Osteosarcomas (OS)

36

Piero Picci

Definition: Malignant tumor composed of mesenchymal cells producing osteoid and immature bone. Almost constantly intramedullary, rarely it may originate at the bony surface. Osteosarcomas may sometimes present with skip or more distant skeletal metastases, but it can be also skeletally multifocal at presentation. There are, consequently, several varieties of osteosarcomas whose anatomo-clinical presentation, treatment, and prognosis, however, are not as distinctive as to justify a separate classification. Other osteosarcomas types, instead, are different in their clinical, pathologic, and therapeutic-prognostic features, and are classified as separate entities (periosteal osteosarcomas, parosteal osteosarcomas, low-grade central osteosarcomas).

osteosarcomas varieties and their incidence on 100 cases

High-grade OS varieties	**90%**
• Classic osteosarcoma	75
• Telangiectatic	5
• Secondary	4–5
• Of soft tissues	3
• Of jaw bones	2–3
• Small cell	<1
• Of bone surface	1–2
• Multicentric	0.5
Low-grade OS varieties	**10%**
• Parosteal	4–5
• Central	3
• Periosteal	1–2

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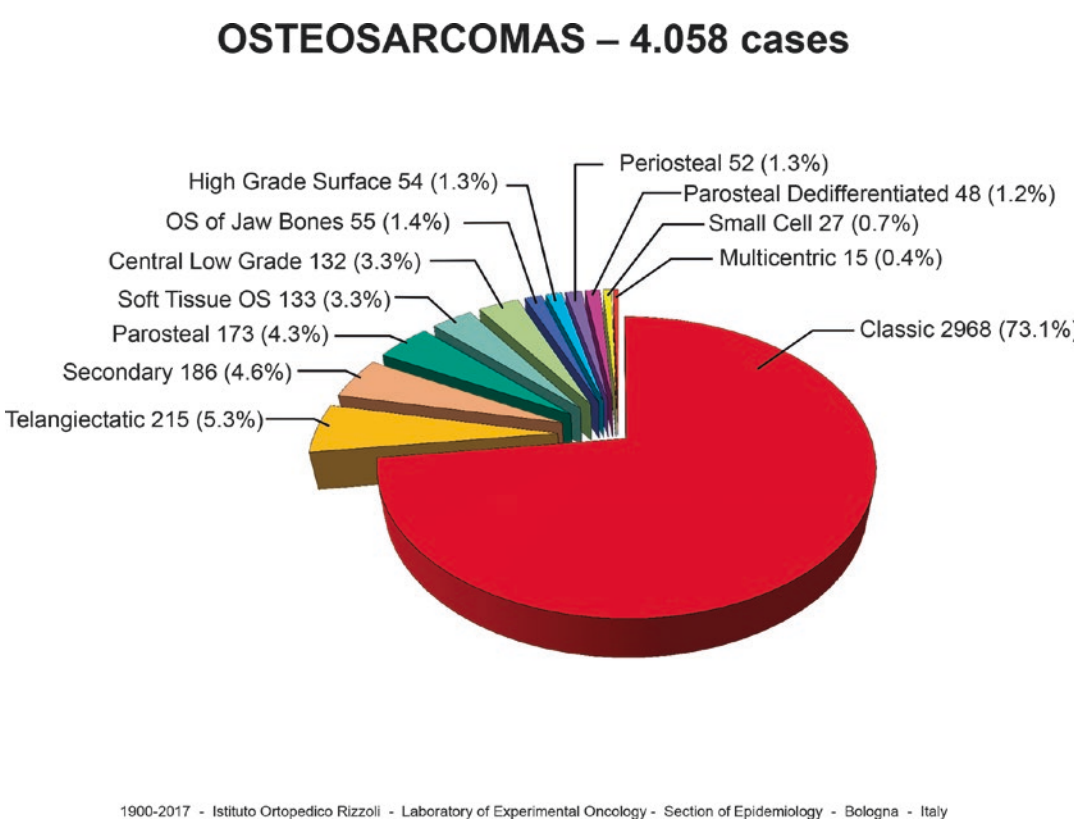
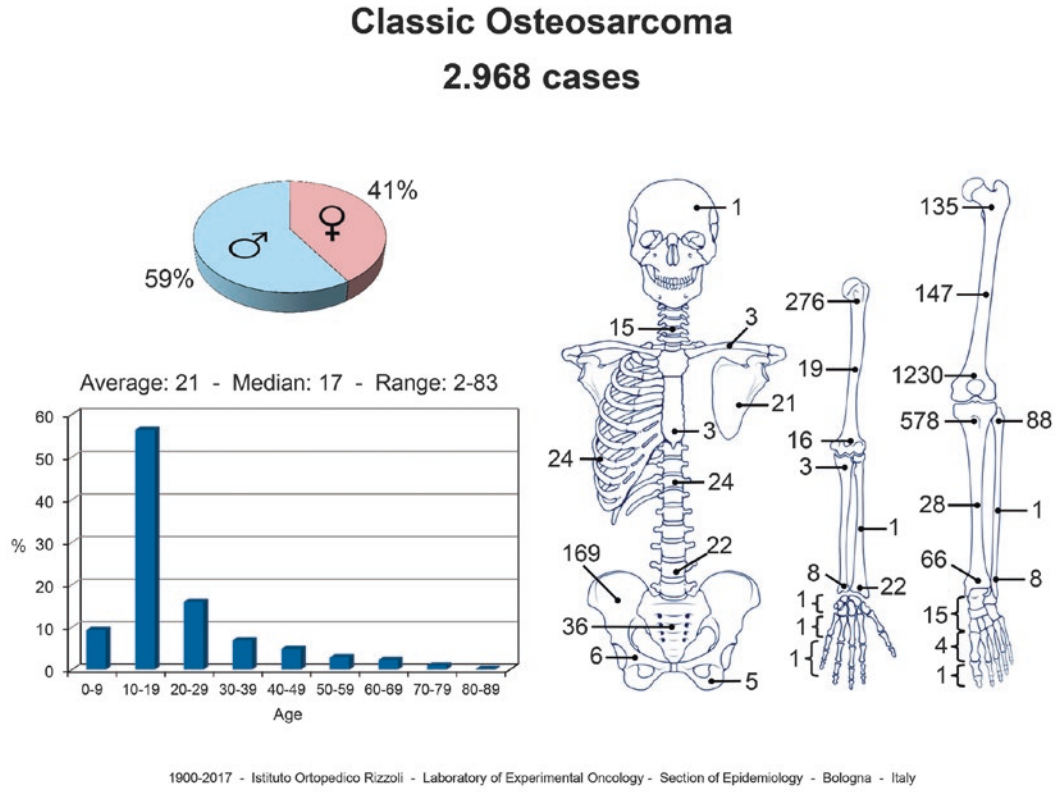


36.1 Classic Osteosarcoma

Epidemiology: It is the most frequent primary malignant tumor of bone, excluding myeloma considered a systemic neoplasm. Its incidence is of 2–3 cases/million/year (only 0.2% of all malignancies). Males are preferred (1.5:1). Most cases occur between 10 and 20 years of age, with a median age of 17. Older patients are usually secondary to radiation, Paget's, chondrosarcoma, other primary bone tumors, or idiopathic.

Localization: Seventy percent of OS are localized around the knee or shoulder. Other locations are proximal or mid-femur, ilium, mid and distal tibia, proximal fibula, spine. Exceptions are the hand and foot. OS usually grow in the metaphysis or meta-diaphysis but tends to invade the epiphysis even in presence of a growth plate.

Clinical: Pain is usually the first symptom, often referred to trauma. In few weeks, it increases and painful swelling appears. High temperature and limited joint motion are advanced signs. Pathologic fracture may occur in osteolytic forms. Alkaline phosphatase is frequently elevated. Less frequently, also LDH may be increased.



Imaging: The plain X-ray is usually diagnostic. Typically, OS starts intramedullary, but breaches the cortex, and expands in the soft tissues. It is usually a combination of radiolucency and radiodensity, sometimes it is entirely eburneus with edges always faded. The pure osteolytic form is typical of the telangiectatic variety. The tumor soft tissue extension shows irregular, cloud-like radiodensities, and/or stripes of density perpendicular to the cortex (sunray image). Occasionally, it is purely radiolucent and it can be appreciated only by CT and MRI. At the periphery of the area where the tumor breaches the cortex, a triangular buttress of immature bone (Codman's triangle) is seen. This is due to reactive bone acutely produced by the periosteum. Isotope bone scan is intensely hot even beyond the radiographic limits of the tumor. Rarely, it may reveal skips or distant bone metastasis. CT demonstrates intraosseous and extraosseous extension of the tumor and intratumoral radiodensities. With MRI, most OS exhibit the usual pattern of low T1, and high T2 signal. Sclerosing OS, however, have a low intensity on both T1 and T2 images. MRI is the best way to determine medullary tumor borders, epiphyseal invasion, skip metastasis. Contrasted CT and MRI show the relationship with vessels; but in some cases, an angiogram may be more reliable. Patient workup always includes CT of the lungs where metastasis may appear as radiodense round nodules.

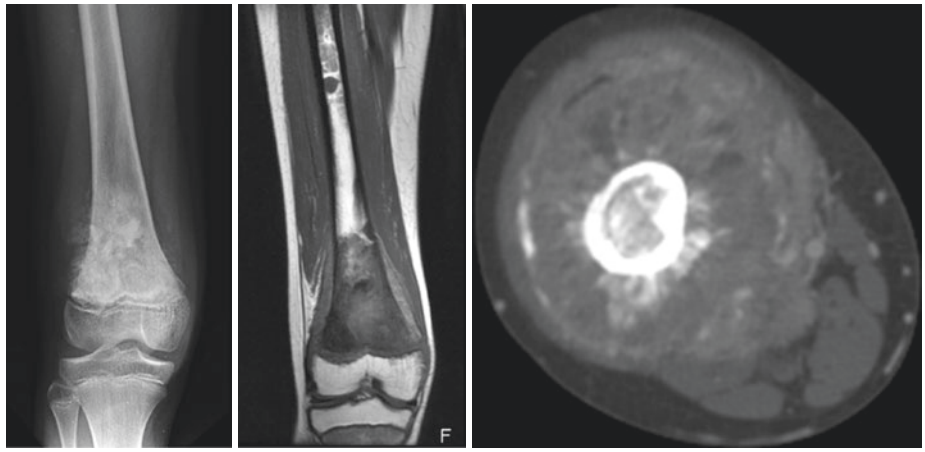
Histopathology: OS is fleshy-soft in cellular areas with little matrix, firm and rubbery in fibroblastic areas with collagen production, gritty to stone-hard in osteogenic areas, and cartilaginous to myxoid in chondroblastic areas. Hemorrhage, necrosis, and cystic alterations are common. The most relevant diagnostic feature is constant permeation of marrow spaces, trapping host trabecular bone along its margins, predominantly. Cortex is also permeated and usually breached. An endosteal and periosteal production of reactive bone is associated. OS may invade the joint capsule and ligaments. Rarely, OS plugs are found in the adjacent veins. Skip metastasis, usually in the same but also in the adjacent cross-joint bone may be detected in a small percentage of cases. Microscopically, OS has a wide range of histological presentations but the characterizing feature is represented by high-grade sarcomatous cells producing osteoid and woven bone. The less osteogenic areas of the tumor (usually the periphery) are highly cellular and show more clear-cut features of high-grade malignancy as compared to more osteoid or bone-rich central areas of the tumor. Cells are large, with striking pleomorphism, hyperchromia, prominent nucleoli, frequent atypical mitoses, although some 10% of cases may show little anaplasia and lead to confusion with benign entities such as osteoblastoma, chondroblastoma, giant cell tumors, and a few others. Tumor osseous matrix varies from slender lace-like seams of osteoid to islands or dense sheets of woven bone. No regular trabeculae rimmed by osteoblasts are produced by OS cells. Where OS is intensely sclerotic, cells are scarce, small, with no mitoses; tissue is scarcely vascular and may be necrotic. In these areas, features of malignancy may be absent and diagnosis of OS is suggested by the permeative pattern of the tumor. Occasionally, OS is extensively chondroblastic (as a high-grade chondrosarcoma), or fibroblastic (similar to a fibrosarcoma). The osteoid-osseous production, which identifies the OS, may be found only in the microscopic study of the entire specimen. Reactive giant cells are seen, particularly in areas of hemorrhage. Particularly at the periphery of the tumor reactive osteogenesis associates and should not be confused with tumorous osteogenesis. Histochemical stains show a high content of alkaline phosphatase in OS cells.

Course and Staging: OS has a rapid course. At presentation, 80% of OS are stage II-B; only 5% are stage II-A. About 15% of OS are stage III. Because, without the use of chemotherapy, 80–90% of OS patients die of metastases, notwithstanding ablation of the primary tumor, it can be said that in 80–90% of cases occult micro metastases are present at the start. Metastatic spread occurs primarily to the lungs.

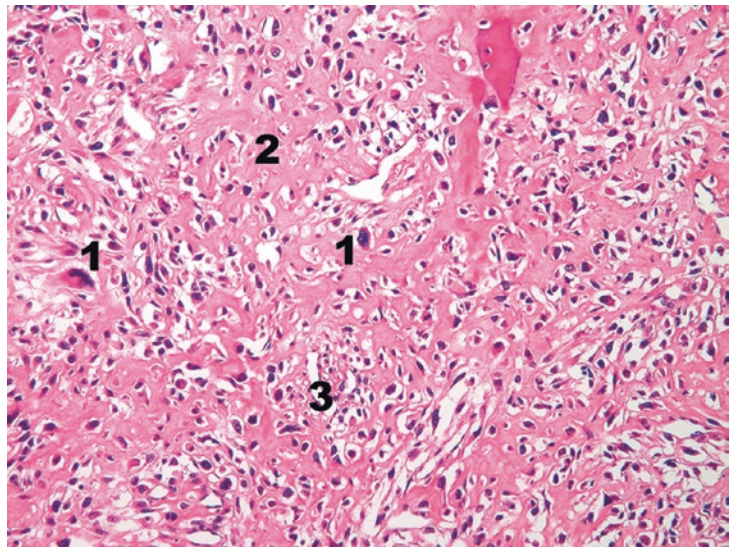
Treatment: Treatment of OS is based on chemotherapy (ctx) and surgery of both the primary tumor and the metastases. Postop ctx (adjuvant) started in 1971, pre- and postop ctx (neoadjuvant) was introduced in 1978. Presently, the most effective drugs are adriamycin (ADM), high-dose methotrexate (HDMTX), cisdiaminoplatinum (CDP), and ifosfamide (IFO). Preoperative ctx is started immediately after diagnosis. After a few cycles (approximately 2 months), the tumor is restaged, evaluating response: clinical (regression of pain, reduction and hardening of the tumor mass), laboratory (<serum alkaline phosphatase), and imaging (arrest of growth, ossification and capsulation of the tumor, regression of vascularity and edema, decreased isotope uptake). A precise method for evaluating response to ctx preoperatively does not exist. Dynamic isotope scan and contrasted MRI, however, are comparatively good indexes of response. Based on post-ctx staging study, surgery is performed. The entire tumor is sampled histologically and examined to quantify tumor necrosis. Good response is indicated by necrosis from 90 to 100%. Postop ctx is continued, starting 1–2 weeks after surgery, and lasting from 4 to 6 months. Usually, the same drugs as used preoperative are given in good responders. In poor responders, different drugs are administered or added in more prolonged trials.

Prognosis: Without chemotherapy, the 10 years survival rate was around 10–15%. With current ctx, the same figure is about 70%, for OS non-metastatic at presentation and involving the appendicular skeleton. Local recurrence was 2–3% after amputation. Presently, it is around 5% after conservative surgery. Metastases (mainly to the lungs) occur usually in the first 2–3 years. There are, however, rare cases of metastasis occurring even 5–10 years after treatment. The second most frequent site for metastasis is the skeleton.

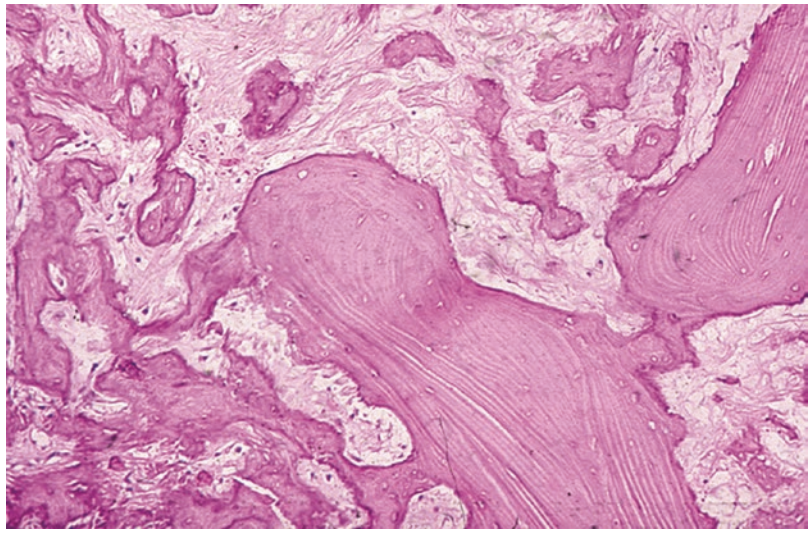
Key points	
• Clinical	Young age, pain and swelling
• Radiological	Central lesion, aggressive with radio-opacities
• Histological	High-grade with osteoid/bone production
• Differential diagnosis	None



Radiograph, CT and coronal T1 MR image. The tumor is metaphyseal, heterogeneous, forms bone, destroys part of the cortex, invades soft tissues. A skip metastasis is detected on MR in the medullary cavity



Sarcomatous tissue with cells producing osteoid and bone. (1) Sarcomatous tissue. The aspects of the high-grade malignancy are fairly evident: large, pleomorphic, and hyperchromic cells are seen. (2) Neoplastic osteoid and osseous material, shaped with an absolutely anarchical architecture. It is nearly impossible to find trabeculae bordered by a regular row of osteoblasts. (3) Abundant blood vessels. They do not have their own well-formed and continuous wall. In some areas, they are directly walled by sarcomatous cells

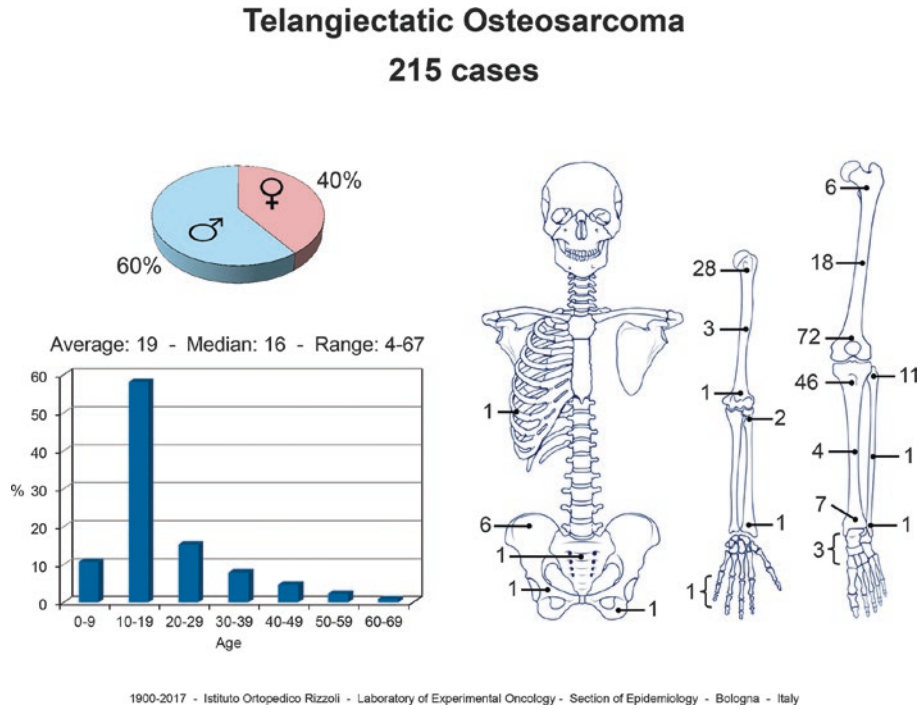


Histology patterns of a good response to preoperative chemotherapy

36.2 Telangiectatic Osteosarcoma

Definition: This variety (about 5/6% of all OS) is a completely osteolytic sarcoma, with a sponge-like structure filled of blood and scarce osteogenesis.

Epidemiology: Sex, age, and localization are the same as in classic OS.



Clinical: Clinically, the tumor has an aggressive course, with an expanding soft tissue mass, soft and tender on palpation, with increased local temperature. Pathologic fracture is not uncommon.

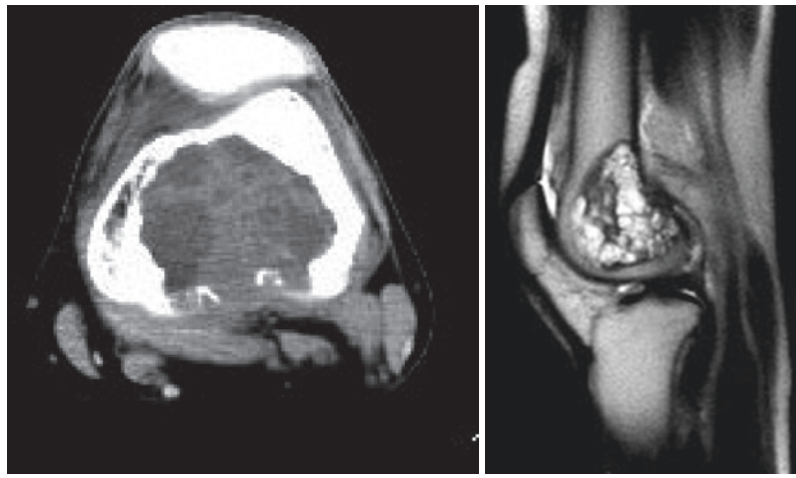
Imaging: Imaging shows a purely osteolytic lesion with ill-defined limits. Isotope scan shows an increased uptake. CT and MRI show the multicystic pattern (high signal in both T1 and T2, because of fluid and hemosiderin content) with fluid levels.

Histopathology: Grossly, the tumor is constituted by large cavities filled with blood. Neoplastic tissue constitutes the septa; it is very soft and can be very scarce, overwhelmed by hemorrhage. The permeative pattern is particularly evident, and cortex and periosteum are often extensively destroyed. Histologically under low power, the pattern is similar to an ABC. Only at higher power, the sarcomatous nature of cells becomes apparent, because all telangiectatic OS are high-grade malignant. Sometimes, however, the hemorrhage and necrosis are so massive that it is difficult to find viable cells and to appreciate anaplasia. Osteogenesis is usually focal and often it must be searched for in numerous sections, and rarely, may not be found at all yet with the overall clinical, gross, and histological patterns are entirely consistent with telangiectatic OS, with minus finding of osteoid or bone production by the sarcoma cells within the aneurysmal bone-cyst-like walls. Atypical mitoses are easily identified.

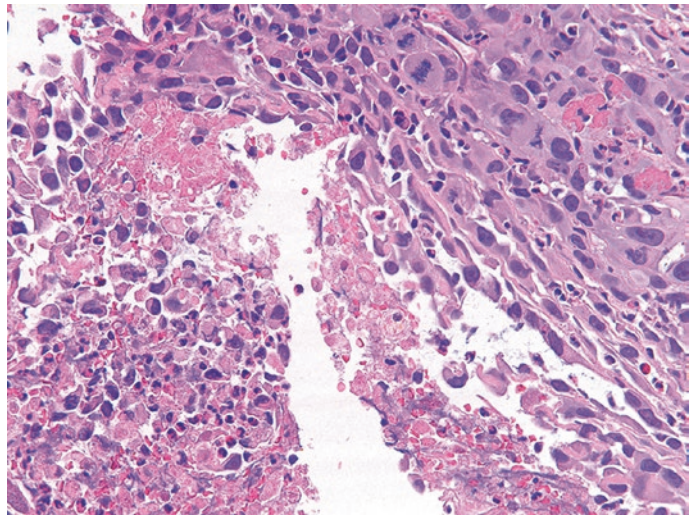
Course: The course is rapid, and the stage is almost regularly II-B or III**.**

Treatment and prognosis: Treatment and prognosis are the same as for classic OS. Some data suggest that response to preoperative ctx is particularly good, which can be explained by the rich vascularity of the tumor, enhancing the ability of the chemotherapeutic agents to reach the malignant cells.

Key points	
• Clinical	Young age, pain and swelling. Pathologic fracture possible
• Radiological	Very aggressive and completely lytic
• Histological	High-grade with lacunae
• Differential diagnosis	Aneurysmal bone cyst



CT and sagittal T2 MR image. Aggressive metaphyseal tumor, destroying the cortex, invading the soft tissues, heterogeneous. Fluid-fluid levels in multiple small cavities are easily detected on MR

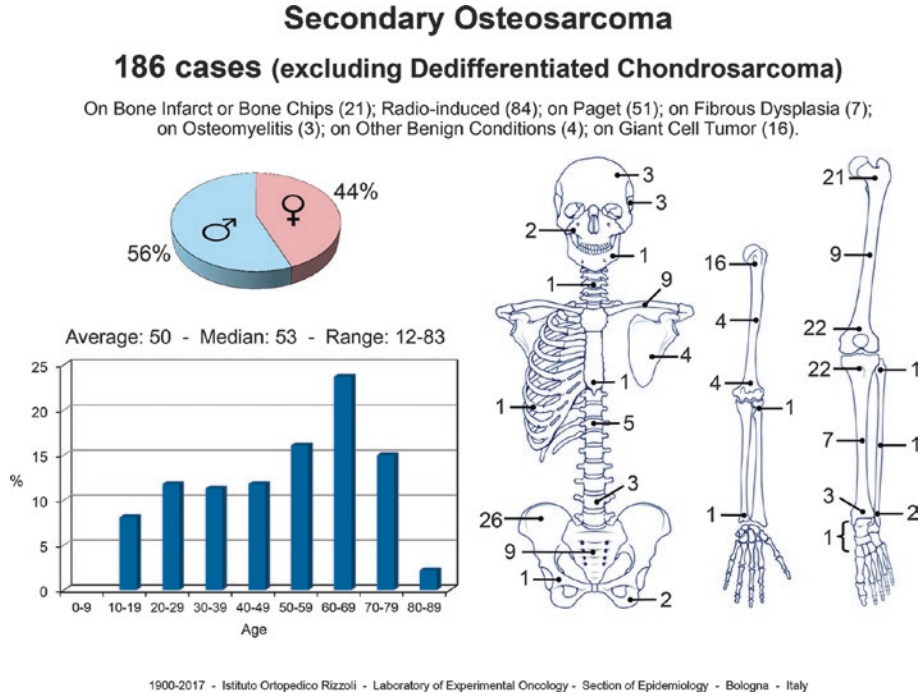


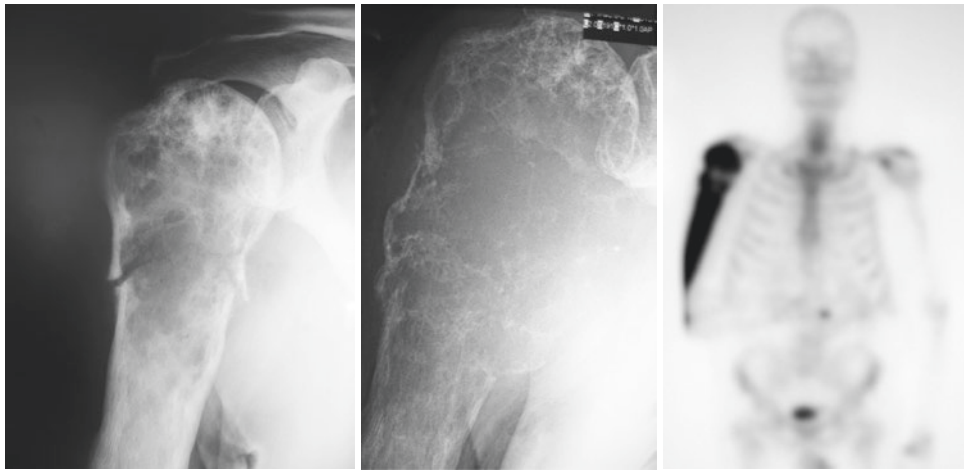
Blood filled cavities rimmed by malignant mesenchymal cells only focally producing osteoid

36.3 Secondary Osteosarcoma

Definition: These OS on pre-existing lesions like Paget's, fibrous dysplasia, bone infarct, chronic osteomyelitis, eventually treated, like after radiation.

Most of these cases are observed in advanced age, usually after the 50 years. Treatment is the same as for usual OS, except for the fact that patient age may contraindicate the use of the same ctx used in youngsters. Prognosis of secondary OS is generally worse as compared to primary OS, since the response to chemotherapy and advanced age of the patients are adverse parameters.



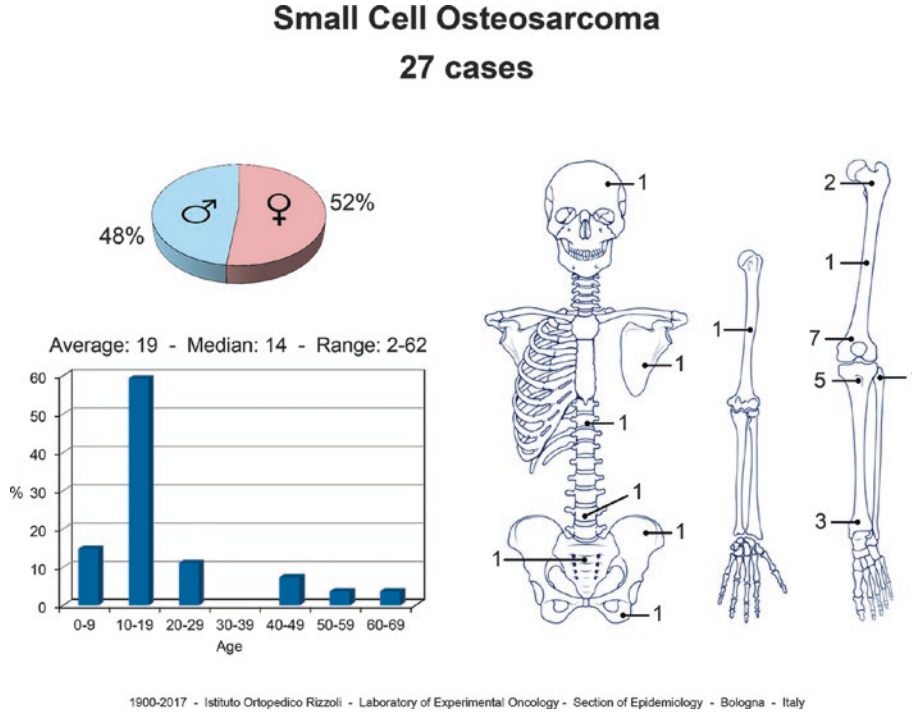


Radiograph at onset and 2 months later, bone scintigraphy. Lytic heterogeneous broken lesion involving the epiphysis and metaphysis. The thick lamellar cortex indicates a pre-existing Paget's disease, confirmed by widespread intense fixation on bone scintigraphy. Two months later, very fast progression of the tumor

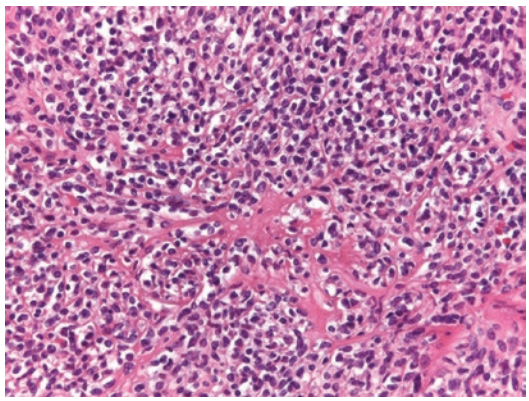
36.4 Small Cell Osteosarcoma

Definition: Tumor composed by small cells, similar to Ewing sarcoma, but producing bone matrix.

This is a rare variety (1–2% of all OS). Epidemiology, clinical presentation, and imaging are not consistently different from usual OS.



Histopathology: Characteristics round to ovoid shaped cells, with scanty cytoplasm, round to oval nuclei with fine to coarse chromatin and inconspicuous nucleoli, similar to Ewing sarcoma cells, but producing osteoid matrix. Immunohistochemical expression of SATB2, CD99 immunonegativity, and the absence of EWSR1 and FUS gene rearrangements are very useful in the differential diagnosis with Ewing sarcoma.

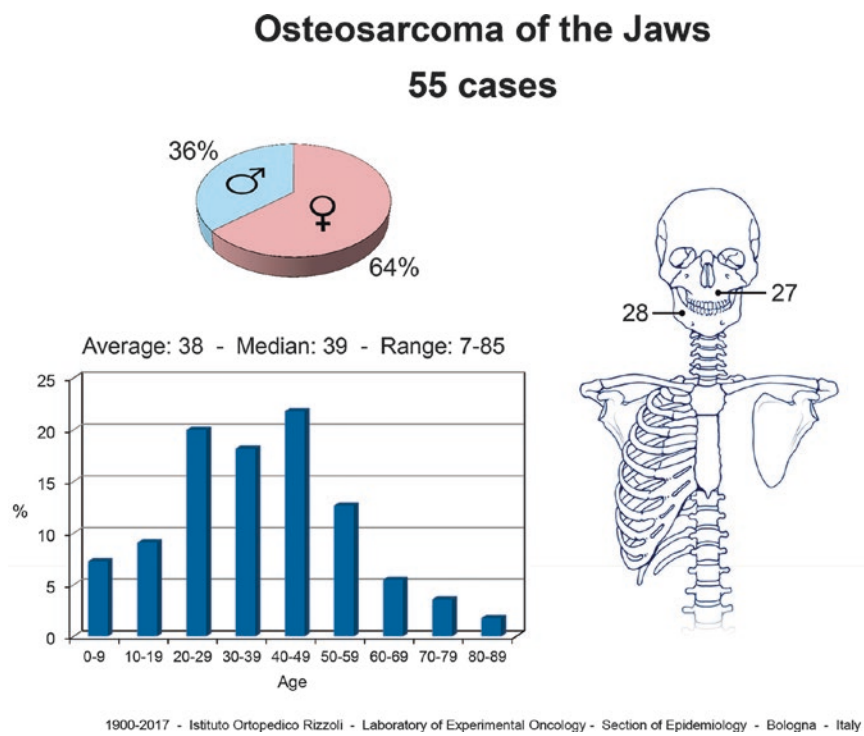


Round to ovoid cells, similar to Ewing sarcoma cells, organized in sheets and nests, with osteoid matrix

36.5 Osteosarcoma of the Jaws

Definition: Osteosarcoma of the jaws is radiologically and morphologically similar to osteosarcoma of other skeletal regions; the main differences involve later development, a high mortality associated with the local disease, fewer incidences of metastases, and its extreme rarity.

Incidence: Osteosarcoma occurring in the jaws is rare, constituting only 2–10% of all osteosarcomas, with an estimated incidence of 0.2–0.3 per million population. Patients affected by osteosarcoma of the jaws are one to two decades older than their peripheral counterparts with an average age of 33–36 years. Men and women are affected nearly equally.



Location: About 55–70% of cases arose in the mandible, and the remaining cases in maxilla or in facial bones.

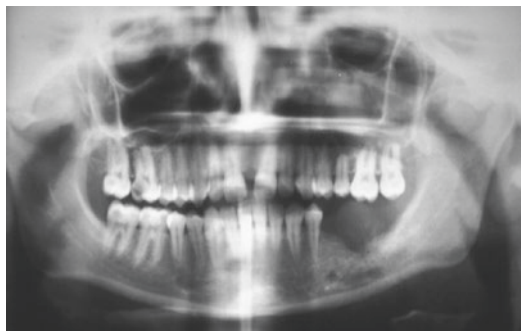
Clinical: Swelling is the most common complaint in patients with osteosarcoma of the jaws often accompanied with pain. The latency period between first symptoms and clinical presentation is around 4 months.

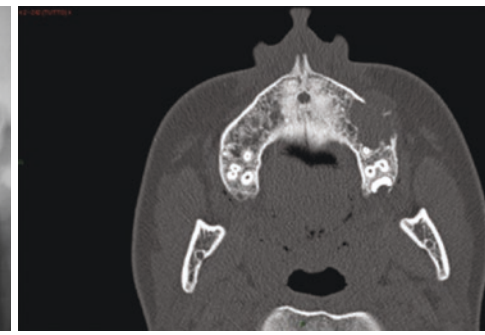
Imaging: Radiographically, osteosarcoma of the jaws presents as mixed radiolucencies reflecting the extent of matrix formation and mineralization. Aggressive features such as cortical permeation and periosteal reaction are generally present in conventional high-grade tumors.

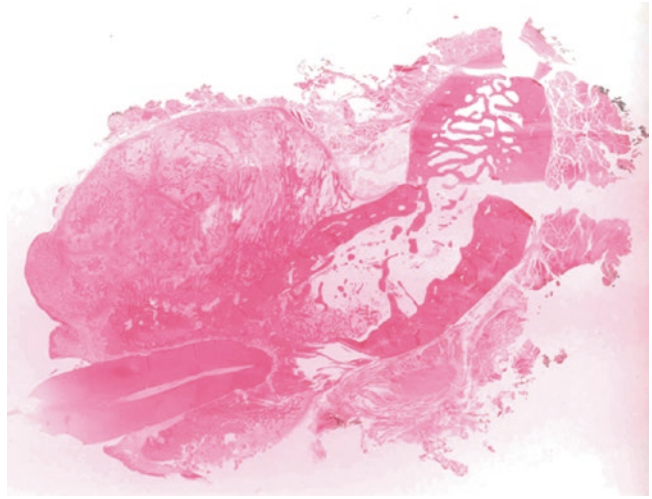
Histology: Histologically, the vast majority of osteosarcoma of the jaws are conventional high-grade tumors, demonstrating highly pleomorphic tumor cells producing a neoplastic bony matrix. The percentage of chondroblastic histotype is higher in osteosarcoma of the jaws than in other skeletal regions and can mimic chondrosarcoma. It should therefore be kept in mind that chondrosarcoma is exceedingly rare in the jaw bones, in particular in mandible. Osteosarcoma of the jaws should always be considered if cartilage is present in a gnathic biopsy and a fracture with callus formation can be ruled out. Immunohistochemistry with antibodies against SATB2 can help to confirm an osteoblastic lineage but is usually not required.

Almost all low-grade cases demonstrate a fibrous dysplasia-like morphology with only minimal atypia but unequivocal osteo-destructive growth. The nuclear immunohistochemical expression of MDM2 and the demonstration of *MDM2* gene amplification using FISH analysis can help to distinguish low-grade osteosarcoma from fibrous dysplasia.

Course and Treatment: The five-year overall survival and disease-free survival range from 50 to 65%, and from 60 to 75%, respectively. Osteosarcoma of jaws have a high tendency toward local relapse (mandible 39–70%; maxilla 15–53%). In osteosarcoma of the jaws, hematogenous metastases are reported to affect only 6–21% of patients after an average time of 17–23 months. Wide resection is therefore widely accepted as the mainstay of treatment with five-year survival rates reaching up to 75% without additional (neo-)adjuvant therapy. Regarding adjuvant treatment in osteosarcoma of the jaws, conflicting results have been reported but there is general consent that postoperative chemo- or radiotherapy cannot cure patients with incomplete resection in the predominant number of cases.





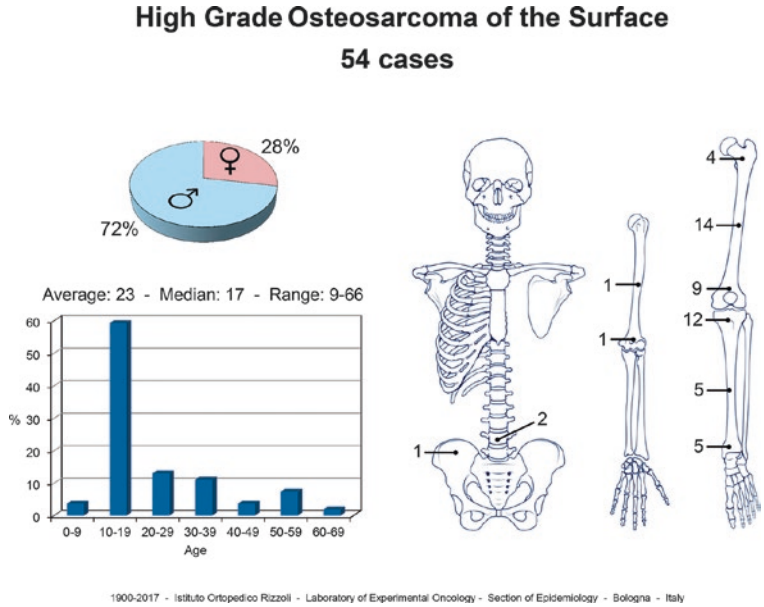


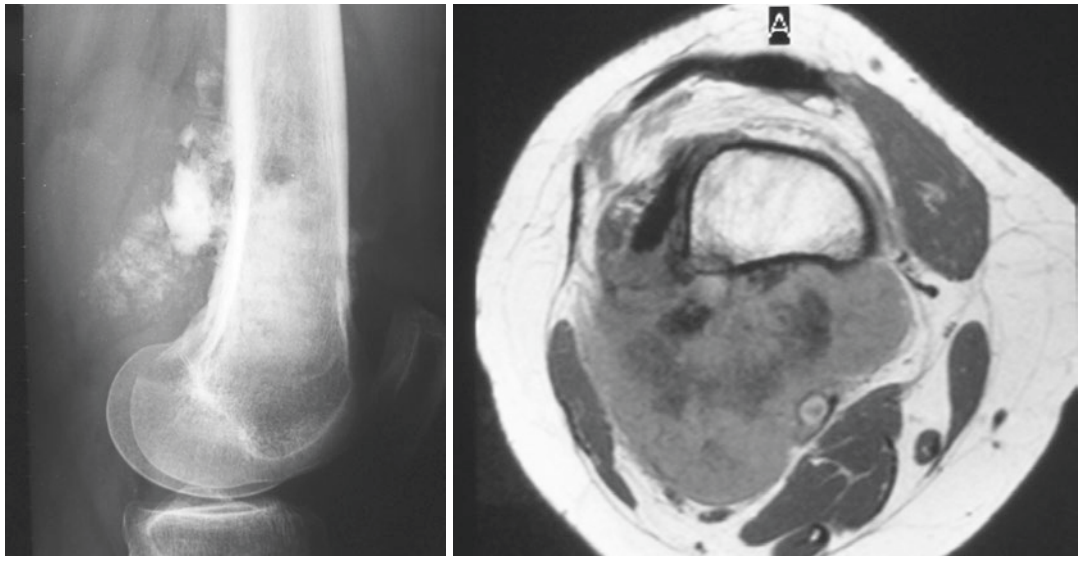
Panoramic radiograph and CT. Aggressive sclerotic and lytic tumour, distroying the cortex, invading the soft tissues, with perpendicular periosteal bone formations

36.6 High-Grade Osteosarcoma of the Surface

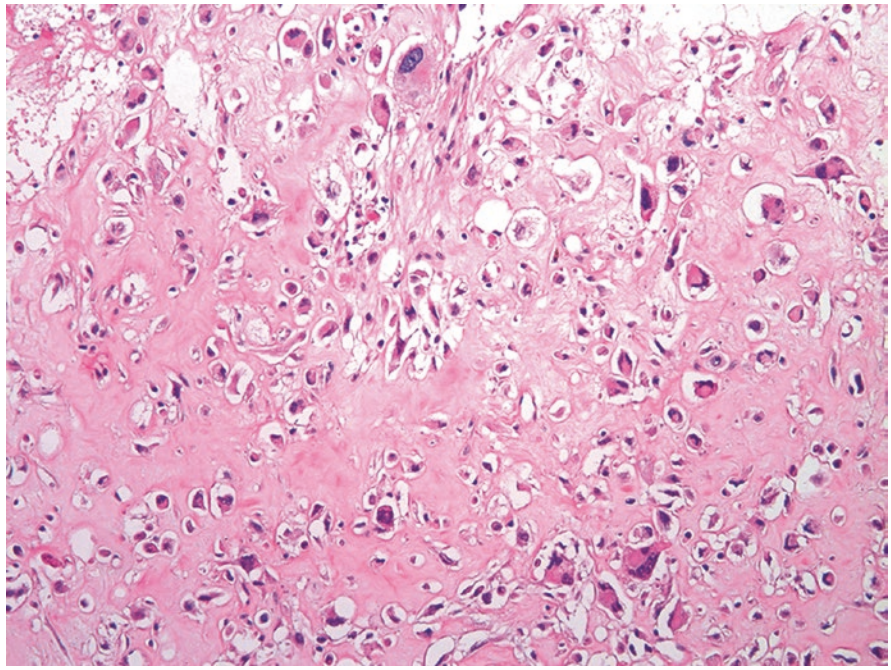
Definition: A high-grade OS arising on the bony surface with minimal involvement of the underlying cortex.

Apart from its site, it does not differ from the usual intramedullary OS in age, site, and histology. Imaging shows mixed non-mineralized and mineralized tumor matrix and some degree of periosteal reactive osteogenesis, but not the features specific of periosteal or parosteal OS. Histology is the same as in conventional OS. Treatment and prognosis also do not differ.





Lateral radiograph of the knee and axial T1 MR image. The tumor forms bone, mainly develops in the soft tissues, but starts from the cortex, which has a limited lysis. Minimal bone extension is visible on MR

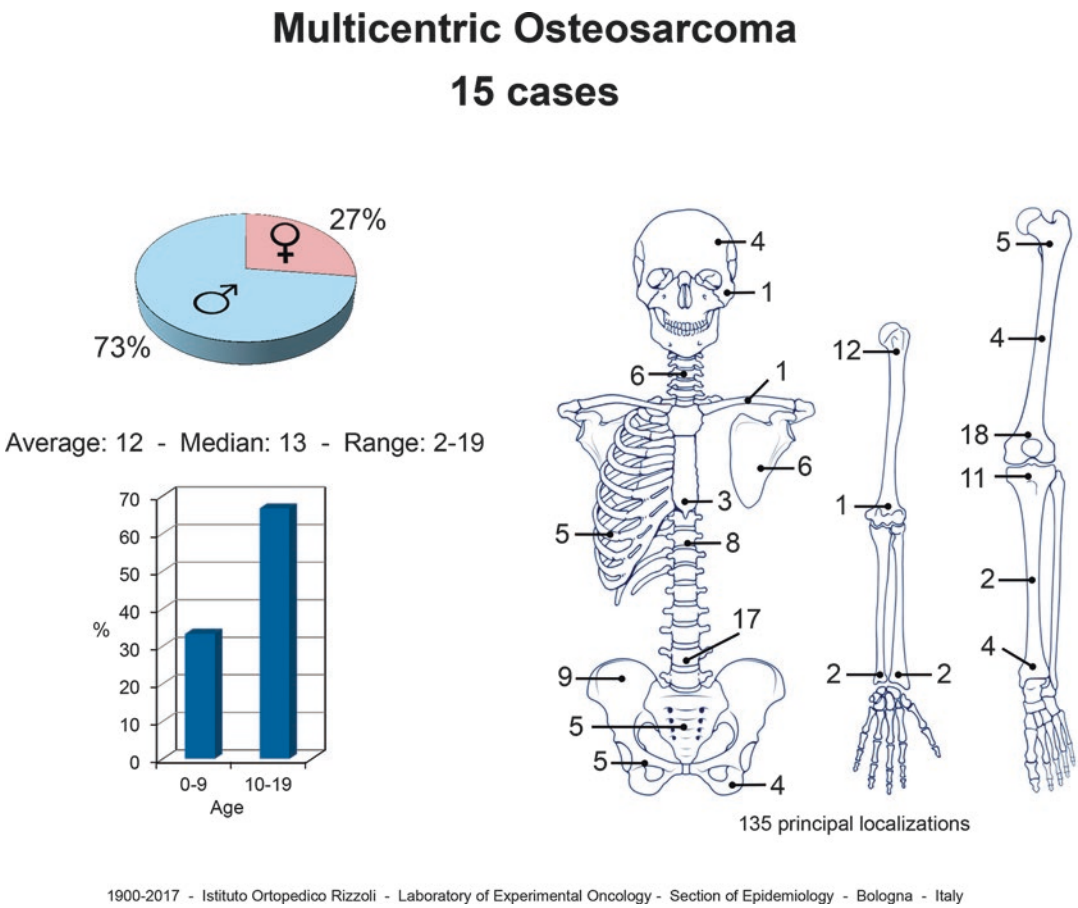


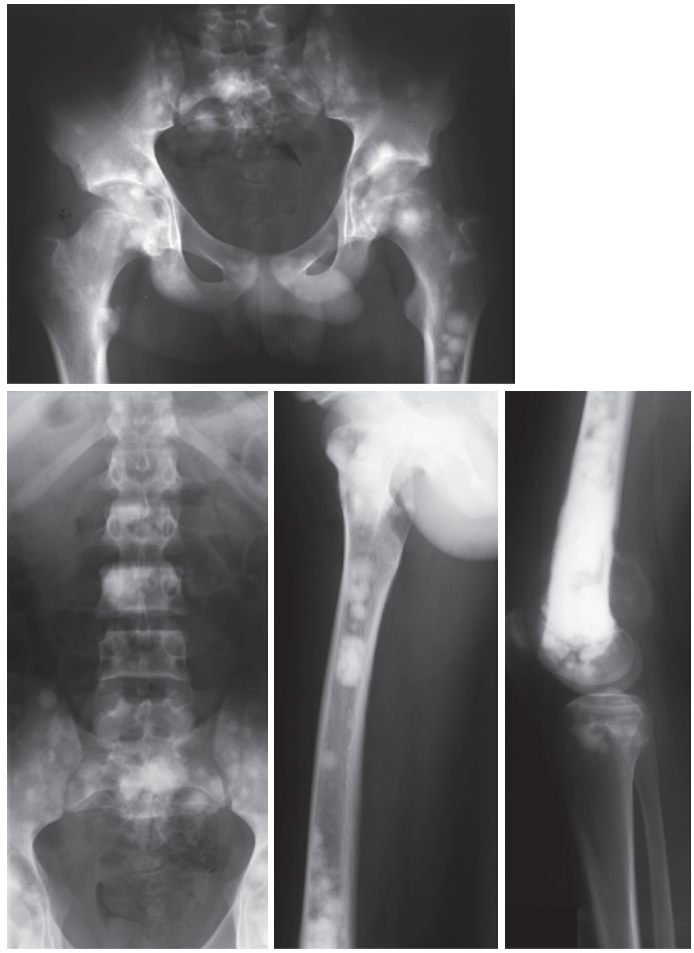
High-grade osteosarcoma identical to conventional central osteosarcoma, situated on the surface of bone. The majority are the osteoblastic variant

36.7 Multicentric Osteosarcoma

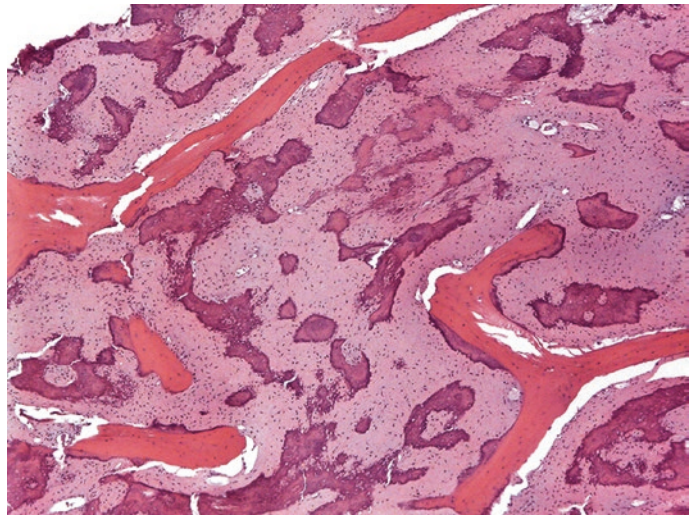
Definition: Almost synchronous appearance of multiple OS in the skeleton usually without pulmonary metastasis.

It is very rare (0.5% of all high-grade OS). Preferred age is from 5–15 years. (lower than usual OS). The number of foci varies from few to many, being distributed in the long bones but also in the trunk. They may involve locations, such as vertebrae, ribs and sternum, skull, hand and foot, epiphyses, where OS occurs very rarely. Usually one larger lesion is considered primary in the hypothesis that the others are metastatic deposits. All lesions are extensively sclerotic and do not easily breach the cortex. Histology is that of a usual osteoblastic generally extensively sclerotic high-grade OS. Whether it represents an early metastatic spread or a multicentric origin is unknown. The course is rapid and prognosis is regularly bad.





On radiographs, multiple mainly sclerotic lesions are easily detected. The epiphyseal involvement is frequent in this lesion

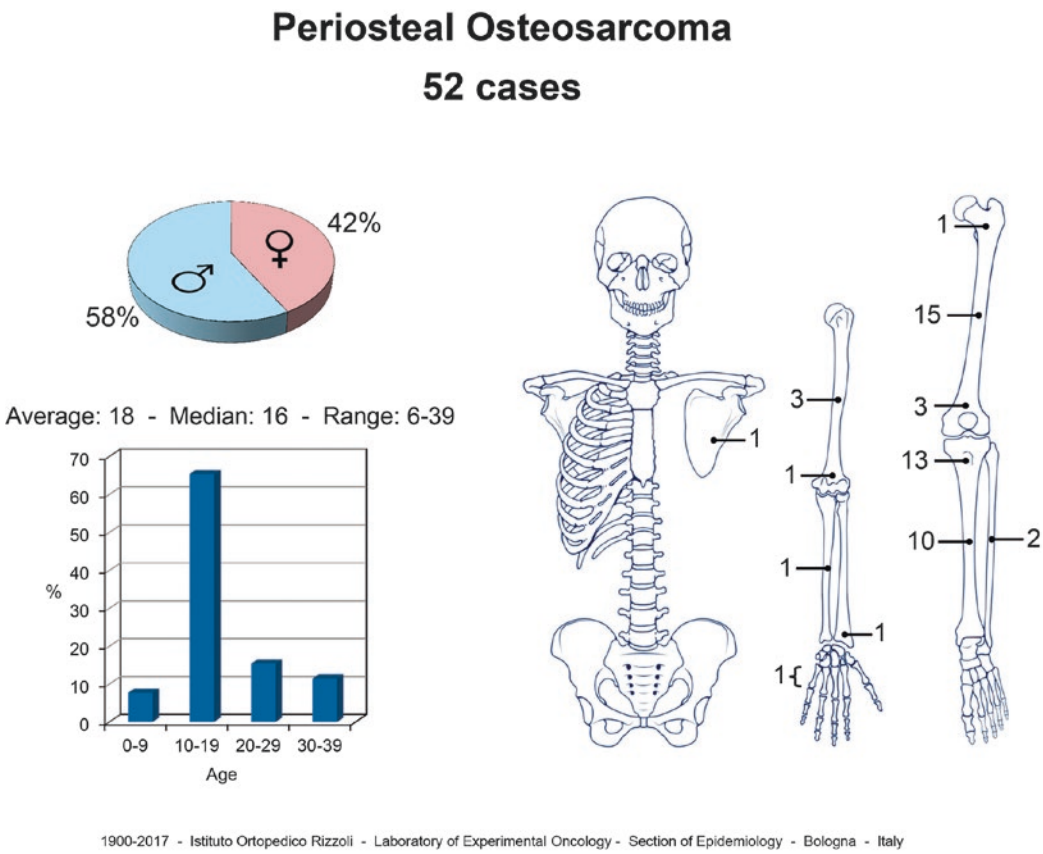


High-grade osteoblastic osteosarcoma usually extensively sclerotic with low cellularity and diminished cytological anaplasia when compared to classic osteoblastic osteosarcoma

36.8 Periosteal Osteosarcoma

Definition: It is a predominantly chondroblastic OS of intermediate malignancy, originating from the periosteum usually in long bone diaphysis.

Epidemiology: Periosteal OS is rare (1/2% of all OS). It has a preference for males, with prevalence in the second decade of life.



Localization: Tibia and femur. Less frequent in humerus, rare in fibula and other long bones. Usually located in the diaphysis, occasionally in the metaphysis.

Clinical: Palpable mass and moderate pain. Slower growth rate than in usual OS.

Imaging: Periosteal, fusiform, radiolucent mass, with well-defined borders. It usually contains spiculated radiodensities perpendicular to the cortex that is either intact or superficially eroded, sometimes with a Codman triangle. Typically, the medullary canal is uninvolved. This is better demonstrated by CT and MRI.

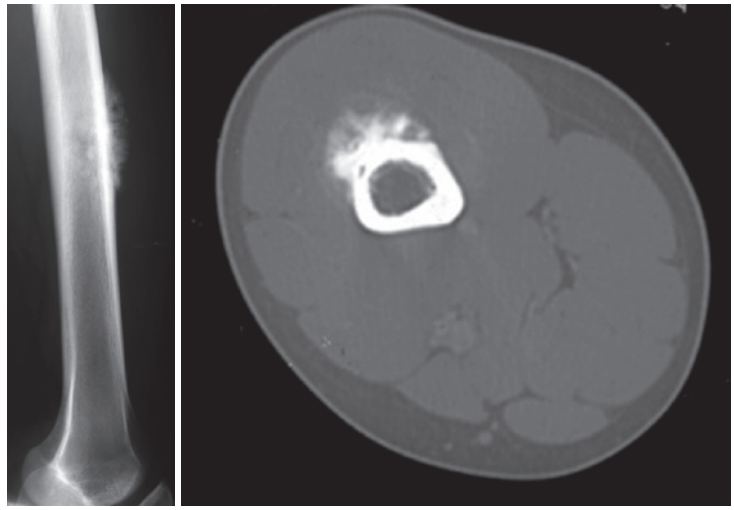
Histopathology: The cut surface of the tumor is soft to rubbery with a translucent aura. The tumor forms large lobules, separated by streaks of ossification perpendicular to the cortex. Tissue is mainly chondroblastic, being more cellular at the periphery, with spindle cells and lace-like osteoid, more chondroid at the center of the lobuli where the tumor is similar to a low- to intermediate-grade chondrosarcoma. At the bony interface, the tumor can permeate for a small thickness into the cortex.

Course and Staging: It generally grows slower than usual OS, but much less slow than

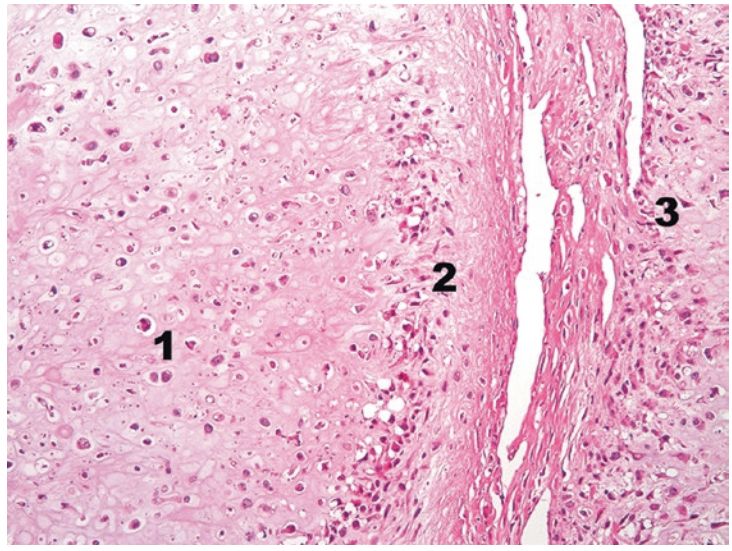
parosteal OS. The stage is I-A or I-B if there is intramedullary involvement.

Treatment and Prognosis: Treatment consists of en bloc resection with wide margins. Metastasis (lung) have been observed in about 15% of cases. Therefore, prognosis is good, after wide surgery and without chemotherapy.

Key points	
• Clinical	Young age, mild symptoms
• Radiological	Surface lesion, diaphyseal with radio-opacities
• Histological	Low-grade cartilaginous lesion, with increased cellularity and osteoid at the periphery of the lobules
• Differential diagnosis	Periosteal chondrosarcoma, high-grade surface osteosarcoma



Radiograph and CT. Diaphyseal lesion of the bone surface, forming bone, with thick perpendicular periosteal bone formations. The cortex is eroded. Bone marrow is not involved

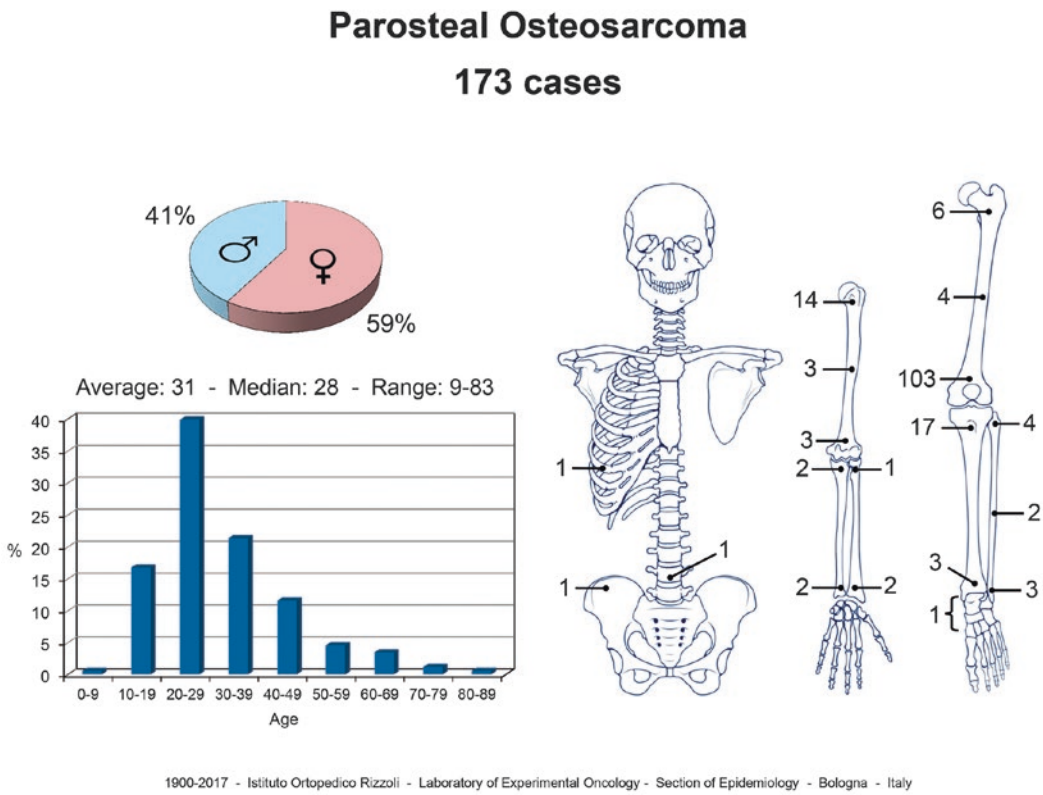


Predominantly chondroblastic tissue of intermediate malignancy that forms large lobules. (1) Chondroid cells. (2) Lake-like osteoid among malignant cells. (3) Spindle cells with minimal matrix at the periphery of the lobules

36.9 Parosteal Osteosarcoma

Definition: This OS originates at the surface of the bone, with abundant production of dense bone and low-grade anaplasia. Progression of malignancy in high-grade OS may occur in about 10% of cases, particularly those with multiple recurrences or those previously mistaken and treated as benign bone tumor.

Epidemiology: It is infrequent (5/6% of all OS). Slight preference for females. Usually it appears between ages 20 and 40, very rare before the end of growth.



Localization: Almost exclusive of the long bones, it originates from the metaphysis. Rare in the diaphysis and exceptional in flat bones. The most typical site is the distal metaphysis of the femur in its posterior aspect (60% of cases).

Clinical: No or slight pain. There is a bony hard mass. Duration of symptoms not infrequently exceeds 1, 2, or even 5 years. It is not uncommon to see patients having undergone one or more surgical excisions and presenting with a local recurrence.

Imaging: Due to slow growth, parosteal OS is usually seen when it is large. It is a lobulated mass of osseous radiodensity, fused to the cortex with a broad base that tends to wrap around the bone. Radiodensity is maximal near the implant base while the outer margin tends to be blurred. Detailed radiographies show a mesh of trabeculae ("steel-wool" pattern), from ground glass to ivory density. Toward the diaphysis, the medullary canal is usually not involved. In metaepiphyses, the thin cortex is frequently breached with extension to the cancellous bone. This involvement increases with malignancy and with the standing duration of the tumor and is appreciated by CT in 60% of cases. CT scan, MRI, and angi-

ography show the tumor adhering to or enwrapping the vascular bundle. Isotope scan is very hot.

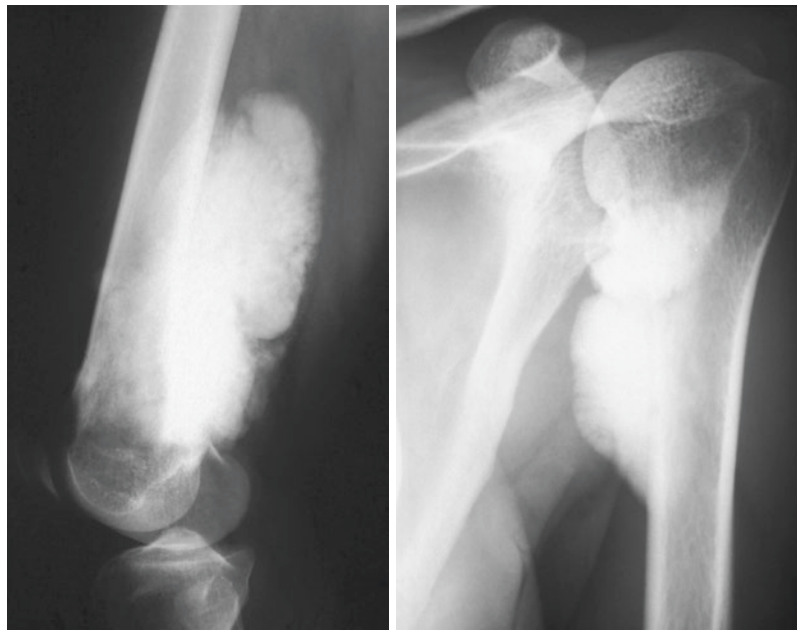
Histopathology: Parosteal OS is composed of spindle cells and collagen fibers, embedding osseous trabeculae. Occasionally cartilage may be associated. Cells form long sweeping fascicles with parallel nuclei. Trabeculae appear also as parallel streamers with broken cement lines as pagetic mosaic. Bone is formed by metaplasia from tumor cells (fibro-osseous metaplasia) and trabeculae may not show osteoblastic rimming. Parosteal OS is a low grade tumor but may progress in malignancy, and transform into a high-grade OS. It is indeed not rare to find areas of different histological grade in the same case. Metastasis (lung, skeleton) have usually the same pattern as the most malignant part of the primary, and are often densely sclerotic. The nuclear immunohistochemical expression of MDM2 and the demonstration of *MDM2* gene amplification using FISH analysis are useful to confirm the diagnosis.

Course and Staging: The course is usually slow. Parosteal OS is usually staged I-A or B. In dedifferentiated tumors, the stage is II.

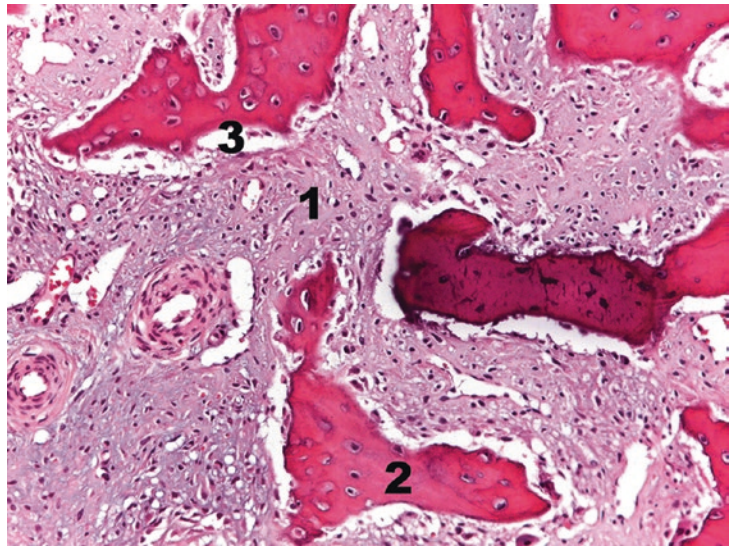
Treatment and Prognosis: Surgery must aim to wide margins. Hemicylindric resection is usually possible in the popliteal region, through a double approach (medial and lateral), elevating the quadriceps. More often, a complete segmental resection of the affected bone is needed. When the tumor impinges on the vascular bundle, wide margins may often require vessel resection and reconstruction. Chemotherapy is only indicated after progression in high-grade lesions and it is the same as that used in classic OS. Local recurrence is the rule after intralesional surgery. Metastasis may be seen mainly when the underlying bone is invaded. Metastasis are less common as compared to conventional OS, about 2–10% in low-grade parosteal OS, but rising to about 60–70% in high-grade dedifferentiated parosteal OS.

Key points	
• Clinical	Long history of mild symptoms, pain, and swelling
• Radiological	Surface, eburneus aspect
• Histological	Low-grade malignancy, spindle cells, bone production
• Differential diagnosis	Dedifferentiated parosteal osteosarcoma, high-grade surface osteosarcoma

Amplicons	
• MDM2 12q15	Gene amplification
• CDK4 12q13-14	Gene amplification

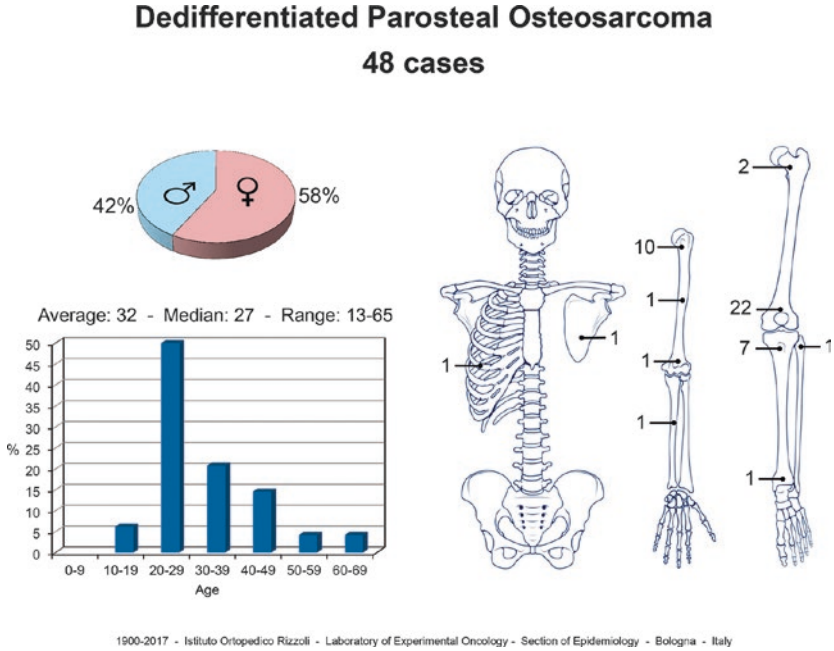


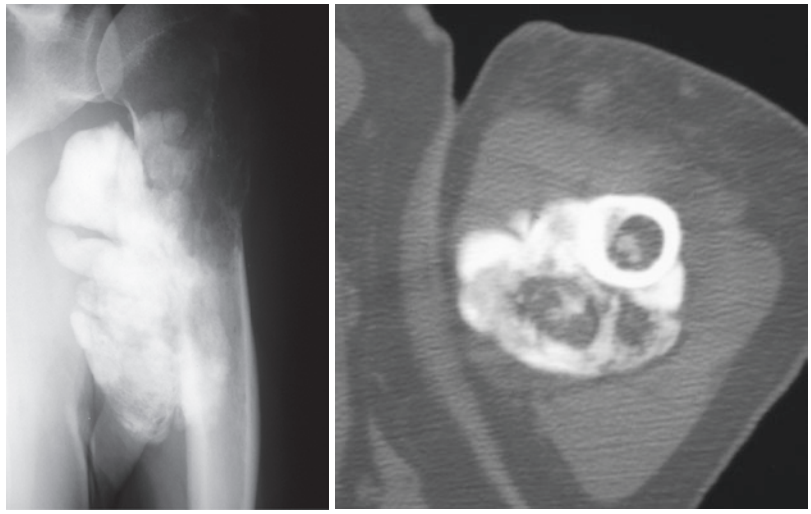
Radiographs. The tumors are homogeneous and sclerotic. They are attached to the bone



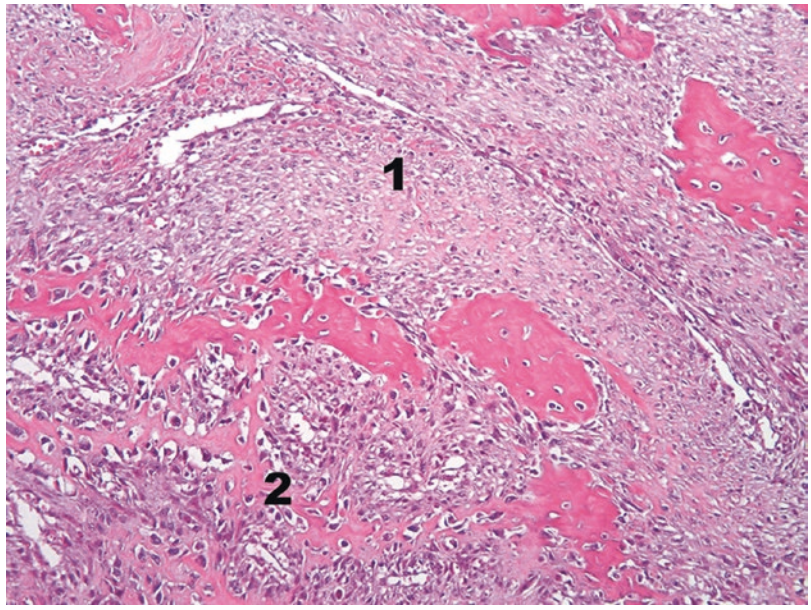
Histopathologic features are substantially represented by bony trabeculae enmeshed in a sarcomatous low-grade malignant spindle cell proliferation in a collagenous stroma. (1) Atypical spindle cells, like those of a low-grade fibrosarcoma. Nuclei are large, oval with low to mild pleomorphism. (2) Bone trabeculae arranged rather regularly. (3) Osteocytes do not present aspects of malignancy. The best place to find anaplasia is in the fibroblastic stroma and sometimes in the cartilage that is produced as caps over the bony portions of the tumor

Dedifferentiated parosteal osteosarcoma. In rare cases, within a typical parosteal osteosarcoma lytic areas (at imaging) can be found corresponding histologically to high-grade areas, showing therefore a dedifferentiation. Dedifferentiated parosteal OS is as malignant as conventional OS.





Radiograph and CT of the humerus. Typical parosteal osteosarcoma on radiograph. The lytic central areas on CT are very suggestive of dedifferentiation

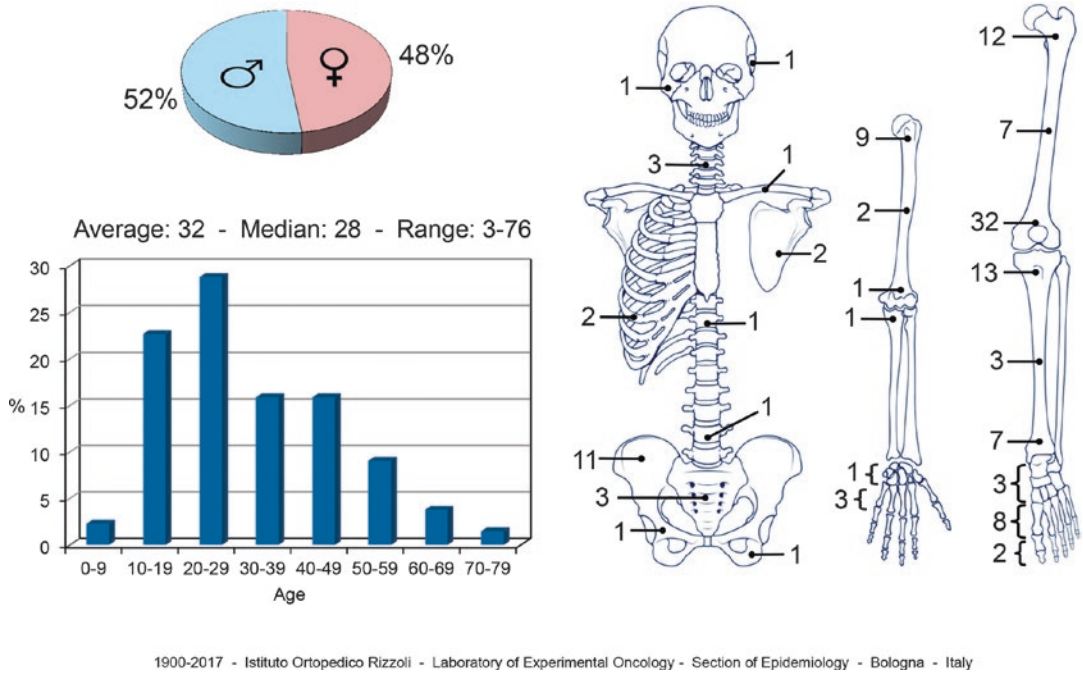


(1) Parosteal low grade osteosarcoma. (2) Dedifferentiation in high grade osteoblastic osteosarcoma

36.10 Central Low-Grade Osteosarcoma

Definition: It is an intramedullary low-grade bone producing tumor. It has been suggested to represent the central counterpart of parosteal OS.

Epidemiology: Rare (2/3% of all OS). There is no preference for sex. Age ranges from 10 to 60 years, the median being around 30.



Localization: Preferred sites are long bones, particularly distal femur and proximal tibia. Rare in flat bones; exceptions are hands and feet. It is usually centered in the metaphysis and, as it occurs mostly in the adult, it usually involves the epiphysis too.

Clinical: Mild to moderate pain and, less frequently, a moderate swelling. Clinical history is often of long duration. Pathologic fracture is rare.

Imaging: Usually, due to the slow course, tumors are large. The lesion appears mixed, lytic, and blastic. Even when lytic, some ground glass density can usually be found. Conversely, when it is sclerotic, some radiolucent areas are usually present. The bone contour may be expanded with a thin cortex that may present some discontinuity. In half of the cases, a soft tissue mass can be found, which can be either radiolucent or densely mineralized. Frequently, the tumor presents a coarse trabeculation similar to desmoid tumor of bone. A chronic periosteal reaction and thickening of the cortex are occasionally observed. Isotope scan is hot. CT and MRI are essential to define the extensions of the tumor.

Histopathology: Spindle cells producing collagen and bone. The tumor closely mimics the histological pattern of parosteal OS. The lesion is generally hypocellular. When osteogenesis is scarce, the tumor is similar to desmoid tumor or low-grade fibrosarcoma. Less frequently, it has the "Chinese characters" appearance of fibrous dysplasia. Bony trabeculae are generally parallel and composed of mature bone, differently from the woven bone of fibrous dysplasia. Occasionally foci of cartilage can be seen. The cells demonstrate slight atypia with few mitotic figures. Osteocytes of the bone trabeculae are normal. Almost regularly, the tumor has a permeative pattern. The nuclear immunohistochemical expression of MDM2 and the demonstration of *MDM2* gene amplification using FISH analysis are useful to confirm the diagnosis.

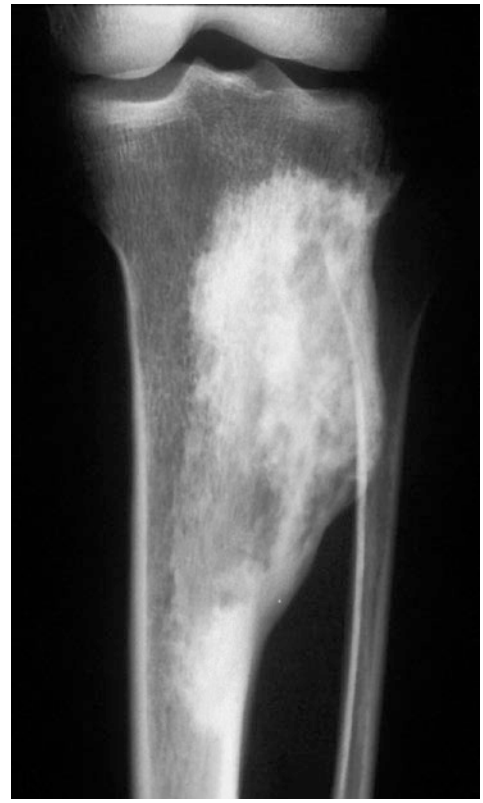
Course and Staging: The course is slow. In about 15% of cases, the tumor shows a progression of malignancy, transforming into a high-grade OS. The stage of the tumor is I-A or I-B. Transformed tumors become stage II.

Treatment: Intralesional or marginal excision is almost regularly followed by local recurrence. Thus, surgery must obtain wide margins, which is usually feasible with conservative resection. Chemotherapy is not indicated, except in case of progression in malignancy.

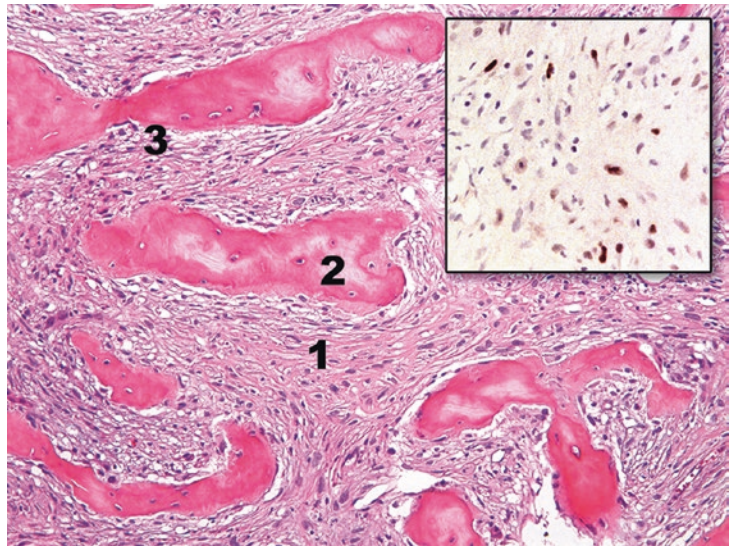
Prognosis: Metastasis (lungs) are reported in 10% of cases, and mostly in tumors that progressed in malignancy. They can occur many years after the onset of symptoms. Thus, prognosis is good, unless the tumor becomes a high-grade OS.

Key points	
• Clinical	Long history of mild symptoms. Usually pain
• Radiological	Central, mixed aspect
• Histological	Low-grade bone production
• Differential diagnosis	Osteoblastoma, high-grade osteosarcoma

Amplicons	
• MDM2 12q15	Gene amplification
• CDK4 12q13-14	Gene amplification



Radiograph. Heterogeneous lytic and sclerotic metadiaphyseal tumor. The lesion is well limited, but destroys the cortex

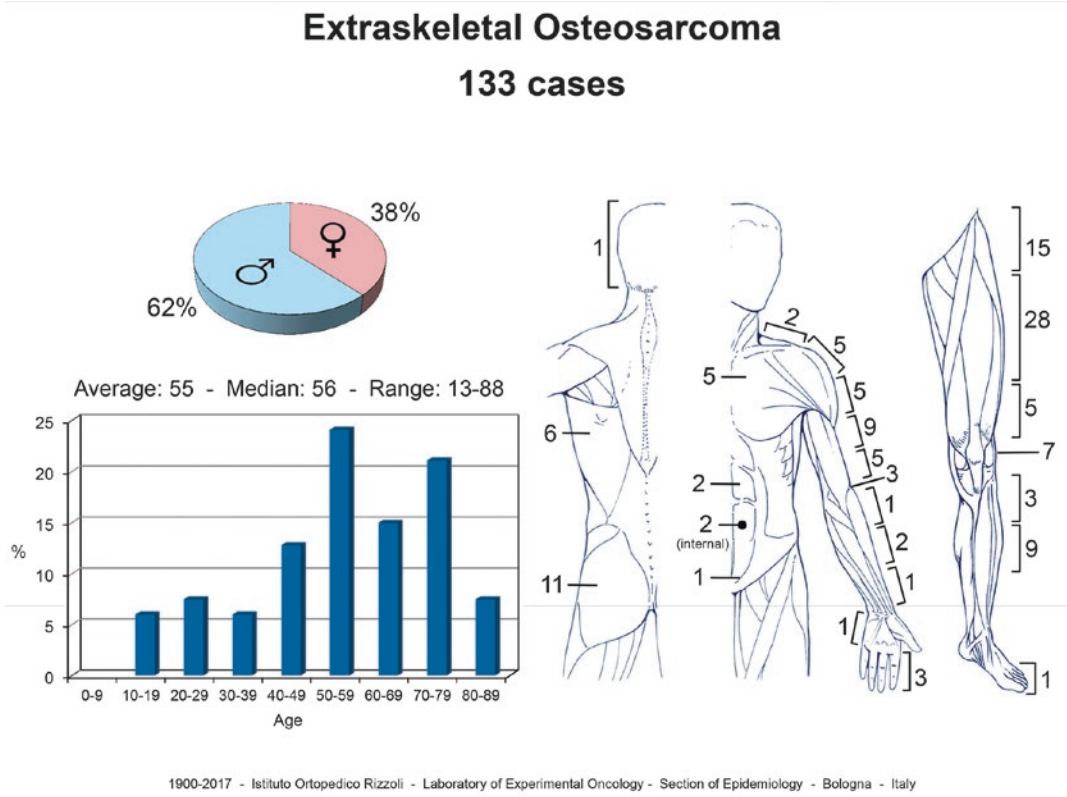


It histologically appears to be identical to parosteal osteosarcoma. (1) Cells surrounding the bony trabeculae are prevalently spindle-shaped, with aspects of minimal atypia. (2) Neoplastic trabeculae. (3) A regular row of osteblasts lining the trabeculae can be absent. Immunohistochemical nuclear positivity for MDM2 in the neoplastic cells *(inset)*

36.11 Extraskeletal Osteosarcoma

Epidemiology: Rare, males, 50–80 years.

Definition: A sarcoma arising in the extraskeletal somatic soft tissues in which neoplastic cells produce osteoid or bone matrix, or both.



Location: Deep soft tissues of the thigh and buttocks.

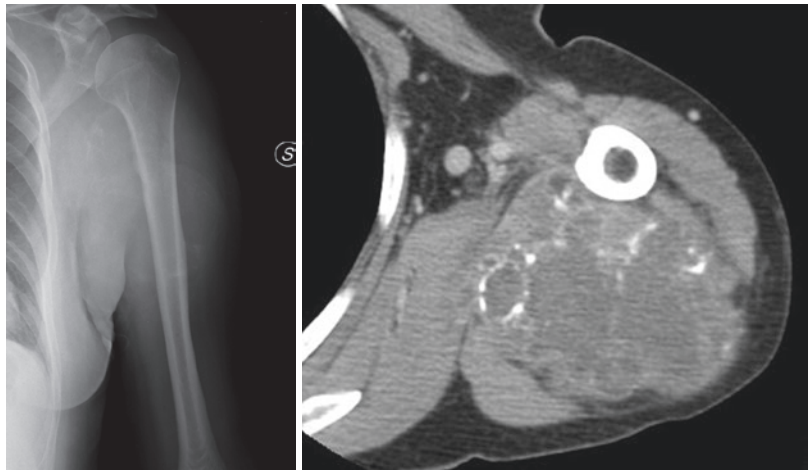
Clinical: Progressively enlarging painless mass.

Imaging: X-rays, CT, and MRI reveal a large deep-seated soft tissue mass with variable mineralization. By definition, these lesions do not arise from bone, but secondarily involve the periosteum, cortex, or medullary canal.

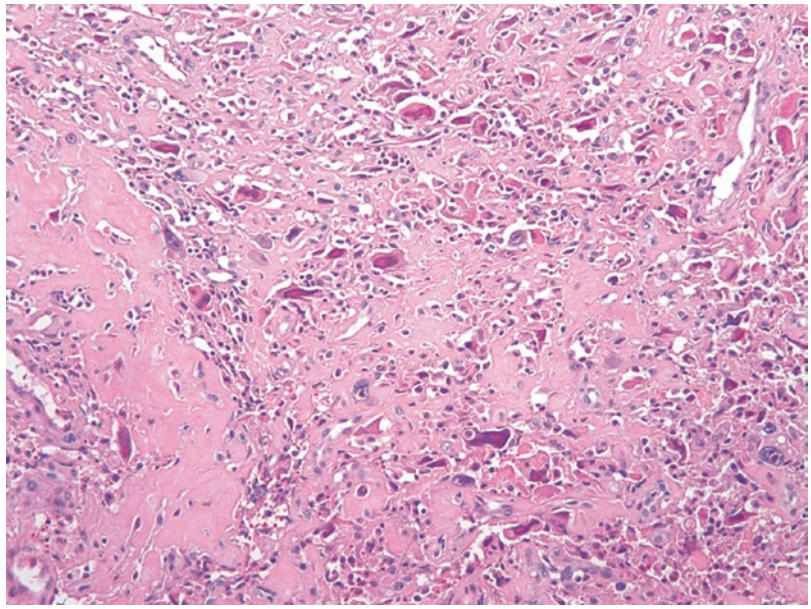
Histopathology: Highly cellular, mitotically active tumors. There is usually considerable nuclear pleomorphism with necrosis and lace-like eosinophilic osteoid outlining individual cells or clusters of cells. Mineralized osteoid (bone) is relatively uncommon. Lobules of malignant cartilage may be present. All histological variants of osseous osteosarcoma may be seen.

Course and Staging: High-grade tumors, poor prognosis, high rate of metastasis.

Treatment: Wide or radical excision with systemic chemotherapy.



Radiograph and CT after contrast media injection. Heterogeneous soft tissue mass containing irregular ossifications. The cortex of the humerus is not involved



Osteoid-producing malignant cells haphazardly organized, growing in the soft tissues

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