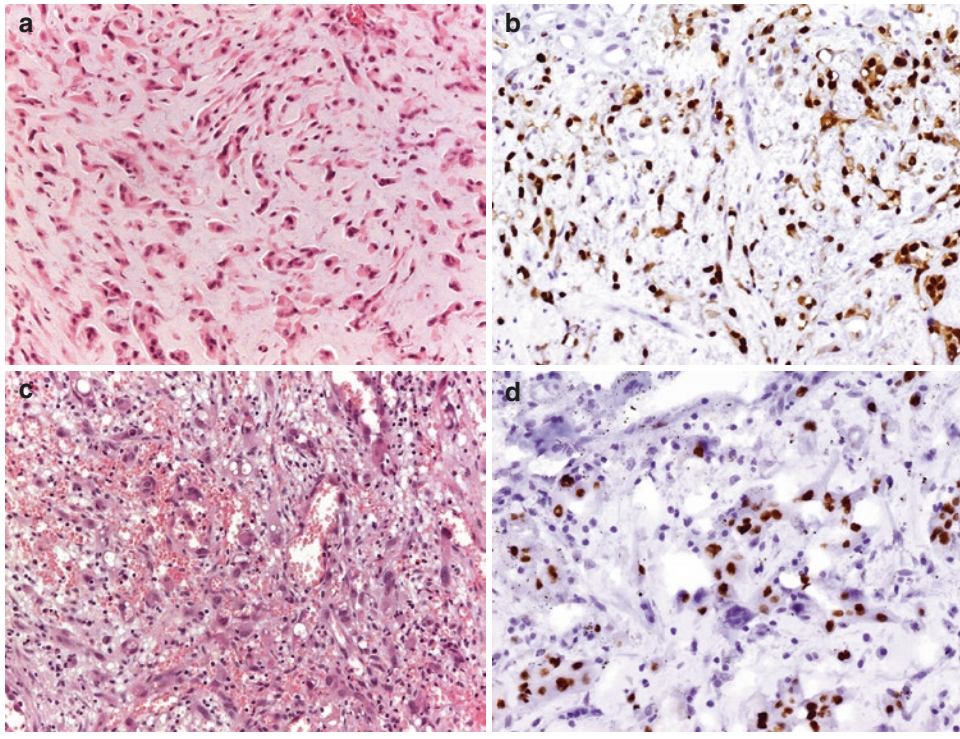
Course and Treatment: Wide resection is the treatment of choice. Although less clinically aggressive than angiosarcoma, epithelioid hemangioendothelioma is associated with metastasis in 20–30% of cases, and 10–15% of patients die of disease. The preferred sites for metastasis are the lungs followed by the skeleton, but it remains unclear whether these skeletal metastases should be considered true metastases or multifocal regional spread. The "aggressive" or "malignant" variant of soft tissue epithelioid hemangioendothelioma is typically associated with a more aggressive clinical course. Conversely, in primary bone epithelioid hemangioendothelioma, this "aggressive" or "malignant" variant does not seem to predict prognosis.

Epithelioid hemangioendothelioma

Chromosomal translocations		
• t(1;3)(p36.3;q25)	WWTR1-CAMTA1	80–90%
• t(x;11) (p11;q22)	YAP1-TFE3	10–20%



Radiograph. Purely lytic lesions. They can be unique, or multiple usually in the same limb

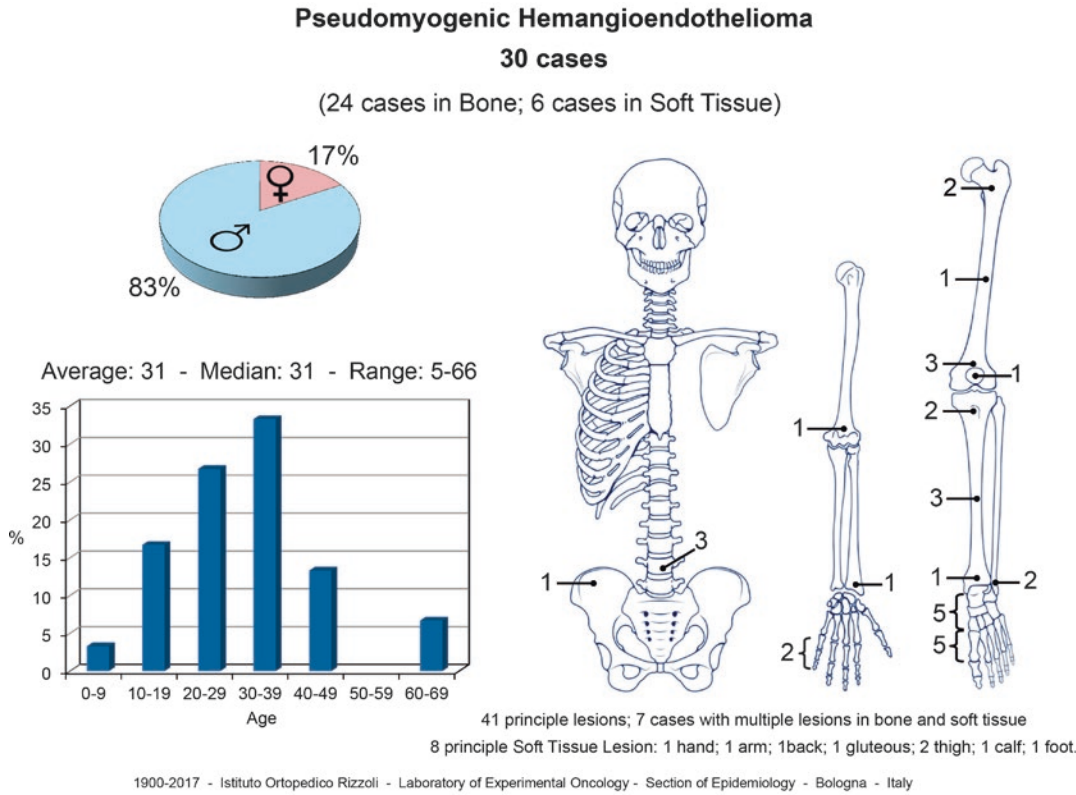


An example of epithelioid hemangioendothelioma constituted of cords, strands, or nests of epithelioid cells in a myxohyaline stroma on hematoxylin and eosin (**a**: ×200 of magnification) associated with a strong nuclear reactivity for CAMTA1 antibody (**b**: ×200 of magnification). A second example of epithelioid hemangioendothelioma (arising in T12) that showed mature vessel lumen formation, in addition to intracytoplasmic vacuoles on hematoxylin and eosin (**c**: ×200 of magnification) associated with a strong nuclear reactivity for TFE3 antibody (**d**: ×200 of magnification)

46.6 Pseudomyogenic Hemangioendothelioma

Definition: Pseudomyogenic hemangioendothelioma, which has also been referred to as epithelioid sarcoma-like hemangioendothelioma, is a rarely metastasizing vascular tumor exhibiting peculiar pathological features.

Incidence: This clinically distinctive tumor typically arises in young adults, with a peak incidence at age 30 years and a marked male predilection (male: female ratio of 4:1).



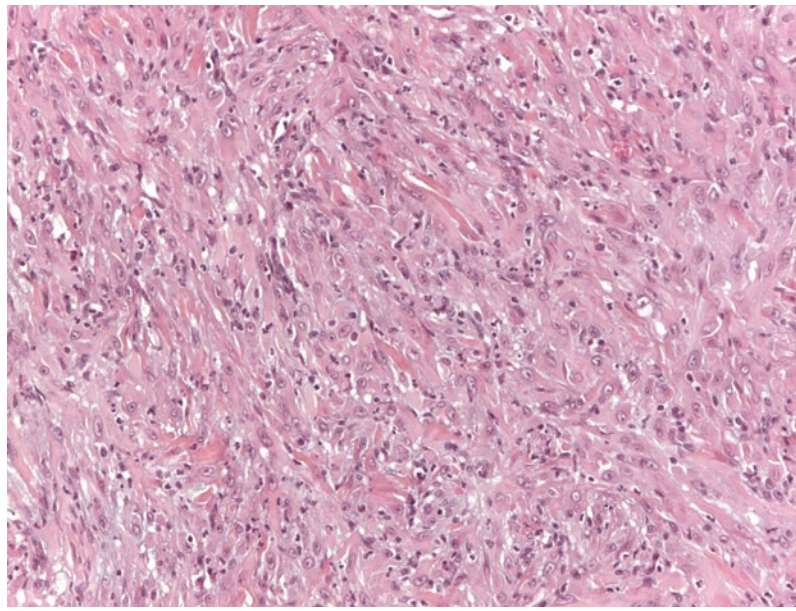
Location: Patients usually present with dermal or subcutaneous nodules on the extremities, most commonly the lower limbs, and 66% of patients have multifocal disease at presentation, often involving multiple tissue planes (deep soft tissue, skeletal muscle, or bone). The bone tissue involvement is reported in more or less 25% of cases, but not more of 100 cases of primary pseudomyogenic hemangioendothelioma of bone have been described in the literature so far.

Imaging: Pseudomyogenic hemangioendothelioma of bone usually shows well-limited purely lytic lesion. Tumors are 18F-fluorodeoxyglucose-avid on positron emission tomography scan, which helps to delineate the extent and multifocality of disease visualizing clinically occult deep lesions.

Histopathology: Tumors are composed of sheets and loose fascicles of spindled cells with abundant brightly eosinophilic cytoplasm, vesicular nuclei, and small nucleoli associated with scattered epithelioid cells, sometimes mimicking rhabdomyoblasts, occasionally organized in small clusters. Tumor cells show mild atypia and low mitotic activity. The neoplastic cells proliferation is usually associated with prominent infiltration by neutrophils and focal chronic inflammatory infiltrate. This tumor is often extremely difficult to diagnose because no morphological evidence suggestive of endothelial differentiation is present

to confirm a radiological pattern of vascular neoplasm. The peculiar immunohistochemical phenotype with co-expression of keratin AE1/AE3 and vascular markers (ERG, FLI1 and CD31) associated with a strong nuclear expression of FOSB offers a diagnostic tool to distinguish pseudomyogenic hemangioendothelioma from histologic and radiological mimics including epithelioid sarcoma, metastatic carcinoma, and other vascular neoplasms. Molecular analysis detected the presence of the *SERPINE1-FOSB* fusion genes in the majority of cases tested.

Course and Treatment: Pseudomyogenic hemangioendothelioma is considered to be a tumor of intermediate biological potential in terms of clinical behavior, given its propensity for local recurrence and the frequent development of additional nodules in the same region, which occur in almost 50% of patients. Rare cases with aggressive clinical behavior resulting in distant metastasis and death have been reported. Conservative management is therefore the mainstay of treatment, often in the form of complete but narrow excision or curettage of bone lesions, avoiding large disfiguring surgeries. Adjuvant chemotherapy (gemcitabine and/or taxane) and/or radiotherapy following curettage of the largest tumoral nodule represent a therapeutic option for these patients.

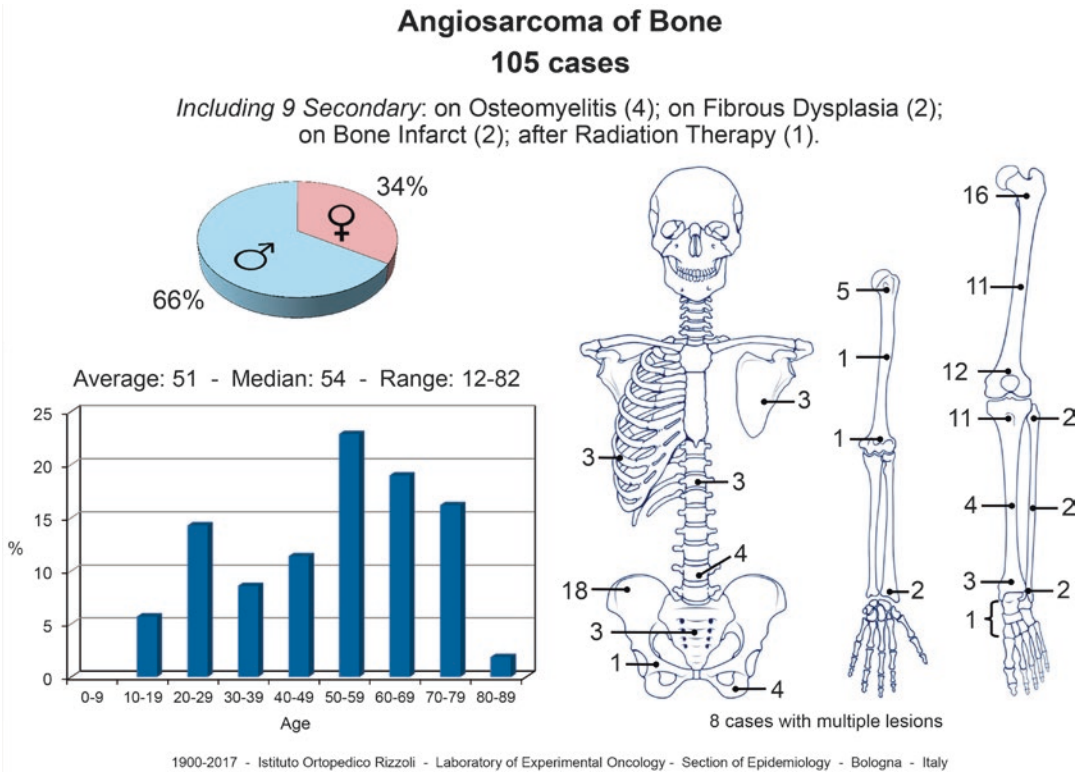


The tumor is composed of sheets and loose fascicles of spindle cells with abundant brightly eosinophilic cytoplasm and small nucleoli. Scattered neutrophils are present (**a**, magnification ×200)

46.7 Angiosarcoma of Bone

Definition: A high-grade malignant vascular tumor, composed of cells that demonstrate endothelial differentiation displaying variable degree of vascular formation.

Incidence: Primary angiosarcomas of bone are rare and account for less than 2% of malignant tumors of bone. Approximately 4% of all angiosarcomas arise primarily in bone and predominantly occur in the seventh decade, with a male predominance.

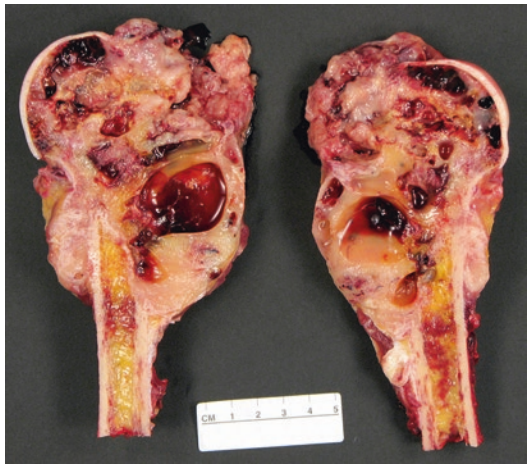


Location: Usually occurring in the long tubular bones, most frequently in the lower extremities. In bone, 30–40% of angiosarcomas are multifocal.

Imaging: Destructive osteolytic mass with well- or poorly defined margins. Cortical destruction is found in 65% of cases.

Histopathology: The majority (>85% of cases) of bone angiosarcomas displays epithelioid morphology with sheet-like growth and plump cells constituted of abundant eosinophilic cytoplasm and marked cellular atypia. In addition to the variable presence of vasoformative areas, solid areas can be found. Malignant endothelial cells can be also arranged in intraluminal buds, projections, or papillae. Mitoses are numerous (>15/10 HPF). Extensive hemorrhage is a characteristic feature of most angiosarcomas. Secondary angiosarcoma (after irradiation, chronic osteomyelitis, bone infarct, and fibrous dysplasia) often shows a prevalent spindle cell morphology. Immunohistochemistry shows positivity for CD31 (95–100%), ERG (96%), and smooth muscle actin (61%). Keratin AE1/AE3 is expressed in 69–80% of the bone angiosarcomas and can often lead to confusion with metastatic carcinoma. To molecular point of view, angiosarcomas of bone evidence different molecular alterations in a subset of cases with mostly non-overlapping genetic signatures across clinical subsets, involving *MYC, CIC, KDR, FLT4, PLCG1,* and *PTPRB* genes.

Course and Treatment: Angiosarcoma of bone has a very poor survival: the 1-year survival is 55% and the 5-year survival is 33%. Wide surgical resection is seldom feasible due to the fast infiltrative behavior and probably unable to prevent systemic spread. Chemotherapy and radiotherapy progresses could be helpful. In this perspective, multidisciplinary approach is mandatory, and surgery should be planned and coordinated according to timing of chemotherapy and allowing the most effective radiation.

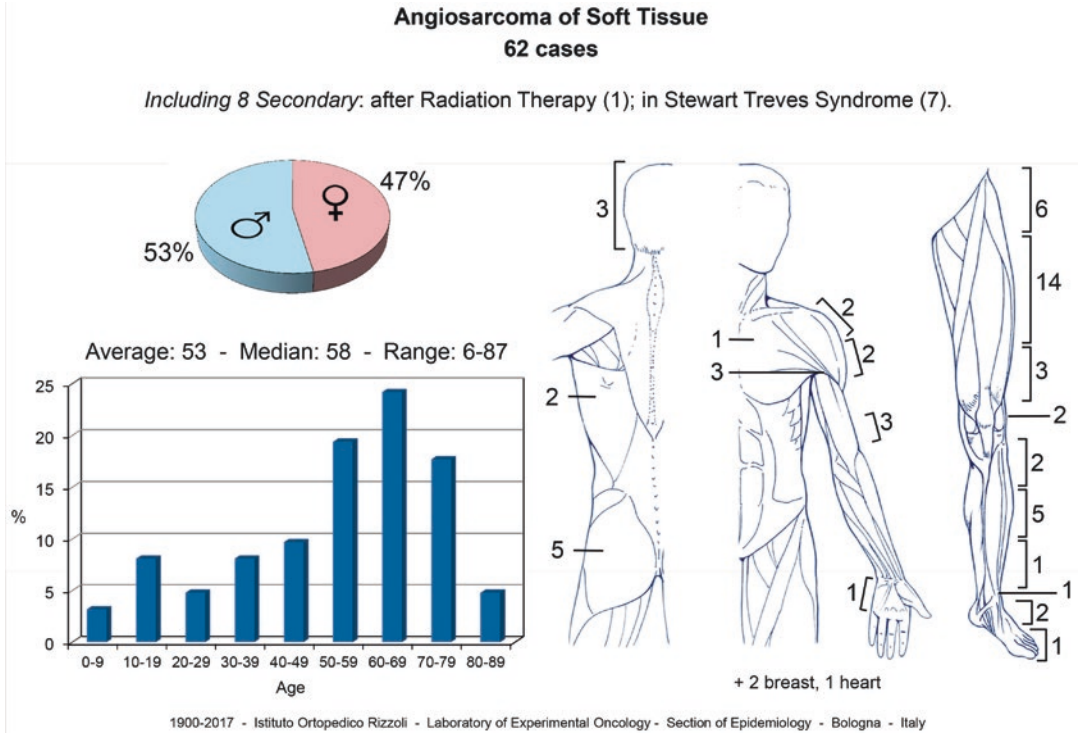


At macroscopy, angiosarcoma is usually a big mass, friable, hemorrhagic, and tan-red that destroys the cortex and extends into the soft tissue

46.8 Angiosarcoma of Soft Tissues

Definition: A malignant vasoformative tumor that recapitulates the morphological and functional features of endothelium to a variable degree.

Incidence: 2–4% of soft tissue sarcomas. This tumor shows a male predilection with a wide age range, although children are rarely affected. Most soft tissue angiosarcomas are sporadic, but a small minority arises at the site of previous radiation therapy. A smaller subset occurs adjacent to synthetic (graft) or foreign material. Evenly distributed throughout the decades with a peak incidence in the seventh decade.



Location: The majority develops as cutaneous lesions, particularly in patients suffering from lymph edema or after radiation for a previous malignancy. Less than 25% are deep-seated soft tissue neoplasms. The most common localizations are the deep muscles of the lower extremities (40% of cases) followed by the arm, trunk, head and neck, and the abdominal cavity. Patients typically present with an enlargement or painful mass. Rarely lesions are multifocal.

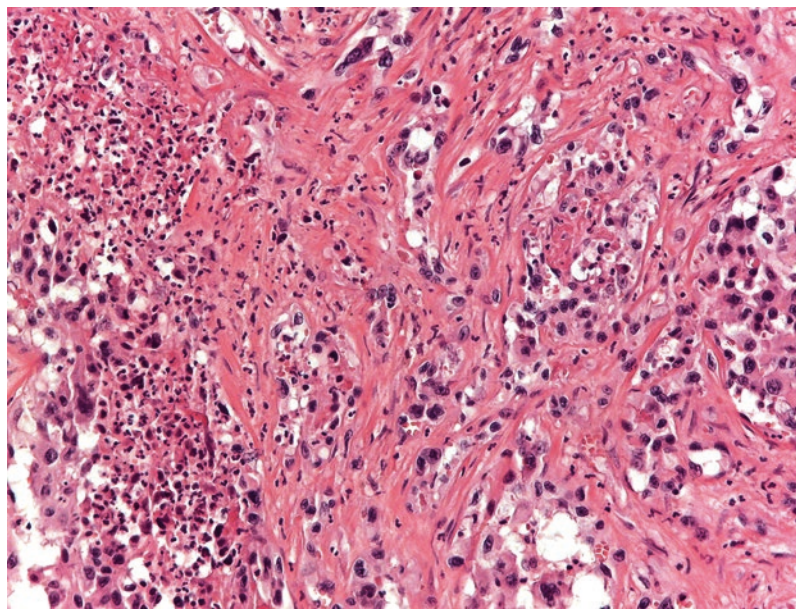
Clinical: Soft tissue angiosarcoma develops as enlarging mass, in 1/3 of patients associated with other symptoms such as coagulopathy, anemia, persistent hematoma, or bruisability.

Imaging: Soft tissue angiosarcomas often show nonspecific characteristics. Presence of intratumoral necrosis may be demonstrated by the use of contrast agents.

Histopathology: Macroscopically, angiosarcomas of soft tissue are multinodular hemorrhagic masses often with secondary cystic degeneration and necrosis. The majority of soft tissue angiosarcomas, as well as primary bone angiosarcomas, are the epithelioid variant, ranging from areas of well-formed, anastomosing vessels to solid sheets of high-grade cells without clear vasoformation. The vast majority of cases are high-grade neoplasms with brisk mitotic activity, coagulative necrosis, and significant nuclear atypia. Intratumoral hemorrhage is common and may result in an organizing hematoma with superimposed papillary endothelial hyperplasia. Careful and extensive sampling may be necessary to document malignant cells.

Immunohistochemically, soft tissue angiosarcomas express vascular markers CD34, CD31, ERG, and FLI1 associated with an expression of lymphatic marker podoplanin (D2-40) in approximately 50% of cases.

Course and Treatment: Angiosarcomas of soft tissue are highly aggressive malignancies with a high rate of tumor-related death. More than half of patients die within the first year from diagnosis with metastatic disease in the lung, lymph nodes, bone, and soft tissues. Some patients are palliated for 1 year or longer with radiation or taxane-based chemotherapy regimens, but long-term survival is uncommon.



An example of the morphology of epithelioid angiosarcoma that shows tumor cells lining vascular lumina and growing in solid nests, the latter mimicking metastatic carcinoma

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