Diagnosis of Musculoskeletal Tumors and Tumor-like Conditions

Clinical, Radiological and Histological Correlations - The Rizzoli Case Archive

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This book is dedicated to
Prof. Mario Campanacci,
Prof. Mario Mercuri,
Dr. Gaetano Bacci, and
Dr. Marco Alberghini
who strongly supported the dissemination
of knowledge of musculoskeletal tumors.

Preface

This is a second book based on the data of the Rizzoli case archive, after the one published in 2014 with the title *Atlas of Musculoskeletal Tumors and Tumorlike Lesions: The Rizzoli Case Archive*.

In this new one, not only the epidemiological data are updated with the addition of about 7000 new lesions diagnosed in 5 years between 2013 and 2017, but also some chapters were added and/or modified based on the more recent discoveries in terms of clinical, histological, and molecular investigations.

In particular, small blue round cell tumors are deeply analyzed and presented, as the whole spectrum of vascular lesions, with the introduction of new entities, as for the presentation of a new classification for those sarcomas of bone in the past simply diagnosed as "malignant fibrous histiocytoma" or "fibrosarcoma." More space is also dedicated to soft tissue lesions and also to those more rare entities not discussed in the previous book.

What presented reflects the experience of the Rizzoli Orthopedic Institute in over 100 years of treatment of musculoskeletal tumors and tumorlike lesions. The first treated case dated September 28, 1900, and the archive contains the original material (clinical charts, imaging, paraffin blocks, and histological slides) of more than 47,000 cases (about 32,000 bone lesions and 15,000 soft tissue lesions).

Each single entity is presented multidisciplinarily, with the pertinent clinical, radiological, and histological correlations. The treatment is briefly reported for each entity. Other separate chapters analyze the more recent biomolecular findings useful for diagnosis, prognosis, and treatment.

The text reflects the improvements in knowledge of musculoskeletal tumors as presented during the yearly international course held at the Rizzoli Institute.

This course, promoted by Prof. Mario Campanacci since 1970, has seen the participation as guest professors of the major international experts in musculoskeletal lesions:

D. Dahlin (Rochester) 1974, 1984
W.F. Enneking (Gainsville) 1984, 1989–1990, 1992–1994, 1998, 2004
N. Jaffe (Houston) 1984
D. Springfield (Gainsville, New York, Boston) 1995, 1997, 2000, 2002–2007
J.M. Mirra (Los Angeles) 1996, 2008

H. Mankin (Boston) 1999
A.L. Schiller (Boston) 2002
D. Vanel (Villejuif-Bologna) 2003, 2005, 2007–2018
P.C.W. Hogendoorn (Leiden) 2006–2008
N. Athanasou (Oxford) 2008
M.C. Gebhardt (Boston) 2008–2017
F.H. Sim (Rochester) 2010–2011
M.I. O'Connor (Jacksonville) 2011–2013
J.M. Coindre (Bordeaux) 2011
M.J. Klein (New York) 2012–2017
N. Fabbri (New York) 2013–2017
J.H. Healey (New York) 2013–2014
A.P. Dei Tos (Treviso) 2013–2019
S. Cammelli (Bologna University) 2016–2019
R. Grimer (Birmingham) 2017–2019
R. Windhager (Wien) 2018–2019

Rizzoli collaborators to the Annual Course of the last years:

Patrizia Bacchini	Pathology
Alberto Bazzocchi	Radiology
Maria Serena Benassi	Biology
Stefania Benini	Biology
Franco Bertoni	Pathology
Roberto Biagini	Orthopaedics
Giuseppe Bianchi	Orthopaedics
Stefano Boriani	Orthopaedics
Laura Campanacci	Orthopaedics
Roberto Casadei	Orthopaedics
Marco Colangeli	Orthopaedics
Massimiliano De Paolis	Orthopaedics
Davide Maria Donati	Orthopaedics
Costantino Errani	Orthopaedics
Nicola Fabbri	Orthopaedics
Stefano Ferrari	Oncology
Andrea Ferraro	Orthopaedics
Tommaso Frisoni	Orthopaedics
Marco Gambarotti	Pathology
Alessandro Gasbarrini	Orthopaedics
Claudia Hattinger	Biology
Marco Manfrini	Orthopaedics
Emanuela Palmerini	Oncology
Piero Picci	Oncology
Alberto Righi	Pathology
Eugenio Rimondi	Radiology
Pietro Ruggieri	Orthopaedics
Katia Scotlandi	Biology
Massimo Serra	Biology

Eric Staals	Orthopaedics	
Daniel Vanel	Radiology	
Licciana Zanella	Biology	
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Bologna, Italy		Davide Maria Donati
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Bologna, Italy		Daniel Vanel
Padua, Italy		Angelo Paolo Dei Tos

Preface of the First Book

The Rizzoli Orthopedic Institute has a proud and dynamic history, with several very famous orthopedic surgeons over the past 120 years. Dr. Mario Campanacci was especially concerned with the diagnosis and therapy of bone and soft tissue tumors, particularly the malignant bone tumors, two of which are very common and often lethal to children, namely Osteosarcoma and Ewing's sarcoma. Beginning in the early 1970s he pioneered the use of chemotherapy in Europe for these two tumors. He organized a team of surgeons and oncologists, who helped make an amazing reversal for most of these unfortunate patients dying of lung metastases within 2 years, to the majority being cured. The Rizzoli Orthopedic Institute has an independent Department dedicated to The Treatment of Malignant Bone Tumors and they now achieve, for osteosarcoma and Ewing's sarcoma an over 70–75% cure rate for their patients (by cure is meant the total eradication of the cancerous tumor).

Prior to the era of modern chemotherapy in the treatment of malignant tumors of bone, most patients died, even if they were diagnosed within days of arriving at a hospital, and even if an amputation was quickly applied as a desperate measure. The reason they died despite appropriate rapid diagnosis and local ablative surgery, is that about 90% of these patients already had microscopic lung metastases, impossible to see on their initial admission to the hospital by standard radiology studies. Months later, however, the tiny, microscopic seeds of metastases to the lungs would grow to grossly visible proportions, and within months, the patient would succumb to death by suffocation. Thanks to the Rizzoli and other Research Institutes throughout the world, not only are most patients with Ewing's and Osteosarcoma now cured, but as amazingly the majority can be cured without even the need for amputation. It is now possible to maintain their limb simply by removing the tumor area en-bloc, with a margin of uninvolved tissue, and using a prosthetic replacement, after a course of pre-operative chemotherapy. The Rizzoli Institute also stands at the cornerstone of these superb surgical advancements in prosthetic replacement techniques. As an effect of these outstanding results the Rizzoli Institute Bone Tumor Treatment Department is now, not only the premier treatment center for such tumors in Europe, treating some 80% of all such malignant tumor patients in Italy, but it may well be the largest and most renowned such treatment center in the world.

Another of the main goals of the Rizzoli has always been centered around the education of young doctors to become some of the finest Orthopedic Surgeons, Oncologists, Pathologists and Radiologists in the world with

respect to all aspects of Orthopedics, and especially for the specialty in the Bone Tumor field. Bone tumors are very rare, representing only about 1% of all benign and malignant tumors. It is extremely important that major bone tumor centers such as the Rizzoli exist, where patients afflicted by very rare tumors can be sent and where the physicians who will, or are directly caring for these patients obtain the necessary training and experience. A standard community hospital serving a local population of some 100,000 individuals will only see about 1 patient per year with a malignant bone tumor. In my opinion, to begin to understand how to accurately diagnose (with over 95% accuracy) and treat these tumors adequately requires a physician to have personally seen at least 500 such patients. In a general hospital that could take 500 physician years, well beyond the lifetime of any ordinary person I know. But at the Rizzoli it is possible for diagnosticians, treating physicians and student doctors to be involved with some 500 bone tumor patients in 2–3 years.

Which now brings us to the "Rizzoli Syllabus" which you now hold in your hands. This is a truly remarkable primer for students and even trained physicians to study the essentials of bone tumor diagnosis and treatment of virtually all of the benign and malignant tumor entities of bone. And for the first time in my experience, this syllabus also includes considerations of basic biology concepts of Giant Cell Tumor, Chondrosarcoma, Osteosarcoma and several other important basic science oriented topics. Many of these topics have been pioneered in the Rizzoli Research Institute under Dr. Piero Picci's direction. In addition, very important principals of Staging and Radiology have been added to The Syllabus, vital to an overall understanding of the treatment and diagnosis of tumors of the bone.

I have been involved with writing my own syllabi for The UCLA Orthopedic residents in years past, and I have seen a number of other syllabi over the years, but for a Bone Tumor Syllabus, this is by far the best I have ever seen published. It is informative, it is accurate, it is concise, and it is beautifully illustrated. The authors are to be highly commended for their efforts and dedication to teaching, from which a new generation of highly competent Bone Tumor Specialists will emerge.

Los Angeles, CA, USA Joseph M. Mirra

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Part I

Introduction

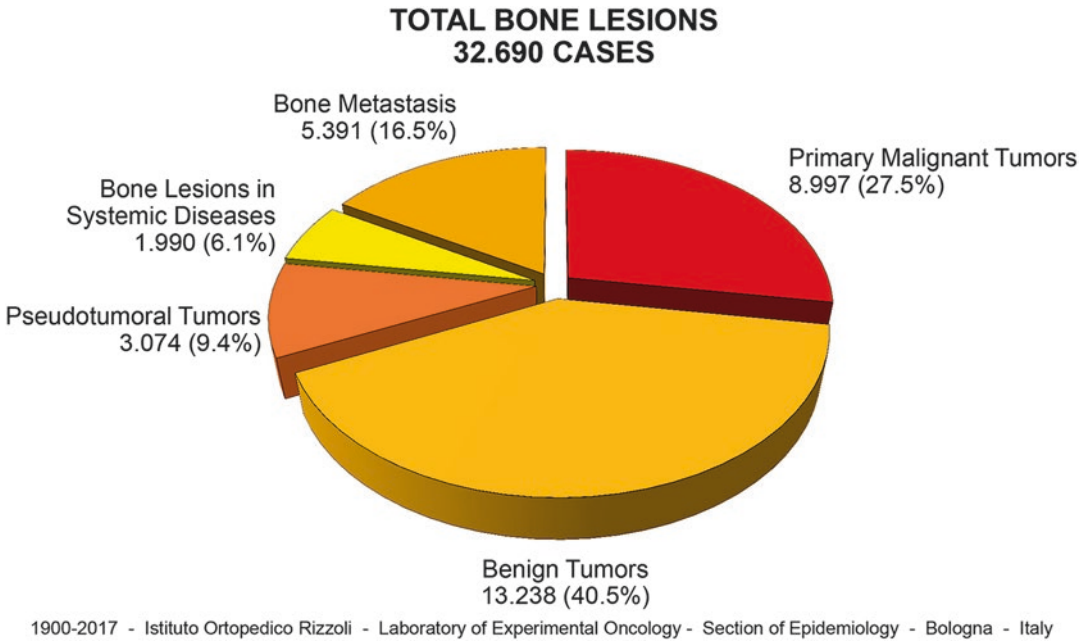
Epidemiology of Bone Lesions

1

Piero Picci

There are no data regarding epidemiology of pseudotumoral and benign bone lesions. Most are incidental findings during examinations for other conditions. As for soft tissue lesions, it is generally accepted that benign conditions are 100 times more frequent than malignant primary bone tumors.

Figures from the Rizzoli archive are not representative of the true incidence, as they represent cases treated in a specialized center and therefore biased for more severe or complicated cases. More reliable are data regarding age, sex, and sites of presentation.



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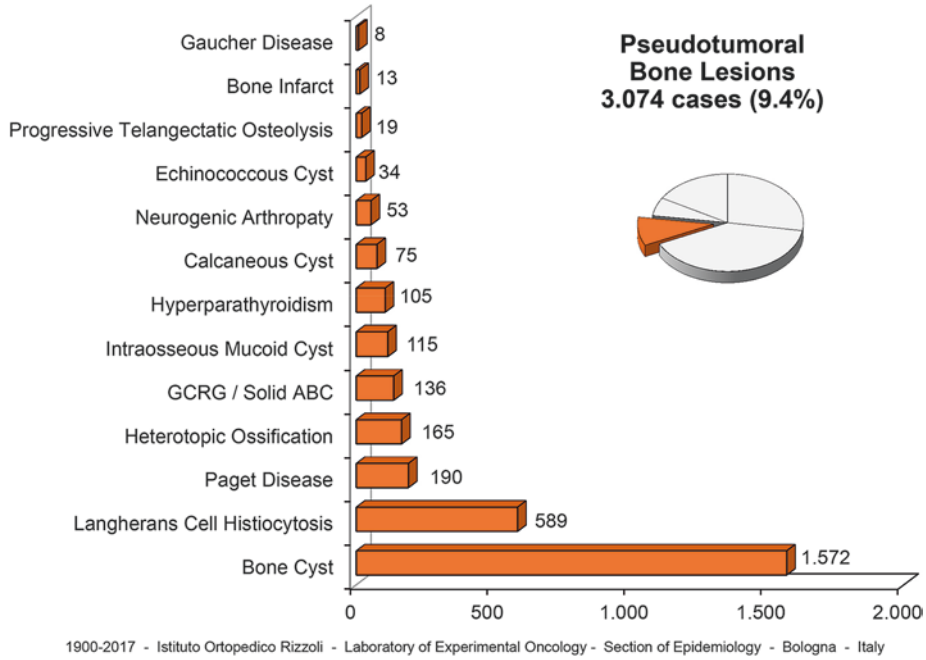
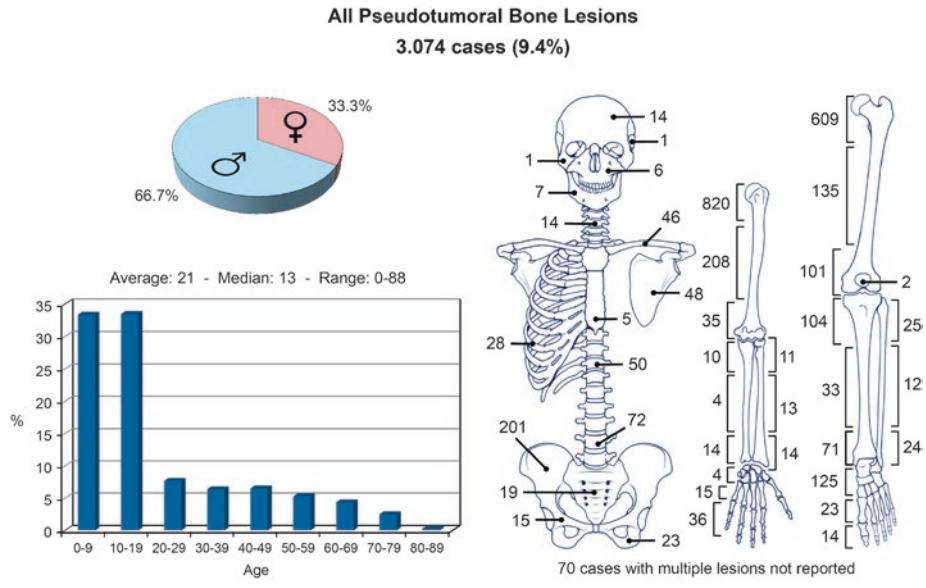
1.1 Pseudotumoral Lesions

The male/female ratio is 2:1. Typically, they affect children and teenagers with a median age of 13 years. In fact, the most represented entities are simple bone cyst and Langherans cell histiocytosis which are typical of young age. Aneurysmal bone cyst, once included in pseudotumoral lesion, is now considered a benign entity, due to the detection of a specific translocation.

These two entities together represent more than 70% of all pseudotumoral lesions. Preferred sites are metaphysis of long bones, especially proximally.

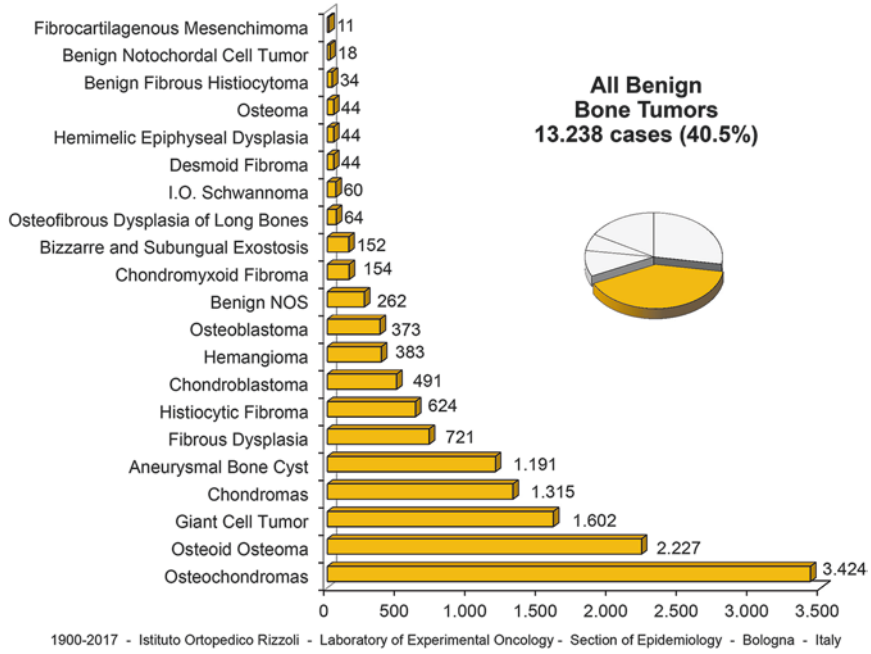


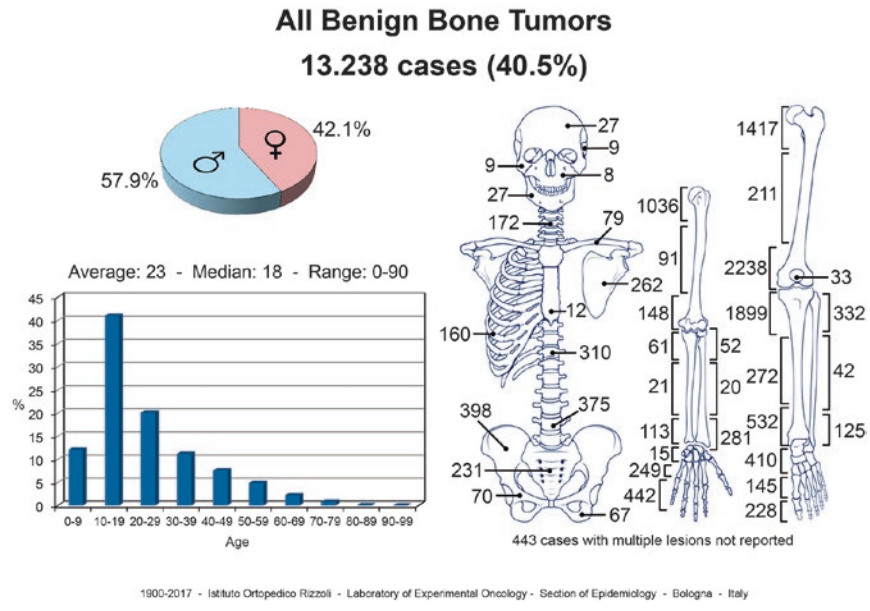


1.2 Benign Tumors

The male/female ratio is 1.5:1. Age comprises the first four decades of life, with a median age of 18 years. They are very rare in the elderly.

The most represented are benign chondroblastic lesions (osteochondromas and chondromas) and osteoid osteoma. Aneurysmal bone cyst is now considered a benign entity, due to the detection of a specific translocation. Preferred sites are in bone around the knee, but practically all bones may be affected with localizations in flat bones that are not rare.





1.3 Primary Malignant Tumors

More reliable epidemiologic data are available for primary malignant bone tumors or with a better definition of bone sarcomas. Incidence is usually evaluated including soft tissue sarcomas. Global incidence reported is around five new cases/100,000 inhabitants/year. This incidence is similar in different countries with about 3,000 new cases per year in Great Britain and Italy (with 60 million inhabitants) and about 12,000 new cases in the USA (with about 300 million inhabitants).

This incidence of bone sarcomas is about 0.2% of all neoplasms.

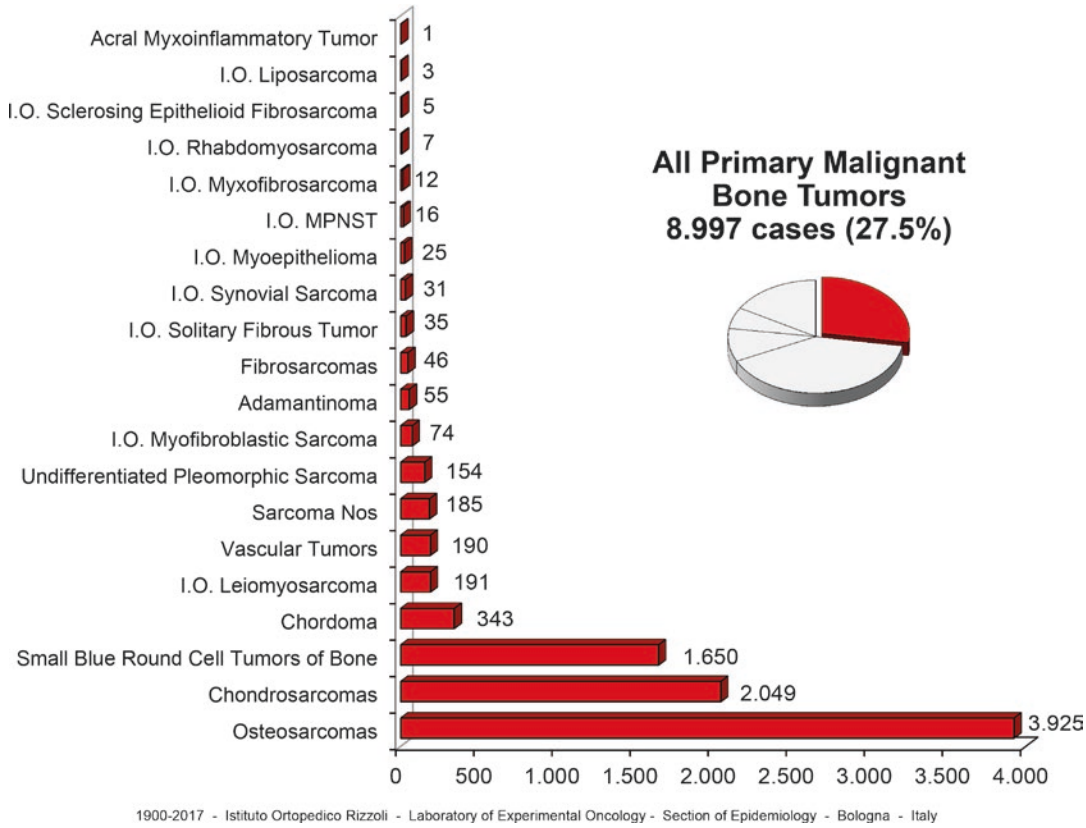
Specifically regarding bone sarcomas, their incidence is considered 1/5–1/6 of all sarcomas, with an incidence of 0.8–1 new case/100,000 inhabitants/year.

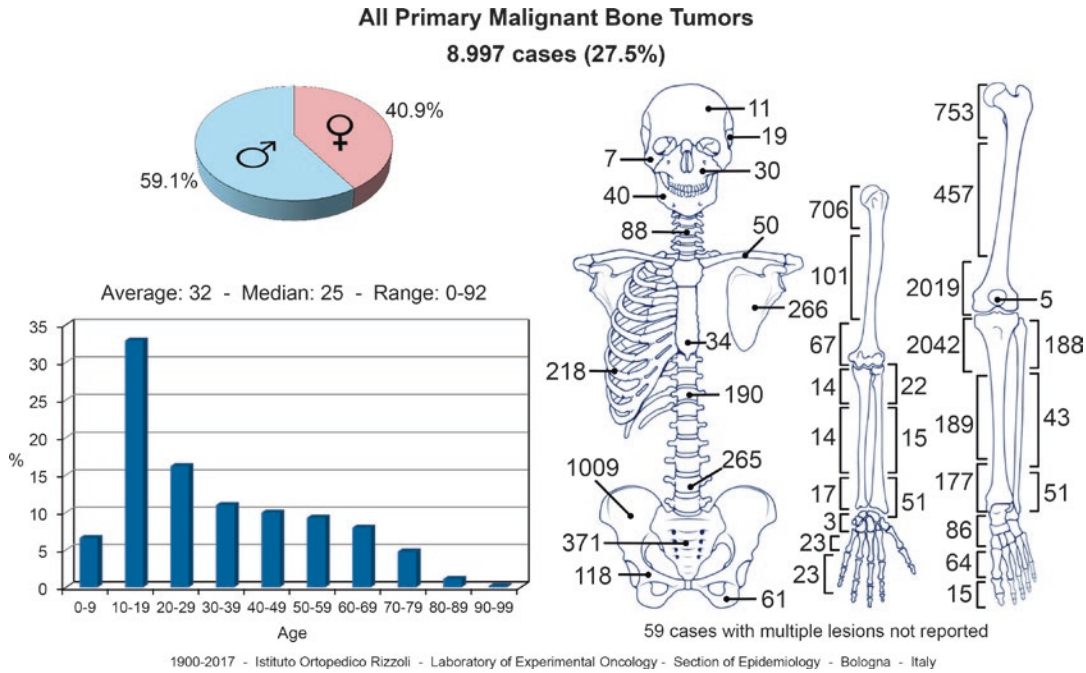
The Rizzoli archive figures are more reliable in comparison to nonmalignant conditions. The only bias is related to the lack of registration of those localizations generally not treated at an orthopedic hospital as the trunk and skull.

The male/female ratio is again 1.5:1, as for the benign lesions. Median age is 25 years, with a peak in the second and third decades of life. Incidence is also evident and constant for all the adult age.

Osteosarcomas are the most frequent with an incidence of about 0.2 new cases/100,000 inhabitants/year.

A similar incidence is also reported for chondrosarcomas, followed by Ewing sarcoma with an incidence considered one-half in comparison to osteosarcomas. All other entities are very rare. Affected sites are the same as those of benign tumors.



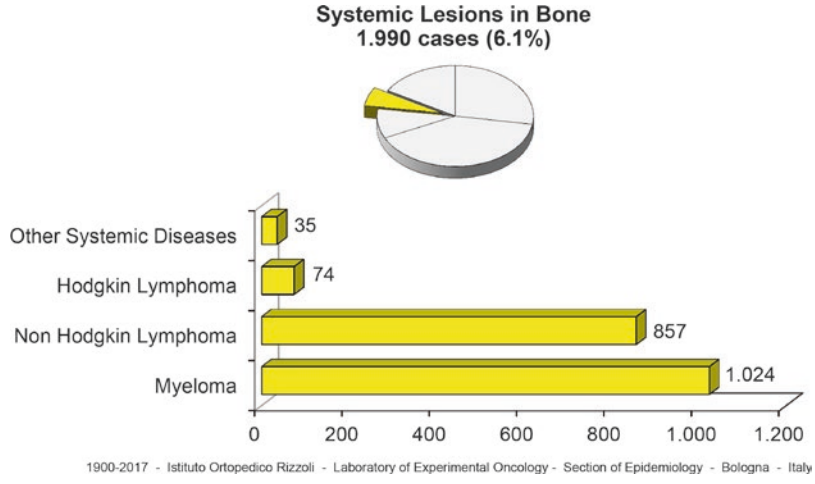


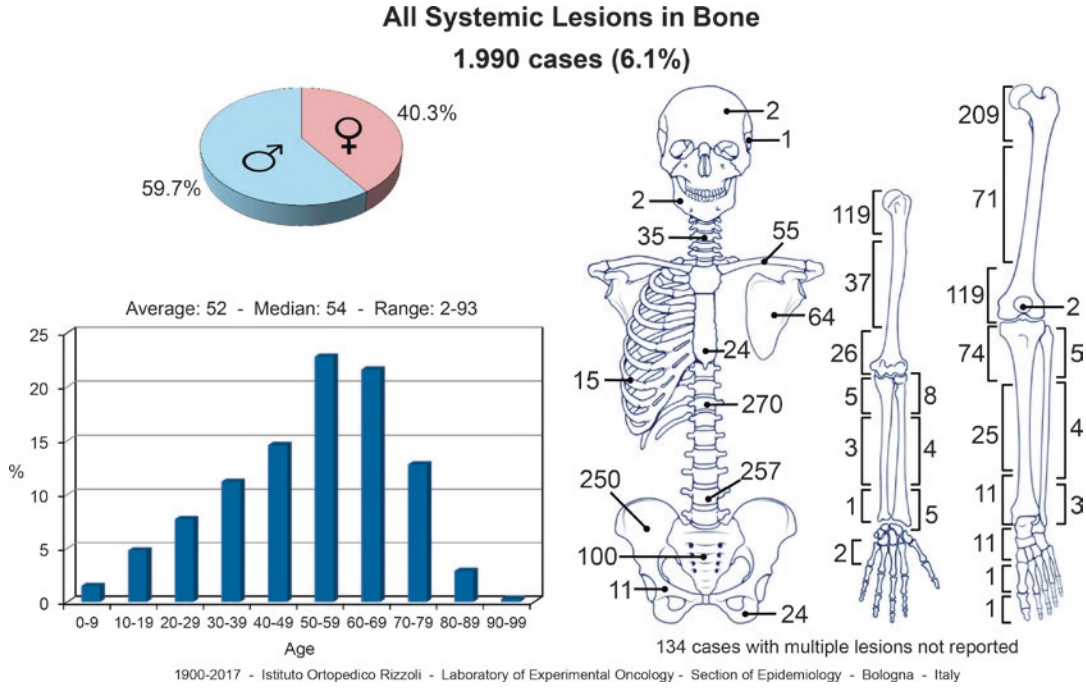
1.4 Systemic Lesions and Metastasis

The figures reported in this book, and therefore the incidence, reflect only those lesions requiring orthopedic attention and treatment and therefore are non-representative of the true data.

Systemic lesions comprise mainly myeloma and non-Hodghin lymphomas, rarely Hodgkin disease or leukemic disorders.

The male/female ratio is again 1.5:1. Median age is 54 years, and these lesions are very rare before the adult age.





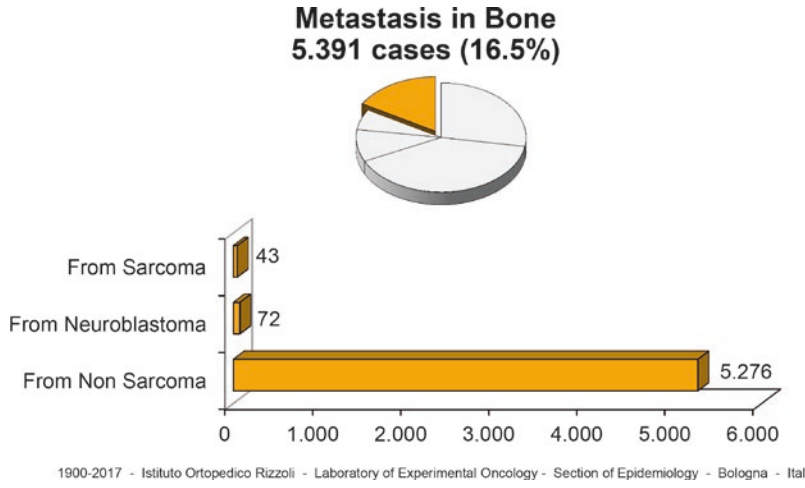
Metastasis is by far more frequent than primary bone sarcomas, but considering that they do not always deserve orthopedic treatment, they are therefore underestimated in this book.

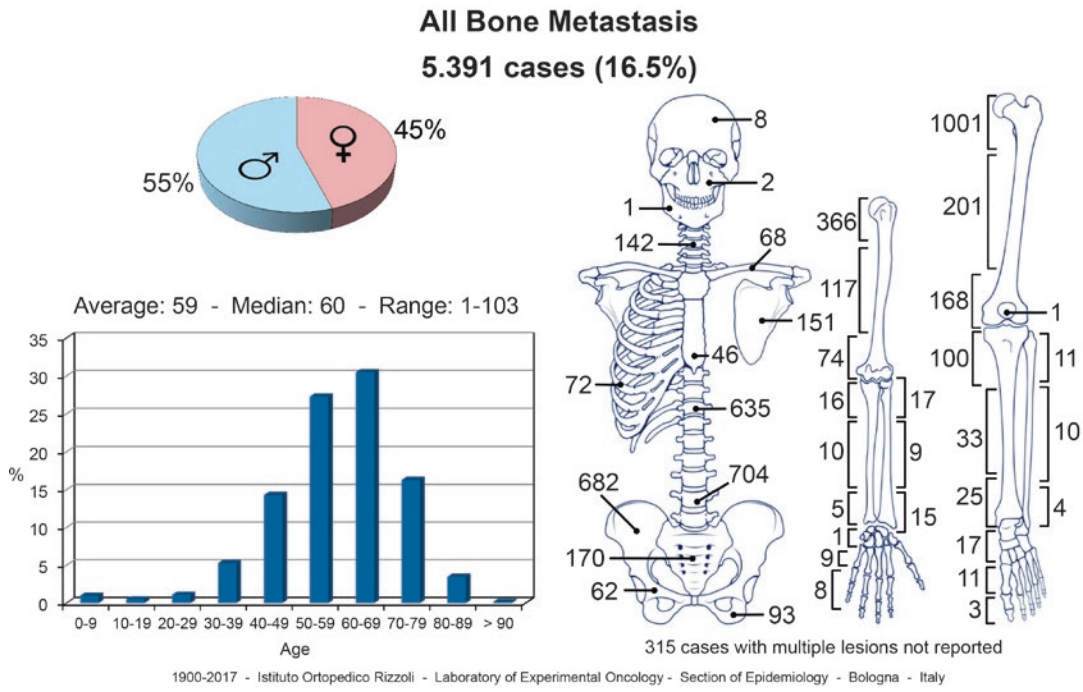
The prevalence is slightly higher in the male gender, with a median very advanced age (60 years).

The site of origin of the tumors are represented by breast, kidney, and lung in more than 60% of the all cases, followed by gastroenteric, prostate, and thyroid in another 20% (see table in dedicated chapter).

Rarely the bone metastases may originate from sarcomas. In our experience, in our series this is due in 60% of the cases from leiomyosarcoma of the uterus.

Bone metastasis from neuroblastoma, typical of infancy with a median age of 6 years, must be considered in the differential diagnosis with small blue round cell tumors of bone.





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2 Classification of Primary Bone Lesions

Piero Picci, Marco Gambarotti, and Alberto Righi

Primary bone tumors are classified on the base of their histological differentiation, as reported in the following table. Thay are divided into "benign" (with a limited capacity of local recurrence), "intermediate" (locally aggressive: local recurrence, also in a destructive way; rarely metastasizing: as above also with possible distant metastasis in occasional cases, not predictable on the basis of the morphology), and "malignant," the latter furtherly divided into low-grade and high-grade malignant.

Classification of primary bone tumors (WHO 2013)

Histogenesis	Benign	Intermediate (locally aggressive and/or rarely metastasizing)	Malignant [(∗) low-grade lesions if not dedifferentiated]
Fibrogenic and fibrohistiocytic	Histiocytic fibroma Benign fibrous histiocytoma	Desmoplastic fibroma	Fibrosarcoma
Chondrogenic	Osteochondroma Hemimelic epiphyseal dysplasia Enchondroma Periosteal chondroma Osteochondromyxoma Subungual exostosis Bizarre parosteal osteochondromatous proliferation Synovial chondromatosis	Chondromyxoid fibroma Chondrosarcoma grade 1 Chondroblastoma Fibrocartilaginous mesenchymoma	Chondrosarcoma grade 2 Chondrosarcoma grade 3 Dedifferentiated chondrosarcoma Mesenchymal chondrosarcoma Peripheral chondrosarcoma (∗) Periosteal chondrosarcoma (∗) Clear cell condrosarcoma (∗)

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Histogenesis	Benign	Intermediate (locally aggressive and/or rarely metastasizing)	Malignant [(∗) low-grade lesions if not dedifferentiated]
Osteogenic	Osteoma Osteoid osteoma	Osteoblastoma	Low-grade central osteosarcoma (∗) Conventional osteosarcoma Telangiectatic osteosarcoma Small-cell osteosarcoma Secondary osteosarcoma Parosteal osteosarcoma (∗) Periosteal osteosarcoma (∗) High-grade surface osteosarcoma
Osteoclastic giant cell rich	Giant cell reparative granuloma	Giant cell tumor of bone	Malignancy in giant cell tumor
Vascular	Hemangioma Lymphangioma	Epithelioid hemangioma	Epithelioid and other hemangioendothelioma (∗) Angiosarcoma
Nervous	Schwannoma Neurofibroma		MPNST
Lipogenic	Lipoma		Liposarcoma
Myogenic	Leiomyoma		Leiomyosarcoma
Notochordal	Benign notochordal cell tumor		Chordoma (∗)
Hematopoietic neoplasms			Primary non-Hodgkin and Hodgkin lymphoma Plasmocytoma of bone/ plasma cell myeloma
Tumors of undefined neoplastic nature/ miscellaneous tumors	Simple bone cyst Fibrous dysplasia Osteofibrous dysplasia Chondromesenchymal hamartoma Rosai-Dorfman disease	Aneurysmal bone cyst Langerhans cell histiocytosis Erdheim-Chester disease	Adamantinoma (∗) Ewing sarcoma Undifferentiated pleomorphic sarcoma

3 General Principles of Bone Pathology

Marco Gambarotti and Alberto Righi

Bone tumors are among the rarest neoplasms in humans. Bone sarcomas account for 0.2% of all neoplasms arising in the human body. Considering that and the fact that more than 40 malignant histological types have been described, it is reasonable to think that only specialized centers can have enough experience in managing these neoplasms. The peculiar "multidisciplinary-team" approach is mandatory in bone tumors, in order to avoid dramatic mistakes in the diagnosis and treatment of these tumors. The pathologist dealing with bone must follow a diagnostic flowchart that starts from the accurate collection of clinical information, followed by the careful examination of the imaging, then the decision about the kind of diagnostic procedure to apply, and finally the histological diagnosis. All these steps must be shared with the other colleagues of the team, such as the orthopedic surgeons, the radiologists, and the oncologists. Examining in detail every single step of the diagnostic approach, analysis of clinical features, such as patient age, symptoms and anatomic location of the lesion, are necessary for a preliminary assessment of the lesion. Bone tumors like Ewing sarcoma and osteosarcoma usually occur in young patients. Tumors like chordoma, myeloma, and chondrosarcoma are typical of adults or elderly patients. When osteosarcomas occur in patients older than 50, they are frequently secondary to pre-existing bone conditions, such as Paget's disease, bone infarcts, or arising after radiation therapy. Symptoms and features are frequently of great clue for diagnosis. Pain during night that can be treated with salicylates is typical of osteoid osteoma; the presence of fever favors for the diagnosis of Ewing sarcoma rather than lymphoma. Laboratory tests can also be very useful; for example, the blood levels of parathormone are the key features for the diagnosis of hyperparathyroidism. The site of the tumor within the bone and the specific bone segment are very important, as some tumors occur usually in the epiphysis, such as giant cell tumor, chondroblastoma, and clear cell chondrosarcoma, while other tumors are centrally located, and others are eccentrically located in the bone cortex; others, such as adamantinoma occur almost exclusively in the tibial diaphysis. In low-grade chondroid lesions, the site of the lesion is very important for a correct interpretation of histology: if the lesion is in the small bones of the hands and feet, it is usually benign, while, with similar histological features, it is usually malignant if located in the ribs and sternum. Tumors that arise in the periostium are generally clinically less aggressive than the intramedullary counterparts. The radiographic features of the lesion are very important for the pathologists:

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they have to be considered like a negative image of the macroscopic appearance of the neoplasm. Bone lesions can cause osteolysis or reactive bone production (osteosclerosis). Combinations of these two processes give rise to three typical patterns of bone destruction:

(a) The geographic bone destruction pattern, typical of slow growing lesions
(b) The "moth-eaten" pattern, that is typical of more aggressive lesions, that usually have a faster growth rate, and for this reason the osteosclerosis in this situation is less evident
(c) The permeative growth that can be observed in the most aggressive lesions, such as lymphomas and Ewing sarcoma

Finally, periosteal reaction gives a great clue for the interpretation of biological features of a bone neoplasm. Fast-growing lesions do not cause a periosteal reaction that usually requires about 2 weeks to be detectable on radiographs. Some kinds of periosteal reactions suggest a specific diagnosis (onionskin reaction is frequently present in Ewing sarcoma). A careful examination of all these aspects helps the pathologist to achieve a correct interpretation of the histology of a given bone lesion.

In the last years, pathologists have started to collect biologic samples of fresh tumor tissue to store in biobanks, which are necessary for the study of these rare tumors, in order to perform molecular diagnostic and research tests and to share these samples with other institutions in the context of large international scientific projects.

The 2013 WHO classification of bone tumors is based on cytologic and histogenetic criteria and on the kind of matrix produced by the tumor (see previous table). It represents the classification used today. Bone producing lesions together with cartilaginous lesions and Ewing sarcoma account for about 80% of all bone tumors; the remaining entities are by far rarer. The use of ancillary techniques such as immunohistochemistry is very important for the assessment of the possible origin of a bone metastasis, but also in some primary bone tumors. Molecular techniques are widely used in the validation of the diagnosis of Ewing sarcoma and, recently, also in other situations, such as aneurysmal bone cyst, fibrous dysplasia, giant cell tumor of bone, chondroblastoma. The grading system for bone sarcomas used at the Rizzoli institute is a four grading system according to Broders (grade 1–2: low grade; grade 3–4: high grade); the grading system in WHO classification is a three grading system based on the histological type or subtype of the tumor.

The Rizzoli's syllabus is based on the study of the most numerically important series in the world, and the use of a schematic approach for every single entity gives the reader a useful diagnostic tool, very practical for such rare diseases.

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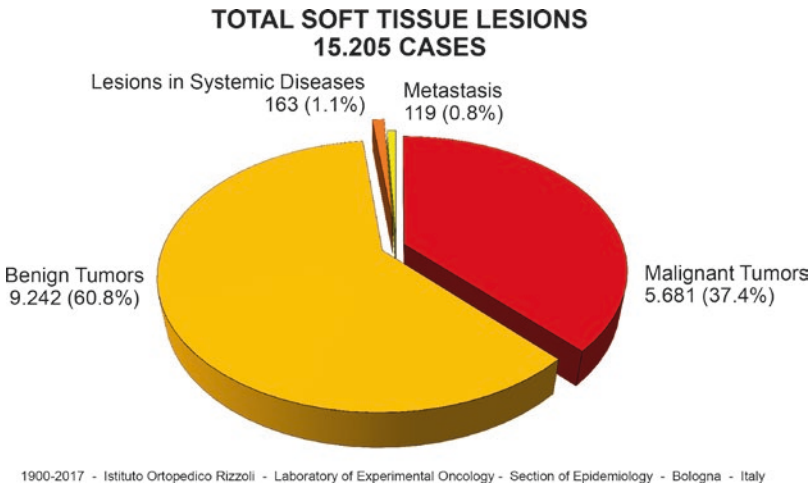
4 Epidemiology of Soft Tissue Lesions

Piero Picci



Soft tissue tumors (STT) are a heterogeneous group of benign and malignant processes. Some are assumed reactive, and others are clearly neoplastic. These lesions account for less than 4% of all tumors in adult patients, and for 7–10% of all tumors in pediatric patients. More than 99% of STT are benign, and the incidence of malignant STT is about 4–5 times that of malignant tumors arising from bone.

The rarity of STT causes problems with respect to diagnosis, grading, or optimal therapeutic approach. Over the last few decades, there have been significant changes in diagnostics and treatment of STT. Several developments in the field of radiology, pathology, and surgery have significantly changed the way STT are currently diagnosed and treated, improving prognosis and quality of life for patients with these rare diseases.

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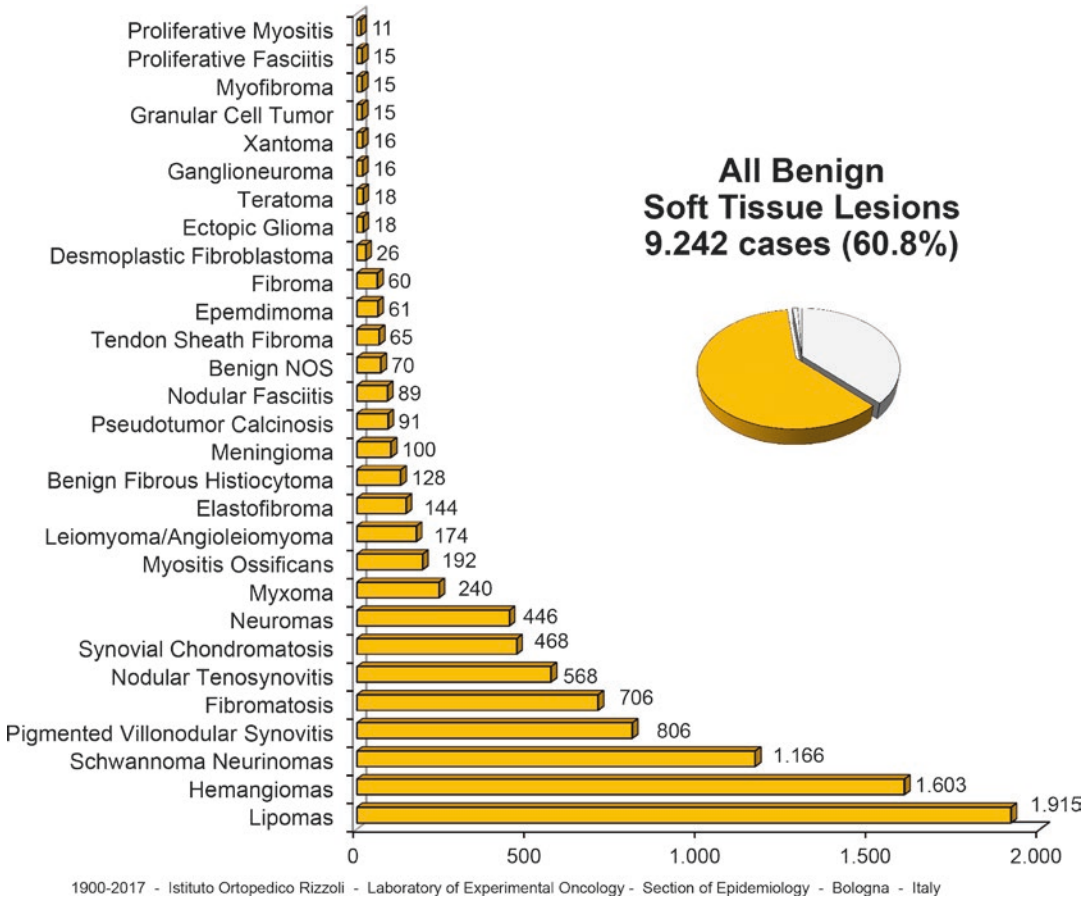
All Benign
Soft Tissue Lesions
9.242 cases (60.8%)
Proliferative Myositis 11
Proliferative Fasciitis 15
Myofibroma 15
Granular Cell Tumor 15
Xantoma 16
Ganglioneuroma 16
Teratoma 18
Ectopic Glioma 18
Desmoplastic Fibroblastoma 26
Fibroma 60
Epemdimoma 61
Tendon Sheath Fibroma 65
Benign NOS 70
Nodular Fasciitis 89
Pseudotumor Calcinosis 91
Meningioma 100
Benign Fibrous Histiocytoma 128
Elastofibroma 144
Leiomyoma/Angioleiomyoma 174
Myositis Ossificans 192
Myxoma 240
Neuromas 446
Synovial Chondromatosis 468
Nodular Tenosynovitis 568
Fibromatosis 706
Pigmented Villonodular Synovitis 806
Schwannoma Neurinomas 1.166
Hemangiomas 1.603
Lipomas 1.915
0
500
1.000
1.500
2.000
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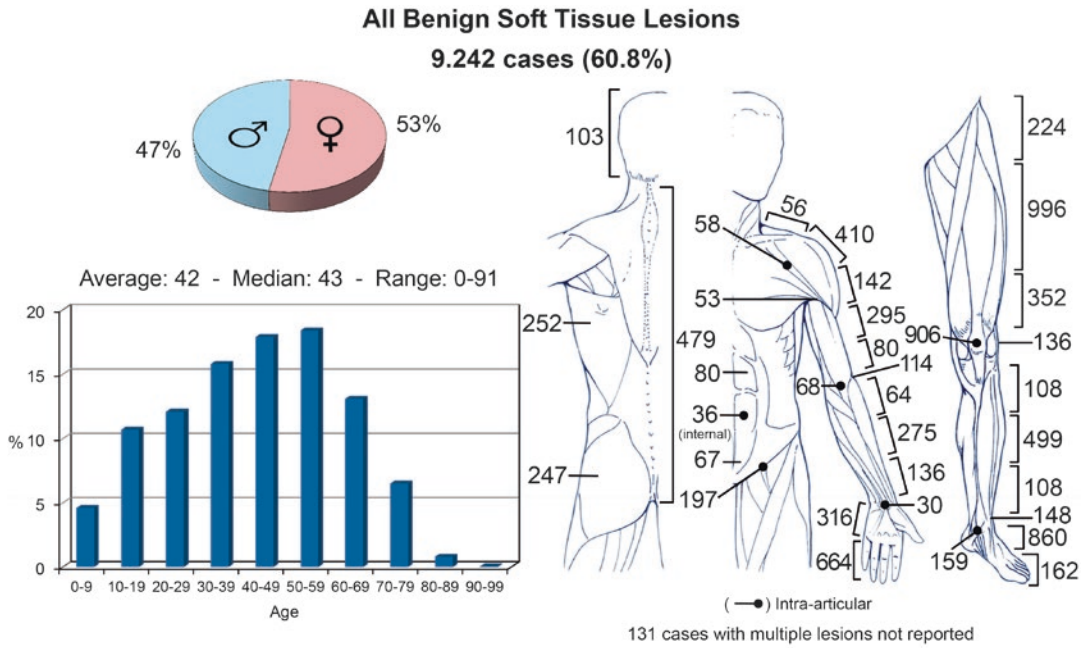
All Benign Soft Tissue Lesions
9.242 cases (60.8%)
47%
53%
Average: 42 - Median: 43 - Range: 0-91
%
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99
Age
103
252
247
479
80
36
(internal)
67
197
58
56
410
53
142
295
80
114
68
64
275
136
30
316
664
906
224
996
352
136
108
499
108
148
860
159
162
( ) Intra-articular
131 cases with multiple lesions not reported
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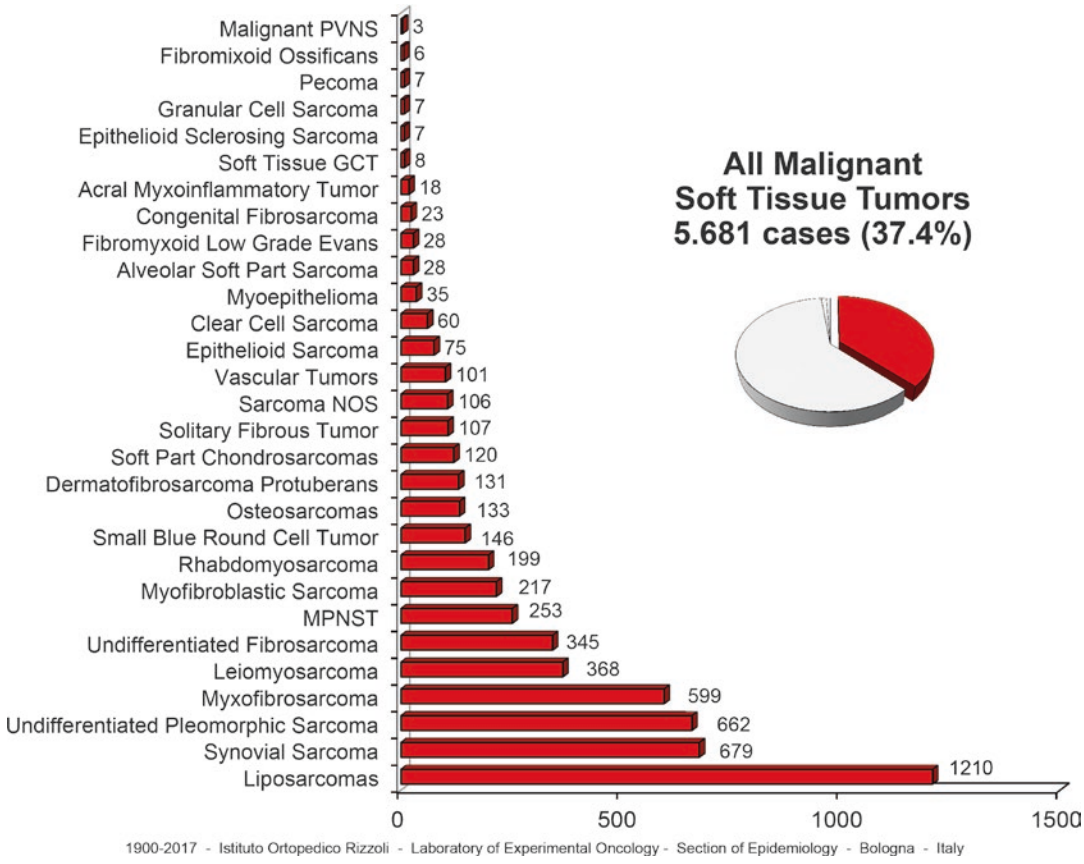
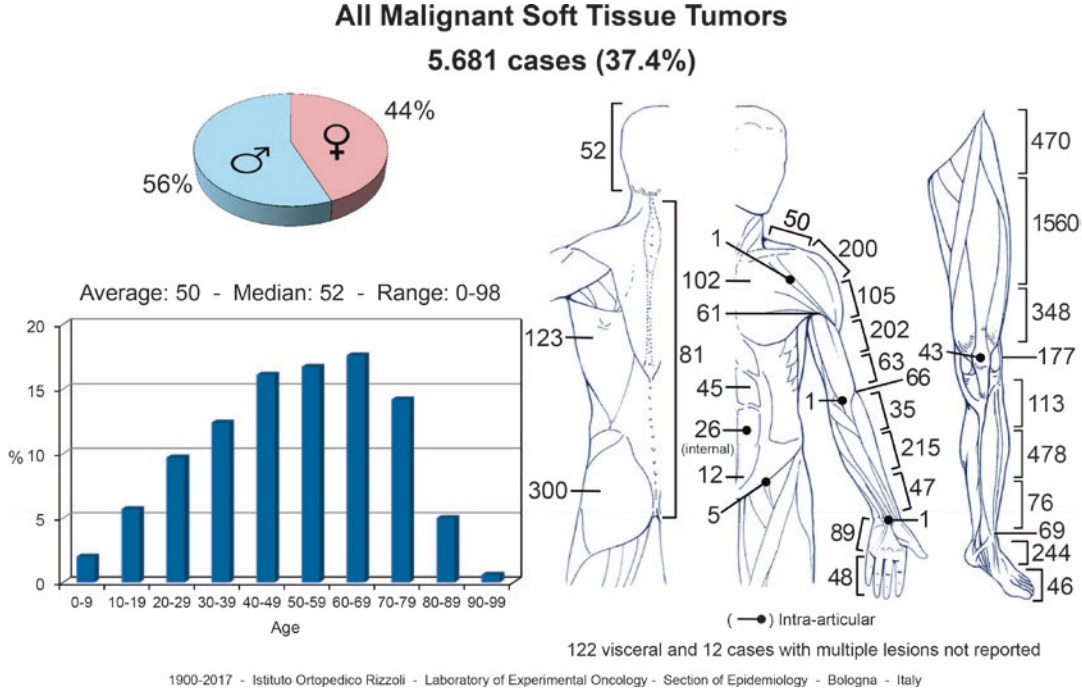

Malignant PVNS 3
Fibromixoid Ossificans 6
Pecoma 7
Granular Cell Sarcoma 7
Epithelioid Sclerosing Sarcoma 7
Soft Tissue GCT 8
Acral Myxoinflammatory Tumor 18
Congenital Fibrosarcoma 23
Fibromyxoid Low Grade Evans 28
Alveolar Soft Part Sarcoma 28
Myoepithelioma 35
Clear Cell Sarcoma 60
Epithelioid Sarcoma 75
Vascular Tumors 101
Sarcoma NOS 106
Solitary Fibrous Tumor 107
Soft Part Chondrosarcomas 120
Dermatofibrosarcoma Protuberans 131
Osteosarcomas 133
Small Blue Round Cell Tumor 146
Rhabdomyosarcoma 199
Myofibroblastic Sarcoma 217
MPNST 253
Undifferentiated Fibrosarcoma 345
Leiomyosarcoma 368
Myxofibrosarcoma 599
Undifferentiated Pleomorphic Sarcoma 662
Synovial Sarcoma 679
Liposarcomas 1210
0
500
1000
1500
All Malignant
Soft Tissue Tumors
5.681 cases (37.4%)
1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy


All Malignant Soft Tissue Tumors
5.681 cases (37.4%)
44%
56%
♂
♀
Average: 50 - Median: 52 - Range: 0-98
20
15
% 10
5
0
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99
Age
52
50
1
200
102
105
61
202
63
66
1
35
215
47
1
123
81
45
26
(internal)
12
5
300
89
48
470
1560
348
43
177
113
478
76
69
244
46
(—●) Intra-articular
122 visceral and 12 cases with multiple lesions not reported
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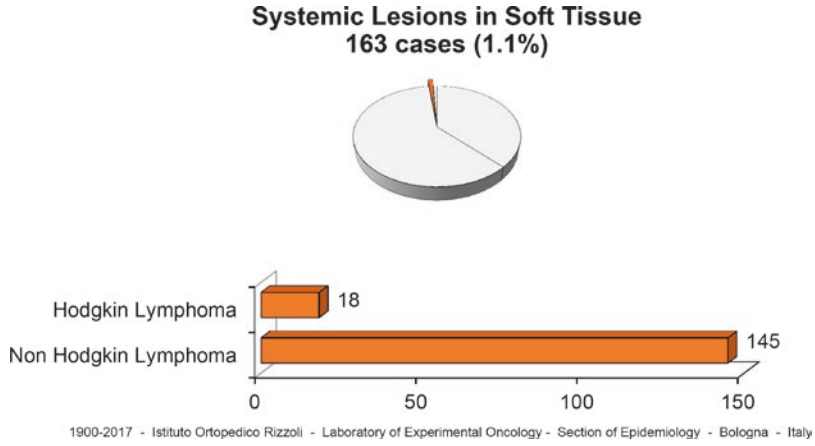
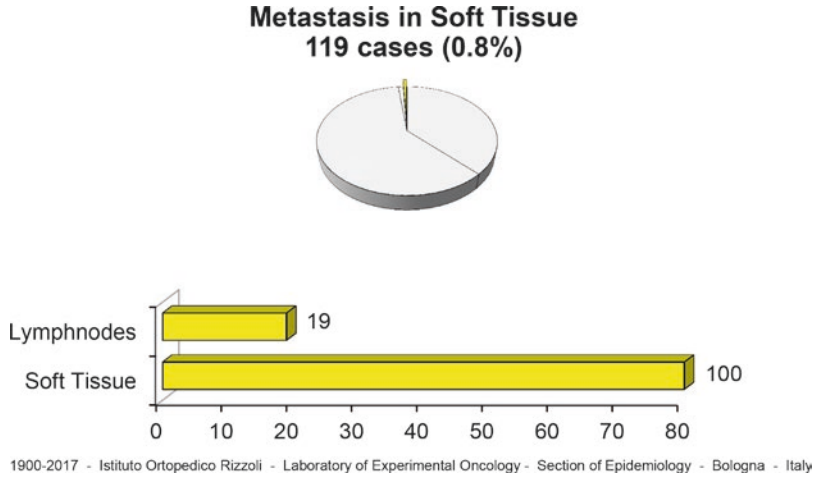

Systemic Lesions in Soft Tissue
163 cases (1.1%)
Hodgkin Lymphoma
Non Hodgkin Lymphoma
18
145
0
50
100
150
1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy


Metastasis in Soft Tissue
119 cases (0.8%)
Lymphnodes
Soft Tissue
19
100
0
10
20
30
40
50
60
70
80
1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

5 Classification of Soft Tissue Lesions and General Principles of Soft Tissue Pathology

Marta Sbaraglia, Marco Gambarotti, Alberto Righi, and Angelo Paolo Dei Tos

Soft tissue sarcomas are currently classified on the basis of the 2013 WHO classification of soft tissue tumors. WHO classifies the different entities on the basis of histomorphology and includes all available immunophenotypic and genetic data since the 2002 edition. This perfectly matches a diagnostic approach that integrates sequentially the microscopic features of the lesion with its immunophenotype and its genetic profile. Soft tissue sarcomas and soft tissue tumors of intermediate malignancy currently recognized by WHO classification are listed in Table 5.1.

Despite the intrinsic challenge of sarcoma diagnosis, it is possible to achieve a correct classification in most instances, provided that cases are approached following a rigorous methodology. The diagnosis of sarcoma relies upon the evaluation as well as the integration of four main features:

1. The predominant shape of the neoplastic cells. Neoplastic cells can be classified on the basis of their shapes into four main categories: spindle, epithelioid, round, and pleomorphic.
2. The pattern of growth. Main patterns are as follows: fascicular, herringbone, storiform, alveolar, solid, and biphasic.
3. The quality of the background. Main variants are fibrous, sclerotic, myxoid, myxochondroid, and osteogenic.
4. The architecture of the vascular network. Blood vessels can organize in plexiform architecture, archiform architecture, and hemangiopericytoma-like architecture.

This approach possesses the great merit of reducing dramatically the number of diagnostic options, also allowing a rational choice of ancillary immunohistochemical and molecular tests. Of course this approach needs some degree of flexibility as numerous entities may at times exhibit a combination of different major morphologic features.

Immunohistochemical characterization plays a key role in the diagnostic workup of soft tissue sarcomas. However, a blind application of a broad range of immunophenotypic markers unsupervised by morphology most often leads to

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Table 5.1

Histogenesis	Benign	Uncertain behavior (locally aggressive and/or rarely metastasizing)	Malignant
Adipocytic	Lipoma Lipomatosis Lipomatosis of nerve Lipoblastoma/lipoblastomatosis Angiolipoma Myolipoma Chondroid lipoma Extrarenal angiomyolipoma Extra-adrenal myelolipoma Spindle cell/pleomorphic lipoma Hibernoma	Atypical Lipomatous Tumor / Well Differentiated Liposarcoma (ALT/WDL)	Dedifferentiated liposarcoma Myxoid liposarcoma Pleomorphic liposarcoma Liposarcoma, NOS
Fibroblastic/myofibroblastic	Nodular fasciitis Proliferative fasciitis Proliferative myositis Myositis ossificans Fibro-osseous pseudotumor of digits Ischemic fasciitis Elastofibroma Fibrous hamartoma of infancy Fibromatosis colli Juvenile hyaline fibromatosis Inclusion of body fibromatosis Fibroma of tendon sheath Desmoplastic fibroblastoma Mammary-type myofibroblastoma Calcifying aponeurotic fibroma Angiomyofibroblastoma Cellular angiofibroma Nuchal-type fibroma Gardner fibroma Calcifying fibrous tumor	Palmar/plantar fibromatosis Desmoid-type fibromatoses Lipofibromatosis Giant cell fibroblastoma Dermatofibrosarcoma protuberans (DFSP) Solitary fibrous tumor Inflammatory myofibroblastic tumor Myxoinflammatory fibroblastic sarcoma Infantile fibrosarcoma	Adult fibrosarcoma Myxofibrosarcoma Low-grade fibromyxoid sarcoma Sclerosing epithelioid fibrosarcoma Myofibroblastic sarcoma Fibrosarcomatous DFSP Malignant solitary fibrous tumor
Fibrohistiocytic	GCT of tendon sheath Benign fibrous histiocytoma	Pigmented villonodular synovitis (PVNS) Plexiform fibrohistiocytic tumor Giant cell tumor of soft tissues	Malignant PVNS

Smooth muscle	Leiomyoma		Leiomyosarcoma
Skeletal muscle	Rhabdomyoma		Rhabdomyosarcoma
Pericitic (perivascular)	Glomus tumor Myopericytoma/myofibroma Angioleiomyoma		Malignant glomus tumor
Vascular	Hemangiomas Epithelioid hemangioma Angiomatosis Lymphangioma	Kaposiform hemangioendothelioma Retiform hemangioendothelioma Papillary intralymphatic angioendothelioma Composite hemangioendothelioma Pseudomyogenic hemangioendothelioma	Kaposi sarcoma Epithelioid hemangioendothelioma Angiosarcoma
Nerve Sheath	Schwannoma Neurofibroma Perineurioma Granular cell tumor Dermal nerve sheath myxoma Solitary circumscribed neuroma Ectopic meningioma Nasal glial heterotopia Benign Triton tumor Hybrid nerve sheath tumors	Melanotic schwannoma	Malignant Peripheral Nerve Sheath Tumor (MPNST) Epithelioid MPNST Malignant Triton tumor Malignant perineurioma Malignant granular cell tumor Ectomesenchymoma
Cartilaginous and osseous	Soft tissue chondroma		Mesenchymal chondrosarcoma Extraskeletal osteosarcoma
Tumors of uncertain differentiation	Acral fibromyxoma Intramuscular myxoma Juxta-articular myxoma Deep (“aggressive”) angiomyxoma Ectopic hamartomatous thymoma	Hemosiderotic fibrolipomatous tumor Atypical fibroxanthoma Angiomatoid fibrous histiocytoma Pleomorphic hyalinizing angiectatic tumor Myoepithelioma Ossifying fibromyxoid tumor Phosphaturic mesenchymal tumor PEComa	Synovial sarcoma Epithelioid sarcoma Alveolar soft part sarcoma Clear cell sarcoma Extraskeletal myxoid chondrosarcoma Extraskeletal Ewing sarcoma Desmoplastic small round cell tumor Extrarenal rhabdoid tumor Intimal sarcoma Malignant myoepithelioma Malignant ossifying fibromyxoid tumor Malignant phosphaturic mesenchymal tumor Malignant PEComa Undifferentiated/unclassified sarcoma

diagnostic errors. The number of potential diagnostic markers has grown exponentially through the years; however, in consideration of the natural evolution of the field, some markers have lost their role while others have gained diagnostic relevance. It has to be underlined that, with some exceptions, the majority of classic differentiation markers tend to show good sensitivity however associated with rather limited specificity. This may not represent a problem only if interpretation is strictly handled in association with morphology. The most commonly used immunohistochemical diagnostic markers are listed in Table 5.2.

As will be discussed in a separate chapter, diagnostic accuracy can be improved by a wise use of molecular genetics that however also needs to be evaluated in context with morphology.

Once a firm diagnosis of malignancy is made, a useful prognostic parameter is represented by grading. As suggested also by WHO we adopt the FNCLCC grading system that scores the degree of differentiation, the amount of necrosis, and the mitotic index.

Table 5.2 Useful immunohistochemical markers in soft tissue tumors diagnosis

Tumor	Marker
Smooth muscle tumors	Smooth muscle actin, h-caldesmon, desmin
Striated muscle tumors	Desmin, myogenin, MyoD1
Neural tumors	S100, SOX-10, GFAP,
Vascular tumors	CD31, ERG, CAMTA1, TFE3, FOSB
Osteogenic tumors	SATB2
Dermatofibrosarcoma protuberans (DFSP) / Fibrosarcomatous DFSP	CD34
Ewing sarcoma	CD99
Synovial sarcoma	EMA, cytokeratin, TLE1
Epithelioid sarcoma	EMA, cytokeratin, loss of INI1, CD34
PEComa	Smooth muscle actin, desmin, HMB45, Melan-A
Myoepithelioma	EMA, cytokeratin, S100
Alveolar soft part sarcoma	TFE3
Low grade fibromyxoid sarcoma	MUC4, EMA
Well differentiated / Dedifferentiated liposarcoma	MDM2
Malignant peripheral nerve sheath tumors	H3K27me3

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6 Molecular Alterations in Musculoskeletal Lesions

Marta Sbaraglia, Marco Gambarotti, Alberto Righi, and Angelo Paolo Dei Tos

The marriage of molecular genetics and soft tissue tumor pathology certainly represents one of the most fruitful events of the last decade. The close relationship between morphology (including immunohistochemistry) and molecular genetics was certified by the 2002 WHO classifications of bone and soft tissue tumors and further expended in the 2013 update.

This integration has impacted on several aspect of pathology:

- More accurate definition of disease entities and validation of classification schemes.
- Improved diagnostic accuracy.
- Identification of molecular predictive and prognostic markers.
- Discovery and validation of therapeutic molecular targets.

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6.1 Definition of Disease Entities and Validation of Classification Scheme

Molecular genetics has significantly contributed to a more accurate definition of histologic subtypes. This is particularly true whenever new entities are described but also applies to the revision of classification schemes. In addition, molecular genetics has helped refining histologic classification.

6.2 Improvement of Diagnostic Accuracy

In the last two decades it has become clear that molecular testing may add diagnostic accuracy in important subsets of challenging soft tissue tumors. In fact many of these lesions are known to harbor a variety of relatively specific point mutations, gene amplifications, and chromosome translocations. Gene fusion seems to be particularly frequent in soft tissue neoplasm, the most common of which are listed in Table 6.1. Their occurrence can be routinely assessed using FISH, Sanger-based techniques, or next-generation sequencing.

The diagnostic utility of molecular genetics can be best exemplified in the following situations:

- Distinguishing specific subtypes of sarcomas
- Supporting diagnosis in non-canonical clinical presentations
- Distinguishing sarcomas from benign mimickers

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Table 6.1 Gene fusions in soft tissue neoplasm

Tumor	Gene fusion	Cytogenetics
Myxoid/round liposarcoma	FUS-DDIT3 EWSR1-DDIT3	t(12;16)(q13;p11) t(12;22)(q13;q12)
Dermatofibrosarcoma protuberans	COL1A1-PDGFB	t(17;22)(q21;q13)
Low-grade fibromyxoid sarcoma	FUS-CREB3L2 FUS-CREB3L1 EWSR1-CREB3L1	t(7;16)(q34;p11) t(7;16)(p11;p11) t(11;22)(p11;q12)
Solitary fibrous tumor	NAB2-STAT6	inv(12)(q13;q13)
Infantile fibrosarcoma	ETV6-NTRK3	t(12;15)(p13;q25)
Sclerosing epithelioid fibrosarcoma	FUS-CREB3L2 FUS-CREB3L1 EWSR1-CREB3L1	t(7;16)(q34;p11) t(11;16)(p13;p11) t(11;22)(p11;q12)
Myxoinflammatory fibroblastic sarcoma/hemosiderotic fibrolipomatous tumor	MGEA5-TGFBR3	der(10)t(1;10)(p22;q24)
Inflammatory myofibroblastic tumor	CARS-ALK SEC31A-ALK ATIC-ALK RANBP2-ALK CLTC-ALK TPM3-ALK TPM4-ALK PPFIBP1-ALK RREB1-TFE3	t(2;11)(p23;p15) t(2;4)(p23;q21) inv(2)(p23;q35) t(2;2)(p23;q13) t(2;17)(p23;q23) t(1;2)(q21;p23) t(2;19)(p23;p13) t(2;12)(p23;p11) t(X;6)(p11;p24)
Myxofibrosarcoma	KIAA2026-NUDT11 CCBL1-ARL1 AFF3-PHF1	t(9;X)(p24;p11) t(9;12)(q34;q23) t(2;6)(q12;p21)
Alveolar rhabdomyosarcoma	PAX3-FOXO1 PAX7-FOXO1 PAX3-FOXO4 PAX3-NCOA1 PAX3-NCOA2 FOXO1-FGFR1	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q36) t(2;2)(p23;q36) t(2;8)(q36;q13) t(8;13;9)(p11;q14;q32)
Spindle cell rhabdomyosarcoma	SRF-NCOA2 TEAD1-NCOA2	t(6;8)(p21;q13) t(8;11)(q13;p15)
Angiomatoid fibrous histiocytoma	EWSR1-CREB1 FUS-ATF1 EWSR1-ATF1	t(2;22)(q33;q12) t(12;16)(q13;p11) t(12;22)(q13;q12)
Ossifying fibromyxoid tumor	EP400-PHF1 MEAF6-PHF1 ZC3H7B-BCOR	t(6;12)(p21;q24) t(1;6)(p34;p21) t(X;22)(p11;q13)
Myoepithelioma/mixed tumor	EWSR1-ATF1 EWSR1-PBX1 EWSR1-POU5F1 EWSR1-ZNF444 EWSR1-KLF17 EWSR1-PBX3 FUS-KLF17 LIFR-PLAG1 SRF-E2F1	t(12;22)(q13;q12) t(1;22)(q23;q12) t(6;22)(p21;q12) t(19;22)(q13;q12) t(1;22)(p34.1;q12) t(9;22)(q12.2;q33.3) t(1;16)(p34.1;p11) t(5;8)(p13;q12) t(20;6)(q11;p21)
Clear cell sarcoma	EWSR1-ATF1 EWSR1-CREB1 IRX2-TERT	t(12;22)(q13;q12) t(2;22)(q33;q12) del(5)(p15.33)
Synovial sarcoma	SS18-SSX1 SS18-SSX2 SS18-SSX4 SS18L1-SSX1	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;20)(p11;q13)
Alveolar soft part sarcoma	ASPSCR1-TFE3	t(X;17)(p11;q25)
Extraskeletal myxoid chondrosarcoma	EWSR1-NR4A3 TAF15-NR4A3 TFG-NR4A3 TCF12-NR4A3 HSPA8-NR4A3	t(9;22)(q31;q12) t(9;17)(q31;q12) t(9;3)(q31;q12) t(9;15)(q31;q21) t(9;11)(q31;q24)
Desmoplastic small round cell tumor	EWSR1-WT1	t(11;22)(p13;q12)

Table 6.1 (continued)

Tumor	Gene fusion	Cytogenetics
Ewing sarcoma and Ewing-like sarcomas	EWSR1-FLI1	t(11;22)(q24;q12)
	EWSR1-ERG	t(21;22)(q22;q12)
	FUS-ERG	der(21)t(16;21)
	EWSR1-ETV1	t(7;22)(p21;q12)
	EWSR1-ETV4	t(17;22)(q21;q12)
	EWSR1-FEV	t(2;22)(q35;q12)
	EWSR1-NFATC2	t(20;22)(q13;q12)
	EWSR1-PATZ1	inv(22) (q12;q12)
	EWSR1-SMARCA5	t(4;22) (q31;q12)
	EWSR1-POU5F1	t(6;22) (p21;q12)
	EWSR1-SP3	t(2;22)(q31;q12)
	FUS-FEV	t(2;16)(q35;p11)
	CIC-DUX4	t(4;19)(q35;q13)
	CIC-FOXO4	t(X;19)(q13;q13)
	BCOR-CCNB3	inv(X)(p11.4;p11.22)
	FUS-NCATc2	t(16;20) (p11;q13)
Perivascular epithelioid cell tumors	SFPQ-TFE3	t(X;1)(p11;p34)
Mesenchymal chondrosarcoma	HEY1-NCOA2	del(8)(q13;q21)
	IRFBP2-CDX1	t(1;5)(q42;q32)
Epithelioid hemangioma	ZFP36-FOSB	t(19;19)(q13.32;q13.2)
Epithelioid hemangioendothelioma	WWTR1-CAMTA1	t(1;3)(p36;q25)
	YAP1-TFE3	t(x;11)(p11;q22)
Pseudomyogenic hemangioendothelioma	SERPINE1-FOSB	t(7;19)(q22;q13)
Angiosarcoma	CIC-LEUTX	t(19;19)(q13.11;q13.2)

6.2.1 Distinguishing Specific Subtypes of Sarcomas

The distinction of specific sarcoma subtypes is becoming increasingly important as more specific local as well as systemic treatments are being developed. Molecular genetics/pathology has proved diagnostically useful in all morphological groups of mesenchymal malignancies. Round cell sarcomas represent the perfect example to underline how clinically relevant molecular diagnostics has become. Round cell sarcomas include Ewing sarcoma, desmoplastic small round cell tumor (DSRCT), alveolar rhabdomyosarcoma, poorly differentiated round cell synovial sarcoma (PDSS), CIC-rearranged and BCOR-rearranged undifferentiated round cell sarcomas, and a minority of cases or high-grade liposarcoma featuring a round cell morphology. They all represent aggressive neoplasms, and their distinction is crucial because the therapeutic approach may differ significantly. As morphologic overlap may be at time extreme, to the extent that even immunohistochemical characterization cannot help in achieving a definitive classification (i.e., keratin-positive Ewing sarcoma vs. poorly differentiate round cell synovial sarcoma), molecular genetics may play a key diagnostic role. As shown in Table 6.1, all these entities harbor relatively specific genetic aberrations that can be routinely assessed contributing to increase diagnostic accuracy. The demonstration of EWSR1, SS18 and FOXO1 rearrangements in Ewing sarcoma, RMS, and PDSS is of great diagnostic help.

The identification of gene copy number variations has also proved extremely helpful. The perfect example is represented by dedifferentiated liposarcoma, a pleomorphic adipocytic malignancy that, in contrast with other sarcoma such as leiomyosarcoma, exhibits the tendency to recur locally with a comparatively lower rate of metastatic spread. The recognition of dedifferentiated liposarcoma is generally based on the identification of a well-differentiated lipogenic component associated with a high-grade, most often non-lipogenic, sarcoma. In consideration of the increasing tendency to use core biopsies for diagnostic purposes, not infrequently the well-differentiated lipogenic component is not made available. In this context, the detection of MDM2 amplification by FISH or quantitative RT-PCR certainly represents a useful diagnostic adjunct.

6.2.2 Supporting Diagnosis in Non-canonical Clinical Presentations

As a result of the widespread use of molecular pathology as a confirmatory diagnostic tool, the range of clinical presentations of many entities has broadened. In fact, the combination of morphological criteria and genetics validates the recognition of rare diseases even when arising at non-canonical anatomic locations. Molecular genetics has undoubtedly greatly contributed for instance to the identification of primary Ewing sarcoma of the skin, kidney, and meninges, as well as of synovial sarcomas occurring at visceral sites such as the lungs and the gastrointestinal tract.

6.2.3 Distinguishing True Sarcomas from Benign Mimics

The morphological appearance of mesenchymal lesions not always parallels the clinical behavior. The distinction of sarcomas from benign mimics most often relies on morphologic criteria; however, in some cases molecular genetics may also prove diagnostically helpful, for instance, when dealing with low-grade fibromyxoid sarcoma (LGFMS), a bland-looking spindle cell sarcoma, actually characterized by aggressive clinical behavior. The differential diagnosis of LGFMS includes benign lesions such as perineurioma, neurofibroma, cellular myxoma, and nodular fasciitis, as well as locally aggressive neoplasms such as desmoid fibromatosis. Even if MUC4 expression is currently regarded as a key diagnostic feature, the identification of FUS rearrangement represents an extremely useful diagnostic tool. As mentioned, desmoid fibromatosis enters the differential diagnosis, and in addition to immunohistochemical detection of nuclear accumulation of β-catenin, mutational analysis of the CTNNB1 gene also represents a valuable diagnostic tool.

6.3 Identification of Molecular Predictive and Prognostic Markers

During the last decade, several attempts have been made to assess the prognostic value of molecular genetic findings. Most analyses have focused on Ewing sarcoma, alveolar rhabdomyosarcoma, and synovial sarcoma. We have to admit that results have been contradicting, and at this moment no meaningful molecular prognostic stratification can be foreseen. A potential exception is represented by a molecular signature named “CINSARC” that reportedly allows better separation of grade 2 sarcomas.

It has also to be stressed how molecular pathology/genetics represents the most valuable tool in order to identify and validate new therapeutic targets. Good examples are represented by ALK in inflammatory myofibroblastic tumor, MDM2, and CDK4 in dedifferentiated liposarcoma, PDGFB in dermatofibrosarcoma protuberans, and CSF1 in giant cell tumor of tendon sheath.

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General Principles of Imaging

7

Daniel Vanel

7.1 Bone Tumors

Bone imaging has undergone significant changes during the last decades. Ultrasounds, CT, MR imaging, and PET have been added to arteriography, scintigraphy, and radiographs. At the same time, survival of primary malignant tumors has improved with chemotherapy and local results with conservative surgery. Imaging plays a major role in diagnosis, local and general staging, monitoring the treatment, and detecting recurrences.

7.1.1 Diagnosis

Patient age, location (bone or part of the bone involved), size (small is usually benign), calcifications and ossifications, limitation (the better seen, the slower the lesion growth), periosteal bone formations, and soft tissue involvement must be added to reach a reliable diagnostic probability. Combining clinical information, imaging and histology lead to the most accurate results. Diagnosis of a bone tumor must be teamwork.

Radiographs remain the mandatory first step. They allow diagnosis of "leave-me-alone" lesions, and nothing more is usually added. If the lesion on radiographs is probably malignant, the next step should be immediate MR to stage the lesion.

Radiographs have limitations: superimpositions, partial cortex destruction could be overlooked, flat and short bones and soft tissues are poorly analyzed.

CT is used in case of a diagnostic problem on radiographs. It allows a better study of the cortex, to detect and analyze small calcifications and thin periosteal bone formations. The nidus of an osteoid osteoma is well found (much better than on MR). Measuring tissue density can help characterize fat, fluid, blood, and calcification. After injection of contrast medium, soft tissue extension and vessels are well located.

The contrast remains however much lower than on MRI, which is the main modality for local staging. Its diagnostic role is limited, as calcifications and periosteal bone formations are more difficult to analyze (a black signal on MRI may be a calcification, but also fibrous tissue or chronic bleeding with hemosiderine). Fluid-fluid levels are better depicted than on CT, because of higher contrast and longer examination time. They are frequently seen in aneurysmal bone cysts, but are non-specific. Peritumoral imflammatory reaction is very well detected and frequent in some benign tumors (osteoid osteoma, osteoblastoma, chondroblastoma, Langerhans cell histiocytosis), and infections are rarer and more limited in malignant tumors.

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7.1.2 Local Staging

On MRI, the precise location of the tumor is well analyzed.

Intramedullary extension (and the level of surgical resection), skip metastases, soft tissue involvement, and extension to vessels and nerves are easily and reliably detected. The main limitation is articular extension, which could change the surgical technique: if the tumor abuts on the cartilage, joint involvement cannot be reliably predicted.

In case of contraindications (pace makers and metallic ocular foreign bodies), CT is used, but has a lower accuracy.

7.1.3 Distant Spread

Bone metastases and multiple lesions are detected on scintigraphy. Total body MRI is more sensitive without irradiation. Pulmonary metastases are seeked by chest CT. Its sensitivity is good, but specificity is lower (or if we detect a lesion, we are not sure that it is actually a metastasis).

PET, now combined with CT, or even MRI allows a global study of the patient, studying the tumor metabolic activity as well as the distal extent. Its spatial resolution is limited (lesions of less than 5 mm may be overlooked), and some malignant lesions are not very active metabolically (such as sclerotic metastases).

7.1.4 Evaluation of Treatment Effectiveness

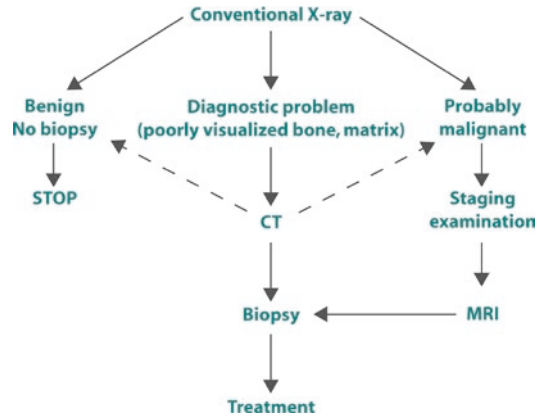
Most primary malignant tumors are treated with preoperative chemotherapy. Decrease of lesion size, ossification, and decrease of early contrast medium uptake on scintigraphy and most of all dynamic MRI are signs of an efficient treatment. They become reliable only late after the beginning of chemotherapy. The initial results of PET are not (yet?) much better.

7.1.5 Detection of Local Recurrences

In case of suspicion, a local MR can be performed if the prothesis is non-paramagnetic (that is in titanium).

7.1.6 Summary

Radiographs remain the first step to image a bone tumor. In case of diagnostic problems, the next step is CT. MR is the main imaging modality for local staging, treatment evaluation, and detection of recurrences. PET is still under evaluation.



7.2 Soft Tissue Tumors

Imaging problems are completely different from bone tumors. The main responsibility of the radiologist is to think of a possible sarcoma in front of a big (more than 5 cm of diameter), deep, or pediatric mass and refer it to a reference center before the first biopsy. That would prevent inadequate treatments with sometimes disastrous local or general consequences.

Radiographs are the first imaging modality. They detect calcifications and check the state of the underlying bone and fracture risk.

Ultrasound examinations are used very often; the improvements of machines and level of radi-

ologists make them an useful tool. They are cheap, easily available, and safe. They confirm the mass, its exact location, help diagnose typical benign lesions, and guide biopsy. But they are difficult to reproduce and analyze for surgeons.

CT detects calcifications and local extension and can guide needle biopsy.

MRI is the main imaging modality. Its contrast is much higher. Thanks to its high contrast resolution and multiplanar imaging capability, MRI provides an anatomic and topographic depiction of the lesion, defining with great precision the relationship to muscle compartments, fascial planes, bones, and neurovascular structures. The usual tumor that has a low signal on T1-weighted sequences, high on T2, is heterogeneous. A different signal, high on T1w sequences, helps diagnose fat, blood, or melanin, a low signal on T2 calcium, fibrous tissue, or hemosiderin. A rapid and strong uptake of contrast medium is very sensitive and specific of malignancy.

Modern imaging techniques are not only of great importance for differential diagnosis of STT, they also play an important role in monitoring the effects of nonsurgical treatments and are sometimes useful in the detection of local and distant recurrence during postoperative follow-up.

Most recent developments are the introduction of positron emission tomography (PET) often combined with CT and the application of new MRI modalities (spectroscopy, perfusion, and diffusion). Although experience with these new techniques is still rather limited for STT, it is likely that they will have an increasing role in diagnosis, monitoring, and follow-up of these lesions in the nearby future.

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Staging

8

Piero Picci

Tumors are labeled and classified according to their clinical (natural history) and histologic features. Such assessment however does not suffice to describe the actual behaviour of a given tumor in an individual patient. Moreover, to determine the anatomo-clinical diagnosis, staging of the tumor is necessary for each individual case.

Different staging systems are adopted for musculoskeletal lesions. The one preferred by orthopedic surgeons and in fact called "surgical staging system" has been devised by Enneking (1980). Oncologists prefer the American Joint Committee System (AJCS).

Surgical Staging System (SSS). According to Enneking (1983) "by compartment is meant an anatomical structure or space bounded by natural barriers to tumor extension." Natural barriers are the cortical bone, fascia and fascial septa, articular cartilage, joint capsule, tendons, and tendon sheaths. Fat and interstitial areolar tissues outside these compartments are extra-compartmental, like the tissue around neurovascular bundles. Natural barriers as cortical bone or fascia can be breached especially along their vascular perforations. The most resistant barrier is the articular cartilage, having no vascular perforations and probably an intrinsic resistance to tumor. The growth plate functions as a relative barrier, depending on anatomical site and age (perforated by vessels in early infancy and again at puberal age). The periosteum, the synovial membrane (until it is ulcerated and bleeding, producing a hemarthrosis containing neoplastic cells), and the sheath of the major nerves (perinervium) can be considered relative although very thin barriers. Where the joint capsule and synovium, the ligaments, and tendons insert into an epiphysis, apophysis or metaphysis, the only barrier is a thin bony cortex with vascular perforations, and therefore, the tumor easily extends from the cancellous bone to these structures and vice versa.

The system is based on the three classic parameters, **G**, **T**, and **M**.

G is the grade of the tumor, mainly dictated by histology. G0 is benign, G1 is low-grade malignant, and G2 is high-grade malignant. When a four-grade classification of malignancy is used, histological grades 1 and 2 are low; grades 3 and 4 high.

T is the tumor anatomic extension. T0 means a benign tumor contained by a true capsule (intracapsular). T1 is a benign or malignant tumor not having a true capsule, yet confined within an anatomical compartment. T2 is a benign or malignant tumor without a true capsule, originating in an extra-compartmental space, or expanded extra-compartmentally by violating the natural barriers.

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M are the metastases, either regional (skip, lymph nodes) or distant. M0 means absence and M1 presence of metastases.

Benign tumors of both bone and soft tissues are staged 1 (latent, inactive), 2 (active), and 3 (aggressive).

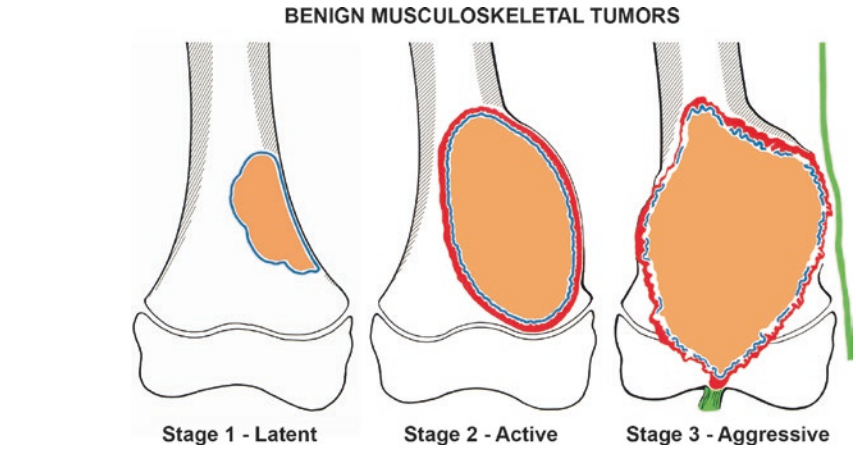
Sarcomas (bone and soft tissues) are staged I (low-grade malignancy), II (high-grade malignancy), and III (with metastases). Each of the three stages is subdivided into A and B: whether the tumor is intra- or extra-compartmental in stage I and II, and if it is low or high grade in stage III.

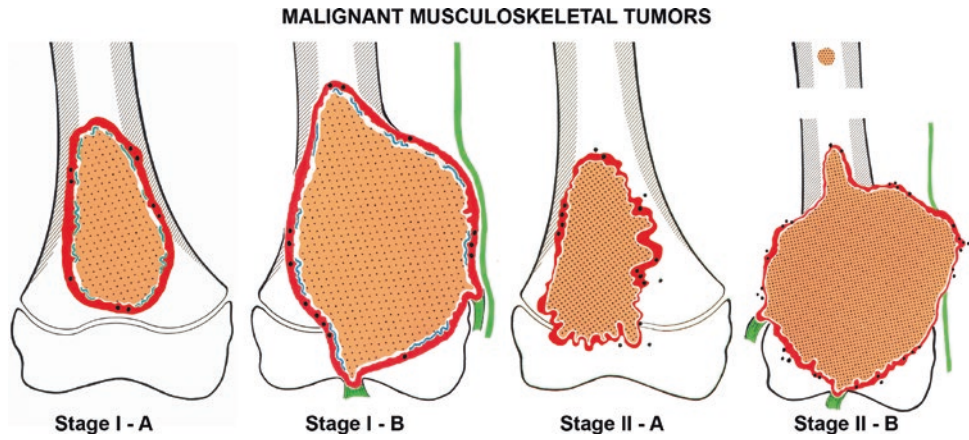
Surgical stages for benign musculoskeletal tumors

Stage	Grade	Site	Metastases	Definition
1	G0	T0	M0	Latent or inactive
2	G0	T0	M0	Active
3	G0	T1–T2	M0–1	Aggressive

Surgical stages for malignant musculoskeletal tumors

Stage	Grade	Site	Metastases	Definition
				Low-grade
IA	G1	T1	M0	A intra-compartmental
IB	G1	T2	M0	B extra-compartmental
				High-grade
IIA	G2	T1	M0	A intra-compartmental
IIB	G2	T2	M0	B extra-compartmental
				Metastatic
IIIA-B	G1–2	T1–T2	MI	Either grade (A or B) Distant metastases





The Enneking system is best suited for well-documented sarcomas arising in the extremities. It does not include the type, size, and depth of the tumor as separate parameters, its two-tier grading system is too narrow for the wide biological range of soft tissue tumors.

American Joint Committee System (AJCS). Oncologists prefer the American Joint Committee system (AJCS) because it is applicable for any site. Based on the TNMG system, it uses size and tumor extension (T), involvement of lymph nodes (N), presence of metastasis (M), and the type and grade of tumor (G).

T1: < 5 cm; **T2:** 5 cm. o greater; **T3:** involvement of bone, vessels, nerve

N0: no metastasis to regional lymph node; **N1:** lymph node metastases

M0: no distant metastasis; **M1:** distant metastasis

G1: low grade, well-differentiated; **G2:** moderate (moderately well-differentiated)

G3: high grade, poorly differentiated

Stage	Grade	Site	Lymph node metastases	Distant metastases	Definition
IA	G1	T1	N0	M0	Low grade without metastases
IB	G1	T2	N0	M0	
IIA	G2	T1	N0	M0	Moderate grade without metastases
IIB	G2	T2	N0	M0	
IIIA	G3	T1	N0	M0	High grade without metastases
IIIB	G3	T2	N0	M0	
IIIC	G1–3	T1–2	N1	M0	Any tumor with lymph node metastases
IVA	G1–3	T3	N0–1	M0	Tumor involving bone, vessel, nerve with or without lymph node metastases
IVB	G1–3	T1–3	N0–1	M1	Any tumor with distant metastases

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Part II

Pseudotumoral and Benign Lesions of Bone

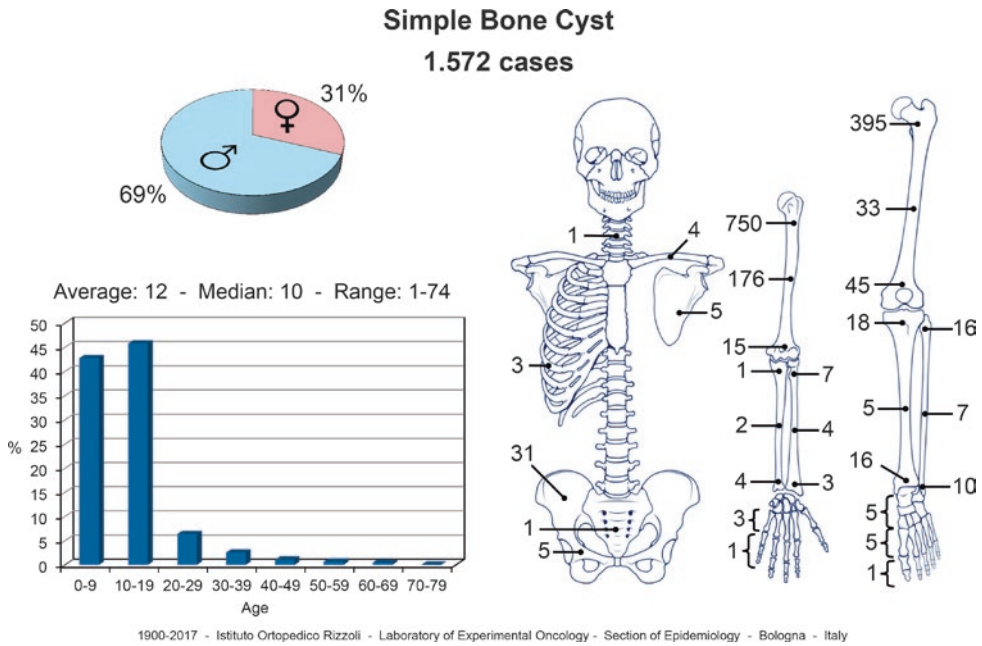
Simple Bone Cyst (Unicameral Bone Cyst)

9

Laura Campanacci

Definition: Central cystic lesion of bone, with a fluid content similar to serum, starting in the metaphysis during childhood and becoming inactive around or soon after the skeletal maturity. It is the only true cyst of bone that conforms to the pathologic definition of cyst. Simple bone cyst cavity will only contain blood if associated with a pathologic fracture.

Epidemiology: The simple bone cyst represents one of the most frequent osseous lesions. Males are more affected than females (2:1). It usually occurs in infancy and teenage (highest incidence between 5 and 15 years of age).



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Localization: It usually arises in the metaphysis of long bones, beneath the growth plate, but along with patient growth, the cyst migrates toward the diaphysis. Most common location is proximal humerus, followed by proximal femur.

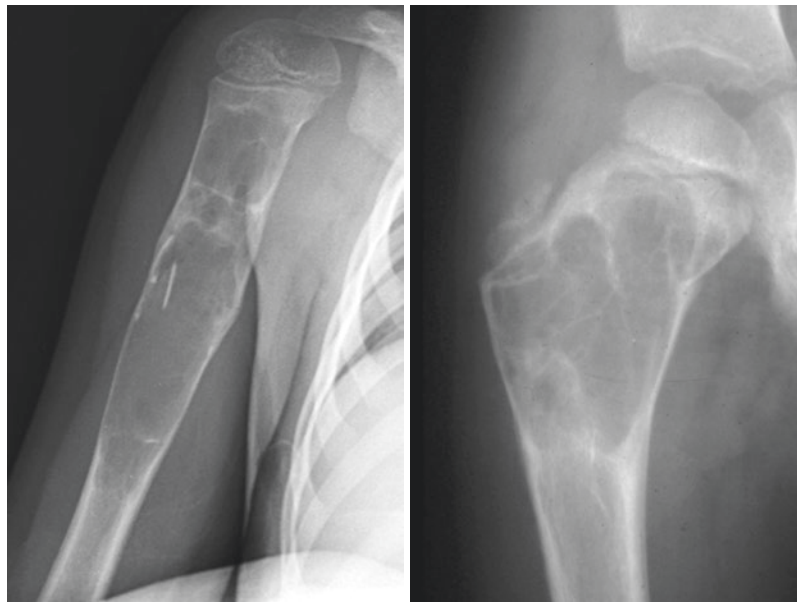
Clinical: Simple bone cyst is painless and asymptomatic; it becomes painful if a pathologic fracture develops. Sometimes it presents as an incidental finding.

Imaging: The characteristic radiographic appearance is a pure osteolysis, extended to the whole cross section of the bone, thinning and "inflating" the cortex. Bony septa are usually present, giving the appearance of a multiloculated cyst. When fracture occurs, a small fragment of the wall may be seen on X-rays in the cavity, also known as "fallen fragment" sign. The cyst usually initiates centrally in the metaphysis, close to the growth plate, and progressively and slowly extends toward the diaphysis. The MRI shows an homogeneous liquid content in the cyst, bright in the T2-weighted images. The cortex even if very thin is well defined and continuous, with no periosteal reaction (except if there is a fracture).

Histhopathology: Grossly it appears as a cavity filled by serous or serosanguineous fluid. The cavity is lined by a thin membrane made of fibroblasts and few (if any) multinucleated giant cells. Cholesterol slits and hemosiderin deposits can be present. About 20% of the cyst walls contain clumps of pink, granular amorphous material (so-called wooly bone) composed of degenerated fibrinoid cementum-like material that is quite diagnostic of SBC when seen.

Course and Staging: Bone cysts are staged according to their activity. Lesions abutting to the growth plate usually have an internal pressure > 30 cm H_2O, a shiny membrane, and overall clinical features of activity, being considered stage 2. Lesions located far from the physis usually have an internal lower pressure, a thicker membrane, and overall features of inactivity, being considered stage 1. Occasionally the fracture may induce spontaneous healing of the cyst.

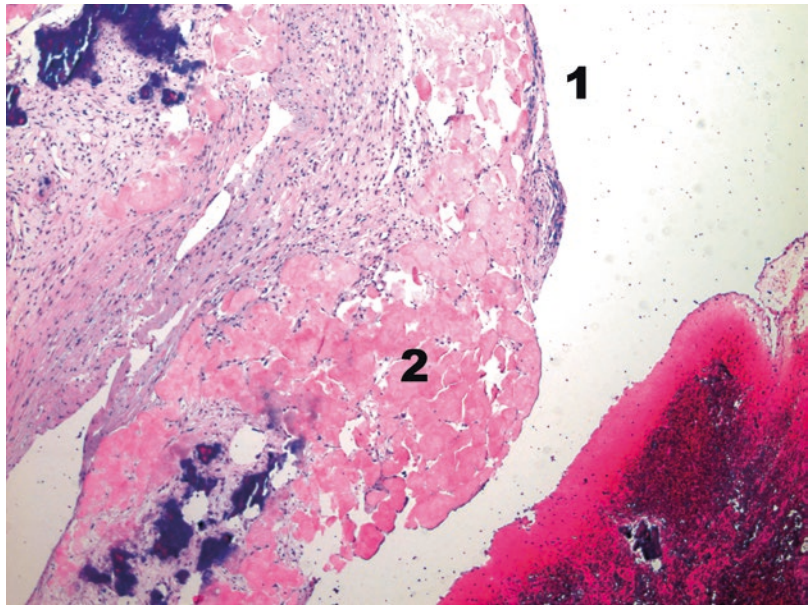
Treatment and Prognosis: Treatment depends on the stage of the cyst, patient's age, and presence or not of a pathological fracture. In young patients and active cysts, percutaneous injections (with methylprednisolone or bone marrow) appear to have a reasonable success rate in the majority of active cysts. Pathological fracture usually induces ossification of the cyst. Curettage and bone grafting of the cyst +/− internal fixation in fracture or risk of fracture in weight bearing sites.



Radiographs of the proximal humerus and femur in two patients. Lesions are metaphyseal, start from the epiphyseal plate, are purely lytic, and in the middle of the bone. The cortex is thin. The humeral lesion is broken (compound fracture with a small cortical fragment fallen into the cystic cavity: "fallen fragment")

Key points	
Clinical	Incidental findings or pain if fractured
Radiological	Pure lytic, central, metaphyseal
	After fracture, “fallen fragment” sign

Key points	
Histological	Pure cavity, lined by a thin connective tissue
Differential diagnosis	None



(1) Thin and shiny membrane made up of loose collagen. In the wall of the cyst, there are fibroblasts, macrophages, and scattered lymphocytes. (2) Fibrinoid material, considered pathognomonic of SBC, associated with calcifications

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Langerhans' Cell Histiocytosis

10

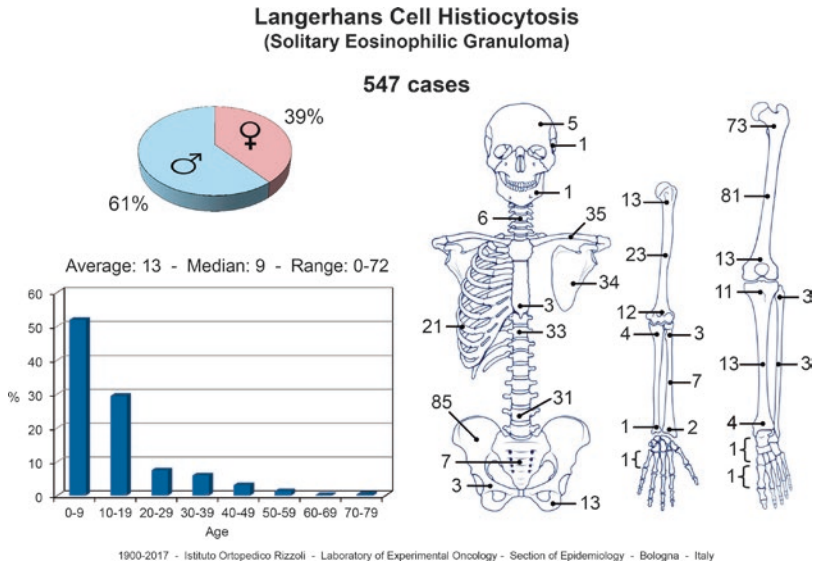
Laura Campanacci

Definition: Group of multiple-systemic diseases may involve bone marrow, internal organs, skin, and mucosae, characterized by a histiocytic proliferation of granuloma-like aspect. The pathogenesis is unclear; viruses, bacteria, and genetic factors have been implicated. An immunological dysfunction has also been reported; familial occurrence is very rare.

(a) Localized in the skeleton: solitary or multiple eosinophilic granuloma
(b) Chronic disseminated: including Hand–Schuller–Christian disease
(c) Acute/subacute diffused: including Letterer–Siwe disease

10.1 Eosinophilic Granuloma

Epidemiology: More frequently solitary, multiple <10%. Males. 5–10 years of age.



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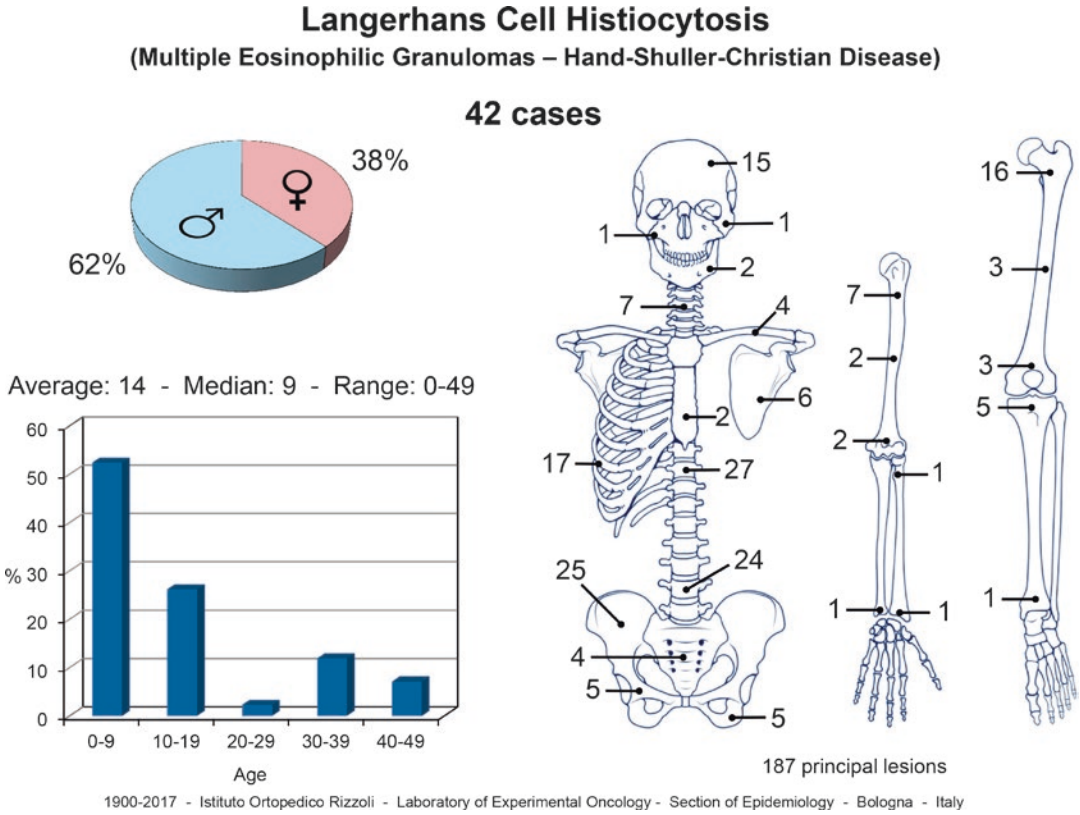


Location: Flat and short bones of the trunk: skull (parietal, frontal site), ribs, pelvis, vertebral body, clavicle, and scapula. Among long bones: proximal half of the femur, humerus, and tibia (diaphyseal localization is typical). Very rare in the hand and foot.

Clinical: Pain, wide swelling in superficial bones, rare pathologic fracture; radicular pain, rarely signs of medullary compression and deformities of the column in vertebral lesions. Rare mild increase in sedimentation rate and mild eosinophilia.

Imaging: Imaging varies according to the age, localization, and phase of the lesion. Standard X-rays usually show an osteolytic lesion with variable features. Sometimes rounded, often polycyclic, well-defined margins, thin sclerotic rim, and overall benign-looking appearance. Sometimes "moth-eaten" pattern with ill-defined margins, no sclerotic rim, "onion-skin" periosteal reaction mimicking a malignant process (e.g., Ewing sarcoma). Uniform, rapid flattening of the vertebral body reduced to a thin bony lamina (vertebra plana) is typical. Bone scan sometimes shows multiple lesions, but usually does not show an intense uptake, sometimes it can even appear almost negative. On MRI light gray, intermediate low signal on T1, and a higher than fat, bright signal on T2.

Histopathology: Soft, semi-liquid, yellowish-gray tissue, with areas of hemorrhage or necrosis. Background of inflammatory cells (lymphocytes, plasma cells, macrophages, rare neutrophils, and abundant eosinophilyc granulocytes, sometimes forming eosinophilic abscesses). Langerhans cells are the diagnostic cells. They are characterized by a wide cytoplasm with ill-defined membrane and reniform, indented, pale nucleus, a

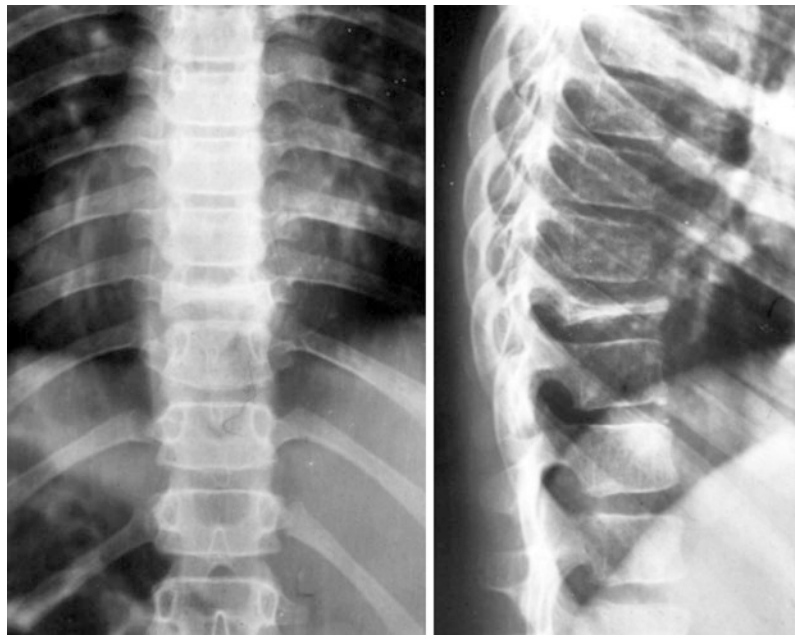
small nucleolus with nuclear grooves, imparting a "coffee bean" appearance. Sporadic giant cells and foam cells can also be present.

Course and Staging: Rapid growth, spontaneously self-limiting, and tendency to healing with at least partial bone repair, rare evolution into multiple type, exceptional transformation into chronic diffused type. Usually stage 2, rarely stage 3.

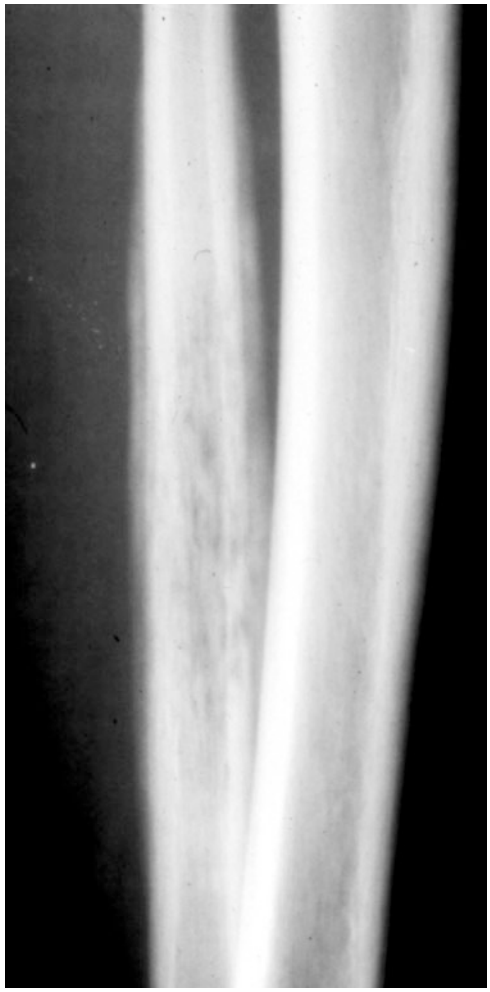
Treatment: Even if not treated tends to a spontaneous healing, or this may happen after a simple needle biopsy. Needle biopsy, frozen section, and steroid injection are treatment of choice. Clinically very successful with complete or almost complete repair in 2 years. Bracing or casting required in the spine. Systemic cortisone and chemotherapy are used in multiple lesions.

Key points	
Clinical	Pain, swelling, rapidly increasing
Radiological	Variable aspects, from benign to aggressive aspects
Histological	Langerhans cells, leukocytes, eosinophils
Differential diagnosis	Osteomyelitis, Ewing sarcoma

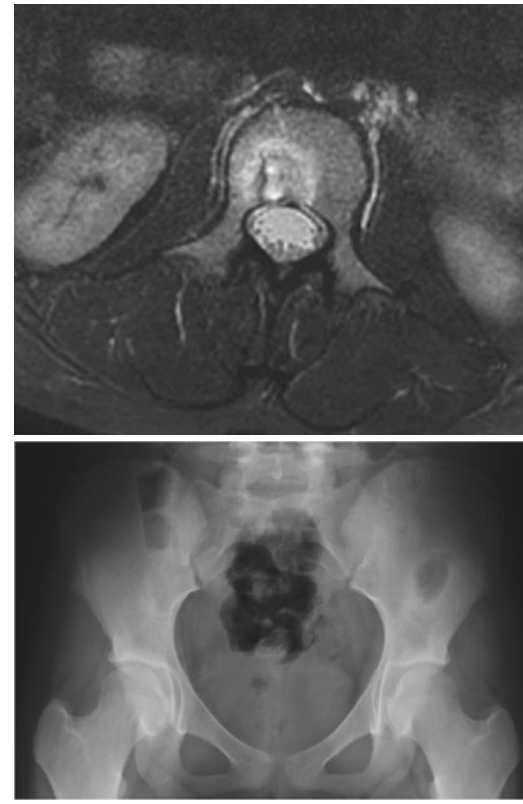
Immunohistochemical panel	
CD1a	+
S100	+
Langerin	+



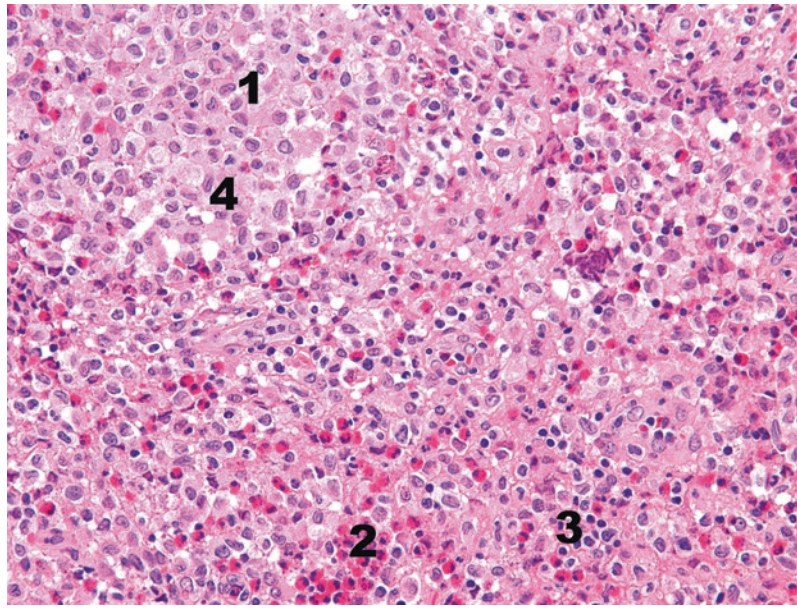
AP and lateral radiographs of the spine: complete vertebral collapse of T9. No soft tissue mass



Radiograph of the fibula: poorly limited lytic lesion of the shaft, with irregular periosteal bone formation. Differential diagnosis with Ewing sarcoma or an acute infection may be very difficult at the onset of disease



Woman 25 years old. MRI (T2 weighted) of L2 shows irregular osteolysis surrounded by bone edema. Standard X-ray of the pelvis shows a roundish osteolysis in the left iliac wing with thin rim of bone sclerosis



(1) Background of large Langerhans cells, generally organized in a more or less loose net, rarely collected in nests or nodules. (2) Infiltration of eosinophilic granulocytes. (3) Mixed inflammatory cells (eosinophils, neutrophils, and lymphocytes). (4) "Coffee bean" nuclei, with indentations in the nuclear membrane, typical and diagnostic feature of Langerhans cells

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Histiocytic Fibroma

11

Laura Campanacci

Synonyms: Non-ossifying fibroma, Metaphyseal fibrous defect, Fibrous cortical defect, Fibrous xanthoma

Definition: It is a common benign lesion essentially consisting of histio-fibroblastic tissue, most frequently originating eccentrically, in the metaphyseal portion of a long bone, in a skeletally immature individual.

The tendency to remain asymptomatic and spontaneously resolve in most instances and the common relationship with tendon and ligament insertions in proximity of the growth plate suggest a posttraumatic or developmental defect producing faulty ossification rather than a true neoplasm. It is not infrequent to see two or three lesions in either one or both lower extremities of the same patient. A different and very rare clinical scenario is the association of numerous multiple histiocytic fibromas, more extensively involving the skeleton, with extraskeletal abnormalities. This condition known as Jaffe–Campanacci syndrome will be discussed separately.

Epidemiology: Overall, it is a very frequent lesion, the incidence of which has been estimated around 30%. However, patients are in most instances asymptomatic, and the true incidence is therefore underestimated. There is slight male sex predominance. It is typical in childhood and adolescence, being rare before 5 and after 20 years of age.

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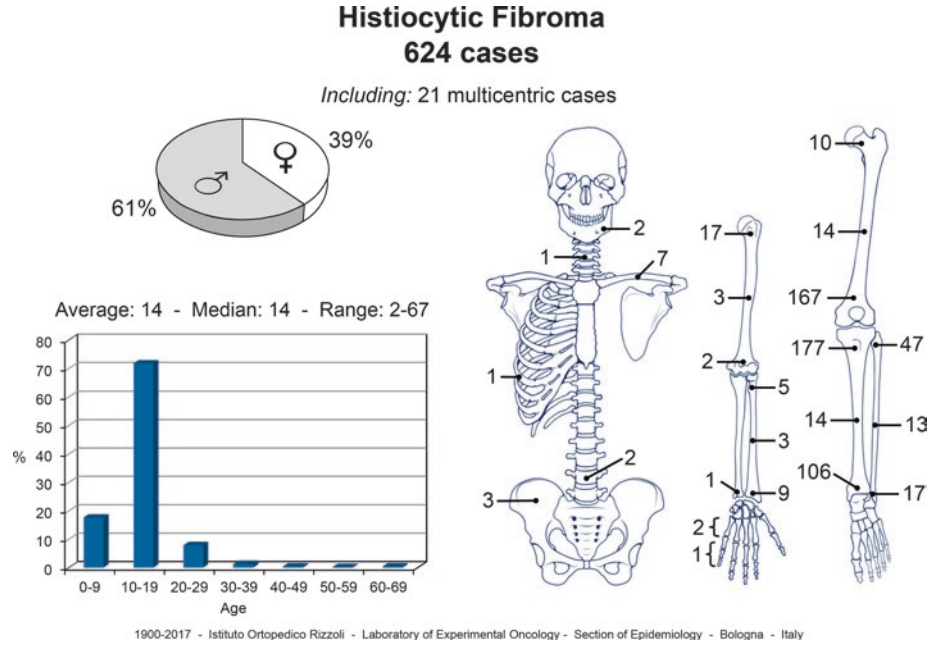


Localization: It is generally localized in the metaphysis at first and then displaced toward the diaphysis. It starts intracortically/subperiosteally. Most of the lesions are located around the knee and ankle. It is rare in the proximal femur and upper limb, exceptional in the trunk, hand, and foot. Two or three lesions may appear in the same or both lower limbs (e.g., distal femur and proximal tibia).

Clinical Aspects: Diagnosis is usually based on a radiogram obtained for unrelated reasons (usually trauma), histiocytic fibroma being the most classic and common lesion diagnosed as incidental finding. Rarely, pathologic fractures may occur in larger lesions (more than 1/2–2/3 of the bone cross section, particularly for the distal tibia and fibula).

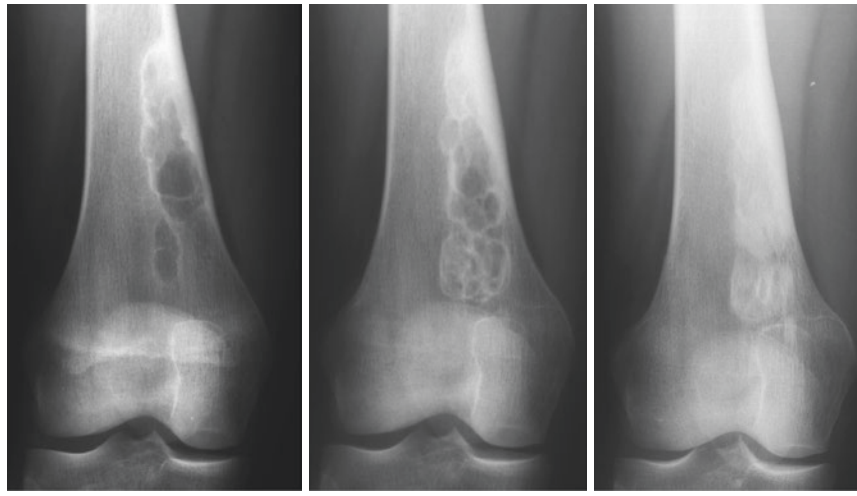
Imaging: Standard X-rays are usually diagnostic. The defect is metaphyseal, intracortical, and/or subperiosteal. Generally lobulated, its inner boundaries are surrounded by a rim of bone sclerosis. The osteolytic image may appear multilocular due to corrugations of the bony wall. The cortex is sometimes attenuated, rarely slightly expanded due to chronic periosteal reaction.

Histopathology: Tissue is compact, rubbery soft, tan brown in color, sometimes containing yellow (foam cells) or dark (hemosiderin) areas. Dense network of cellular typically plump spindle cells with a prominent storiform pattern, and with scattered multinucleated giant cells. Intra- and extra-cytoplasmatic hemosiderin and lipid-loaded foam cells are common findings. Mitotic figures, foci of reactive bone, and infiltration in between the host bony trabeculae can be present.

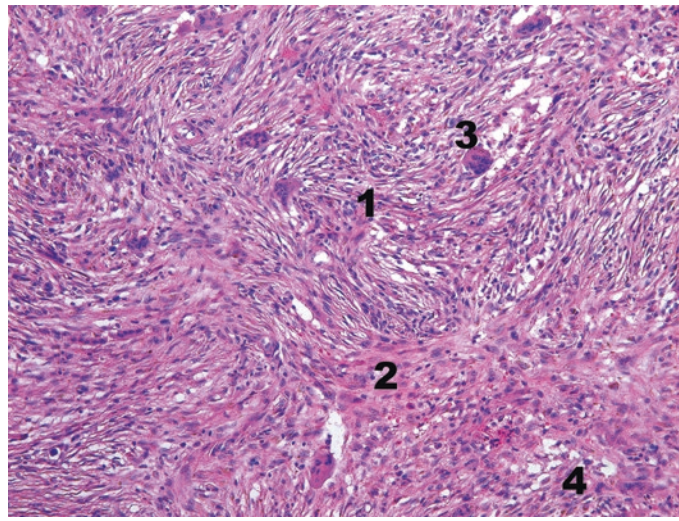
Course and Staging: Tumor growth stops at skeletal maturity and very frequently even before. The lesion then tends to ossify slowly. The stage is initially 1 or 2 and then constantly becomes 1.

Treatment and Prognosis: The majority of histiocytic fibromas do not require treatment; diagnosis can usually be made on clinico-radiographic features avoiding biopsy. Occurrence of a pathologic fracture per se is not an indication for surgery, as fractures heal essentially in a normal fashion. Curettage and bone grafting are rarely needed for large lesions, possibly associated with internal fixation for displaced fractures.

Key points	
• Clinical	Incidental findings
• Radiological	Eccentric, lobulated, subperiosteal or intracortical
• Histological	Bland spindle cells without atypia in a storiform pattern
• Differential diagnosis	Chondromyxoid fibroma (at imaging) Fibrous dysplasia



Radiographs of the knee. The lesion is lytic, metadiaphyseal, centered on the cortex, and limited by a sclerotic line. As it was painless, diagnosis of histiocytic fibroma was sure, and biopsy was not performed. With time ossification that slowly completely regressed appeared in the proximal (older part) lesion



(1) Compact histio-fibroblastic tissue arranged in imbricated and whorled bundles (storiform pattern). (2) Great number of slightly plump and well-stained nuclei; rare and normal mitotic figures (active areas of the lesion). (3) Small and sparse giant cells, less numerous cells, and more abundant collagenous bundles (florid stage). (4) Foam cells (regressive phenomena of the tumor)

11.1 Multiple Histiocytic Fibromas with Extraskeletal Abnormalities (Jaffe–Campanacci's Syndrome)

It is a very rare condition possibly linked to neurofibromatosis. Multiple large histiocytic fibromas extend to the long bones of one or both lower limbs or to the four limbs with prevalence in one side of the body and even including the pelvis. Café au lait skin spots are usually seen. Occasionally, mental retardation, hypogonadism or criptorchidism, ocular and cardiovascular anomalies, and other skin alterations suggestive of neurofibromatosis are associated.

More frequently symptomatic, as compared to the usual histiocytic fibroma, they cause slight

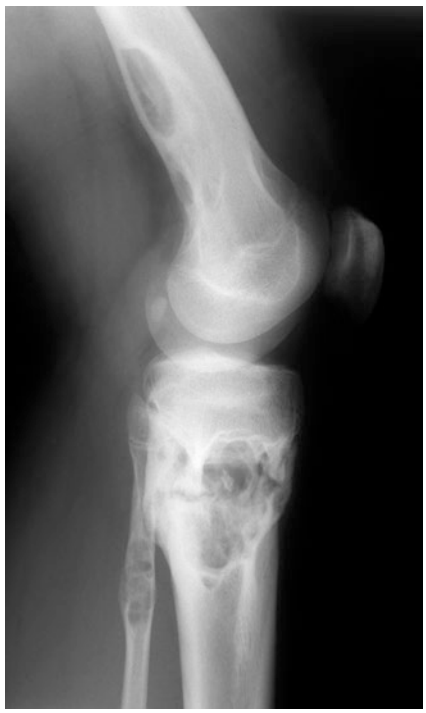
expansion of the bone, stress or pathologic fractures, and sometimes deformity or limb length discrepancy.

Imaging: Lesions are rather extensive and, from the metaphysis, tend to involve the diaphysis. Osteolyses are mostly intracortical or eccentric. The cortex may be very thin or absent. Differential diagnosis includes multifocal fibrous dysplasia, but imaging and histopathology is quite different in the two lesions.

Histopathology: Same as conventional histiocytic fibroma.

Course: Similar to conventional histiocytic fibroma. The lesions do not expand after skeletal maturity and then tend to be replaced by sclerotic bone.

Treatment: Aimed to prevent pathologic fractures and address deformities.



Radiograph of the knee, lateral view. Multiple histiocytic fibromas. The lesion of the tibia is broken. The one on the fibula appears centered and not cortical. This pattern is frequent in thin bones

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Fibrous Dysplasia

12

Piero Picci

12.1 Related Conditions: McCune–Albright Syndrome, Mazabraud Syndrome

Definition: Intramedullary lesion consisting of a peculiar fibro-osseous tissue; it may be either monostotic or polyostotic.

Epidemiology: Monostotic fibrous dysplasia is frequent, polyostotic uncommon, and McCune–Albright syndrome is rare. Difficult to assess true incidence because often asymptomatic. Slight female predominance. Usually diagnosed between age 10 and 30. When asymptomatic, it can be discovered at any age. The polyostotic forms and McCune–Albright syndrome manifest in early childhood.

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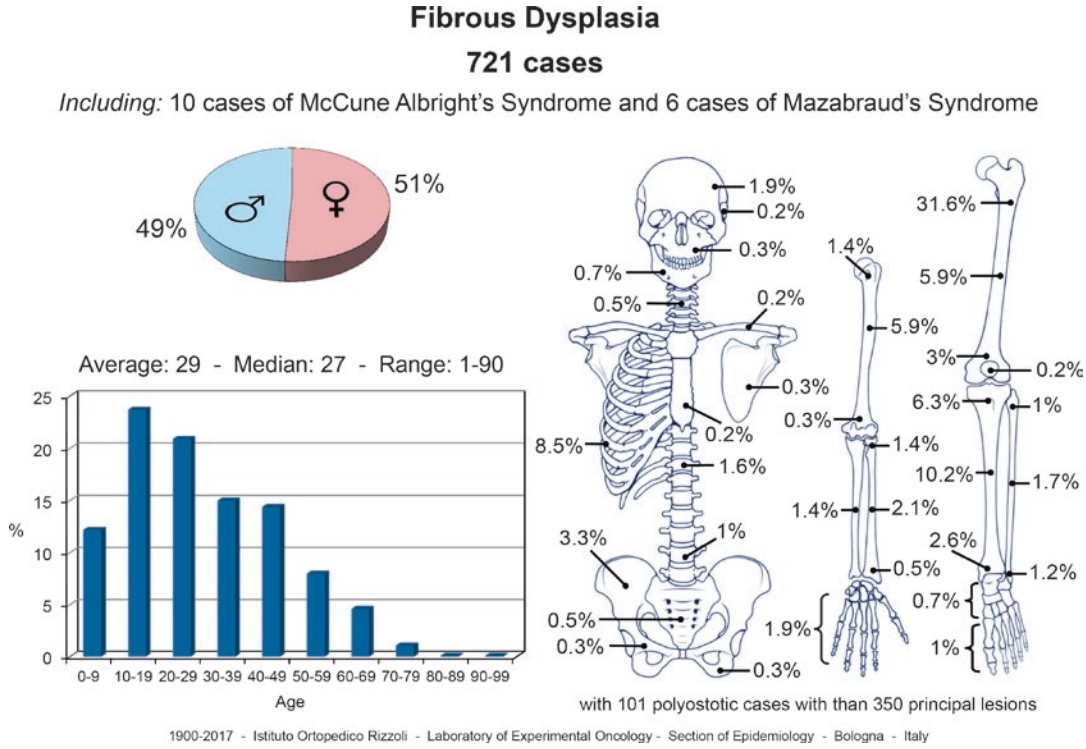


Location: Femur (proximal), tibia, craniofacial bones, and ribs; then humerus, forearm, and pelvis. Same sites in multicentric and polyostotic disease. Frequently more areas in the same long bone or two to three adjacent bones are affected. Lower limb more frequent than upper limb. Hand and foot are involved almost only in extensive polyostotic forms. Spine, scapula, and clavicle are rarely affected. Poliostotic type is usually prevalent in one body side.

Clinical: Monostotic is usually asymptomatic representing an incidental finding. Polyostotic: discontinuous pain (fatigue fractures), bony expansion in superficial bone, pathologic fracture, deformity, and lower limb length discrepancy. In polyostotic forms also cafè au lait spots ("coast of Maine"), multiple endocrine abnormalities (McCune–Albright syndrome), and intramuscular mixomas (Mazabraud syndrome).

Imaging: Standard X-rays show defined defect involving cortical and cancellous areas. Margins are well defined, sometimes marked by a rind of bone sclerosis. The cortex is sometimes thinned and expanded but continuous. No periosteal reaction. Radiolucency of "ground glass" appearance depends upon the amount of intratumoral trabeculae of woven bone. Severe "shepherd's crook" deformity of the proximal femur, usual in polyostotic form. Isotope scan: rather hot (diffuse dysplastic bone formation) and corresponding to radiographic extent. CT: homogeneity of ground glass radiolucency; cystic cavities and cartilaginous areas (sometimes calcified) when present. MRI: fairly homogenous low signal in T1.

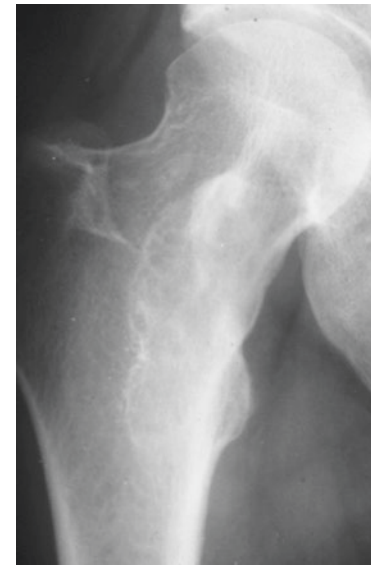
Histopathology: Periosteum is not involved; underlying cortex is regularly smooth but thin. Lesional tissue, well defined from surrounding bone, whitish to pink, from fibrous to gritty, to

hard bony. Sometimes, hemorrhagic areas or cystic spaces with serohematic content are present. Rarely, sparse lobules of hyaline cartilage are embedded in the above-described tissue. Histologically, it is characterize by a mixture of plump not atypical spindle cells and islands of woven bony trabeculae irregularly shaped, in the so-called "chinese letters" or "alphabet letters" fashion. Usually, bony trabeculae show no clear-cut osteoblastic rimming. Benign giant cells and foam cells are commonly found. Mitotic figures are uncommon and never atypical. Islands of cartilage may dominate the histologic appearance (so-called "fibrocartilaginous dysplasia"). It may show secondary aneurysmal bone cyst like areas.

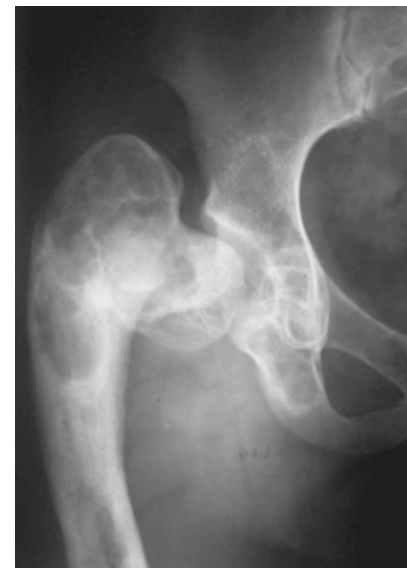
Course and Staging: Lesions are usually stage 2 in children and adolescents and stage 1 in adults. If a lesion expands and becomes symptomatic in an adult, this may be due to hemorrhage (during pregnancy). Rarely (less than 0.5% of the reported cases) a sarcoma may develop on a fibrous dysplasia. It usually occurs in adult of advanced age, both in monostotic and in polyostotic fibrous dysplasias, more frequent after radiation therapy.

Treatment: Frequently not needed. Curettage and grafting of active lesions should be avoided. Deformities may need corrective osteotomies and internal fixation, preferably by intramedullary devices.

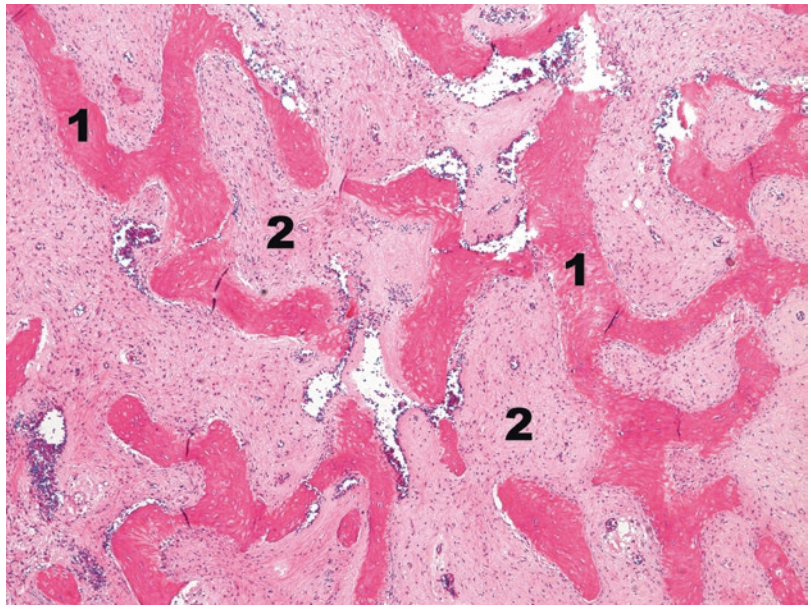
Key points		
• Clinical	Incidental findings	
• Radiological	"Ground glass" appearance	
• Histological	Benign fibroblastic lesion producing immature woven bone. No osteoblasts	
• Differential diagnosis	Low-grade central osteosarcoma	
Chromosomal translocations		
• Point mutations GNAS1	20q13.32	93%



Radiograph of the proximal femur. The lesion is metadiaphyseal, eccentric, sclerotic, and heterogeneous. It is well limited by a sclerotic ring



Radiograph of the hip. Lytic and sclerotic well-limited lesions. Typical femoral neck deformity (Shepherd's crook)



Histopathologic features are represented by immature bone trabeculae enmeshed in immature histio-fibroblastic tissue. (1) The dysplastic bone trabeculae are generally small and shaped like Chinese ideograms; they are usually not bordered by rows of osteoblasts. Trabeculae have a woven structure. (2) Undifferentiated fibrous connective tissue surrounding the trabeculae. The histio-fibroblasts are numerous and plump, with rare mitotic figures

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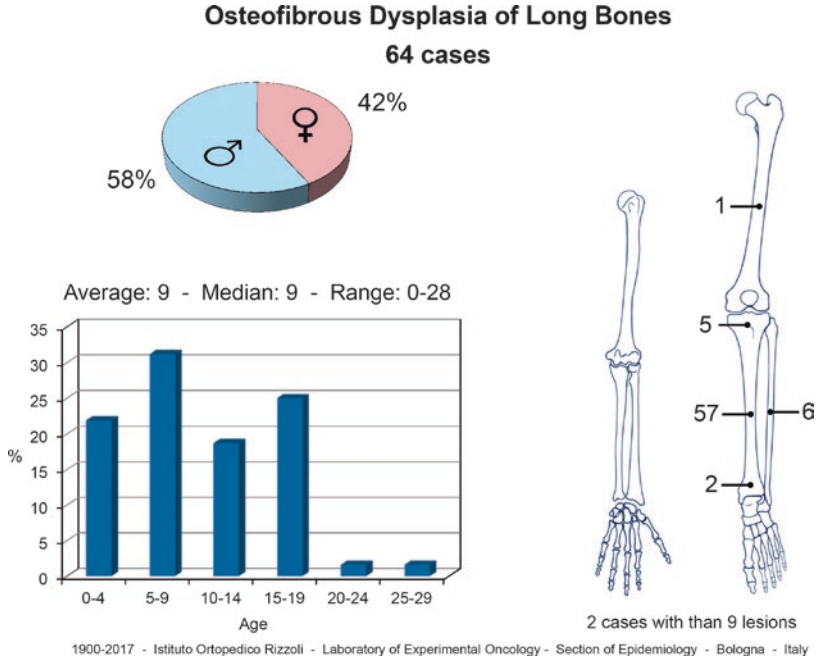
13 Osteofibrous Dysplasia of Long Bones

Alberto Righi

Definition: Benign fibro-osseous lesion of bone, characteristically involving cortical bone of the anterior mid-shaft of the tibia of young patients. This lesion is also called osteofibrous dysplasia of long bones (DOFOL), Kempson-Campanacci disease, and ossifying fibroma of long bones.

Epidemiology: Rare (<1% of all bone tumors). No clear sex predilection. Usually observed in infantile age, below 5 or 10. Rare cases are congenital.



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Localization: The lesion is almost exclusively localized in the anterior cortex of the mid-shaft of the tibia, occasionally involving the ipsilateral or contralateral fibula. Exceptionally in ulna, radius, and humerus.

Clinical: The symptoms are moderate expansion of the bone, anterior or valgus-varus bowing of the diaphysis. The lesion is painless. Stress and pathologic fractures are not uncommon. Pseudoarthrosis is exceptional.

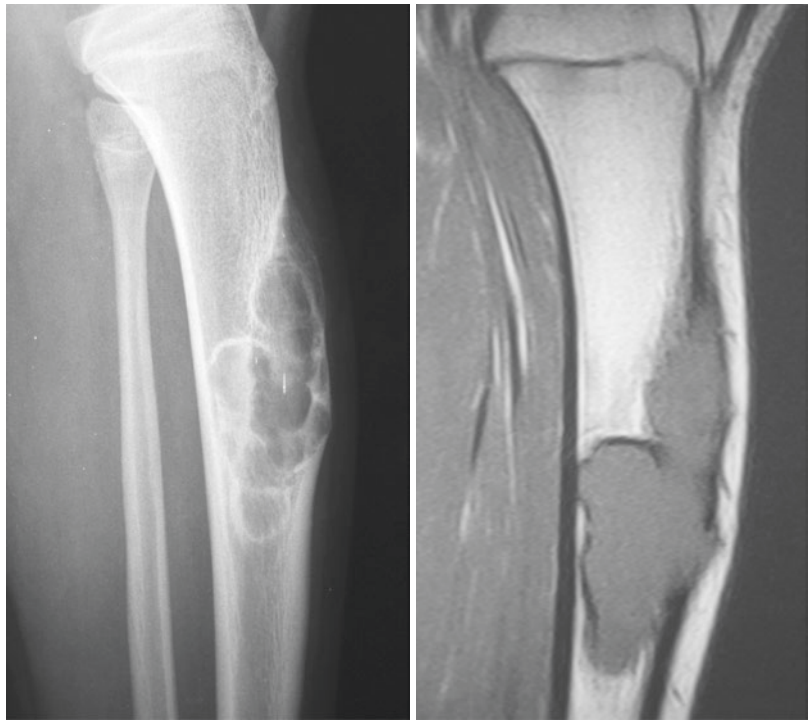
Imaging: The lesion typically appears as an intracortical osteolysis of the anterior cortex of the tibia, often associated with an anterior bowing of the diaphysis. The cortex is regularly and moderately expanded, very thin, and with a smooth surface. Toward the medulla, the osteolysis is bordered by a rim of sclerotic bone, so that the medullary canal is frequently narrowed or closed. The osteolysis can be multilocular, with a bubbly appearance. Some of the lesions are veiled by a tenuous ground-glass radiodensity. Bone scan is typically hot. On MR, the lesions show high intensity on T2-weighted images and mixed signals on T1-weighted images and fat-suppressed images.

Histopathology: Grossly, it is composed of yellow, gray, or white tissues, generally firm and gritty in consistency. Histologically, it is characterized by irregularly shaped, curvilinear woven bony trabeculae, rimmed by cubic osteoblasts, sometimes with scattered osteoclasts. Between the bony trabeculae, an hypocellular proliferation of bland not atypical spindle cells in a storiform pattern is present. The intercellular stroma is collagenous to myxoid. The bone trabeculae tend to be sparse, thin, and woven in the center of the lesion, to gradually become more abundant, anastomosing, and lamellar toward the periphery, where both the trabeculae and the fibrous tissue blend with the surrounding host bone (zonal architecture). Secondary changes such as hemorrhagic areas, foam cells, and cystic changes may be present. Isolated cytokeratin-positive epithelial cells are present in about 90% of cases, not obvious on the hematoxylin-eosin stain.

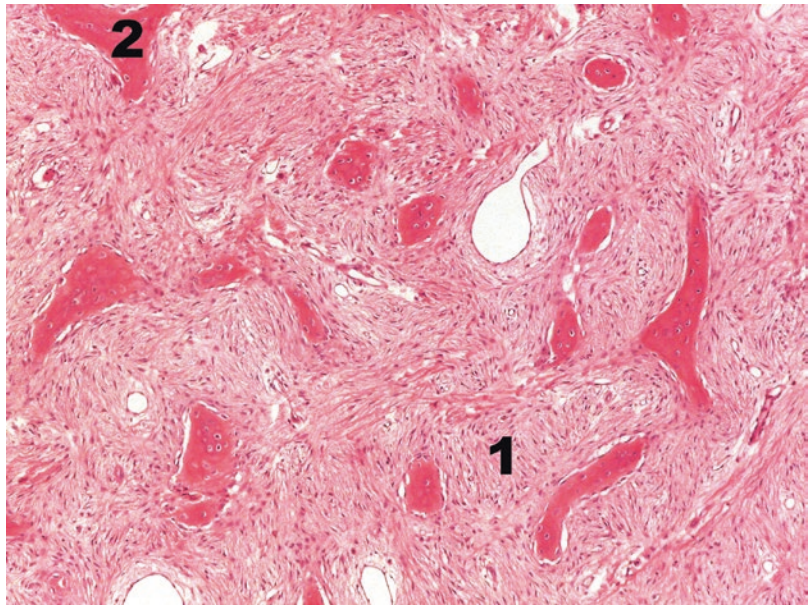
Course and Staging: The lesion may progress considerably in the first years of life, thereafter stabilizes, and after 10–12 years of age, slowly repairs through peripheral bone thickening.

Treatment and Prognosis: Attempts to intralesional excision before the lesion has stabilized are regularly followed by local recurrence. Surgery (not even biopsy) is usually not indicated. The child should be protected, when indicated, by bracing, and monitored until spontaneous repair occurs. The prognosis is good, except for the more severe cases ending up with leg deformity and shortening. Progression into adamantinoma has been reported in rare cases.

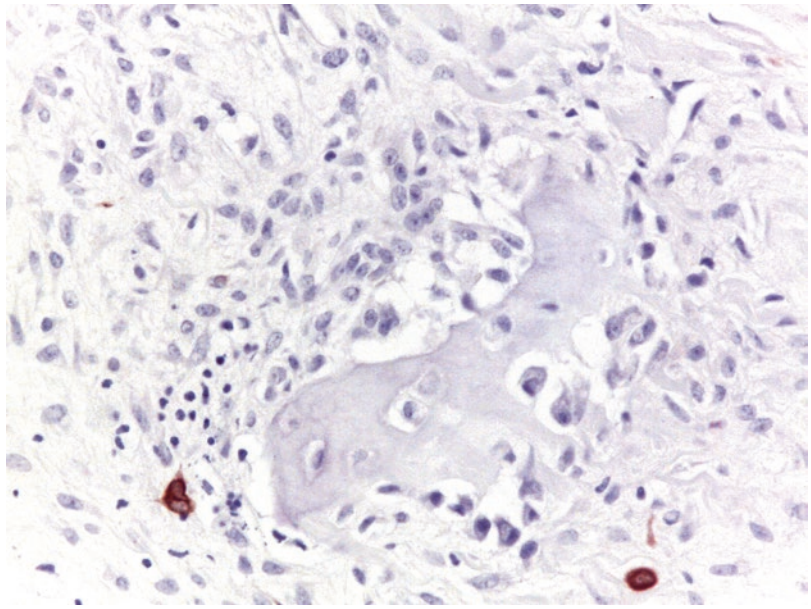
Key points	
• Clinical	Tibia (or fibula) in children, moderate expansion of the bone
• Radiological	Intracortical expansion with deformity
• Histological	Bland spindle cell proliferation with immature woven bone bordered by osteoblasts
• Differential diagnosis	Adamantinoma
Immunohistochemical panel	
• CK	Rare isolated positive cells



Lateral radiograph and sagittal T1 MR image. There is bowing of the tibia. The lesion is centered on the anterior cortex of the shaft of the tibia, lytic, and well limited



Benign fibro-osseous proliferation: (1) bland spindle cell proliferation with a storiform pattern, in a collagenous to myxoid stroma, (2) irregularly shaped woven bony trabeculae with osteoblastic rimming. Open vessels are characteristics



Isolated cytokeratin-positive epithelial cells

13.1 Osteofibrous Dysplasia and Adamantinoma

These two lesions are so related as to deserve to be described under the same heading. Both are rare, but adamantinoma is three times rarer than osteofibrous dysplasia. Osteofibrous dysplasia is a benign even spontaneously regressing lesion, while adamantinoma is a low-grade malignant tumor capable of metastasizing. Osteofibrous dysplasia is typical of childhood, while adamantinoma generally occurs in young adults; there are, however, exceptional cases of adamantinoma in children. Osteofibrous dysplasia and adamantinoma are almost exclusive of tibia and fibula. The clinical and radiological presentations of these two lesions can be different, but frequently they are similar if not identical. Histologically, osteofibrous dysplasia is characterized by a fibro-osseous component containing isolated epithelial cells quite always visible only in keratin immunostaining, while adamantinoma contains large nests of epithelial cells, evident on hematoxylin-eosin stain. Progression of osteofibrous dysplasia into adamantinoma has been reported in rare cases. Osteofibrous dysplasia and adamantinoma are related clinically, radiologically, immunohistochemically, and genetically. Two main hypotheses exist to describe the relationship between these two lesions. According to Dorfman, osteofibrous dysplasia results from a secondary reparative process of overgrowing matured and regressing epithelial tumor tissue; this means that adamantinoma can regresses in osteofibrous dysplasia, with the osteofibrous component being reparative and with a quite total disappearance of the epithelial cells (similar to regressing neuroblastoma). According to Mirra, osteofibrous dysplasia contains foci of epithelial cells which can originate a malignant tumor; this means that osteofibrous dysplasia can evolve in adamantinoma (similar to benign notochordal cell tumor originating chordoma).

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Desmoid Fibroma

14

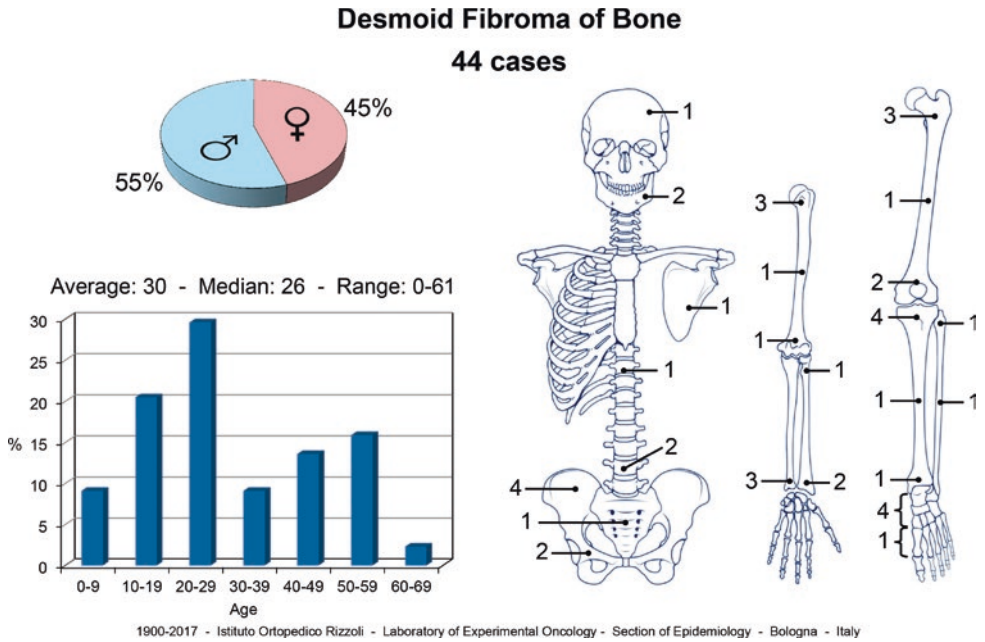
Laura Campanacci

14.1 Desmoplastic Fibroma of Bone

Definition: It is a benign neoplasm composed of spindle cells and collagen, similar to desmoid-type fibromatosis of soft tissues.

Importance: Slow-growing benign tumor with a high tendency to local recurrence.

Epidemiology: Tumor occurs rarely and more frequently in males. The majority of the cases are aged less than 30 years at diagnosis.



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Localization: Desmoid fibroma is more frequent in the mandible, long bones, and pelvis. In the long bones, it is more often observed in the meta-diaphysis, but it may be diaphyseal. During adult age, it usually extends to the epiphysis.

Clinical: Symptoms are mild and late (the lesion grows slowly and is not very vascularized) and include moderate pain and possible pathologic fractures.

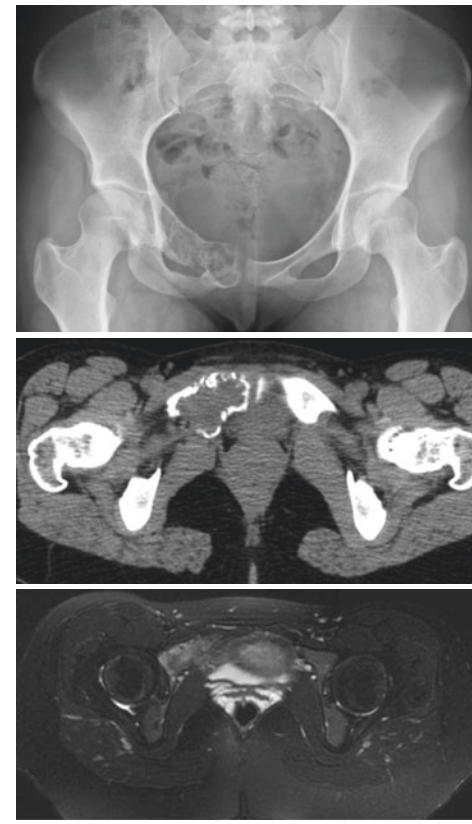
Imaging: The radiographic picture shows a large osteolysis, usually with expansion of the bone. The original cortex may be replaced by a thin shell of newly formed bone. Occasionally and focally, the tumor breaches the cortex with no clear demarcation toward the surrounding tissues. Rather typically, osteolysis has a finely trabeculated, reticulated, or bubbly appearance. Reactive chronic hyperostosis can produce a rind of sclerosis at the edges of the tumor. On angiography and CT, the tumor only moderately takes the contrast, and it appears relatively "cold" on isotope scan. MRI gives a low signal in T1 and T2 suggestive of dense collagenous tissue.

Histopathology: Hypocellular spindle cell tumor associated with large amounts of collagen. Nuclei have a bland appearance with no atypia and few mitotic figures. Areas of relative hypercellularity can be present, but are not common. β-Catenin pathway does not seem to have the same role in the tumorigenesis of desmoid tumor, as it has in the desmoid-type fibromatosis.

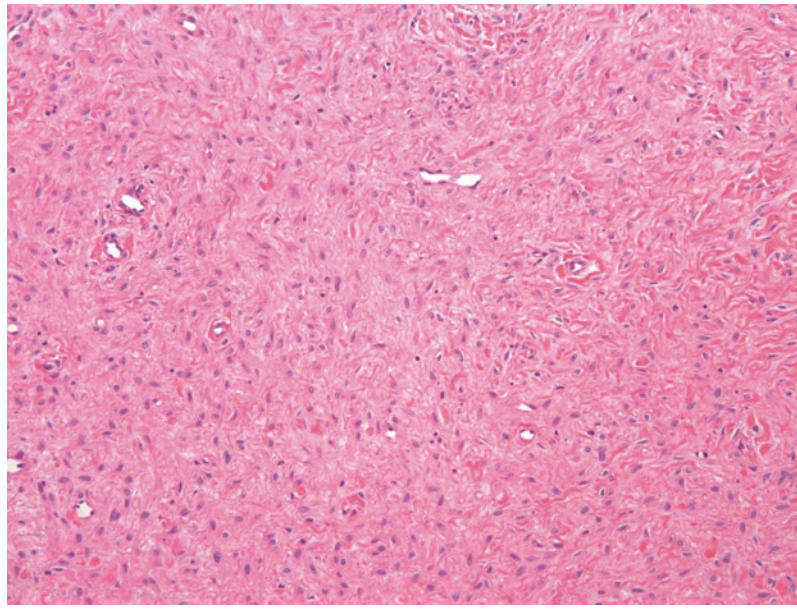
Course and Staging: Growth of the tumor is very slow; it may even take several years prior to causing symptoms. The stage is 2 or 3.

Treatment and Prognosis: Although historical data indicated wide en bloc resection as the treatment of choice, recent experiences show that aggressive curettage is about equally effective providing better functional results. Desmoid fibroma does not metastasize.

Key points	
• Clinical	Mild symptoms
• Radiological	Slow growing lytic lesion with possible expansion of the cortex
• Histological	Bland spindle cells resembling desmoid-type fibromatosis of soft tissues
• Differential diagnosis	Low-grade fibrosarcoma
Immunohistochemical panel	
• Smooth M Act	+/–
• β-Catenin	+ (nuclear staining, occasionally)



Lytic well-limited lesion of the ilio pubic ramus. At the periphery the lesion has a slight infiltrating pattern, and this is the reason for the high tendency of local recurrence. The lesion has a low–intermediate signal on T2 image, indicating fibrous tissue



Hypocellular proliferation of spindle cells with slender nuclei associated with large amounts of fibrillar, hyalinized, or keloid-like collagen. “Open” vessels are typical

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Chondromas

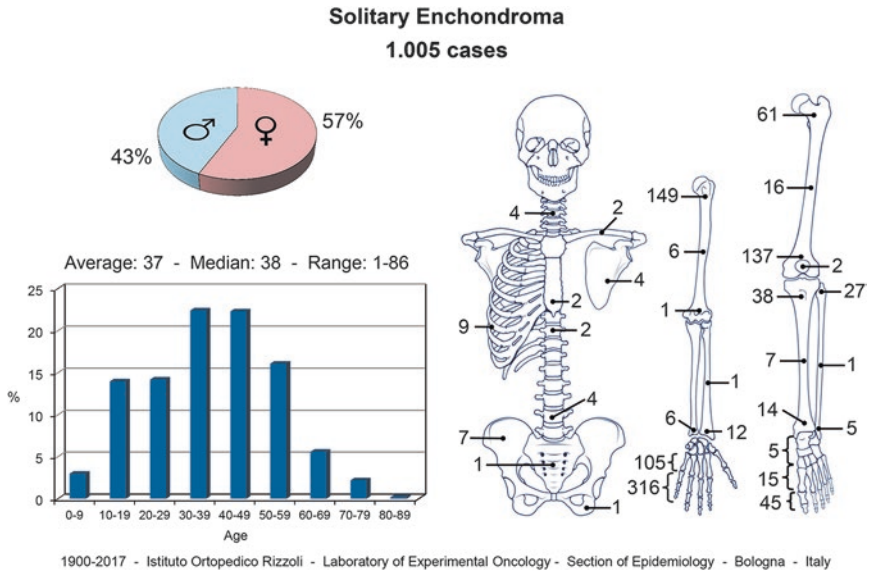
15

Davide Maria Donati and Eric L. Staals

15.1 Solitary Chondroma (Enchondroma)

Definition: Intramedullary neoplasm made of well-differentiated hyaline cartilage.

Epidemiology: Relatively frequent. No predilection for either sex. May be diagnosed at any age.



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Localization: Chondromas occur only in bones that undergo secondary ossification of cartilage during skeletal development. They are very frequently seen in the tubular bones of the hand, where they represent the most common bone tumor. The other chondromas are mainly distributed in the long bones, with preference for the femur. The real incidence of chondroma is unknown, as most of these lesions do not cause any symptoms.

Clinical: Most chondromas are incidental findings on imaging studies. Pain can be due to small cracks or pathological fractures that often occur after minor trauma of the hands. A mild expansion of the cortex can be seen or palpated in superficial bones, such as tubular bones of the hand or foot, ribs, fibula.

Imaging: The lesion is frequently central, sometimes eccentric or intracortical. On radiographs it is usually an osteolysis, with rounded, lobulated, well-defined edges with a thin rind of reactive sclerosis. Often the lesion contains granular, popcorn, ring-like opacities that represent calcification and ossification at the periphery of the cartilage lobules. Chondroma can reach considerable extension in major long bones but rarely exceeds 10 cm. In the long tubular bones, the cortex is intact and does not show erosions. In small bones (hand, ribs), the cortex can be thinned and the bone expanded creating a palpable deformity. CT scan demonstrates the lobular or multi-island nature of the lesion, its sharp limits, and its radio-densities, as well as status of the cortex. MRI at best defines longitudinal extension; the lesion has low signal in T1, high signal in T2, and calcifications are seen as black signal-voids in both T1 and T2. Isotope scan is hot in most lesions and regularly reveals asymptomatic chondromas when performed as a staging examination in case of malignancies.

Histopathology: Lesion consists of lobules of cartilage. The aspect is typical of hyaline cartilage. Calcified areas appear as white opaque granules. Reactive or enchondral ossifications manifest as white-yellow hard rings and streaks around and between the lobules. The limits of the lesion are often irregular, as lobules of cartilage push toward the cancellous bone and excavate little niches in the cortex, but always well defined. The chondrocytes are sparse, with small, round, dense nuclei, of relatively uniform size. Occasionally, isogenous groups of cells can be seen. Double-nucleated cells are present, usually rare, but can be moderate. This does not really distinguish well benign enchondroma from chondrosarcoma. While diagnosis of cartilage tumor is usually easy even on clinico-imaging findings alone, the real problem is to differentiate chondroma from grade 1 chondrosarcoma. Histologically, this distinction is difficult:

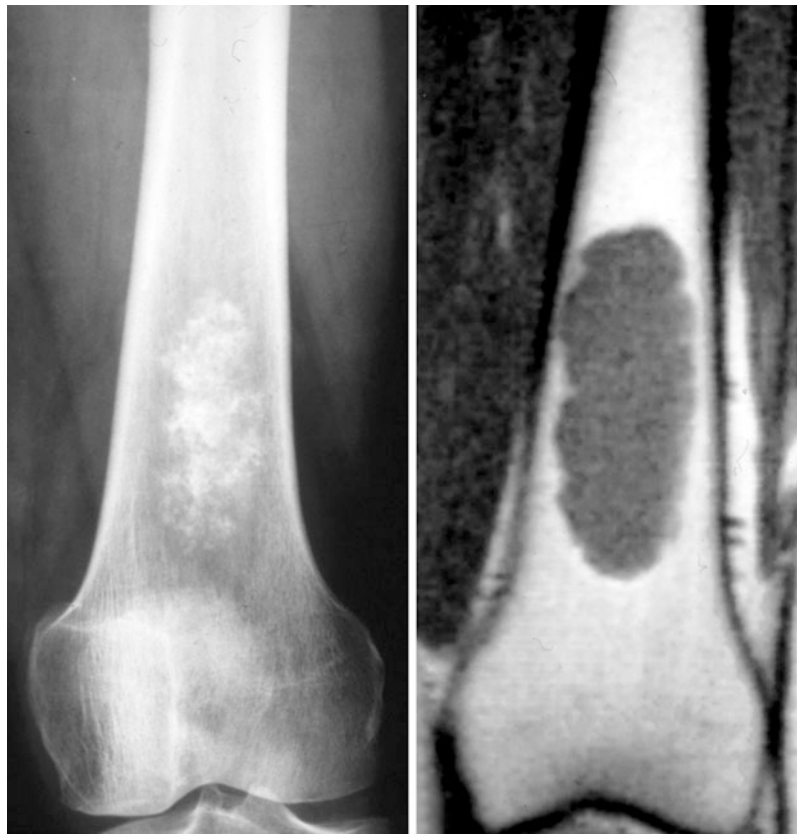
(a) Grade 1 chondrosarcoma has a higher cellularity, more plump nuclei, more than 4–5 double-nucleated cells per high-power field, but such features are subjective.
(b) Areas of chondroma and grade 1 chondrosarcoma may be found in the same tumor.
(c) The histological indicators of low-grade malignancy are meaningless if the lesion is in the hand, or in a child, or periosteal, or in chondromatosis. A useful differential element is represented by the relationship between tumor and host bone. Chondroma may present with cartilage islands scattered in the bone, usually encased by a shell of mature lamellar bone. Chondrosarcoma, on the contrary, permeates marrow spaces and haversian channels of the host in at least 90% of cases. The permeative pattern is 99% accurate, although cartilage permeation-like areas can be found in advanced osteoarthritis and in post fracture epiphyses.

Course and Staging: Until skeletal maturity, chondroma grows slowly, and then it tends to stop. Thus, chondroma is stage 2 in children and stage 1 in adults. The exact incidence of malignant transformation of a solitary chondroma is

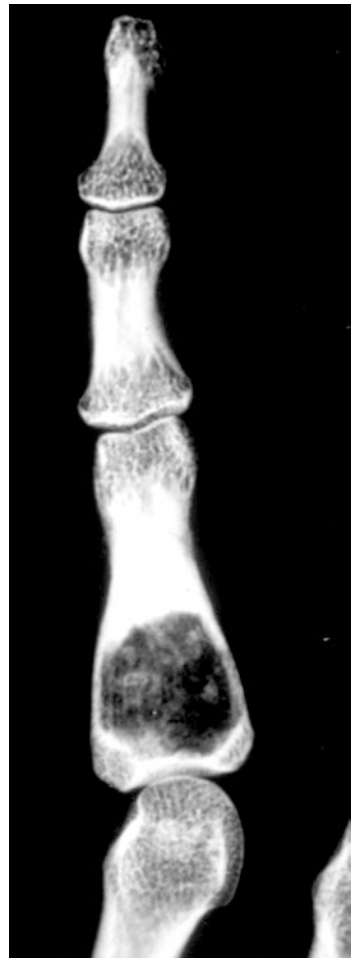
unknown and controversial. Transformation is very rare in the hands, probably less rare in the trunk and limb girdles.

Treatment and Prognosis: Diagnosis can usually be made on clinico-radiographic features. The majority of chondromas do not require biopsy or surgical treatment. Enchondromas of the hand are sometimes treated with curettage and bone grafting because of pain, pathologic fracture, or cosmesis. Rarely, biopsy may be indicated if the diagnosis of enchondroma is unclear and a chondrosarcoma is suspected. Follow-up with serial radiographs or MRI is helpful in the differential diagnosis vs. grade 1 chondrosarcoma. After the epiphyseal plate is closed, enchondromas show little to no growth, chondrosarcoma growth is slow but continuous, and is associated with increasing pain, also at rest.

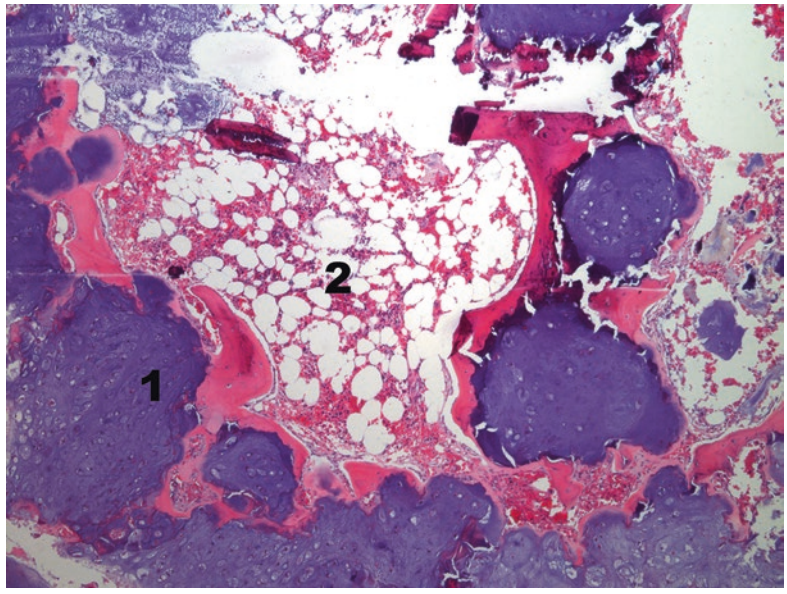
Key points	
• Clinical	Incidental findings
• Radiological	Central, lobulated, granular, and ring-like calcifications
• Histological	Lobules of benign cartilage ossified at the periphery without infiltration of the cancellous host bone
• Differential diagnosis	Low-grade central chondrosarcoma



AP radiograph and coronal T1 MR of the distal femur. Well-limited lesion, centered in the medullary cavity, with typical cartilaginous calcifications (round with a clear center). The cortex and soft tissues are not involved



Radiograph of a finger. Well-limited lesion, containing cartilaginous calcifications



(1) Cartilaginous lobules with mature matrix. (2) Normal fatty marrow in between the cartilaginous lobules

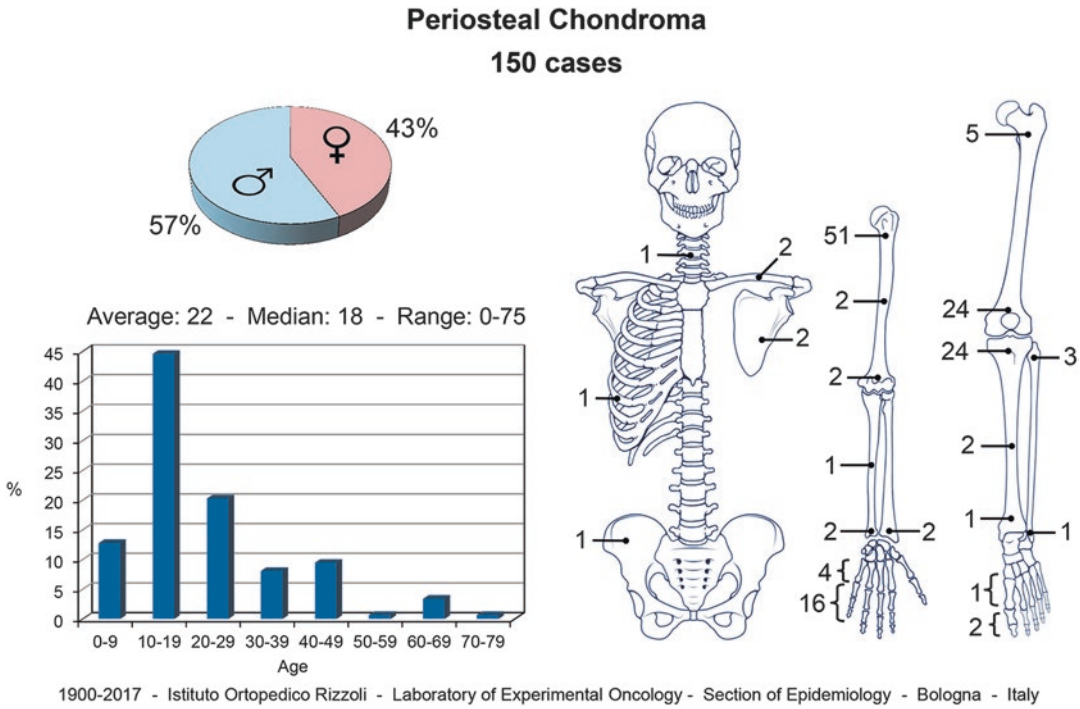
15.2 Periosteal Chondroma

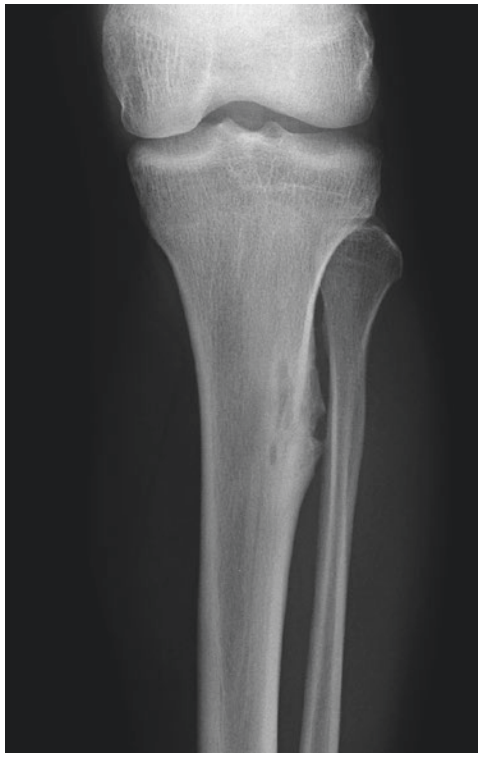
Definition: Benign cartilage neoplasm originating at the surface of the bone.

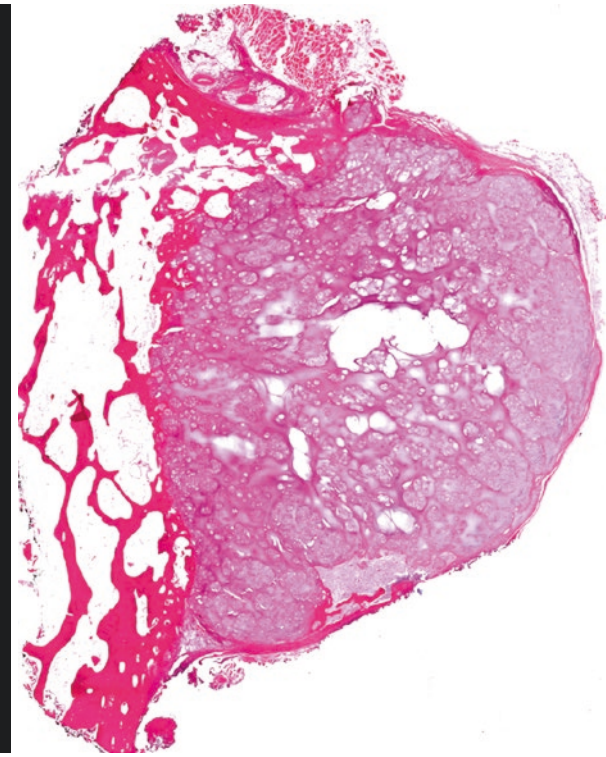
Rather rare, it is usually observed in children or young adults. It prefers the metaphysis of the long bones, particularly the proximal humerus. It is usually moderately painful because of nociception by the periosteum and typically presents as a hard, bony, swelling. Imaging shows a superficial erosion of the bone cortex, at times slightly scalloped, with regular borders. Such erosion is caused by a hemispherical periosteal cartilaginous mass, usually of small to moderate size (<3 cm). Granular or popcorn densities due to calcifications may be seen within the tumor.

Histologically the tumor is very similar to enchondroma, but it more frequently displays features of cell proliferation (high cellularity, nuclear plumpness, and frequent double nucleated cells). Being somewhat painful and causing some swelling in most instances, it usually requires surgical management consisting of either en bloc marginal excision or thorough curettage, equally effective.

Key points	
• Clinical	Some pain, young patients
• Radiological	Subperiosteal, metaphyseal, with erosion of the cortex, granular calcifications
• Histological	Lobules of benign cartilage. Possible hypercellularity
• Differential diagnosis	Periosteal chondrosarcoma



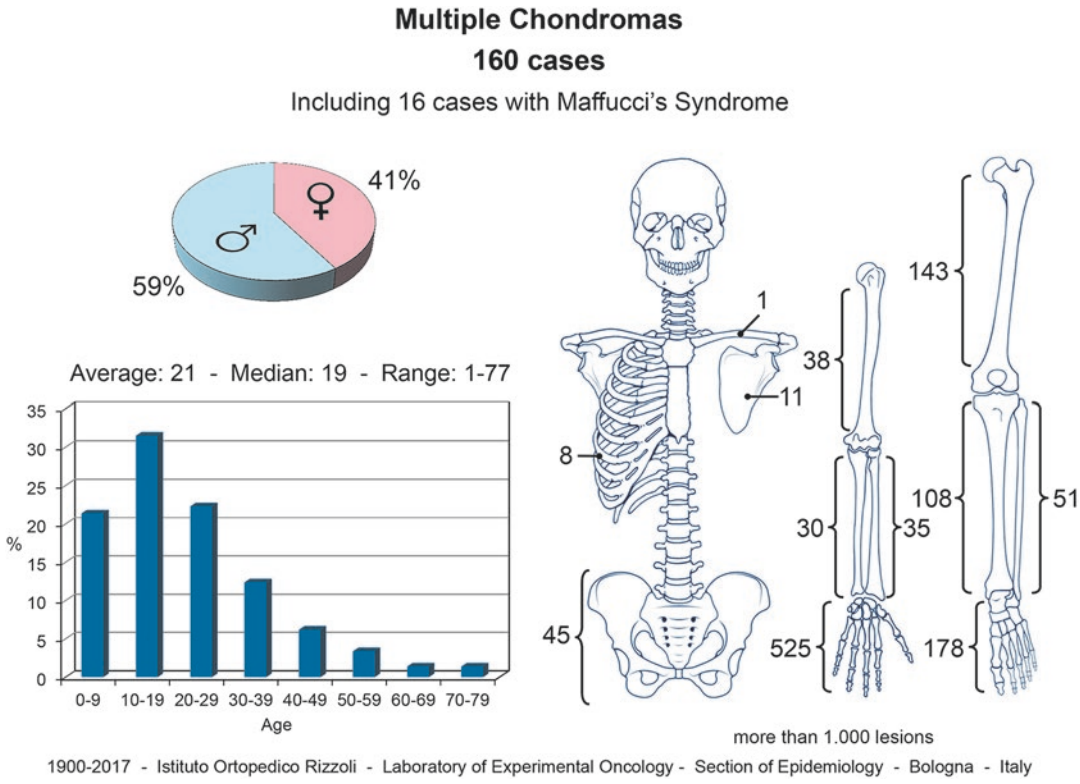




Male, 22 years old. Small (less than 3 cm) well-circumscribed lobulated lesion composed of hyaline cartilage. The lesion is beneath the periosteum with a sharp margin with the underlying cortex. The chondrocytes are frequently enlarged and hyperchromatic with increased cellularity and variability in nuclear size and shape. Chondrocytes are arranged in lobules. The lesion shows sharp borders, in particular without infiltration of the surrounding soft tissue (if present, this is consistent with periosteal chondrosarcoma)

15.3 Multiple Chondromas (Chondromatosis, Ollier's Disease) Associated Condition: Maffucci's Syndrome

Multiple chondromas are infrequent. The condition is not inherited and prevails in males**.** Their distribution and spectrum of presentation are extremely variable. It can present with only a few chondromas limited to the hands or one limb with minimal symptoms or show a hemisomic distribution. It can also be extended to the entire body with overall features of diffuse chondrodysplasia, known as Ollier's disease. The most affected bones are the small tubular bones of the hand and foot, but chondromas may present anywhere in the skeleton. Knobby swelling, bowing deformities, and lower limb length discrepancy (even >10 cm) are the dominant symptoms. Relationship between the polyostotic limited form and the fully expressed diffused chondrodysplasia (Ollier's disease) remains unknown.



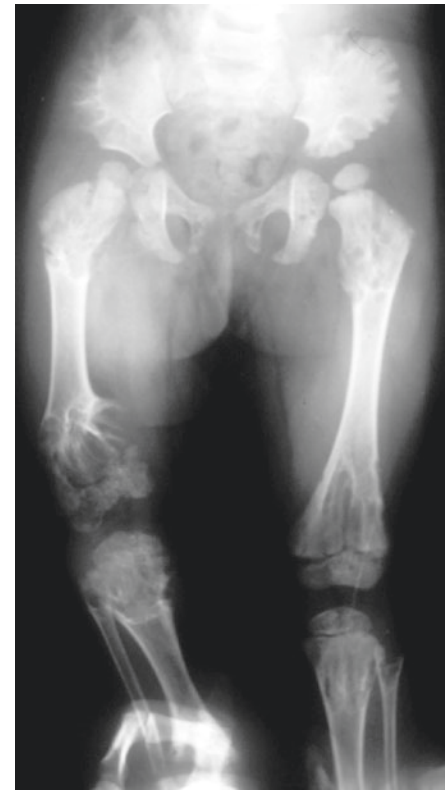
In Maffucci's syndrome (very rare), multiple, diffuse chondromas are associated with multiple hemangiomas. The hemangiomas can be either cutaneous, subcutaneous, or located in the deep soft tissues (not in the bone). Basic imaging is the same as described for solitary chondroma. In the metaphysis, longitudinal columns of radiolucency extend toward the diaphysis. They are divided by longitudinal bony septae. Chondromas can be very extensive, sometimes bubbly or trabeculated, with expansion of the bone, very thin cortex, or lack of any cortex. In Maffucci's syndrome, phleboliths reveal on X-rays the angiomas. MRI scans are useful to detect and follow up the lesions. Histologically, compared to solitary enchondroma, lesions in chondromatosis show features of more pronounced and persistent proliferative potential. Cartilage is more cellular, nuclei are sometimes hyperchromatic, and the histology overlaps with low-grade chondrosarcoma by cytology alone. The stage is 2 in children, more frequently 1 in adults. Transformation to secondary sarcoma, most commonly chondrosarcoma is frequent and probably ranges from 20% to 30% in Ollier and certainly higher in Maffucci (estimated >40%). Also in chondromatosis, malignant transformation to sarcoma is usually seen in adults but may occur even before age 20, especially in Maffucci.

Both Ollier and Maffucci are conditions at increased risk to develop extraskeletal malignancies, such as breast, liver, ovarian cancers and CNS tumors, suggesting an underlying genetic disorder predisposing to cancer in

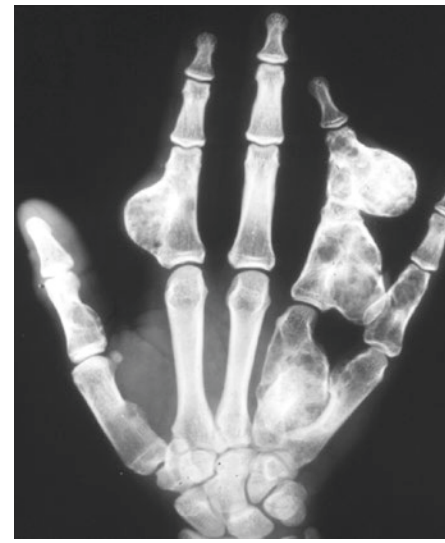
general. IDH1/IDH2 mutations are seen in approximately 90% of enchondromas in enchondromatosis (vs. 50% in solitary enchondromas). Surgical treatment is aimed to relieve symptoms, rather than excise chondromas. Skeletal deformities and limb length discrepancy are addressed by osteotomies and/or lengthening procedures. Prognosis is burdened by the incidence of malignant change.

15.4 Concept of "Active" Chondromas and Differential Diagnosis with Chondrosarcoma

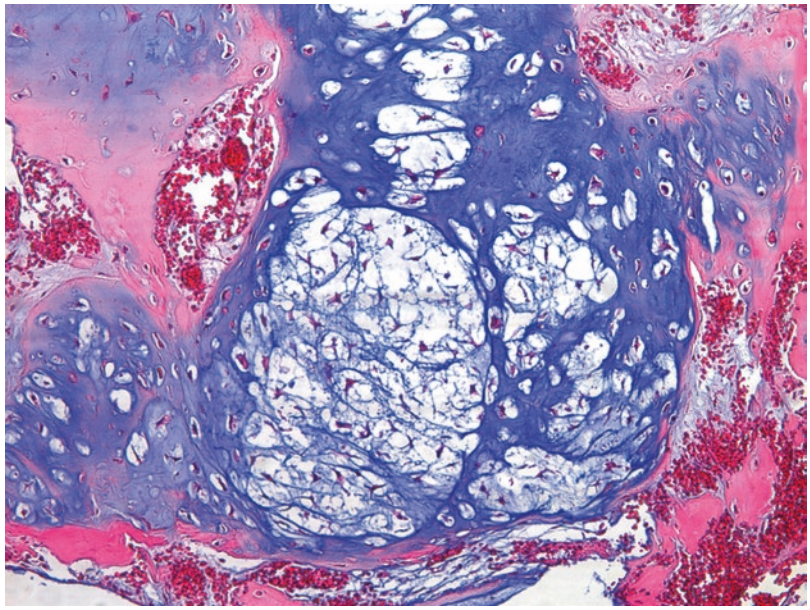
It is important to keep in mind that certain chondromas may show a histological pattern essentially similar to chondrosarcoma. In fact, multiple chondromas in Ollier and Maffucci, periosteal chondroma, enchondromas of the hands and feet, synovial chondromatosis, and soft tissue chondromas all show histologic features consistent with low-grade chondrosarcoma of bone. In other words, a grade 1 chondrosarcoma is cytologically indistinguishable from a benign lesion encountered in the abovementioned clinical settings. Therefore, diagnosis of malignant change is based on clinico-radiographic features and on the permeative growth pattern of tissue toward bone trabeculae. Secondarily, it is of paramount importance that the pathologist reviewing the slides has adequate clinical information, including site of biopsy and imaging studies, and discusses the case with the orthopedic surgeon before making the diagnosis of chondrosarcoma. Quite important to the recognition of malignant change is to have good radiologic baseline studies taken in early adulthood. Malignancy is characterized by a focal change in a bone of the baseline pattern often demonstrating a more "windblown" pattern often with a new soft tissue mass best seen on an MRI scan The patient also experiences chronic pain and may feel a mass.



Radiograph of the pelvis and proximal limbs. Multiple cartilaginous lesions, mainly metaphyseal, with bone deformations



Radiograph of the hand: multiple chondromas



Cartilaginous lobules show evident atypia with a pseudomalignant appearance of the lesion. This histology has to be considered benign if the lesion is in a child, or in Ollier/Maffucci disease, or in a periosteal site, in hands and feet, or in a joint (synovial chondromatosis)

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Osteochondromas

16

Davide Maria Donati and Eric L. Staals

16.1 Solitary Osteochondroma

Definition: Benign cartilaginous neoplasm arising from the surface of the bone, histologically mimicking abnormal epiphyseal plate which grows and matures according to normal enchondral ossification.

It originates from a misplaced, subperiosteal island of physeal cartilage. It may also be seen in children secondary to radiation therapy. Presumably irradiation favors the exclusion of a cartilaginous island, by partially arresting and disorganizing proliferation of the physeal plate. Chomosomal aberrations involving 8q22-24.1 (where the *EXT1* gene is located) or 11p11.2 (where *EXT2* gene is located), causing biallelic inactivation of the *EXT1* and *EXT2* genes in the cartilaginous cap support the neoplastic nature of these lesions.

Epidemiology: Osteochondroma is very frequent. It prefers male sex by 1.5–2 : 1. Originating in early infancy, it is usually first noticed between 6 and 20 years of age.

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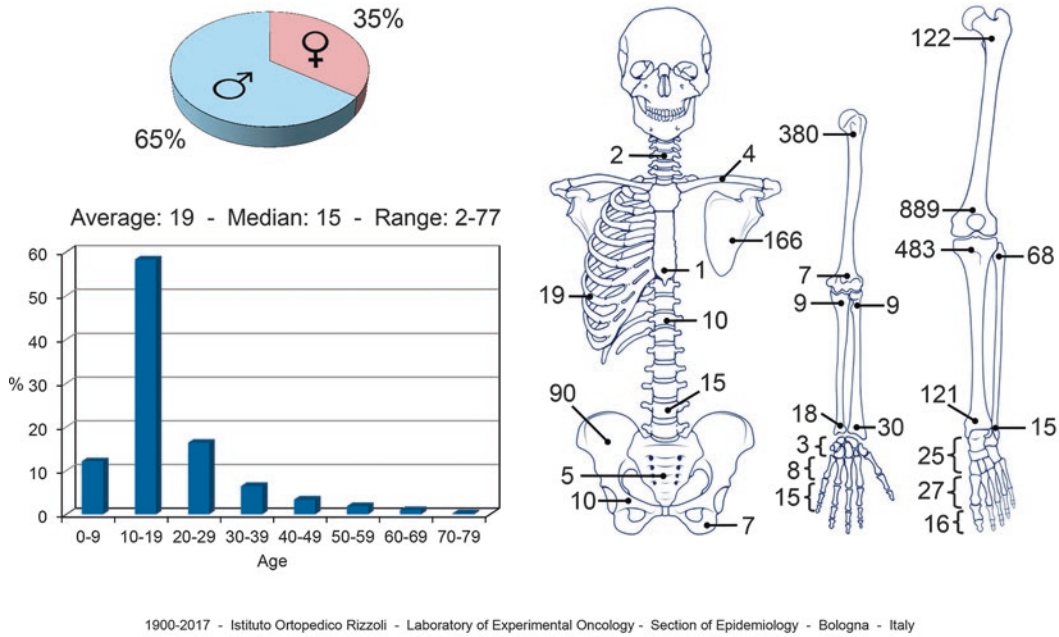


Localization: The most frequent localization is in the long bones: distal femur, proximal humerus, and proximal tibia. It originates from the metaphysis, but, with skeletal growth, it tends to move toward the diaphysis (growing away from the physis). The most frequently involved sites in the trunk are the scapula and ilium. Osteochondroma is exceptional in the hands and feet, and it does not occur in bones originating from membranous ossification (skull), nor in the epiphyses, carpal, and tarsal bones (except the calcaneus).

Clinical: A hard swelling is the main symptom, slowly increasing during skeletal growth. Osteochondroma is usually painless. Sometimes, pain is caused by an overlying bursitis or tendinitis. Occasionally, the overlying bursa, giving rise to increased volume and pain, may arise the suspicion of a malignant change. Exceptionally, osteochondroma compresses a peripheral nerve, causing neurological symptoms; or it rubs against a large artery thus producing a false aneurysm (femoropopliteal artery). Also exceptionally, as a result of traumatic fracture of its stalk, osteochondroma becomes painful and mobile, clinically simulating a muscular ossification or a loose articular body. An osteochondroma close to the physis may interfere with skeletal growth and cause axial deviations or a limb length discrepancy.

Imaging: Osteochondroma is a bony protuberance with well-defined limits, having a thin outer cortex and an internal cancellous structure. The pathognomonic radiographic feature is that the cortex of the host bone flares into the cortex of the osteochondroma, and the cancellous bone of the osteochondroma is continuous with the cancellous bone of the metaphysis. In large lesions, areas or rarefied bone may alternate with irregular blotches of intense radio density, due to

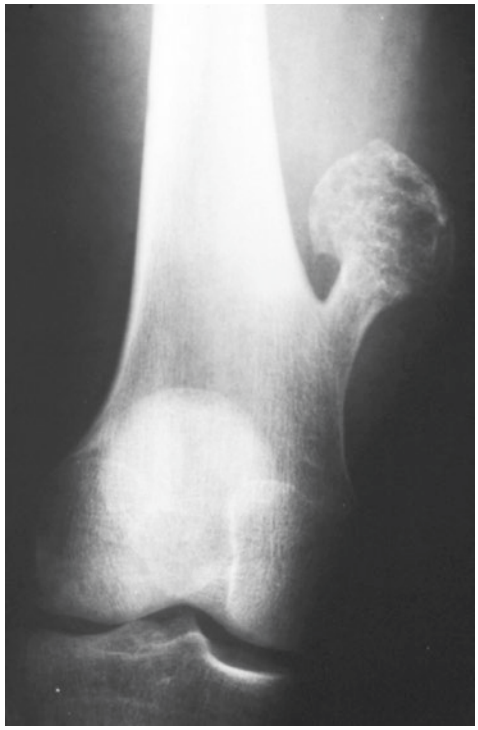
remnants of calcified cartilage, focal thickening of bone trabeculae, and bone necrosis. Some are pedunculated with a globose, cauliflower-like cap, or with a sharp horn-like extremity. Others have a broad sessile base. Pedunculated osteochondromas are usually inclined toward the diaphysis. Rarely osteochondroma becomes very large (even 15–20 cm), which is not a proof of malignancy. By chronic compression osteochondroma can cause scalloping and bowing of an adjacent bone. CT and MRI are useful (a) to confirm the diagnosis; (b) to perform preoperative planning (considering the relationship with the nearby neurovascular structures); (c) to measure the thickness of the cartilage cap or identify a reactive bursitis in case of suspicion of malignant transformation. Isotope scan is hot in active osteochondromas during childhood and adolescence and remains weakly positive or becomes negative after skeletal maturity, becoming again positive in malignant changes or when adjacent to a bursitis.

Histopathology: There is continuity between the cortex of the host bone and the cortical bone of the osteochondroma (so-called flaring of the cortex); similarly there is continuity between the medullary bone of the host bone and the medullary bone of the stalk of the osteochondroma. In children, osteochondroma is covered by a cartilage cap with a thickness ranging from a few millimeter to approximately 1.5–2 cm, and it appears as a light blue cartilage similar to that of the physeal plate. In the adult, this cap decreases in thickness, and in some areas, it disappears; residual cartilage is white and similar to articular cartilage. Limits of the cartilage with the underlying bone are well-defined. The inner part of osteochondroma is irregularly cancellous, with fatty or occasionally hemopoietic marrow. When osteochondroma is covered by a bursa, this may contain serous or hematic effusion, rarely osteo-cartilagenous loose bodies. In its active stage, the cartilage cap presents, although irregular, the same features of the normal growth plate. Some cellularities, plumpness of the nuclei, hypertrophy of the cells are to be expected in children and adolescents. The bony trabeculae of osteochondroma are originated by enchondral ossification of cartilage. Cancellous bone may include remnants of calcified cartilage and/or areas of necrotic bone.

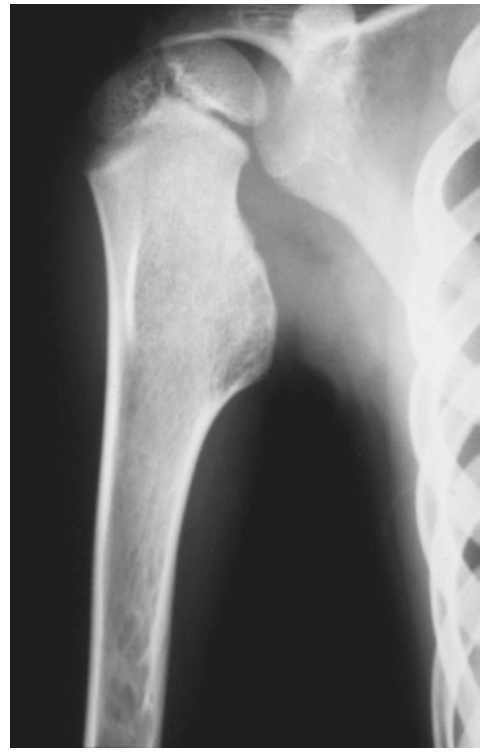
Course and Staging: Growth occurs during childhood and adolescence. After skeletal maturity, osteochondroma stops growing. Thus, it is a benign stage 2 lesion in children and adolescents, becoming stage 1 in the adult. The change of a solitary osteochondroma into a peripheral chondrosarcoma is rare (<1%) and does not occur before puberty. Risk of transformation depends on the site. It is exceptional in the more distal extremities, rare around the knee, and less rare in the trunk and limb girdles.

Treatment and Prognosis: There is no absolute indication for removal of an osteochondroma, and given the low risk of malignant transformation, prophylactic excision is not encouraged. Relative indications for surgery are pain, chronic bursitis/tendinitis, neurovascular symptoms, functional limitations, or growth disturbances due to the osteochondroma. In some cases, patients request excision of a large osteochondroma for cosmesis.

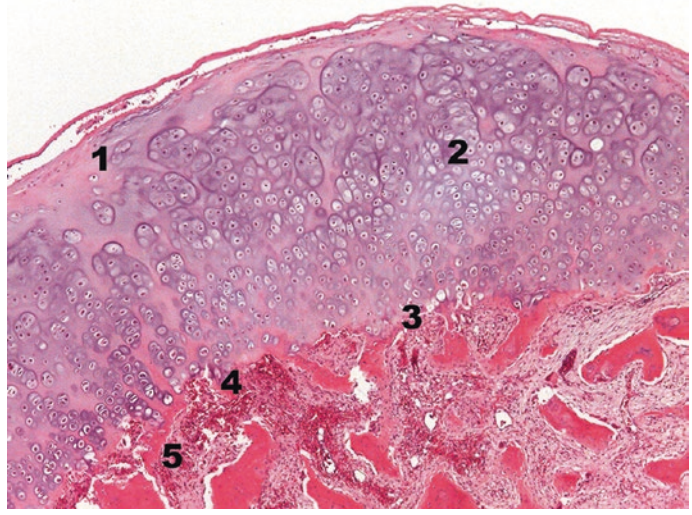
Key points	
• Clinical	Increasing swelling during growth age
• Radiological	Bony protuberance with continuity of the cortex and cancellous bone
• Histological	Cartilage cap (maximum 2 cm) covering normal cancellous bone
• Differential diagnosis	Low-grade peripheral chondrosarcoma



Pedunculated osteochondroma. Radiographs of the distal femur. The cortex of the osteochondroma is in continuity with that of normal bone



AP radiograph. Sessile osteochondroma of the proximal humerus



It commonly arises in bones formed by enchondral ossification, at the region of the edge of the epiphyseal plate. During the growth phase, the cartilage cap presents the same aspects of normal growth cartilage, although less regular. Progressive transformation of proliferating cartilage in underlying bone also mimics the epiphyseal growth mechanism, but it is much less orderly. (1) Chondrocytes arranged in clusters at the top of the cartilaginous cap. (2) Chondrocytes arranged in columns at the bottom of the cartilaginous cap. (3) Enchondral ossification at the interface between the cartilaginous cap and the underlying medullary bone. (4) Vascular mesenchymal cells invading calcified cartilage. (5) Seams of osteoid formed by the osteoblasts are laid on the framework of calcified cartilage

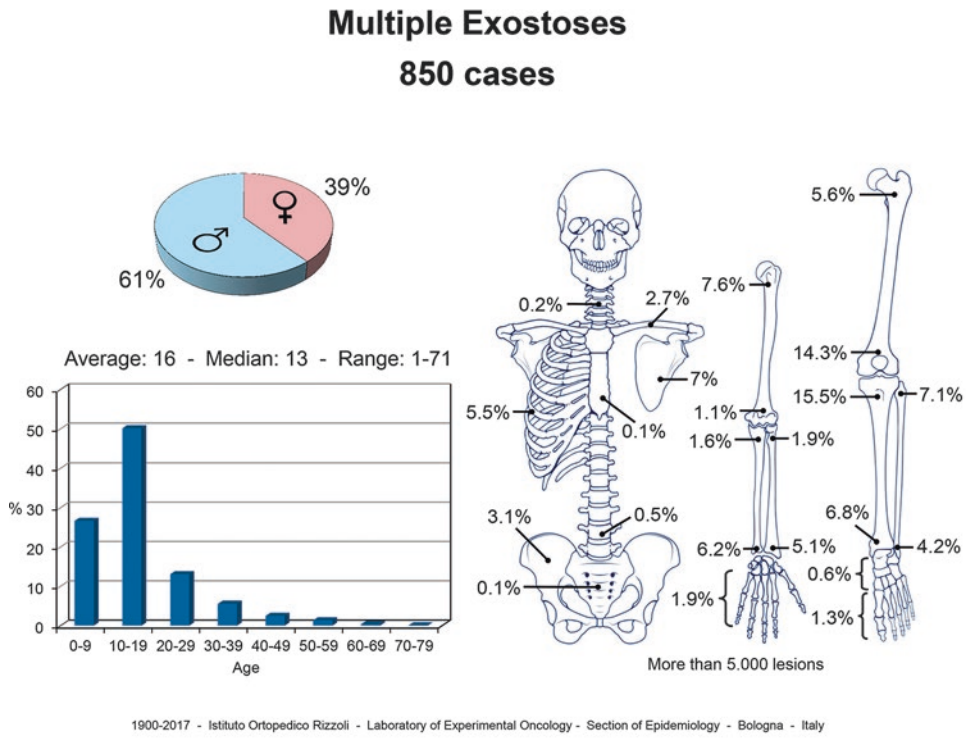
16.2 Multiple Osteochondromas

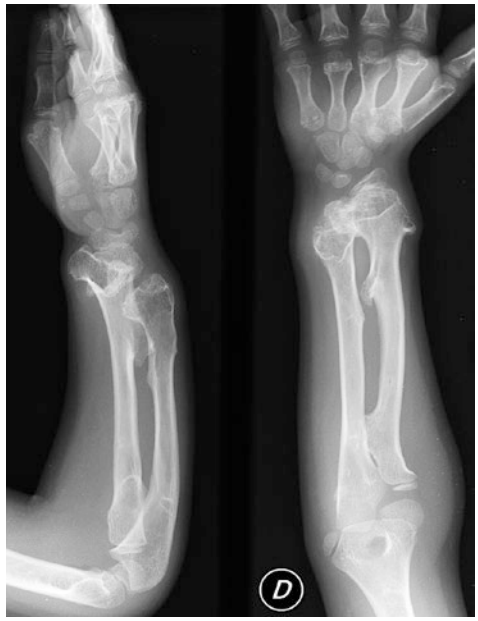
Multiple exostoses or osteochondromas are infrequent (prevalence 1/50,000). Male sex is preferred, by 1.5:1. The osteochondromas usually manifest before the age of 5–6 years, earlier as compared to solitary osteochondroma. Heredity is present in 80% of cases. Transmission is autosomal dominant. Recent studies suggest a role for other *EXT* genes. Basic research has identified several genetic abnormalities determining the disease. Most common mutations involve gene *EXT1* on chromosome 8 and gene *EXT2* on chromosome 11; a third gene named *EXT3* has been identified on chromosome 19. Cytogenetic aberration (biallelic inactivation, deletions ± mutations) of *EXT1/EXT2* genes are present in up to 90% of cases.

Multiple skeletal lesions are usually diffused and relatively symmetrical. Typically, exostoses involve the bone circumferentially, mostly surrounding the metaphyseal regions, causing swelling and sometimes limiting joint motion. Pain is a frequent symptom due to inflammation of adjacent tissues (bursitis, tendinitis). Limb shortening and deformity are frequently seen. Clinically, there is a large spectrum of presentation, from no deformity to severe impairment of upper and lower extremities, also within the same family. Relationship between type of genetic abnormality, severity of the disease, and risk of malignant transformation is under investigation in several centers. Overall, *EXT1*-positive patients seem to have a more severe clinical presentation.

Treatment principles are prevention and correction of deformity and shortening, by removal variably combined with stapling, osteotomies, and lengthening procedures. Most patients do surprisingly well and have satisfactory function without surgery.

The incidence of sarcomatous change in adult patients is low, ranging about 0.5–5%. Preferred sites for sarcoma are trunk, limb girdles, and knee. As for solitary osteochondroma, prognosis is dependent on the risk of malignant transformation. Patients should be followed clinically at regular intervals, monitoring the deeper exostoses (pelvis, spine) with serial radiograms every 2–3 years.





Radiographs of the arm and hand. Multiple exostoses. Bone deformation and shortening

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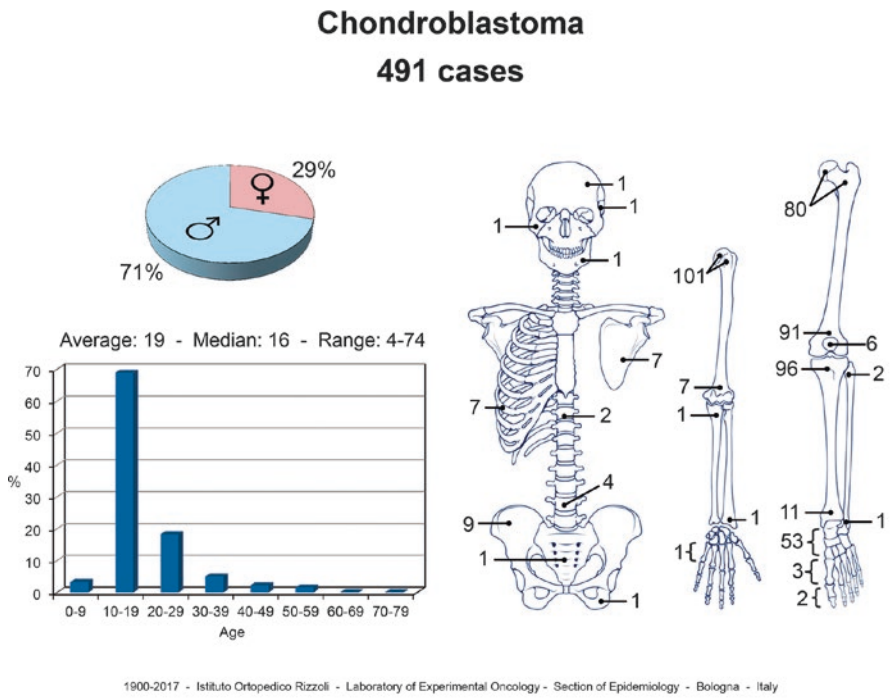
Chondroblastoma

17

Eric L. Staals

Definition: Benign cartilaginous tumor of childhood, usually epiphyseal.

Epidemiology: Infrequent (less than 1% of all bone neoplasms, 4–5% of all benign lesions); it prefers male sex by 2–3 to 1. Most cases (around 60%) are diagnosed in the second decade of life: rare after 35 years of age and exceptional before age 10.



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https://doi.org/10.1007/978-3-030-29676-6_17

Location: Usually at the end of long bones (femur, tibia, humerus), involving the epiphysis or both the epiphysis and the metaphysis. Less frequently it is located in an apophysis. Less common locations are tarsal bones and pelvis, quite rare elsewhere.

Clinical: Moderate to severe pain is usually present; relatively common symptoms are joint effusion, muscular hypotrophy, and stiffness.

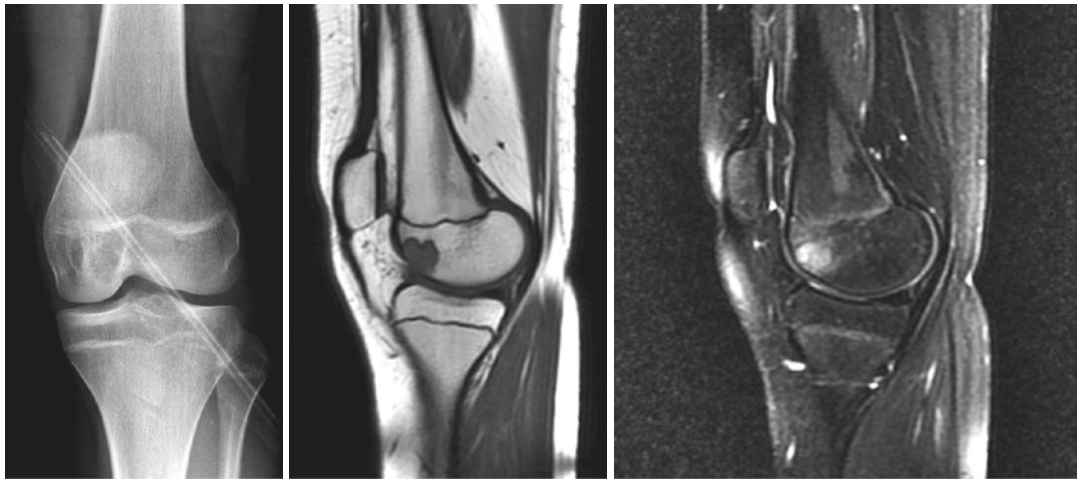
Imaging: Typically round or oval radiolucent lesion, small to moderate in size (1–7 cm) within the epiphysis or an apophysis, sometimes crossing the growth plate; sharp margins and usually a sclerotic rim are present. The cortex may be expanded but is preserved in most cases. Usually no periosteal reaction. Calcifications are visible inside the defect in 30–40%. A soft tissue recurrence tends to be well circumscribed by a shell of ossification. Isotope scan: coinciding with radiographic limits and merging into uptake of the physeal plate. CT: fine punctate calcifications; presence of cystic areas. MRI: homogenous high signal in T2, low to intermediate signal in T1, presence of joint effusion and/or synovitis.

Histopathology: Gross: pink-grey to tan-brown, overall "wet sawdust" aspect; areas of chondroid matrix, calcification, and hemorrhage may be easily recognized. Histology: combination of mononuclear cells and giant cell. Mononuclear oval cells with nuclei typically characterized by longitudinal grooves, resulting in a "coffee bean" appearance. Eosinophilic fibrochondroid matrix can be present; basophilic hyaline cartilage is infrequent. Chicken-wire calcifications are present in a third of cases (pathognomonic). Eosinophilic matrix similar to osteoid can be present. Mitotic figures are present, but generally not very numerous and never atypical. Secondary ABC-like areas in about 35% of cases. *H3F3B* gene mutations are present in more than 90% of the cases; this can be highlighted with immunohistochemistry for H3F3B protein.

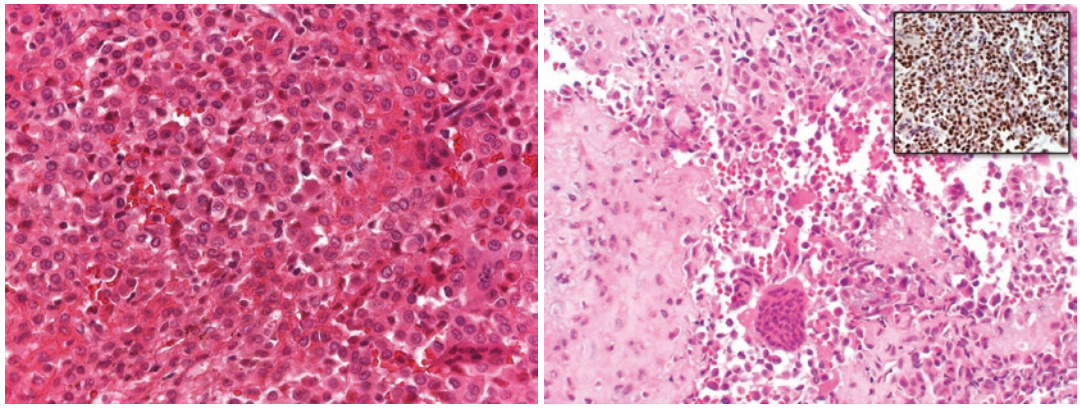
Course and Staging: Slow growth, normally stage 2 at presentation; stage 1 rare, stage 3 infrequent (recurrences, pelvic lesions).

Treatment: Curettage: stage 1, stage 2, and very rarely stage 3 lesions. Be careful to avoid damage to the physis and to the joint surface, if possible. Very rarely, en bloc resection for extensive stage 3 lesions with massive bone destruction and/or tissue mass, large recurrences. Recurrence rate: about 10% after curettage, minimal following en bloc resection. In small lesions in difficult-to-reach areas, the use of radiofrequency thermoablation has been reported.

Key points		
• Clinical	Pain in young, possible important inflammatory symptoms	
• Radiological	Epiphyseal (or metaepiphyseal) with calcifications	
• Histological	Mononuclear oval cells with "coffee bean" nuclei, giant cells, chicken-wire calcifications	
• Differential diagnosis	Clear cell chondrosarcoma	
Genetic alteration		
• Mutation of *H3F3B* gene (17q25.1)	p.Lys37Met (NP_005315)	96%



Radiograph, and sagittal T1 and T2FS MR images. Well-limited epiphyseal lesion. An inflammatory reaction is well detected on T2 image



Mononuclear cells with plasmacytoid, sometimes with “coffee bean” appearance. Multinucleated giant cells are present. Immunohistochemical nuclear positivity for H3F3B in the neoplastic cells (*inset*)

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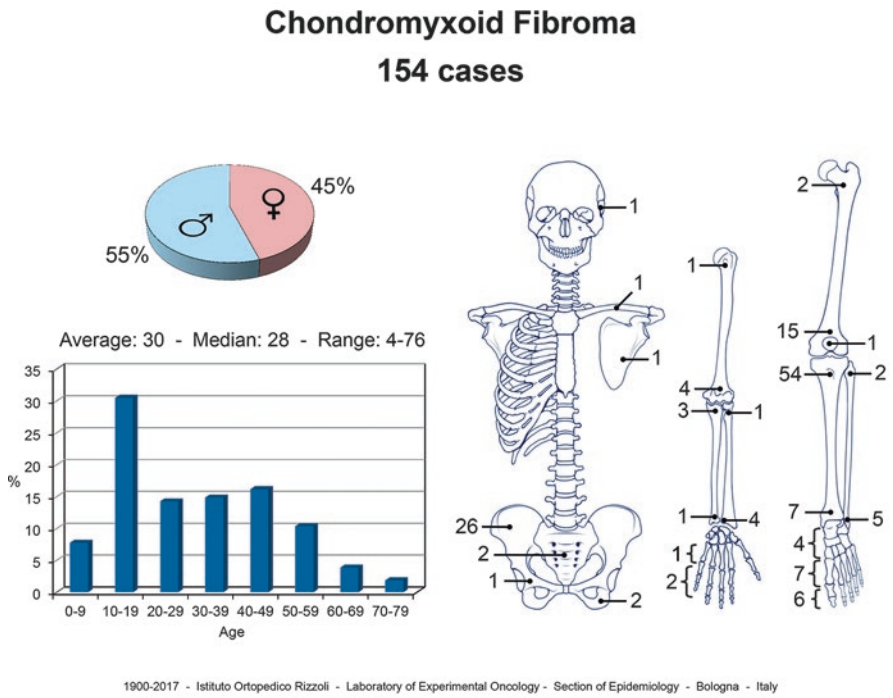
Chondromyxoid Fibroma

18

Eric L. Staals

Definition: Benign cartilaginous tumor made of lobulated, fibromyxoid, and chondroid tissues.

Epidemiology: It is definitely rare (0.5% of all bone tumors, about 2% of all benign neoplasms) and prefers male sex by 1.5:1. Generally seen between 5 and 30 years of age, it has a predilection for the second and third decades of life.



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Location: Typically located in the metaphysis of long bone; it can invade the epiphysis, especially in adults. Preferred sites: proximal tibia (30% of cases), small bones of the foot, pelvis. Rare in the upper limb and in the trunk besides pelvis.

Clinical: Usually a slow-growing lesion with a relatively long history of mild to moderate pain, sometimes associated with bland local swelling. Occasionally asymptomatic and discovered as incidental finding on radiographs.

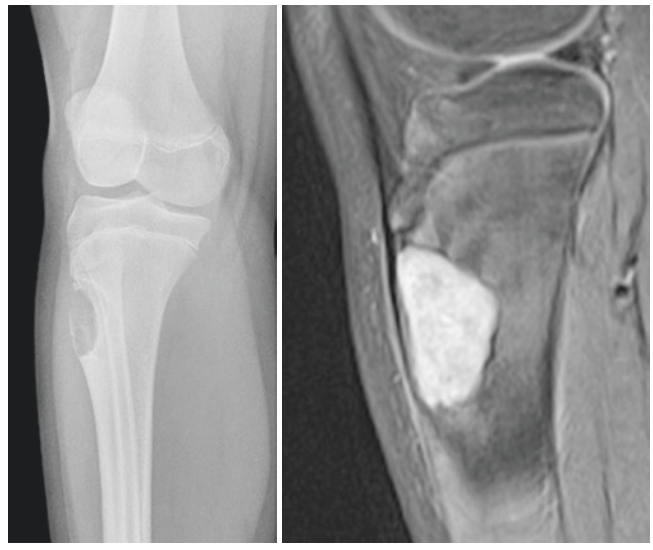
Imaging: Small (generally ≤5 cm), metaphyseal, and eccentric radiolucent defect, usually with the long axis parallel to the bone of origin; sometimes, especially in small bones, fusiform expansion of its entire contour. Sharply marginated by a lobulated shell of endosteal reactive bone because of a sclerotic rim. The cortex is usually cancelled, with the tumor "bubbling out" into soft tissue. Little and peripheral periosteal reaction, chronic in nature and similar to that of periosteal chondroma. Intratumoral calcification is unusual. Isotope scan: moderately hot and corresponding to radiographic extent. CT: metaphyseal, eccentric and subperiosteal, heavily marginated radiolucency, usually without any mineralization. MRI: homogenous intratumoral signal (intermediate-high in T2, low-intermediate in T1).

Histopathology: Gross: the tumor is rubbery soft, distinctly lobular, and clearly separated from the surrounding bone. Tissue is whitish or bluish and semitranslucent in chondromyxoid areas, tannish-red in the undifferentiated and vascularized zones. Histology: lobular pattern better appreciated at low power, a light center, and a dark periphery. In the centers of the lobules, spindle–stellate cells in a myxoid background are present; the center of lobule is hypocellular, while at the periphery a condensation of polyhedral cells is evident, often with multinucleated giant cells. Mitotic figures are not common. Cellular atypia may be present (15–20% of cases).

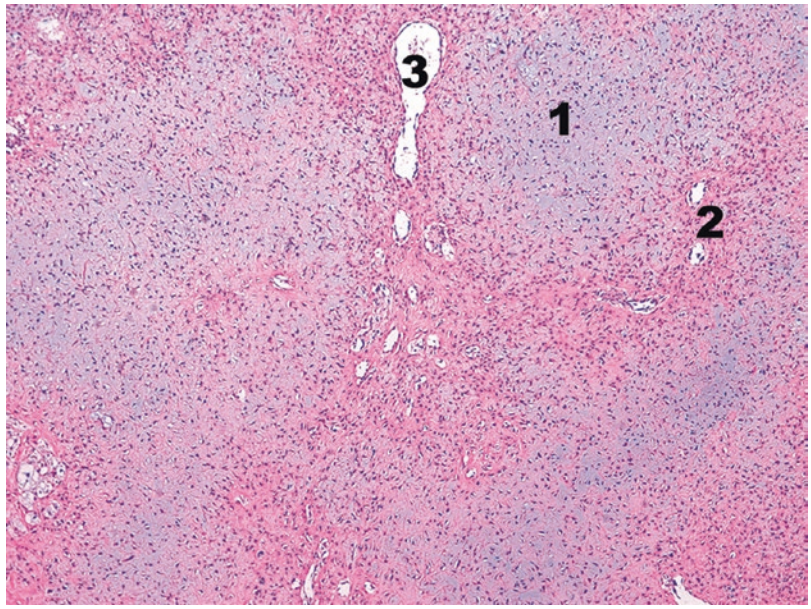
Course and stage: The tumor grows slowly and is generally small; at presentation usually stage 2 and occasionally stage 3.

Treatment: Aggressive curettage is usually indicated and frequently curative for either stage 2 or stage 3 tumors; recurrence rate probably lower than GCT of bone and chondroblastoma. Consider en bloc resection for recurrent lesions and expendable bones.

Key points	
• Clinical	Mild symptoms
• Radiological	Lobulated, subperiosteal lytic lesion
• Histological	Myxochondroid lobules of cartilage surrounded by more cellular bundles with vessels
• Differential diagnosis	Histiocytic fibroma (at imaging)



Radiograph and sagittal T2W image. Metaphyseal cortical well-limited lytic lesion in a 13-year-old boy



Histologic characteristics are particularly evocative at low power view. This shows the typical lobular architecture of the tumor. (1) Clear center of the lobuli. They are composed of spindle–stellate cells interspersed in an abundant and fluid ground substance. (2) Dark periphery of the lobuli. There are more densely cellular areas composed of well-stained cells with plump nuclei. (3) Numerous ectatic blood vessels run through these peri- and interlobular bands

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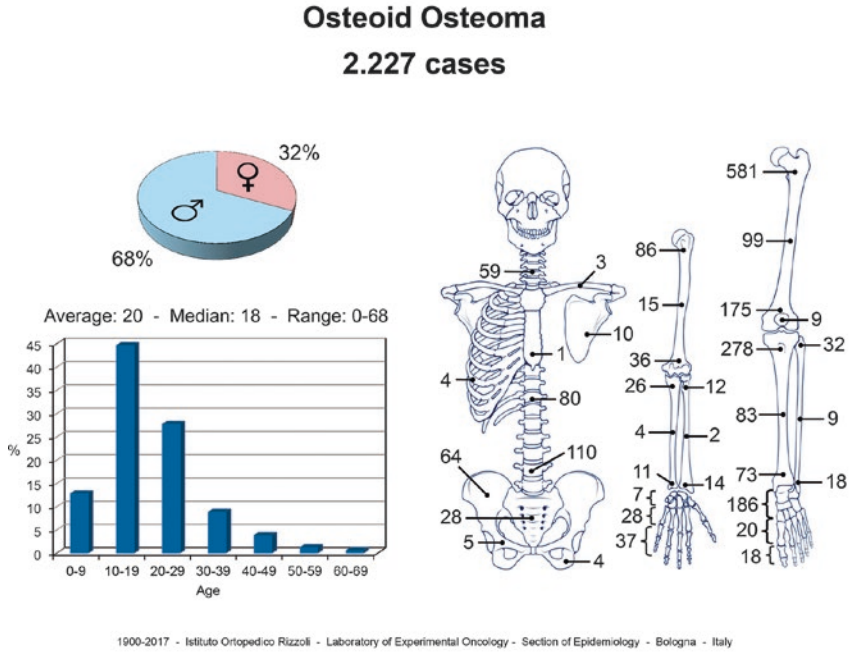
Osteoid Osteoma

19

Laura Campanacci

Definition: Small benign tumor, usually very painful, producing osteoid and woven bone, surrounded by a halo of reactive bone. The lesion has a limited growth potential; for this reason it is generally less than 2 cm in its major diameter.

Epidemiology: Relatively frequent in young patients (3% of primary bone tumors). It has predilection for males (ratio of 2:1). Rarely observed before 5 and after 30 years of age.



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Localization: It prevalently occurs in the appendicular skeleton, while it is rare in the trunk, except for the spine (mostly localized in the posterior arch). In the limbs, it prevails in the proximal femur, but it is also common in the other long bones where it is more often diaphyseal or meta-diaphyseal. It may occur also in the short bones, like talus. When occurring in long shafts, it involves the cortex, but also in cancellous areas it is localized at the surface rather than in the center of the bone.

Clinical: The almost constant and often only symptom is pain, with a typical tendency to increase during the night, relieved by nonsteroidal anti-inflammatory drugs. When localized close to a joint, limited motion and chronic synovitis can be observed. In the spine, it may cause muscular spasm with stiff scoliosis.

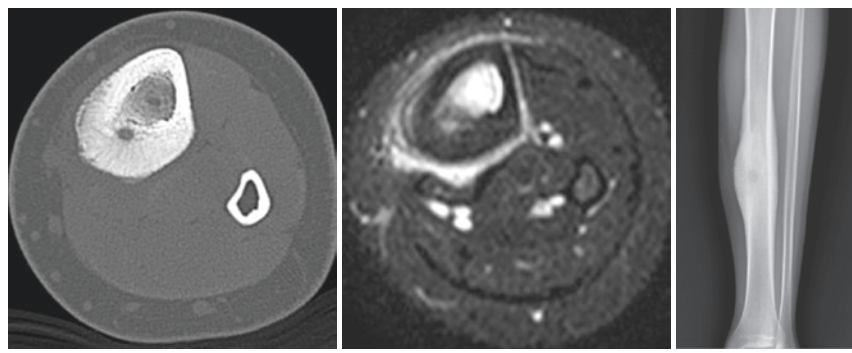
Imaging: The basic radiographic element is a small (1–2 cm) rounded area of osteolysis ("nidus"), surrounded by a halo of bone sclerosis. The lesion is located at the center of this sclerosis that can be so thick that the small nidus cannot be seen except by CT. In cancellous bone areas, the halo of sclerosis may be less prominent. Isotope bone scan is constantly positive, showing a small, rounded area of intense uptake centered in a more diffused halo, thus resembling a "headlight in the fog." CT always demonstrates the nidus and its localization, thus permitting an adequate surgical plan. Angiography may demonstrate the high vascularity of the nidus. MRI, instead, is of little value because it is inferior to CT in depicting the nidus, showing inflammation of the surrounding tissue; it may even confuse diagnosis.

Histopathology: Small roundish, reddish, and hyperemic tumor, softer than the surrounding bone. Microscopic view shows a packed mesh of thin, contorted woven bone trabeculae, with osteoblastic rimming, osteoclasts, and numerous dilated capillaries. This calcified center corresponds to the radio dense nucleus of the nidus. The surrounding host bone appears as reactive bone, mature, and sclerotic. The soft tissues around the lesion show chronic inflammation.

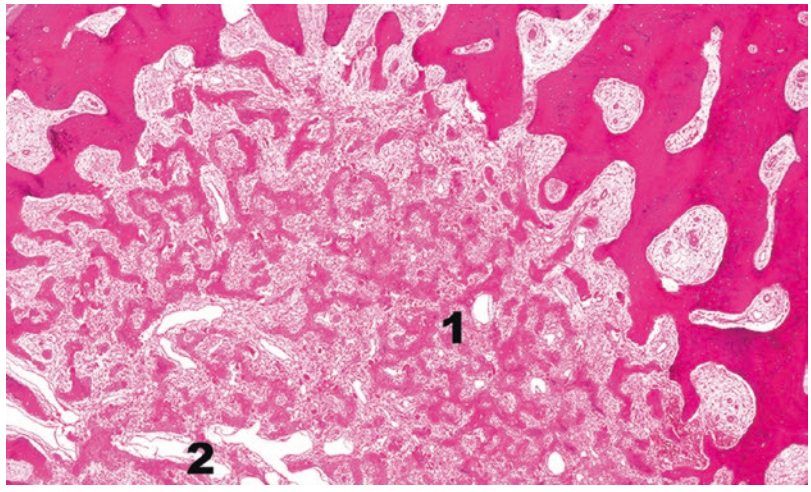
Course and Staging: If left untreated, it increases very slowly. There are cases, managed by nonsteroidal anti-inflammatory drugs, where pain subsided after some years of treatment and eventually even the nidus regressed. The tumor can be staged 1 or 2 in all cases.

Treatment and Prognosis: Surgery has been historically the mainstay of treatment; accurate intralesional curettage has been the treatment of choice in most centers until the late 1990s. Nowadays CT-guided percutaneous radiofrequency, laser or focused ultrasound (FUS) ablation is considered the treatment of choice. Success rate of this approach is usually more than 90% based on pain relief. Surgery remains an option in cases refractory to percutaneous ablation or when the nidus is close to the skin or to a nerve root.

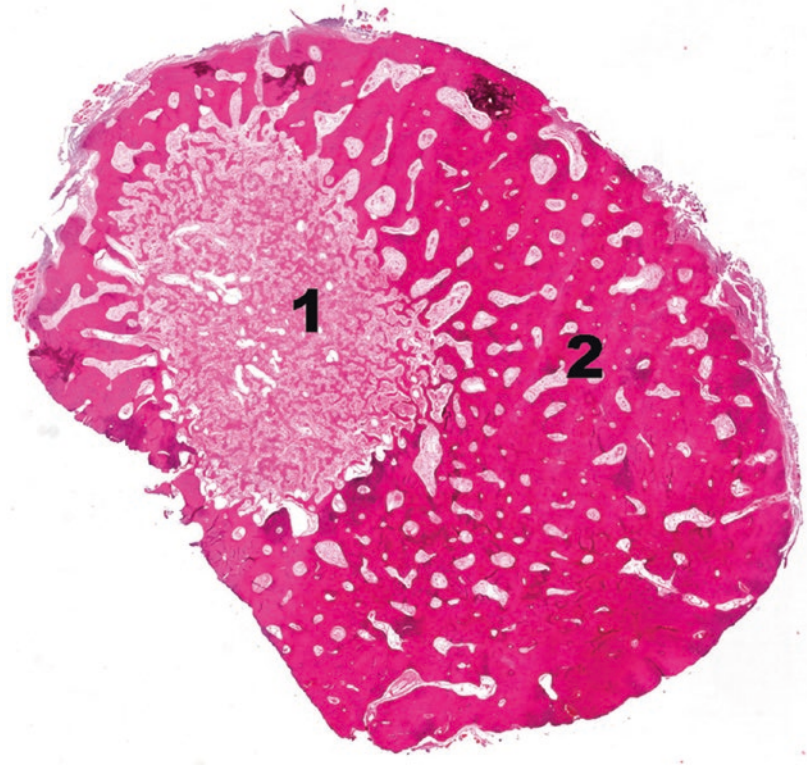
Key points	
• Clinical	Pain increasing during the night, relieved by nonsteroidal anti-inflammatory drugs
• Radiological	The "nidus" surrounded by bone sclerosis
• Histological	Woven bone formed by active osteoblasts and rich vascularization
• Differential diagnosis	Intracortical osteosarcoma (very rare), osteoblastoma



A 16-year-old boy. The X-ray shows a small and roundish osteolysis surrounded by a thick, sclerotic bone reaction. On CT scan, the nidus is evident in the posterior tibial cortex, surrounded by the chronic bone reaction. On MRI the nidus is less evident



(1) Randomly arranged thick bars of osteoid with variable amounts of mineralization. (2) Capillaries and fibroblasts are present between the bony trabeculae



Macrosection of osteoid osteoma, with the nidus (1) and the sclerotic reactive bone (2)

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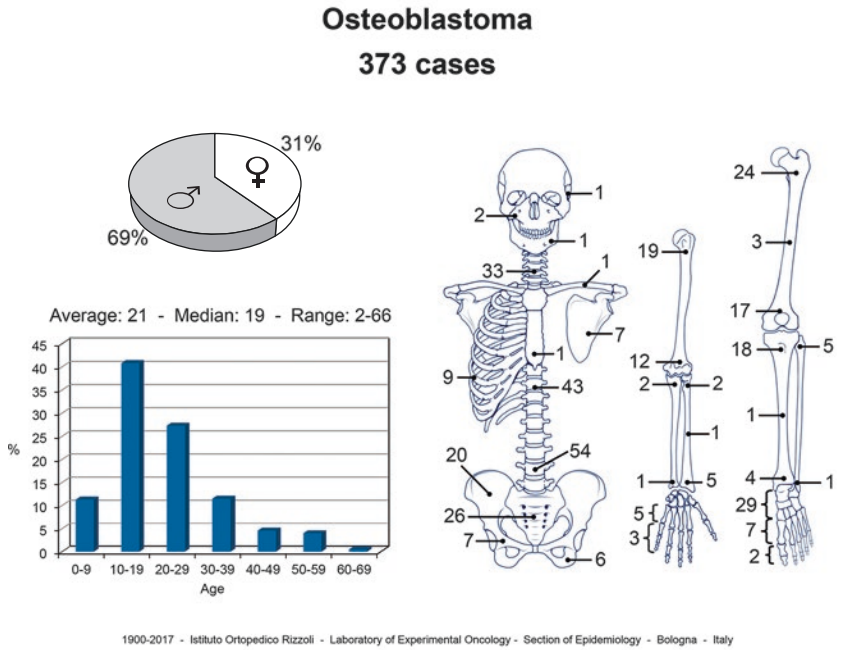
Osteoblastoma

20

Laura Campanacci

Definition: Benign tumor producing osteoid and woven bone. Differently from osteoid osteoma, it does not have a limited growth potential; for this reason it can become very big, generally more than 2 cm in larger diameter, up to more than 10 cm.

Epidemiology: It is rare. It has predilection for males (2–3:1). Rarely observed prior to 8 and after 40 years of age.



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Localization: Osteoblastoma shows evident predilection for the vertebral column (posterior arch) and the sacrum, but it may occur in any skeletal site.

Clinical: In the spine, it presents symptoms similar to osteoid osteoma (pain, scoliosis) with frequent signs of root compression. Usually it grows slowly but aggressive lesions manifest a rapid growth with severe symptoms due to the peritumoral inflammation.

Imaging: It is an osteolytic tumor containing a variable extent of osseous-type mineralization. Its size varies from 2 to 10 cm, majority being between 3 and 5 cm. The tumor may be central, eccentric, and rarely periosteal. It tends to be roundish, with margins often demarcated by a rind of bone sclerosis (not as dense as in osteoid osteoma). The cortex may be destroyed with intense periosteal reaction. In aggressive lesions, the limits may appear blurred. Rarely the tumor blows the bone out or contains cystic spaces like ABC. A regional osteoporosis may be associated (due to peritumoral inflammation). Isotope bone scan is very hot. CT at best depicts intratumoral densities (mineralization of the woven bone formed by the tumor). MRI may show extensive peritumoral inflammatory reaction. It is highly vascularized.

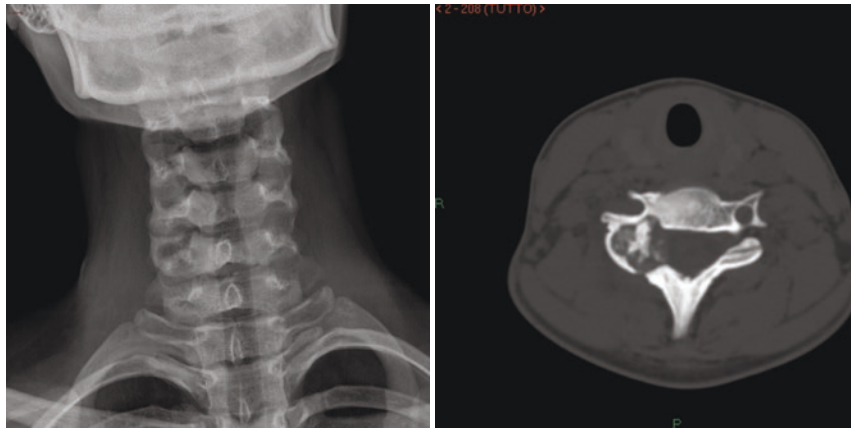
Histopathology: The tissue is compact, reddish-brown, of soft to gritty consistency. Occasionally wide cavities typical of ABC are observed. The cortex is thinned, expanded, sometimes absent, with a pseudo capsule covering the tumor.

Microscopically the tumor consists of large osteoblasts producing osteoid and woven bone. Trabeculae are usually thin, with a regular "organoid" pattern. Osteoblasts rim the trabeculae. Cytologic features of activity (large cytoplasm, plump dark nuclei, and evident nucleolus) may be present. Scattered mitotic figures can be seen but never atypical. Large cells with bizarre hyperchromatic nuclei may be seen: they are never in mitosis and are interpreted as regressive cells (the so-called pseudo-malignant osteoblastoma). Intertrabecular tissue contains a loose fibrovascular stroma, with abundant capillaries. The interface between tumor and surrounding bone is sharp with no permeative pattern (differential diagnosis vs. osteosarcoma). Multifocal growth defines the so-called multifocal osteoblastoma. Aggressive osteoblastoma is characterized by large epithelioid osteoblasts with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli; in the last WHO classification, it is reported that there is no evidence that aggressive osteoblastoma seems to have a worse prognosis than conventional osteoblastoma.

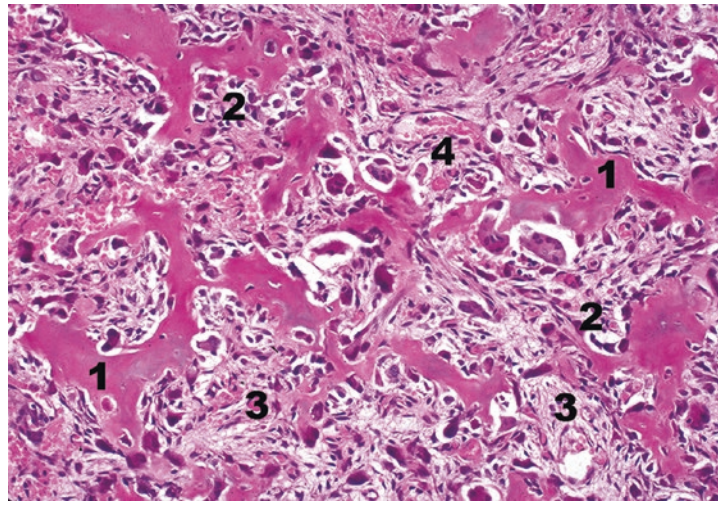
Course and Staging: Most osteoblastoma are actively growing but well contained (stage 2). Occasionally they are more invasive, bulging into the soft tissues (stage 3). Rarely the tumor appears almost quiescent and heavily mineralized, so that it can be approximated to a stage 1 lesion. The vast majority of "osteoblastomas" that end up metastasizing to lungs, leading to patient demise, were probably osteoblastoma-like osteosarcomas from the beginning. It is very important to assess the matrix of the "osteoblastoma" lesion with the host bone. If it permeates the marrow spaces and traps host lamellar bone, the lesion is an osteosarcoma, osteoblastoma-like.

Treatment: In stage 1 (latent) or stage 2 (active): intralesional curettage. In stage 3 lesions (aggressive): marginal or wide resection is indicated. In vertebral localizations, aggressive curettage or resection. Selective preoperative arterial embolization may be useful to reduce bleeding during surgery.

Key points	
• Clinical	Pain and swelling, depending on the site. Frequent in the spine (posterior aspect)
• Radiological	Mixed lesion (lytic/mineralized)
• Histological	Osteoblasts producing osteoid and woven bone in a regular organoid pattern
• Differential diagnosis	Low-grade central osteosarcoma



Radiograph and CT of the cervical spine. The lesion is well limited, contains ossifications, and is surrounded by reactive sclerosis



(1) Irregular bars of neoplastic osteoid. (2) Plump, deeply stained, and slightly pleomorphic osteoblasts encircling woven bone trabeculae. (3) Proliferation of mesenchymal cells that tend toward osteoblastic differentiation. (4) Rich capillary vascularization

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Aneurysmal Bone Cyst (ABC)

21

Laura Campanacci

Definition: Benign tumor characterized by cystic cavities lined by septa containing spindle cells, inflammatory cells, giant cells, and histiocytes with hemosiderin deposition.

Production of variable amounts of reactive bone is frequently encountered. The cavities are filled with flowing blood. This lesion, when primary, is now considered to be tumoral, because in about 40–50% of cases, it has been demonstrated the presence of typical translocation t(16; 17) (q22; p13) and t(17; 17) (q22; p13) that produce the chimeric proteins CDH11-USP6 and COL1A1-USP6, respectively. When this lesion is described side by side with another bone tumor (e.g., giant cell tumor, chondroblastoma, or fibrous dysplasia), it is considered reactive and does not display any kind of genetic abnormality.

Importance: It is often mistaken for a malignant tumor because of its possible radiological and pathological aggressiveness.

Epidemiology: Primary lesions represent about 2% of primary bone tumors. No differences in gender. They are found mostly in the second decade of life (85% under 20 years of age; rare above 50).

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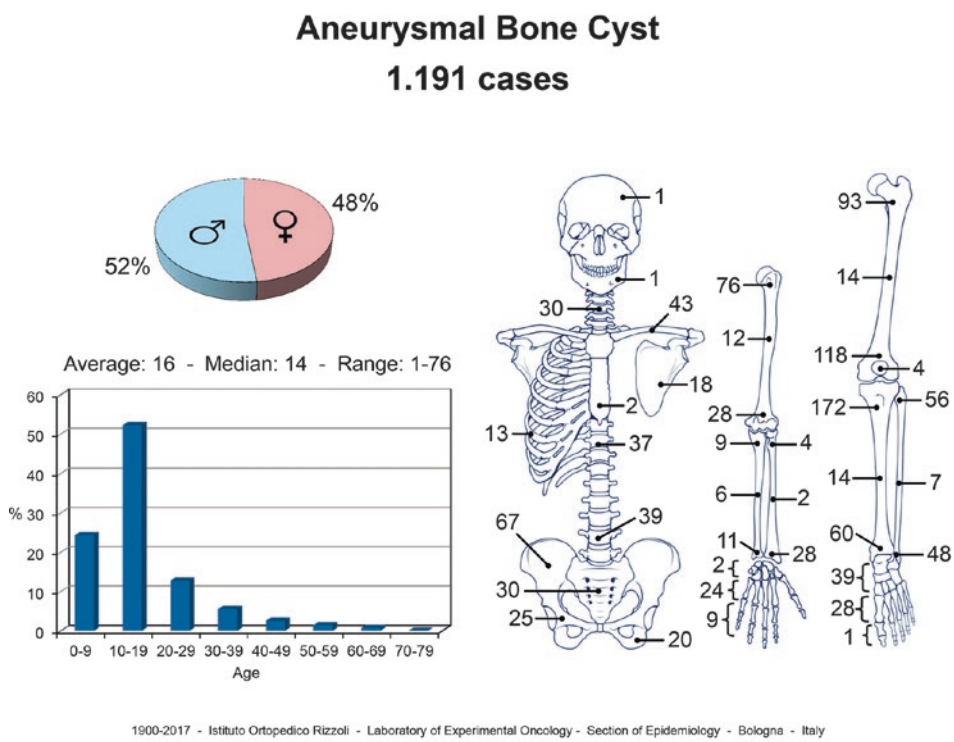


Localization: Any osseous segment may be affected, but the most common sites are the metadiaphyses of the long bones and the spine.

Clinical: Pain and swelling generally of less than 3 months duration. Frequent report of a previous trauma in the same skeletal site. Onset or progression of symptoms has been observed in some cases during pregnancy.

Imaging: The characteristic radiographic appearance of ABC is a subperiosteal, poorly defined osteolysis, elevating and inflating the periosteum, and progressively eroding the cortex. CT and MRI are often helpful in showing fluid levels within the cyst. Angiograms show intense and persistent accumulation of contrast media. Isotope scan commonly reveals an increased uptake with a cold central area.

Histopathology: Grossly it appears as a blood-filled sponge limited by fibrous septa. The wall of the cystic cavities is not formed by endothelial cells but by mesenchymal tissue rich in fibroblasts, histiocytes, thin capillaries, and scattered multinucleated giant cells. Immature trabeculae of reactive bone may be seen. Blotchy purple calcifications (considered pathognomonic by some authors) can be seen. Brisk mitotic activity is frequent.

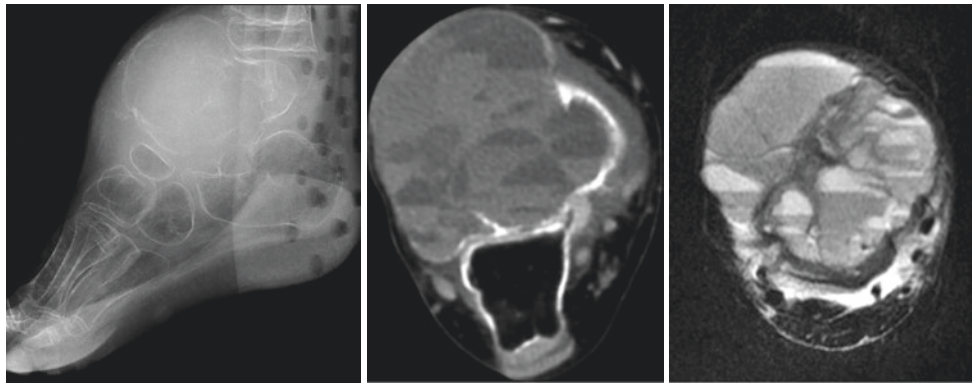
Course and Staging: The lesion may progress very rapidly, but in some cases it may heal spontaneously, after a fracture or a biopsy. Recent cytogenetic data have demonstrated the presence of fusion oncogenes in a subgroup of ABCs. Nevertheless, its origin is controversial, ABC is commonly staged as a benign tumor.

Treatment and Prognosis: After intralesional surgery, local recurrence occurs in a 20% of cases. Selective arterial embolization of the nutrient vessels represents the standard treatment in difficult locations (spine or pelvis) or big proximal lesions (proximal femur, proximal humerus). Various minimally invasive treatments have been used with satisfactory results, as curopsy, sclerotherapy, cryotherapy, injection with concentrated bone marrow, and demineralized bone matrix. Radiation therapy (30–40 Gy) has been proven effective in inducing cyst ossification, but it is charged by the risk of sarcoma induction, or growth plate damage in children.

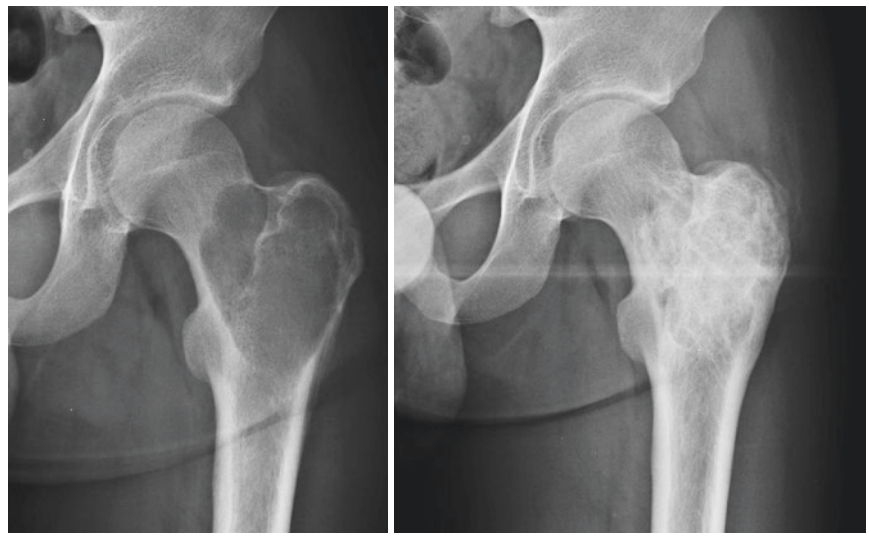
Key points	
• Clinical	Pain and swelling in young people
• Radiological	Eccentric, lytic lesion. Fluid/fluid levels
• Histological	Cystic cavities and septa not lined by endothelial cells
• Differential diagnosis	Telangiectatic osteosarcoma

Chromosomal translocations		
• t(16;17)(q22;p13)	CDH11-USP6	30–50%
• t(17;17)(q12;p13)	COL1A1-USP6	5%

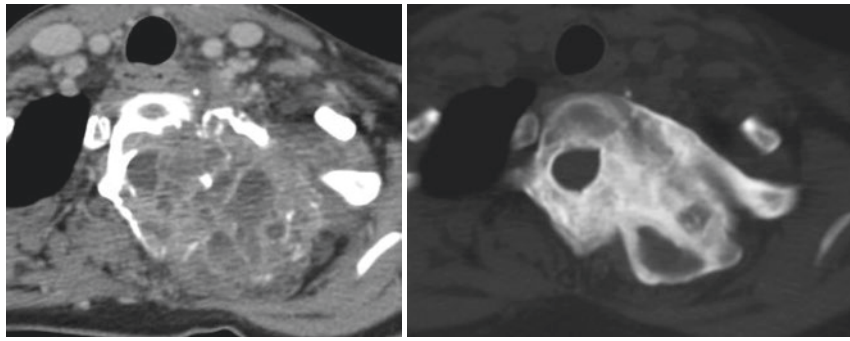
Chromosomal translocations		
• t(1;17)(p34,3;p13)	THRAP3 (TRAP150)-USP6	Rare
• t(3;17)(q21;p13)	CNBP(ZNF9)-USP6	Rare
• t(9;17)(q22;p13)	OMD-USP6	Rare
• t(17;17)(q13.3;p13)	PAFAH1B1-USP6	Rare
• t(6;17)(q21.1;p13)	RUNX2-USP6	Rare
• t(3;17)(p22.1;p13)	CTNNB1-USP6	Rare
• t(4;17)(q21.22;p13)	SEC31A-USP6	Rare
• t(17;17)(q21;p13)	EIF1-USP6	Rare
• t(2;17)(p23.2;p13)	FOSL2-USP6	Rare



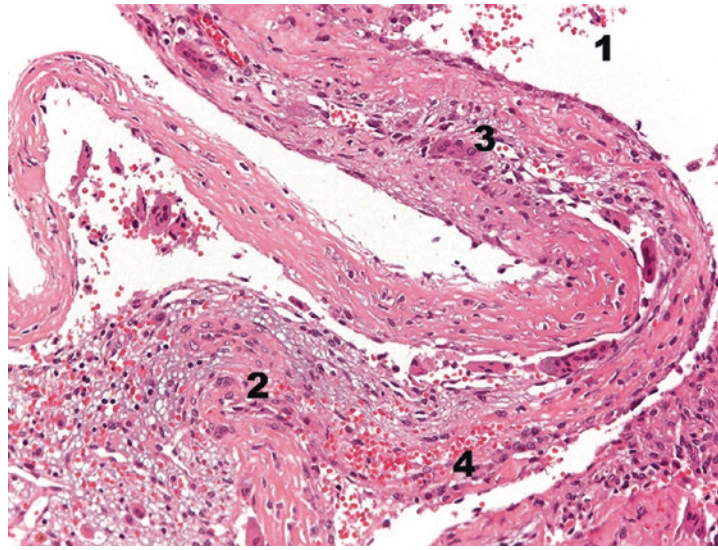
Radiograph, CT, and MR T2 axial image. The lesion is limited by a thin calcified periosteal reaction, indicating, despite a huge mass, slow growth. Fluid-fluid levels are detected on CT, but better seen on MR



Radiograph of ABC in a boy 16 years old, before and 9 months after curettage and bone grafts



CT scan of aggressive, stage 3, ABC in the first thoracic vertebra in a girl 15 years old. Two years after selective arterial embolization, the lesion was completed ossified and healed



The typical spongy structure is observed: multiloculated cystic spaces of varying size filled with blood are interspaced with solid areas of benign appearing fibrous tissue. (1) Blood-filled lacunae, (2) The walls of the cavities are formed by histio-fibroblastic tissue, (3) Multinucleated giant cells, (4) Thin blood capillaries

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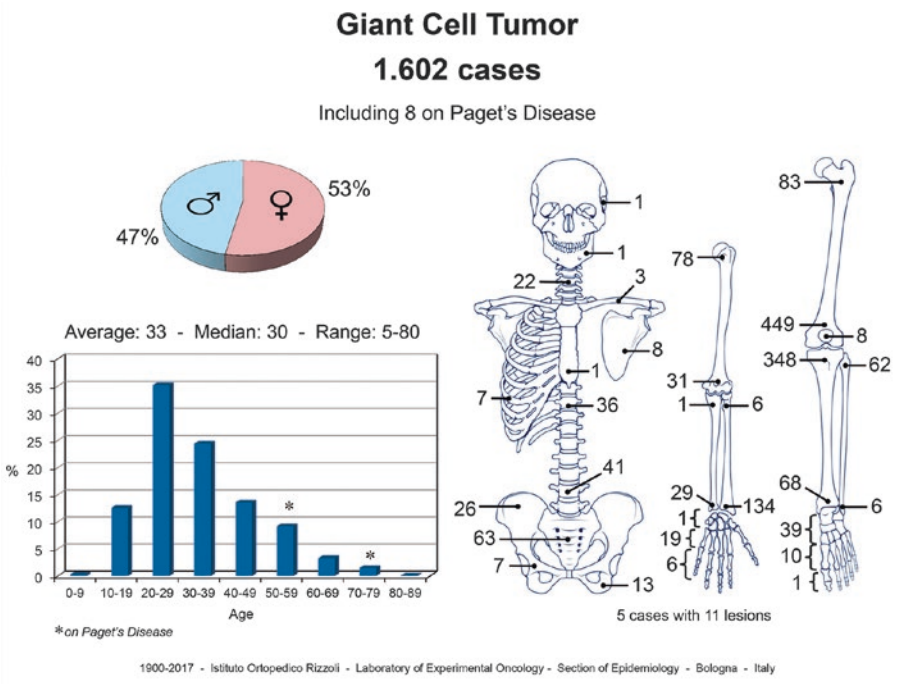
Giant Cell Tumor

22

Marco Manfrini

Definition: Intermediate bone tumor with a variable and unpredictable potential for growth, consisting of a background of undifferentiated mononuclear stromal cells with uniformly scattered osteoclast-like multinucleated giant cells. Over 90% of GCTs present histone variants in the *H3F3A* gene.

Epidemiology: Roughly, 5% of all bone tumors and 20% of all benign tumors. Slight preference for females. Usually young adults (about 65% aged 20–40), uncommon after 50 years of age and rare in the immature skeleton (about 2% of the cases).



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Location: Long bones, metaepiphyseal and eccentrical: distal femur, proximal tibia, and distal radius (65% of the cases). It may occur also in small bones of hand, foot, spine, sacrum, and pelvis. When occurring in long bones before closure of growth plate, the tumor is metaphyseal. Exceptionally multicentric (less than 0.5%). In differential diagnosis, rule out hyperparathyroidism.

Clinical: Pain is the first symptom, but swelling and muscular hypotrophy are also frequently encountered; severe stiffness and pathologic fracture are less common.

Imaging: On X-ray, purely lytic lesion with relatively well defined margins ("puddle on the sand") but without sharp definition as other benign tumors. The cortex is usually thinned, often expanded, sometimes violated with little if any periosteal reaction. Soft tissue recurrence usually has an ossified rim. In isotope bone scan, the uptake usually corresponds with the limits of the lesion, often it may show a cooler center with hotter rim; in aggressive forms the uptake is beyond the radiographic limits. The CT images show an usually isodense lesion that occupy the bone with small outpockets in the borderline spongiosa. In some case cystic areas with fluid levels may be evident. MRI images may reveal both homogeneous and less homogenous signals, low in T1 and high in T2.

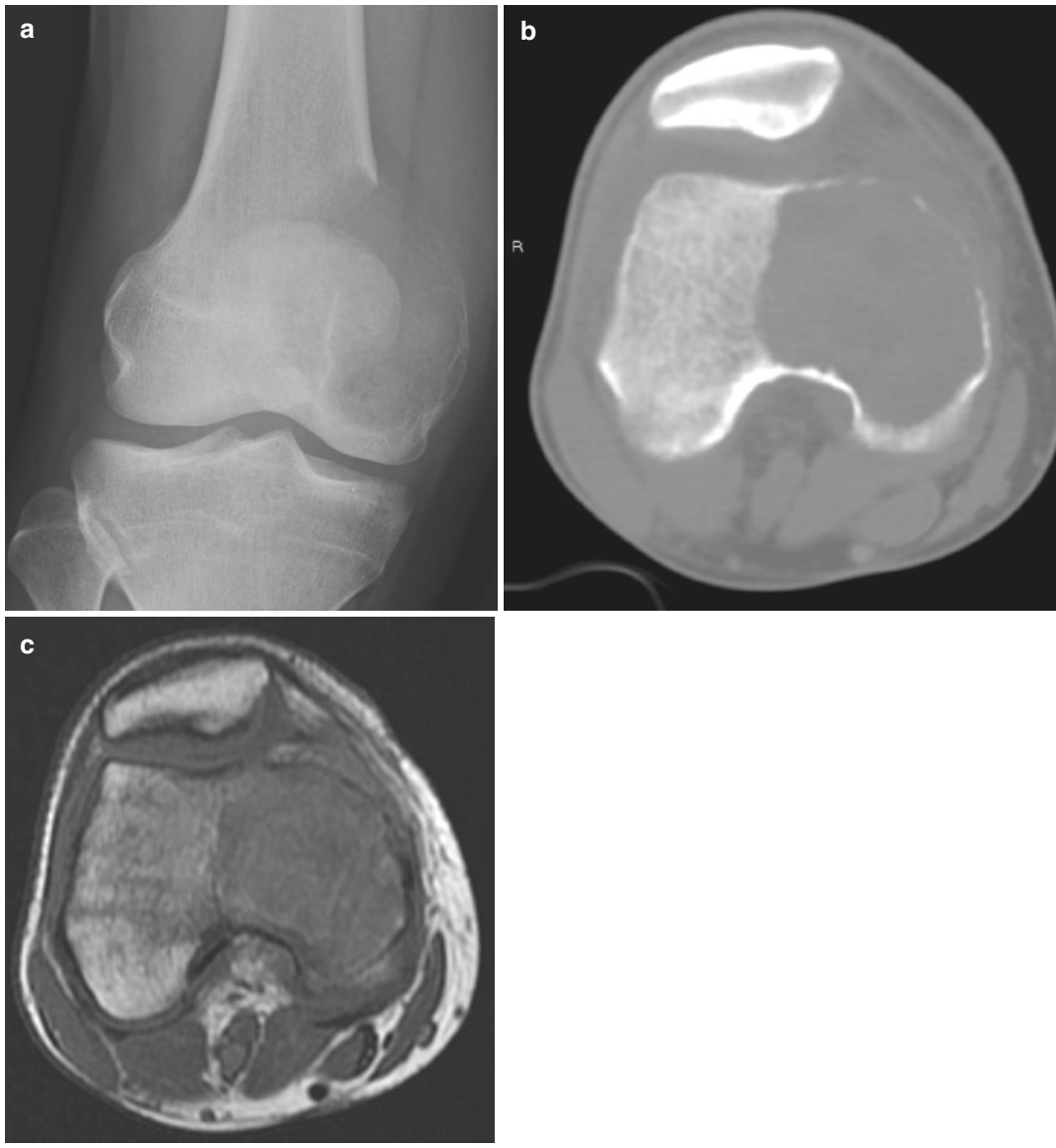
Histopathology: Grossly, the tumor appears as a meaty reddish-purple tissue sometimes merged with soft yellow areas and often cystic areas (ABC-like areas). Histologically, the lesions are composed of a carpet of mononuclear round-oval cells (not neoplastic, of monocytic lineage, RANK+) with stromal ovpid-to-spindle cells (neoplastic, RANKL+) with many reactive multinucleated giant cells (40–60 up to 100 nuclei) more or less uniformly distributed. Nuclei of mononuclear cells and giant cells identical. Mitotic activity but no atypical mitoses or cytological atypia. Necrotic "infarct-like" areas without an inflammatory response, and collection of foam cells are common, sometimes rich of spindle cell areas in a "fibrohistiocytic pattern." Reactive bone formation can be present. Vascular invasion can occasionally be found. *H3F3A* gene mutations are present in the neoplastic cells in more than 90% of the cases; this can be highlighted with immunohistochemistry for H3F3A protein.

Course and Staging: Course unpredictable if untreated: rarely indolent, sometimes rather aggressive. Histological grading has no value. Local recurrence rate depends upon stage and treatment. About 2–5% present metastatic nodules, usually to lung. Malignant transformation may occur spontaneously in about 1%; if radiation therapy is applied, the risk increases to 5–15%. Presentation: less than 10% as stage 1, 60–70% as stage 2, and 20–30% as stage 3.

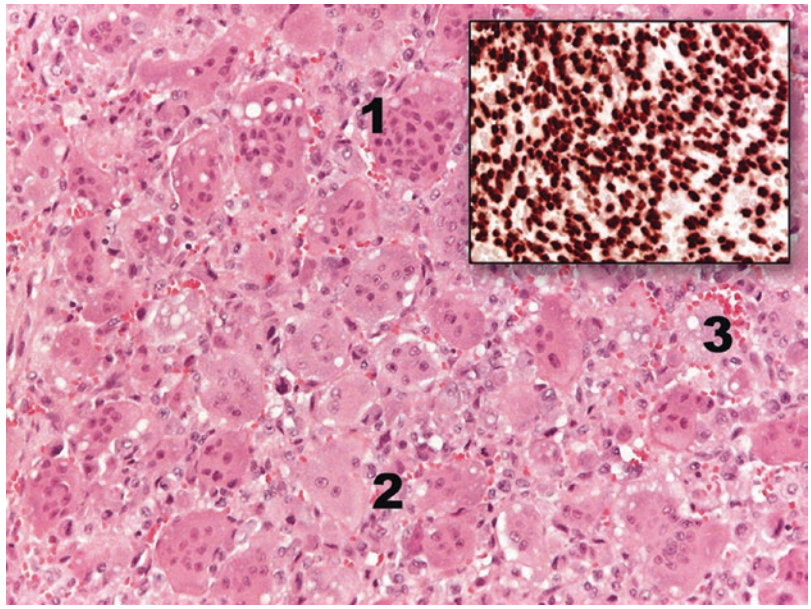
Treatment: Curettage represents the preferred surgery in stage 1 and stage 2 lesions. Recurrence rate ranges between 10 and 15% with local adjuvants (cement, phenol, liquid nitrogen) and 15–30% without local adjuvants. En bloc resection is recommended in small bones of the hand, expendable bones and in stage 3 lesions with massive periarticular bone destruction or after displaced pathologic fracture. Adjuvant radiation therapy following intralesional surgery has been associated with malignant transformation. The medical treatment with anti-RANK-L antibodies (Denosumab) has been demonstrated to be very effective (see biology) to stop the tumor growth, but, if discontinued, the tumor restarts growing. Some concern about a possible risk of iatrogenic malignant transformation under Denosumab treatment has been reported, and currently, the treatment with Denosumab is accepted in surgically difficult cases (spine, pelvis, pathological fracture) as short-term induction treatment before a wide resection, in the treatment of metastatic nodules in the lung and in patients with inoperable large tumors of pelvis or spine.

Key points	
• Clinical	Periarticular pain and swelling in adult age
• Radiological	Eccentric lytic metaepiphyseal lesion with small periosteal reaction
• Histological	Mononuclear and giant cells with similar nuclei
• Differential diagnosis	ABC in youngers, lytic bone tumors in adults

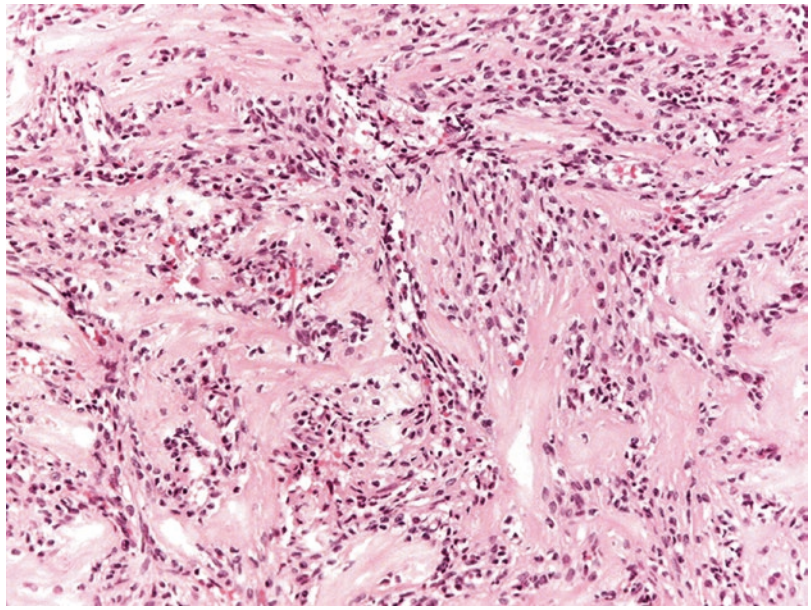
Genetic alteration		
• Mutation of H3F3A gene (1q21)	p.Gly35Trp (NP_002098.1)	96%
	p.Gly35Leu p.Gly35Val p.Gly35Met p.Gly35Glu p.Gly35Arg	Rare



Radiograph (**a**), CT (**b**), and MRI-T1 (**c**) of the knee. Purely lytic, well limited but without sclerosis, epi-metaphyseal tumor. The cortex is thinned, but not destroyed



The lesion is composed of very cellular tissue with a dense population of cells of average size and with a single nucleus, constellated nearly everywhere by a large number of multinucleated giant cells. (1) The multinucleated giant cells stud the tissue. Giant cells have a large number of nuclei (even 50–100 in the section plane) gathered at the center. (2) Mononuclear cells. They have the same nuclei as those of the giant cells. (3) Blood vessels. Immunohistochemical nuclear positivity for H3F3A in the neoplastic cells (*inset*)



After treatment with Denosumab, the tumor appears as a proliferation of bland spindle cells, without multinucleated giant cells, and with abundant osteoid production

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Biology of Giant Cell Tumour

23

Maria Serena Benassi

Giant cell tumour of bone (GCTb) is a locally aggressive osteolytic tumour characterized by a network of spindle-shaped mononuclear stromal cells, round mononuclear monocytes and multinucleated giant cells [1, 2].

Giant cells are osteoclast-like cells originating from hematopoietic stem cells. They are positive to CD68 and CD14 belonging to macrophage/monocyte lineage and express the markers for bone resorption including tartrate-resistant acid phosphatase (TRAP), cathepsin K, vitronectin and calcitonin receptors.

Mononuclear stromal cells that represent the proliferating pattern are osteoblast-like cells originating from bone marrow mesenchymal stem cells. They express markers of bone apposition including FGFR (fibroblastic growth factor receptor) that is involved in osteoblastic differentiation by increasing osteopontin, osteocalcin and alkaline phospatase activity.

Stromal proliferating cells also release a soluble factor, RANKL (receptor activator for nuclear factor-kB ligand), a component of tumour necrosis factor (TNF) family, that interacts with its receptor, RANK, expressed by osteoclast precursors. This binding promotes osteoclast differentiation in presence of cytokines and macrophage colony stimulating factor (M-CFS).

When the bone remodelling system is in a homeostatic state, the balance between the activity of osteoblast and osteoclast is regulated by the tried RANK/RANKL/OPG (osteoprotegerin). OPG is an endogeneous RANKL antagonist, regulating its activity through a competitive mechanism for RANK.

In GCTb, RANK/RANKL activity overcomes the effect of OPG promoting a massive osteoclastogenesis and osteolysis. The release of growth factors, cytokines and hormones entrapped into bone matrix promotes the stromal cell proliferation [3, 4].

The agents targeting the key end-points of RANK/RANKL cascade as well as the osteoclast lineage may be considered suitable for cancer therapy and include bisphosphonates, small inhibitors of proteinases and antagonists of pro-survival and pro-adhesion molecules [5–7].

However, the evidence that RANKL may also influence the cell proliferation in an osteoclast-independent way [7] focused the studies on the RANKL antagonists [8].

The first study used a recombinant OPG molecule (AMGN0007) in patients with bone metastasis, but the potential adverse effects led to the selection of other approaches [9, 10].

Denosumab is a fully monoclonal anti-RANKL antibody that inhibits bone turnover in patients with osteolytic disease, including myeloma multiple and carcinoma bone metastasis [11, 12].

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Phase II clinical studies in patients with recurrent and/or not resectable GCTb observed a tumour response in terms of giant cell disappearance and absence of radiological progression in a high percentage of cases [13, 14]. Recent studies confirmed variation of the tumour cell morphology associated with disappearance of osteoclast-like giant cells and environmental changes, while few alterations in immunohistochemical and genetic markers were seen [15].

Chromosome instability characterizes GCTb and telomeric associations or telomeric fusions are cytogenetic aberrations commonly implicated in the tumorigenesis [16, 17]. Our previous results show that ploidy determination combined with FISH analysis may predict the cell malignant potential and suggest that chromosomal abnormalities superimposed on telomeric associations could be responsible for a more aggressive clinical course [18].

More recently, driver somatic mutations in the *H3F3A* gene have been detected in more than 90% of primary GCTb, resulting in histone H3.3 aminoacid substitution. The point mutations are restricted to stromal component and are currently useful for differential diagnosis with giant cell-rich sarcomas, chondroblastoma and aneurysmal bone cyst [19–21].

The majority of GCTb presents H3.3 G34 W (glycine to tryptophan substitution), and the immunoreactivity in mononuclear cells may significantly improve the diagnostic accuracy [22].

Similarly, H3F3A mutation was seen in metastatic and malignant GCTb [22, 23], but not in malignant GCTb originating from Paget's disease [24].

A study carried out on GCTb patients treated by Denosumab reported that the matrix and osteoid formation was accompanied by the reduction of H3.3 G34W-positive cells [25].

However, the identification of candidate prognostic factors useful in clinical management of GCTb requires a more profound knowledge of molecular mechanisms controlling tumour progression.

In a previous study, we defined an aggressive-related signature including molecules that control cellular redox state and survival as well as growth factor signalling pathways. In particular, Kaplan–Meier analysis revealed that the probability of disease-free survival significantly decreased for patients with glutathione-peroxidase 1 (GPX1) overexpression, while FGFR and EGFR signalling in neoplastic stromal cells may contribute to disease progression, promoting stromal cell proliferation and osteoclastogenesis [26–28].

In addition, the expression of key molecules that control the interaction between tumour cells and bone microenvironment has been evaluated in a wide series of GCTb specimens from patients with different clinical course.

A significantly higher risk of metastasis was seen in the subset of patients presenting co-overexpression of RANKL, RANK and the transcriptional factor NFIB, suggesting that the cross-talk between bone proteins and intracellular pathways may represent a predictive biological model [29].

Accordingly, *NF1B* gene showed significantly higher mRNA levels in metastatic tumours and was inversely correlated with its microRNA regulator, miR-136, providing a list of activated pathways in GCTb development [30].

Finally, by the evidence that serum protein fragments generating from tumour tissue [31] and markers of bone turnover may have a diagnostic and prognostic value in an early phase of disease, our studies are currently addressed toward the identification of circulating indicators of pathway activity and predictors of disease progression, also useful for therapy monitoring. Proteoma cluster analysis separeted metastasis-free from metastatic patients in two well-defined groups where serum levels of signalling transduction mediators and regulators of kinase activity presented a high descriminatory power [32].

In conclusion, the identification of prognostic molecules may be useful to identify a subset of high-risk GCTb patients prone to receive a different clinical management in terms of a closer follow-up and medical adjuvant therapy.

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Other Rare Pseudotumoral Lesions

24

Alberto Righi

24.1 Paget Disease

Paget disease is a disorder in which progressive deformity of the skeleton is associated with thickening of the involved bone. It affects older persons with a male predominance. Patients present with pain and progressive deformity. Any portion of the skeleton may be involved, but the innominate bone is the common site, followed by the sacrum, lumbar, spine, skull, femur, and tibia. Radiologically, Paget disease has typical radiographic features, namely a sharply demarcated lucency associated with thickened cortex and medullary bone. Histologically, the bony trabeculae are thickened and irregular with multiple blue cement lines. Osteoblasts and osteoclasts are prominent, and the bone marrow is replaced with loose connective tissue. Calcitonin and bisphosphonates have shown promise in arresting the progress of the disease. Development into sarcoma can be expected in fewer than 1% of patients.

24.2 Mucoid Cyst

Mucoid cyst is a term that considers both intraosseous and soft tissue ganglion. These lesions are uniloculated or multiloculated cystic swellings that often appear in or around joints and tendons. Intraosseous ganglion cyst can be found in any periarticular joint although they are most commonly seen in medial malleolus, proximal tibia, acetabulum, and carpal bones. The radiographic appearance of intraosseous ganglion cyst is a well-defined epiphyseal lucency with a sclerotic margin which occurs in the absence of degenerative features that can be mistaken for giant cell tumor of bone, chondroblastoma, and clear cell chondrosarcoma. Microscopically, a thick fibrous-walled cyst, which is either denuded of cells or lined by a single layer of flat cells, is characteristic of intraosseous ganglia. Soft tissue ganglion is most commonly found in the wrist and elsewhere in the hands and feet. They may occur in the menisci of the knee where they are known as meniscal cysts. They tend to affect young adults, and the incidence is three times as high in women as men. Microscopically, the soft tissue ganglion has a thin, fibrous tissue wall, and no lining cell layer with small collections of mucinous fluid.

24.3 Brown Tumor in Hyperparathyroidism

Hyperparathyroidism is associated with skeletal changes due to hyperfunctioning of the parathyroid glands because of neoplasm or hyperplasia.

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Any portion of the skeleton may show localized defects, but generally there is a diffuse demineralization. On radiographs, the brown tumor in hyperparathyroidism presents as an area of lucency. Histologically, brown tumors are composed of a proliferation of giant cells, usually arranged in clusters, with a background of spindle and fibrosis. Hyperparathyroidism should be suspected if a lesion that suggests the diagnosis of giant cell tumor occurs in an unusual site, such as a rib or the metaphysis of a long bone. Treatment should be directed toward surgical removal of the hyperfunctioning parathyroid gland.

24.4 Giant Cell Reparative Granuloma (Solid ABC)

Giant cell reparative granuloma (solid ABC) is a reactive process consisting of giant cells that usually are arranged in clusters, fibroblasts, and new bone formation. It is limited to the jawbones and small bones of the hands and feet. The mean of distribution is the third decade without sex predilection. Patients present with pain and/or swelling. On radiographs, the lesion is predominantly lucent, the bone is commonly expanded, the cortex may be thinned, and the process may extend into soft tissue. The main differential diagnosis is with giant cell tumor of bone. The presence of spindle cells, collagen production, bone formation, and the absence of *H3F3A* gene mutation allow the diagnosis of giant cell reparative granuloma. Curettage is the treatment of choice. Recurrences are common and are managed effectively with recurettage.

24.5 Charcot Joint (Neuropathic Arthropathy)

Charcot joint (neuropathic arthropathy) is one in which there is chronic progressive joint destruction as a consequence of nerve dysfunction around weight-bearing joints. The prime cause of the arthropathy is a loss of or marked reduction in sensitivity to pain. It usually affects adults over 40 years of age and men more than women. Although it can affect any joint, it most commonly involves the weigh-bearing joints of the lower limb. Radiologically, the disease is characterized by complete derangement of the joint structure with subluxation and even disarticulation. The morphologic features are rapidly destructive osteoarthritis with osteosclerosis, subarticular cyst (geode) formation, and intraarticular bone and cartilage loose bodies. It is often difficult to distinguish clinically and radiologically between a severe Charcot joint and septic arthritis or osteomyelitis without histological examination.

24.6 Gaucher Disease

Gaucher disease is a common lysosomal storage disease that is inherited in an autosomal recessive manner and characterized by the accumulation of glucocerebroside in macrophages throughout the reticuloendothelial system. Clinical and radiographic evidence of bone disease occurs in most patients with the common non-neuronopathic-type and subacute neuronopathic-type Gaucher disease. Radiologically, bone marrow infiltration results in generalized osteopenia with radiolucency of bone and cortical thinning and scalloping sparing the epiphyses. Histologically, the peculiar features are the variable infiltration of bone marrow spaces by large, occasionally multinucleated, macrophages. Cells similar to Gaucher disease are seen occasionally in chronic myeloid leukemia, thalassemia, Niemann-Pick disease, and Erdheim-Chester disease. The skeletal effects can be very disabling and result in impaired mobility and significantly diminished quality of life. Recently, the introduction of enzyme replacement therapy has achieved improvement in quality of life with Gaucher disease.

24.7 Bone Infarct

Bone infarct is an area of necrosis in bone associated with localized ischemia. Clinically, avascular necrosis of the femoral head is the most common type of bone infarct associated with pain in the hip. Infarcts in other portion of bone do not cause symptoms. On radiograph, an area of lucency surrounded by calcification is evident.

Morphologically, the bony spicules have empty osteocytic lacunae and the bone marrow shows fat necrosis and calcifications, similar to that seen in fibrous dysplasia and enchondromas. Femoral head necrosis is treated by total hip arthroplasty; other infarcts do not require treatment. The risk of a sarcoma arising in an infarct is low.

24.8 Echinococcus Cyst

Echinococcus cyst is a manifestation of hydatidosis, a worldwide zoonosis in sheep- and cattle-raising region, that is caused by the larval tapeworms of the genus Echinococcus. The incubation period of echinococcosis depends on the location of the infection and is often prolonged for several years. Bone lesions are usually localized in the spine, pelvis, femur, tibia, and rib. On radiographs, the lesions are evident in the advanced stage that reveal single or multiple expansile cystic radiolucent lesions with coarse trabeculations which may suggest fibrous dysplasia, hemangioma, plasmacytoma, giant cell tumor, cartilaginous tumor, or metastatic tumor in the differential diagnosis. Histological identification of protoscolices, hooklets, calcareous corpuscles, or the typical laminated hydatid membranes is diagnostic of hydatidosis. Echinococcus cyst may be confused with bone cyst, cystic osteomyelitis, cavitary mycobacterial fungal infections, and tumors. Response to treatment with drugs or surgery depends on the size and location of the cyst. Bone cysts respond less well to drug therapy and have to be surgically removed.

24.9 Gorham Disease

Gorham disease (also called disappearing bone disease, massive osteolysis, vanishing bone disease, and Gorham-Stout disease) is characterized by the gradual and progressive disappearance of bone from a particular osseous site, along with loss of structure and function. Most individuals affected are children or young adults. The disease is sporadic and has equal gender distribution. Often, the limb girdles and proximal appendicular skeleton are involved, and there is a tendency for the process to cross the joints. Radiologically, contiguous radiolucent lesions affected both the compact and cancellous bones are evident. These lesions become progressively destructive. Histologically, the lesion may be active or inactive. Active lesions are benign vascular lesions (hemangiomas, lymphangiomas, or compound lesions) associated with bone resorption. Inactive lesions consist mainly of fibroconnective tissue, which becomes more abundant as the lesion stabilizes. The treatment is mainly symptomatic and palliative, consisting of stabilization of the affected part for pain control.

24.10 Heterotopic Ossifications

Heterotopic ossification is a reactive, self-limited condition in which fibroblast proliferate in the soft tissues, producing bone and, occasional, cartilage. Patients evidence a rapidly enlarging swelling, usually of a few weeks' duration. The process affects any age group but especially young adults without sex predilection. Any part of the body may be involved, but the anterior thigh is the most common site. On radiographs, an ill-defined mass is evident that shows a mineralization at the periphery with a lucent center. Histologically, the central area of the lesion is composed of proliferating fibroblasts that appear less mature than those in the periphery, and the periphery is composed of more mature bone and cartilage. Parosteal osteosarcoma and extraskeletal osteosarcoma are the main differential diagnosis of heterotopic ossification. Conservative excision is adequate therapy.

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Other Rare Benign Lesions

25

Alberto Righi

25.1 Dysplasia Epiphysealis Hemimelica

Dysplasia epiphysealis hemimelica, also called Trevor disease or Fairbank disease, is a rare nonfamilial disease of unknown etiology. It presents in early childhood between the ages of 3 and 15 years with osteochondroma-like swelling close to a joint, a limited range of movement, and occasional "locking" of the involved joint. A cartilaginous lesion that continues to grow and undergo endochondral ossification until skeletal maturity is reached and generally requires surgical treatment causes the swelling. The majority of children have more than one lesion affecting a single limb, usually a lower limb. Radiologically and macroscopically, the features of dysplasia epiphysealis hemimelica overlap with those of osteochondromas. Histologically, dysplasia epiphysealis hemimelica is composed of multiple nodules of cartilage with centers of active endochondral ossification in the epiphysis functioning as accessory secondary ossification centers. By 3–4 years of age, most of the nodules have fused with epiphysis, and the accessory ossification centers have disappeared. The cartilage cap contains chondrocytes arranged in a fibrillar matrix in a somewhat disorganized manner compared with the surrounding normal cartilage. The differential diagnosis includes enchondroma, synovial chondromatosis, and chondrosarcoma. Radiologic correlation is required for diagnosis.

25.2 Osteoma

Osteoma is a benign tumor composed of mature bone arising on the surface of the bone with a predilection for the craniofacial bones, and when developing in the medullary cavity is known as enostosis. Multiple osteomas can occur in the autosomal dominantly inherited Gardner syndrome, a variant of familial adenomatous polyposis. Osteomas are clinically asymptomatic but can provoke obstruction of the paranasal sinuses or lead to local swellings. On radiographs, osteoma appears a well-circumscribed radio-opaque masses, usually measuring less than 2 cm. On histology, osteomas are predominantly composed of lamellar bone and can be divided into compact, spongious, and mixed subtypes. If cancellous areas occur, the bone can show osteoblastic rimming and a well-vascularized and moderately cellular fibrous stroma, which could be confused with a parosteal osteosarcoma. Usually, osteomas do not require treatment and follow an indolent clinical course.

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25.3 Intraosseous Schwannoma

Intraosseous schwannoma is a very rare benign neoplasm of Schwann cell origin located within the medullary cavity of bone, which can occur sporadically or in association with neurofibromatosis type 2. Many patients are asymptomatic, and the tumor is an incidental finding. Most patients are in the second or third decade of life, and there is a slight female predominance. The mandible and sacrum are the sites most commonly involved, although other bones such as the skull and ribs have been reported to be involved. On radiographs, intraosseous schwannoma presents as well-defined lucencies, occasionally with a sclerotic border. Macroscopically, these tumors are soft, gray-white, well-circumscribed nodules with the same histological features of soft tissue counterpart. The neoplastic cells are strongly and uniformly positive for S100 protein. Conservative surgical removal is appropriate therapy, and the prognosis is excellent.

25.4 Benign Fibrous Histiocytoma

Benign fibrous histiocytoma is a primary bone neoplasm that is composed of fibroblasts and histiocytes whose cytologic features do not suggest a malignant neoplasm. Patients range in age from 5 to 75 years with a slight male predominance. Pain is the usual symptom. The iliac wing is the most common site, followed by the femur. On radiographs, the tumor presents as a well-defined lytic defect localized in the diaphysis or metaphyseal regions, when a long bone is affected. Histologically, spindle cells with plump or slender nuclei are arranged in a loose storiform pattern without atypical features associated with clusters of foam cells and multinucleated giant cells. Treatment consists of thorough curettage. Some recurrences have been reported in literature.

25.5 Nora's Disease

Nora's disease, also called bizarre parosteal osteochondromatous proliferation, is an osteochondromatous proliferation involving the surface of bone, usually affects the proximal small bones of the hands and feet. It has a peak of incidence in the third and fourth decades of life. Swelling with or without complaints of pain is the typical clinical presentation. On radiographs, a well-marginated, heterotopic, mineralized mass attached to the cortex is seen. Macroscopically, the lesion resembles an exostosis with lobulated cartilage cap and a bony stalk. Histologically, a hypercellular cartilage with enlarged chondrocytes associated with a peculiar purplish blue mineralization ("blue bone") is the main histological feature of this lesion. The main differential diagnosis is with osteochondroma. Simple excision is sufficient treatment. Recurrences are common but managed adequately with re-excision.

25.6 Subungual Exostosis

Subungual exostosis in a benign osteochondromatous proliferation involving the nail bed of the distal phalanx of the great toe. Other toes and fingers are rarely affected. It usually occurs in the second or third decade of life, and there is a pronounced male predominance. Radiographs show a mineralized mass attached to the surface of the distal phalanx. The cortex and medulla of the phalanx are not continuous with the lesion. Histologically, there is a gradual maturation from a peripheral spindle cell proliferation to hyaline cartilage to trabecular bone. Loosely arranged spindle cells are present in the intertrabecular spaces. The proliferating spindle cells and cartilage may lead to a misdiagnosis of osteosarcoma or chondrosarcoma. The orderly arrangement and maturation are important clues for recognizing the reactive nature of the lesion. Simple excision is sufficient treatment. Recurrences are rare and are controlled by re-excision.

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Part III

Benign Lesions of Soft Tissues

Myositis Ossificans

26

Tommaso Frisoni

Definition: Myositis ossificans is a self-limiting benign lesion that can arise in any type of soft tissue most frequently in muscle as a solitary lesion. It consists of a process in which soft tissues are interested by mature lamellar bone formation in association with inflammation mostly caused by traumatic or neurological injury surgery burns or other diseases.

Fibrodysplasia ossificans progressiva (also called Munchmeyer's disease) is a hereditary type of myositis configuring an extremely rare genetic disease. Usually sporadic via a gene mutation, but it may also be due to an autosomal dominant hereditary disorder (mutations in a BMP type 1 receptor).

Epidemiology: Classic and fibrodyslpasia ossificans progressiva are very rare. Young active males are the most commonly affected.

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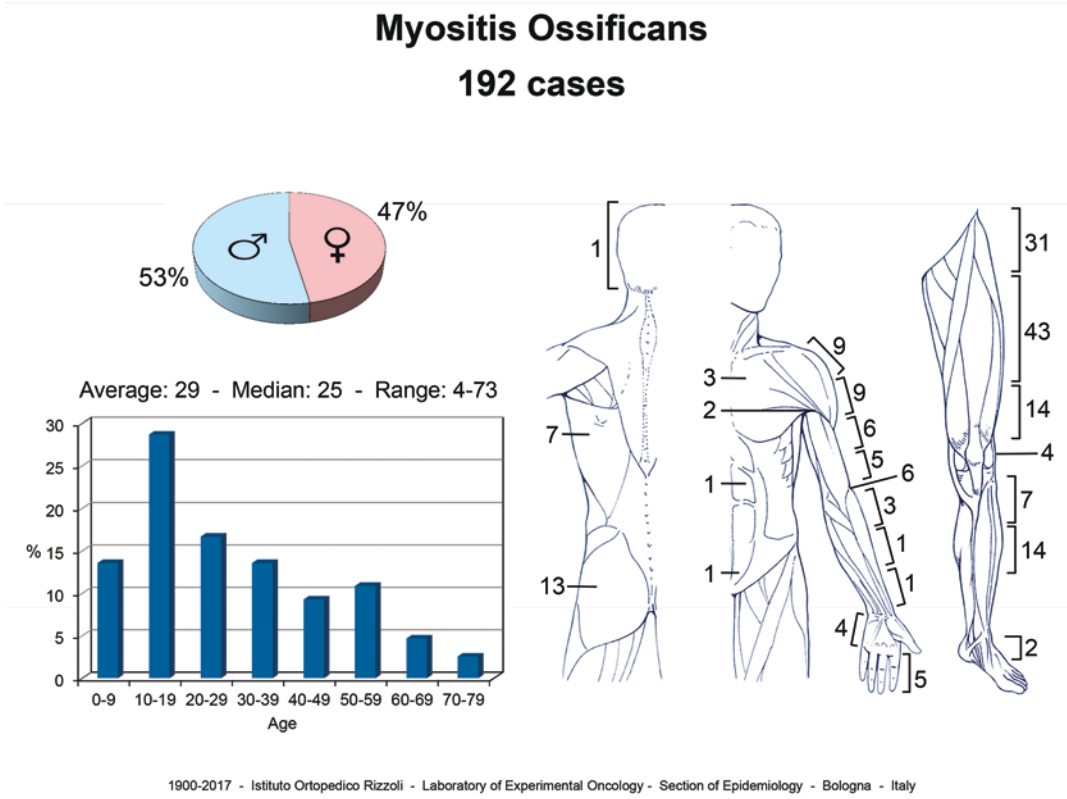


Clinical: The classic MO scenario is pain associated with a growing soft tissue mass usually after a trauma or injury. Even repetitive minor trauma can lead to the development of MO. At the beginning of symptoms, tissues are involved by intense inflammatory response as well as swelling, warming, and rubbishness. Then inflammation and swelling tend to decrease even without any treatment after few days. Pathophysiology is under discussion. During this phlogistic process, a cascade of cytokines activates endothelial mesenchymal cells and induces their differentiation in osteoblasts and chondroblast cells. The final result is bone formation within soft tissue.

The entire process passes through an early, intermediate, and mature stages; each stage has a correspondence between clinical, radiographic, and histopathological aspects (Table 26.1).

So a painful enlarging mass with intense inflammation of the surrounding tissues can be appreciated. Inflammation resolves itself with rest, then the mass slowly regresses. After that a maturation of the mass occurs in several months up to 1 year.

Genetic type: progressive and diffused ossification of tendons, ligaments and connective tissue around muscles, micro-clinodactyly.

Localization: The post-traumatic type may develop in any site. More frequent in the extensor muscles of the thigh, flexor muscles of the arm, then adductor or gluteal muscles. MO of psoas muscle has been reported as well. The genetic type usually starts in the neck, shoulder, axilla, or paraspinal muscles.

Imaging: Standard X-rays in the early stage usually are negative, even if a periosteal reaction can be detected in the first 2 weeks if the process

Table 26.1 Clinical and radiographic findings of myositis ossificans at each stage

Stage	Early	Intermediate	Mature
Clinical aspects	Pain and swelling, functional limitation, rubbishness	Tender soft tissue mass, persistence of functional limitation, decreasing pain	Reduction or absence of symptoms, a hard mass can be appreciated
Imaging	Standard X-ray usually negative	Calcified peripheral border with a radiolucent central area	Radiodense mass with persistent radiolucent central area
Histology	Spindle bland-appearing and mitotic activity	Central immature woven bone associated with peripheral lamellar mature bone formation (zonation)	Maturation of the whole mass into lamellar bone

arises close to the bone. After 3–4 weeks, soft tissue calcifications become evident. Then calcifications tend to mature and organize themselves in a mature ossification at the periphery with a radiolucent central area (6–8 weeks). At the end a rounded calcific mass is clearly shown (6–12 months).

US scan: It is often the first approach to such a lesion. In the early stage three concentric zones can be detected: a peripheral hypoechoic area, an intermediate hyperechoic area with calcification, and an inner hypoechoic area corresponding to immature zone. Despite these characteristics, it remains dependent on the operators' skill, so further examination is the rule.

CT scan can address and lead to the diagnosis, showing the classic pattern of peripheral calcification and radiolucent central area only after few weeks. In the early stage a hypo/isodense soft tissue lesion is visible. So CT scan is very useful and diagnostic in the intermediate stage, while it is neither specific nor helpful in the early stage.

Although MRI is the gold standard examination for soft tissue masses, in MO it can be confounding in particular in the early stages. In the first phase, inhomogeneous T1 and hyperintense T2 and STIR signals are present at the same time corresponding to various phenomena (hematoma, fibroblast proliferation, hemosiderin deposit, edema). These findings may lead to erroneous diagnosis of sarcoma.

After the acute phase (4–6 weeks), the central part of the lesion becomes iso-hypointense in T1 and slightly hyperintense in T2 to surrounding muscles and a low T2 signal at the periphery can be appreciated (peripheral ossification), and in STIR, edema has been resolved.

Then in the mature phase, the lamellar bone pattern and a low signal in all the sequences are the MRI features.

Histopathology: Histology depends on the phase. In the early phase a proliferation of bland-appearing spindle cells with plump nuclei, arranged in a storiform pattern with mitotic activity and scattered inflammatory cells, similar to nodular fasciitis, is seen. In the intermediate phase, the lesions show a central areas with the same spindle cell proliferation, surrounded by immature woven bone (zonation). In the last phase, mature lamellar bone at the periphery is evident.

Course and treatment: Although classic type MO has a benign course, with a self-limiting behavior, a biopsy is often performed in the early stage due to differential diagnosis with more aggressive lesions. The best approach is a US-guided needle biopsy in which the different areas (from periphery to the inner part) must be included.

Treatment is rest, cryotherapy, and anti-inflammatory drugs. Genetic type: progressive severe disability. If respiratory muscles are involved, disease may be fatal.

Treatment: No surgical treatment is usually required. In genetic diseases, good general care and avoidance of trauma (particularly the iatrogenic ones from i.m. injections, biopsies, surgery) are emphasized (Figs. 26.1, 26.2, and 26.3).

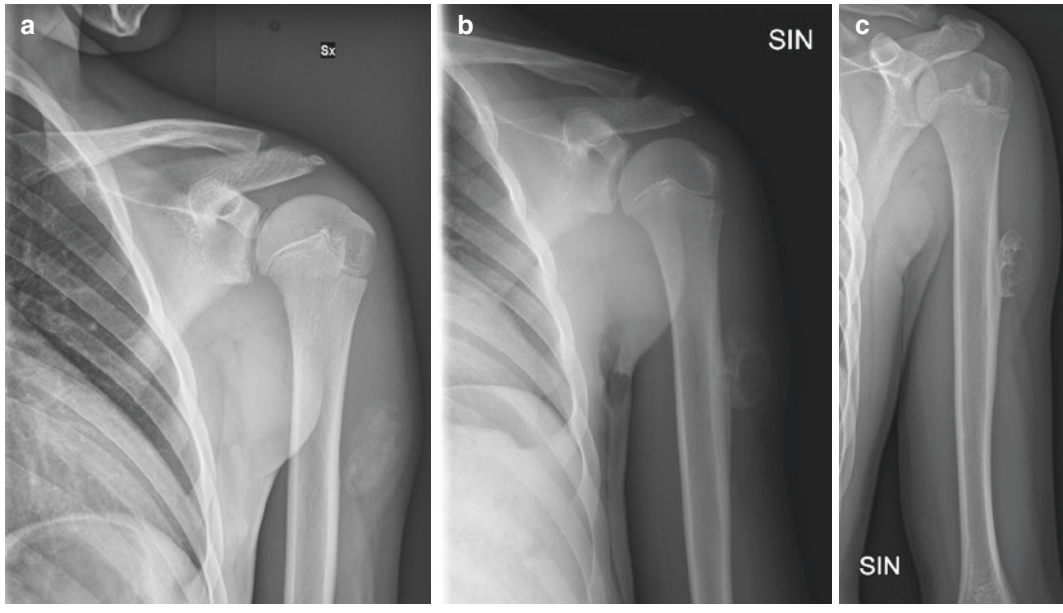


Fig. 26.1 (**a**, **b**, **c**) Evolution of myositis ossificans on standard X-ray. (**a**) X-ray at 3 weeks after clinical onset shows soft tissue calcification in the left arm, (**b**) X-ray at 3 months shows a calcified peripheral border with a radiolucent central area, (**c**) X-ray at 8 months shows a radiodense mass with a persistent radiolucent central area

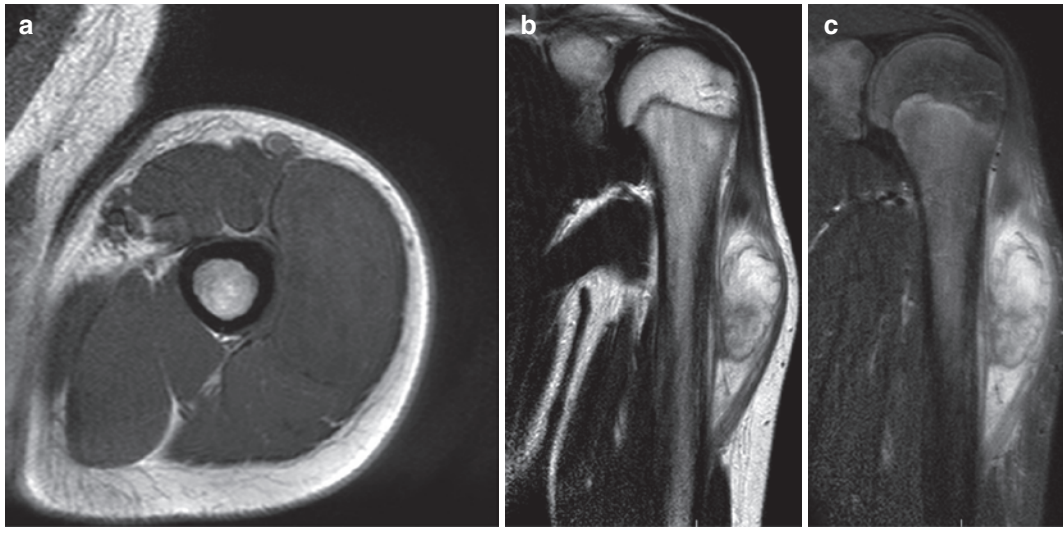


Fig. 26.2 MRI with T1 (**a**), T2 (**b**), and STIR (**c**) signals at 1 month after the onset of symptoms. Inhomogeneous T1 and hyperintense T2 and STIR signals are present at the same time

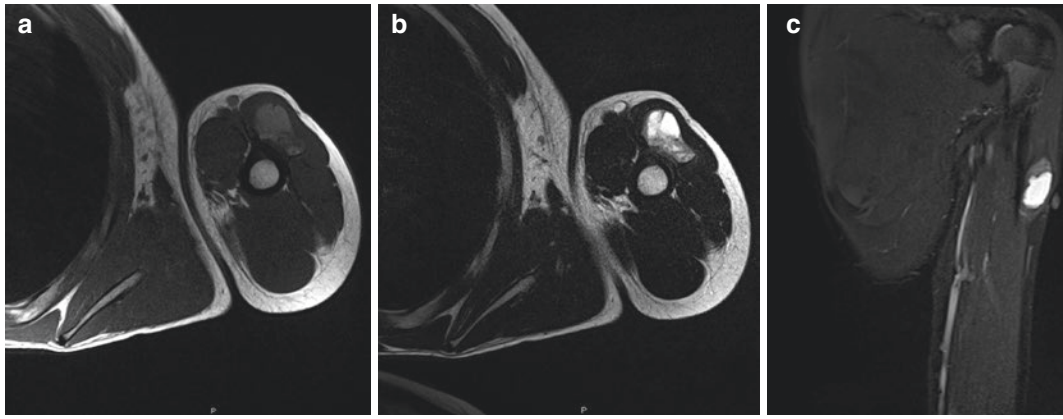
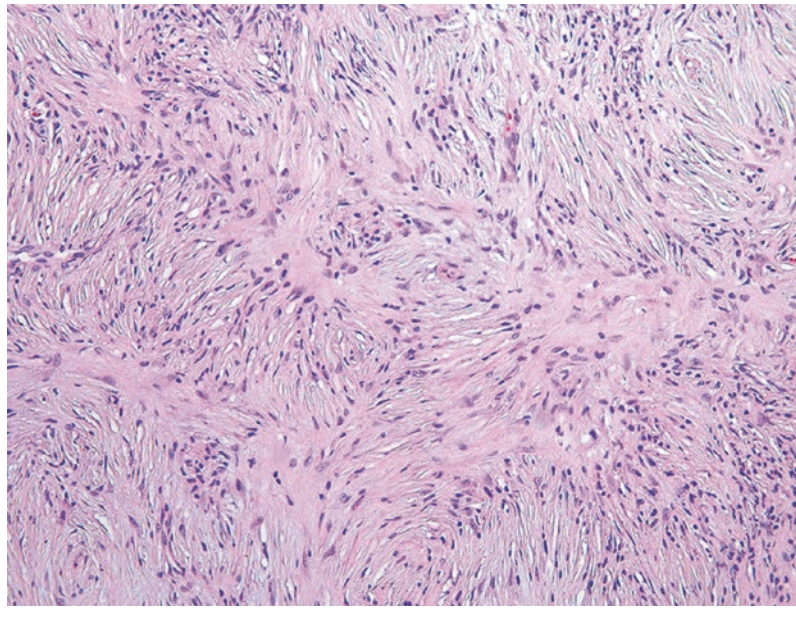
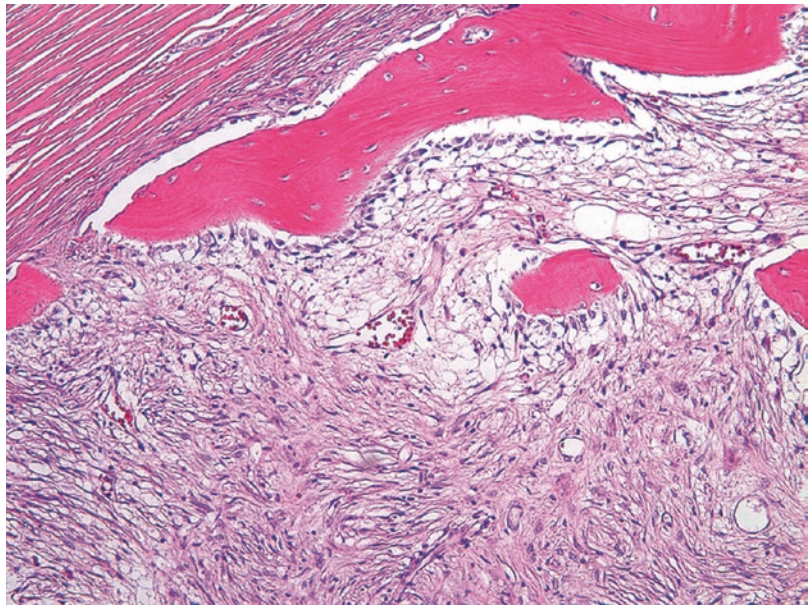


Fig. 26.3 MRI with T1 (**a**), T2 (**b**), and STIR (**c**) signals at 3 months after the onset of symptoms. The central part of the lesion becomes iso-hypointense in T1 and slightly hyperintense in T2 to surrounding muscles, a low T2 signal at the periphery can be appreciated (peripheral ossification) and in STIR edema has been resolved



Storiform pattern of bland-appearing spindle cells and scattered inflammatory cells in the center of the lesion



Ossified rim at the periphery (zoning phenomenon)

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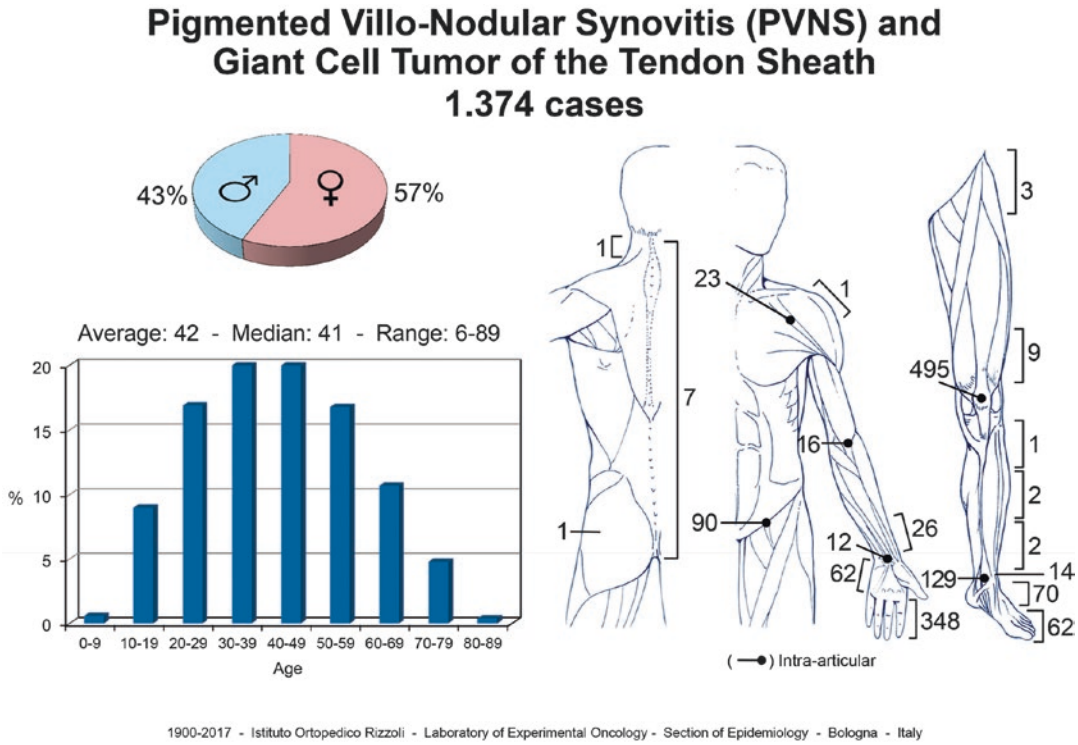
27

Pigmented Villonodular Synovitis and Giant Cell Tumor of the Tendon Sheaths (Tenosynovial Giant Cell Tumor)

Eric L. Staals

Definition: Benign neoplasm, composed of synovial-like mononuclear cells, creating a progressive inflammatory process in the joint, tendon sheaths, or bursae.

Epidemiology: No sex predilection. 20–40 years of age.



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Location: (a) paratendinous (frequent): in the sheath of a flexor tendon of the fingers, in the palm of the hand close to a metacarpophalangeal joint, in the wrist, on the dorsum of a finger adjacent to an extensor tendon, rare in the foot; (b) in the joint (rare): >75% in the knee, then in the hip, wrist, ankle, shoulder; (c) in the bursae (exceptional).

Clinical: The diffuse type, creating multiple nodules and usually involving the whole joint, often causes pain, swelling and stiffness. On the long term, degenerative changes and secondary osteoarthritis are frequently seen. The localized type is usually a single nodule and may cause blocking, clicking, and sometimes swelling of a joint. Pain is generally mild to moderate and if the nodule is small, this type can be (almost) asymptomatic.

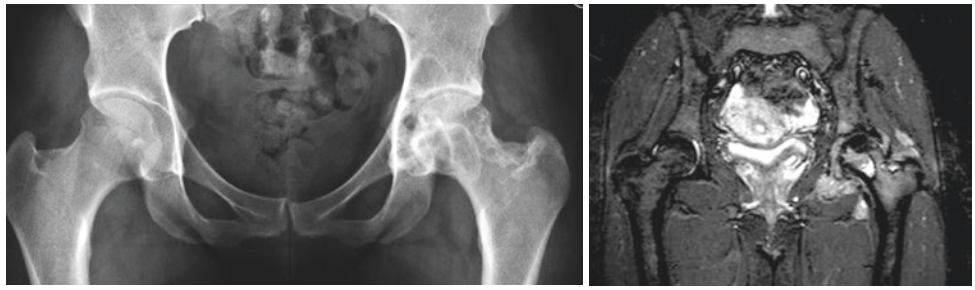
Diagnosis: On X-ray joint effusion may be detectable, with thickening of the synovial tissue. Skeletal erosions due to long standing nodular lesions creating osteolytic lesions with well-defined sclerotic margins, on the perimeter of the joint. On CT—lobulated newly formed tissue in the joint with considerable contrast enhancement. On bone scan—uptake may be increased due to bone compression/erosion. On MRI—heterogeneous, mostly low signal both in T1 and T2 is characteristic. Intra and peritumoral enhancing curvilinear regions on contrast T1. A PET-scan typically shows very high SUVmax values in TGCT, mimicking a malignant process.

Histopathology: Roughly lobulated, single, soft, yellow-white to pale brown nodules with smooth surface. In advanced stages it matures in a fibrous scar. It becomes hard, compact, white with some yellow or brown bands and adheres to the surrounding tissues, to bone, to tendon. The synovial membrane appears thickened, leathery-yellow, matted by long large villi like a "ruffled beard," with multiple, soft, yellow-brown, lobulated nodules of varying size. Fibrin membranes cover the villi surface. Histologically, sheets of mononuclear cells with plasmacytoid features, dense intercellular collagen, multinucleated giant cells, hemosiderin pigment, and scattered groups of foam cells.

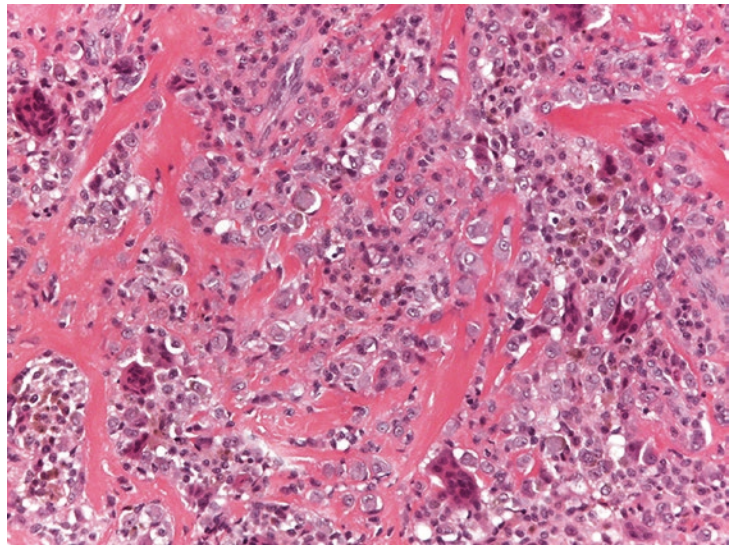
Soft, pasty, friable, and yellow-brown tissue fills joint space in more advanced lesions. Pathologic tissue may be easily enucleated from the bone lesions that have a smooth bony wall. The diffuse type TGCT may invade the joint capsule and expand into the muscles, between the tendons, but it never infiltrates them. It may dislocate or encase the neurovascular structures.

Course and Staging: The clinical course is rather unpredictable. TGCT is usually slowly growing, and clinical presentation may remain stable for many years. However, recurrent disease is very frequent in the diffuse type and may lead to significant functional loss and impaired quality of life. Malignant TGCT has been reported in exceptional cases.

Treatment: Excision of the nodular type is usually curative and may be performed either through an open excision or arthroscopically. In diffuse type TGCT surgery is difficult and often it is impossible to eradicate the whole lesion. Complete synovectomy is indicated, but postoperative complications are frequent and local recurrence rates are as high as 40%. When the disease destroys the joint cartilage an arthrodesis or prosthesis may be required, and in rare cases amputation is necessary. External or intrarticular radiotherapy has been suggested as adjuvant treatment when complete excision is not feasible. Recent studies have underlined the important role of the CSF1-CSF1R pathway in the pathogenesis of TGCT and several target therapies have been proposed with promising short-term results.



Radiograph and T2 coronal MR image. Hip lesion with multiple erosions of the bone of both parts of the joint. Lesions have a low signal on T2 image due to iron deposits



Sheets of synovial mononuclear cells, hemosiderin pigment, scattered multinucleated giant cells, and foam cells. Vaguely nodular pattern on panoramic view

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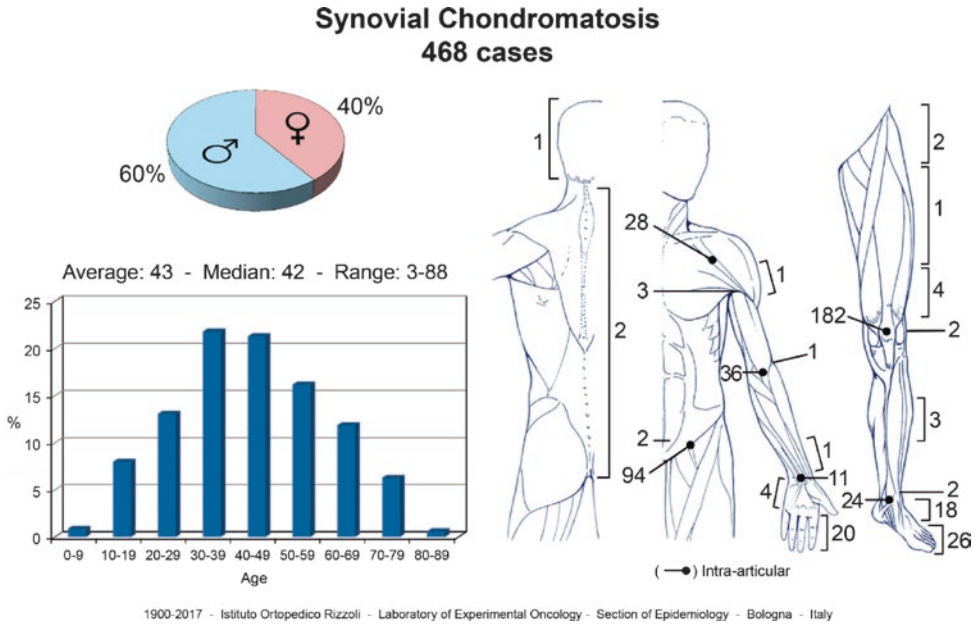
Synovial Chondromatosis

28

Eric L. Staals

Definition: A benign neoplasm of well-differentiated hyaline cartilage originating from the synovial membrane of the joint, the tendinous sheath or the bursae mucosae.

Epidemiology: Rare. Males. 30–50 years old.



The original version of this chapter was revised.
A correction to this chapter can be found at
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Location: >50% knee, then elbow, shoulder, wrist, hip, and ankle. Extra-articular form in the fingers.

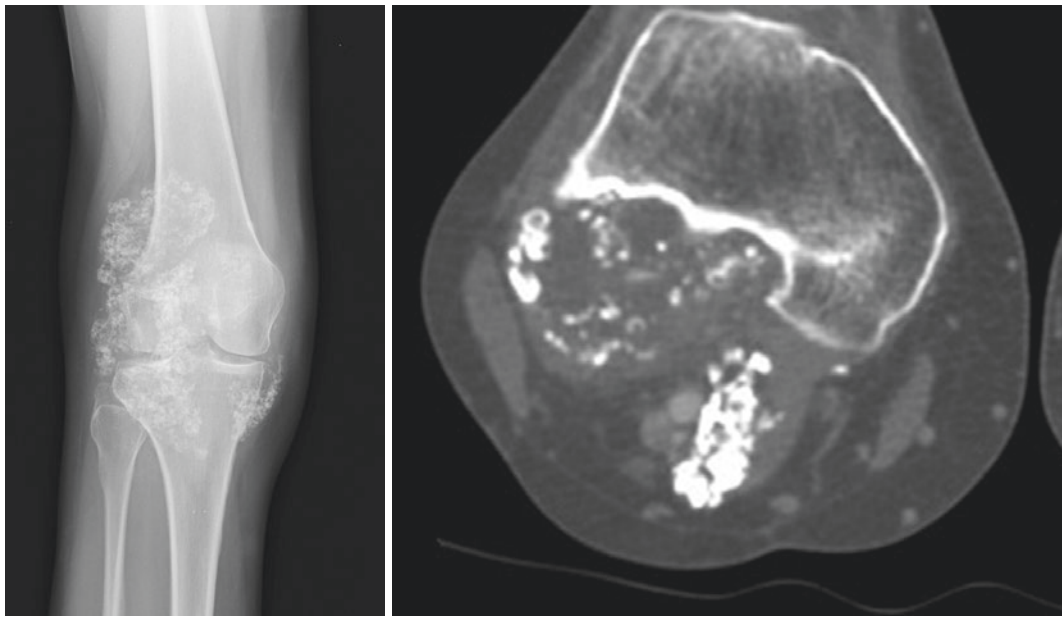
Clinical: Pain, limited joint motion, sensation of joint crackling. Rarely blocking of the joint and effusion. Solid nodules, sometimes loose bodies, may be palpable. Recurring and slowly progressive symptoms. Plurilobulated hard-elastic mass expanding around a joint in aggressive type.

Imaging: X-ray might show intrarticular calcified nodules. Osteoarthitis is frequently seen in longstanding lesions and bone erosion or cortical scalloping in the aggressive ones. On CT intrarticular nodules, calcifications, bone lesions, and invasion of the surrounding tissues is better appreciated. On MRI—increased joint fluid, lobular intra-articular mass, intermediate intensity if uncalcified or with white punctuated appearance if ossified on T1, round, ring-like, dark signal voids in strong enhancement of the synovial tissue on contrast T1 and in bright signal of the joint fluid on T2.

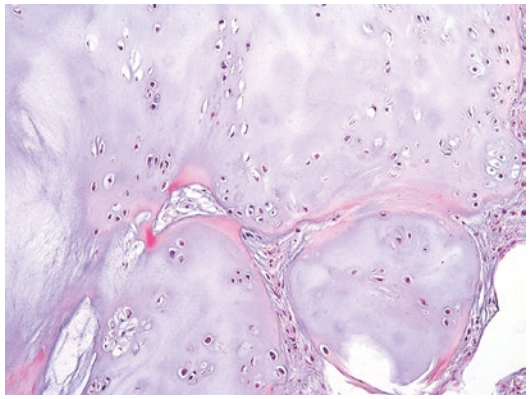
Histopathology: White, smooth, lucent, translucid soft or firm, loose bodies of different size. Thickened and seeded with cartilaginous nodules synovial membrane; hard, granular, yellowish ossified areas in the nodules. Lobules of well-differentiated rather cellular hyaline cartilage. Clustering of the chondrocytes is characteristic. Cartilaginous lobules are surrounded by fibrous bands.

Course and Staging: Slow growth, surgery is often curative, although late recurrences may be seen. Usually, stage 2 or 3. Rarely spontaneous regression. Very rare cases can transform into chondrosarcoma.

Treatment: Intralesional excision with (complete) synovectomy.



Radiograph and CT. Mass in the joint, eroding bone in a well limited way, and containing cartilaginous calcifications



Lobular pattern, clustering of chondrocytes, hyaline matrix

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Fibromatosis (All Types)

29

Davide Maria Donati and Tommaso Frisoni

Fibromatosis consists in a wide group of benign mesenchymal proliferation. In WHO 2013 it belongs to the group of fibroblastic/miofibroblastic neoplasms not metastasizing but with a potential locally aggressive behavior. They can arise either from fasciae (superficial type) or from deep tissue:

(a) Superficial: (1) palmar f. (Dupuytren's contracture); (2) plantar f. (Ledderhose's disease); (3) penile f. (Peyronie's disease); (4) knuckle pads.
(b) Deep (desmoid-type fibromatosis): (1) extra-abdominal f.; (2) abdominal f.

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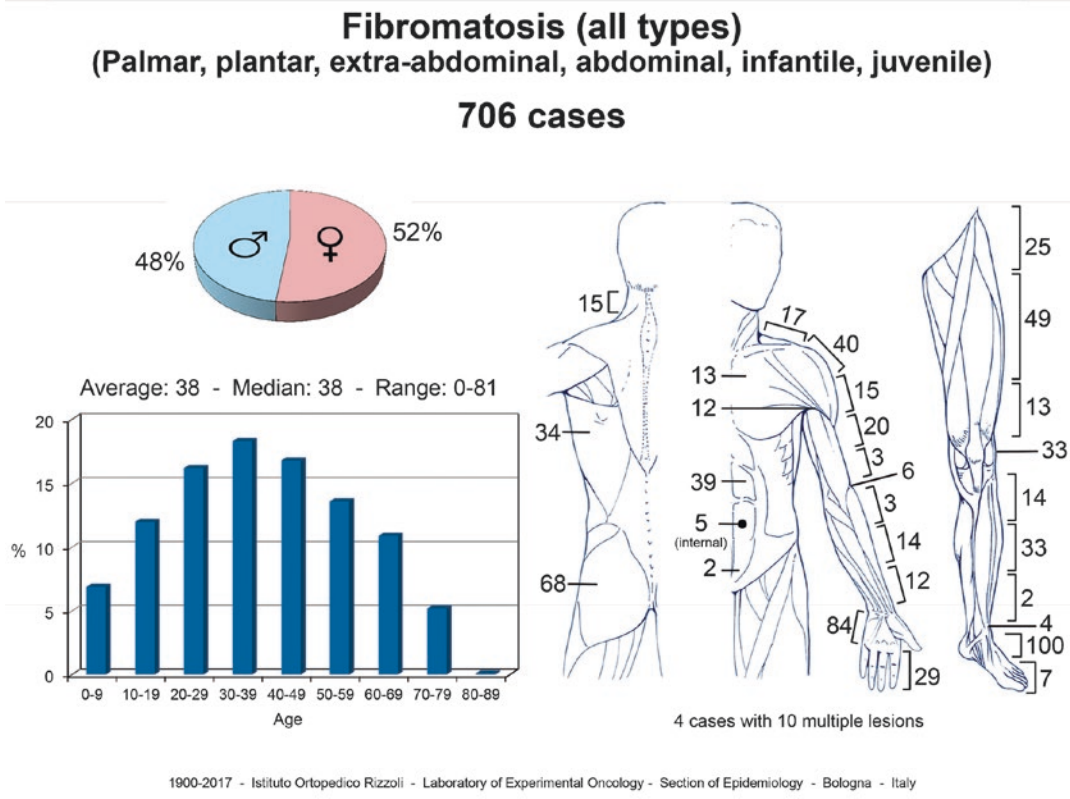
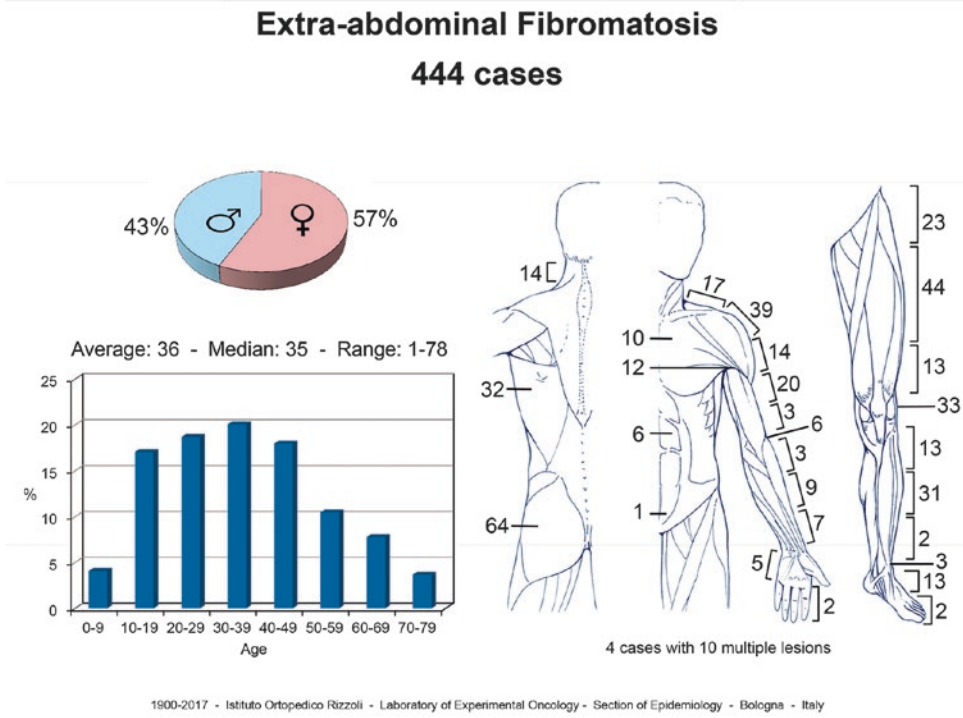


29.1 Desmoid Type: Fibromatosis

Definition: This tumor consists in a locally aggressive proliferation of small bundles of spindle cells (monoclonal fibroblasts) in an abundant fibrous stroma with an infiltrative growth. Not metastasizing but with an high local recurrence rate after surgical excision.

Epidemiology: Young adults and women are mostly involved. Occurs more often in patients with FAP. In women tumor growth may be related to pregnancy. Peak incidence 25–35 years. Three percent of all soft tissue tumors rising to 13% in FAP.

Localization: Ubiquitous. Scapular girdle, pelvic girdle, lower limbs, and upper limbs. Usually deep. Skin invasion is rare.



Clinical: Clinical features depend on localization. Symptoms are mainly related to the structures involved. Tumor is usually a slowly growing, painless, hard mass, often very adherent to surrounding tissues. The infiltrative pattern leads the tumor grow into the muscles and along fasciae with multiple nodules (multifocality) that can arise proximally and distally even in different compartment of the same limb configuring an high morbidity evolution although the lack of metastasizing potential with an tendency to recur. When it develops close to a joint, a functional impairment may occur due to stiffness and muscular/tendon/capsular retraction. Neurological symptoms are rare but possible when nerves are involved.

Imaging: On standard X-ray, it may be not detectable even if sometimes a calcific mass in soft tissue or a bony erosion when the tumor is seated on cortical bone can be revealed. US scan appearance is variable, usually hypoechoic and inhomogeneus; if performed with contrast medium, it shows an early enhancement of the contrast agent and a long washout, typical aspect of benign lesions probably due to the presence of fibrotic tissue.

CT scan reveals a isodense lesion, thus is recommended to conduct the exam with contrast medium, in order to distinguish the mass from surrounding tissue and recognize its multinodular shape. It's very useful in studying the bony erosion.

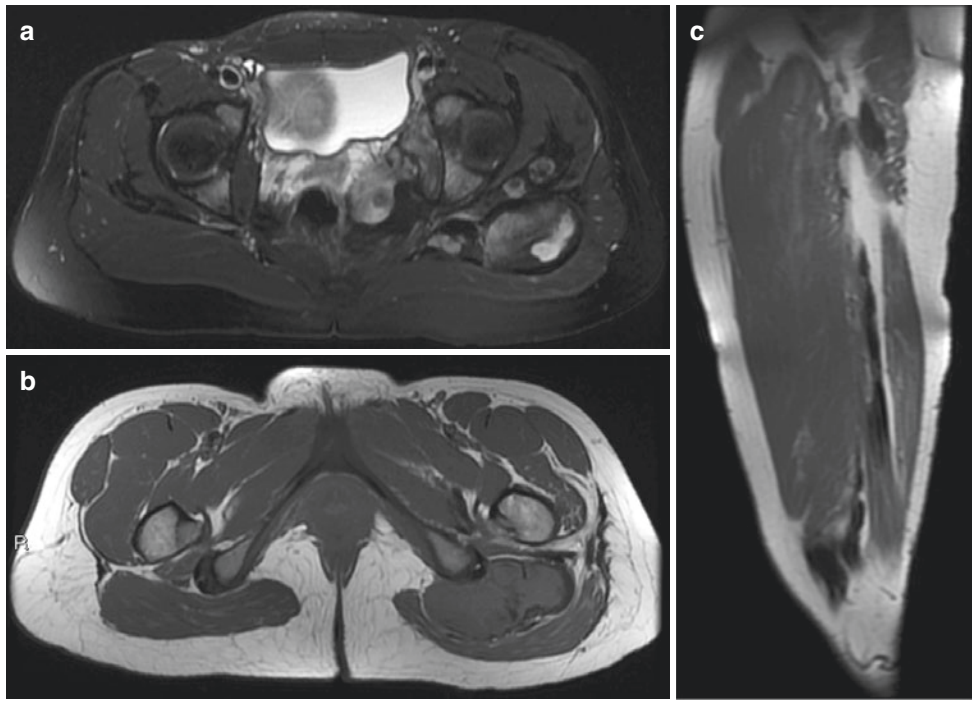
The gold standard is MRI in which active desmoid fibromatosis is often heterogeneously isointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. An inhomogeneus contrast enhancement is present. Bands of low signal on all sequences are due to the presence of hypocellularity and abundant collagen areas, within high T2 signal and enhancement reflecting the cellularity and active disease, whereas low T2 signal denotes collagenization and maturation.

Changes in MRI imaging features are used as evaluation for treatment response; however, a large consensus for what can be considered a good response is necessary. RECIST criteria are not applicable as assessment because usually they do not reduce in volume but they change becoming "biologically inactive" with an increased hypointensity in T2 and a decreased contrast enhancement.

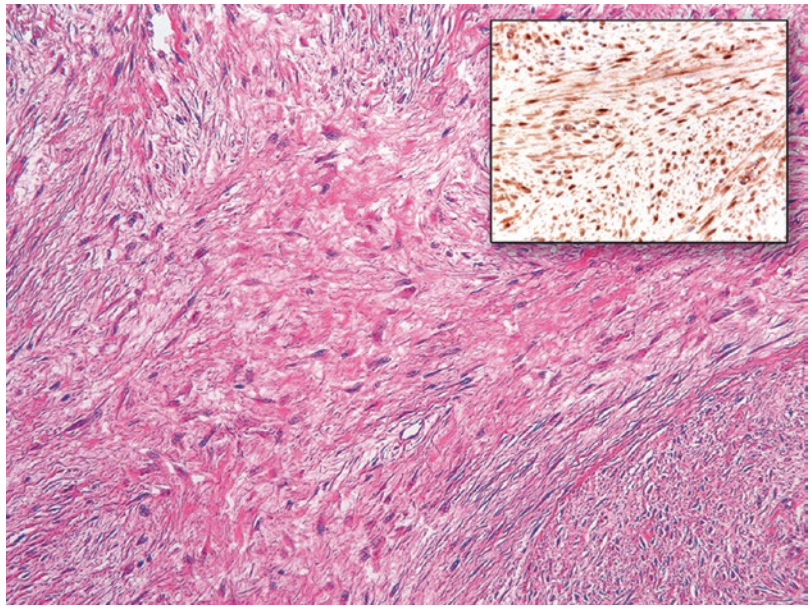
Histopathology: Grossly a solid and hard mass with infiltrative pattern can be appreciated; difficult to recognize well-defined margins and separate from the surrounding tissues even if they usually are not invaded. It's a spindle cell proliferation in a very dense and mature fibrous connective tissue. Cellularity is quite low as well as mitoses. Spindle cells are bland in appearance and grow in intersecting fascicles. Open vascular clefts are characteristics. Abnormal expression of β-catenin is due to *CNTTB1* gene mutations. In FAP, APC gene pathway is involved in pathogenesis.

Course and Staging: Locally aggressive tumor not metastasizing. Clinical behavior is unpredictable. Usually slowly growing; sometimes a rapid growth is observed but it can also tend to self limit with a spontaneous involution or regression associated to MRI changes. Local recurrence is frequent even if removed with adequate margins. Malignant transformation has never been observed.

Treatment: DT fibromatosis treatment is controversial and under debate. The standard of care has been surgical treatment with wide or radical excision (including amputation). This approach has been associated with adjuvant radiation therapy in particular when inadequate margins were obtained. During the last decades, a "wait and see" approach has become more indicated as first line regardless to symptoms. According to localization or symptoms, if resistant to painkiller treatment, systemic or adjuvant therapies such as chemotherapy or radiotherapy can be suggested. Nevertheless surgery and adjuvant therapies should be considered only in case of progression after an observational period or for not responsive tumors. The most used chemotherapy regimen have been low-dose MTX-VBL, tamoxifen, and more recently pazopanib. Prognosis is good.



(**a**, **b**) T1 and T2 FAT SAT MRI sequences show a heterogeneously isointense on T1-weighted images, heterogeneously hyperintense on T2-weighted images. In (**c**) the multifocal pattern that involves the whole extension of the thigh in the same patient



Heavily collagenized tissue with low cellularity, spindle cells with bland appearance, intersected fascicles, and ectatic vascular clefts. Immunohistochemical nuclear positivity for β-catenin in the neoplastic cells (*inset*)

Immunohistochemical panel	
• β-betenin	Smooth M Act +
• β-catenin	+ (80% of cases)

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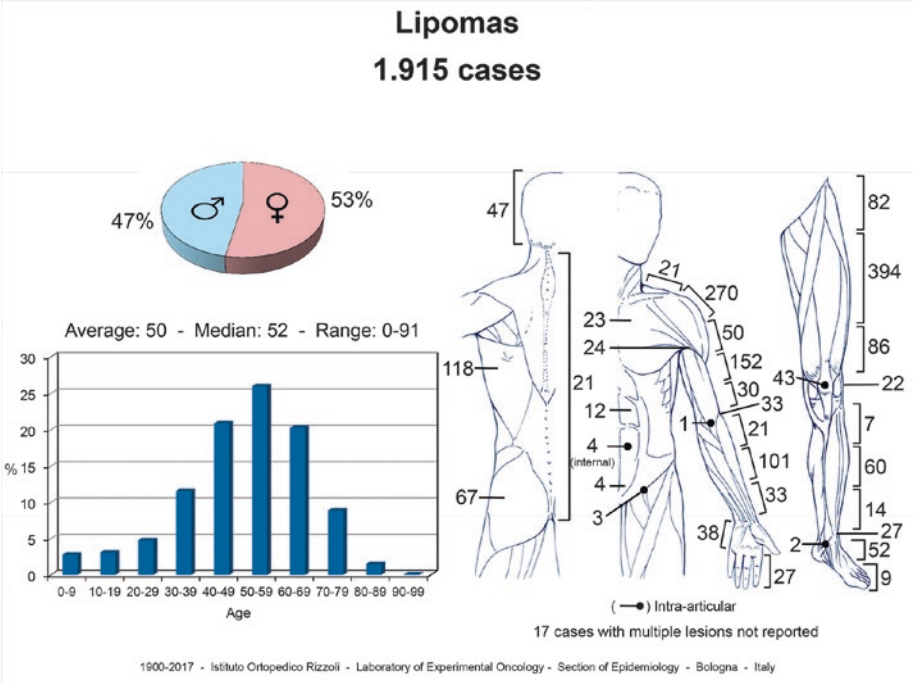
Lipomas

30

Giuseppe Bianchi

Definition: A benign tumor constituted by well-differentiated adipocytes.

Epidemiology: The most common among soft-tissue tumors. It is more frequently observed between 40 and 60 years of age and prevails in females when it is superficial, whereas in males when it is deep and multiple.



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Localization: (a) superficial (frequent): in the subcutaneous tissue of the back, shoulder, neck, proximal extremities. (b) Deep (rare): within or between muscles or adherent to bone, tendons, joints, or nerves. In 5% of cases, lipomas are multiple with symmetrical distribution in the dorsum and proximal upper limb.

Clinical: Solitary lump, slow growing, painless unless there is nerve compression. Superficial lipoma never grows large size (average 4 cm) and it is movable. Deep lipoma tends to be larger (average 10 cm) and with a spherical, fixed, and firm mass. Possible association with hereditary familial multiple lipomatosis (FML).

Imaging: On X-ray, a radiolucent mass rarely with calcification or ossification; mild cortical thickening when parosteal. On CT scan, a lobulated, sharply marginated radiolucency with homogeneous density. On MRI, an encapsulated, bright mass without enhancement after contrast administration; signal intensity equal to that of fat; regular thin septation. On angiography, avascular. On bone scan, there is no uptake.

Histopathology: It is often lobulated with a very thin true capsule. Soft on palpation, pale yellow in color, lipoma is constituted by mature adipocytes with no atypia. Vessels are not very apparent, because they are thin and compressed by lipocytes.

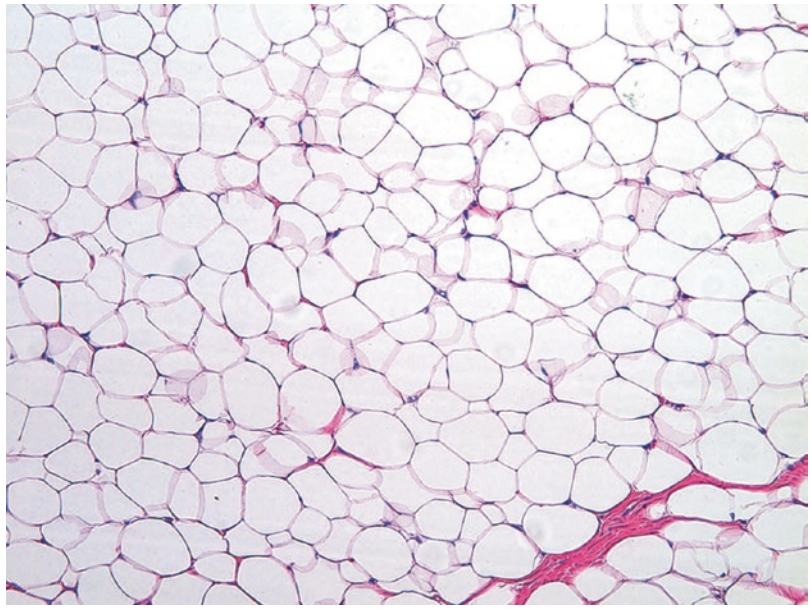
Course and Staging: (a) superficial lipoma: easily diagnosed, asymptomatic, generally stage 1 but it may behave as active stage 2 lesion. According to AJC classification, lipoma is more frequently stage Ia. (b) Deep lipoma: an extensive anatomo-pathological study with multiple specimens is necessary to exclude liposarcoma lipoma-like. Usually, stage 2 or stage Ib according to AJC classification. Malignant changes are exceptional.

Treatment: Marginal excision is curative. Recurrence is rare (<5%).

Variants	Age	Sex	Clinical	Gross	Histology
Angiolipoma	20	Male	<2 cm/forearm subcutaneous pain	Firm yellow/reddish	Lipocytes + network of capillaries with fibrin thrombi
Spindle cell Lipoma	Adult	Male	4 cm/back subcutaneous painless	Soft yellow/whitish	Lipocytes + vessels + spindle cells + myxoid matrix + collagenous bands
Pleomorphic Lipoma	Adult	Male	4 cm/back subcutaneous painless	Firm yellow/whitish	Lipocytes + bizarre floret-like multinucleated cells
Lipoblastoma	<2	Male	3 cm/limbs subcutaneous painless	Lobulated translucid	Like myxoid liposarcoma
Lipomatosis	10	–	Large/diffused pain	Dense tissue infiltrating	Mature adipose tissue
Intranervous L	<30	Male	Hand/wrist pain + neuropathy	Hard	Surrounds and infiltrates the nerve
Hybernoma	Adult	Male	4 cm/scapular subcutaneous painless	Firm	Central nucleus + foam cytoplasm = brown fat

Spindle Cell/Pleomorphic Lipoma

Immunohistochemical panel	
• CD34	+
• Rb	+/–



Mature adipocytic cells organized in lobules with flat nuclei at the periphery and optically empty cytoplasms. No atypia of the cells

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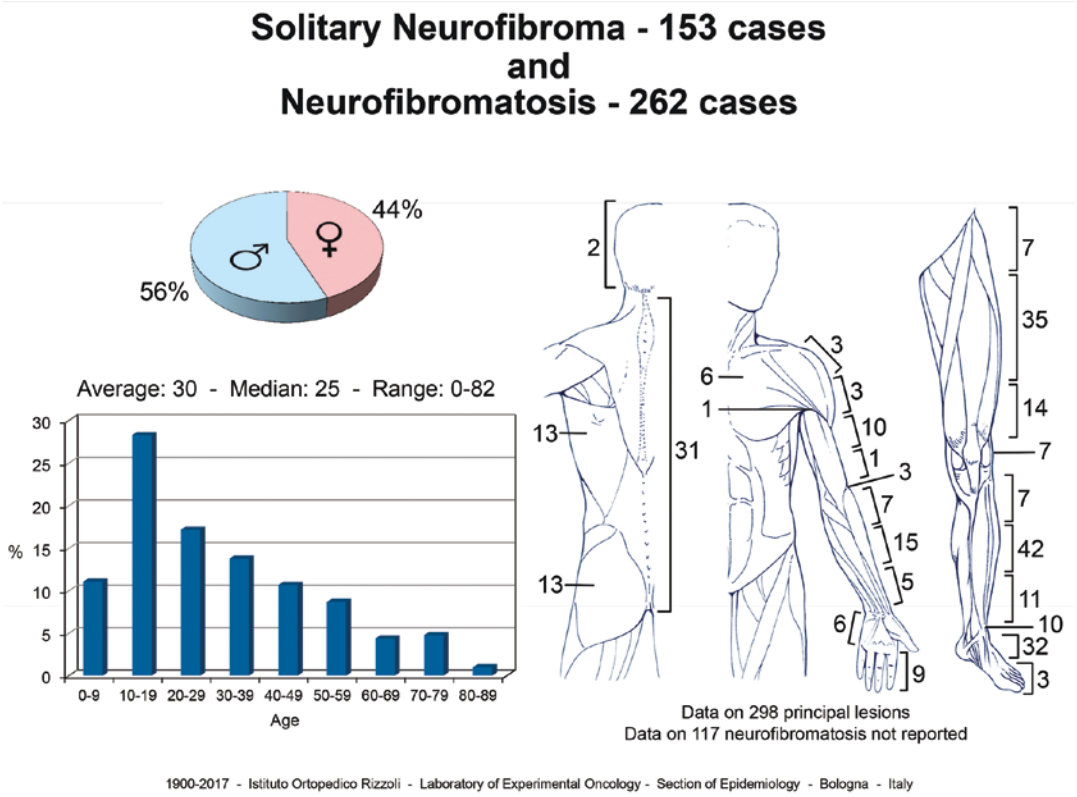
Neurofibromas

31

Marco Gambarotti

Definition: Benign tumor of the peripheral nerve sheath. (a) Solitary. (b) Multiple in neurofibromatosis type 1 (NF1).

Epidemiology: (a) more frequent than (b) (90%). (a): no sex predilection, 20–40 years old. (b): males, younger patients.



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Location: (a): superficial lesion in subcutis or dermis. (b): all sites and organs.

Clinical: (a) painless nodule or few symptoms (pain, swelling); other symptoms depend on location of neurofibromas (b) "café-au-lait" spots, typically in the axilla, pigmented hamartomas of the iris (Lisch nodules), skeletal abnormalities, disorders of growth, and sexual maturation.

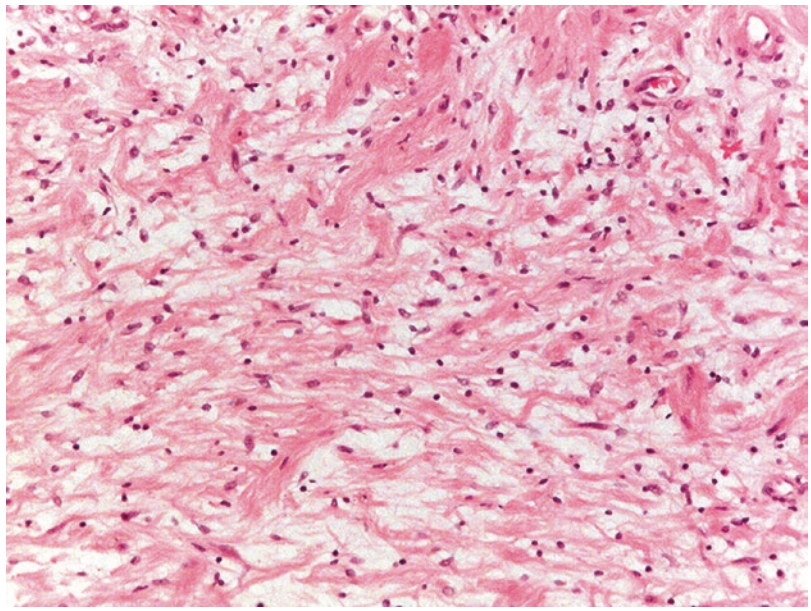
Imaging: On MRI: nerve trapped within or obliterated by the mass. Rarely encapsulated. Much more homogeneous, isointense to muscle with frequent areas of high signal on T1, more inhomogeneous, typical target appearance, higher than fat intensity on T2, centrally higher enhancement never with necrosis on contrast T1.

Histopathology: Some variants are described: localized cutaneous, diffuse cutaneous, localized intraneural, plexiform intraneural, and massive diffuse soft tissue plexiform. Diffused neurofiblomas appear as whitish plaque-like thickening of skin, diffusing along connective septa and among adipose tissue cells. Plexiform neurofibromas appear as cordonal masses of convoluted aspect, a mixture of nerve trunks of different shape and size. Sectioned neurofibromas appear as spindle masses within the nerve, firm, grayish to tan, with pink areas. Histologically, neurofibroma is composed of interlacing bundles of loosely-arranged elongated spindle cells with wavy nuclei, associated with thick "ropey" collagen bundles, and mucoid material. Residual bundles of nerve fibers can be seen inside the tumor. Scattered fibroblastas, mast cells, lymphocytes, and xanthoma cells can be present.

Course and Staging: Malignant transformation in MPNST is rare in type (a), but more frequent (5–10%) in type (b), particularly when in NF1. Usually stage 1 or 2.

Treatment: Marginal excision in (a); in (b) large or painful lesions or lesions located in areas where continued growth would compromise organ function are treated by surgery.

Immunohistochemical panel	
• S100	+ (30–60% of cells)
• Neurofilament proteins (NF)	+ in axons inside the lesion



Loose proliferation of spindle cells with wavy nuclei in a myxoid background containing thick collagen bundles

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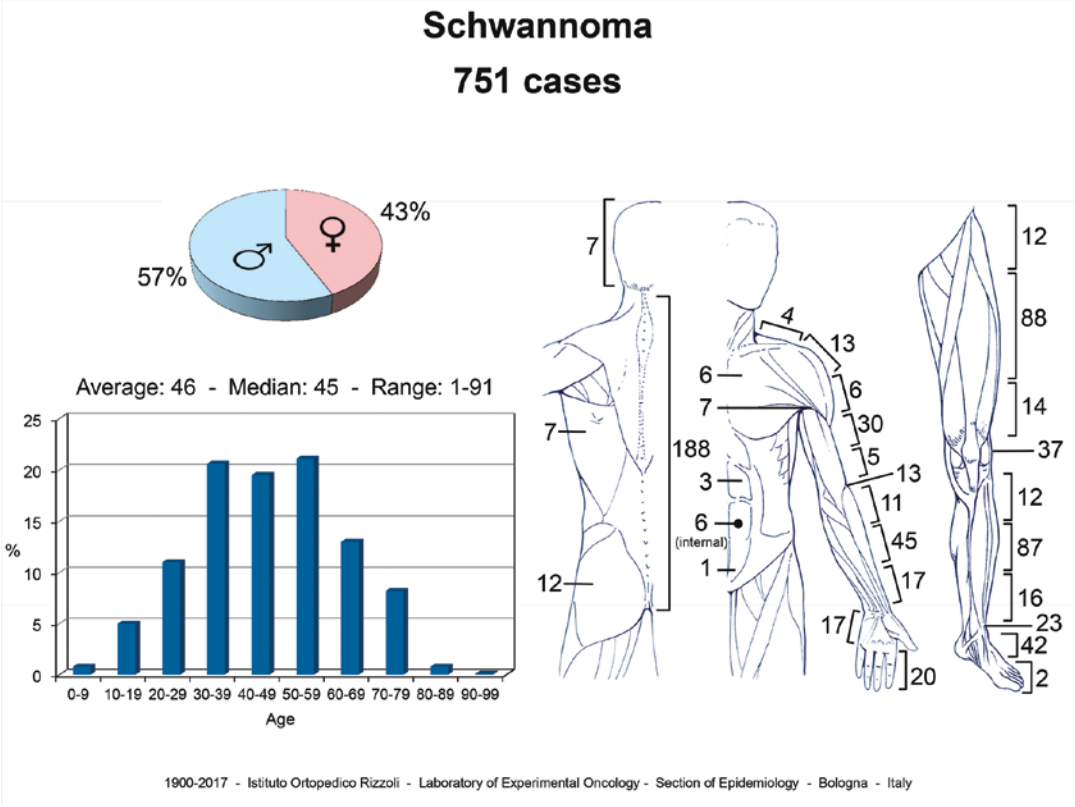
Schwannoma

32

Marco Gambarotti

Definition: Nerve sheath tumor composed of differentiated neoplastic Schwann cells.

Epidemiology: 20–50 years old. No sex predilection. Rarely associated with neurofibromatosis.



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Location: Spinal roots, nerves of the mediastinum or of the retroperitoneum, peroneal, and ulnar nerve. Solitary in more than 90% of cases.

Clinical: Often asymptomatic or slow and progressive pain and neurological symptoms. Liquoral block, compression of the other roots or of the spinal cord, rachialgia, nocturnal increase in pain, stiffness, and spinal contractures. Sometimes sharper irradiated pain, paresthesia, algodystrophic syndrome when in peripheral nerve.

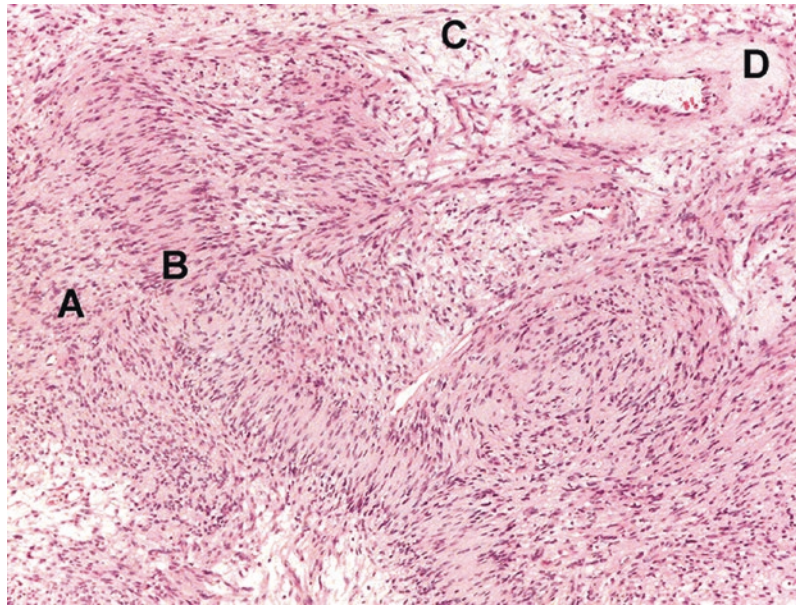
Imaging: On X-ray: scalloping of bone. On CT: well-circumscribed, homogeneous lesion, with muscle density. Frequent non-enhancing necrotic and cystic areas that cause an inhomogeneous hyperdense lesion after contrast administration. On MRI–nerve along the site of the mass. Capsulated. Homogeneous, isointense to muscle with frequent areas of low signal on T1, inhomogeneous, sometimes target appearance, higher than fat intensity on T2, diffused or peripheral enhancement with central necrotic unchanged zones on contrast T1.

Histopathology: Grossly, a globose "sausage-like" or "dumbbell" mass, elongated along the sac, with a smooth well-delimited surface covered by a capsule, connected to a nerve root. Rarely, it expands like an hourglass inside and out of the intervertebral root foramen. Schwannoma of the peripheral nerves can appear as an "onion bulb" or a piece of fruit attached to its stem. Sectioned tumors are soft, pink to white, often with yellow or hemorrhagic areas. Histologically, schwannoma is usually encapsulated. It is composed by a proliferation of spindle cells growing in compact (Antoni A) areas, alternating with loosely arranged (Antoni B) areas. Verocay bodies, formed by parallel rows of well-aligned nuclei, are present in Antoni A areas. Neoplastic cells show ill-defined eosinophilic cytoplasm and elongated tapered nuclei. Rare, if any, mitotic figures. Large, irregularly spaced vessels with hyalinized thickened wall commonly present. Degenerative atypia with extensive hyalinization can be present ("ancient" schwannoma). Cellular schwannoma is composed quite exclusive by Antoni A areas, with high cellularity and mitotic figures. Plexiform schwannoma involves multiple nerve fascicles or a nerve plexus, growing in a multinodular fashion. Melanotic schwannomas are composed of spindle to epithelioid cells, with round large vesicular nuclei and melanotic pigment in the cytoplasm (these cells are immunohistochemically positive for melanocytic markers); the presence of psammoma bodies defines the psammomatous variant.

Course and Staging: Schwannoma is a benign slow growing tumor, with rare recurrences after even incomplete surgery. Usually stage 1 or 2. Malignant transformation in epithelioid MPNST, epithelioid angiosarcoma, primitive neuroectodermal cells, or rhabdomyosarcoma is exceptional. Melanotic schwannoma is a low-malignant potential, rarely metastasizing tumor, with a tendency for late metastasis, and a 15% mortality rate. Although there are no strict criteria for malignancy in melanotic schwannoma, malignant forms often show large vesicular nuclei with macronucleoli, necrosis, and mitotic rate >2/10 HPF. About half of the cases of psammomatous melanotic schwannoma are associated with the Carney complex.

Treatment: Marginal excision is curative for classic schwannoma.

Immunohistochemical panel	
• S100	+
• SOX10	+
• GFAP	+/–
• EMA	+ in perineurial cells of the capsule



Cellular areas composed of elongated spindle cells with tapered nuclei (Antoni A areas, **a**), sometimes organized in palisades (Verocaly bodies, **b**), alternated with loose sheets of cells (Antoni B areas, **c**); hyalinized thickened walled vessels are present (**d**)

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33 Other Rare Conditions of Pseudotumoral and Benign Lesions of Soft Tissues

Alberto Righi

33.1 Myxoma

The myxomas are a group of relatively common, entirely benign probably unrelated lesions, which most commonly involve large muscles (intramuscular myxoma) but may also occur around large joints (juxta-articular myxoma) or in the skin (cutaneous myxoma). All cases are characterized by abundant myxoid matrix, bland stellate to spindled cells, and hypovascularity. These three morphological features are fundamental to differentiate myxoma to myxoid nodular fasciitis and to malignant myxoid neoplasms, such as myxofibrosarcoma and myxoid liposarcoma [1]. Local, complete excision is adequate treatment, but juxta-articular myxoma may recur locally in 30% of cases, particularly if incompletely excised [1].

33.2 Angioleiomyoma

Angioleiomyoma, also called angiomyoma and vascular leiomyoma, is a benign dermal or subcutaneous tumor composed of well-differentiated smooth muscle cells arranged around many vascular channels. It represents 4–5% of benign soft tissue tumors, occurring at all ages but commonest between the fourth and sixth decades of life [2]. Angioleiomyoma can occur anywhere in the body, but is most often seen in the extremities followed by the head and trunk and it typically presents as a small, slowly growing firm nodule measuring <2 cm in diameter associated with pain in half of patients. Incomplete excision or a deeply situated lesion may exceptionally result in local recurrence [2].

33.3 Glomus Tumor

Glomus tumor (also called glomangioma and glomangiomyoma) is mesenchymal neoplasms composed of cells resembling the modified smooth muscle cells of the normal glomus body. This tumor is rare accounting for less than 2% of soft tissue tumor with a similar gender distribution and with a predilection for young adults. The vast majority occur in skin or superficial soft tissue in the distal extremities associated with a long history of pain. Rarely (fewer than 40 cases reported in literature), glomus tumors are morphologically considered malignant when the tumor show marked nuclear atypia and any level of mitotic activity or atypical mitotic figures [3]. "Typical" glomus tumors are benign neoplasms that require only simple excision. Malignant cases are highly aggressive with metastases and death from disease in up to 40% patients.

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33.4 Nodular Fasciitis

Nodular fasciitis is a common, benign, self-limiting, pseudo-sarcomatous reactive process that is mainly composed of fibroblasts and myofibroblasts. It is a solitary, small (<3 cm), sometimes painful subcutaneous nodule that occurs in young and middle-aged adults (20–50 years), with no sex predilection and that develops rapidly (often <1 month). It can be seen anywhere in the body but most common in the upper extremities (50% of cases), especially in the forearm [4]. Morphologically, nodular fasciitis is a highly proliferative lesion and it is commonly mistaken for a sarcoma. Important histological clues to the diagnosis of nodular fasciitis include the short, randomly arranged fascicles, the absence of a well-developed thick-walled vasculature, and the absence of nuclear pleomorphism or hyperchromatism. Simple excision is the treatment of choice with a percentage of local recurrences of less than 2% of cases [4].

33.5 Proliferative Fasciitis and Proliferative Myositis

Proliferative fasciitis and proliferative myositis are morphologically similar to nodular fasciitis but contain ganglion-like myofibroblastic cells, which are usually negative for muscle markers. Proliferative fasciitis is usually seen in the subcutaneous tissue of the upper limbs of middle-aged adults (40–60 years), whereas proliferative fasciitis mainly affects the muscles of the trunk and shoulder girdle. In children, proliferative fasciitis may be cellular and mitotically active, mimicking rhabdomyosarcoma or epithelioid sarcoma [4]. Both these lesions are benign, self-limiting, and reactive process. Simple excision is the treatment of choice. Local recurrences are exceptional.

33.6 Pseudotumoral Calcinosis

Pseudotumoral calcinosis (also called tumoral calcinosis, calcifying collagenolysis, calcifying bursitis, tumoral lipocalcinosis, and hip stone disease) is the designation for an extraskeletal soft tissue hydroxyapatite calcification with a granulomatous response that develops in patients with secondary hyperparathyroidism or hypercalcemia, usually idiopathic or because of end-stage kidney disease [5].

33.7 Hibernoma

Hibernoma is a benign adipocytic tumor characterized by a brown fat cell component variably intermingled with mature white adipose tissue. This tumor, which usually presents as a painless, slow-growing mass, tends to occur in the subcutis of young adult with a predilection for the thigh, followed by the trunk, the upper limbs, and the head and neck area [6]. The main differential diagnosis is with atypical lipomatous tumor with hibernoma-like features: the absence of MDM2 amplification by FISH associated with an immunohistochemical negativity for MDM2/CDK4 in hibernoma can help to differentiate these entities. Local excision is curative.

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Part IV

Primary Malignant Tumors

Chondrosarcomas (CHS)

34

Davide Maria Donati and Giuseppe Bianchi

Definition: Malignant cartilaginous-matrix producing tumors.

CHS varieties and their incidence on 100 cases

Chondrosarcomas varieties	%
• Central	55–60
• Peripheral	15–20
• Dedifferentiated central	15
• Soft tissues	5–6
• Clear cells	2
• Periosteal	2
• Mesenchymal	1–2
• Dedifferentiated peripheral	1

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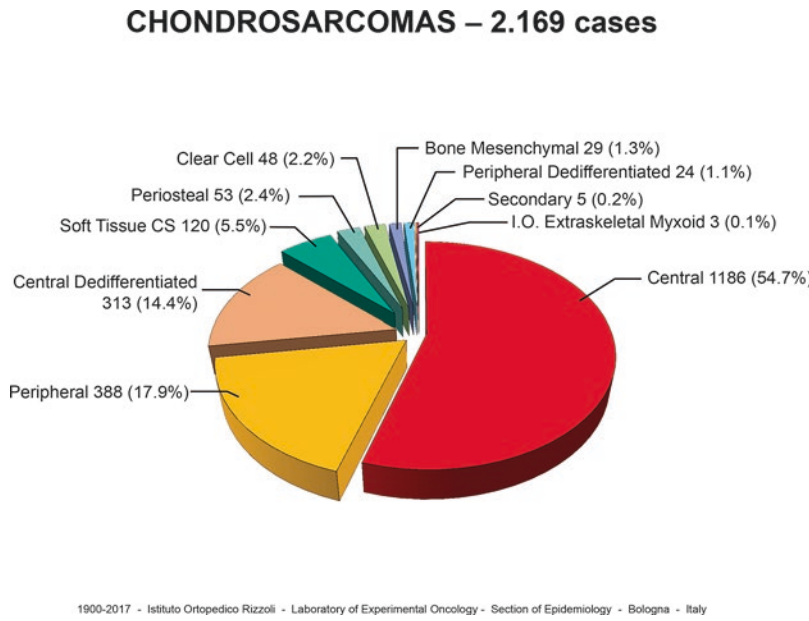
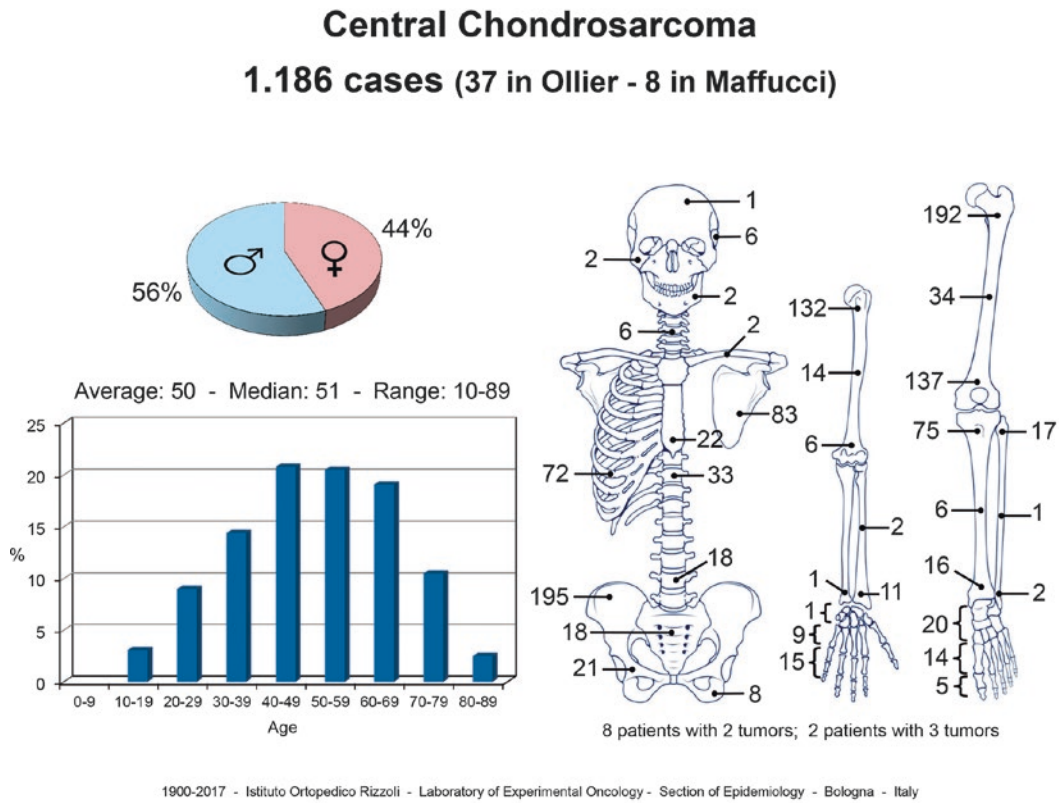


34.1 Central Chondrosarcoma

Epidemiology: Males. Adult age. Extremely rare in children.



Localization: Proximal femur, pelvis, proximal humerus, scapula, proximal tibia. In long bones, it starts at the metaphyseal extending as far as half or more of the entire bone.

Clinical: Deep, discontinuous, mild pain with small swelling. In the pelvis and at more advanced phases large soft tissue mass is present. Pathologic fractures are rare.

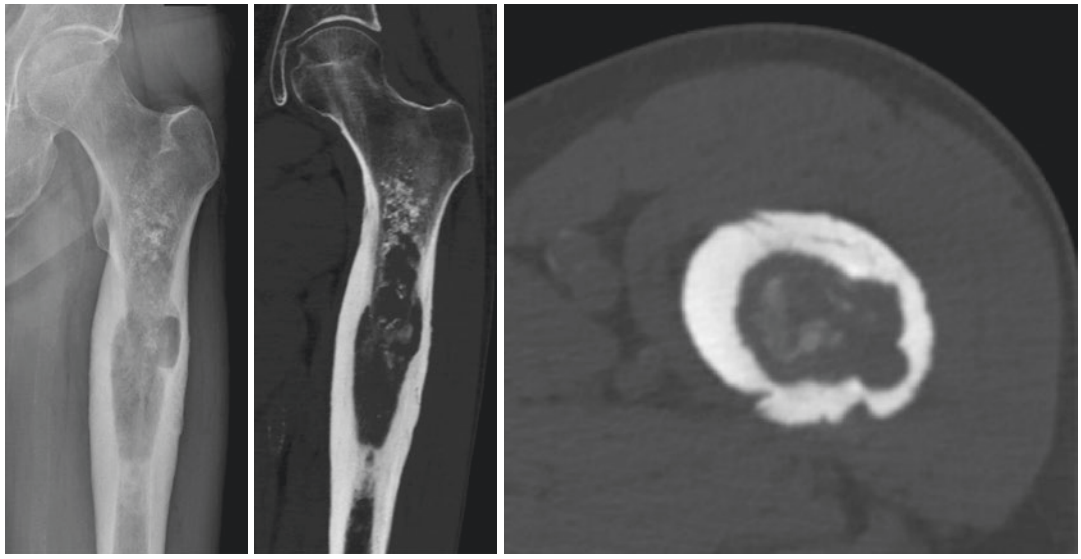
Imaging: On X-ray—intraosseous, osteolytic, geographic lesion with diffused, irregular, granules, nodules, radiopaque rings of calcifications. Sometimes, a bubbling or "honeycomb" feature, metallic or compact opacity. Cortex is scalloped, thinned, and destroyed. Often, it is thickened because the cortical bone reacts to the slow neoplastic infiltration with hyperostosis. Periosteal reaction is faint, with short perpendicular spiculae as a velvet or "beard" appearance. Margins may be sharp, with partial sclerotic rim or ill-defined, faded. It grows where there is less resistance (along the medullary canal). Soft tissue mass are not calcified. On bone scan—increased uptake more than radiographic extension. On angiography—avascular, but there may be a peripheral vascularization around the mass. On CT—typical calcified radiolucency, endosteal scalloping, buttressing, no enhancement, often well contained. May show remnants of prior enchondroma. On MRI—gray homogeneous signal contrasts clearly with white marrow signal on T1, typical bright lesion on T2, unexpected medullary extension on coronal projection.

Histopathology: Lobular, faceted mass of grayer, softer, juicer, more transparent than normal cartilage. Frequent gelatinous, grayish-white, mucoid, hemorrhagic, and necrotic areas. Spots or calcified rings to the periphery of the lobules, hard and gritty, with a chalky yellowish aspect. Grade 1 (20% of the cases): well-differentiated cartilage with increased cellularity compared to enchondroma; chondrocytes are organized in sheets and show slightly nuclear atypia with frequent binucleation; infiltration of the surrounding bony trabeculae is the most important feature in the differential diagnosis with enchondroma. Grade 2 (60% of the cases), hypercellular lesion with hyperchromatic nuclei, frequent binucleate cells, generally in a myxoid matrix; extensive infiltration of the medullary spaces and infiltration of the soft tissues can be present. Grade 3 (20% of the cases): high cellularity with pleomorphic, hyperchromic, gigantic, bizarre cells. Mitotic figures can be found. Diffusely infiltrating the bone marrow spaces with destruction of bony trabeculae and the soft tissue. Point mutations of IDH1/IDH 2 gene are present in about 50% of central chondrosarcomas.

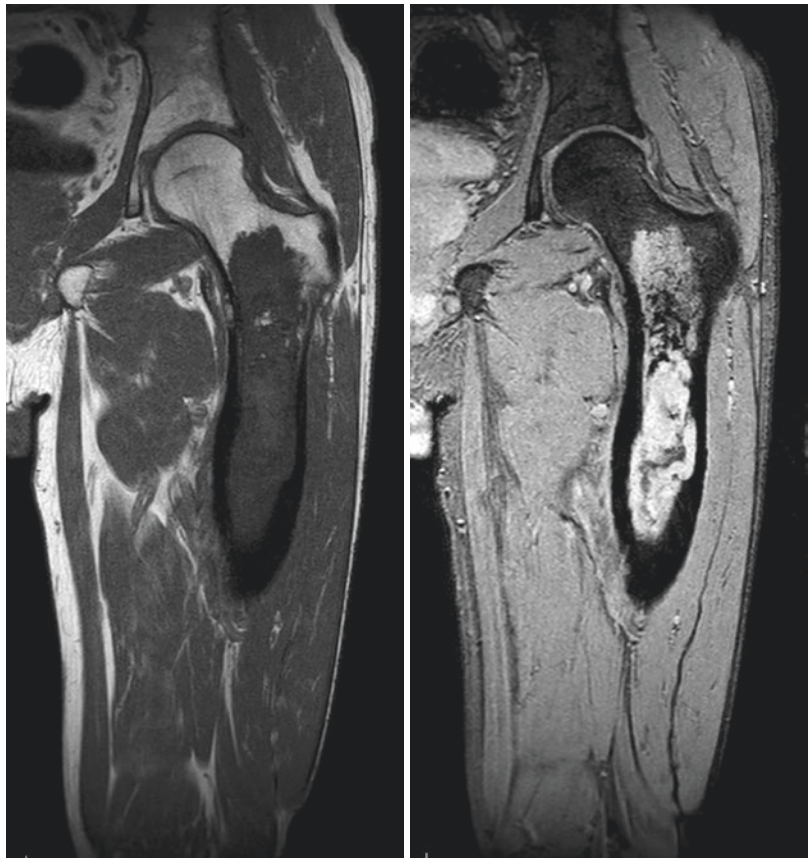
Course and Staging: Very slow growth. Typical progression in malignancy: transformation from a low to high grade or to another malignant tumor. Grade 1: very rare metastases, recurrence even after 10 years. Grade 2: frequent early or late metastases, recurrence within 5 years. Grade 3: higher rate of early metastases, recurrence often within 1 year, usually stage IIB.

Treatment and Prognosis: Wide or radical resections are curative. High risk of recurrence with inadequate margins and when incisional biopsy is not performed carefully because tumoral cells may be implanted in the soft tissue. Lung metastases must be excised. Radio- and chemotherapy are not used because they are poorly effective. Death is rare in grade 1 lesions, but it occurs in 30 and 60% respectively, of grade 2 and 3 lesions.

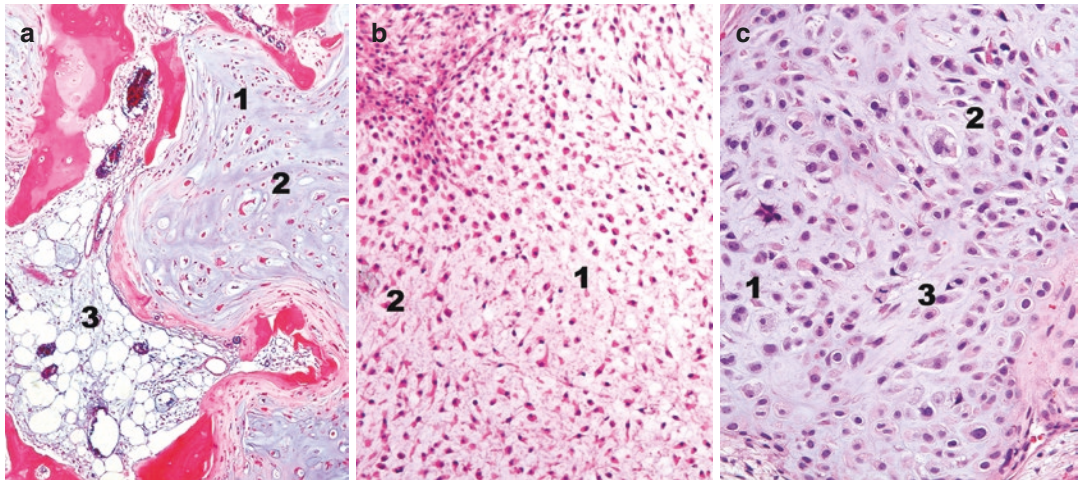
Key points	
• Clinical	Pain, adults, no children
• Radiological	Lytic lesion with granular calcifications. Expanded and invaded cortex
• Histological	Lobules of cartilage infiltrating host trabeculae
• Differential diagnosis	Chondroma, dedifferentiated chondrosarcoma



Radiograph and CT. Central well-limited lesion, containing rare cartilaginous calcifications, thinning the cortex, with an irregular periosteal bone formation



MRI. Chondroid tissue show irregular low signal in T1-weighted sequences and high signal in T2-weighted sequences with characteristic low signal intensity “rings and broken rings”



(**a**) Central chondrosarcoma—Grade 1 Well-differentiated cartilage. (1) Cells are more numerous in relation to most chondromas. (2) Slightly larger and pleomorphic nuclei, generally maintaining their rounded shape. (3) Infiltration of the bony trabeculae. (**b**) Central chondrosarcoma—Grade 2 This is the most frequent variety. Cartilage tissue shows aspects of frank atypia, with hyperchromic nuclei. Binucleated cells are very frequently observed. In nearly half of the cases the tumor is partially or totally myxoid: (1) Cells have generally a spindle-stellate shape and are dispersed, or in small groups, or in short cords in single file. Cytoplasm is ossiphile and clearly visible. The nuclei are fairly plump and hyperchromic. (2) An abundant, semiliquid and tenuously basophilic ground substance is present. (**c**) Central chondrosarcoma—Grade 3 Increased cellularity, severe atypia and pleomorphism are present. (1) Cartilaginous cells are very atypical and very numerous. (2) Severe pleomorphism and intense hyperchromasia of the nuclei are present. (3) Mitotic figures can be found

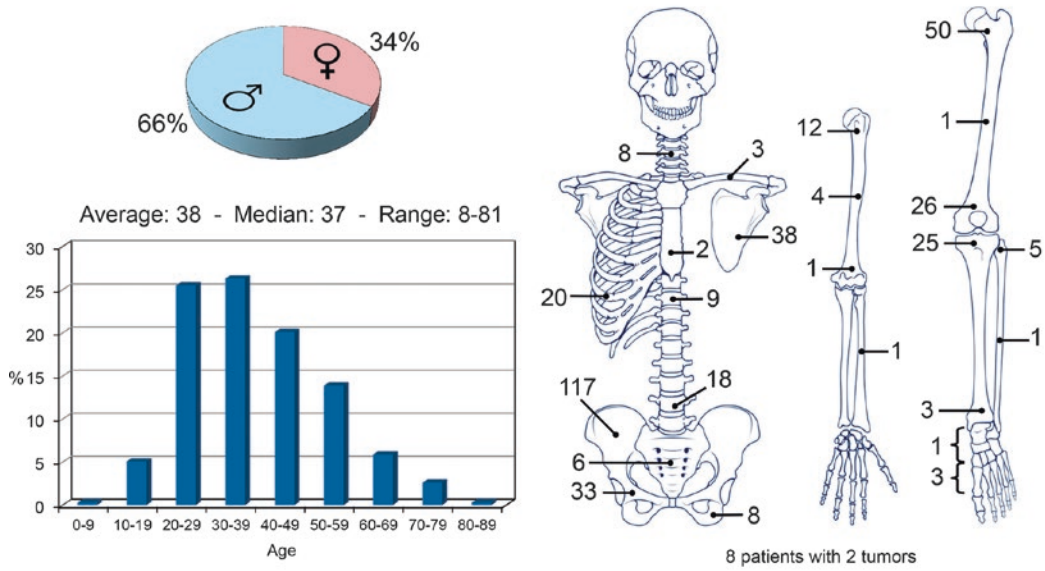
34.2 Peripheral (Secondary) Chondrosarcoma

Definition: It originates from an osteochondroma on the bone surface.

Epidemiology: Males. Less frequent than central but at a younger age. Adults.

Clinical: Slow growing, hard, painful swelling, adherent to bone. At times, asymptomatic and no history of previous osteochondroma. Invading vertebral canal radicular pain and paraplegia may be present. Patients with multiple exostoses, with germiline mutations in EXT1 and EXT2 genes are at increased risk to develop a peripheral (secondary) chondrosarcoma (up to 5%, as compared to <1% in solitary osteochondroma).

Location: Pelvis (iliac wing), proximal femur (metaphyseal region), vertebral column (posterior arch), proximal humerus, ribs.



Imaging: On X-ray—typical aspect of an osteochondroma with more abundant calcifications or ossifications, intense and diffused radiopacities, with thicker superficial uncalcified layer, with fuzzy margins toward the soft tissue. At times, the implant base of the osteochondroma is still visible or the tumor invades the medullary canal. On bone scan—Intense uptake. On CT—Many, large, non-calcified tumoral lobules, ring-like, popcorn-like radiopacities, higher thickness of the cap of cartilaginous tissue. On MRI—lobulated, ill-defined, inhomogeneous muscular signal intensity on T1, extremely heterogeneous signal intensity on T2 with large foci of signal void due to the calcified areas and with a thick peripheral layer of white signal due to the cap of the lesion.

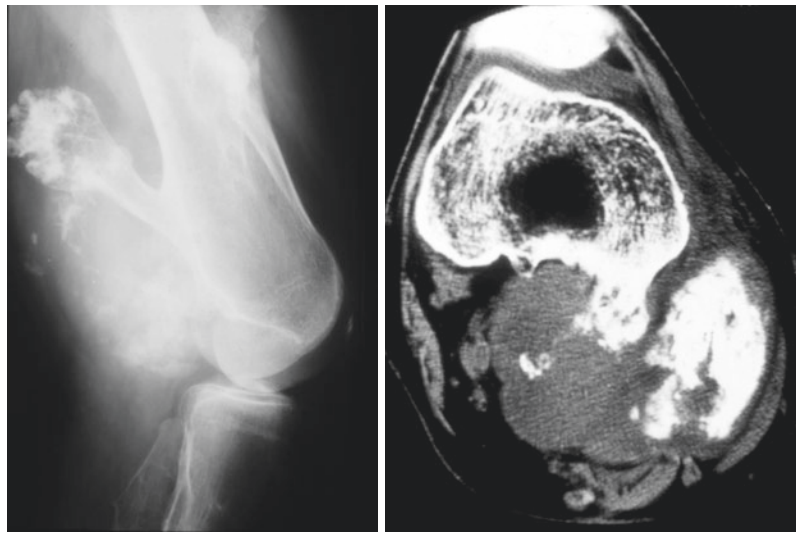
Histopathology: Large, bumpy, cauliflower-like, with a thin pseudocapsule and thick cap of cartilage, generally more than 2 cm in thickness, chalky and gritty, with hard consistency. Histologically, lobules of well-differentiated cartilage with loss of the architecture of an osteochondroma. Hypercellular areas, nuclear atypia, binucleation, and myxoid matrix can be observed.

Cartilage can infiltrate the marrow spaces of the underlining cancellous bone. Infiltration of the surrounding soft tissues, sometimes with satellite nodules, is a sign of malignancy, absent in osteochondroma. Cytogenetic aberration (biallelic inactivation, deletions +/− mutations) of EXT1/EXT2 genes are present in about 90% of cases in multiple osteochondromatosis.

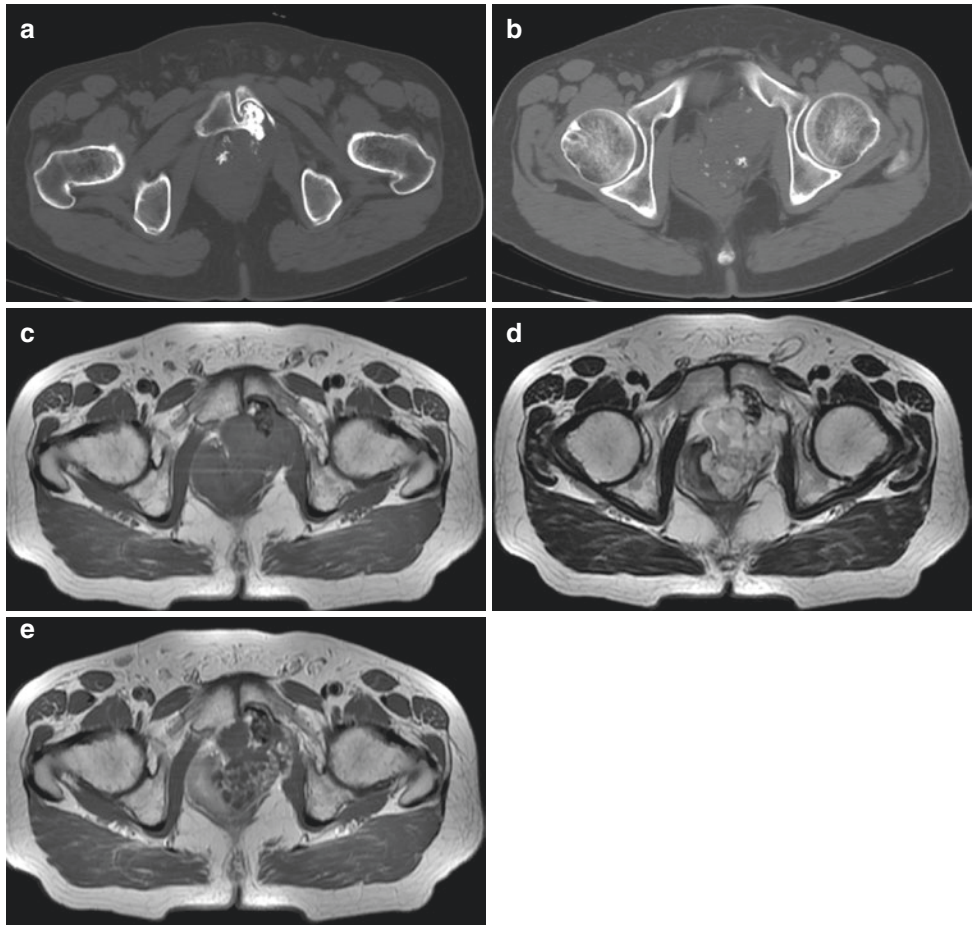
Course and Staging: It grows more slowly than central C, recurrence is observed from a few months to 10 years, <20% of cases have lung and late metastases. Dedifferentiated peripheral C is rare (4%). Usually, stage IB.

Treatment: Wide resection. Inadequate surgery may cause scattered neoplastic nodules in scarring tissue. Radio- and chemotherapy are not effective. Amputation is necessary when it is too large and otherwise inoperable. Peripheral C is less malignant than central because grade 1 forms are frequent and grade 3 rare.

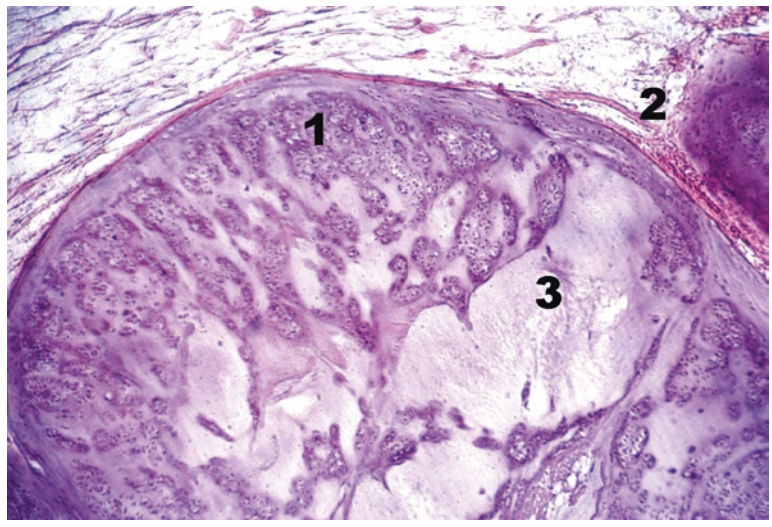
Key points	
• Clinical	Slow increasing swelling
• Radiological	Osteochondroma with lytic areas
• Histological	Thicker cap than osteochondroma with loss of the architecture of the osteochondroma
• Differential diagnosis	Osteochondroma, dedifferentiated peripheral chondrosarcoma



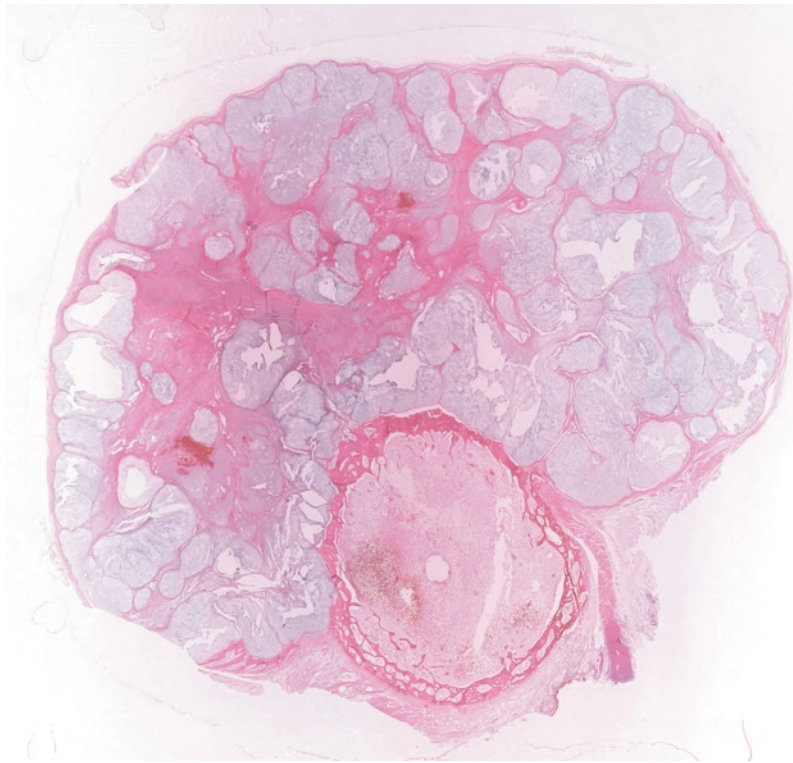
Radiograph and CT: the cortex of the osteochondroma is in continuity with the one of the normal bone. There is a large non-calcified malignant mass



CT (**a**, **b**) and axial R images (**c**: T1, **d**: T2, and **e**: T1 after contrast medium injection). The cortex continuity is well visible on CT (**a**) and MR. The mass contains typical arciform cartilaginous calcifications (**b**), is made of nodules, with a high signal on T2 MR, and no uptake after injection



(1) Clustered chondrocytes. (2) Lobulated architecture. (3) Myxoid change and thickness of the cartilaginous cap exceeding 2 cm

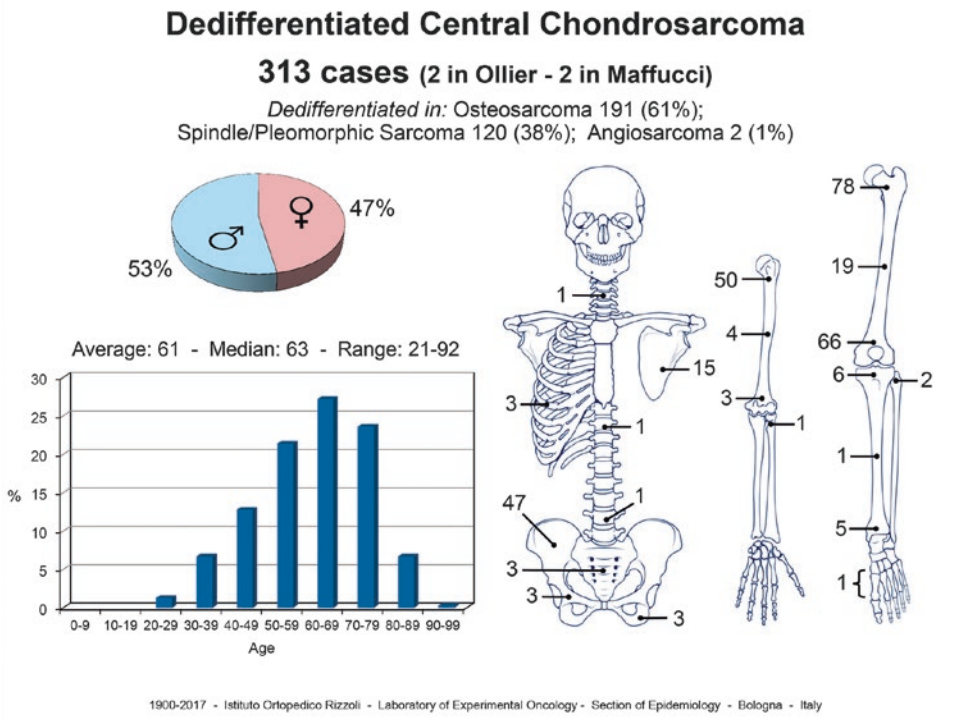


Whole macrosection with cartilaginous cup exceeding 2 cm in thickness

34.3 Dedifferentiated Chondrosarcoma

Definition: Cartilaginous malignant tumor in which a high-grade non-cartilaginous sarcoma occurs.

Epidemiology: 15%. >50 years old. Males.


Dedifferentiated Central Chondrosarcoma
313 cases (2 in Ollier - 2 in Maffucci)
Dedifferentiated in: Osteosarcoma 191 (61%);
Spindle/Pleomorphic Sarcoma 120 (38%); Angiosarcoma 2 (1%)
♀ 47%
♂ 53%
Average: 61 - Median: 63 - Range: 21-92
% 30 25 20 15 10 5 0
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99
Age
1 15 3 1 47 1 3 3 3
50 4 3 1
78 19 66 6 2 1 5 1
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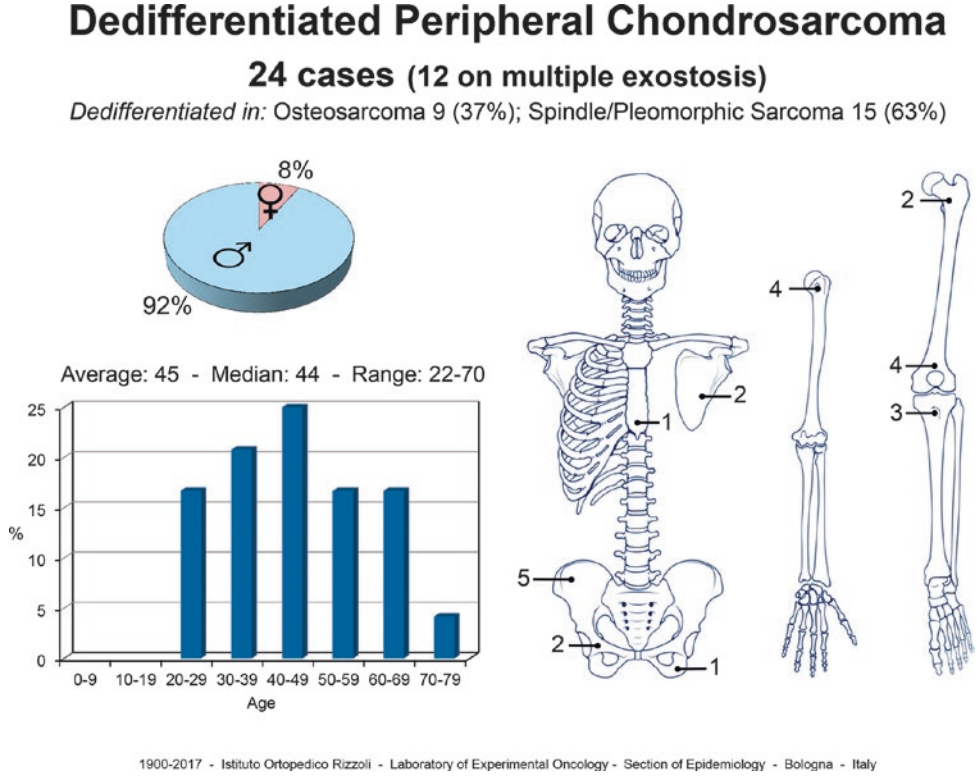

Dedifferentiated Peripheral Chondrosarcoma
24 cases (12 on multiple exostosis)
Dedifferentiated in: Osteosarcoma 9 (37%); Spindle/Pleomorphic Sarcoma 15 (63%)
♀ 8%
♂ 92%
Average: 45 - Median: 44 - Range: 22-70
% 25 20 15 10 5 0
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79
Age
2 1 5 2 1
4
2 4 3
1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

Location: Proximal femur, pelvis, proximal humerus.

Clinical: On a history of long duration with moderate symptoms, a rapid progression of pain and swelling occurs. Pathologic fractures are frequent.

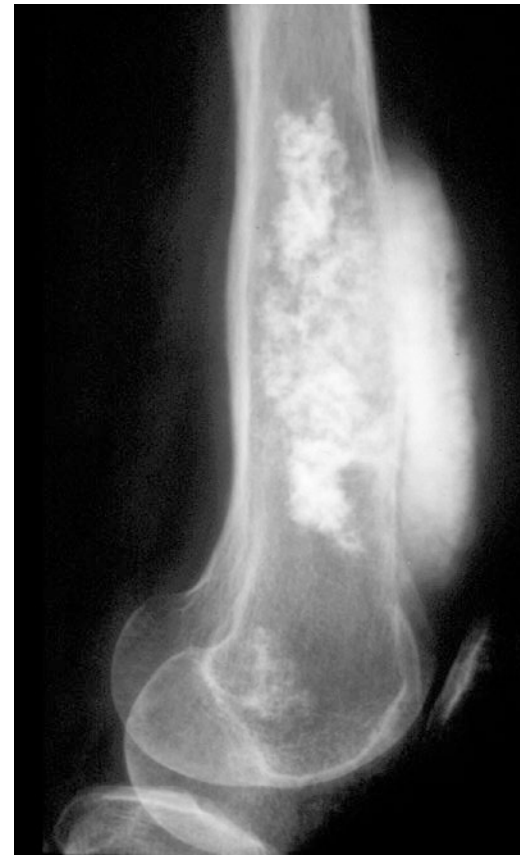
Imaging: On X-ray—(1) old cartilaginous lesion: moderate expansion of the bone with thickened, scalloped cortex, with many calcifications; (2) new lesion: destroying the cortex, involving the soft tissues, dissolving the calcifications, with ill-defined margins. Three different features: (a) pathologic fracture in a new aggressive lytic lesion canceling pre-existing calcifications of an intensely radiopaque old cartilaginous lesion; (b) usual chondrosarcoma aspect with a small high-grade lytic lesion; (c) typical high-grade sarcoma feature with small remnants of chondrosarcoma. On CT—two lesions of different density, matrix, enhancement. On MRI—two different signal intensities on T1 and T2.

Histopathology: Two types of tissue: (1) low-grade cartilaginous tumor; (2) high-grade malignancy, usually an osteosarcoma, an undifferentiated pleomorphic sarcoma, or an undifferentiated spindle cell sarcoma. The transition is sharp. Point mutations of IDH1/IDH2 gene are present in about 50–87% of central dedifferentiated chondrosarcomas.

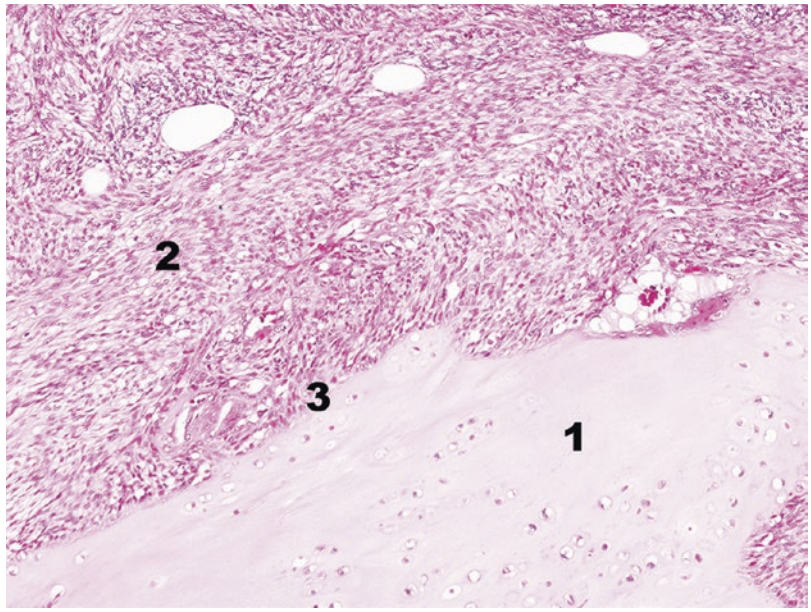
Course and staging: Fast growth, high risk of recurrence with inadequate surgery, and high rate of metastases, often observed at diagnosis. Usually, stage IIB or III.

Treatment: Wide or radical resection. Chemotherapy protocols of OS have been used with effectiveness. Often, an amputation is necessary to obtain adequate margins. Poor prognosis.

Key points	
• Clinical	Symptoms rapidly increasing. Pathologic fracture possible
• Radiological	Very aggressive aspects on a low-grade cartilaginous lesion
• Histological	Two different aspects: low-grade cartilage and high-grade sarcoma
• Differential diagnosis	Central or peripheral high-grade chondrosarcoma



Radiograph: lateral view of the femur. The pre-existing low-grade cartilaginous tumor contains arciform calcifications. The dedifferentiated part of the tumor forms bone, develops in the soft tissues, and corresponds to an osteosarcoma

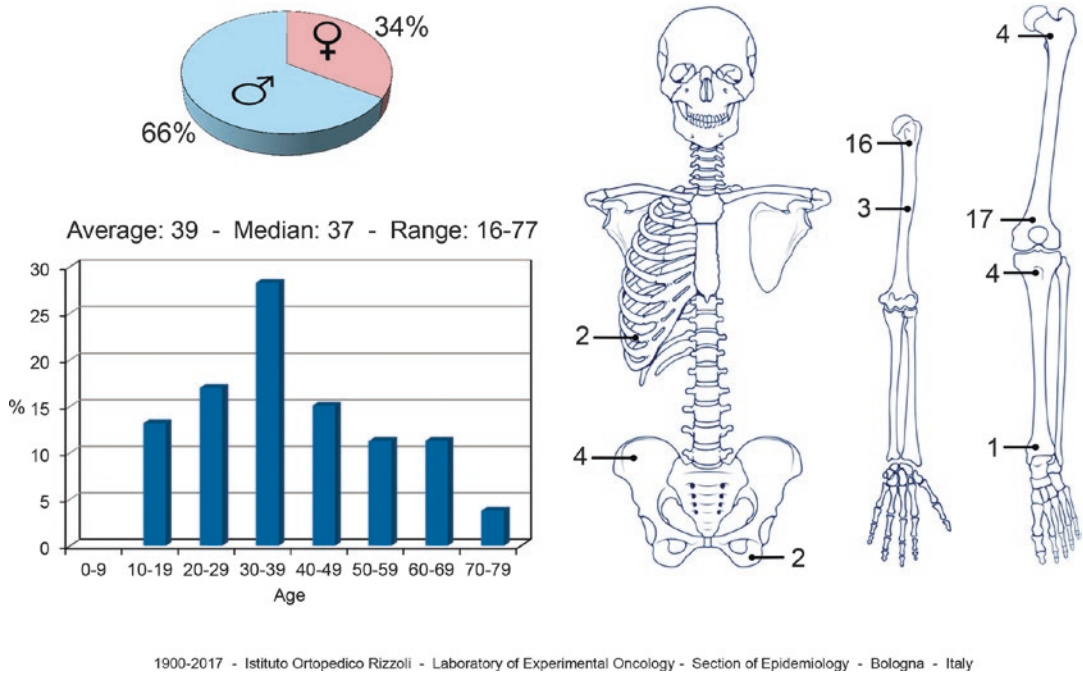


There are two clearly distinct tumor tissues. One is a well-differentiated cartilaginous tumor and the other has a different histotype, characterized by high-grade malignancy. The transition from one type of tissue to the other is abrupt. (1) Chondrosarcomatous tissue. (2) High-grade malignant tumor. (3) Between the two zones the transition is sharp

34.4 Periosteal Chondrosarcoma

Definition: Chondrosarcoma originating on the bone surface. The lesion is generally bigger than 5 cm in major diameter.

Epidemiology: Rare, males, adults.



Location: Mainly in the limbs: distal femur, proximal tibia, proximal humerus.

Clinical: Swelling with little or no pain.

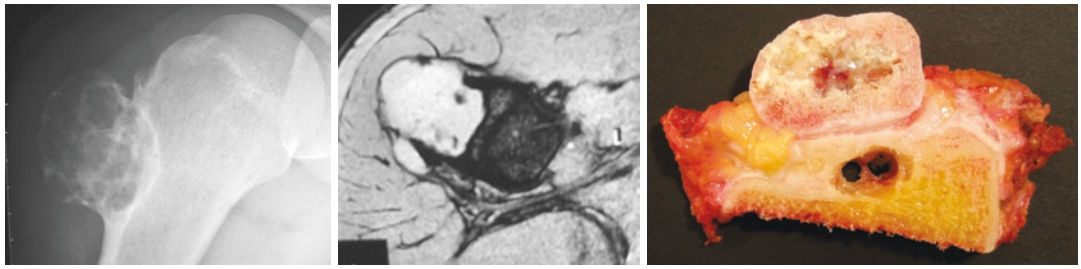
Imaging: On X-ray—globose mass lying on the outer surface of the cortex, very radiolucent or with granules, rings, spots of cartilage, rarely bunches of faded ossifications. Outer cortical erosion, saucer-like cortex, thickness of the adjacent cortex, buttress of periosteal reaction, internal sclerotic rim, sharp margins. On CT—confirms periosteal site of the tumor without involvement of the medullary canal.

Histopathology: The lesion is composed of large lobules of cartilage, with variably hypercellularity and atypical cytological features. Intercellular matrix can be myxoid. Permeation in between the underlining bony trabeculae can be seen. Infiltration of the surrounding soft tissues is a sign of malignancy; absent in periosteal chondroma. Point mutations of IDH1/IDH2 gene are present in a subset of periosteal chondrosarcomas.

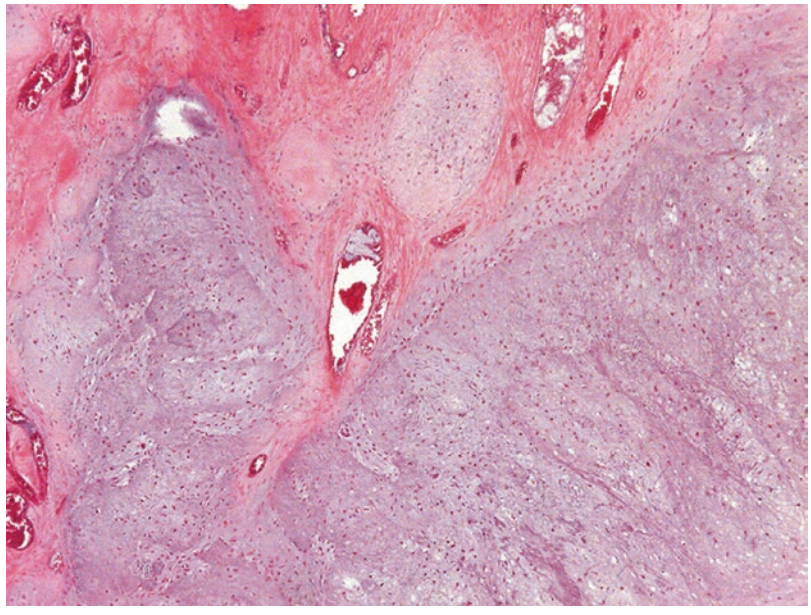
Course and staging: Rare recurrence if surgery is adequate; late, very rare mets. Usually stage IA.

Treatment: Wide resection. Prognosis is good.

Key points	
• Clinical	Adults, swelling
• Radiological	Subperiosteal, metaphyseal, with erosion of the cortex, granular calcifications, periosteal reaction
• Histological	Lobules of cartilage, generally low grade
• Differential diagnosis	Periosteal chondroma, periosteal osteosarcoma



Radiograph, axial GE MR image, and specimen. The lesion contains calcifications and is centered on the cortex, which is eroded in a well-limited way

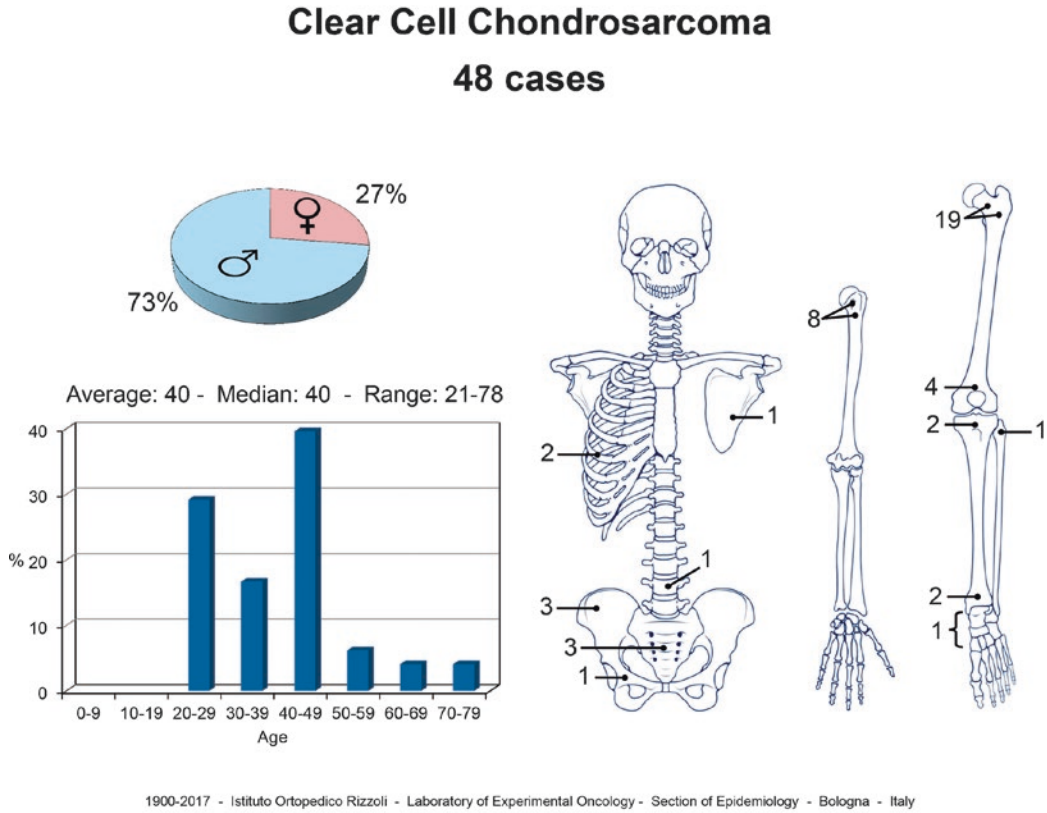


Large (usually more than 5 cm) cartilaginous tumor composed of lobules of cartilage, with myxoid change in the matrix. Permeation into the surrounding soft tissue is unequivocal evidence of malignancy

34.5 Clear Cell Chondrosarcoma

Definition: Chondrosarcoma with large amounts of clear cells.

Epidemiology: Rare, males, adults.



Location: Epiphysis or apophysis of long bones (proximal femur and humerus), flat, short bones.

Clinical: Modest, long lasting pain. Femural pathologic neck fracture may occur at presentation.

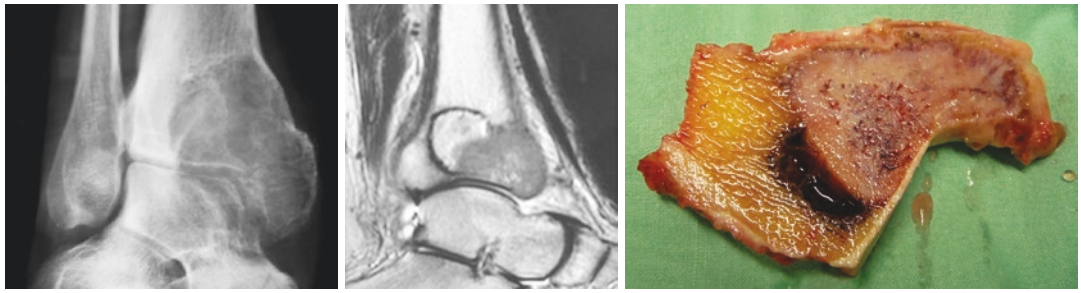
Imaging: On X-ray—like a chondroblastoma. Osteolytic lesion with small calcifications, sharp margins, irregular and ill-defined sclerotic rim. On CT—spots or small granules typical of the cartilaginous tumors.

Histopathology: Lobular tissue with clear cells: central nucleus, extremely vacuolated cytoplasm, strongly P.A.S. positive. Rare mitotic figures. Peripheral reactive giant cells, possible areas of well-differentiated chondrosarcoma, intercellular calcification like chondroblastoma, cystic spaces, osteoid.

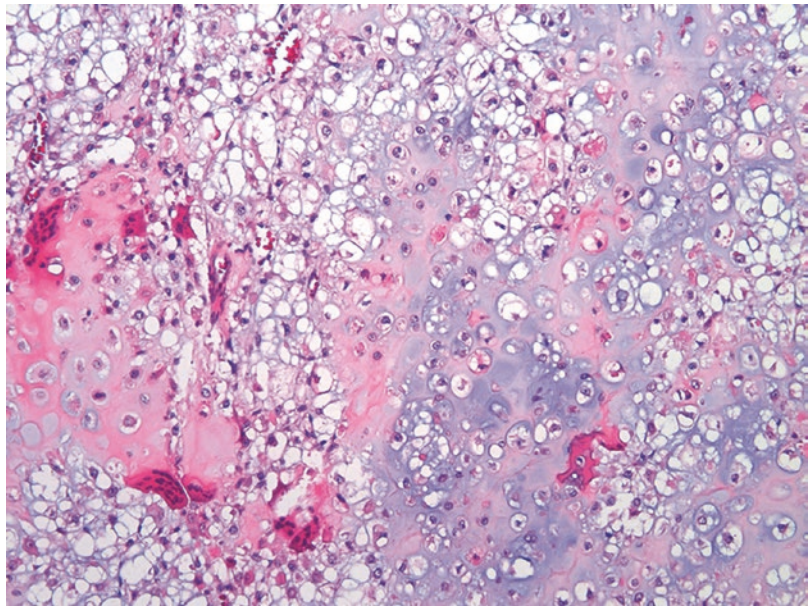
Course and staging: Slow growth, recurrence is possible when intralesional margins are obtained, metastases are exceptional. Usually, stage IA.

Treatment: Wide resection. Prognosis is good.

Key points	
• Clinical	Epiphysis and apophysis in adults
• Radiological	Osteolytic, like a chondroblastoma
• Histological	Lobules of clear cells, possible areas of hyaline cartilage, giant cells, calcifications, osteoid
• Differential diagnosis	Chondroblastoma



Radiograph, sagittal T1 MR image and specimen. Epiphyseal well-limited lesion. The high signal component well visible on MR corresponds to an associated hematoma on the specimen



Proliferation of cells with abundant optically empty or eosinophylic cytoplasm and centrally located vesicular nuclei. Production of immature bone by tumoral cells is a peculiar feature. Scattered giant cells are present throughout

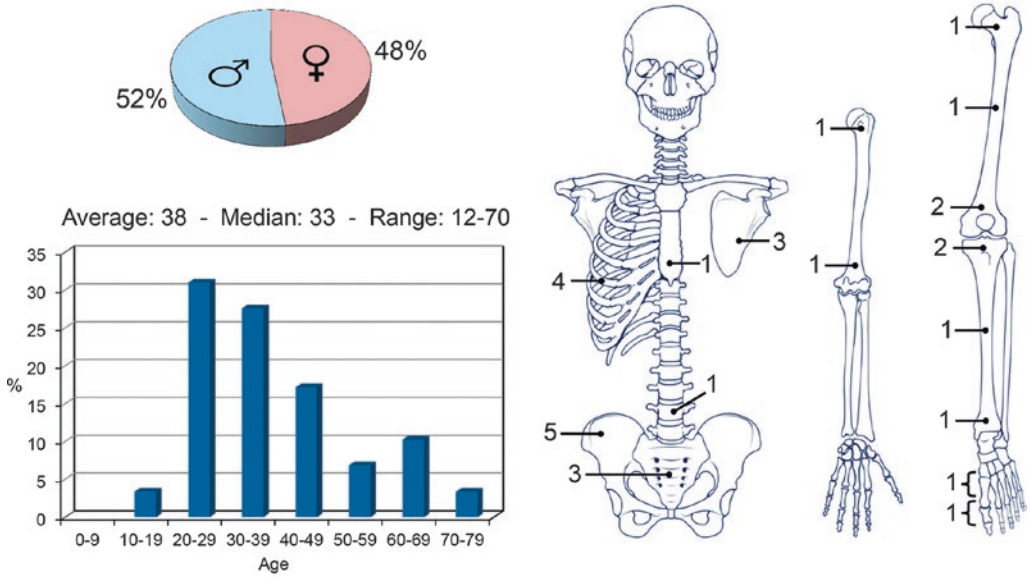
34.6 Mesenchymal Chondrosarcoma

Definition: Malignant neoplasm composed of small round cells and islands of well-differentiated hyaline cartilage.

Epidemiology: Very rare, no sex predilection, young adults and elderly patients.

Mesenchymal Chondrosarcoma in Bone

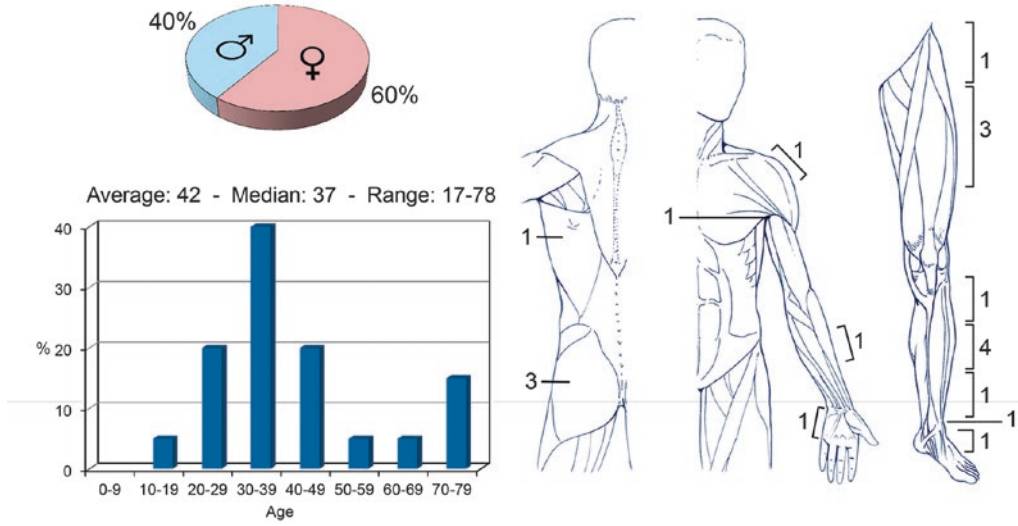
29 cases



1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

Mesenchymal Chondrosarcoma in Soft Tissue

20 cases



1900-2017 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

Location: Trunk and craniofacial bones. Rare in the limbs.

Clinical: Pain and swelling.

Imaging: On X-ray—osteolytic lesion with permeative destruction of bone, ill-defined margins, breaking the cortex, with soft tissue mass, with faded typical calcifications.

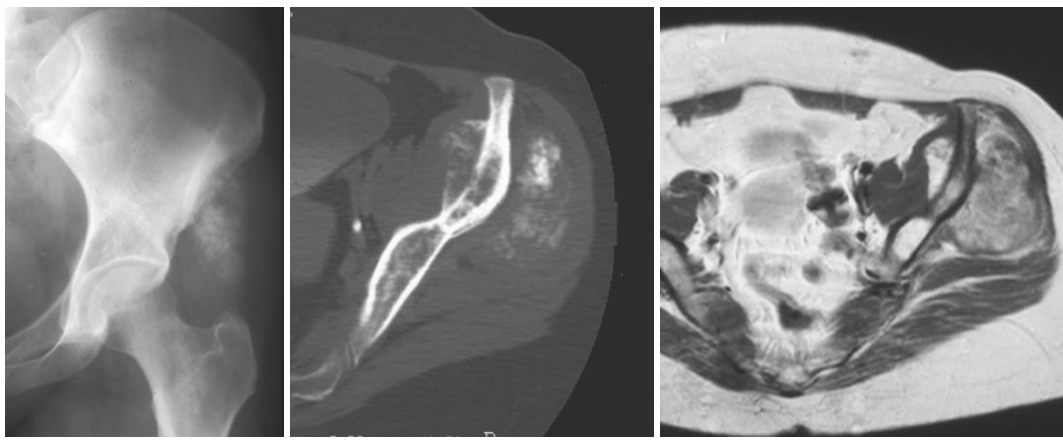
Histopathology: Dense round cells proliferation with hemangiopericytoma-like architecture. Within the tissue there are small foci or larger islands of well-differentiated hyaline cartilage. Osteoid-like matrix can be present.

Course and staging: Fast growth, high rate of recurrence with inadequate surgery and frequent metastases. Usually, IIB.

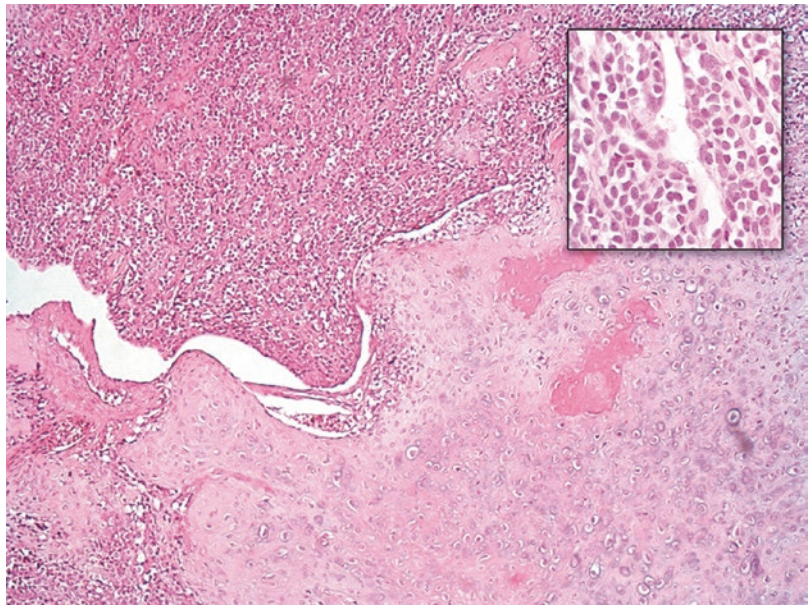
Treatment: Wide or radical resection. Chemotherapy is used but its real effectiveness is not yet known. Prognosis is poor.

Key points	
• Clinical	Very rare in bone, adults, pain and swelling
• Radiological	Aggressive osteolysis, with possible calcification
• Histological	Mixed population with isles of cartilage and undifferentiated round cells
• Differential diagnosis	None

Chromosomal translocations		
• t(8;8)(q21.1;q13.3)	HEY1-NCOA2	>90%
• t(1;5)(q42;q32)	IRF2BP2-CDX1	Rare



Radiograph, CT and axial T1-injected MR image. The tumor contains cartilaginous calcifications, and takes up contrast medium

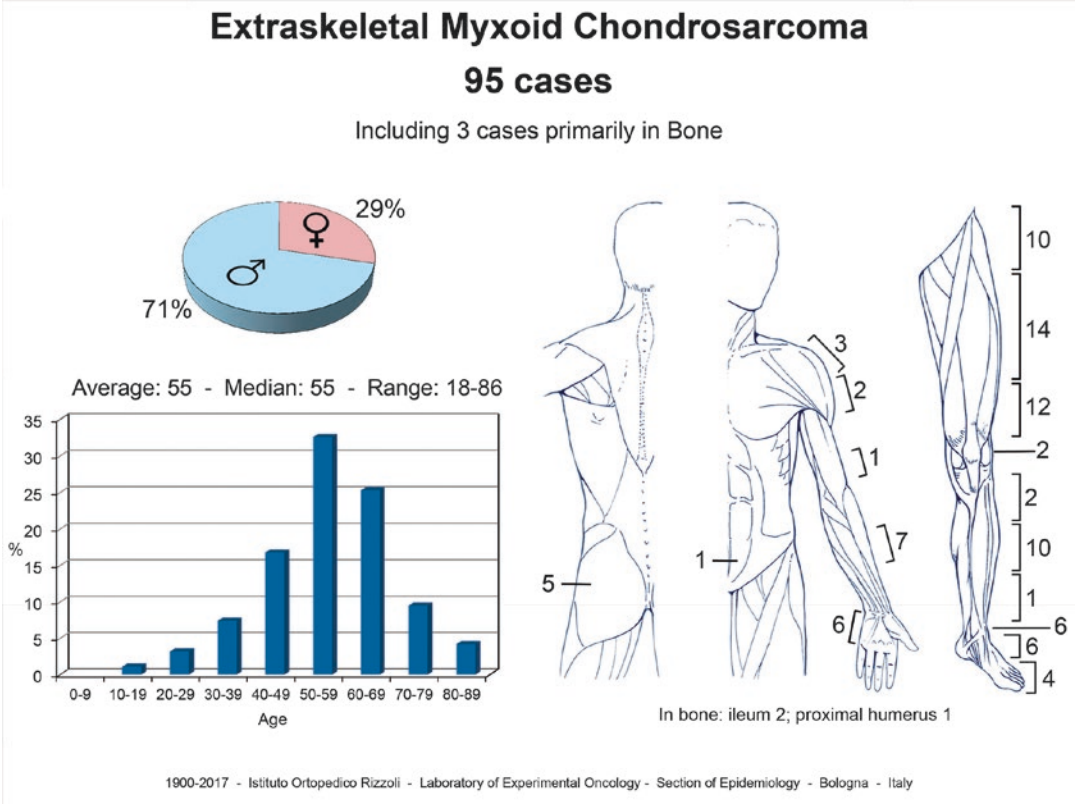


Islands of well-differentiated cartilage are surrounded by a proliferation of small round to ovoid undifferentiated cells. Hemangiopericytoma-like vessels are frequently present in the round cell component (*inset*)

34.7 Extraskeletal Myxoid Chondrosarcoma

Definition: Soft tissue sarcoma composed of spindle and epithelioid tumor cells associated with extracellular myxoid matrix. Extraskeletal myxoid chondrosarcomas are genetically distinct from osseous chondrosarcoma.

Epidemiology: Rare, male/female ratio 2:1, adults (40–70 years).



Location: Deep-seated, proximal extremities and trunk.

Clinical: Enlarging painless soft tissue mass.

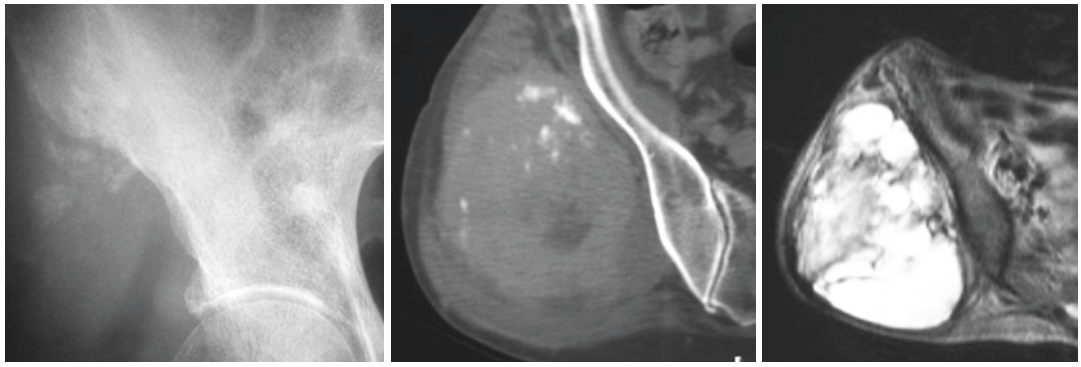
Imaging: Although imaging characteristics are nonspecific, most tumors appear lobulated, and highly myxoid tumors have a homogeneous high intensity signal on T2-weighted MRI images. Tumors with necrosis or hemorrhage have a more heterogeneous appearance.

Histopathology: The tumor is composed of cytologically uniform oval to spindle cells embedded in flocculent myxoid ground substance, with fibrous bands dividing individual lobules of tumor. Cells may be arranged as cords, strands, nests, and sheets and typically show uniform dark staining nuclei with indistinct nucleoli. In hypervascular matrix-poor regions, tumor cells often display larger, more vesicular nuclei with visible nucleoli; some tumor cells may have distinctly rhabdoid morphology. Tumor is hypovascular and the matrix stains alcian-blue positive at pH 4.0 and 1.0 (chondroitin sulfate positive). At the genetic level, the majority of tumors exhibit the t(9,22)(q22;q12) translocation involving EWS and CHN genes.

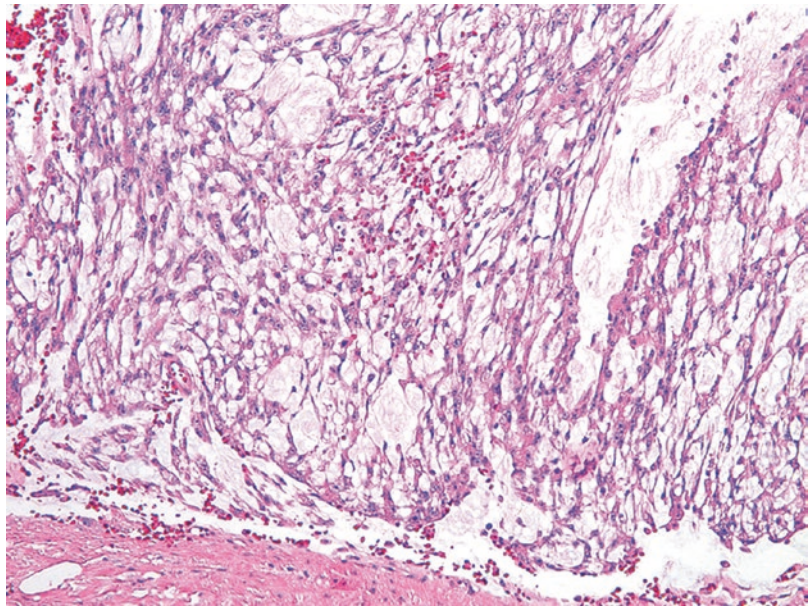
Course and Staging: Five-year survival rates are high (>80%); however, late lung metastases occur, and 10- and 15-year disease free survival rates are considerably lower.

Treatment: Wide surgical excision. Kinase inhibitors' efficacy (pazopanib) in advanced and non-operable disease is under investigation.

Chromosomal translocations		
• t(9;22) (q22;q12)	EWS-NR4A3 (CHN, TEC, NOR1)	72%
• t(9;17) (q22;q11)	TAF2N-NR4A3 (CHN, TEC, NOR1)	16%
• t(9;15) (q22;q21)	TCF12-NR4A3 (CHN, TEC, NOR1)	<1%



Radiograph, CT and T2 axial MR image. The soft tissue mass contains cartilaginous calcifications, is lobulated, and has a high signal on T2 MR image



Cords and nests of eosinophilic cells embedded in a myxoid matrix

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Biology of Conventional Chondrosarcoma

35

Maria Serena Benassi

Conventional chondrosarcoma (CS) (80–85% of all CS) includes central (85–90%) and peripheral (10–15%) CS subtypes that are characterized by complex karyotype and genetic instability. The presence in their benign precursors of specific gene mutations is considered an early event in tumorigenesis [1], and secondary molecular changes are required for the malignant transformation. Currently, the most clinical reliable prognostic factors are age and grade.

Central CS can arises from or enchondromatosis (up to 40%) in patients with somatic mutations in the isocitrate dehydrogenase genes, IDH1 (R132C and R132H) and IDH2 (R172S) [2].

Wild-type IDH1 and IDH2 are important metabolic enzymes involved in lipid metabolism and in Krebs cycle [3]. Heterozygous somatic IDH1/IDH2 mutations, also seen in many other tumours, cause an abnormal production of the potential oncometabolite D-2-hydroxyglutarate (D-2HG) [4, 5] that leads to genome-wide alteration in DNA methylation, thus supporting the causal role for IDHR132H in driving epigenetic instability [6, 7].

Elevated D-2HG concentration has been detected in acute myeloid leukemia and glioma patients with mutant IDH, confirming the role of this potential biomarker for both diagnosis and therapy [8–10]. An antibody against IDH R132H is currently widely used for the differential diagnosis of glioma.

Peripheral CS arises from osteochondroma (15–20% of cases) or multiple osteochondroma (up to 1–5% of cases) that have genetic abnormalities in EXT1 or EXT2 oncosuppressor genes [11, 12], although some data demonstrate that the pathogenesis of secondary peripheral CS may be independent of EXT mutations [13].

EXT1 and EXT2 are located on the chromosome bands 8q24 and 11p11–12 respectively and the loss of their activity impairs the heparan sulfate (HS) biosynthesis, essential for the diffusion of hedgehog proteins involved in chondrocyte differentiation. A disturbance of Indian Hedgehog signaling pathway (IHH) breaks the negative feedback loop with parathyroid hormone-related protein (PTHrP), resulting in an unbalance between chondrocyte proliferation and differentiation [14].

Reactivation of PTHrP signaling and anti-apoptotic Bcl2 protein overexpression promote the progression toward low-grade and high-grade CS, progressively acquiring p53 mutations, defects in the most important cellular signaling pathways and environment structural changes [14].

Conventional CSs are drug-resistant tumours and surgery remains the primary treatment. However, the knowledge of additional genetic or epigenetic changes during malignant progression led to the identification of potential targets that may be useful for planning new

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adjuvant treatments [14]. In conventional CS, cytogenetic studies showed heterogeneity with respect to karyotype complexity. A positive relation between histological grade and degree of karyotype complexity was found associated with high cellular density, chondroid matrix destruction and vascularization. Chromosome 9p21 and 12q13–15 aberrations resulted in loss of CDKN2A tumour suppressor gene activity and amplification of CDK4 that inhibits pRb activity. P53 is inactivated, while overexpression of prosteoglandin COX2, metalloproteinases MMPs, and pro-hypoxia inducible factor HIF, make them candidate targets for therapeutic approaches [15].

While IDH and EXT mutations are no longer essential for tumour growth, representing the initial phase of malignant progression, the activation of key endpoints controlling tumour cell growth and survival differentiates high-grade CS. The evidence that altered IHH and kinase-dependent signaling pathways drive the increase of malignancy has addressed the preclinical and clinical studies to the use of kinase inhibitors or HH antagonists [16–18].

HH, Bcl2, PDGFR, Src, P13K/Akt pathways are considered candidate targets in conventional CS, but the clinical results are not quite satisfactory [19]. Interestingly, Bcl2-dependent drug-resistance of CS cells could be overcome by the treatment with Src kinase inhibitors and doxorubicin in p53-negative cells [20]. A phase II clinical trial using dasatinib observed a prolonged stable disease in more than 10% of patients, suggesting that further evaluations should be considered in future clinical trials [21].

In contrast, a previous study [22] failed in terms of objective response and disease-free survival by using imatinib mesylate, an anti-PDGFR agent.

Currently, phase I phase II clinical studies with agents targeting IDH mutations, PI3K-Akt-mTOR pathway and angiogenesisis are under investigation with the aim to improve the CS patient survival [23].

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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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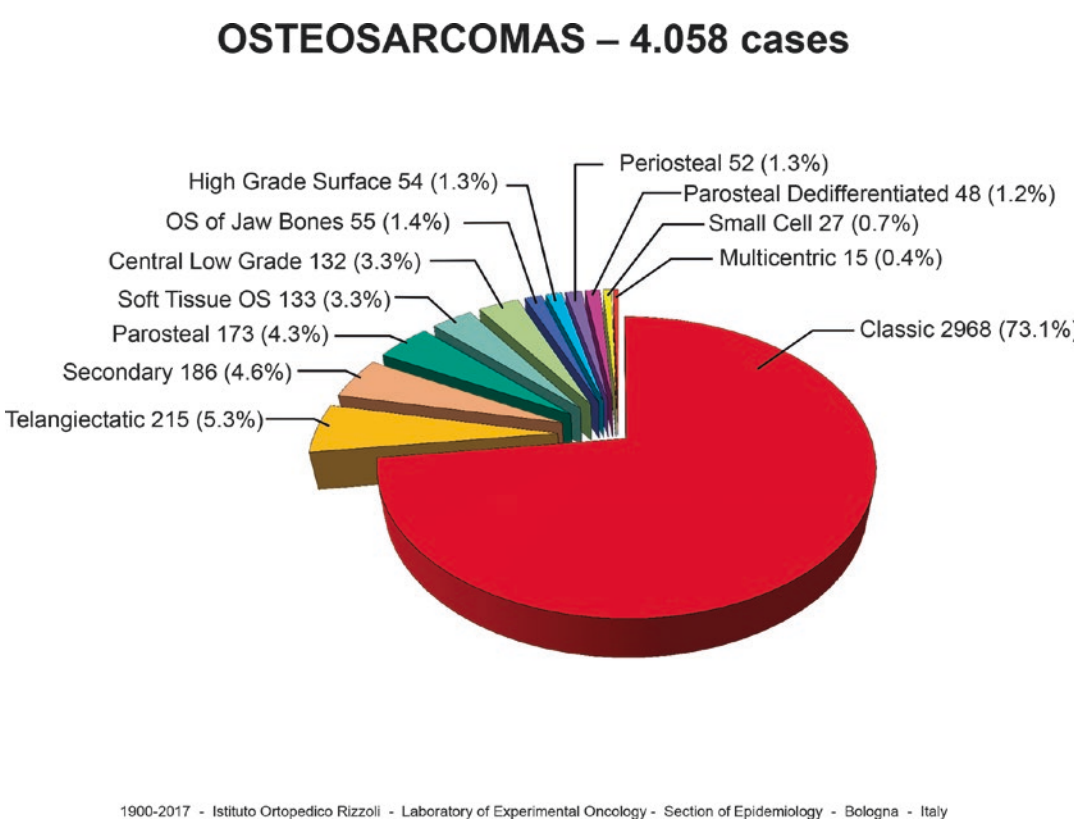
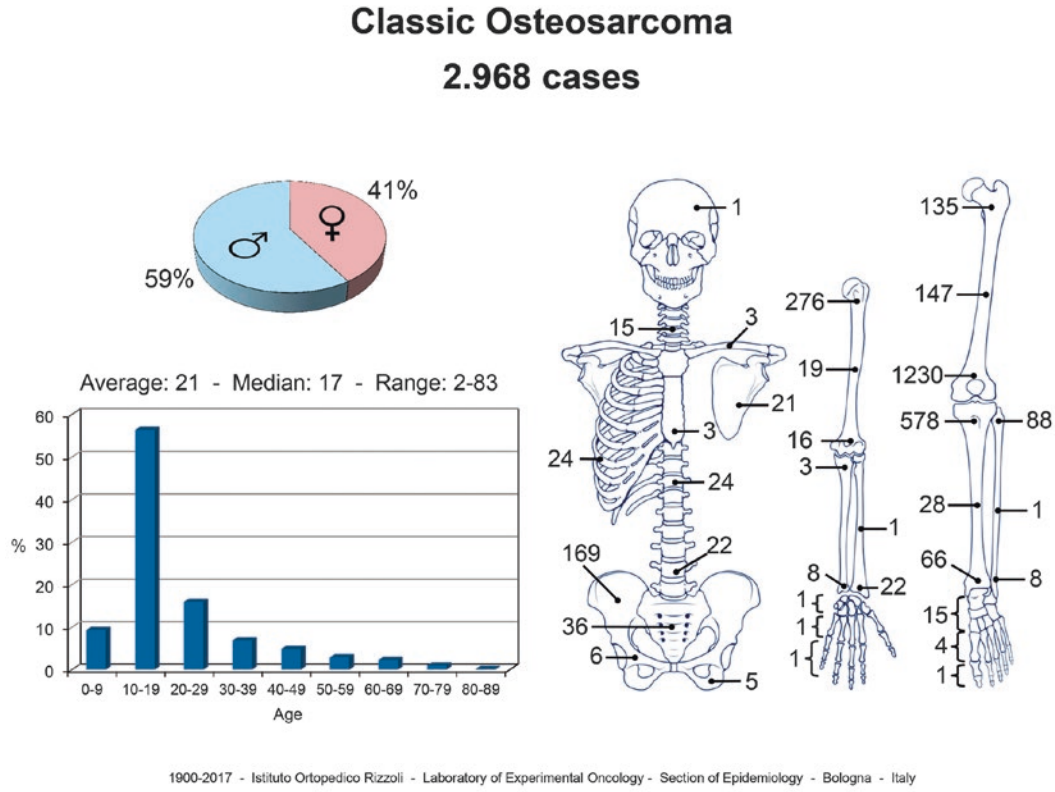


36.1 Classic Osteosarcoma

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.

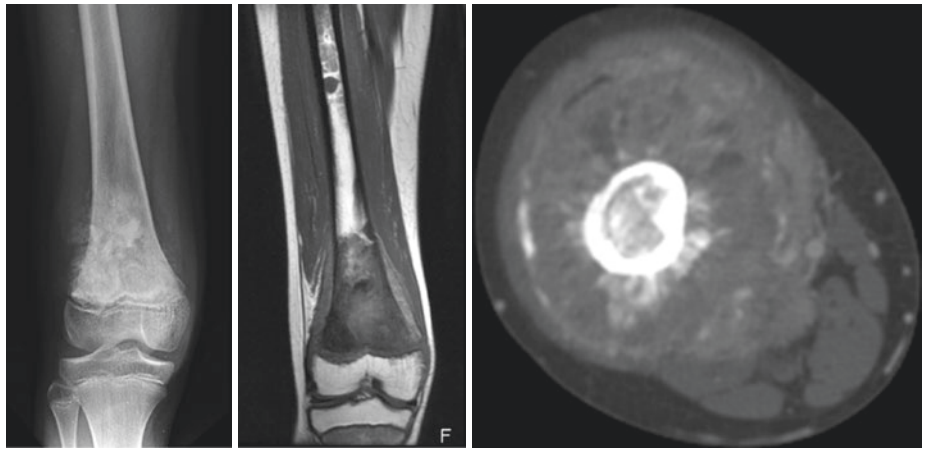
Histopathology: OS is fleshy-soft in cellular areas with little matrix, firm and rubbery in fibroblastic areas with collagen production, gritty to stone-hard in osteogenic areas, and cartilaginous to myxoid in chondroblastic areas. Hemorrhage, necrosis, and cystic alterations are common. The most relevant 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.

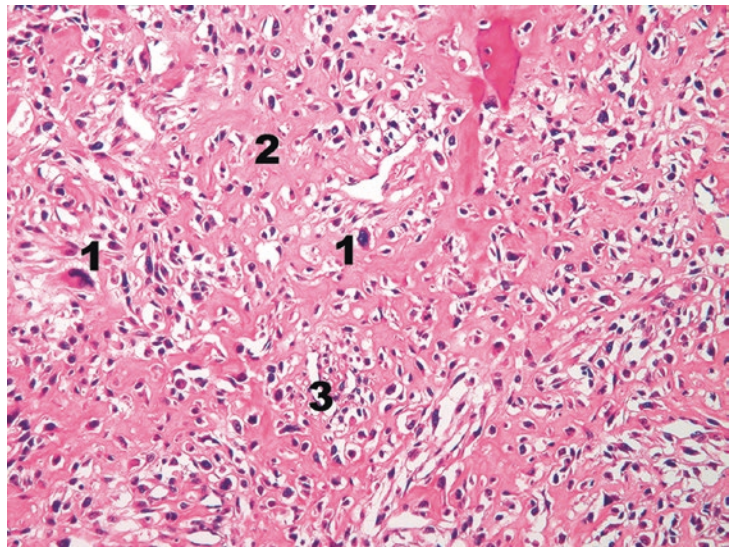
Treatment: Treatment of OS is based on chemotherapy (ctx) and surgery of both the primary tumor and the metastases. Postop ctx (adjuvant) started in 1971, pre- and postop ctx (neoadjuvant) was introduced in 1978. Presently, the most effective drugs are adriamycin (ADM), high-dose methotrexate (HDMTX), 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.

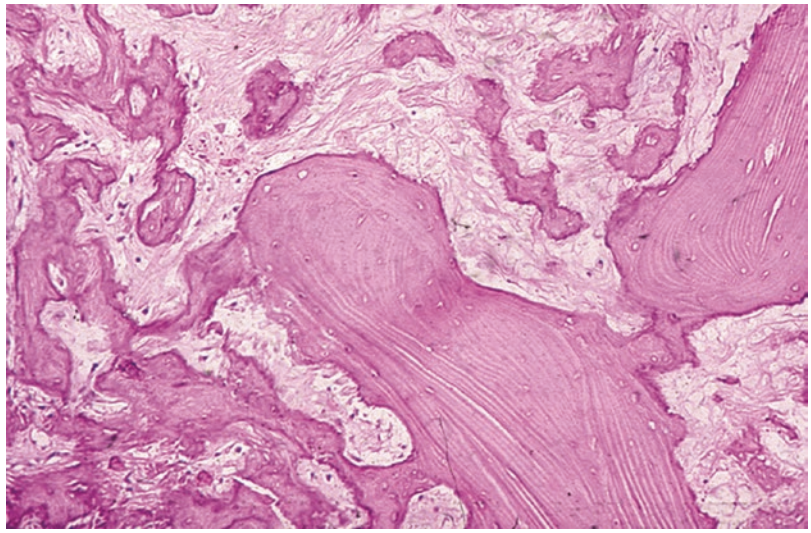
Key points	
• Clinical	Young age, pain and swelling
• Radiological	Central lesion, aggressive with radio-opacities
• Histological	High-grade with osteoid/bone production
• Differential diagnosis	None



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

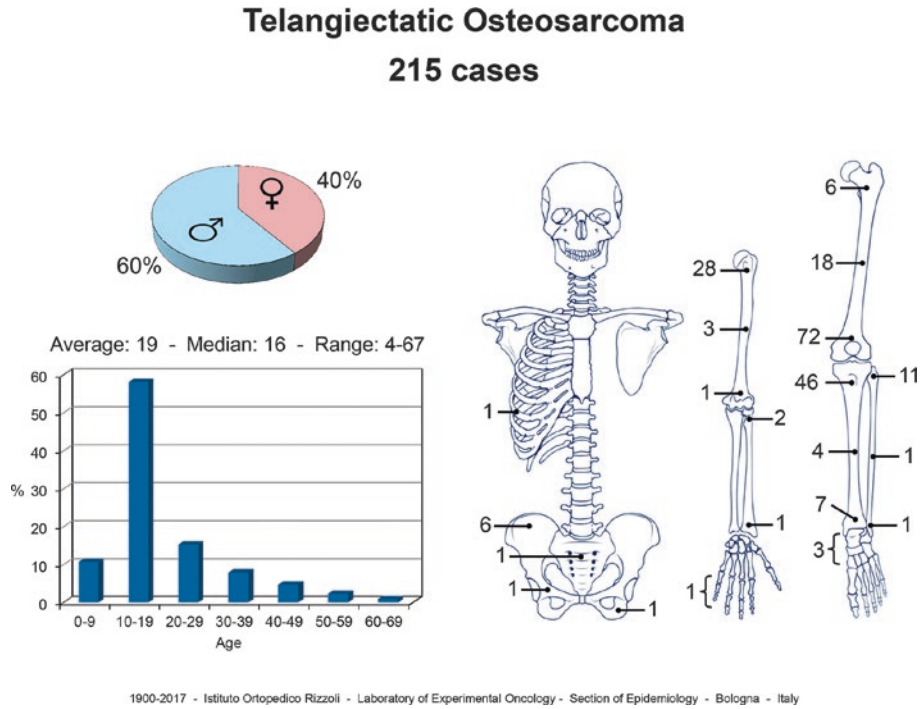


Histology patterns of a good response to preoperative chemotherapy

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.

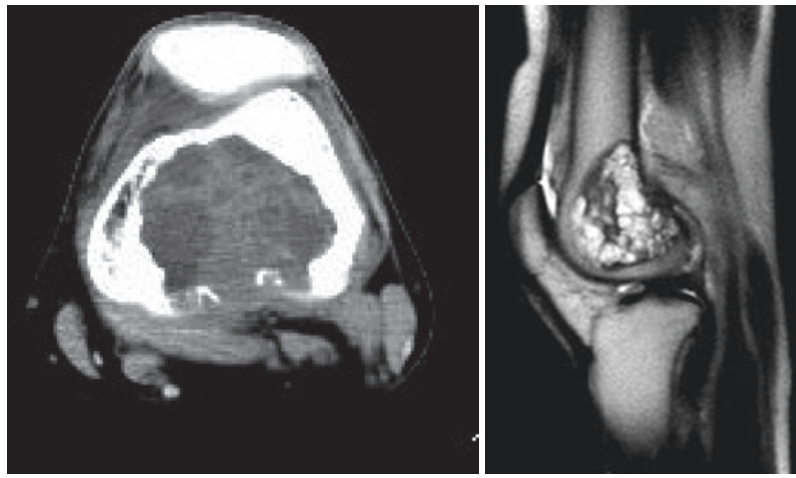
Imaging: Imaging shows a purely osteolytic lesion with ill-defined limits. Isotope scan shows an increased uptake. CT and MRI show the multicystic pattern (high signal in both T1 and T2, because of fluid and hemosiderin content) with fluid levels.

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.

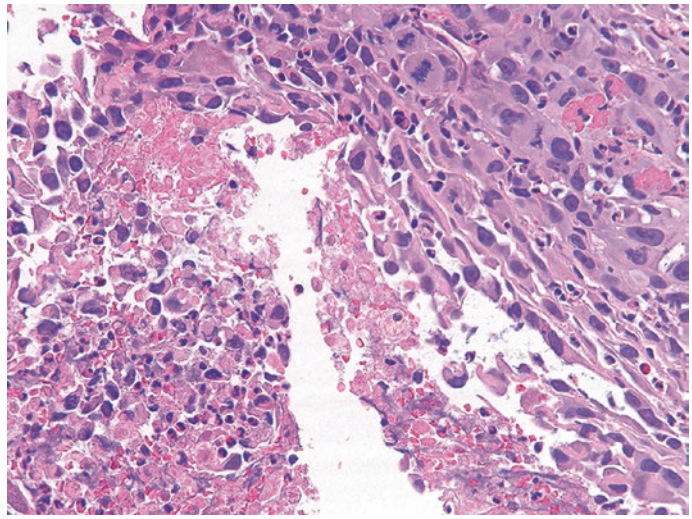
Course: The course is rapid, and the stage is almost regularly II-B or III**.**

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

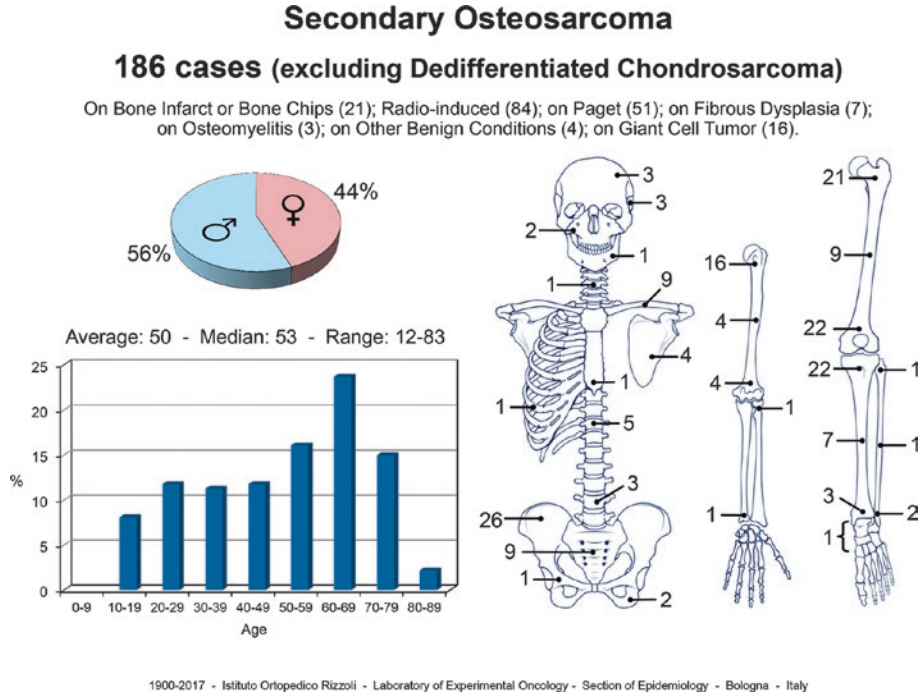


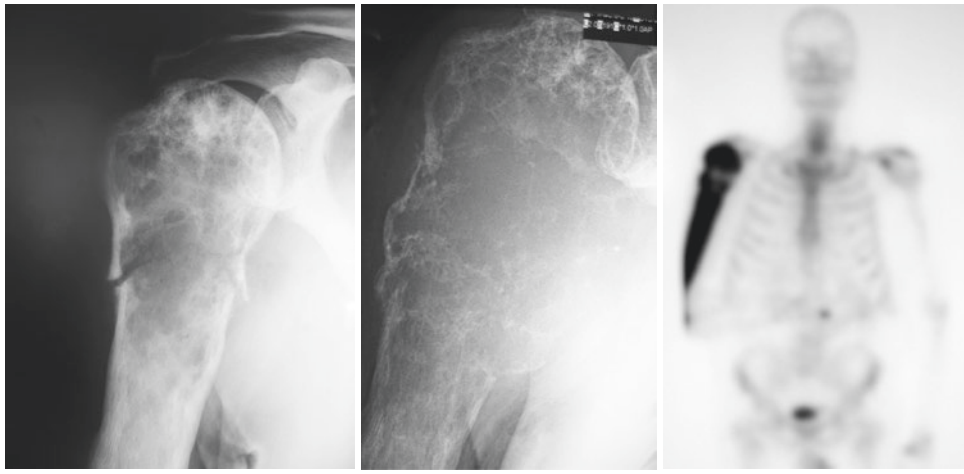
Blood filled cavities rimmed by malignant mesenchymal cells only focally producing osteoid

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.



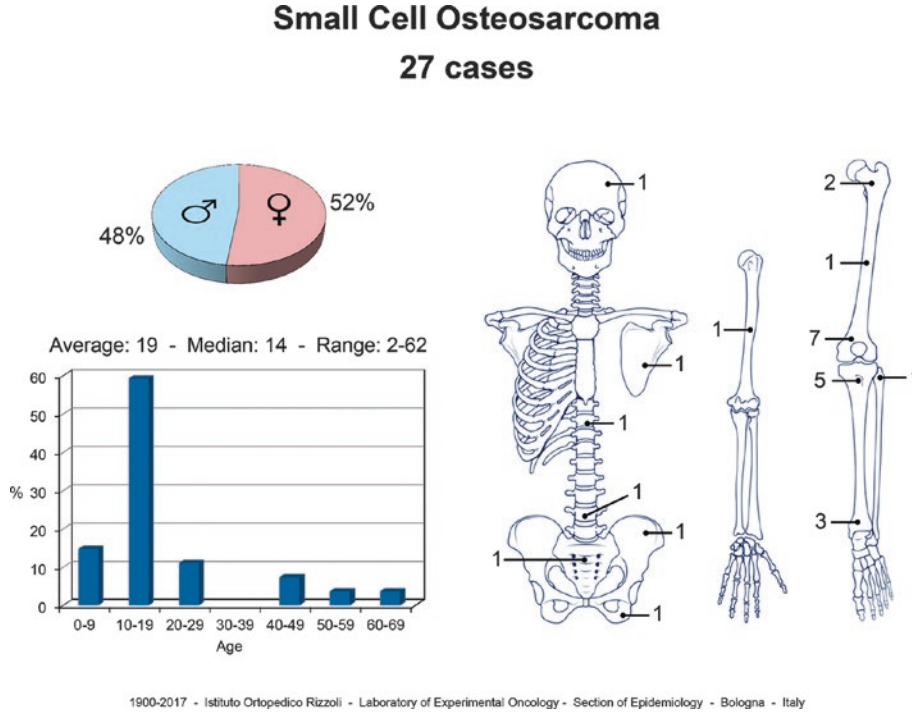


Radiograph at onset and 2 months later, bone scintigraphy. Lytic heterogeneous broken lesion involving the epiphysis and metaphysis. The thick lamellar cortex indicates a pre-existing Paget's disease, confirmed by widespread intense fixation on bone scintigraphy. Two months later, very fast progression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

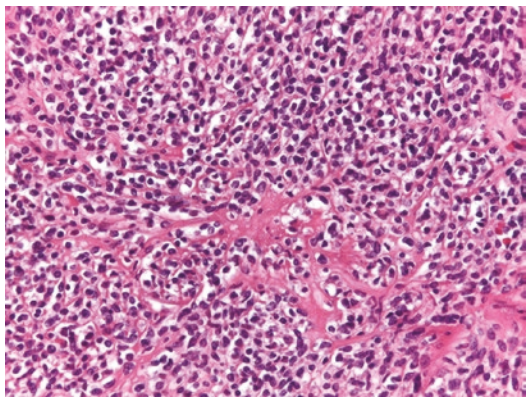
36.4 Small Cell Osteosarcoma

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.

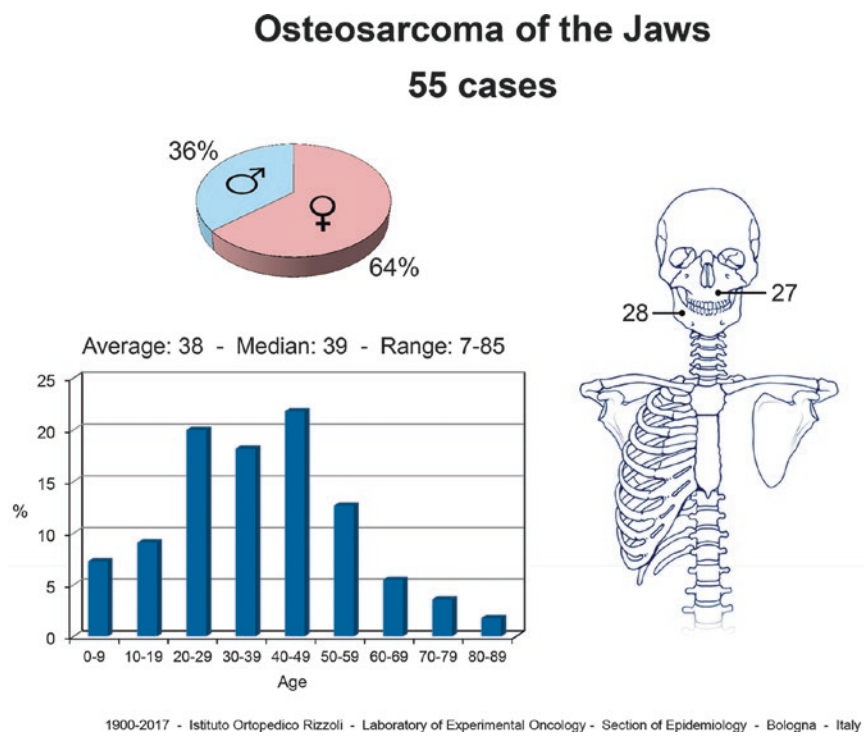


Round to ovoid cells, similar to Ewing sarcoma cells, organized in sheets and nests, with osteoid matrix

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.

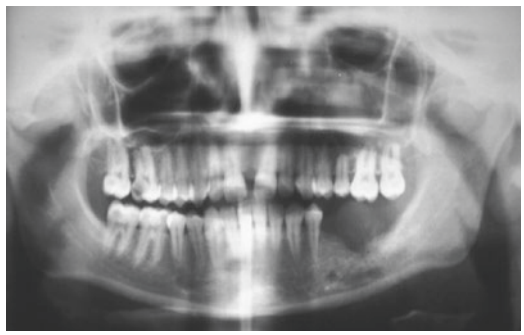
Clinical: Swelling is the most common complaint in patients with osteosarcoma of the jaws often accompanied with pain. The latency period between first symptoms and clinical presentation is around 4 months.

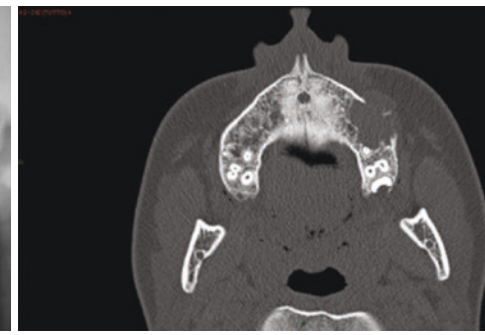
Imaging: Radiographically, osteosarcoma of the jaws presents as mixed radiolucencies reflecting the extent of matrix formation and mineralization. Aggressive features such as cortical permeation and periosteal reaction are generally present in conventional high-grade tumors.

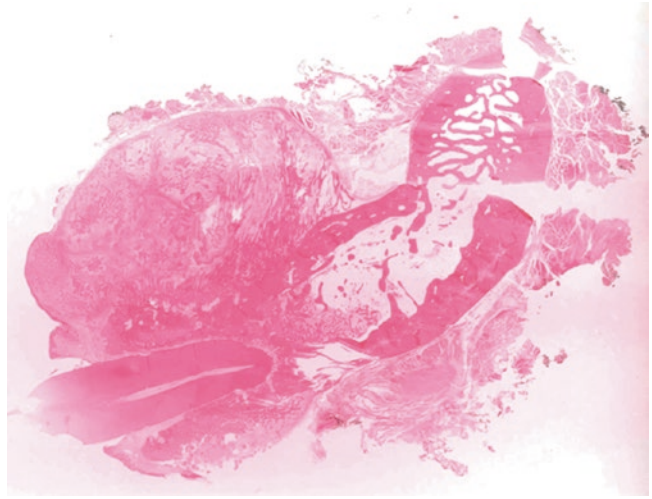
Histology: Histologically, the vast majority of osteosarcoma of the jaws are conventional high-grade tumors, demonstrating highly pleomorphic tumor cells producing a neoplastic bony matrix. The percentage of chondroblastic histotype is higher in osteosarcoma of the jaws than in other skeletal regions 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.





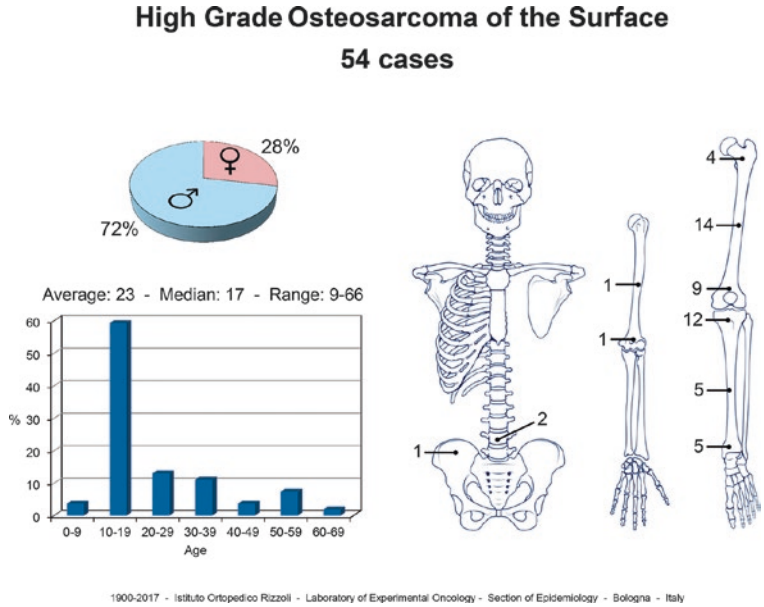


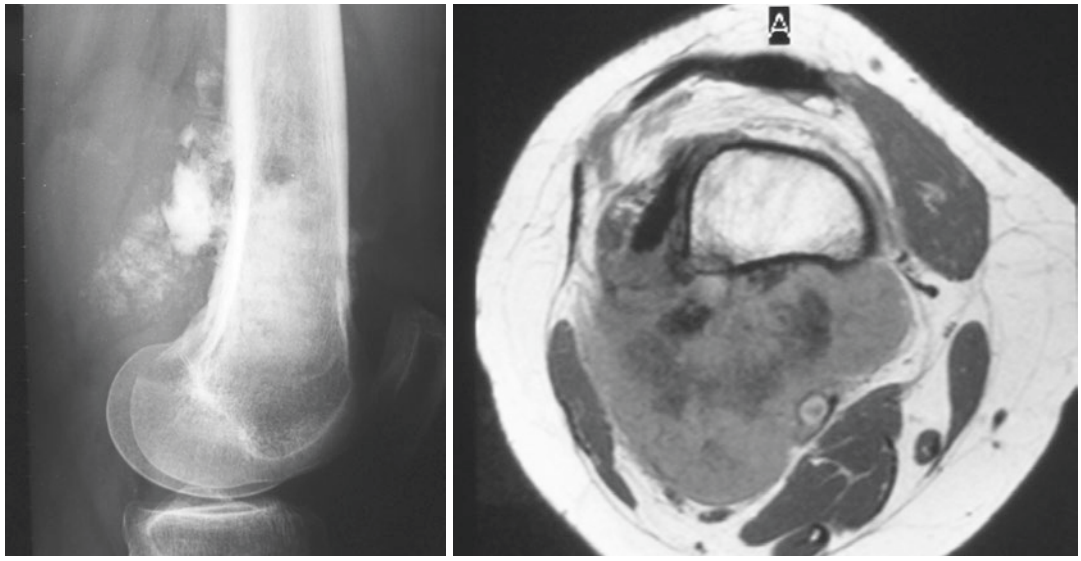
Panoramic radiograph and CT. Aggressive sclerotic and lytic tumour, distroying the cortex, invading the soft tissues, with perpendicular periosteal bone formations

36.6 High-Grade Osteosarcoma of the Surface

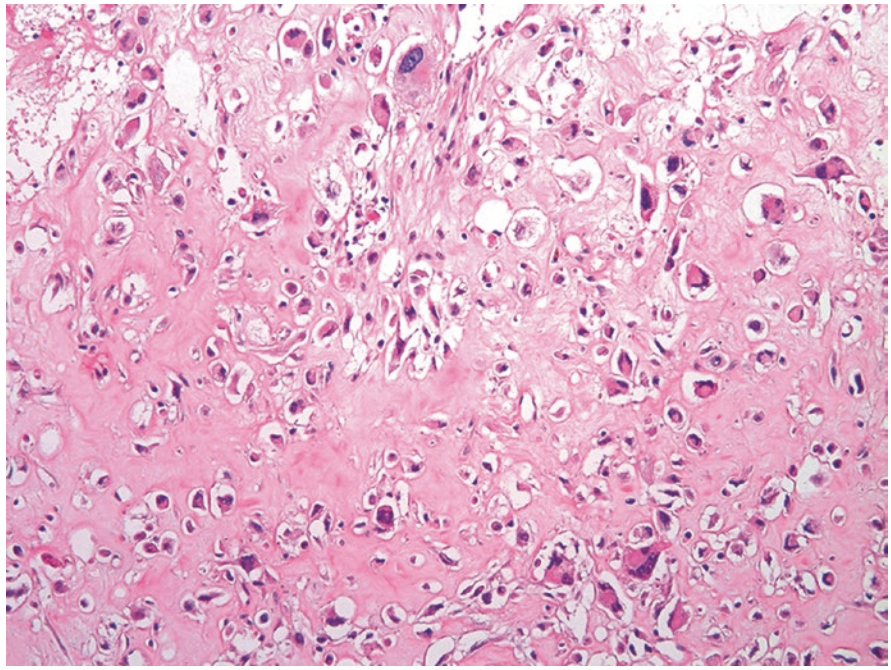
Definition: A high-grade OS arising on the bony surface with minimal involvement of the underlying cortex.

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

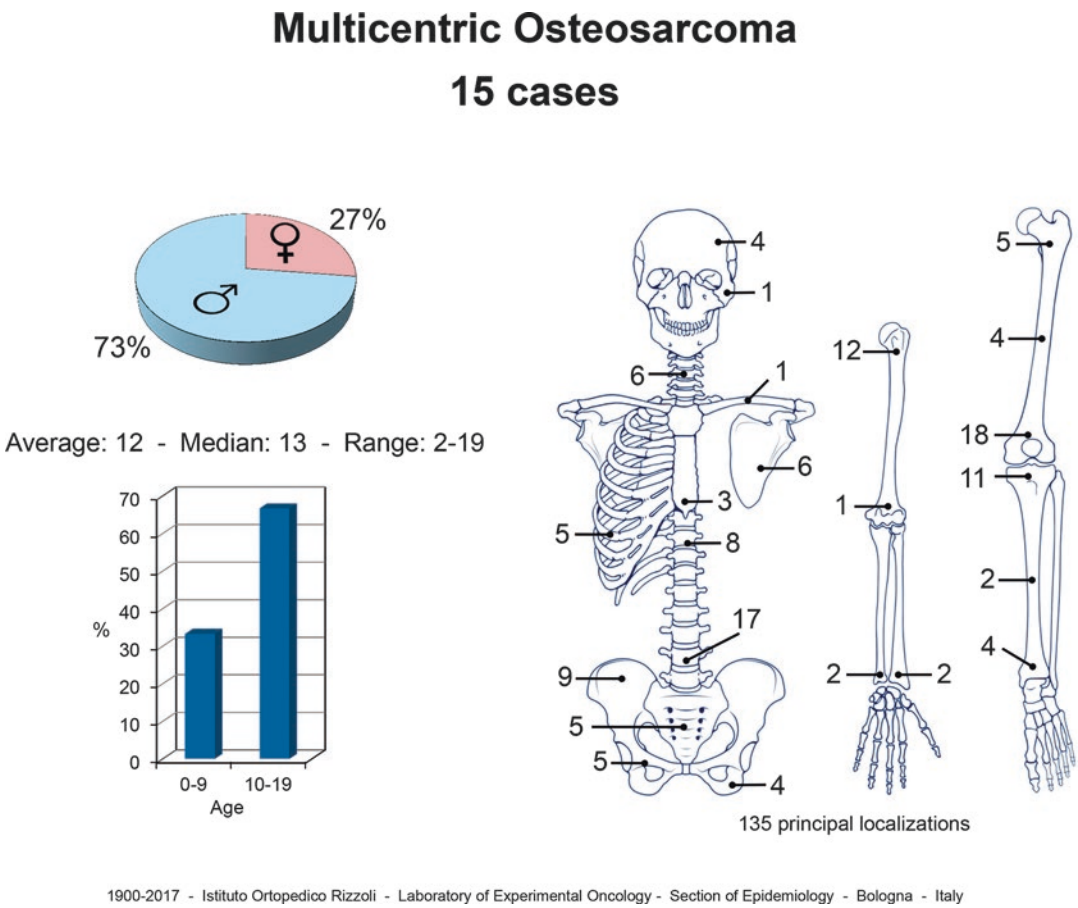


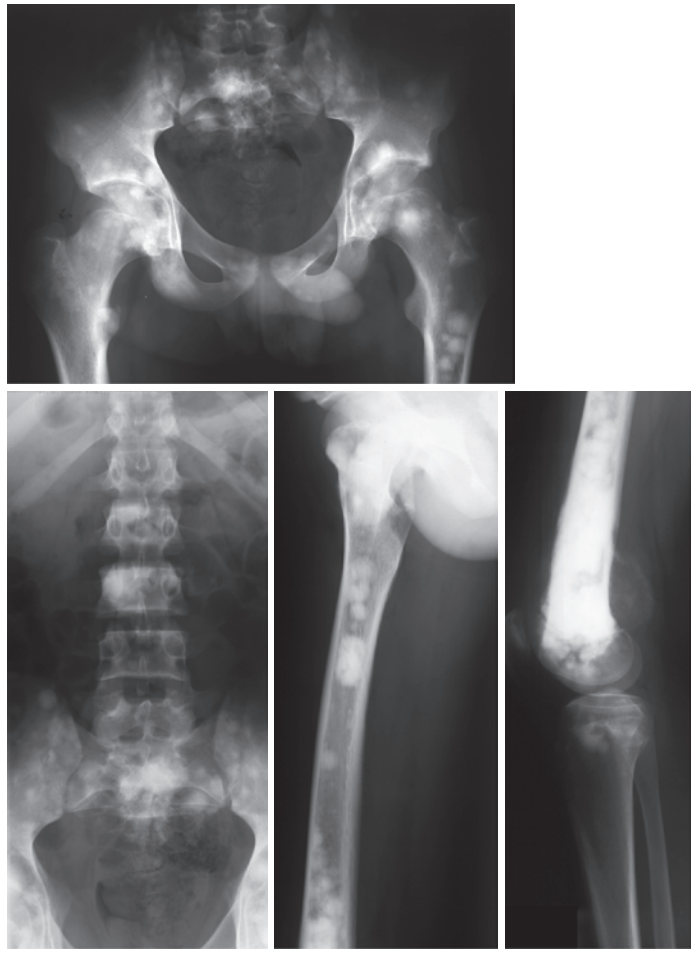
High-grade osteosarcoma identical to conventional central osteosarcoma, situated on the surface of bone. The majority are the osteoblastic variant

36.7 Multicentric Osteosarcoma

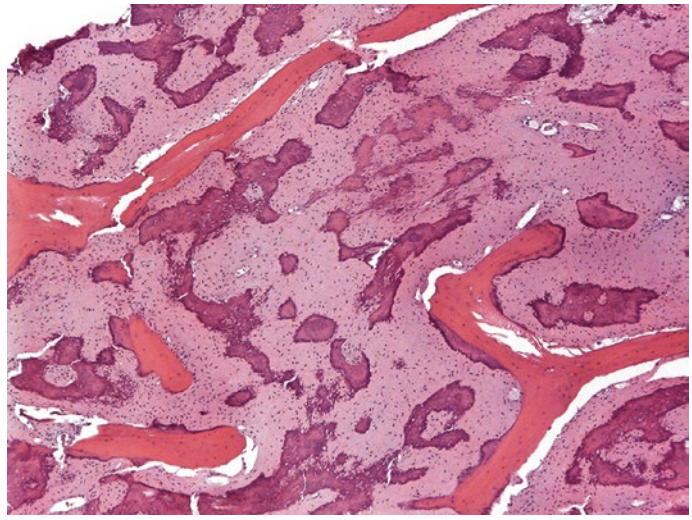
Definition: Almost synchronous appearance of multiple OS in the skeleton usually without pulmonary metastasis.

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

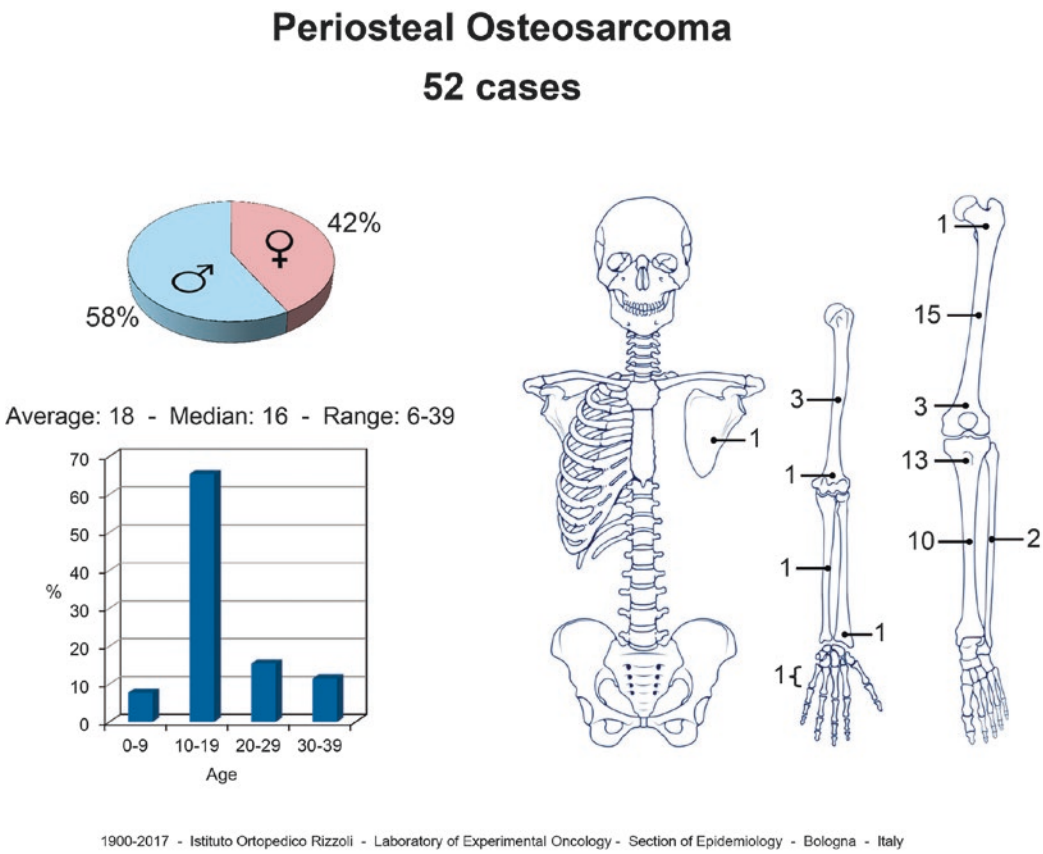


High-grade osteoblastic osteosarcoma usually extensively sclerotic with low cellularity and diminished cytological anaplasia when compared to classic osteoblastic osteosarcoma

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.

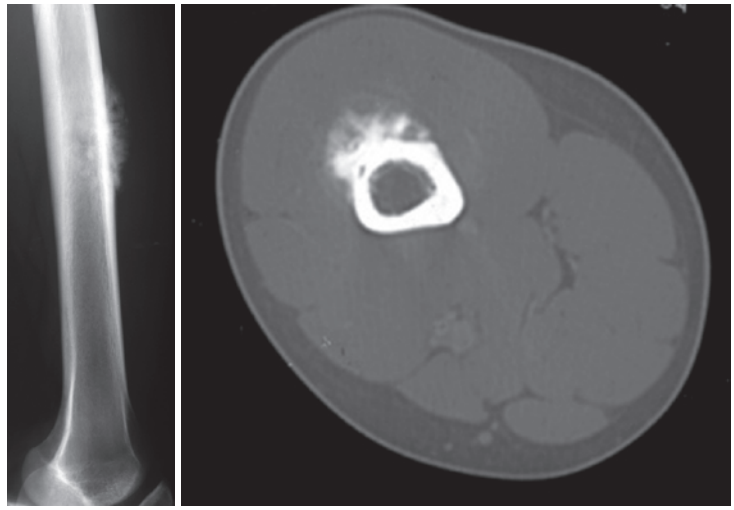
Histopathology: The cut surface of the tumor is soft to rubbery with a translucent aura. The tumor forms large lobules, separated by streaks of ossification perpendicular to the cortex. Tissue is mainly chondroblastic, being more cellular at the periphery, with spindle cells and lace-like osteoid, more 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

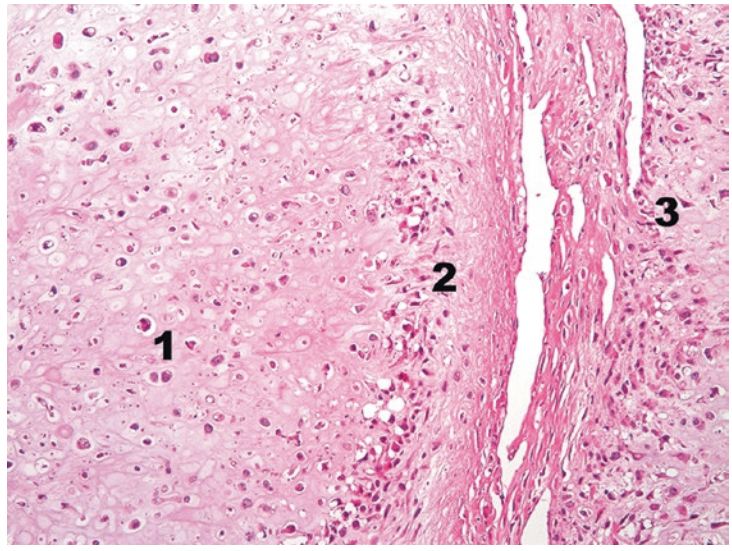
parosteal OS. The stage is I-A or I-B if there is intramedullary involvement.

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

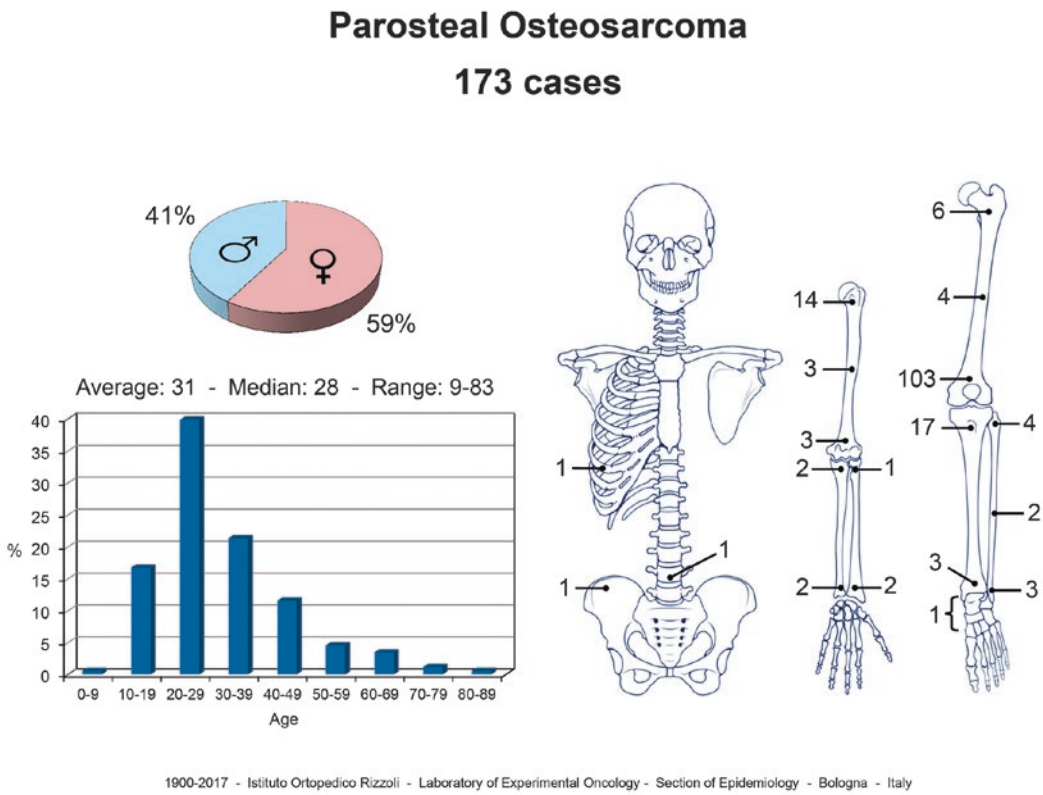


Predominantly chondroblastic tissue of intermediate malignancy that forms large lobules. (1) Chondroid cells. (2) Lake-like osteoid among malignant cells. (3) Spindle cells with minimal matrix at the periphery of the lobules

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.

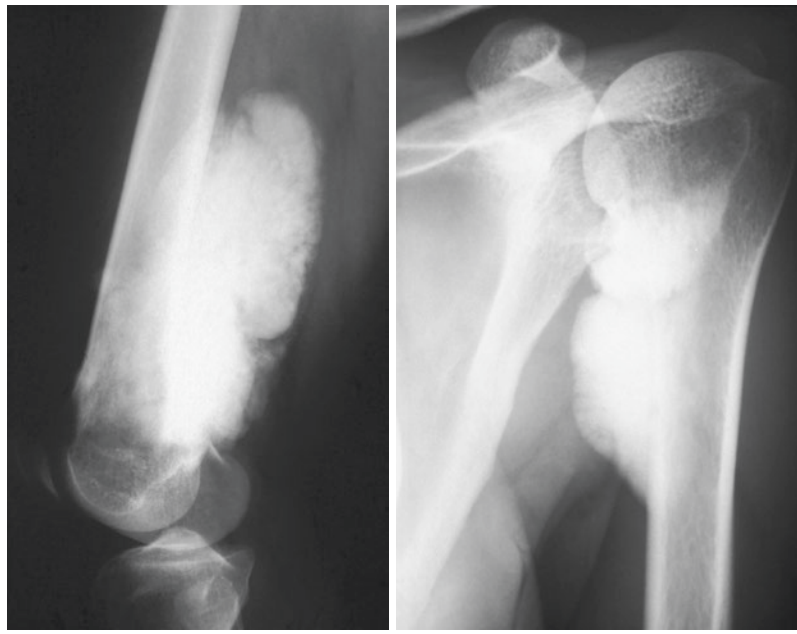
Histopathology: Parosteal OS is composed of spindle cells and collagen fibers, embedding osseous trabeculae. Occasionally cartilage may be associated. Cells form long sweeping fascicles with parallel nuclei. Trabeculae appear also as parallel streamers with broken cement lines as pagetic mosaic. Bone 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.

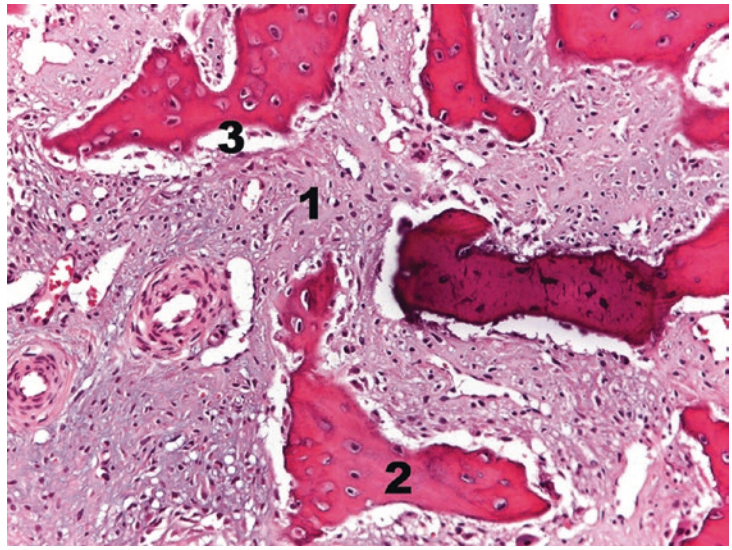
Treatment and Prognosis: Surgery must aim to wide margins. Hemicylindric resection is usually possible in the popliteal region, through a double approach (medial and lateral), elevating the quadriceps. More often, a complete segmental resection of the affected bone is needed. When the tumor impinges 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

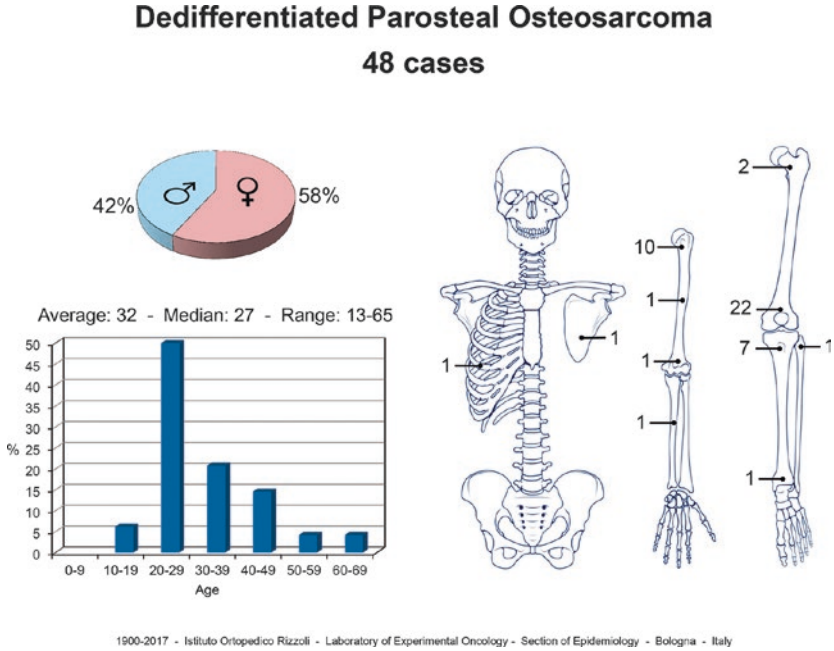


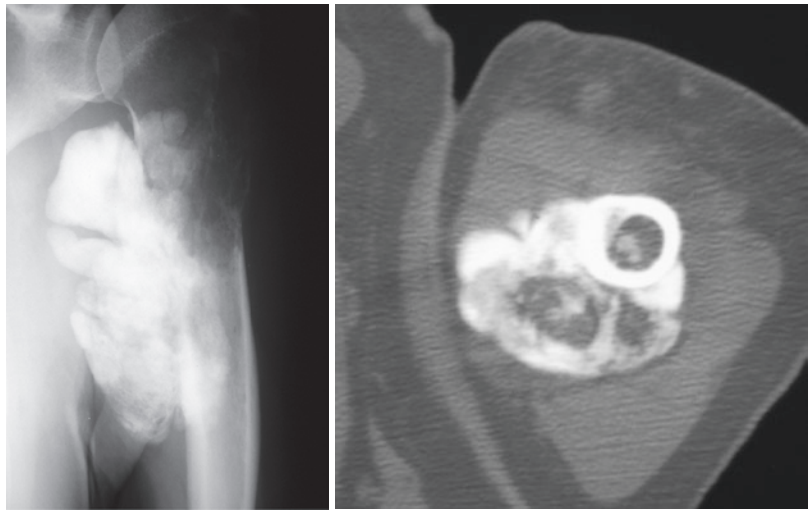
Radiographs. The tumors are homogeneous and sclerotic. They are attached to the bone



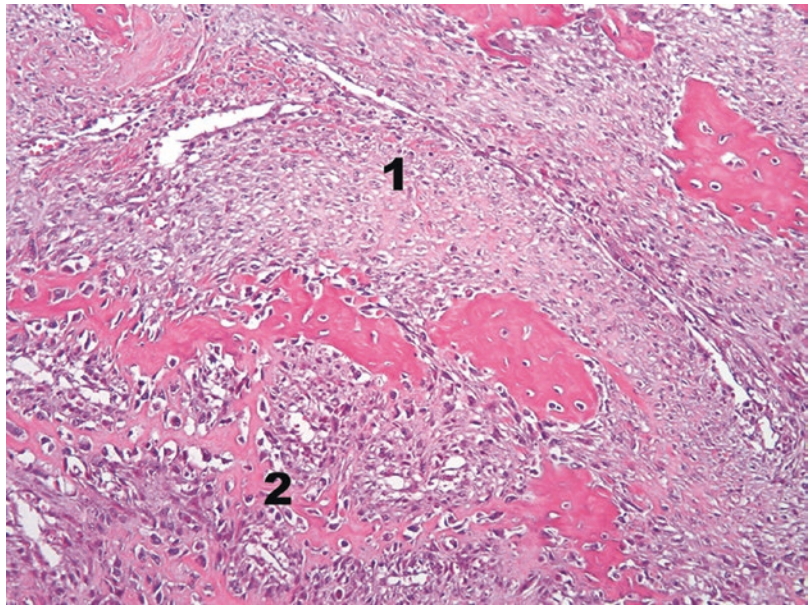
Histopathologic features are substantially represented by bony trabeculae enmeshed in a sarcomatous low-grade malignant spindle cell proliferation in a collagenous stroma. (1) Atypical spindle cells, like those of a low-grade fibrosarcoma. Nuclei are large, oval with low to mild pleomorphism. (2) Bone 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

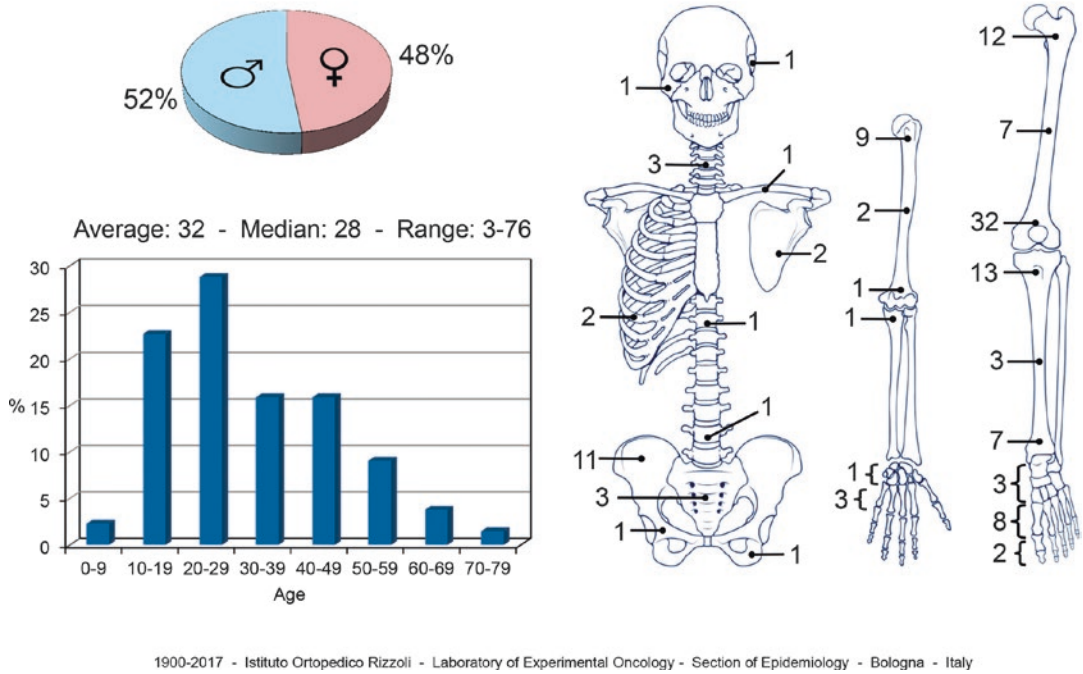


(1) Parosteal low grade osteosarcoma. (2) Dedifferentiation in high grade osteoblastic osteosarcoma

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.

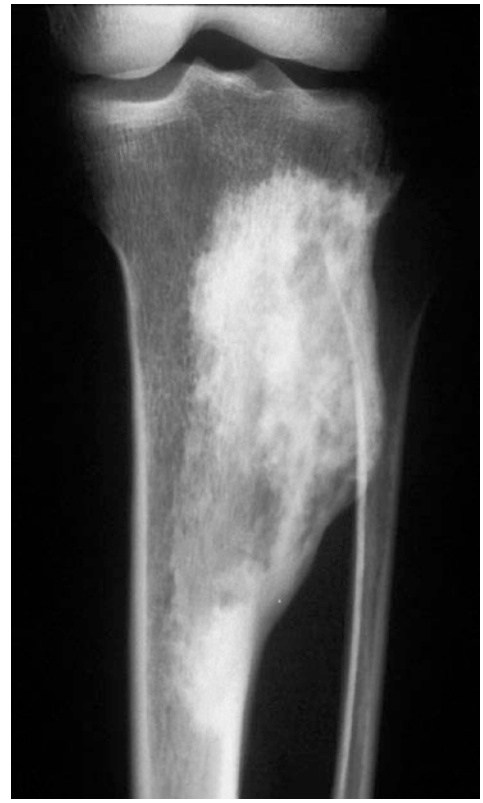
Course and Staging: The course is slow. In about 15% of cases, the tumor shows a progression of malignancy, transforming into a high-grade OS. The stage of the tumor is I-A or I-B. Transformed tumors become stage II.

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.

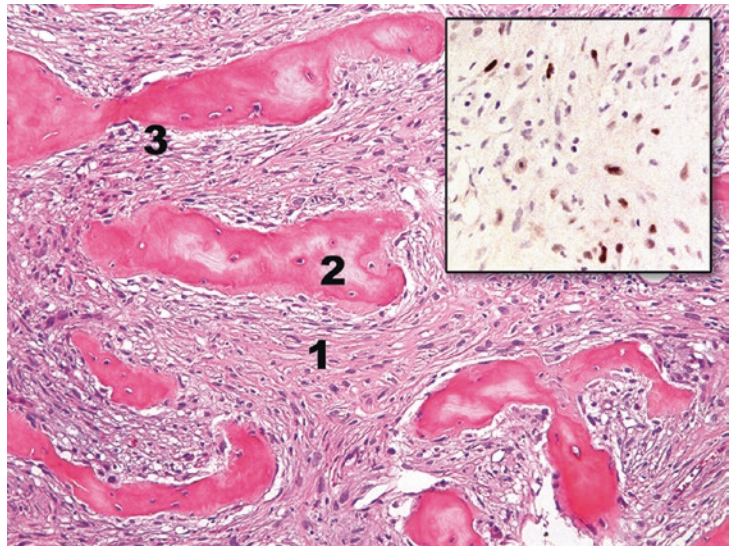
Prognosis: Metastasis (lungs) are reported in 10% of cases, and mostly in tumors that progressed in malignancy. They can occur many years after the onset of symptoms. Thus, prognosis is good, unless the tumor becomes a high-grade OS.

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

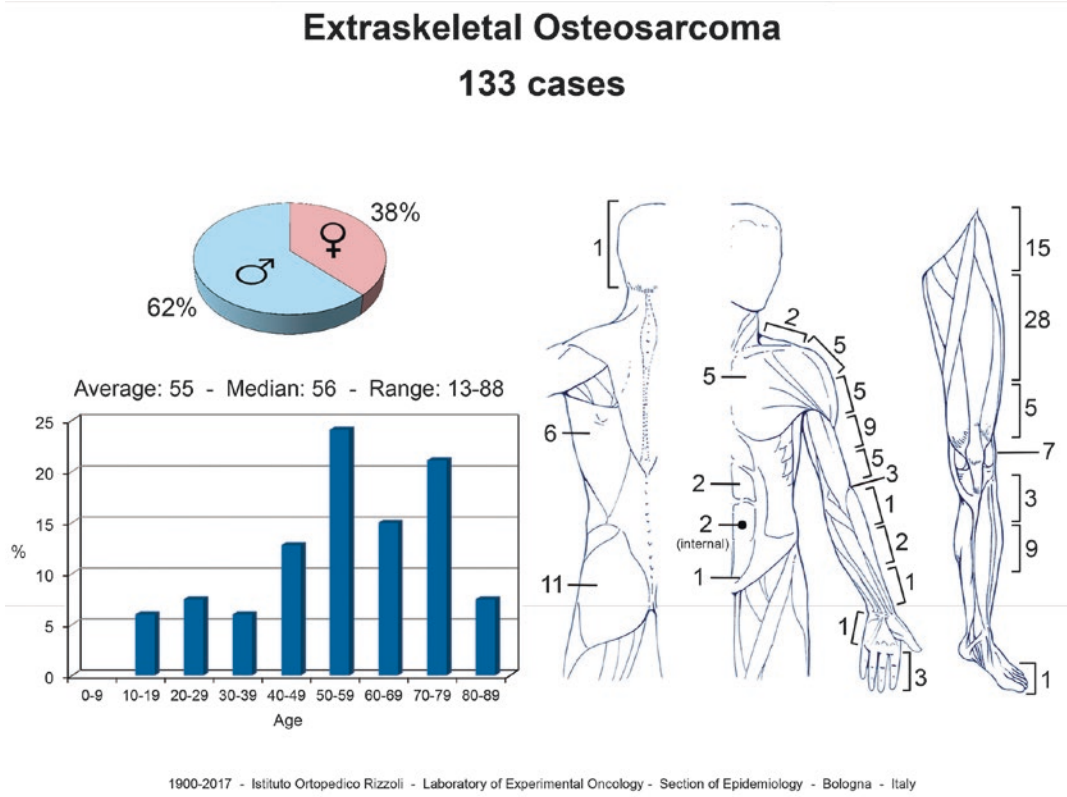


It histologically appears to be identical to parosteal osteosarcoma. (1) Cells surrounding the bony trabeculae are prevalently spindle-shaped, with aspects of minimal atypia. (2) Neoplastic trabeculae. (3) A regular row of osteblasts lining the trabeculae can be absent. Immunohistochemical nuclear positivity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

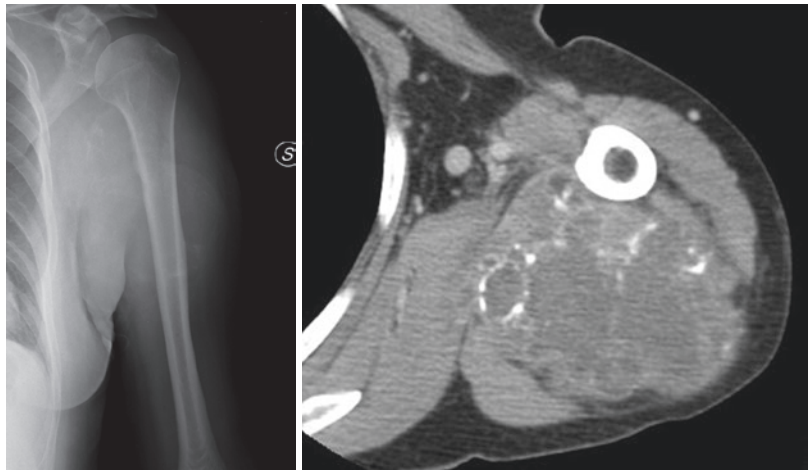
Clinical: Progressively enlarging painless mass.

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.

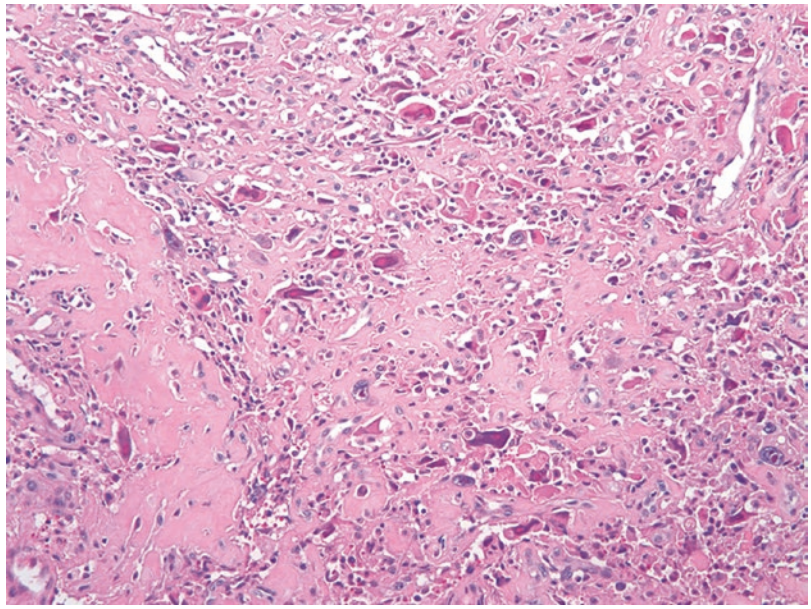
Histopathology: Highly cellular, mitotically active tumors. There is usually considerable nuclear pleomorphism with necrosis and lace-like eosinophilic osteoid outlining individual cells or clusters of cells. Mineralized osteoid (bone) is relatively uncommon. Lobules of malignant cartilage may be present.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

37

Massimo Serra and Claudia Maria Hattinger

Unlike other sarcomas, high-grade osteosarcoma (HGOS) is characterized by complex, unbalanced karyotypes and alterations in multiple genes and pathways. Due to HGOS high genetic instability, recurrent chromothripsis (a massive genomic rearrangement due to a cataclysmic event in which chromosomes are fragmented and subsequently aberrantly assembled), kataegis (high number of genetic changes due to localized hypermutation areas), and chromoplexy (a process generating chimeric chromosomes) are rather common events and lead to multiple malignant cell populations within the same tumor [1, 2].

The pathways governed by the TP53 and retinoblastoma 1 (RB1) tumor suppressor genes are those that have most consistently been found to be involved in HGOS pathogenesis. In fact, the majority (around 80%) of HGOS patients have alterations of one or both pathways [3]. The TP53 gene product plays a major role in the cell response to DNA damage and RB1 regulates cell cycle progression. Therefore, alterations of pathways governed by these two genes may allow cells to proliferate and become malignant after the acquisition of additional genetic aberrations. This is the reason why children affected by the Li–Fraumeni syndrome (carrying germline deletion/mutations of TP53) or familial retinoblastoma (carrying germline mutations of RB1) have a dramatically higher risk to develop HGOS [3].

Biologic and genetic studies of HGOS have clearly shown that during development and progression, tumor cells acquire several genetic changes, which may account for not only the aggressive behavior of this neoplasm but can also be responsible for the development of resistance to chemotherapeutic drugs [4, 5]. Taking these features into consideration, research on new drugs for novel treatment modalities of HGOS has been devoted to identify and validate agents against new candidate therapeutic targets, which have proved or appeared to be relevant for HGOS pathogenesis, treatment response, or clinical outcome. The current research goal of drug development for HGOS consists in the identification and validation of agents that can be administered as adjuvant to conventional chemotherapeutics to better control the local and metastatic disease, as well as to improve the efficacy of standard chemotherapy regimens without increasing their collateral adverse toxicity [6]. These facts offer the hope for not only an increased survival probability, but also for an improved quality of life of cured patients, which is particularly relevant for tumors mainly affecting young people like HGOS.

As a complement to these goals, the validation of predictive and prognostic markers for HGOS

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is highly needed in order to allow a patient stratification based on specific characteristics of each tumor and on a precise risk evaluation aimed to identify those subgroups of patients with the highest probability to benefit from each innovative treatment.

An information that clearly emerged from clinical studies is that the major cause of failure of the current treatment protocols for HGOS is the natural or acquired drug resistance, which occurs in 35–45% of patients. Therefore, the identification and validation of drug resistance-related markers as prognostic factors and potential new therapeutic targets are highly warranted.

Several studies have indicated that the ATP-binding cassette (ABC) transporter ABCB1 (also named as MDR1 or P-glycoprotein) plays an important role in drug resistance and treatment response of HGOS patients [7–11]. Therefore, targeting this molecule appears to be an interesting therapeutic option to improve treatment results in HGOS patients who are unresponsive to conventional regimens.

In the past 30–35 years, several ABC transporter modulators or inhibitors have been described and entered clinical Phase I-II-III trials for different human tumors. The clinical use of such modulators has however, been limited by the severe collateral toxicity that has been encountered at the concentrations required to enable these drugs to significantly inhibit the ABC transporters activity [6]. More recently, a new generation of ABC transporter inhibitors has been developed, few of which showed promising preclinical activity at significantly lower dosages also in HGOS [6, 12]. If this evidence will be further confirmed, in the next years we should have enough information about the possibility to include ABC transporter inhibitors in association with conventional chemotherapeutics in the treatment of HGOS patients unresponsive or with reduced sensitivity to conventional drugs.

The provided evidence about the clinical relevance of ABCB1 expression level in HGOS has been however, taken into account to stratify patients and modulate treatment in the Phase II-III Italian Sarcoma Group (ISG) trial ISG/OS-2 (https://ClinicalTrials.gov/show/NCT01459484). In this protocol, HGOS patients are stratified on the basis of ABCB1 expression level at diagnosis and, subsequently, of the extent of tumor necrosis after preoperative chemotherapy. Patients overexpressing ABCB1 receive a more intensified treatment regimen, which also includes mifamurtide. It is however, worthwhile noting that mifamurtide is not an inhibitor of ABCB1 but a nonspecific immunomodulator, which has successfully been used in clinical trials for metastatic and nonmetastatic HGOS patients [13–15]. In the next 2–3 years, on the basis of the results obtained by this protocol, it will be possible to estimate the actual effectiveness of this treatment strategy.

One important challenge that has recently emerged as a possibility to improve the clinical results of conventional treatments in several human cancers is to consider not only the tumor features that are directly associated with treatment unresponsiveness, but also those related to development of adverse treatment-related toxicities. This approach is aimed to potentiate the efficacy of conventional chemotherapeutic drugs without increasing their adverse collateral toxicities.

In the past decade, pharmacogenomic studies applied to HGOS have started to provide information on the understanding of how genes can affect individual drug response and susceptibility to toxic events [16, 17]. This body of evidence may be of great help to select the drugs and treatment dosages which adapt best for each patient guiding the modulation and individualization of specific therapeutic approaches. As a future perspective, it could be also predicted that the application of high-throughput genetic analyses, such as next-generation sequencing, may extend pharmacogenomics to the entire genome instead of single genes or pathways, leading to the rapid identification of new markers to be considered for improving the standard HGOS clinical treatment protocols [18].

On the basis of the information which has been reported so far, it can be predicted that, in the next 5–10 years, there is a concrete possibility to identify agents with efficacy and safety profiles superior or complementary to those of conventional drugs, which may be considered for

innovative treatment strategies for groups of HGOS patients selected by using novel validated biomarkers.

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Chemotherapy of Osteosarcoma

38

Stefano Ferrari and Emanuela Palmerini

38.1 Osteosarcoma Treatment Strategy

Treatment of osteosarcoma requires a combined approach of surgery of the primary tumor and systemic chemotherapy.

The use of chemotherapy has significantly changed prognosis of patients with osteogenic sarcoma. In the past, when patients received only surgery, survival rate was lower than 20% [1].

Standard strategy of chemotherapy for osteosarcoma is based on primary chemotherapy and delayed surgery followed by adjuvant chemotherapy.

The use of chemotherapy before surgery (neoadjuvant) was introduced in the 1970s and was widely adopted since it offers the opportunity of evaluating chemotherapy-induced tumor necrosis by histological examination of the resected surgical specimen [2].

The degree of tumor necrosis used as a marker of chemosensitivity proved to be an important factor predictive of survival. Also, in a recent paper exploring several prognostic factors of survival in nonmetastatic osteosarcoma, chemotherapy-induced tumor necrosis still retains prognostic significance [3]. Imaging techniques such as PET and dynamic magnetic resonance have been assessed to predict the pathological response [4, 5].

Microarray technology has been recently investigated to predict chemotherapy response and a multigene predictive model was developed to classify good and poor responders to preoperative chemotherapy [6].

38.1.1 Choice of Chemotherapy

Most chemotherapy regimens adopted for osteogenic sarcoma are based on methotrexate (MTX), cisplatin (CDP), doxorubicin (ADM), and ifosfamide (IFO).

It is well known that when only cisplatin and doxorubicin are used, a probability of DFS around 45% can be expected [7].

Strategies of chemotherapy based on the use of the four active drugs lead to a probability of DFS around 60–65% [8–11].

A notable study from The Children's Cancer Group and Pediatric Oncology Group combined classic cytotoxic chemotherapy to immunotherapy. The study evaluated whether the addition of ifosfamide and/or muramyl tripeptide-phosphatidylethanolamine (MTP-PE) to methotrexate, cisplatin, and doxorubicin could improve prognosis [11]. MTP-PE is a compo-

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nent of the bacterial cell wall conjugated to phosphatidylethanolamine and incapsulated in liposomes with immunostimulating activity. Overall, the probability of survival was higher in those patients treated with MTP-PE and a trend was reported in terms of EFS [11].

Based on these data EMA licensed the drug for the commercial use in Europe.

The mifamurtide is now under further investigation in an Italian and Spanish joint study presently ongoing and recently closed to the enrollment (ISG/OS-2 https://clinicaltrials.gov/ct2/show/NCT01459484).

It is matter of discussion whether all patients require intensive and prolonged treatment based on all four active drugs [12].

The Italian Sarcoma Group (ISG) demonstrated that ifosfamide can be given postoperatively and only to patients with a poor pathological response (PR) to primary chemotherapy based on methotrexate, cisplatin and doxorubicine [13]. This approach allowed the same results with lower toxicity than a chemotherapy regimen that used all four drugs since the primary phase and for all patients.

More recently, results of two important randomized clinical trials have been published: EURAMOS-1 and OS2006. EURAMOS-1 [14], performed by the Children's Oncology Group (COG), Cooperative Osteosarcoma Study Group (COSS) of the German Society for Pediatric Oncology and Hematology, European Osteosarcoma Intergroup (EOI), and Scandinavian Sarcoma Group (SSG), aimed to optimize treatment strategies for resectable osteosarcoma based on histological response to preoperative chemotherapy. After a preoperative chemotherapy regimen of cisplatin, doxorubicin, and methotrexate (MAP), patients received postoperative therapy, which was determined by tumor histological response. Good responder patients (≤10% viable tumor cells) were randomized to continue with MAP, or to receive interferon-alpha (IFN) as maintenance therapy following MAP (MAP-IFN). Poor responder patients (>10% viable tumor cells) were randomized either to continue with MAP or to receive the same regimen with the addition of ifosfamide and etoposide (MAP-IE). The trial started in March 2005, overall 2260 patients were registered from 326 centers across 17 countries. No advantages from the use of IFN were observed in GR patients [15] and in PR patients the addition to MAP of the "salvage chemotherapy" with ifosfamide and etoposide not only did not improve the survival, but also induced a higher incidence of secondary malignancy [16].

The French multicenter OS2006 randomized trial investigated the use of zoledronic acid added to chemotherapy in patients with osteosarcoma [17]. A complex strategy of treatment characterized this study. Pediatric and adult patients were treated according to different chemotherapy regimens. For pediatric patients, primary treatment was based on MTX, IFO and etoposide, whereas adult patients received primary chemotherapy with IFO, ADM, and CDP. Postoperative treatment was tailored on the basis of chemotherapy-induced tumor necrosis. All patients with a good pathological response continued with the same drugs as in the preoperative phase. In case of poor response, in pediatric patients, ifosfamide and etoposide were replaced by CDP and ADM. Adult patients received postoperative treatment with ifosfamide and etoposide.

The study started in April 2007 and closed in February 2014 with 318 patients enrolled. The activity shown in the preclinical models of osteosarcoma by zoledronic acid was not confirmed. The French study is of clinical interest because the survival data reported in the group of patients preoperatively treated with a combination of metotrextate and ifosfamide/etoposide [18] with the use of cisplatin and doxorubicin only in PR patients are similar to those of the EURAMOS-1 trial and those of the ISG/OS-1 study. The data of the French study emphasize the role of methotrexate in the treatment of osteosarcoma showing that it is possible to effectively treat patients with osteosarcoma only with methotrexate, ifosfamide, and etoposide, avoiding drugs such as cisplatin and doxorubicin. Overall, these three experiences suggest that from different, but intensive chemotherapy treatments for osteosarcoma, a similar probability of EFS survival (around 60–65%) and overall survival (70–75%) can be expected.

The MAP regimen is now the backbone for the treatment of pediatric and young patients with non-metastatic osteosarcoma. The French experience indicates that good results can be achieved with the use of a chemotherapy regimen based on MTX, IFO, and etoposide, and this indication is of clinical relevance in case of medical contraindication to the use of ADM or CDP.

38.1.2 Osteosarcoma in Patients Older than 40 Years

There is wide agreement on the fact that patients with osteosarcoma older than 40 who also receive chemotherapy have a better probability of survival compared to those treated with surgery alone. Recently, the results of a joint ISG, COSS, and SSG prospective study (EURO.B.O.S.S.) have been published [19].

EURO.B.O.S.S. was the first prospective multicenter international study for patients 41–65 years old with high-grade bone sarcoma. The first aim of the study was to assess the feasibility and the toxicity profile of an intensive chemotherapy treatment derived from chemotherapy protocols for younger patients.

Chemotherapy treatment consisted of combinations of CDP/ADM (CDP 100 mg/m^2/ADM 60 mg/m^2), IFO/CDP (IFO 6 g/m^2/CDP 100 mg/m^2) and IFO/ADM (IFO 6 g/m^2/ADM 60 mg/m^2) repeated three times for a total of 9 cycles. Surgery was planned after 3 cycles. MTX (8 g/m^2) was postoperatively added in poor responders. Overall the planned cumulative dose was ADM: 360 mg/m^2, CDP: 600 mg/m^2, IFO 36 g/m^2, MTX: 40 g/m^2. Immediate surgery was allowed and, in this case, 9 cycles with CDP, ADM, IFO were given postoperatively. Overall the study has enrolled 218 patients with high-grade osteosarcoma. The percentage of patients with a good pathological response was lower than that usually reported in young patients and the probability of OS was 66% in patients with localized disease.

These data, prospectively collected in a large collaborative intergroup study, confirm that also in adult and elderly patients with osteosarcoma, good results can be achieved and that the probability of survival are not so different compared to those reported in younger patients. These good results are paid by a remarkable toxicity, not only bone marrow toxicity, but also neurological and renal toxicity, at a level unknown in younger age groups.

38.2 Extraskeletal Osteosarcoma

A recent study promoted by the European Musculoskeletal Oncology Society (EMSOS) has focused on this rare entity [20]. Retrospectively, data have been collected from 274 patients treated in 16 EMSOS centers. Five-year overall survival (OS) for was 47% (95% CI 40–54%). Five-year OS was 27% for metastatic patients and 51.4% in localized patients who achieved complete remission after surgery. A favorable trend was seen for osteosarcoma-type chemotherapy versus soft tissue sarcoma-type ADM ± IFO) regimens. Age, size, and use of chemotherapy significantly influenced the survival in patients in complete remission after surgery. Based on these data, a chemotherapy strategy close to that adopted in bone osteosarcoma can be recommended in extraskeletal osteosarcoma.

38.3 Parosteal, Periosteal, and Low-Grade Central Osteosarcoma

Wide resection is standard treatment for this low-grade osteosarcomas. Chemotherapy as used in classic high-grade osteosarcoma is indicated in case of dedifferentiated parosteal osteosarcoma, or in case of progression of malignancy in recurrences.

38.4 Small Cell Osteosarcoma

Small cell osteosarcoma is a rare variant, for which standard treatment is the same as for classic osteosarcoma. There is some controversy over the type of chemotherapy, since small cell

osteosarcoma seems to have a somewhat different chemosensitivity and a worse prognosis. Some authors have recommended treatment with the same chemotherapy as that used for Ewing sarcoma, but this is still investigational, while good results have also been reported with chemotherapy used for conventional osteosarcoma.

38.5 Multicentric Osteosarcoma

Multicentric osteosarcoma is extremely rare and has a poor prognosis, whatever the treatment. Aggressive neoadjuvant chemotherapy, followed by, or combined with, radiation therapy to involved sites, and possibly surgical excision of selected lesions, may be considered standard treatment. Nonetheless, the course of the disease is usually rapid and fatal.

38.6 Secondary Osteosarcoma

Secondary osteosarcoma may occur in several benign diseases of bone: Paget's disease, fibrous dysplasia, bone infarcts, chronic osteomyelitis, irradiated bone, as well as in dedifferentiated chondrosarcoma. Poor prognosis has usually been reported, but the issue now raised is that in some cases, this could be due to the older age of these patients, resulting in a less aggressive treatment, and thus that prognosis does not necessarily differ from that of conventional osteosarcoma provided adequate treatment is given. Consequently, aggressive neoadjuvant chemotherapy and wide surgery are strongly recommended also for these rare osteosarcomas.

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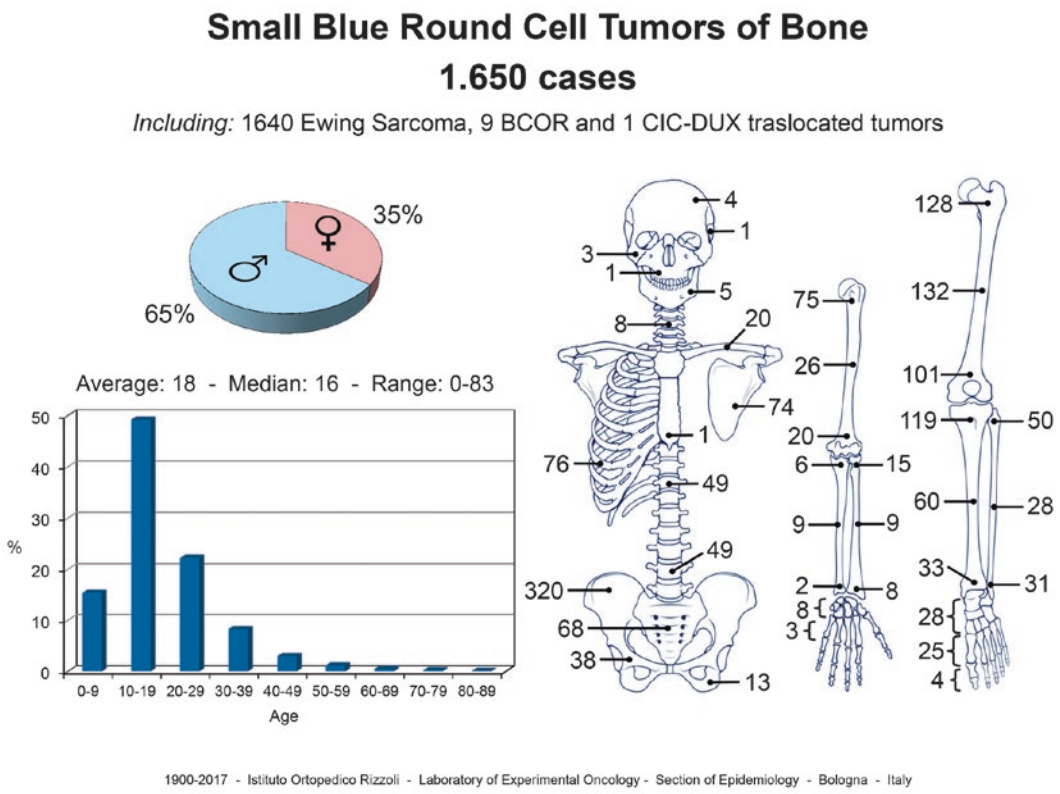
Small Blue Round Cell Tumors

39

Marco Manfrini and Marco Gambarotti



39.1 Ewing Sarcoma of Bone

Definition: High-grade malignant poorly differentiated tumor composed of small round cells. The current definition includes several historical entities, such as Ewing sarcoma, peripheral primitive neuroectodermal tumor (PNET), and Askin's tumor (Ewing sarcoma of the chest wall), all of which share the same oncogenic fusions and similar biologic behavior, and therefore are currently considered as a unique entity defined as Ewing family tumors (EFTs).

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Epidemiology: 6–8% of primary malignant bone tumors, two-third times less frequent than osteosarcoma. It represents the second most common bone malignancy affecting children and adolescents. Male to female ratio is 1.5–1. It is more common in Caucasians and rarely appears in individuals of African heritage. About 90% of cases occur from age 5–25.

Localization: EFT may occur in all the skeleton, as frequent in flat and short bones as it is in long bones. In the limbs, the most common localization is the femur, followed by the tibia, humerus, fibula, and forearm bones. Rare in hands and feet. In the trunk, the most frequent localization is the pelvis, followed by vertebrae and sacrum, scapula, ribs, and clavicle. Rare in the skull. In long bones, tumor is common in the midshaft but it may involve a larger portion or even the entire bone.

Clinical: Pain is the earliest symptom (intense and radiating if nerve impingement is present, as in sacral and vertebral locations). Low-grade fever may be associated. Swelling is also common as early sign. Occasionally, however, no soft tissue mass is appreciated, even for a long time. An increase of serum HDL and erythrocyte sedimentation rate are frequently seen, sometimes associated with leukocytosis and anemia.

Imaging: Imaging presentation is variable: the most frequent is a permeative, infiltrative, poorly defined osteolysis that can also be more destructive, uniform, or vaguely trabeculated. Increased bone radiodensities may associate (bone necrosis and/or deposition of reactive bone). The cortex is almost regularly breached by the tumor or destroyed, and a radiolucent extraosseous tumor mass is usually present. Particularly in flat bones (pelvis, scapula) this mass may be prominent, in contrast with a minimal cortical osteolysis. Rarely, however, the tumor remains intramedullary for a long time. Periosteal reaction is common in the diaphyses of young patients. The most typical, but unspecific sign is an onionskin appearance, leading to a fusiform enlargement of the shaft. Rarely EFT is predominantly periosteal, with a mass expanding in the soft tissue and erosion of the outer cortex. CT defines alterations of bone and the extraosseous mass (density similar to muscle). MRI is the best way to study tumor extension in marrow spaces (better demonstrated by T1 FSE and T2 FAT SAT technique) and in the soft tissues. Isotope scan and PET scan are hot and may show skeletal metastasis at presentation. PET scan is also useful to demonstrate lymph node or visceral metastases. Typically, extension of EFT, as shown by MRI, CT, and isotope scan is much more than what appears on X-rays.

Histopathology: Grossly, Ewing sarcoma is a soft, grayish mass, often with hyperemic, and hemorrhagic areas. Necrosis is common, particularly in the center with a semiliquid appearance, similar to that of purulence. Histologically, the tumor is composed of sheets of small round cells closely packed. Sometimes tumoral cells form rosette-like structures, composed of a central fibrillary core with nuclei at the periphery; Ewing sarcomas with these features—considered indicative of a neural differentiation—were formerly known as PNET. Neoplastic cells are relatively monotonous and uniform in appearance, with round to oval hyperchromatic nuclei showing a distinct nuclear membrane, powder-like chromatin, and one or more tiny nucleoli. Cytoplasm is scarce, pale, granular, eosinophilic to clear (do to the presence of glycogen), with poorly defined limits. Mitotic figures are usually rare. Adamantinoma-like Ewing sarcoma shows complex epithelial differentiationalso with immunohistochemica positivity for cytokeratins; squamous areas can be present. The tumor diffusely permeates the marrow spaces, generally with a prominent neovascular and inflammatory response and a fibro-osseous reaction unable to provide a significant encapsulation. At the edges of the tumor, frequently satellite nodules are present, in and beyond the reactive zone, and even skip metastasis can be found. Reticulin fibers are lacking between cells but may enwrap cells islands. P.A.S.-diastase staining shows the intracytoplasmatic glycogen. Electron microscopy shows glycogen in the cytoplasm.

Course and Staging: The tumor usually displays an aggressive growth. There are, however, cases where EFT remains intraosseous causing only discontinuous pain for a time ranging from one to several years. EFT may display a multiple metastatic spread to the lungs, but also to lymph nodes, skeleton, brain or other organs.

In order to stratify metastatic patients, nowadays EFTs are usually staged by the TNM system from American Joint Committee on Cancer (AJCC). In this system used also for other cancers, the stage of bone neoplasms is based on four parameters

- **T** describes the size of the tumor and if involves different areas of the affected bone segment.
- **N** describes whether the tumor has reached local lymph nodes.
- **M** describes whether the tumor has spread to other parts of the body.
- **G** is the grade of the tumor. EFTs are always high-grade tumors (G2).

Localized EFT may be staged as Stage IIA or IIB according to size (below and above 8 cm).

Stage III is for EFTs that involves the same skeletal segment with more than one lesion (skip lesions).

Stage IV is for EFT that present distant metastases, IVA for cases with lung metastases only, IVB for cases with metastases to lymph nodes, other skeletal segments or other organs.

Treatment: EFT is sensitive to chemotherapy and radiotherapy but surgery plays an essential role in treatment of the primary tumor. Thus, treatment is based on a combination of chemotherapy (always), surgery, and radiotherapy (alternative to surgery or associated to surgery). Currently, trials employ 4–6 cycles of chemotherapy, followed by the local treatment, and another 6–10 cycles of chemotherapy, usually applied at 2- to 3-week intervals. Most active agents include adriamycin, cyclophosphamide, ifosfamide, vincristine, dactinomycin D, and etoposide. Preoperative chemotherapy in responsive patients, which are the vast majority, causes an extensive necrosis of tumor cells. Because tumor cells do not produce any matrix and disappear short after necrosis, effective chemotherapy determines a remarkable shrinkage of the tumor with recession of inflammation. Local treatment (surgery alone, surgery and radiotherapy, radiotherapy and delayed surgery or radiotherapy alone) is planned according to stage and several individual factors (age, location, radiological response to chemotherapy, histological necrosis on the resected specimen), and by balancing the risk of local recurrence against functional loss secondary to local treatment. In patients staged IVA, at the end of the chemotherapy, total lung radiotherapy (14 Gy) is usually performed.

Prognosis: Before the use of chemotherapy, long-term survival was less than 10%, also in localized cases. Presently, with multimodal treatment, the same figure is around 70%.

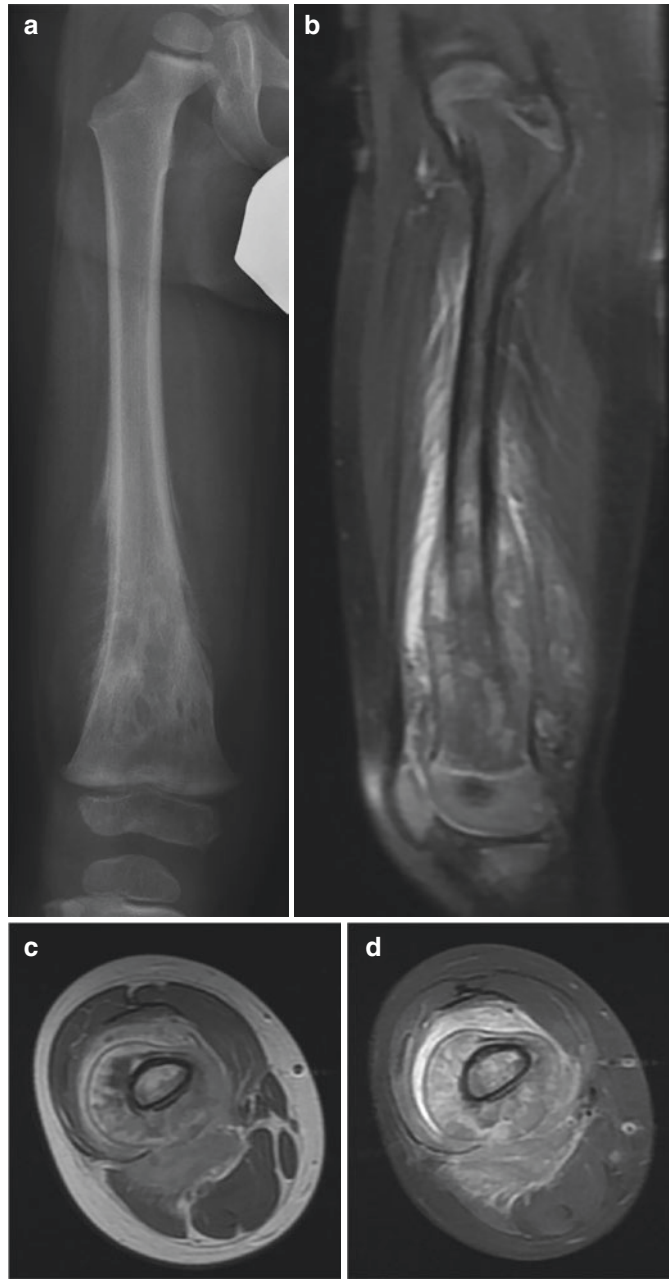
Local recurrence occurs in about 20% of cases treated with radiation (without surgery) plus chemotherapy. It is rare after wide surgery plus chemotherapy (without radiation). The postoperative association of radiotherapy when the surgical margins are evaluated as inadequate or the histological response to chemotherapy is scarce seems to decrease the risk of local relapse.

Metastases, usually multiple or disseminated, appear most frequently in the lungs, followed by the skeleton and the lymph nodes. Treatment with aggressive chemotherapy and bone marrow transplantation is still experimental but seem to improve the survival in high-risk patients. A more favorable prognosis can be expected in children, distal appendicular localizations, small tumor volume, normal H.S.R. and HDL values, use of adequate surgery, and good to complete response to preoperative chemotherapy.

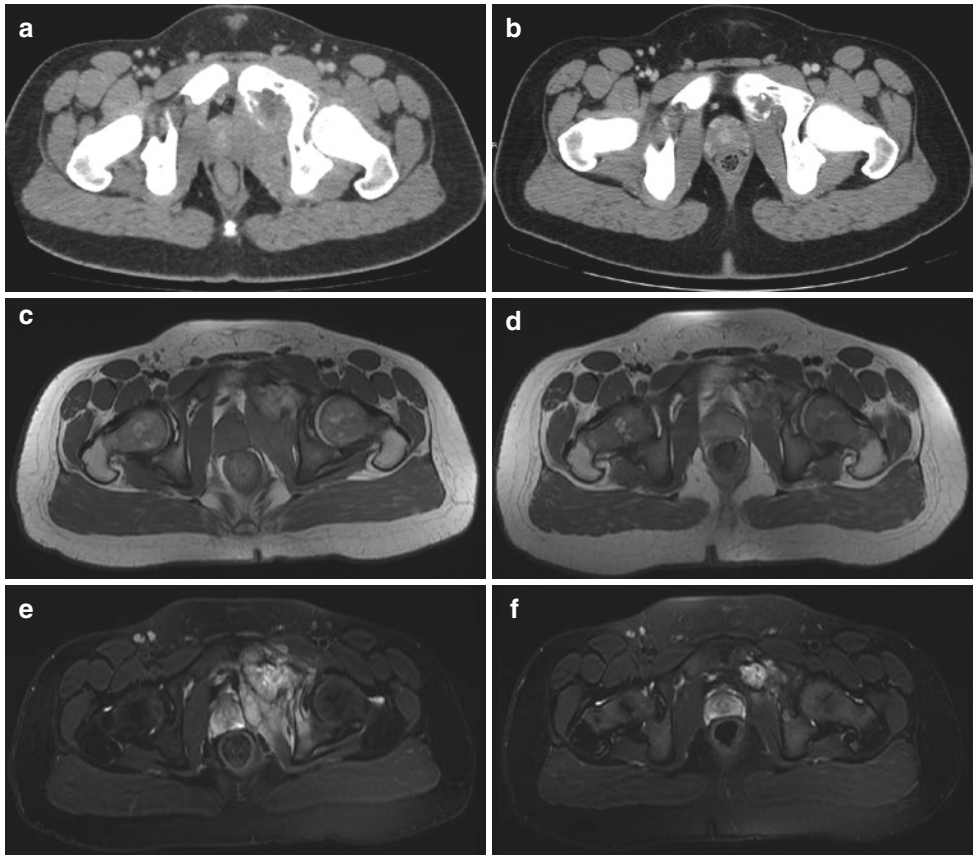
Key points	
• Clinical	Young patients, pain, swelling and general symptoms
• Radiological	Variable, usually aggressive, with infiltrative pattern
• Histological	Monomorphic blue round cell tumor
• Differential diagnosis	Langerhans cell histiocytosis, osteomyelitis, lymphoma

Immunohistochemical panel	
• CD99	+
• Caveolin-1	+
• Fli1	+
• CAM 5.2	+/−
• S100	+/−
• LAC	−
• TdT	−
• PAX7	+
• NKX2-2	+

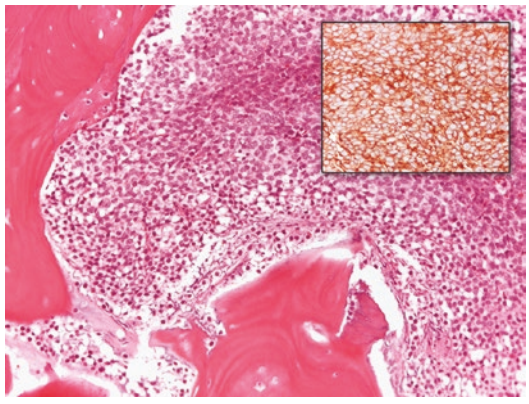
Chromosomal translocations		
• t(11,22)(q24;q12)	EWSR1-FLI1	85%
• t(21;22)(q22;q12)	EWSR1-ERG	10%
• t(2;22)(q35;q12)	EWSR1-FEV	Rare
• t(7;22)(p22;q12)	EWSR1-ETV1	Rare
• t(17;22)(q21;q12)	EWSR1-ETV4	Rare
• t(2;16)(q35;p11)	FUS-FEV	Rare
• t(16;21)(q11;p22)	FUS-ERG	Rare



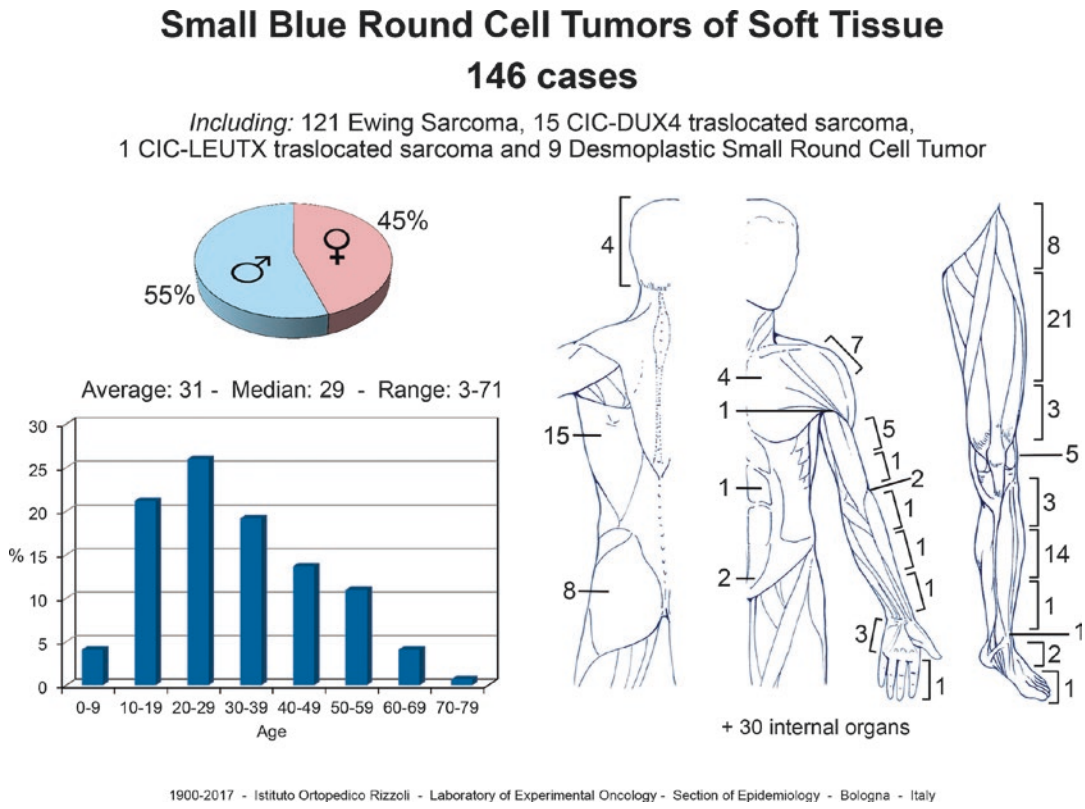
3 year old patient. EFT of the right femur at presentation. Standard radiograph (**a**) MR T1 FSE sagittal view (**b**) and T1 (**c**) and T1 FSE (**d**) axial views. Radiograph and CT. Metaphyseal tumor of the tibia. The lesion is poorly limited, partially sclerotic (not rare in Ewing sarcoma because of the reaction of the remaining bone), destroys the cortex and invades soft tissues



15 year old patient. EFT of the left pelvis. Pre-chemo and post chemo CT with contrast injection (**a** & **b**), T1 MR (**c** & **d**) and T2 MR FAT SAT (**e** & **f**) axial images. Radiograph (**a**), CT with contrast injection (**b**), and T1 (**c**) and T2 (**d**) W axial MR images



Highly cellular tissue composed of a uniform mat of small round cells, infiltrating in between the host bony trabeculae in a permeative fashion. Cytoplasms are rather scarce, pale, often clear, and with faded boundaries. Nuclei are hyperchromatic, twice as large as those of lymphocytes, round-oval in shape, with pulvurent chromatin, and one or more very small nucleoli. Nearly all nuclei appear to be of the same size and with a rather regular shape. Mitotic figures are rare. Immunohistochemical strong and diffuse membranous positivity for CD99 in the neoplastic cells (*inset*)



39.2 Extraskeletal Ewing Sarcoma

Definition: High-grade malignant poorly differentiated tumor composed of small round cells. It is the soft tissue counterpart of the more frequent Ewing sarcoma of bone.

Epidemiology: Soft tissue Ewing sarcoma is by far less frequent than the bone variant. Most common in adults but it may occur at any age. It is more frequent in males.

Location: Any soft tissue site can be involved, but the most common are the paravertebral region, retroperitoneum, and the chest wall, followed by the extremities.

Clinical: Large, destructive mass.

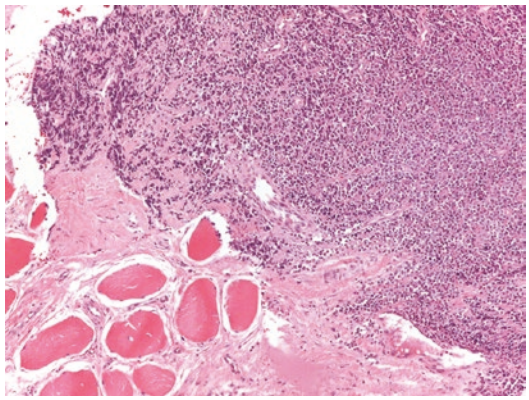
Histopathology: Grossly it is a large, destructive mass, frequently with necrosis, and hemorrhage. Histologically, it is composed of a uniform cell population of round blue cells with small amounts of clear to light eosinophilic cytoplasm, regular nuclear contours, finely dispersed chromatin, and small nucleoli, growing in sheet or in a vaguely lobular growth pattern, with a well-developed capillary vascularization.

Course and Staging: 10-year survival rate of 60% with current treatment regimens.

Treatment: Current multimodal therapy (surgery, chemotherapy, and radiotherapy).

Immunohistochemical panel	
• CD99	+
• Caveolin-1	+
• Fli1	+
• CAM 5.2	+/–
• S100	+/–
• LAC	–
• TdT	–
• PAX7	+
• NKX2-2	+

Chromosomal translocations		
• t(11;22)(q24;q12)	EWSR1-FLI1	85%
• t(21;22)(q22;q12)	EWSR1-ERG	10%
• t(2;22)(q35;q12)	EWSR1-FEV	Rare
• t(7;22)(p22;q12)	EWSR1-ETV1	Rare
• t(17;22)(q21;q12)	EWSR1-ETV4	Rare
• t(2;16)(q35;p11)	FUS-FEV	Rare
• t(16;21)(q11;p22)	FUS-ERG	Rare



Population of uniform small round to ovoid undifferentiated blue cells infiltrating soft tissues, nearly identical to the more frequent bony counterpart

39.3 Other Small Blue Round Cell Tumors in Bone and Soft Tissues

Definition: Round cell sarcomas lacking the specific translocations of Ewing sarcoma and other round cell sarcomas represent new specific entities. The most frequent are CIC-DUX4 fusion-positive sarcomas (characterized by the fusion of the CIC gene with one of the DUX4 retrogenes, located either on 4q35 or on 10q26.3) and BCOR-CCNB3 fusion-positive sarcomas (characterized by a paracentric inversion of the X chromosome).

39.4 CIC-DUX4-Positive Sarcomas

Epidemiology: Very much rarer than Ewing sarcoma. Mean age at presentation is 32 years. There is a slight male predominance.

Location: The vast majority affects soft tissues, rarely viscera, and exceptionally bone. Trunk and the extremities are the most frequent site involved.

Clinical: Very frequent lung metastasis at presentation.

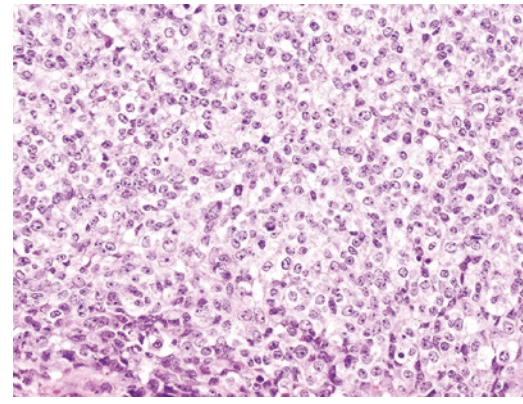
Histopathology: Histologically composed of a proliferation of roundish cells arranged in lobules separated by thin fibrous septa, with confluent geographic areas of necrosis. Neoplastic cells show moderate pleomorphism, vesicular nuclei, abundant cytoplasm, often with clear cell change. A myxoid stroma is frequently present.

Course and Staging: Generally have a dismal prognosis (overall survival at 5 years is about 43%).

Treatment: Multimodal therapy (surgery and chemotherapy). Sometimes responsive to ES CT-regimens (RECIST) but when included in clinical protocols designed for ES, it seems justified to evaluate these patients separately.

Immunohistochemical panel	
• CD99	+/–
• WT1 (N and C terminus)	+/–
• ETV4	+
• CAM 5.2	+/–
• DUX4	+

Chromosomal translocations	
• t(4;19)(q35;q13)	CIC-DUX4
• t(10;19)(q26;q13)	CIC-DUX4L



Proliferation of roundish cells, with moderate pleomorphism, vesicular nuclei, and abundant often clear cytoplasms

39.5 BCOR-CCNB3-Positive Sarcomas

Epidemiology: Very much rarer than Ewing sarcoma. Mean age at diagnosis is 15 years. There is a strong male predominance (male to female ratio is 31 to 5), due to the fact that the characteristic mutation is a paracentric inversion of the X chromosome.

Location: More frequent in bone than in the soft tissues.

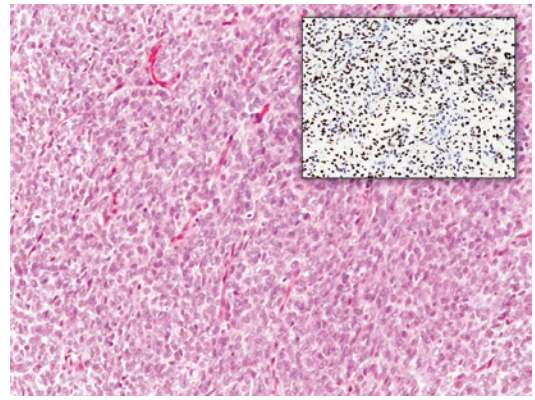
Histopathology: Histologically characterized by a proliferation of relatively monotonous undifferentiated round and spindle cells, so that the tumor shows morphological features similar to synovial sarcoma and Ewing sarcoma. Neoplastic cells show finely dispersed chromatin and occasional tiny nucleoli. They are arranged without a distinct architectural pattern or in short fascicles with whorling, sometimes comprised of areas with high cellularity alternating with less cellular areas. Mitotic activity is often brisk. Small thin-walled arciform and plexiform vessels are generally present.

Course and Staging: Seem to have a better prognosis than Ewing sarcoma (5-year overall survival is about 72%). Recurrence rate is about 30% and metastases (often to the lung) are present in about 35% of cases.

Treatment: Multimodal therapy (surgery and chemotherapy).

Immunohistochemical panel	
BCOR	+
CCNB3	+
PAX8	+/−
SATB2	+/−

Chromosomal translocations	
t(X;X)(p11.4;p11.22)	BCOR-CCNB3



Proliferation of relatively monotonous undifferentiated round and spindle cells arranged in short fascicles. Immunohistochemical nuclear positivity for CCNB3 in the neoplastic cells (*inset*)

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Biology of Ewing Sarcoma

40

Katia Scotlandi

Sarcomas are a heterogeneous group of malignant tumors that are derived from mesenchymal tissues, including bone, muscle, and cartilage. In the last decade, we have gained significant new insights into the genetic abnormalities that underlie the pathogenesis of these tumors. Specific molecular alterations have been associated with specific histological subtypes of sarcomas, leading to a new classification of many sarcomas. Conventionally grouped in either soft-tissue or bone sarcomas according to the site of their origin, these tumors can now be genetically distinguished in two main groups: those carrying tumor-specific recurrent chromosome aberrations and those with complex karyotypes and variable genetic alterations [1, 2]. Sarcomas with recurrent molecular changes include, among others, Ewing sarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, myxoid liposarcoma and myxoid chondrosarcoma.

Ewing sarcoma is a genetically well-characterized disease. Its main driver alteration is a specific chromosomal translocation that fuse a member of the FET family of proteins (encoded by FUS, EWSR1, and TAF15), which are RNA-binding proteins involved in transcription and splicing, with different members of the ETS (E26-specific) family of transcription factors, which are involved in cell proliferation, cell differentiation, cell-cycle control, angiogenesis and apoptosis—most commonly FLI1 (85% of cases) [3]. In the remaining cases of Ewing sarcomas that are negative for EWSR1–FLI1 fusions, variant fusions between EWSR1 and other members of the ETS family occur, most commonly ERG (encoding transcriptional regulator ERG) followed by ETV1, ETV4, or FEV [4–7]. Some variant fusions were described between ETS genes and EWSR1 paralogues of the FET gene family (namely, FUS and TAF15). Ewing sarcomas harboring EWSR1–FLI1 or EWSR1–ERG were found to have similar clinical behavior [8].

Large-scale genomic sequencing studies have demonstrated that Ewing sarcoma has one of the lowest mutation rates among all cancers (0.15 mutations/Mb) [9–11]. This highlights the relevance of fusion transcripts and epigenetic mechanisms in controlling Ewing sarcoma pathogenesis and progression. Chimeric fusion proteins act as aberrant transcription factors and deregulate hundreds of genes through DNA binding at either ETS-like sequences that contain a single GGAA motif or at GGAA microsatellites (which are composed of multiple iterative GGAA motifs) [12, 13]. Comprehensive epigenome profiling [14–16] has revealed that EWSR1–FLI1 drives widespread epigenetic reprogramming by inducing de novo enhancers (Ewing-specific enhancers) and by repressing enhancers that are active in

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many cell types, including putative mesenchymal cell of origin. As a result, EWS-FLI orchestrates multiple oncogenic hits that lead to the transformation and disruption of normal developmental processes.

Despite being a necessary condition, EWS-FLI is however, not sufficient to generate a fully transformed phenotype and requires adjuvant factors, which may include mutations of *STAG2* (Cohesin subunit SA2) and *TP53* genes, which are detected at diagnosis in 15–21% and 5–7% of cases, as well as deletion of CDKN2A, a cyclin-dependent kinase that regulates cell proliferation, in 10–22% of cases, respectively [9–11]. In addition, the presence of an intact IGF pathway as well as of CD99, a 32-kD integral membrane glycoprotein that is highly expressed in most cases of Ewing sarcoma, is also required for EWS-FLI transformation [17, 18]. In addition, Ewing sarcoma is frequently characterized by chromosomal gains or loss, such as chromosome 8, chromosome 2, chromosome 1q, and chromosome 20 gains and chromosome 16q loss. These alterations have been described as associated with different patient outcome [19, 20].

The presence of specific chimeric product is very attractive from a therapeutic point of view. Unfortunately, the chimeric transcription factors that give raise to Ewing sarcoma are not druggable at the best of our current knowledge. Thus, the most interesting therapeutic options are small-molecule inhibitors, such as YK-4-279 [21], which blocks protein–protein interactions with EWSR1–FLI, or druggable pathways regulated by EWS-FLI1, such as the IGF-1R mediated signaling pathway. Antibodies or tyrosine kinase inhibitors directed against the IGF-1 receptor protein have shown therapeutic potentials in around 15% of patients [22, 23]. Several studies have focused on targeting the epigenetic deregulation present in Ewing sarcoma. For example, therapeutic option can be offered by inhibiting EWS-FLI activity by using inhibitors of lysine-specific histone [24]. Additionally, Ewing sarcoma cells are particularly sensible to poly(ADP-ribose) polymerase (PARP) inhibitors [25, 26]. PARPi have been preclinically explored as enhancers of drug sensitivity in combination with agents such as trabectedin [27] or temozolomide [28].

Finally, new immunotherapeutic approaches have been tested in preclinical models. Unfortunately, Ewing sarcomas are considered as "immune deserts" or "cold" tumors, typically depleted of immune infiltrates. Programmed cell death protein 1 (PD1) and programmed cell death 1 ligand 1 (PDL1) are expressed only in a fraction of Ewing sarcoma cells [29, 30] and therefore checkpoint inhibitors may not be the best approach in this type of tumors. Further studies to establish whether other mechanisms are in place in Ewing sarcoma to elude immune response are required.

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Chemotherapy of Ewing Sarcoma

41

Stefano Ferrari and Emanuela Palmerini

Ewing sarcoma (ES) shares with osteosarcoma similarities in the strategy of treatment.

Neoadjuvant chemotherapy with the aim of reducing tumor mass, increasing the likelihood of local control, and facilitating conservative surgical approaches is considered the standard in patients with ES [1].

Vincristine, dactinomycin, adriamycin, cyclophosphamide, ifosfmide, and etoposide are the drugs that, in different combinations, are recommended for the neoadjuvant treatment of ES [2].

In patients who undergo surgery of the primary tumor, the pathological evaluation of the chemotherapy-induced tumor necrosis identifies patients with different probability of survival, higher in those with a good pathological response [3, 4].

The more recent chemotherapy protocols are based on different strategies of dose intensification [5–7]. The results of Protocol AEWS0031 indicate that a dose intensification obtained by an interval compression (every 2 weeks) of the chemotherapy courses is more effective compared to a standard approach based on chemotherapy courses given every 3 weeks. This strategy seems to be more beneficial in pediatric patients, rather than in adults [6].

In a joint study between Italian Sarcoma Group (ISG) and Scandinavian Sarcoma Group (SSG), the dose intensification with high-dose chemotherapy and peripheral blood stem cell rescue (HCT) was applied only to patients with a poor response to a six-drug primary chemotherapy. The results showed that poor responder patients had the same probability of event-free survival obtained in good responder patients [7].

To investigate the role of HCT in ES in 1999, a randomized clinical trial (EURO-EWING) was activated. The results of the group of patients randomized to receive or not high-dose chemotherapy have been presented at the ASCO meeting in 2016 [8]. In localized patients with a poor pathological response or large tumor volume who received HCT, the survival was significantly higher compared to that obtained in those who were treated with standard chemotherapy. Interestingly, the probability of survival reported in the HCT arm of the EURO-EWING study is similar to that obtained in the poor responder group of the joint ISG/SSG study [7].

The strategy of treatment for patients with synchronous metastases is based on chemotherapy combined with local and metastatic control by the use of aggressive surgical and/or radiotherapy approach.

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The probability of survival of patients with metastastic disease is lower than 30% even when intensive but standard chemotherapy regimens are used [9, 10].

Use of HCT has been adopted and in a recent joint study of the Italian Sarcoma Group and Scandinavian Sarcoma Group, a survival higher than 50% has been reported in patients with lung metastases and/or one bone metastasis [11]. In patients with very high risk, such as those with multivisceral involvement, multiple skeletal lesions, and/or bone marrow infiltration, the probability of survival reached 30% when high-dose chemotherapy was delivered in addition to aggressive surgery and/or radiotherapy for all the sites of disease [12]. The recent results of the EURO-EWING study for metastatic patients pose some doubts about the use of HCT in this setting, since the arm randomized to receive HCT did not obtain better results compared to that randomized to receive standard chemotherapy. These data have to be considered with some caution since the study design was biased by a different use of the total lung irradiation (TLI) that was not permitted in those patients randomized for HCT [13].

In case of patients with only pulmonary recurrent disease, the relapse-free interval is the main prognostic factor [14]. Standard treatment of patients with isolated lung metastases is polychemotherapy, to be selected considering the previous chemotherapy treatment [1]. High-dose treatments with autologous stem cell rescue are still investigational, but frequently adopted in several centers. In case of isolated lung metastases with a long (>36 months) relapse-free survival, chemotherapy can be omitted and surgical resection with radiation therapy of the lungs is recommended [15].

For patients with extrapulmonary metastases, prognosis is dismal and also in this condition, chemotherapy is to be defined according to the previous treatment. High-dose treatments with peripheral stem cell rescue have been used by various investigators, with encouraging results. Generally, they are reserved to optimal responders after some kind of induction therapy willing to enter open clinical studies on such approaches.

Irinotecan and temozolamide, topotecan and cyclophosphamide and high-dose ifosfamide have shown activity in recurrent ES of bone [16–19].

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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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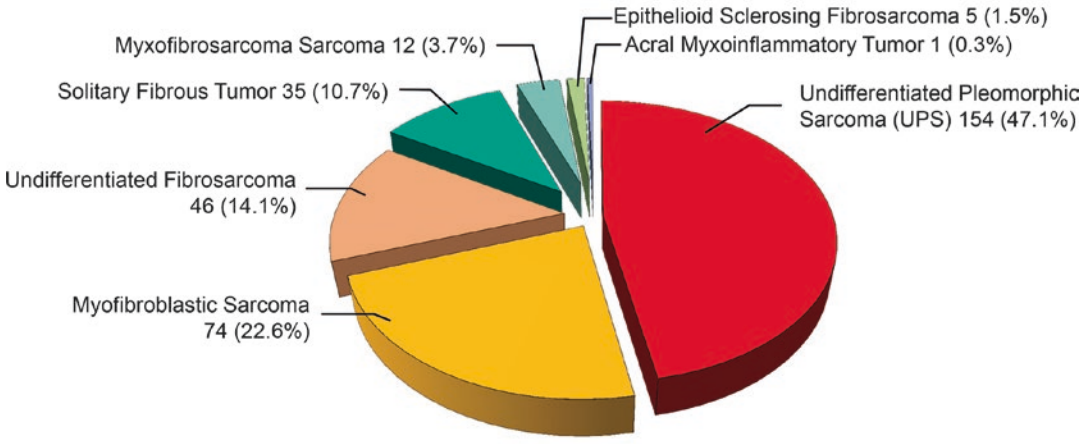
FIBROBLASTIC / MYOFIBROBLASTIC SARCOMA OF BONE
327 cases



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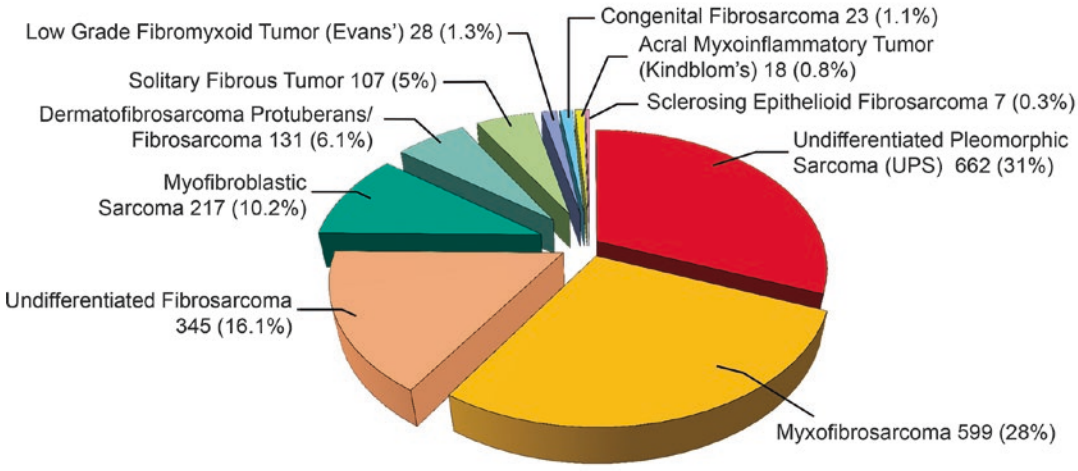
FIBROBLASTIC / MYOFIBROBLASTIC SARCOMA OF SOFT TISSUE
2.137 cases



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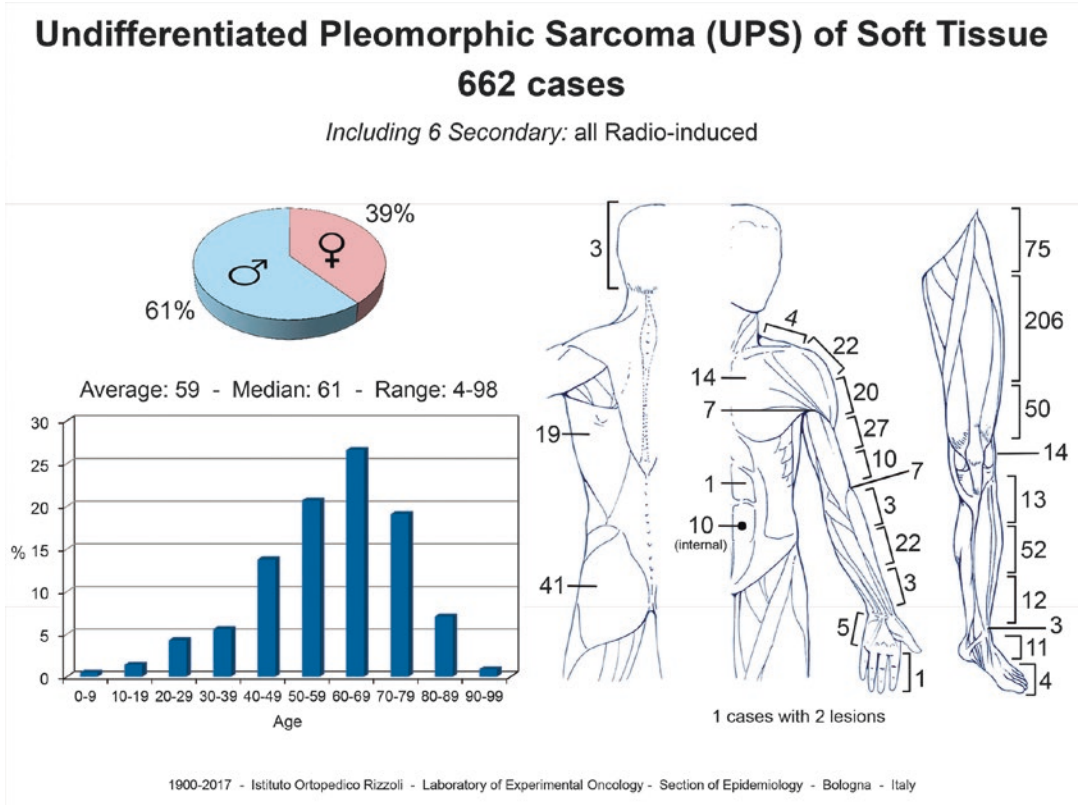
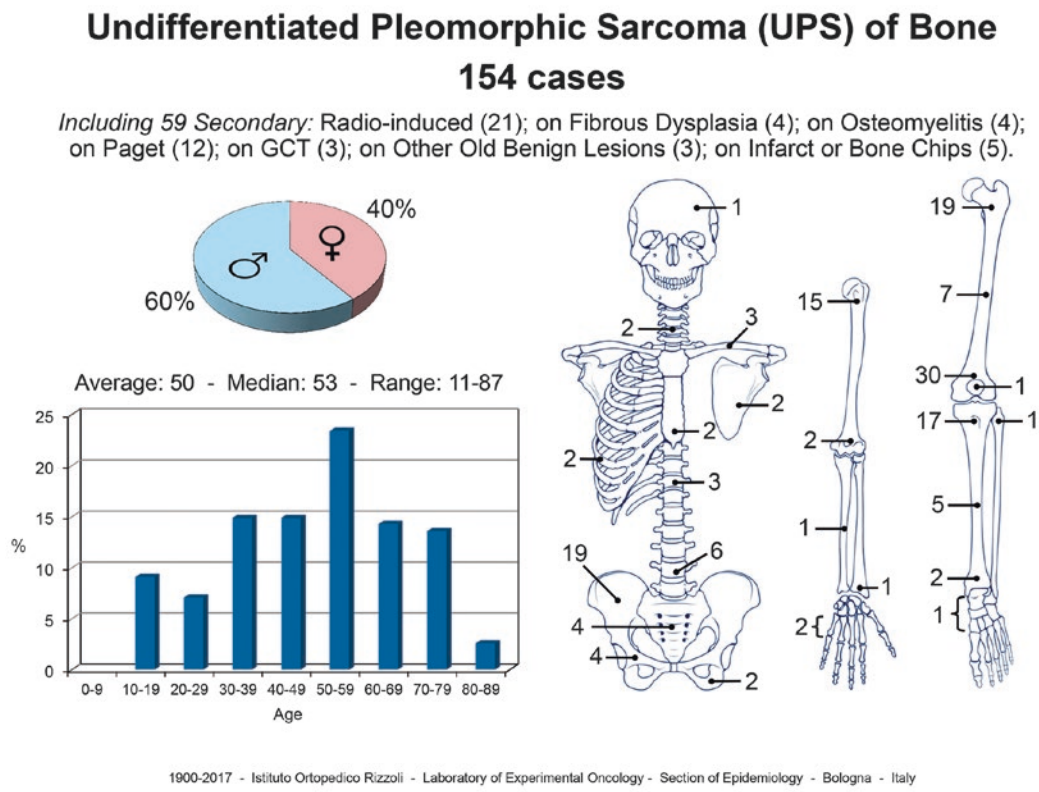
42.1 Undifferentiated Pleomorphic Sarcoma (UPS)

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-

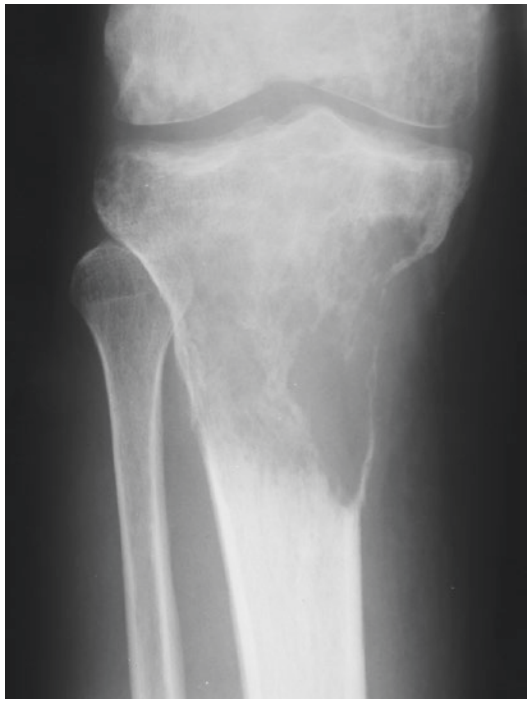
sue, with large cavities with fluid contents and a thick wall that are mistaken with a hematoma. On MRI: poorly defined margins, homogeneous, muscular intensity on T1 and heterogeneous high signal intensity on T2, dark central necrotic zones and strong enhancement at the periphery on contrast T1, internal 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).

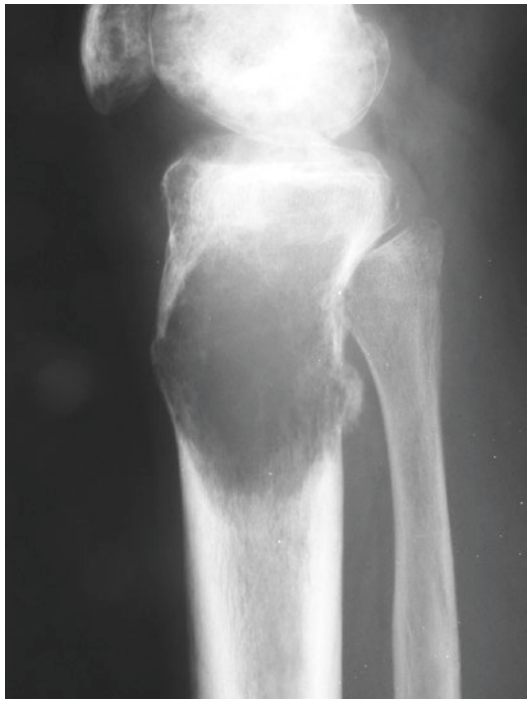
Course and Staging: The majority of UPS are high-grade sarcomas with a metastatic incidence that varies between 30 and 50%, with the common metastatic sites being lung, bone, and liver; regional lymph node metastases are decidedly uncommon. Usually, this tumor is stage IIB. IIIB presentation due to lymphatic 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.

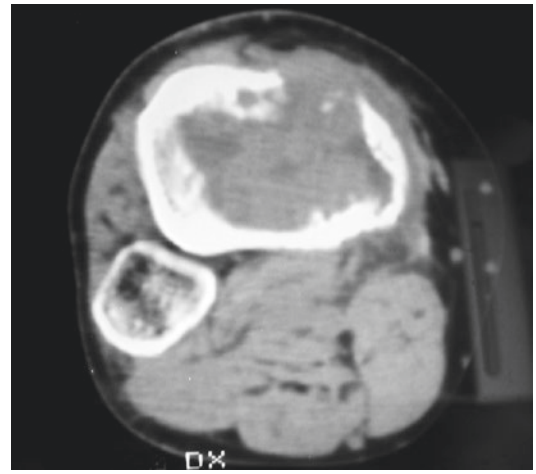
Key points	
• Clinical	Adults, pain and swelling
• Radiological	In bone pure lytic lesion; in ST no specificity
• Histological	High-grade spindle and pleomorphic cells
• Differential diagnosis	In bone, metastasis and all other primary purely osteolytic lesions of the adults. In ST, all other sarcomas



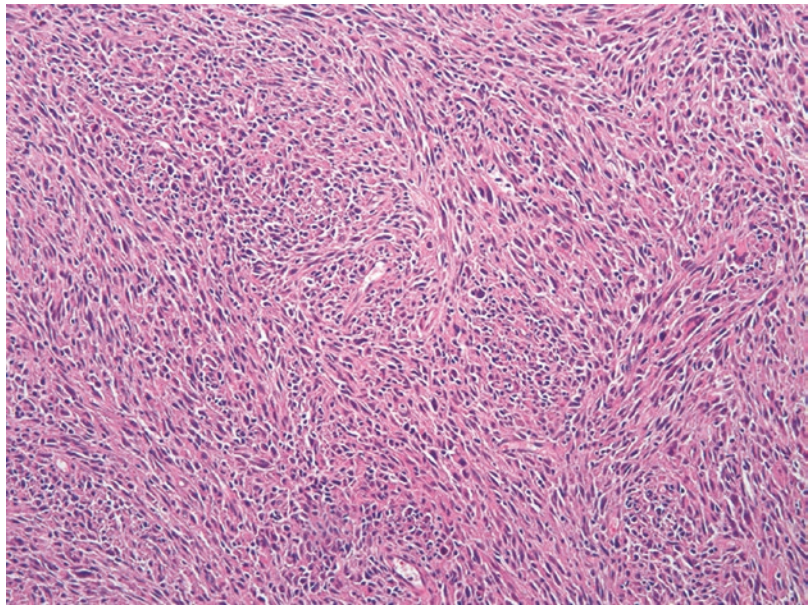
Radiographs and CT with contrast medium. Metaphyseal purely lytic, poorly limited lesion, destroying the cortex



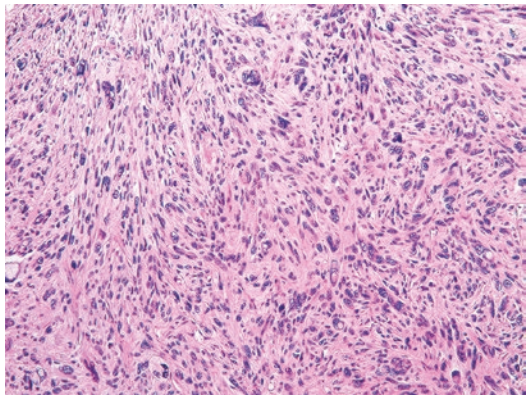
Radiographs and CT with contrast medium. Metaphyseal purely lytic, poorly limited lesion, destroying the cortex



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

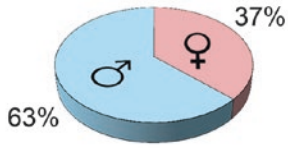
42.2 Undifferentiated Fibrosarcoma

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

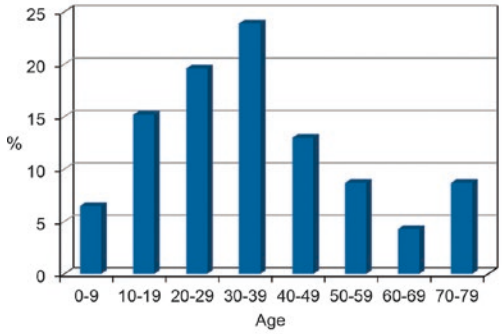
Epidemiology: <1% of adult soft tissue sarcomas. Medium age 40–45 years. No sex predilection.

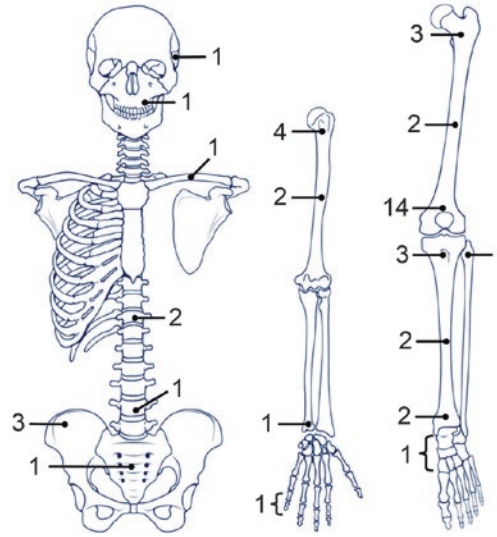
Undifferentiated Fibrosarcoma of Bone
46 cases

*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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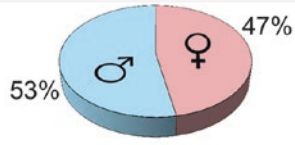
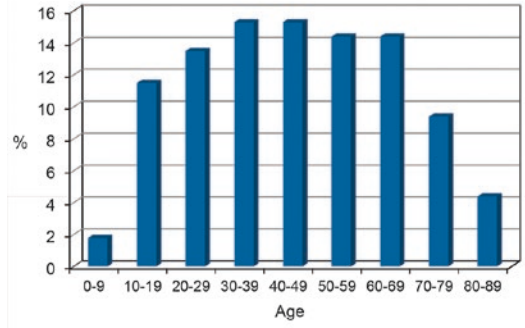
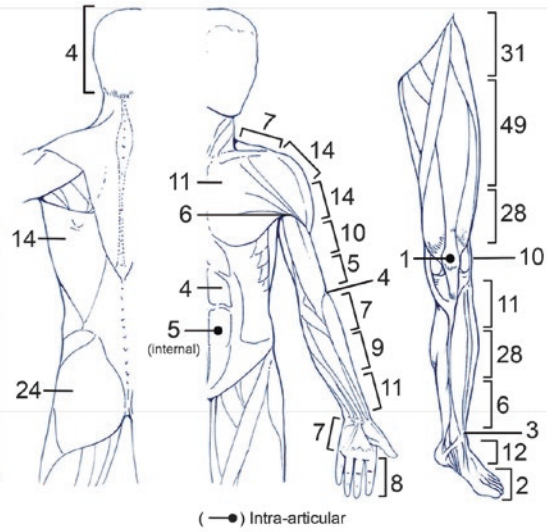
Undifferentiated Fibrosarcoma of Soft Tissue
345 cases

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.

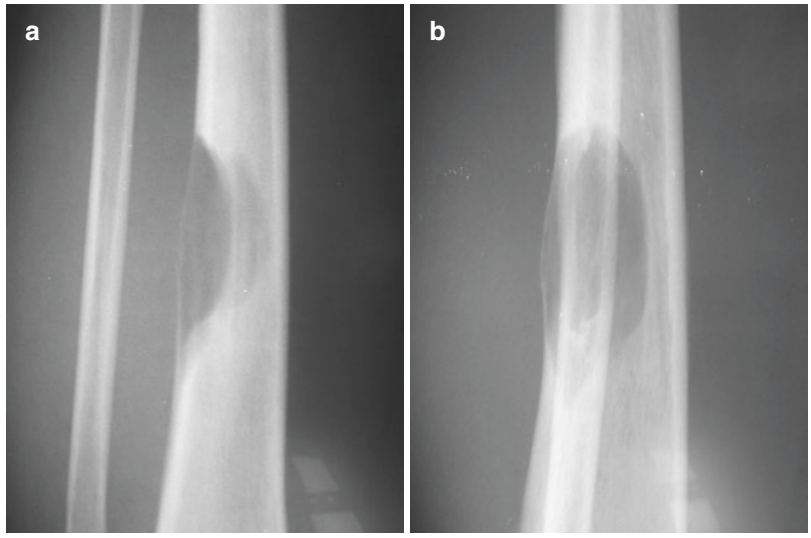
Histopathology: Fibrosarcoma tends to be firm and whitish when containing more collagen (low-grade); pink-gray and soft to encephaloid, when the cells prevail (high-grade). Low-grade well-differentiated tumor are firm and scar-like in consistency, white-yellow, with rounded limits, growing in an expansile 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%).

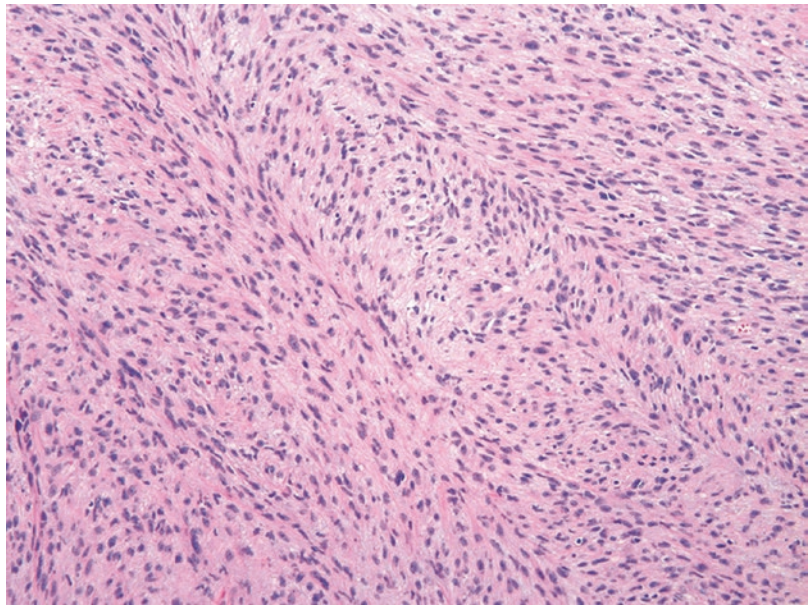
Treatment: Wide excision. In the adult and in a high-grade lesion, radical margins may be indicated. Radiotherapy is less effective and it is used as adjuvant in high-grade tumors in soft tissue lesions.

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.

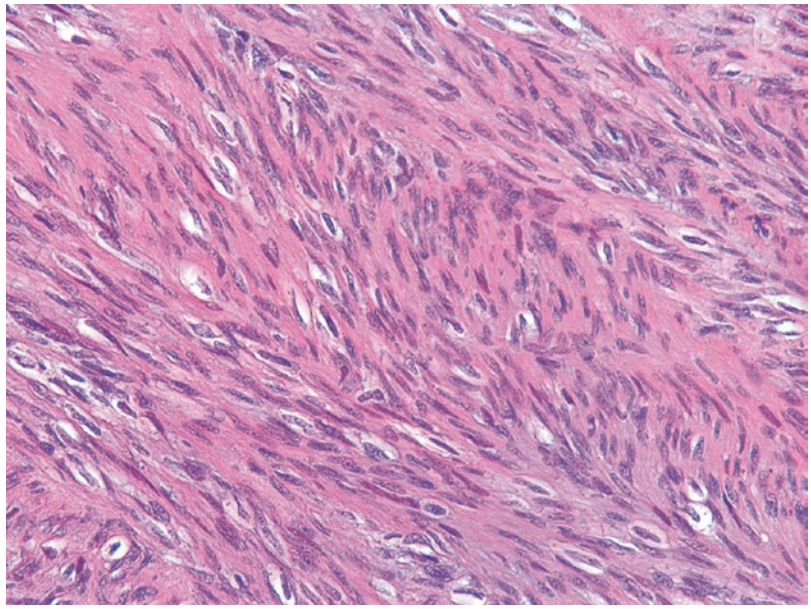
Key points	
• Clinical	Adults, pain and swelling
• Radiological	In bone pure lytic lesion; in ST no specificity
• Histological	High-grade spindle cells
• Differential diagnosis	In bone, metastasis and all other primary purely osteolytic lesions of the adults. In ST, all other sarcomas



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

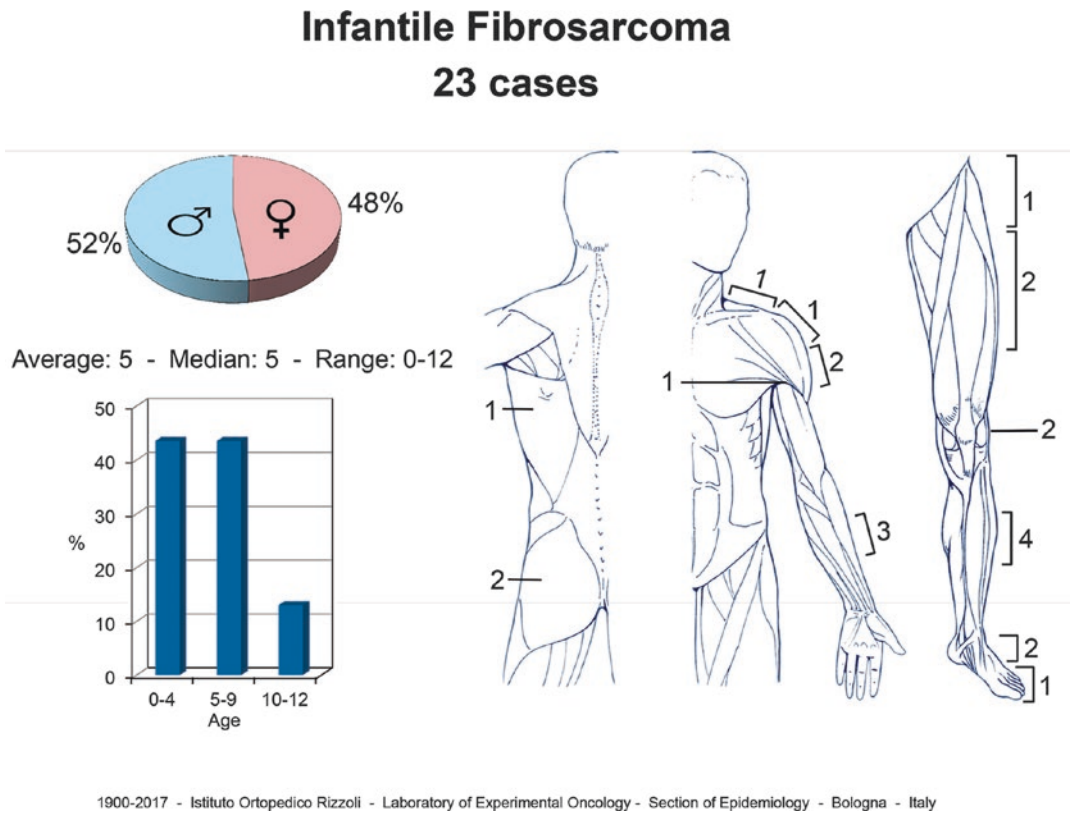


Spindle cell neoplasm with variable grade of atypia arranged in a herringbone pattern with intercellular fibrillary collagen

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.



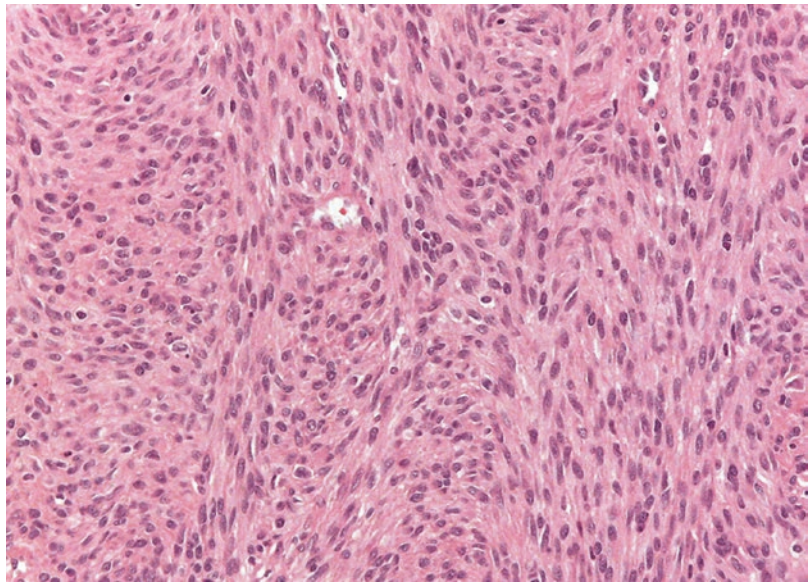
Location: Superficial or deep soft tissues of distal extremities, head and neck, trunk**.**

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%

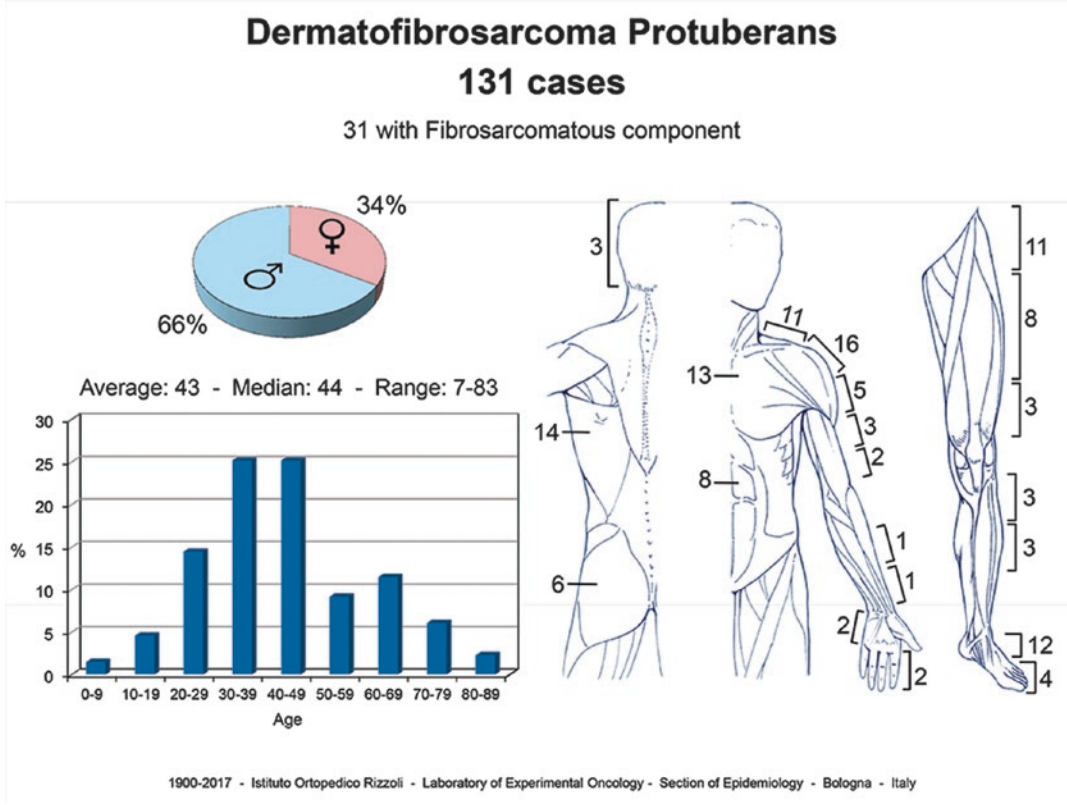


Spindle cell sarcoma with mild pleomorphism, growing in intersecting fascicles with a herringbone pattern

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

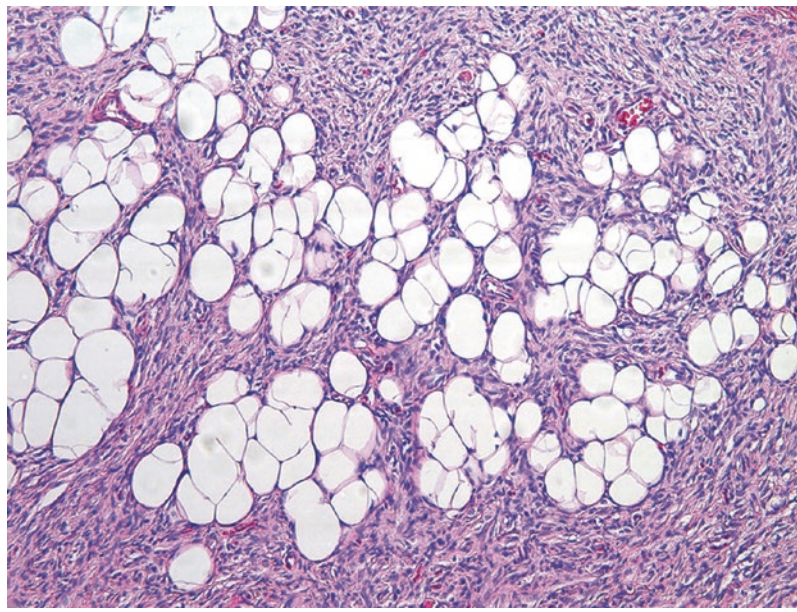
gene that encodes a growth factor. Ring chromosomes are predominantly observed in DFSP of adult patients, whereas the t(17;22) translocation is mostly seen in DFSP of children and in giant cell fibroblastoma.

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%



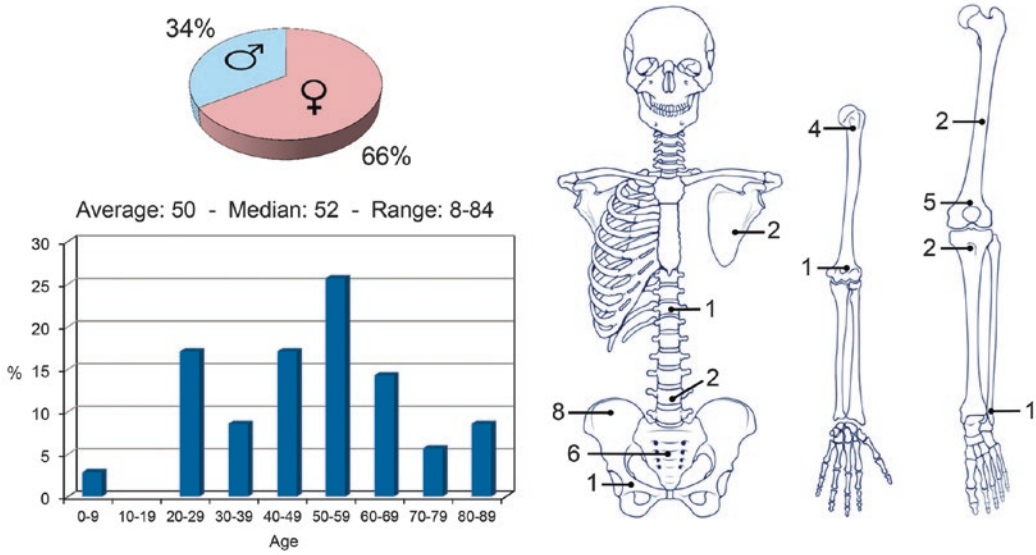
Bland-appearing spindle cells organized in a monotonous storiform pattern, with infiltrative margins that frequently surround lobules of fat

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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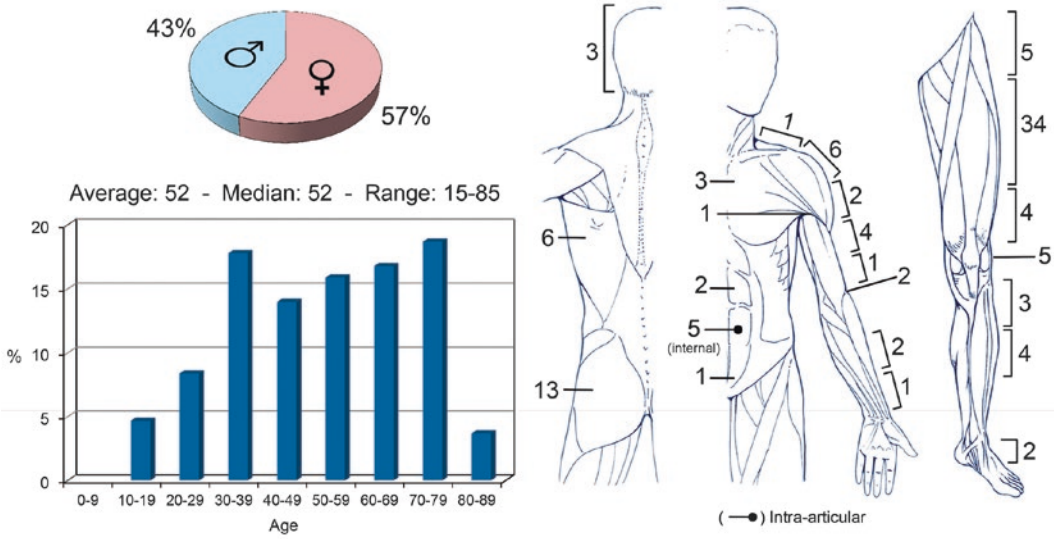
Solitary Fibrous Tumor of Soft Tissue
107 cases



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

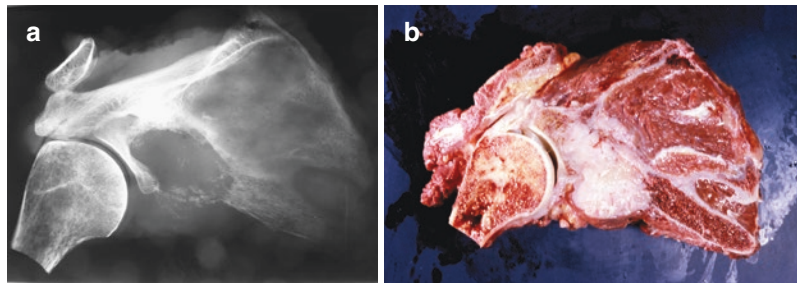
Clinical: Enlarging painless mass.

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.

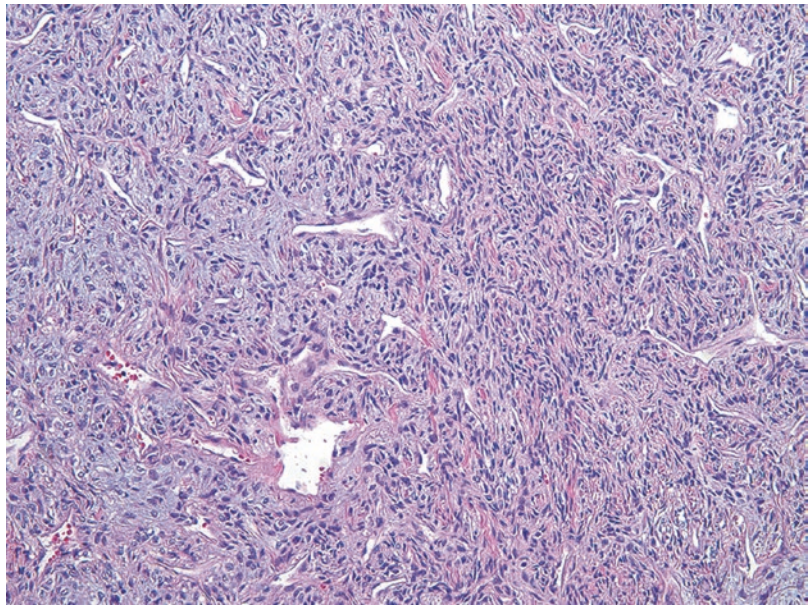
Histopathology: Soft, from pale to dull red or brownish red, heavily bleeding, thin pseudocapsule, cystic hemorrhagic necrotic areas. Thick, diffused network of capillaries, totally collapsed or wide-open sinusoids, surrounded by a compact proliferation of bland-appearing cells with oval nuclei, distinct 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	+

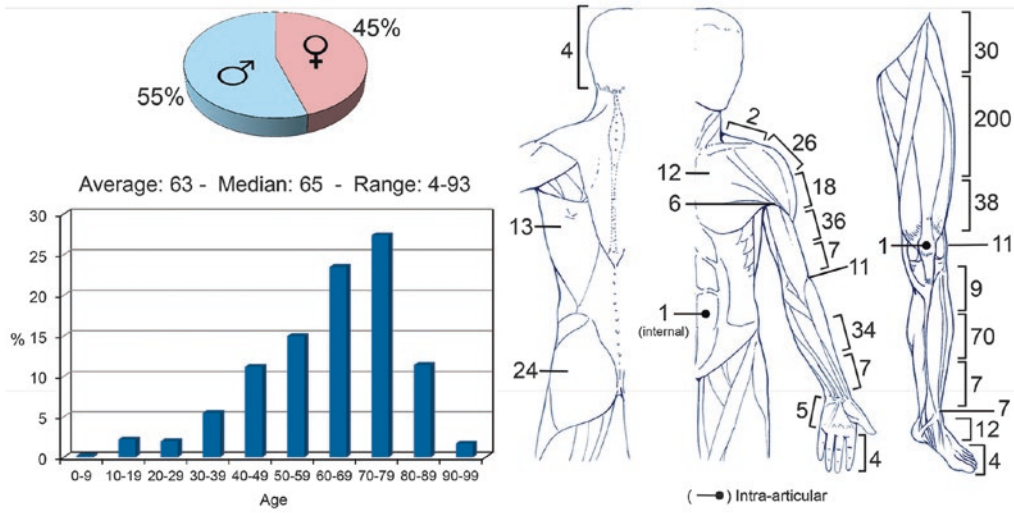
Genetic alteration		
• Intrachromosomal inversion	Inv12 (q13q13) NAB2-SATB6	90%

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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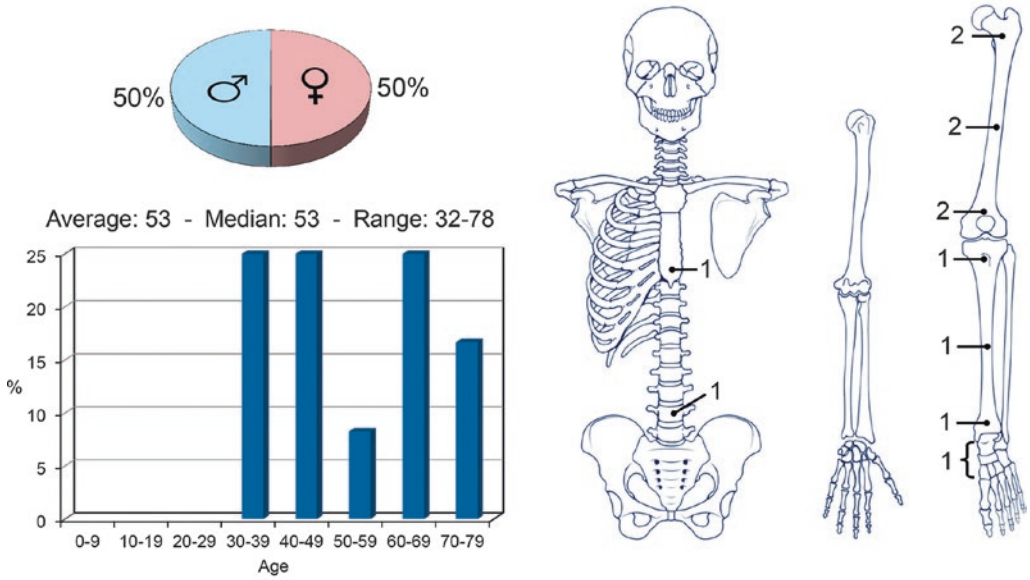
Myxofibrosarcoma of Bone
12 cases

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



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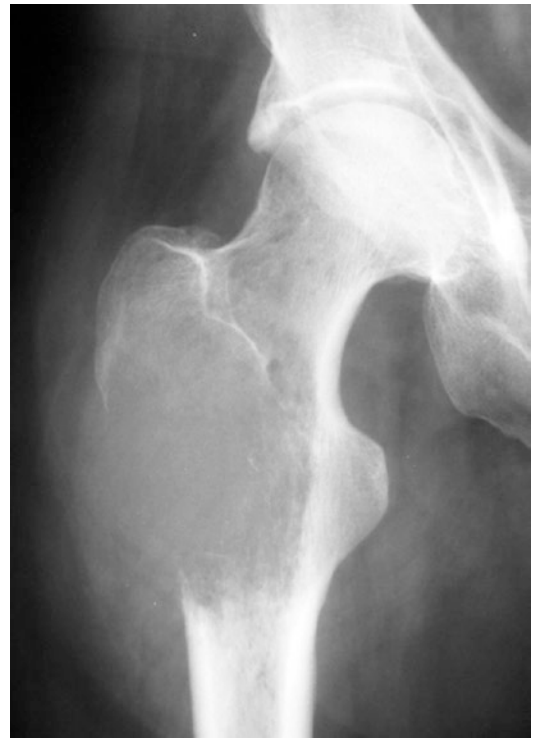
Location: The most frequent sites are the lower limbs, followed by upper limbs and limb girdles. Rare in trunk, head and neck, hands and feet. Most cases described in the retroperitoneum and in the abdominal cavity represent dedifferentiated liposarcomas. About half of cases arises in dermal/subcutaneous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

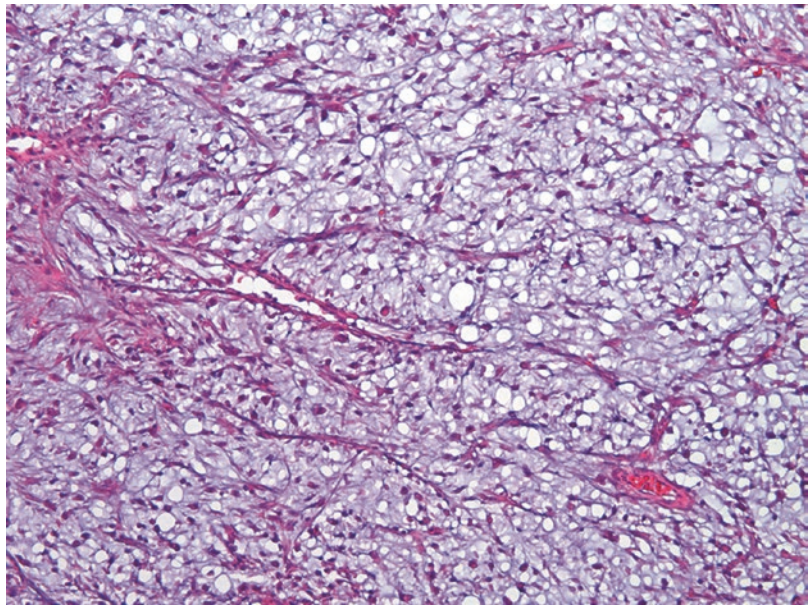
Histopathology: Grossly they appear as multiple gelatinous to firm nodules with infiltrative margins. Histologically all cases share distinct morphological features: multinodular growth with incomplete fibrous septa, a myxoid stroma composed of hyaluronic acid and prominent elongated, curvilinear, thin 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

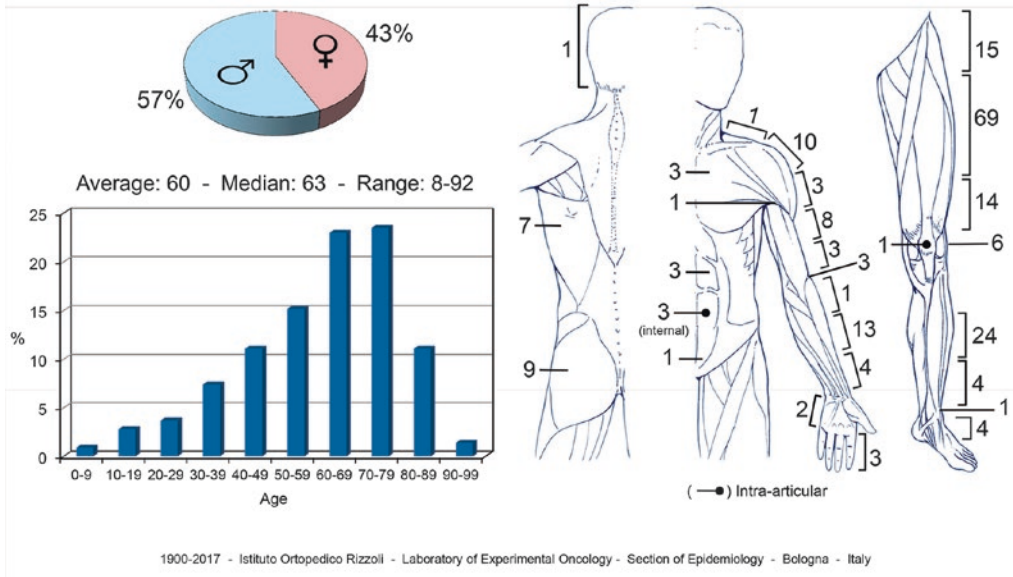
42.7 Myofibroblastic Sarcoma

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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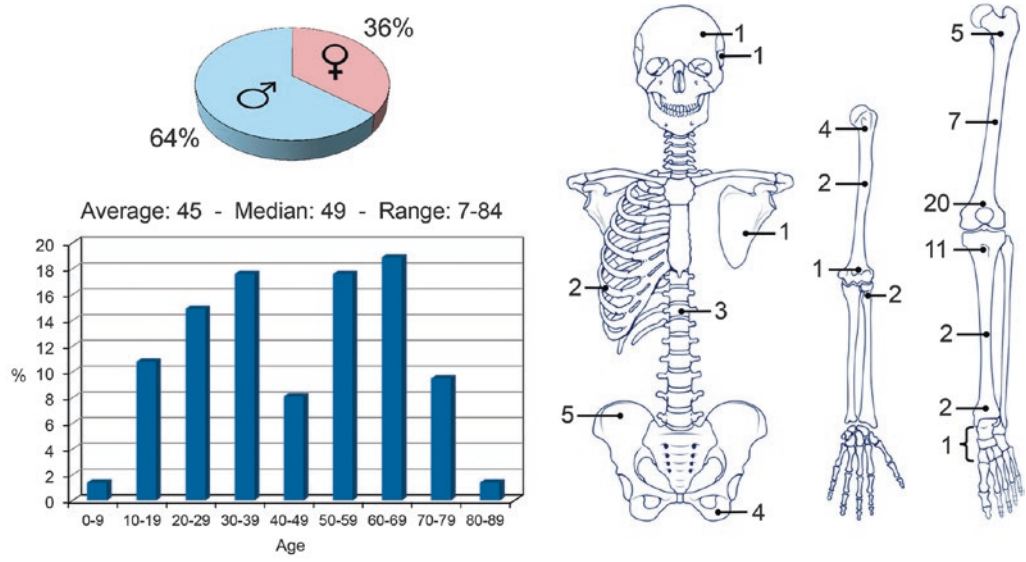
Myofibroblastic Sarcoma of Bone
74 cases

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



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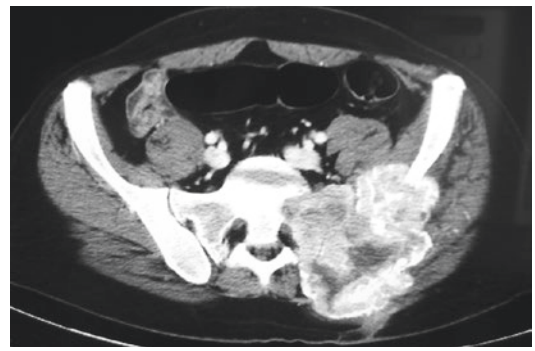
Location: Low-grade myofibroblastic sarcomas most commonly occur in the head and neck region, including the oral cavity, pharynx and parapharyngeal regions, proximal extremities and trunk; occasional cases can occur in the abdomen or pelvis. They usually arise in the deep soft tissues but cases have 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.

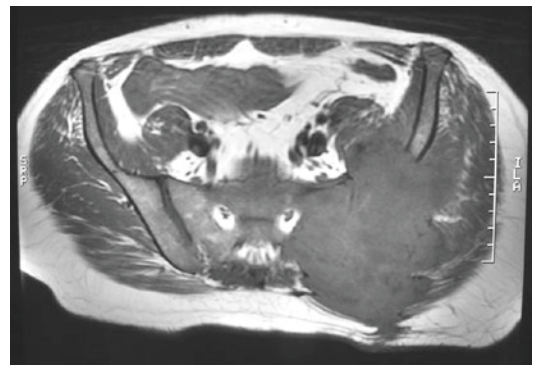
Histopathology: Grossly, low-grade myofibroblastic sarcomas are firm with a pale fibrous-appearing cut surface, ill-defined infiltrative margins, or sometimes with pushing margins. High-grade myofibroblastic sarcomas are large solid tumors with hemorrhage and necrosis. Histologically, low-grade myofibroblastic 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.

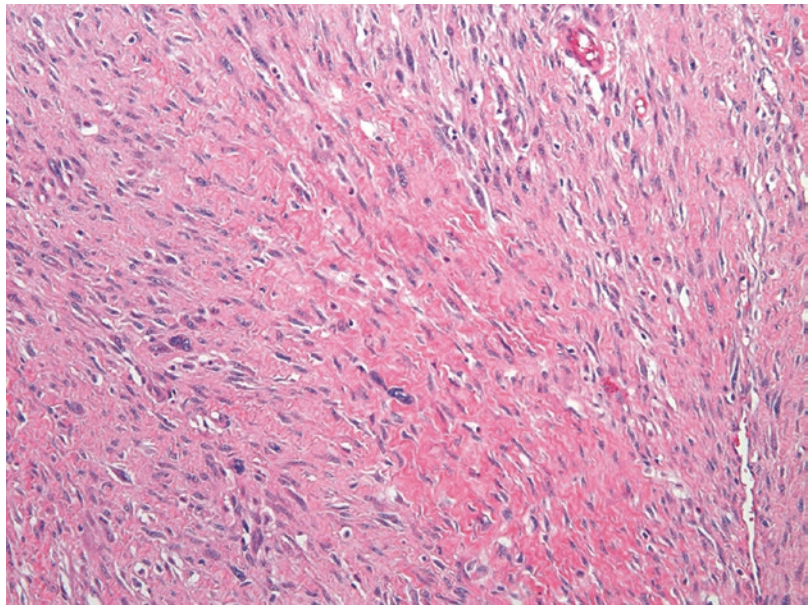


Axial CT with contrast medium and T1W MR. Purely lytic lesion of the left iliac wing and sacrum, with a strong heterogeneous uptake of contrast medium, destruction of the bone and soft tissue invasion



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	–



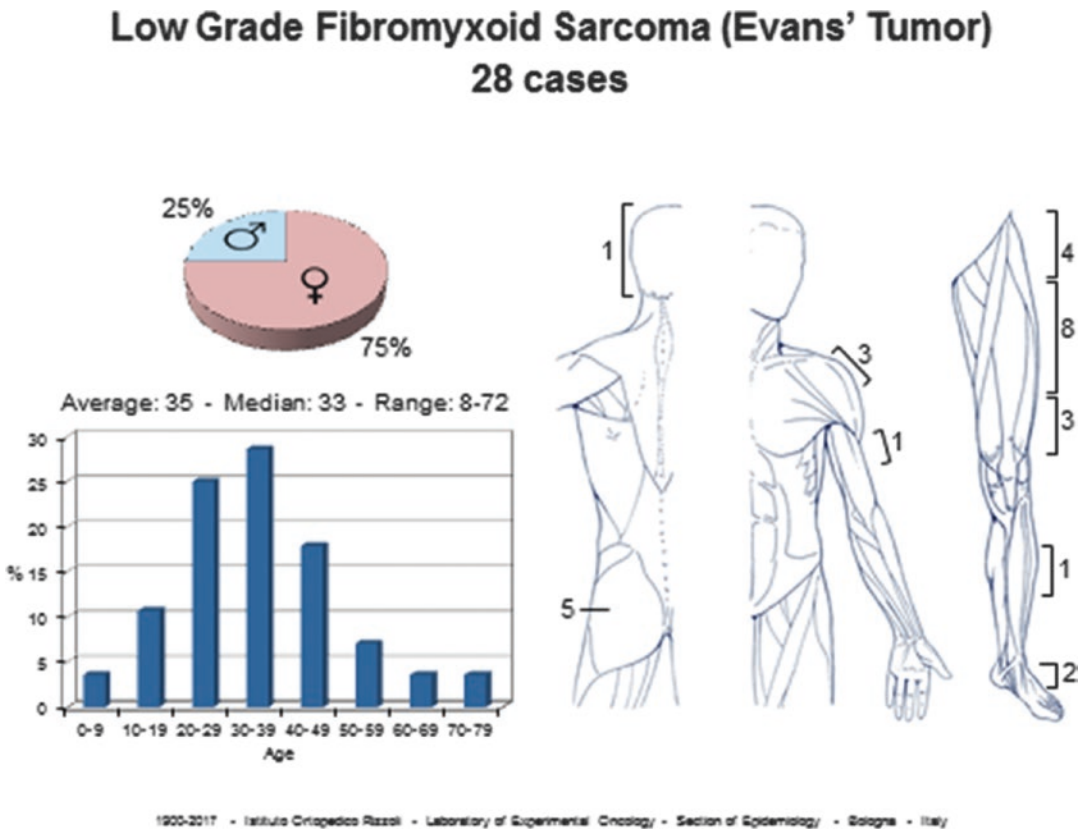
Fascicular to storiform arrangement of malignant spindle cells with short tapered wavy nuclei. Stroma is variably collagenous. Some tumors show a tissue culture-like growth pattern that resembles nodular fasciitis

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.

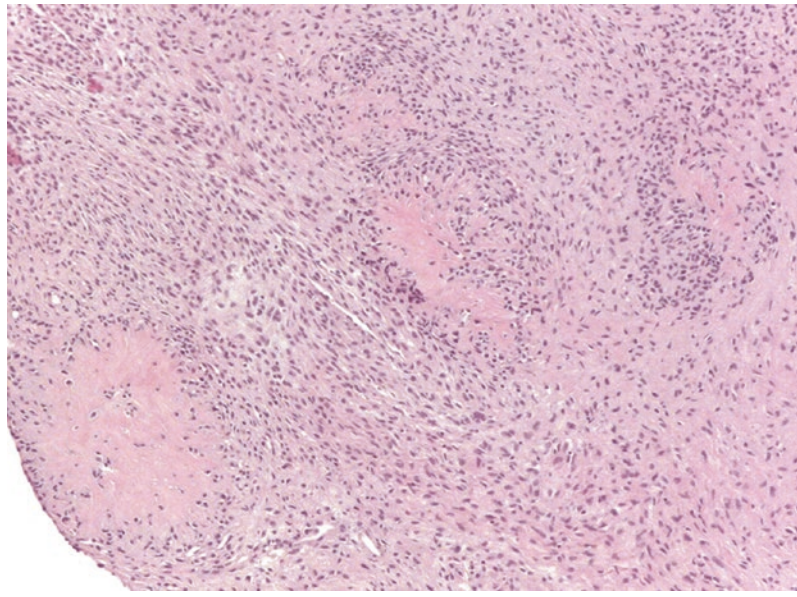


Location: The most frequent locations are the deep soft tissues of the limbs (thigh), limb girdles (shoulder), and trunk.

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).



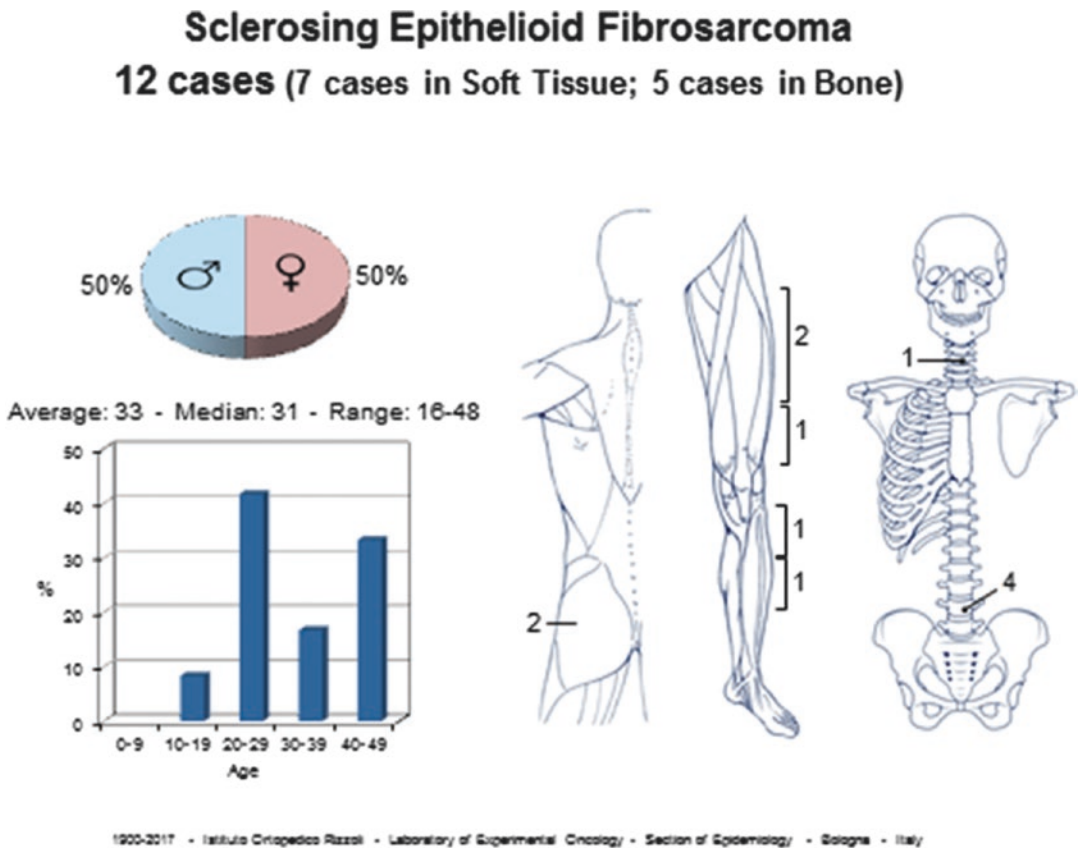
Slender spindle cells in a and myxo-collagenous stroma; large hyalinized collagen rosettes are present

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.

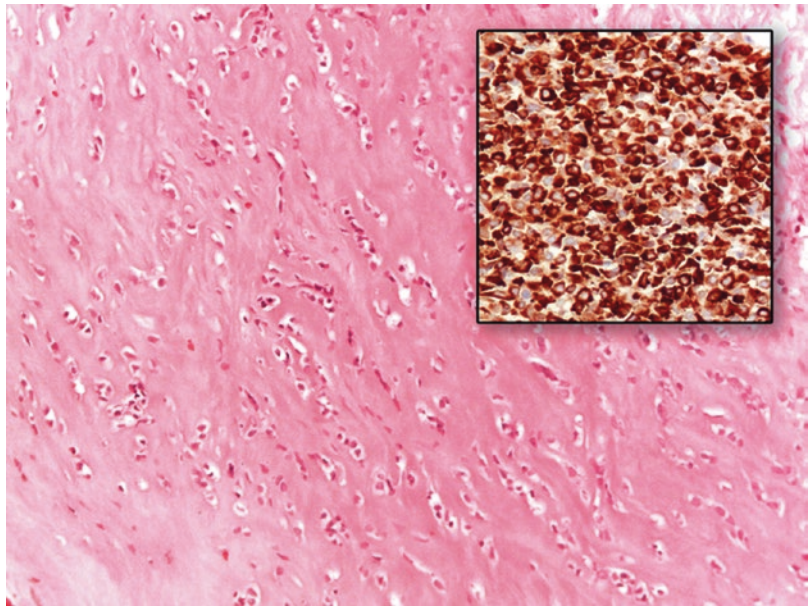
Imaging: On imaging, a mass, sometimes calcified, is evident showing on MRI low signal intensity on T1-weighted images and hypointense to intermediate signals on T2-weighted images

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.



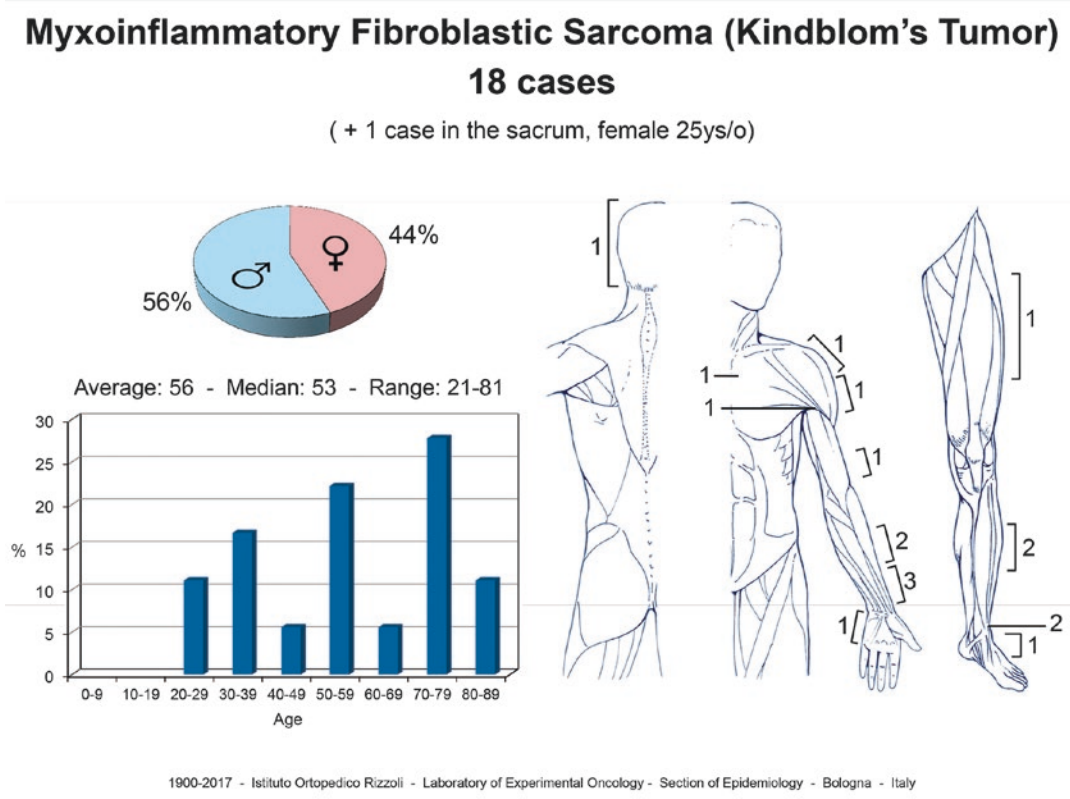
Moderately pleomorphic epithelioid cells arranged in cords within a densely hyalinized stroma. Immunohistochemical cytoplasmic positivity for MUC4 in the neoplastic cells (*inset*)

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.



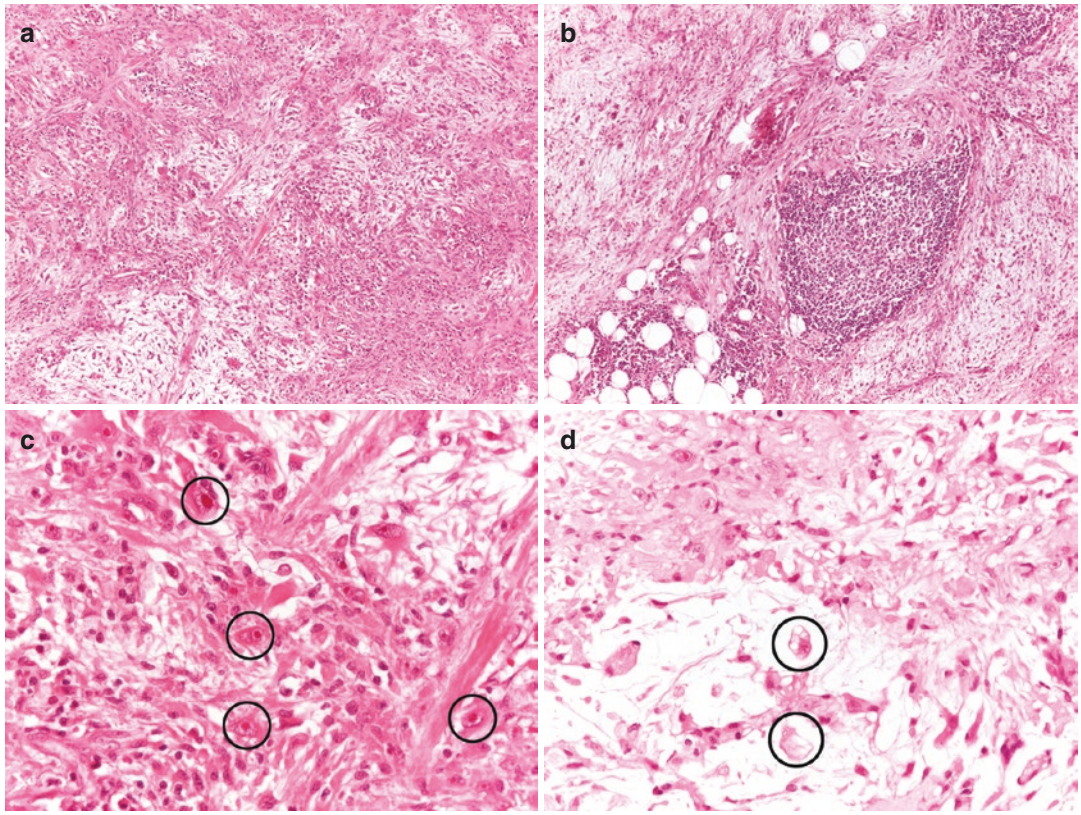
Location: The vast majority occurs in the subcutaneous tissues of the distal extremities, mostly in the upper limbs.

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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Nerve Sheath Tumor

43

Piero Picci and Angelo Paolo Dei Tos

43.1 Malignant Schwannoma (Malignant Peripheral Nerve Sheath Tumor—MPNST)

Definition: Malignant tumor that rises from a peripheral nerve, from a pre-existing benign nerve sheath tumor, in a patient with neurofibromatosis type 1, or with features of Schwann cells differentiation.

Epidemiology: 5% of all soft tissues sarcomas. Fifty percent in neurofibromatosis. Males prevail in patients with neurofibromatosis with a medium age of 30 years. Females prevail in sporadic cases in the adult age (>40 years).

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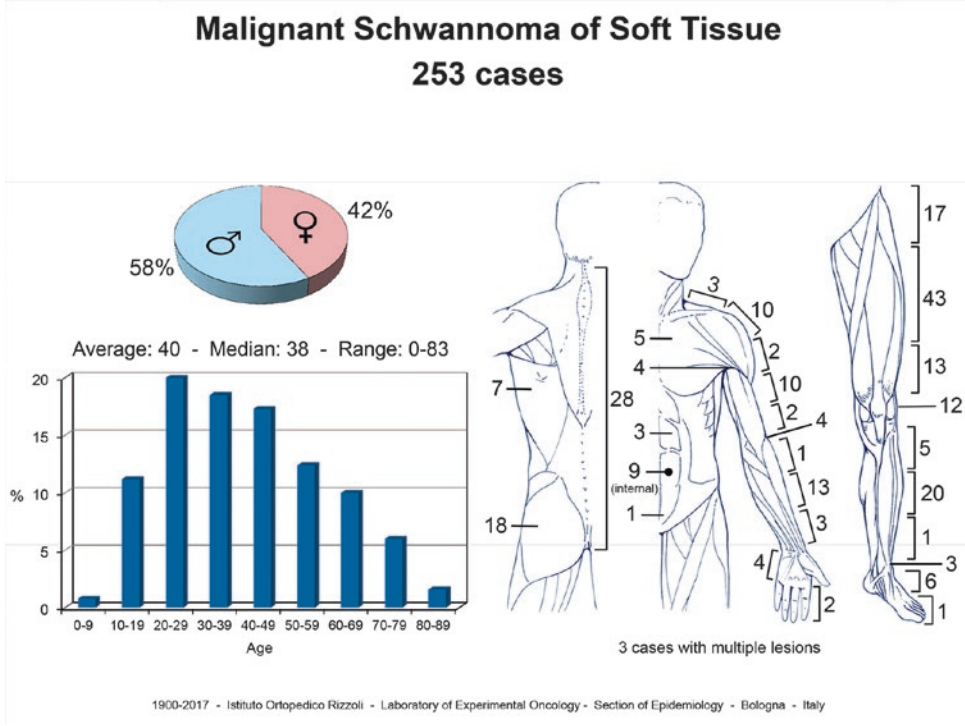
Malignant Schwannoma of Soft Tissue
253 cases
42%
58%
Average: 40 - Median: 38 - Range: 0-83
%
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89
Age
3 cases with multiple lesions
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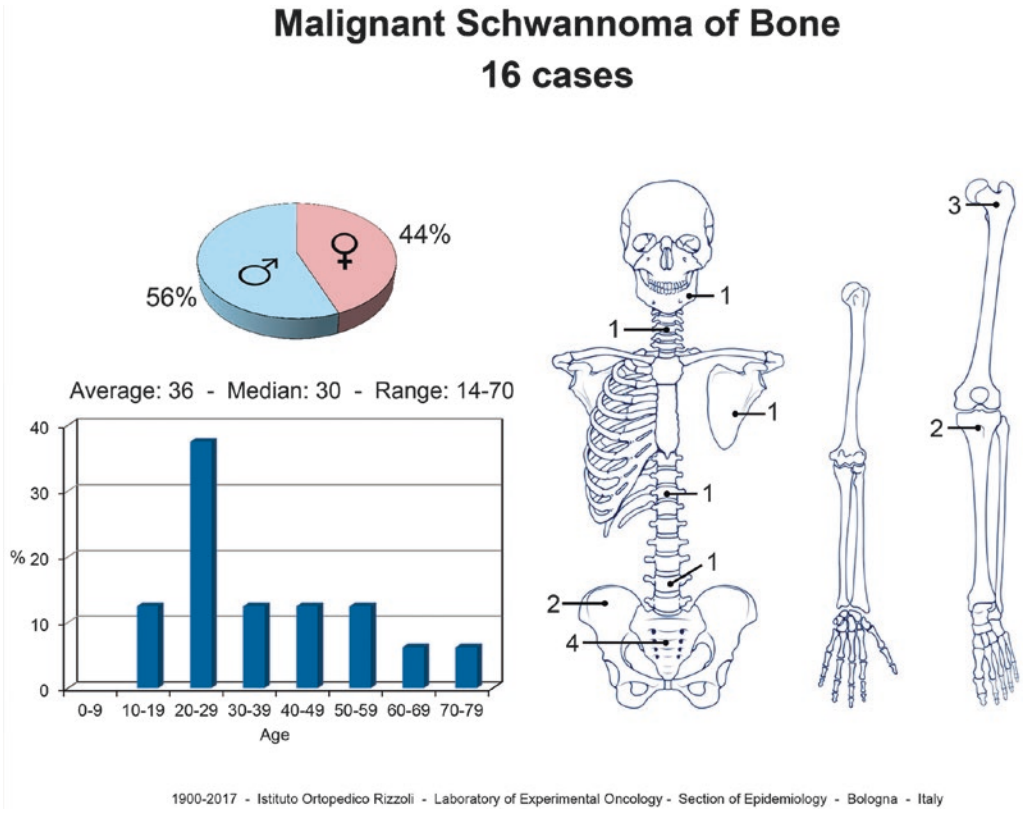
Malignant Schwannoma of Bone
16 cases
44%
56%
Average: 36 - Median: 30 - Range: 14-70
%
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79
Age
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Location: In association with major nerve trunks: sciatic nerve, brachial plexus, sacral plexus. Gluteal region and pelvis, thigh region, shoulder region, and axilla are the most frequent sites.

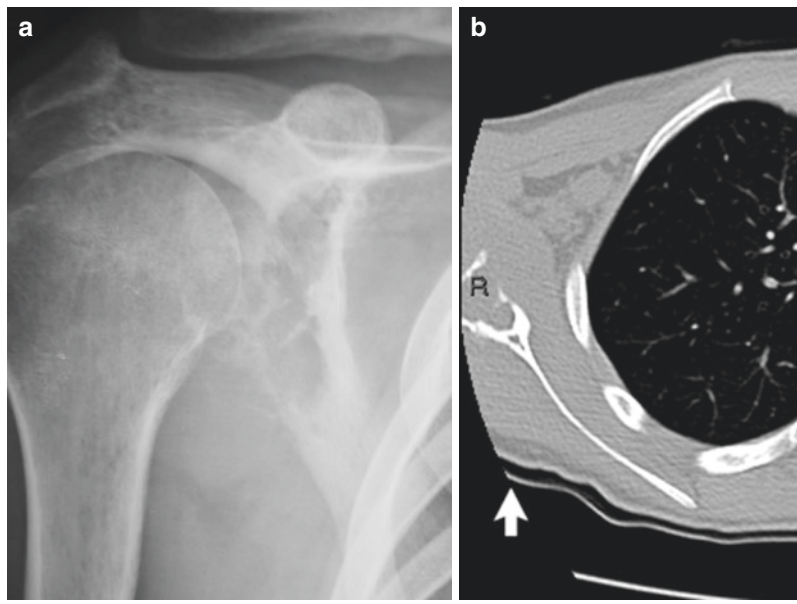
Clinical: Rapidly enlarging mass with pain. Sensory and motor symptoms including projected pain, paresthesias, weakness.

Imaging: Neither CT nor MRI can establish a definite diagnosis. On CT: mild enhancement with some nonenhancing areas of necrosis. On MRI: inhomogeneous and higher intensity than muscle on T1, markedly inhomogeneous and bright on T2, common necrosis in the center of the mass with peripheral capsule-like or irregular enhancement on contrast T1, a wide halo of edema unusual in benign lesions.

Histopathology: Large fusiform or eccentric mass within a major nerve. When the tumor spreads along the epi- and perineurium, it has a rosary bead aspect proximal or distal to the principal mass. Tumor is usually >5 cm, deep seated, but rarely superficial, fleshy, with hemorrhagic and necrotic diffused areas. Spindle cells with markedly irregular contours with wavy, buckled or comma shaped nuclei, lightly stained and usually indistinct cytoplasm. Densely cellular sweeping fascicules alternate with hypocellular, myxoid zones in the so-called "marble-like" pattern. A peculiar nodular or whorled arrangement of cells can be present. Focal nuclear palisading is present in only 10% of cases. Hemangiopericytoma-like vascular pattern can be present, with condensation of the neoplastic cells around blood vessels is characteristic. Heterologous elements such as glandular differentiation, skeletal muscle (malignant triton tumor), bone, cartilage, and angiosarcomatous areas are present in about 15% of cases. Epithelioid MPNST is a rare variant composed of epithelioid cells with abundant eosinophilic cytoplasm; it is not associated with NF1 and it is the most common type arising in schwannoma. On immunohistochemistry focal S-100 protein expression in classic MPNST. Epithelioid MPNST shows diffuse positivity for S100 protein and Sox10; it retains expression of H3K27me3 and mostly show loss of SMARCB1 expression.

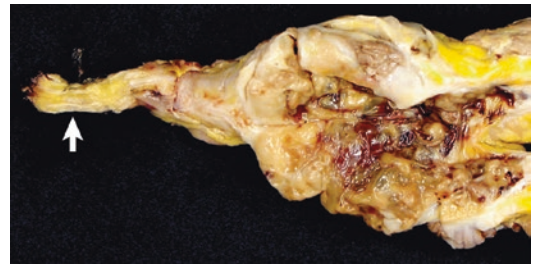
Course and Staging: Frequent local recurrence when surgery is inadequate. Metastases frequently develop in the lungs, liver, subcutis and bone, rarely in the lymph nodes. Usually, stage IIB.

Treatment: Very wide or radical local excision. Often, multicentric origin and diffusion along the nerve makes even radical surgery ineffective. Overall 5-year survival is 30% in patients with neurofibromatosis and 75% in sporadic cases. In neurofibromatosis, prognosis is worse because the tumor involves the trunk and proximal extremities with late diagnosis, it is larger and of higher grade, and multiple sarcomas may occur. Usefulness of radiotherapy and chemotherapy is uncertain.

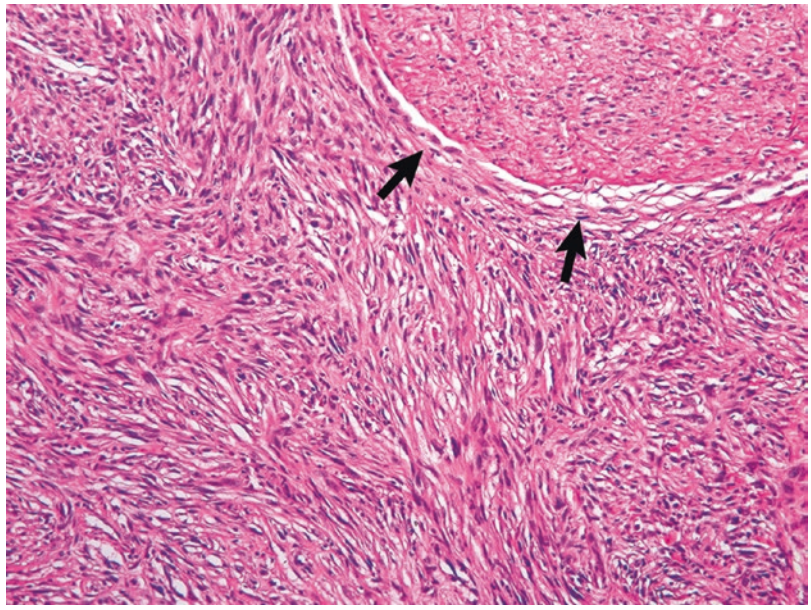


Radiograph (**a**), and CT (**b**) images. Poorly limited lytic and sclerotic lesion, destroying the cortex and invading the -soft tissues

Immunohistochemical panel	
• S100	+ (30% of cells in 30% of cases)
• GFAP	+ (30% of cells in 30% of cases)
• SOX10	+/–
• H3K23me3	–



The tumor arises from a peripheral nerve (*arrow*)



Highly atypical spindle cells with wavy or plump nuclei organized in storiform or fascicular pattern, frequently close to a peripheral nerve (*arrows*)

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Smooth and Striated Muscle

44

Piero Picci and Angelo Paolo Dei Tos

44.1 Leiomyosarcoma

Definition: Malignant tumor showing smooth muscle differentiation. Type (a) retroperitoneal; (b) cutaneous; (c) vascular.

Epidemiology: 7% of soft tissue sarcomas. Type (a): females. Median age 60 years. Type (b): 2–3% of superficial sarcomas. No sex predilection. 40–70 years old. Type (c): rare, female in leyomiosarcomas of the inferior vena cava, no sex predilection in the other cases. Median age 50 years.

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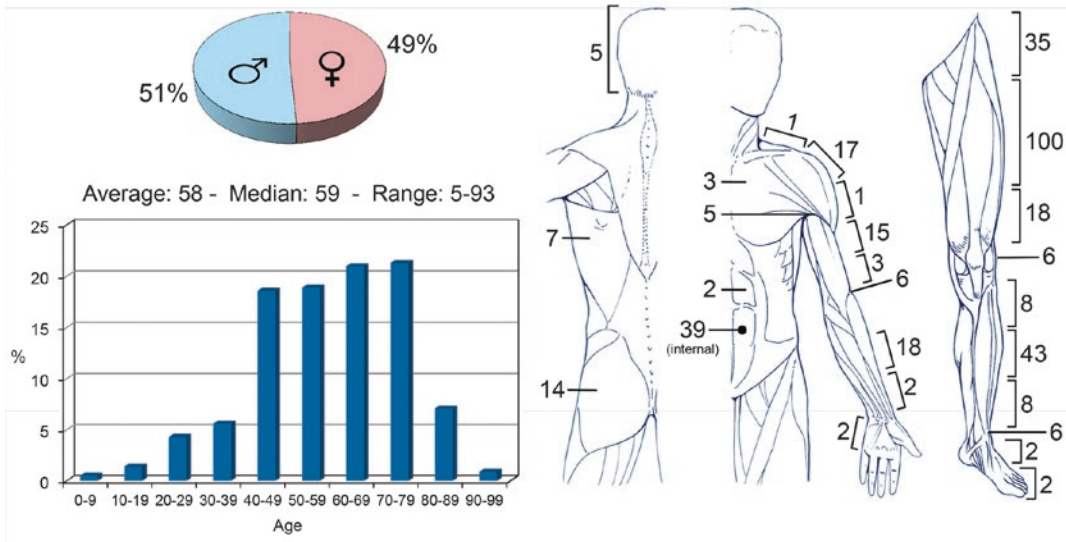
Leiomyosarcoma of Soft Tissue
368 cases



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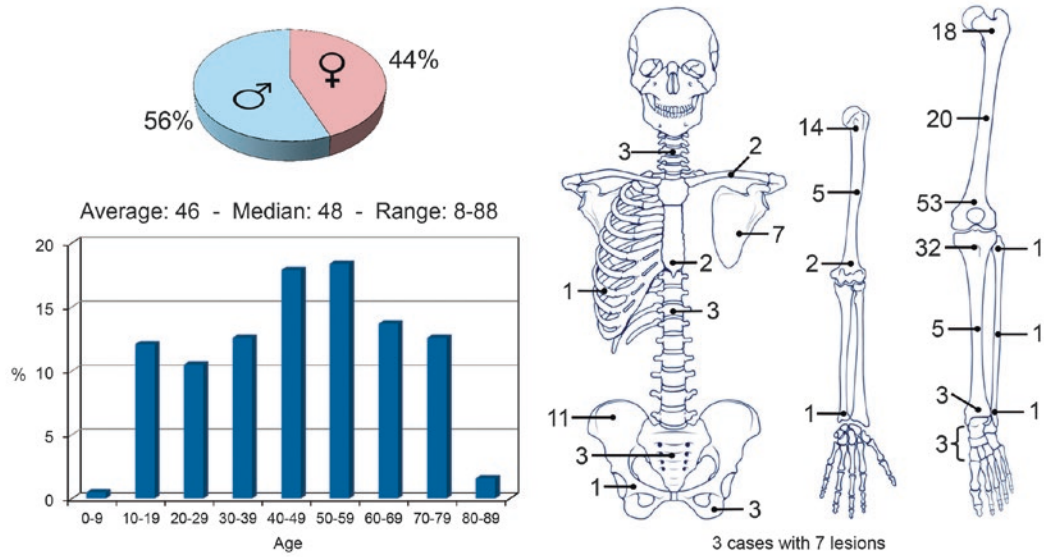
Leiomyosarcoma of Bone
191 cases

Including 18 Secondary Tumors: after Radiation Therapy (6),
on Bone Infarcts or Bone Chips (6), on Paget's (3), on GCT (2), on Fibrous Dysplasia (1)



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Location: In soft tissues, Type (a): retroperitoneum. Commonly involves kidney, pancreas, vertebral body for direct extension. Type (b): in the limbs, from piliferous areas. Quite small, less 2 cm subcutaneous tumors grow faster and reach a larger size. Type (c): in the lower limbs, more frequently involving the veins, exceptionally the arteries. In bone in the metaphysis around the knee, the proximal femur and proximal humerus.

Clinical: Type (a): abdominal mass, pain, weight loss, nausea, or vomiting. Type (b): pain, surface changes in the epidermis. Type (c): pain for pressure on nerve close to the affected vessel, edema due to venous compression. In bone, pathological fracture is possible. The tumor is typical of the adult age.

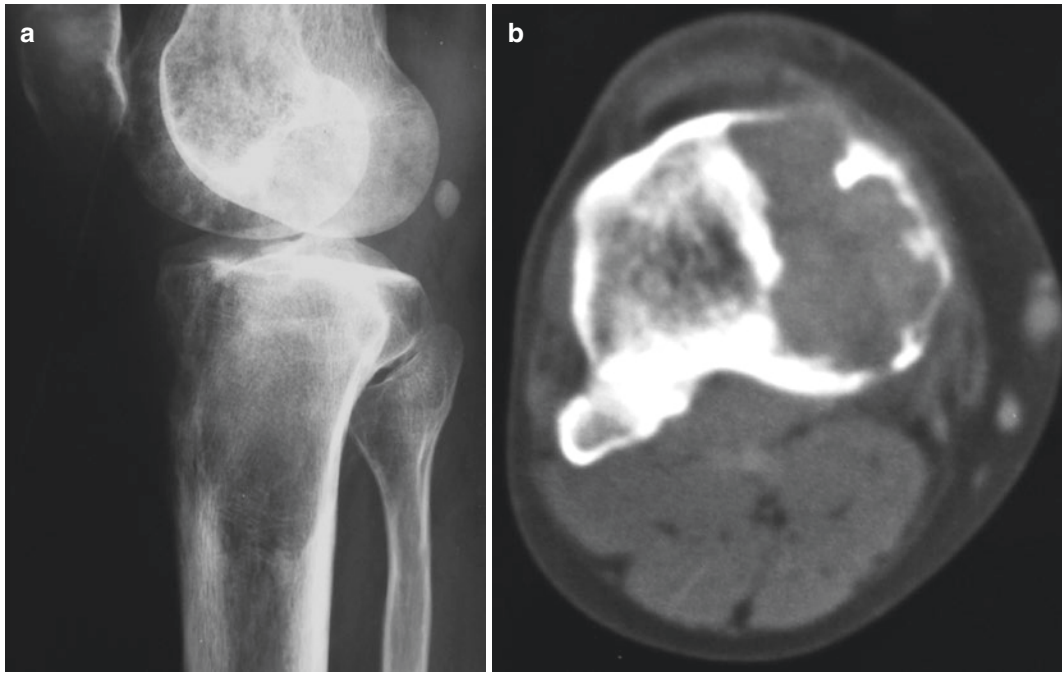
Imaging: On CT—hypo or moderately vascular lesions, type (a): found by CAT scan or angiography that do not show typical aspect. Dislocation of the most important vessels is usual. Type (c): angiographically highly vascularized. On MRI—inhomogeneous, isohypointense on T1, with a thick, irregular rim enhancement on contrast T1, marked inhomogeneity with mixed but mainly high signal intensity on T2. In bone no specific characteristic in respect to all the lytic lesions of the adults.

Histopathology: White-gray whorled appearance, more often fleshy masses with foci of necrosis and hemorrhage, frequent cyst formation. Proliferation of spindle cells with an elongated nucleus with abundant cytoplasm. The nucleus is central and blunt-ended or "cigar-shaped." A vacuole close to one end of the nucleus produces a slight indentation so that it becomes concave rather than convex in the contour. Sometimes, cytoplasm may have a "clotted" appearance because of clumping of the myofilaments. Cells are arranged in bundles that form wide waves intersecting with different orientation. A right angle is frequent. Stroma is a delicate mesh between cells. At times, a palisade-like aspect of the nuclei similar to neurinoma is observed. Pleomorphic appearance with highly anaplastic to epithelioid cells is common. Mitotic figures are frequent. Type (b) is whitish-gray or pinkish, fasciculated aspect, ill-defined margins by virtue of the intricate blending of tumor fascicles with surrounding collagen and pilar arrector muscle in dermis tumors, well-circumscribed lesions by a pseudocapsule in subcutis tumors. Mitotic figures are frequent. Pure cutaneous (dermal without subcutaneous involvement) leiomyosarcomas have been recently designed as "atypical smooth muscle tumors" because they show a 30% rate of locale recurrence and no metastasis. Immunohistochemistry is positive for pan-muscle actin, smooth muscle actin, desmin, and caldesmon.

Treatment: Type (a): Wide excision, but it is often so large that total resection is impossible. Local recurrence is frequent. Type (b): Wide excision.

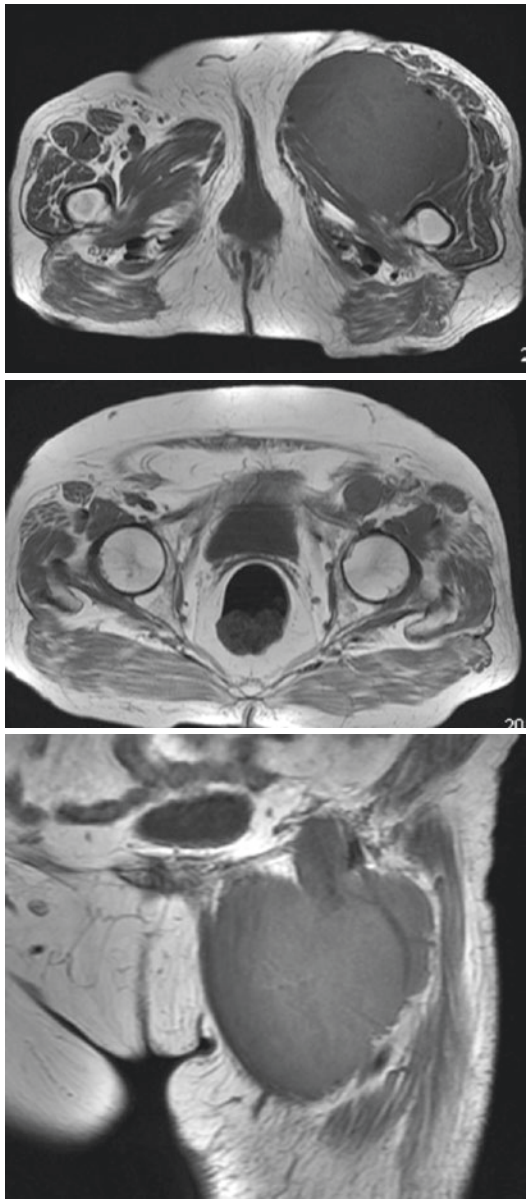
Type (c): Wide excision is often impossible in large veins (hepatic, inferior or middle cava). Necessary in tumors of the small veins.

Course and Staging: Type (a) highly aggressive, so they may cause death also by local extension. Survival from 0 to 29% at 5 years. Usually, stage IIB. Type (b): good prognosis, metastases infrequent, local recurrence frequent (50%), usually stage IA–B. Type (c): poor prognosis, 50% have metastases; tumors of the small veins seem to have a better prognosis, usually stage I–IIB.

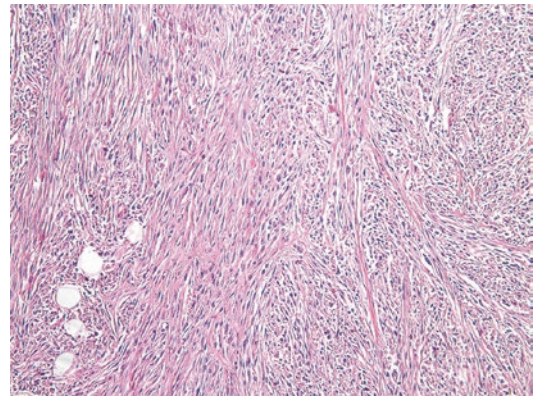


Radiograph, lateral view (**a**), and CT (**b**). Mainly lytic lesion, with a sclerotic component better seen on CT, rather well limited, with a longitudinal interrupted periosteal bone formation, and destroying the cortex

Immunohistochemical panel	
• Smooth M Act	+
• Desmin	+
• Caldesmon	+



Axial and coronal T1 MR images. Mass of the root of the thigh, involving the femoral vein



Spindle cell neoplasm with smooth muscle differentiation with variable pattern

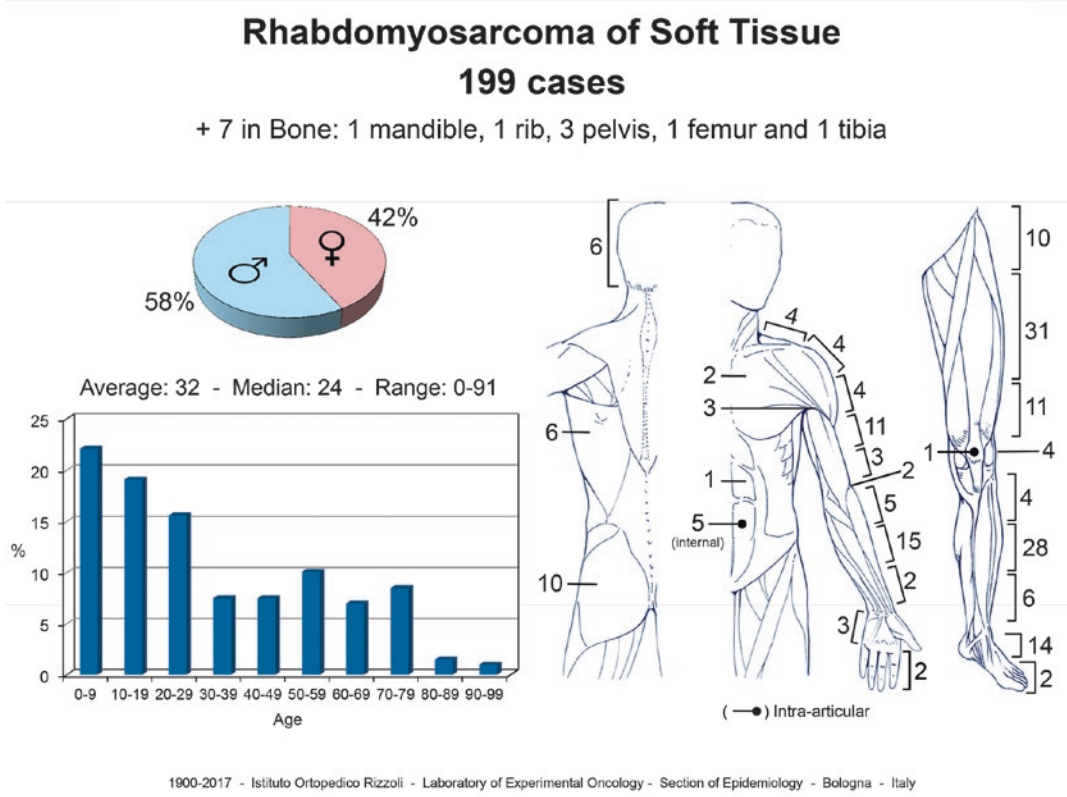
44.2 Rhabdomyosarcoma

Definition: Malignant tumor with phenotypical and biological features of skeletal muscle cells.

Epidemiology: 20% of all soft tissue sarcomas. Most frequent under 20 years. Male. Very rare primarily in bone (seven cases in our series).

Varieties: (a) embryonal, (b) alveolar, and (c) pleomorphic. Spindle cell/sclerosing rhabdomyosarcoma is a rare variant that can occur in children, adolescent, and in adults; it was originally classified in the embryonal category but it is now considered a distinct histological subtype.

Type (a): The most common type (60%), prevalent from birth to 15 years of age. Type (b): frequent (30%), prevalent in 10–25 years old. Type (c): rare, almost exclusively in 40–60 years old.



Location: Rhabdomyosarcoma of the limbs of the limbs constitutes 15% of all tumors. Type (a): head, neck, genito-urinary tract (botryoid variety), retroperitoneum. Type (b): limbs (forearm, hand, foot). Type (c): limbs (prevails in the thigh).

Clinical: Type (a): rapidly, invasive, infiltrative growth. Symptoms and signs depend on anatomic location. Type (b, c): Deep, painless unless it compresses a nerve, rapidly enlarging mass in a striated muscle.

Imaging: On X-ray—erosion of flat bone in 20% of cases. In type (b, c) is rare, but it occurs mainly in the hand and foot. Periosteal reaction is minimal. Nevertheless, tumor is frequently tightly bound to bone. On arteriography—common aspects to all well-vascularized tumors: neovascularity and tumoral blush. On CT—large, lobulated mass with central hypodensities, septation, rimlike enhancement surrounding areas of necrosis after contrast administration. On MRI—Type (a): homogeneous, slight hyperintensity on T1, bright on T2 with some dark internal strands, no enhancement of large parts of the mass on contrast T1, no necrosis. Type (b): inhomogeneous, intermediate intensity with multiple, central hypointensity areas on T1, heterogeneous, with white central zones on T2 (necrotic areas), strong peripheral enhancement on contrast T1. Type (c): mixed signal intensities on T1, more inhomogeneous on T2 with central fluid collection near to low signal intensity areas, ringlike, peripheral enhancement around these.

Histopathology: Firm or soft mass, with myxoid and cystic component, mottled white-gray to pink-tan, with frequent hemorrhage and necrotic areas. Immunostains for desmin and myogenin are essential for diagnosis. Type (a): Usually undifferentiated small round cells with round-oval, hyperchromic nucleus. Nuclear membrane is evident. Chromatin granules are distinct and nucleoli are clearly evident. Thin, perinuclear cytoplasmatic ring. Mitotic figures and pleomorphism are fre-

quent. Cells are distributed without any order with scarce collagen stroma among them. At other times, in more differentiated zones, the volume of the cells increases, nucleus becomes larger, vesicular, eccentric, with a large nucleolus. Cytoplasm is eosinophilic, granular, more abundant, with filaments wrapped around the nucleus. Transverse striation may be recognized with progressive rhabdomyoblastic differentiation. Neoplastic cells can show a racket, tadpole, strap, or ribbon shape. Globose cells may have a vacuolated cytoplasm and this may be reduced to filaments that from the nucleus irradiate to the periphery (so-called "spider-web" cells). Type (b): Undifferentiated, small, round-oval cells, collected in solid islands and forming alveolar aspect. Rough bands of dense collagen, convoluted and ramified, containing dilated capillaries, surround these cellular zones. Peripheral cells adhere in a single layer to the fibrous septa. Cells in the center are more loosely arranged or freely floating. Rhabdomyoblasts are much rarer. Type (c): Association of loosely arranged, haphazardly oriented, small and large, round or pleomorphic cells. Larger and more irregular in outline racket-shaped and tadpole-shaped rhabdomyoblasts with stringy, granular, and vacuolated cytoplasm can be present. Transverse striations are extremely rare. Much less collagen stroma between cells is observed. Immunohistochemistry is positive for pan-muscle actin, desmin, MyoD1, and myogenin (diffuse positivity in type b), but negative for smooth cell actin. There are two main karyotypic aberrations in alveolar rhabdomyosarcoma: t(2;13) that fuses the PAX3 gene on 2q35 with the FOXOA1 gene on 13q14 and is present in 60–80% of cases; and t(1;13) that fuses PAX7 on 1p36 with FOXOA1 on 13q14 and is present in 10–20% of cases. The latter translocation is associated with a better prognosis, the first with a worse prognosis.

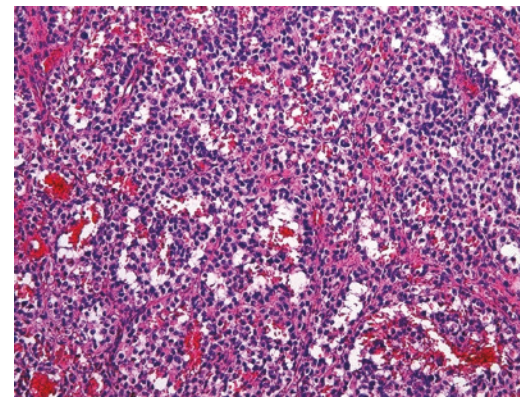
Course and Staging: Rapid and aggressive. Frequent recurrence if inadequately treated and metastases in lungs and lymph nodes. Usually, stage IIA, within one of the major muscles of the limb, or stage IIB. Stage I is rare. American rhabdomyosarcoma intergroup study distinguishes four stages: Stage 1: localized tumor, completely resected; stage 2: marginal excision with or without lymph-nodes metastases; stage 3: intralesional excision; stage 4: distant metastases at time of diagnosis.

Treatment: Optimal treatment is preoperative chemotherapy, wide excision with resection of regional lymph nodes, postoperative chemotherapy plus radiation therapy when excision is not wide. Overall 5-year survival is excellent for stage 1 (83%) and for stage 2 (75%), less favorable for stage 3 (52%), and poor for stage 4 (20%). Tumors in the head and neck, retroperitoneum, abdomen, extremities have a worse prognosis than neoplasms in the orbit and in paratesticular region. Alveolar type has a less favorable prognosis than embryonal.

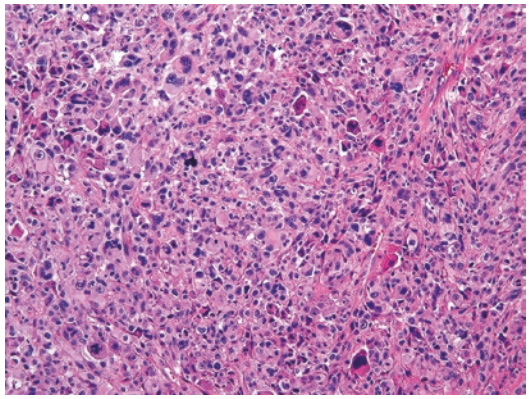
Immunohistochemical panel	
• Desmin	+
• Myogenin	+
• MyoD 1	+
• Smooth M Act	–

Alveolar rhabdomyosarcoma

Chromosomal translocations			
• t(2;13) (q35;q14)	PAX3-FOXOA1	60–80%	Worse prognosis
• t(1;13) (p36;q14)	PAX7-FOXOA1	10–20%	Better prognosis



Alveolar rhabdomyosarcoma
Undifferentiated small cells with skeletal muscle differentiation organized in nodules with loosening of cohesiveness of cells in the center of nodules, resulting in an alveolar-like appearance



Pleomorphic rhabdomyosarcoma
Pleomorphic high-grade neoplasm, similar to undifferentiated pleomorphic sarcoma, with skeletal muscle differentiation

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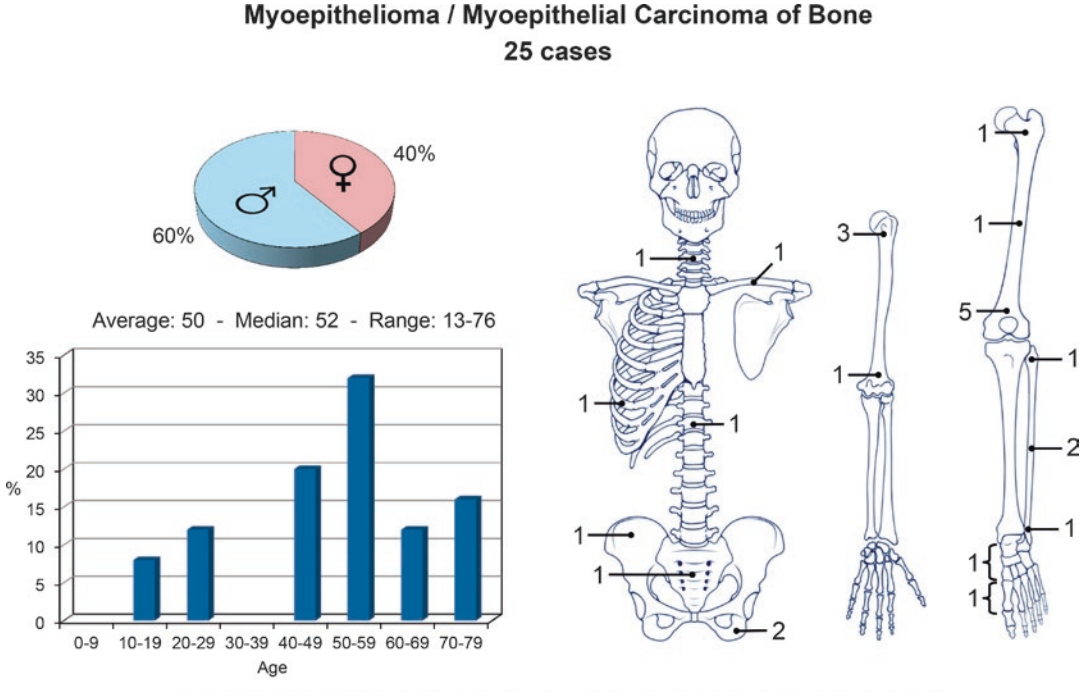
45 Sarcomas with Uncertain Differentiation

Marco Gambarotti and Alberto Righi

45.1 Myoepithelioma/ Myoepithelial Carcinoma

Definition: Spectrum of lesions morphologically similar to those arising in the salivary glands. Malignant forms are called myoepithelial carcinomas.

Epidemiology: Uncommon tumors. Equally distributed between the sexes. Median age: 40 years old, but with a wide age range; frequent in children. Very rare bone tumors, generally affecting adult patients.



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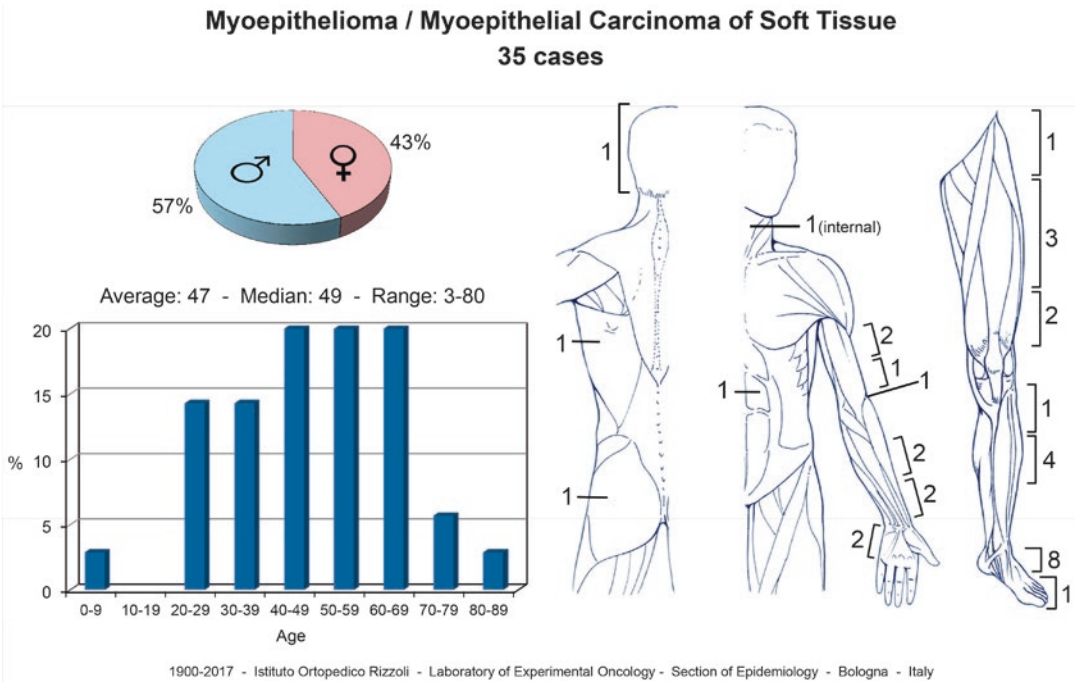


Location: Limbs and limb gilders are the most frequent site involved, followed by trunk and head and neck.

Clinical: Superficial or deep-seated, usually painless mass.

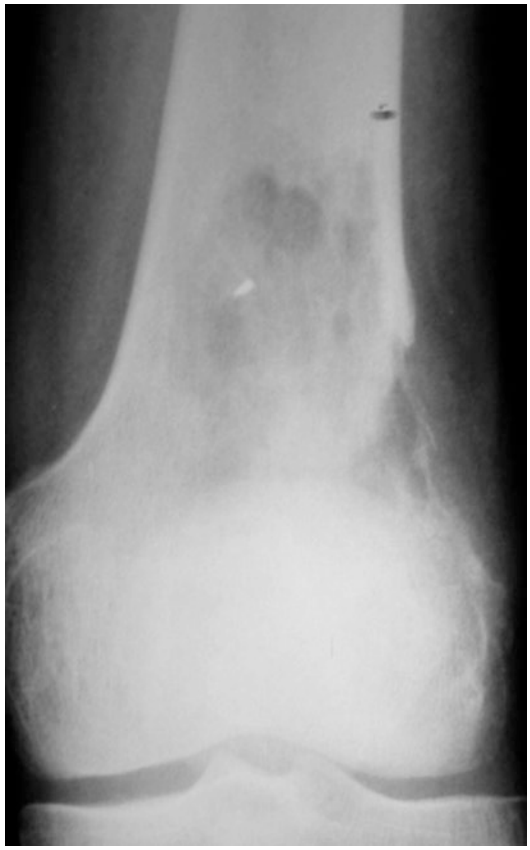
Imaging: Not specific. The lesion may be calcified. There is a hypointense signal on T1W images on MRI, a high signal on T2W images, because of the myxoid component. Cystic, necrotic, or hemorrhagic parts are possible. The uptake of contrast medium after injection is usually late and heterogeneous.

In bone, benign forms generally appear as well-circumscribed lesions with sclerotic margins, while malignant forms tend to be lytic and to invade the soft tissues.

Histopathology: Grossly, generally well circumscribed, gray-whitish, sometimes glistering or mucoid. Histologically, composed of spindle to epithelioid cells organized in chords, strand, trabeculae, or nests, often in a chondromyxoid stroma. Neoplastic cells generally show eosinophilic cytoplasms and sometimes eccentrically placed "plasmocytoid" nuclei. Prominent cytoplasmic vacuolations mimicking chordoma define the so-called "parachordoma"; a ductal component defines the so-called "mixed tumor." Immunohistochemically, tumoral cells typically coexpress EMA and/or cytokeratins and S100 and/or GFAP. Malignant forms are defined by the severe nuclear atypia, often with high mitotic count, tumor necrosis, and an infiltrative pattern of growth.

Course and Staging: Most myoepitheliomas behave in a benign fashion, with local recurrences in 20% of cases and rare metastasis. Malignant myoepitheliomas recur and metastasize in 40–50% of cases.

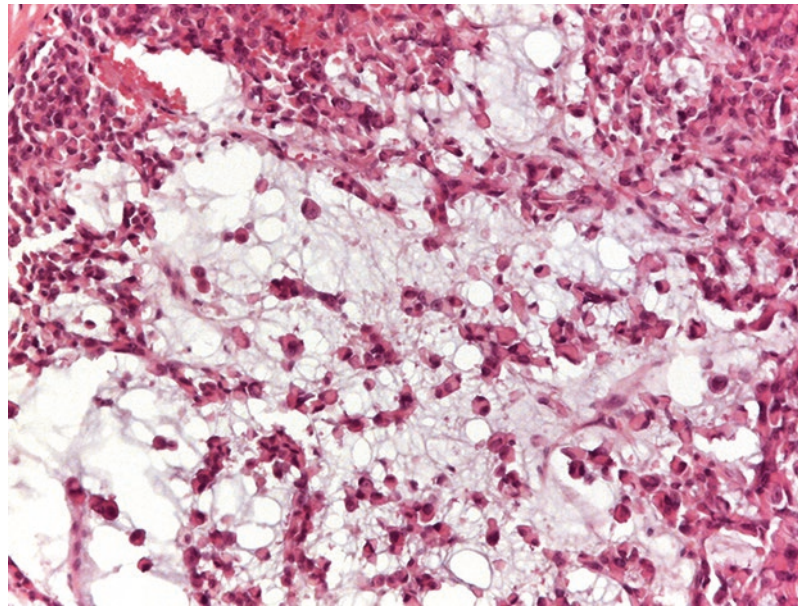
Treatment: Wide excision.



Radiograph. Lytic poorly limited metaphyseal lesion, with a sclerotic component, destroying the cortex and invading the soft tissues

Immunohistochemical panel	
• Pan-cytokeratin	±(90%)
• EMA	±(70%)
• S100	±(90%)
• GFAP	±(50%)
• SMA	±(30%)
• p63	±(45%)
• INI-1 (SMARCB1)	– in 40% of pediatric cases and in 10% of adult cases

Chromosomal translocations		
• t(6;22)(p21;q12)	EWSR1-POU5F1	16%
• t(1;22)(q23;q12)	EWSR1-PBX1	16%
• t(19;22)(q13;q12)	EWSR1-ZNF444	<2%

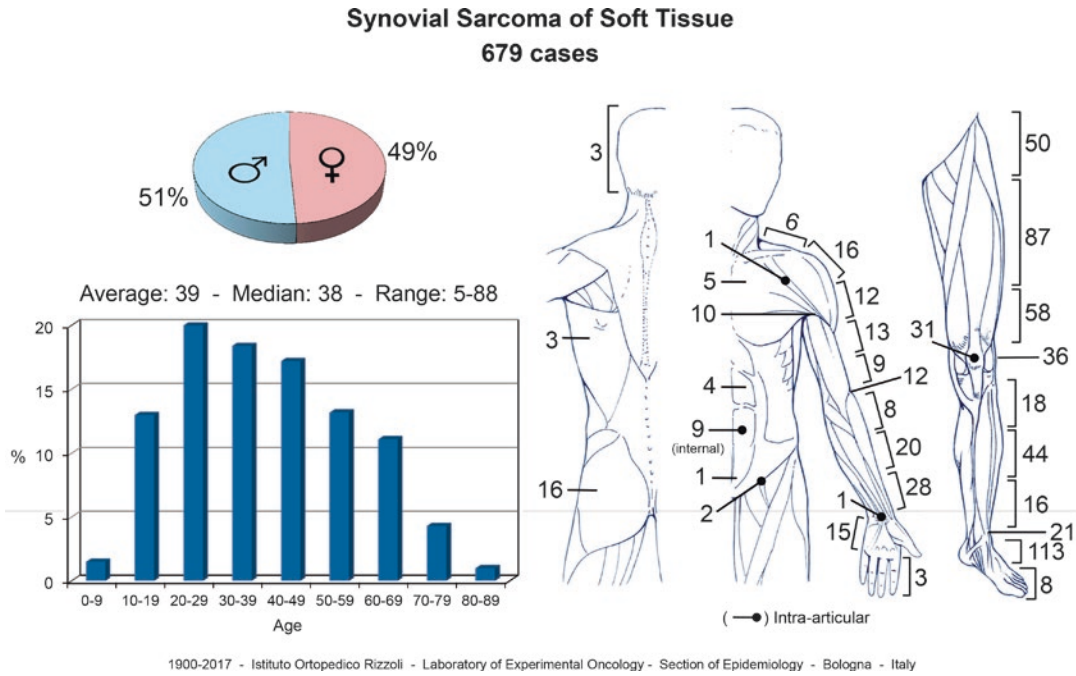


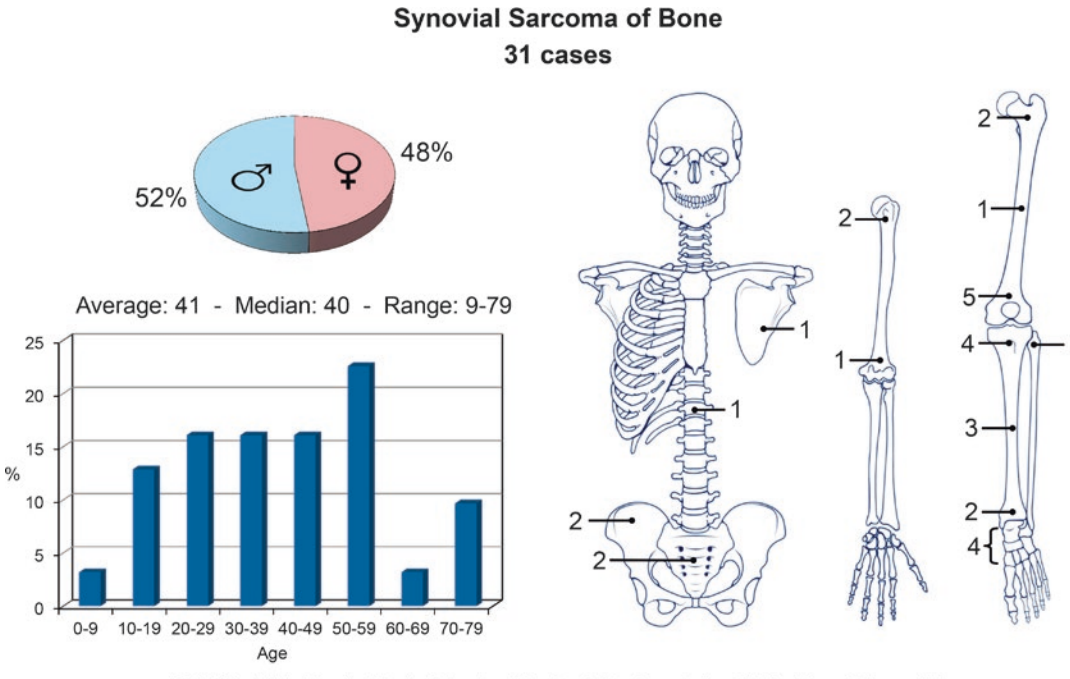
Chords and nest of epithelioid cells in a chondromyxoid stroma, often with "plasmocytoid" appearance

45.2 Synovial Sarcoma

Definition: Malignant mesenchymal tumor displaying a variable degree of epithelial differentiation and the specific translocation t(X;18).

Epidemiology: 5–10% of all sarcomas of soft tissues. Very rare in bone. Quite equally distributed between male and female. More frequent between 15 and 40 years old.





Location: More frequent in deep soft tissue of the extremities (80% of cases); lower limbs (thigh, knee, foot, ankle) account for 60% of cases, while upper limbs (forearm, wrist, shoulder) account for 23% of cases.. Only 10% arise within a joint. Usually close to a major joint, intimately related to tendons, tendon sheaths, bursae, beyond the confines of the joint capsule. In bone predominantly occurs in the long bones (femur and tibia are the more frequent sites), followed by pelvic bones

Clinical: A palpable deep-seated often painful mass. Pain may be the first symptom of the disease. Tumor grows slowly and insidiously; the duration of symptoms generally ranges from 2 to 4 years, up to 20 years.

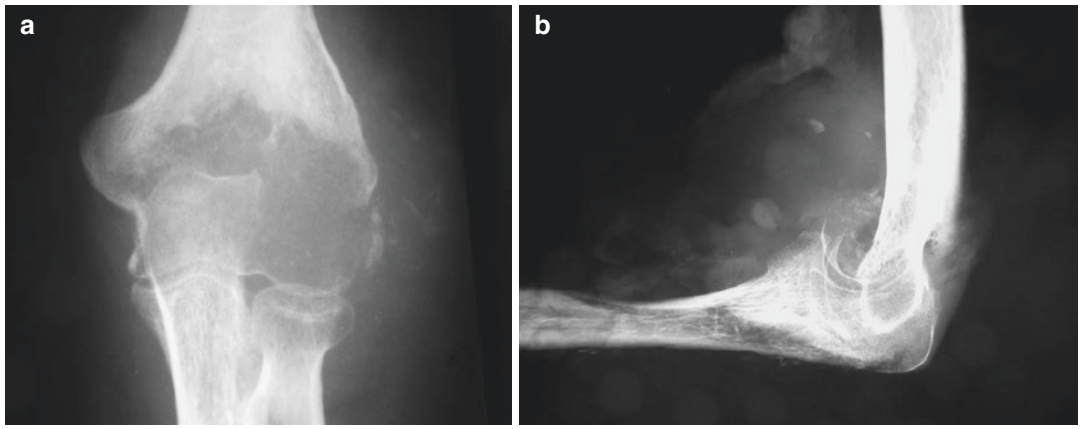
Imaging: On X-ray—a round or oval, lobulated swelling of moderate density near a joint. Usually, bone is uninvolved. Periosteal reaction, bone erosion, or bone invasion (15–20%). Multiple, small and spotty calcifications, or cloudy and faded shadow or massive and dense radiopacities of bone formation (40%). Radiopacities more frequent in the periphery. On angiography richly hypervascularized. On CT—infiltrating soft tissue mass with slightly higher density than muscle, markedly enhanced, with easily detected calcifications, cortical erosion, joint invasion when tendons or ligaments are involved. On MRI—90% hypointense on T1, hyperintense on T2. Fluid levels (15%). Marked inhomogeneity, enhancement, and septation on T2. A triple signal pattern on T2 (30%): white-like fluid, gray-like fat, dark-like fibrous tissue. Small high signal areas on T1 (45%) are foci of hemorrhage. This and the triple pattern are suggestive of synovial sarcoma. In bone, lytic lesions sometimes with sclerotic areas, generally infiltrating the surrounding soft tissues.

Histopathology: Grossly, tumors range in dimension from 1 to 20 cm; they are slow-growing lesions that appear as a firm, lobular mass, fairly well circumscribed, attached to surrounding tissues, from yellow to gray-white on cut surface. More rapidly growing lesions can appear as a soft, globose mass, poorly encapsulated, with a variegated friable or shaggy appearance, from mottled pink yellow to light brown, with frequent necrosis and hemorrhage and multicystic areas. Calcifications can be seen. Histologically, two different types of cells can be present: spindle and epithelial cells. Based on the type of the cells, three subtypes are identified: (1) monophasic spindle cell type (the most frequent; only spindle cells); (2) biphasic type (both spindle and epithelial cells in varying proportions); (3) poorly differentiated type (20%; hypercellular areas with round cells similar to Ewing sarcoma or spindle to epithelioid cells with severe nuclear atypia and high mitotic activity). A monophasic epithelial type (only epithelial cells) was also described in the literature, but according to the last WHO classification it does not exist, since a spindle cell component, although very focal, is always present in these tumors. Spindle cells have a uniform appearance, with scant and indistinct cytoplasm and oval, dark bland nuclei. They grow in a solid fascicular pattern, often with a herringbone appearance. A fine net of pericellular collagen fibers is often present. "Staghorn-like" vessels can be present, resulting in a hemangiopericytoma-like appearance. Epithelial cells are globose, cubic or cylindrical, with large vescicular nuclei, abundant pale cytoplasm, with well-defined limits. They are arranged in cords, whorls, nests, or glandular structures often containing mucus; rarely, they show squamous features with keratinization. Calcifications are present in about 1/3 of cases.

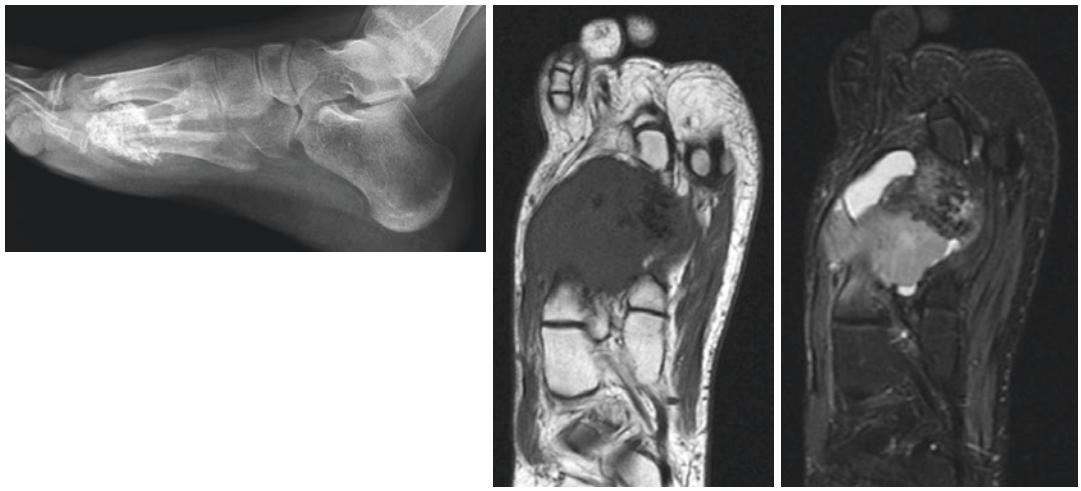
Course and Staging: Usually it grows between and adheres to the tendons, joint capsules, bursae mucosae, fasciae, skeleton, muscles, and interosseous membranes. It pushes its growth along these multiple planes, infiltrating these structures and creating intravascular plugs. Local recurrence is common also 10 years after an inadequate surgery. Metastases develop in about 50% of cases. Usually, stage IIB. In bone, it seems to behave more aggressively than the soft tissue counterpart.

Treatment: Surgery aims at obtaining wide margins, also sacrificing functionally important structures or amputating the limb. Wide conservative surgery can be difficult for the characteristic growth of the tumor. It may be useful to associated adjuvant chemotherapy and pre- or

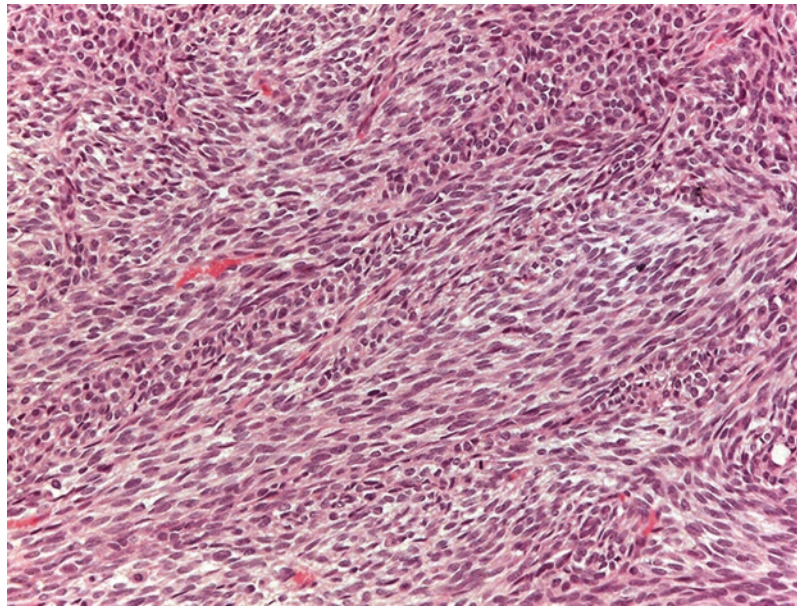
postoperative radiation therapy. Overall survival at 5 years and 10 years varies from 36% to 76% and from 20% to 63%, respectively. Favorable prognostic factors are: size <5 cm, young age, distal location, calcifications, <10 mitosis per 10 HPF, biphasic morphology, and absence of intravascular plugs. Tumors with SSX2 translocation showed a higher local recurrence rate. Grade 3 according to FNCLCC classification identified high-risk patients.



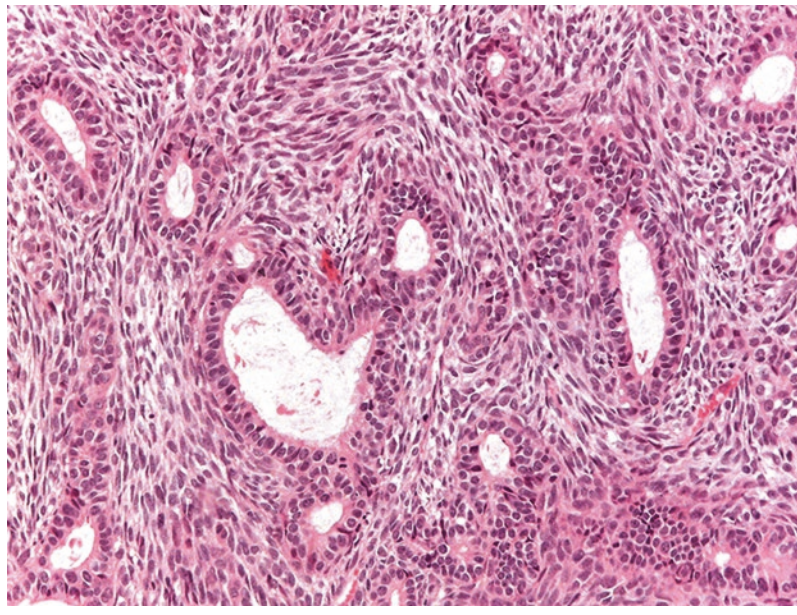
Radiograph (**a**, **b**). Purely lytic poorly limited lesion. The cortex is thin, partially destroyed with soft tissue involvement



Radiograph, axial and sagittal T1 and T2 FS MR images. The mass is calcified, displaces the bones, and has a heterogeneous signal on MR



Monophasic spindle cell synovial sarcoma: spindle cell sarcoma composed of cells with a relatively uniform appearance, growing in intersecting fascicles



Biphasic synovial sarcoma: glandular component and spindle cell component intermixed in the same tumor

Immunohistochemical panel	
• CK	±
• EMA	±
• TLE1	+
• CD99	±
• S100	±

Chromosomal translocations		
• t(X;18) (p11;q11)	SS18-SSX1 and SS18-SSX2	95%
	SS18-SSX4	<1%

45.3 Alveolar Soft Part Sarcoma (ASPS)

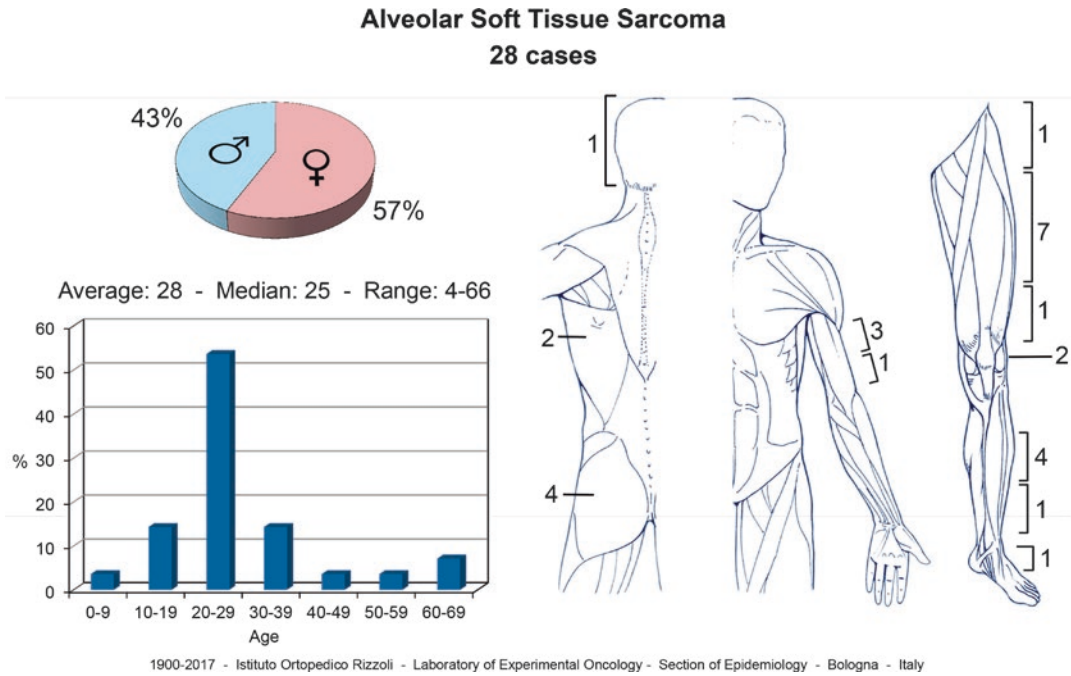
Definition: Sarcoma composed of epithelioid cells arranged in alveolar organoid structures.

Epidemiology: Very rare, less than 1% of all soft tissue sarcomas. Fifteen to 35 years old. More frequent in females in the first three decades of life, while more frequent in males after the third decade.

Location: Deep-seated, lower limb, thigh.

Clinical: Slow-growing painless mass. Tumor may be richly vascularized with pulsation on the mass.

Imaging: On CT: an intense uptake of contrast medium. On angiography: tumoral neoangiogenesis and indirect signs of artero-venous shunt. On MRI: bright both on T1 and T2, homogeneous on the first, inhomogeneous with sharp peripheral demarcation of the mass on the second.



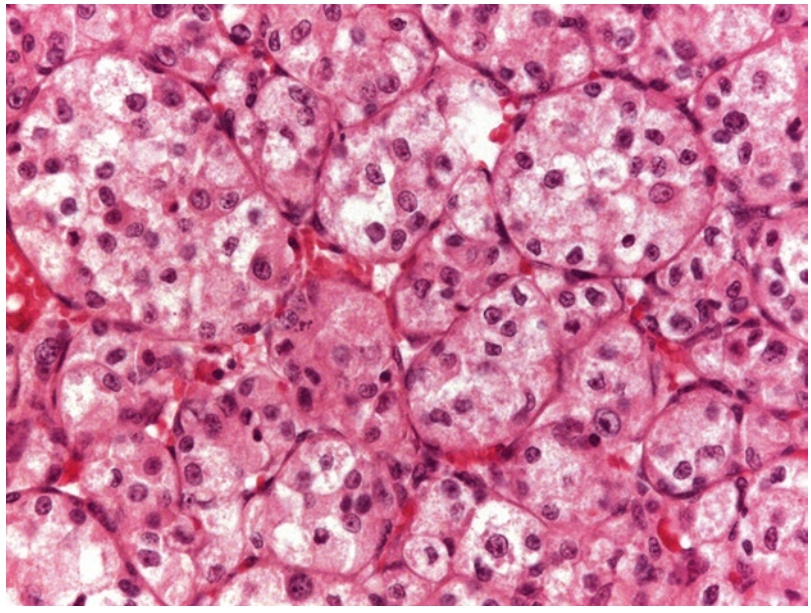
Histopathology: Grossly, soft, yellowish-white or gray-red-purple, with hemorrhagic and necrotic areas, poorly delimited. Histologically, nests of cells separated by thin-walled vascular spaces; loss of cellular cohesion and necrosis in the center of the nests gives the typical pseudoalveolar appearance. Neoplastic cells are large, epithelioid, globose to polyhedric, with eosinophilic granular to clear cytoplasm, often containing rhomboid to rod-shaped inclusions that can be highlighted on PAS stains after diastase digestion. The nucleus is vesicular with a prominent nucleolus. Mitotic figures are rare.

Course and Staging: Recurrences when treated inadequately. Metastases may be present at the time of the diagnosis or even decades after the diagnosis. Survival rate for patients with localized disease at the time of the diagnosis is about 60–70% at 5 years. Usually stage II B or III B.

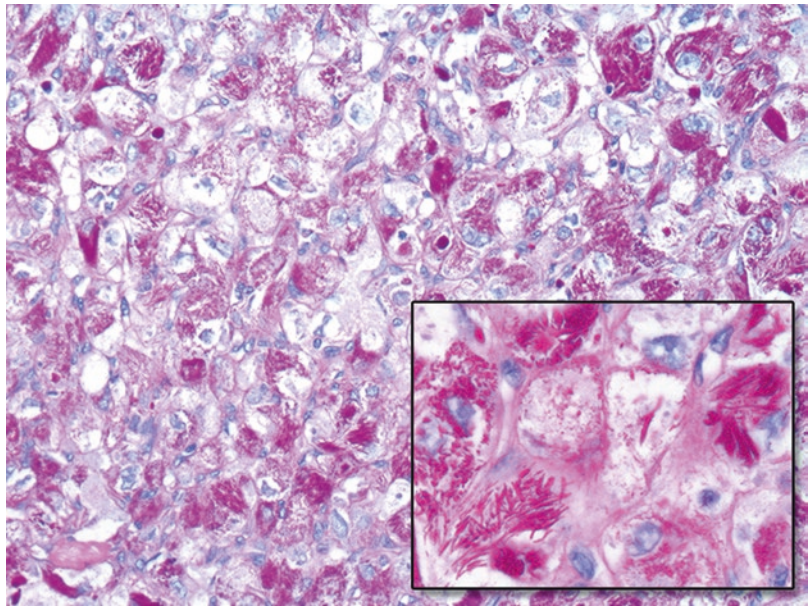
Treatment: Wide or radical excision associated to adjuvant radio- and/or chemotherapy.

Immunohistochemical panel	
• DESMIN	±
• TFE3	+
• S100	±

Chromosomal translocations		
• t(X;17) (p11;q25)	ASPL-TFE3 (type 1, type 2)	100%



Eosinophilic epithelioid cells arranged in nests with loss of cohesion in the center, giving a psuedoalveolar appearance

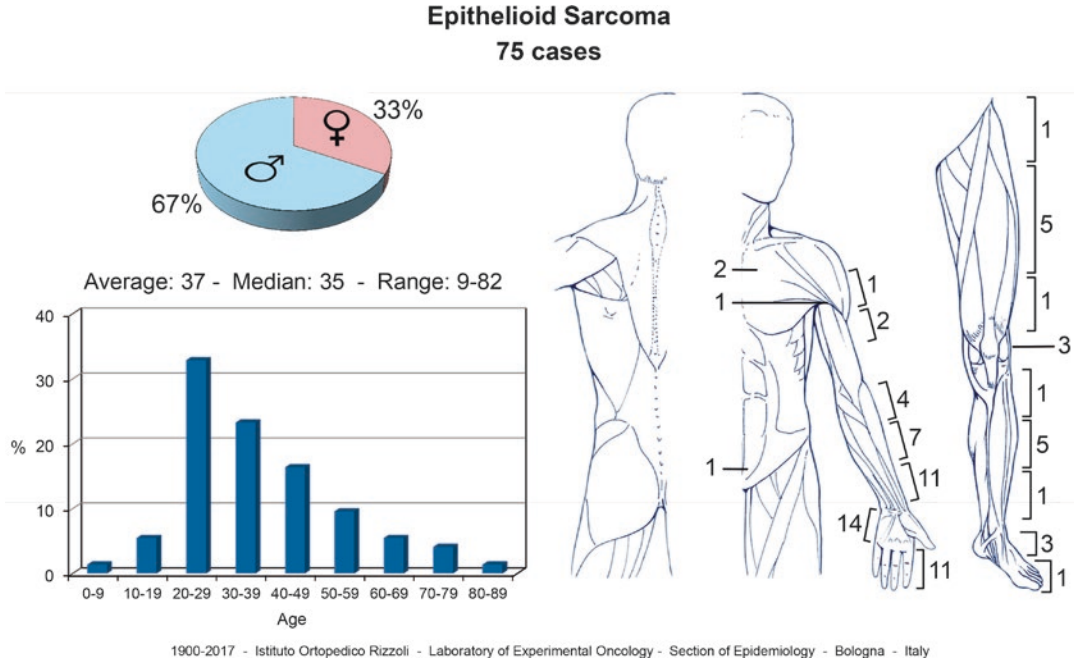


PAS stain after diastase digestion demonstrates rod-shaped inclusions (*inset:* higher magnification)

45.4 Epithelioid Sarcoma

Definition: Malignant mesenchymal neoplasm that exhibits a predominantly epithelial phenotype.

Epidemiology: 1% of sarcomas. More frequent in males. Twenty to 60 years old. Classic distal type nearly twice more frequent that proximal type



Location: Classic type generally occurs in the distal extremities and is among the most frequent sarcomas occurring in the hand and forearm. Proximal type generally occurs in deep soft tissues of the pelvic-perineal, genital, and inguinal regions.

Clinical: Usually one or more small, hard, superficial nodules, adherent to the derma, slightly elevated on the skin; they grow slowly ulcerating the skin surface. Some nodules are deep. Painless. Almost woody, nodules adhere and fixed to the surrounding tissues.

Imaging: On X-ray—Calcifications (20%), bone erosion rare. On MRI—Isointense with muscle on T1, inhomogeneous, hyperintense, with an irregularly outlined lesion on T2.

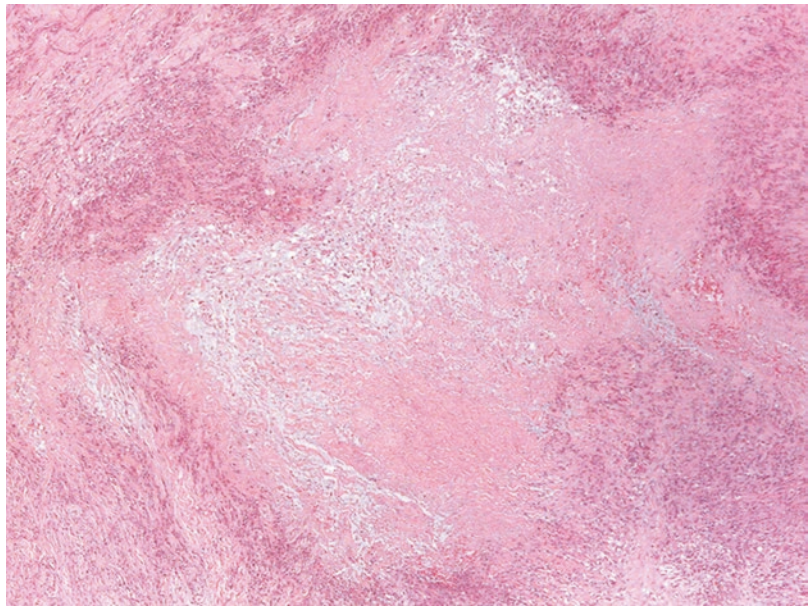
Histopathology: Grossly, multinodular, hard, gray-white, infiltrating and adhering to the skin, fascia, tendon sheaths, muscles, vessels, nerves, periosteum. Histologically, classic type shows a pseudo-granulomatous pattern with a central area of necrosis surrounded by proliferation of large epithelioid to polygonal cells with abundant eosinophilic cytoplasms, vescicular nuclei, and evident nucleoli. At the periphery, neoplastic plump spindle cells arranged in bundles and chronic inflammatory cells are present. Proximal type is composed of larger cells showing carcinoma-like to rhabdoid appearance, with vescicular nuclei and prominent nucleoli; the pseudo-granulomatous pattern is generally absent.

Course and Staging: Frequent metastases in regional lymph nodes and lungs. It diffuses in the limb in a proximal direction along the tendons, muscles, neurovascular bundles, and the lymphatic network of the derma; it can produce multiple superficial ulcerated nodules. Five-year overall survival rate is about 60–80%, while at 10 years is about 40–60%. Proximal type has a worse prognosis. Usually, stage IIB.

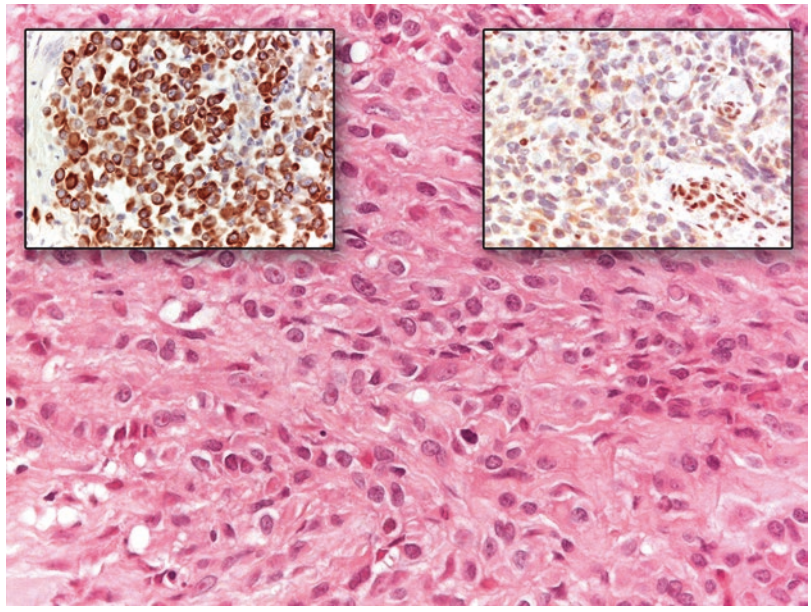
Treatment: Radical excision with dissection of the regional lymph nodes.

Immunohistochemical panel	
• Pan-cytokeratin	+
• EMA	+
• CD34	±
• INI-1 (SMARCB1)	− in more than 90% of cases

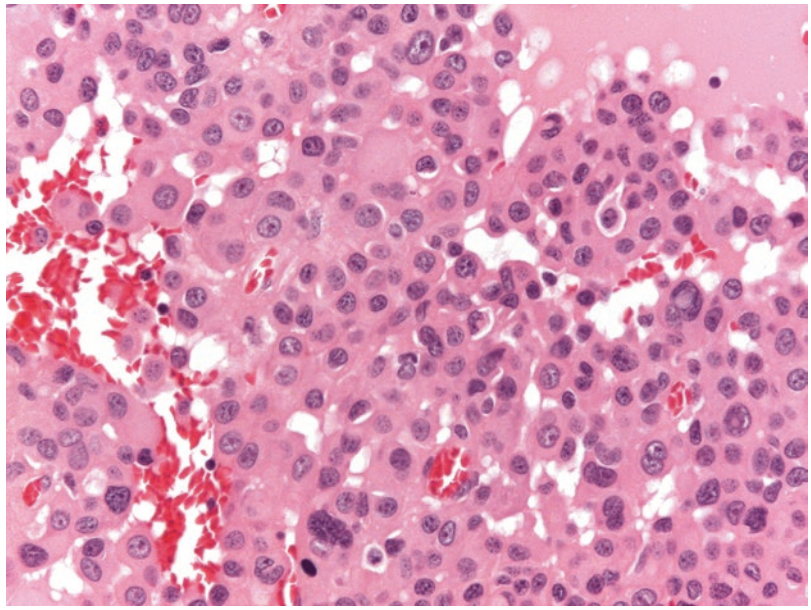
Genetic alteration		
• Deletion/mutation of SMARCB1 gene	Biallelic inactivation of 22q11.2	90%



Classic-type epithelioid sarcoma (low power view): pseudo-granulomatous structures with necrotic centers surrounded by tumoral cells



Classic-type epithelioid sarcoma (high power view): malignant epithelioid cells with abundant eosinophilic cytoplasm, showing immunohistochemical positivity for cytokeratin (*left inset*) and loss of INI-1/SMARCB1 (*right inset*)

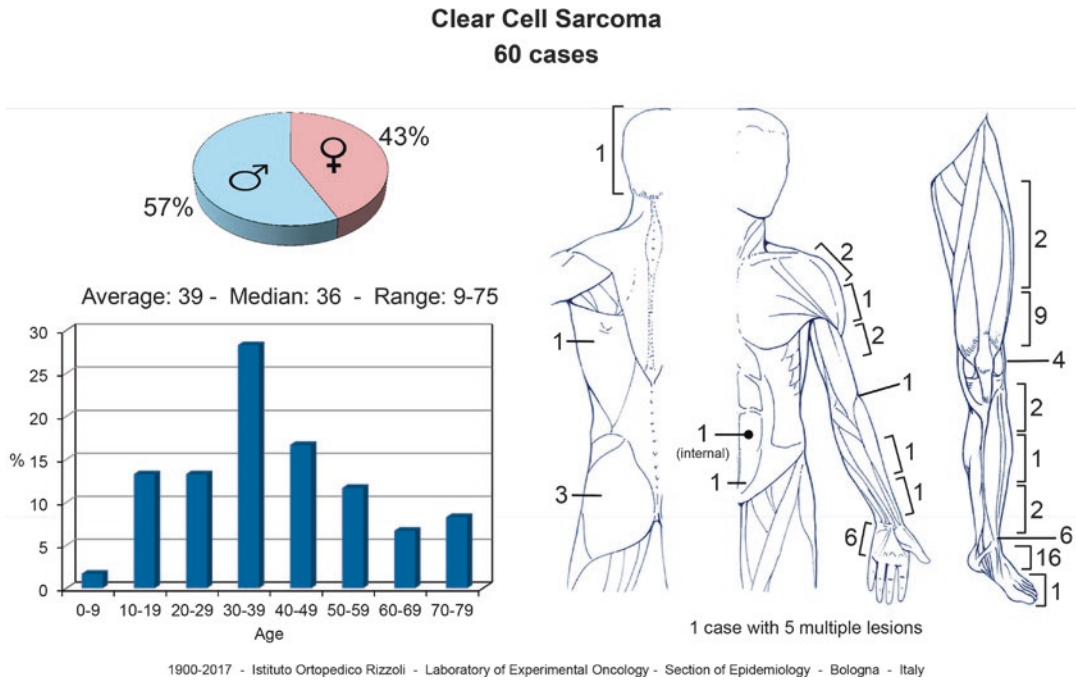


Proximal-type epithelioid sarcoma: Large malignant epithelioid cells with marked cytologic atypia

45.5 Clear Cell Sarcoma

Definition: Sarcoma with melanocytic differentiation, typically close to tendons and aponeuroses.

Epidemiology: Very rare. 20–40 years old.



Location: Foot, ankle, knee, and upper limb. Deep-seated, often associated with tendons and aponeuroses.

Clinical: Slowly growing, moderate size, painless, globose mass.

Diagnosis: On MRI, elliptical, smoothly outlined mass, slightly or markedly hyperintense on T1, white lesion with multiple low intensity septations on T2, homogeneous enhancement after gadolinium.

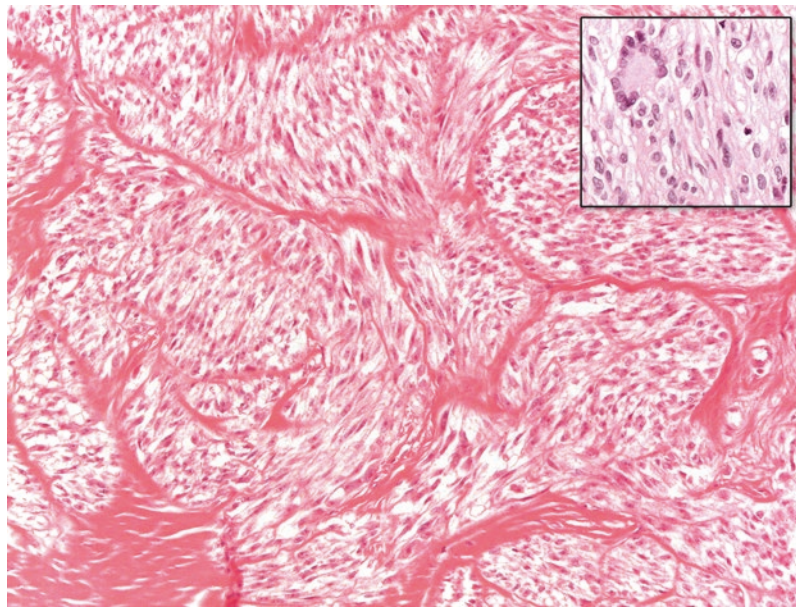
Histopathology: Grossly, firm, globose, gray-white mass with well-defined boundaries. Histologically, nests surrounded by a fine reticular stroma or rough collagen bands. Neoplastic cells are epithelioid, oval, or spindle, with eosinophilic or amphophilic or clear cytoplasm; nuclei are round to elongated, vescicular, with a large nucleolus. Mitotic figures are rare. Scattered wreath-like multinucleated giant cells are often present.

Course and Staging: Not very aggressive clinical presentation but frequent local recurrences. Late metastases (also >10 years) in lymph nodes (50% of cases), bone, and lungs. Poor prognosis with survival rate of 10% at 20 years. Usually stage II B.

Treatment: Wide or radical excision with dissection of the regional lymph nodes.

Immunohistochemical panel	
• S100	+
• HMB45	+
• MART-1	+
• MITF	+

Chromosomal translocations		
• t(12;22) (q13;q12)	EWSR1-ATF1 (type 1, type2)	>90%
• t(2;22) (q33;q12)	EWSR1-CREB1	<6%



Epithelioid and spindle cell with optically clear cytoplasms arranged in nests surrounded by rough collagen bands; wreath-like multinucleated giant cells can be present (*inset*)

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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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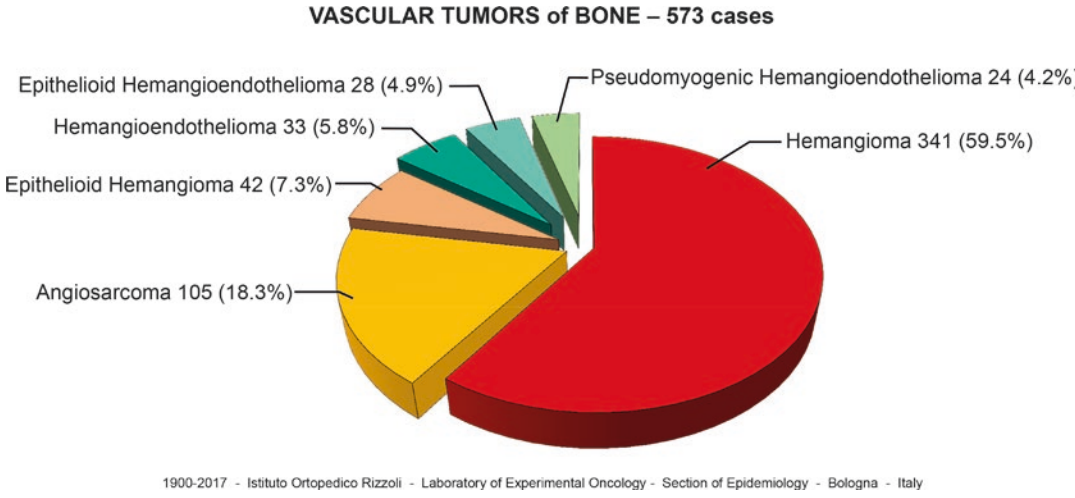
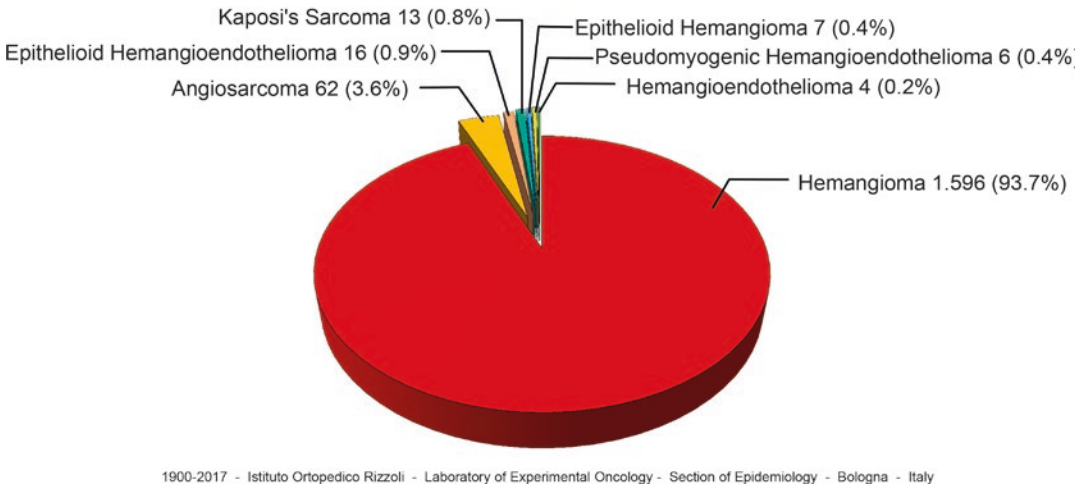




Key points	
• Clinical	Adults, pain and swelling
• Radiological	Frequently multifocal, pure lytic lesion
• Histological	Proliferation of endothelial cells at various grade of differentiation
• Differential diagnosis	Bone metastasis, myeloma, and all other primary purely osteolytic lesions of adults

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

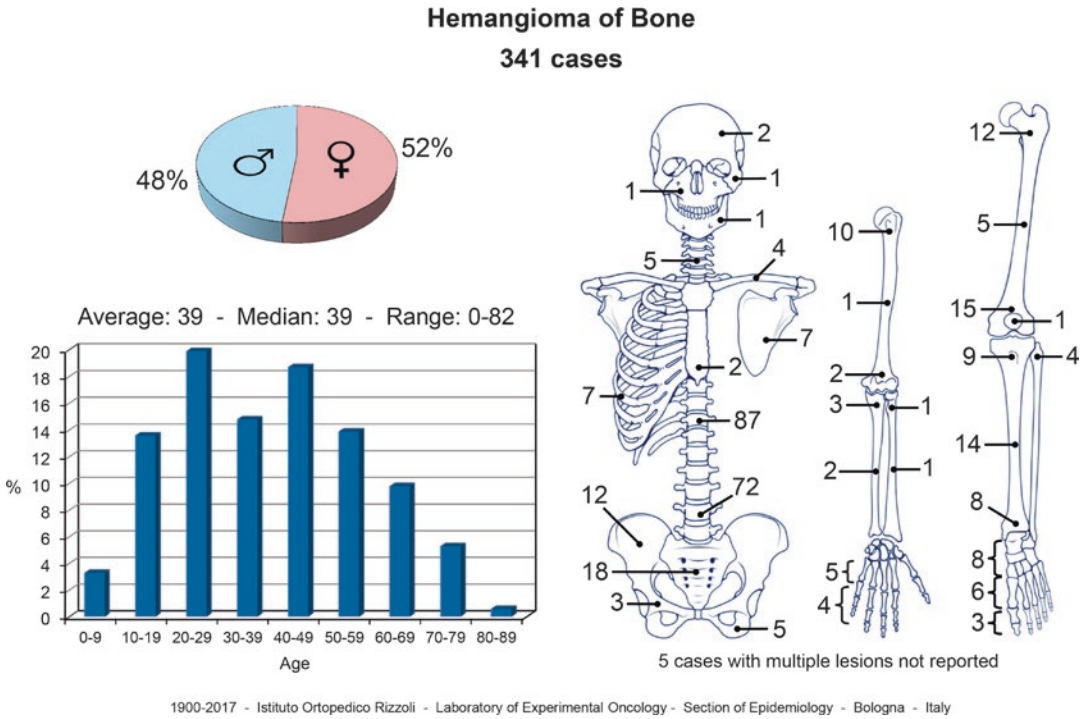
Prognosis
Hemangiomas (with epithelioid variant) → benign lesions
Hemangioendothelioma → good prognosis
Angiosarcoma → poor prognosis

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.

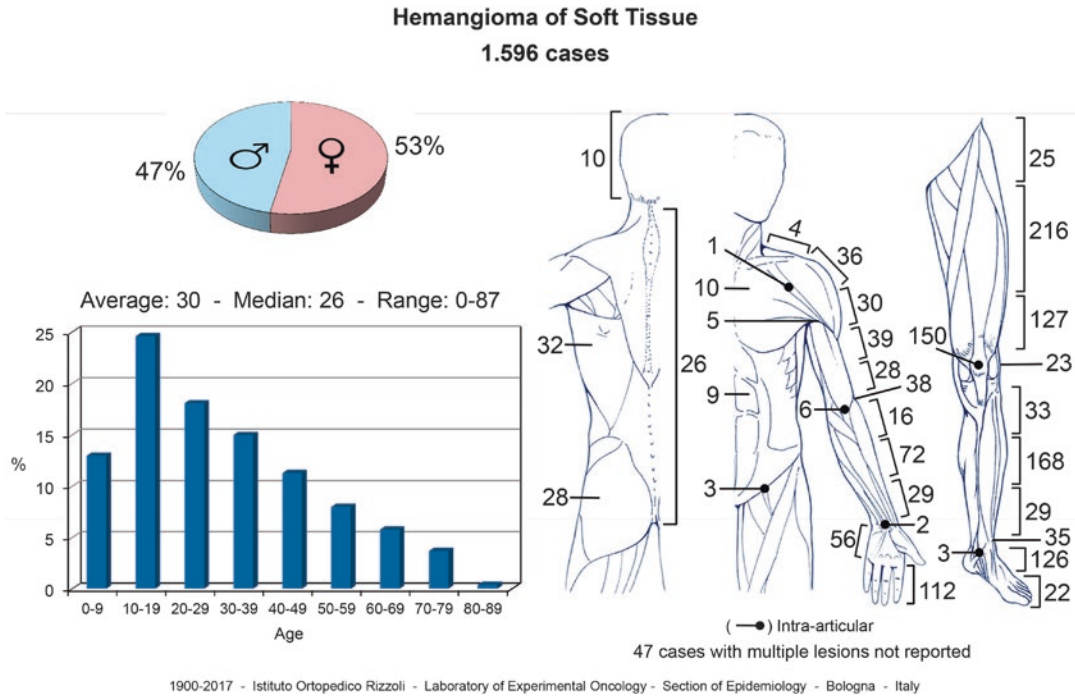
Histopathology: Hemangiomas of bone have variable histological features. Capillary and cavernous hemangiomas, that represent the vast majority of hemangiomas, show numerous blood-filled spaces, lined by a thin layer of flat endothelial cells, without atypia. The vascular spaces are surrounded by loose 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.

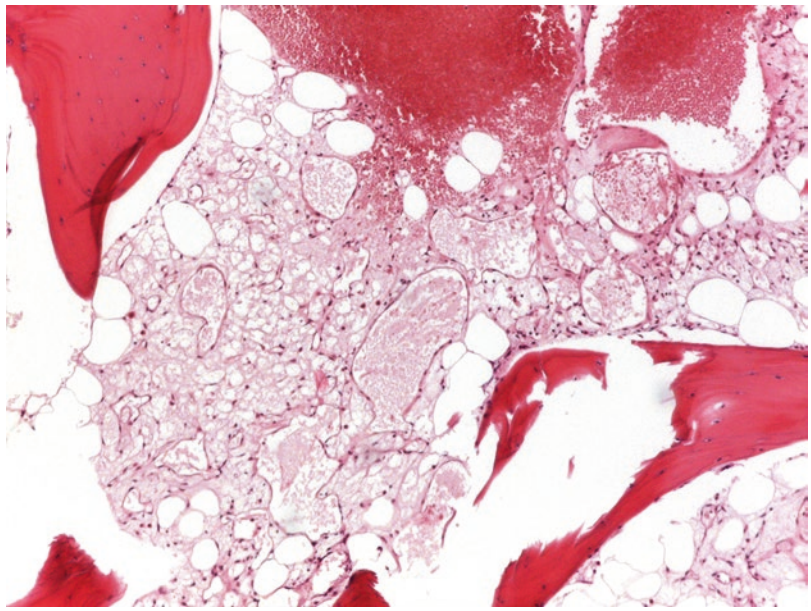
Clinical: Superficial (cutaneous/subcutaneous) hemangiomas are reddish-wine colored, painless lesions, generally present at birth. Intramuscular hemangioma arises within the belly of a single muscle; only in the hand and foot it may expand between the fascia, muscles, and tendons. Pain is sharp and becomes 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.

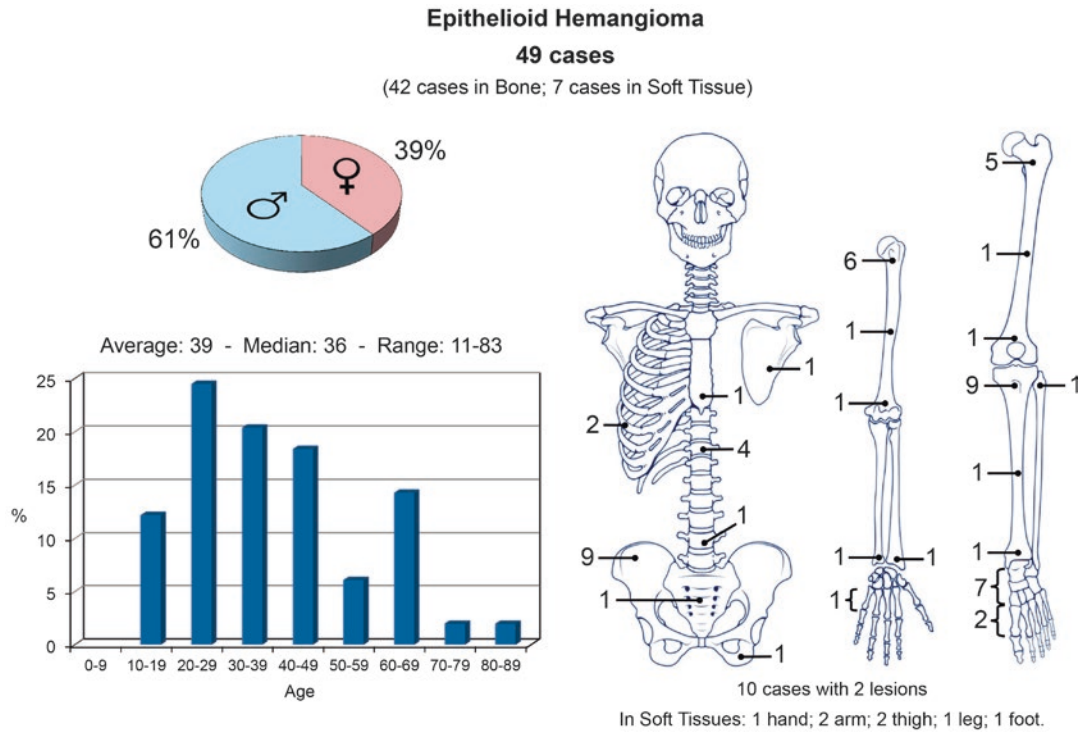


On histology, hemangioma shows thin-walled blood vessels lined by a single layer of endothelial cells with the marrow and between bony trabeculae.

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.

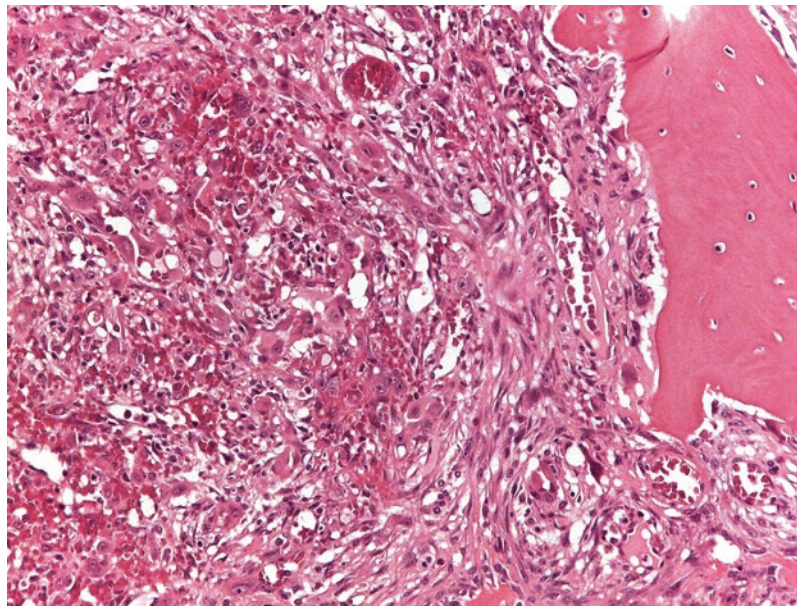
Clinical: Patients usually present with pain localized to the involved anatomical site. In soft tissues, the majority of epithelioid hemangioma presents as subcutaneous masses of a year or less in duration. The process is usually uninodular, but multinodularity, generally in contiguous areas, can be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

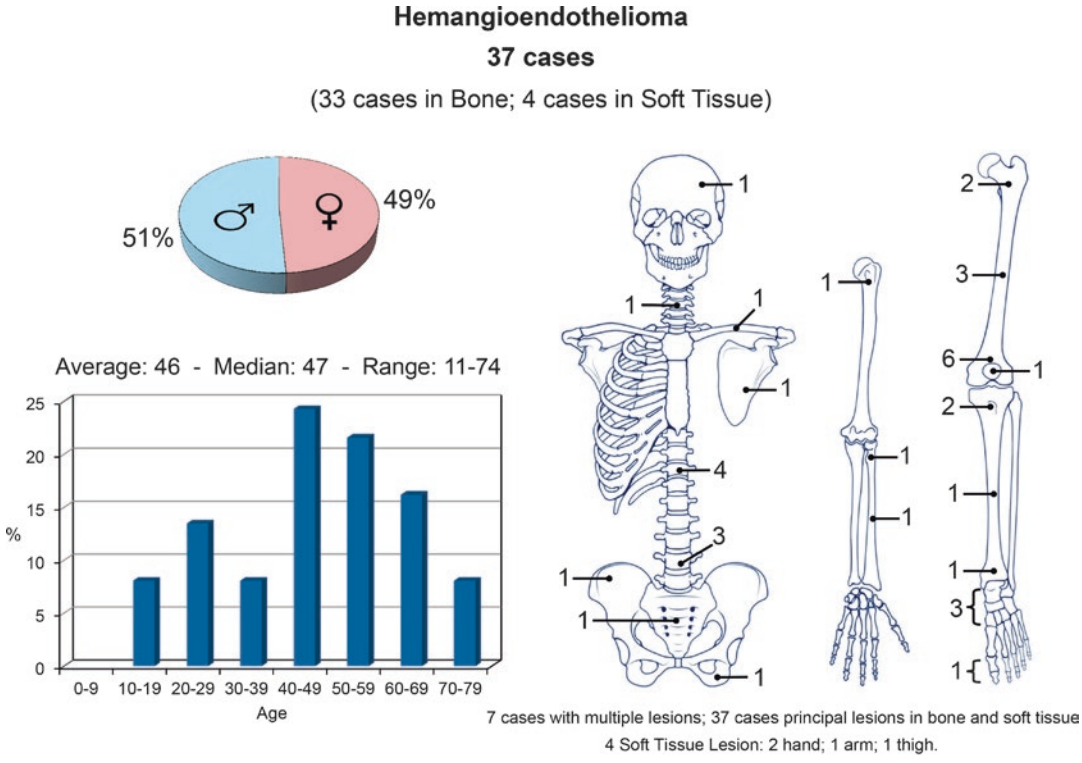
Course and Treatment: Epithelioid hemangioma of bone is a locally aggressive lesion and treatment usually consists of curettage and less frequently, marginal en-bloc excision of the tumor. Radiotherapy could be used for tumors in inaccessible locations. Local recurrence is reported to occur in 1/3 of 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.

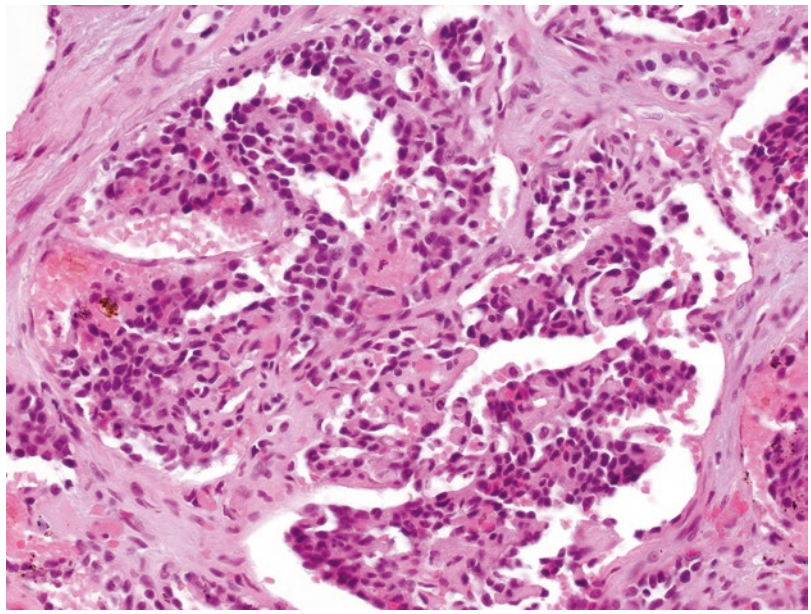


Large epithelioid cells line well-formed vascular spaces associated with isolated prevalent epithelioid or slightly spindled cells adjacent to a well-formed neoplastic vessel

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.



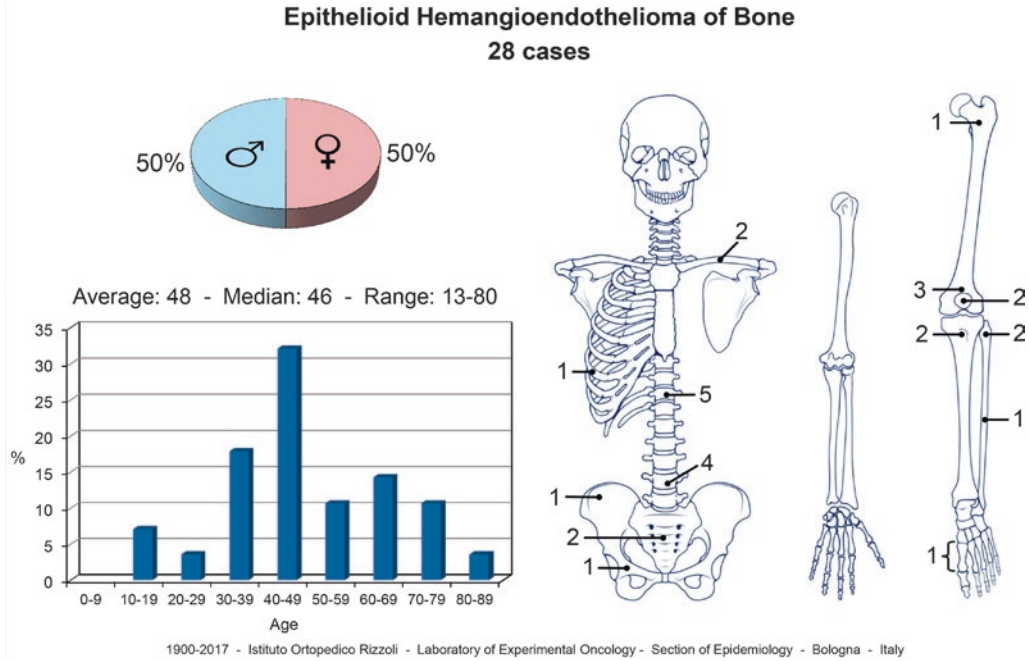


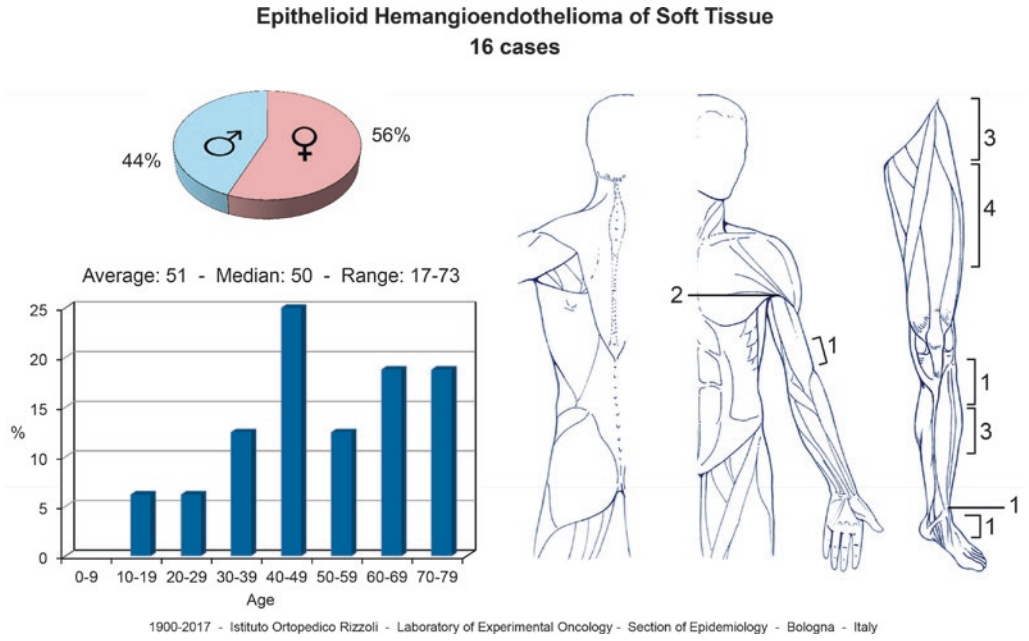
Histological features of papillary intralymphatic angioendothelioma, composed of glomerulus-like structures with papillary structures projecting into the lumen, covered by plump “hobnail” endothelial cells

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.

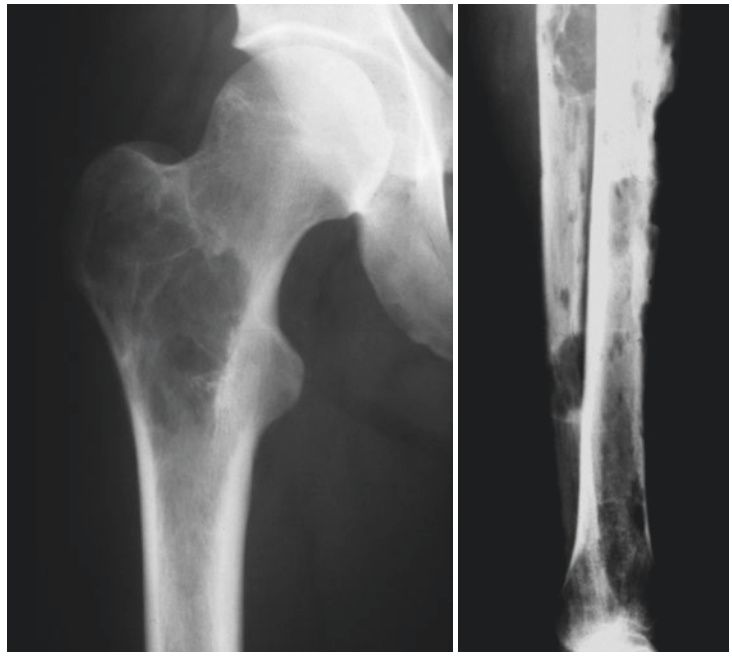
Imaging: Radiologically epithelioid hemangioendothelioma of bone, like the other vascular tumors in bone, presents as a lytic lesion, without a sharp demarcation and they may be expansile and erode the cortex.

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.

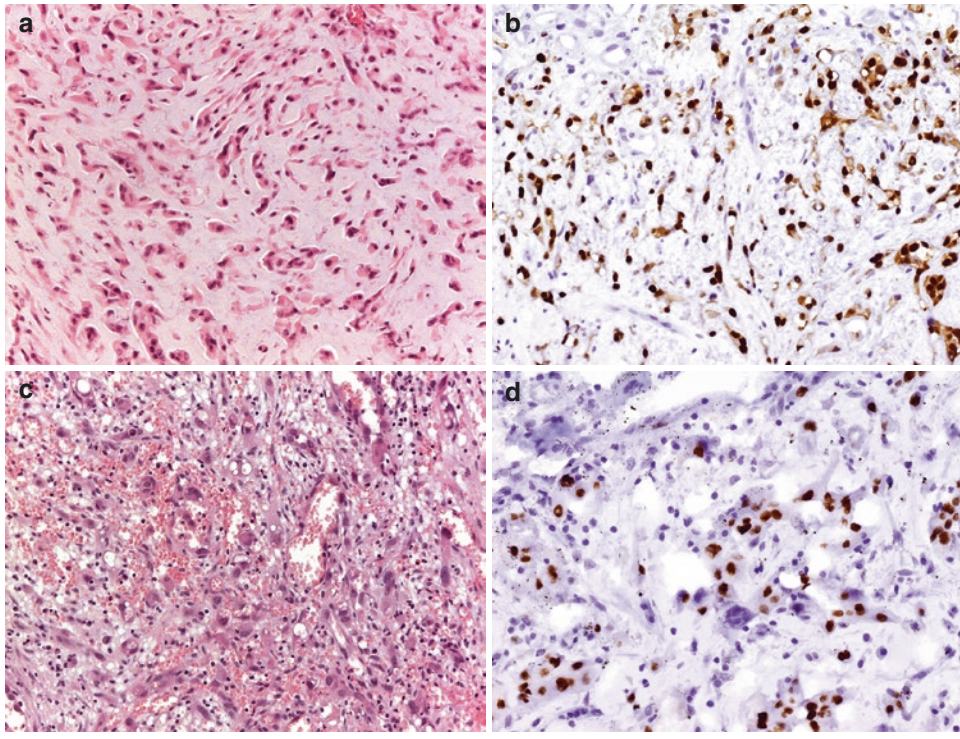
Course and Treatment: Wide resection is the treatment of choice. Although less clinically aggressive than angiosarcoma, epithelioid hemangioendothelioma is associated with metastasis in 20–30% of cases, and 10–15% of patients die of disease. The preferred sites for metastasis are the lungs followed by 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

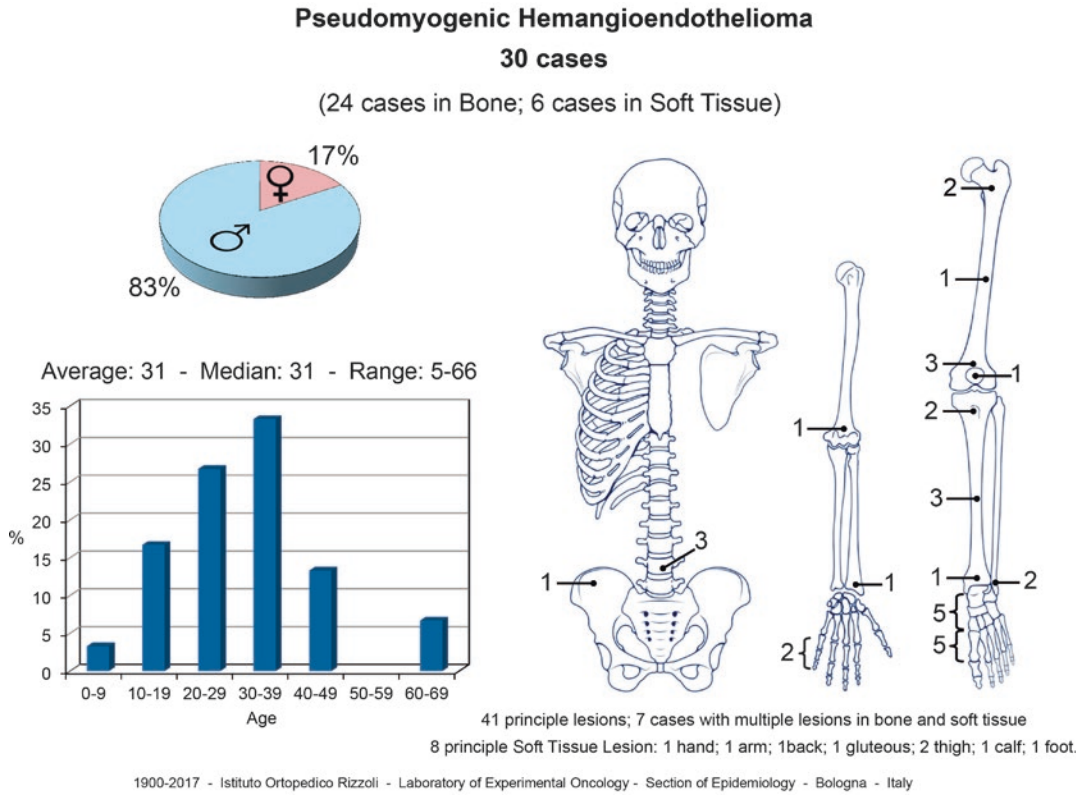


An example of epithelioid hemangioendothelioma constituted of cords, strands, or nests of epithelioid cells in a myxohyaline stroma on hematoxylin and eosin (**a**: ×200 of magnification) associated with a strong nuclear reactivity for CAMTA1 antibody (**b**: ×200 of magnification). A second example 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).



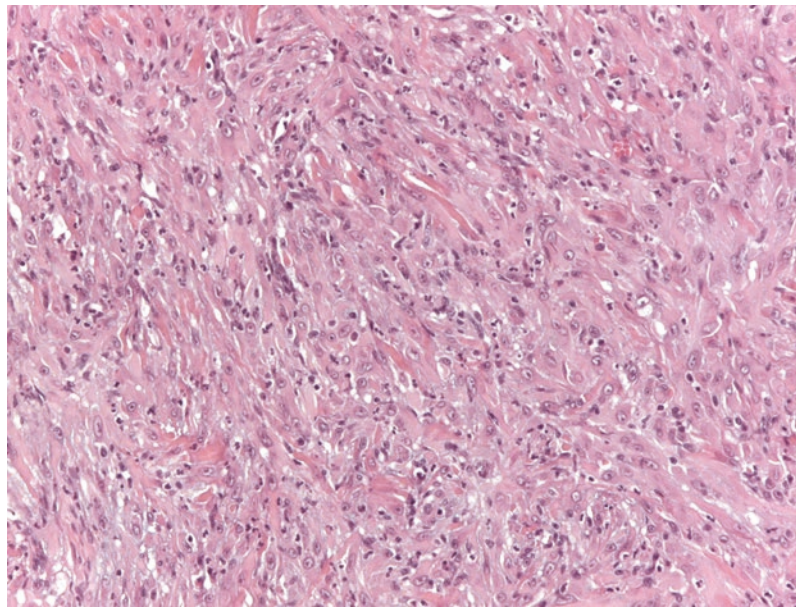
Location: Patients usually present with dermal or subcutaneous nodules on the extremities, most commonly the lower limbs, and 66% of patients have multifocal disease at presentation, often involving multiple tissue planes (deep soft tissue, skeletal muscle, or bone). The bone tissue involvement is reported 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.

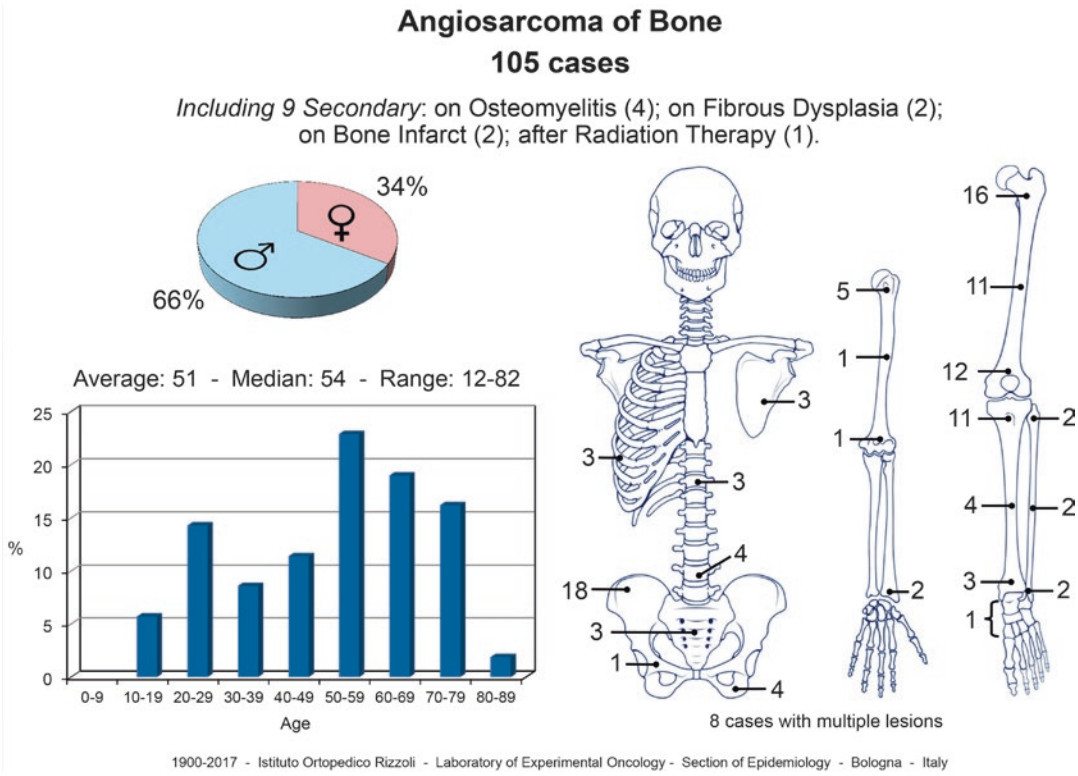


The tumor is composed of sheets and loose fascicles of spindle cells with abundant brightly eosinophilic cytoplasm and small nucleoli. Scattered neutrophils are present (**a**, magnification ×200)

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.

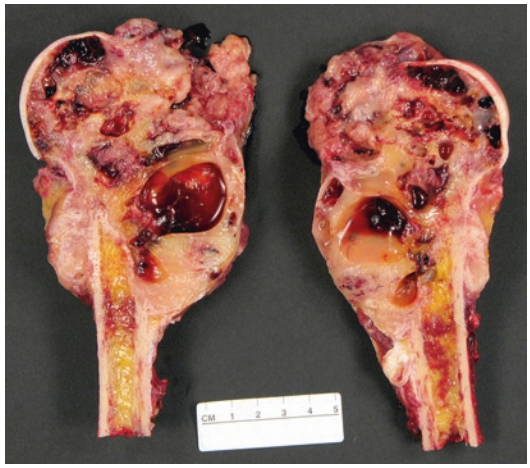


Location: Usually occurring in the long tubular bones, most frequently in the lower extremities. In bone, 30–40% of angiosarcomas are multifocal.

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.

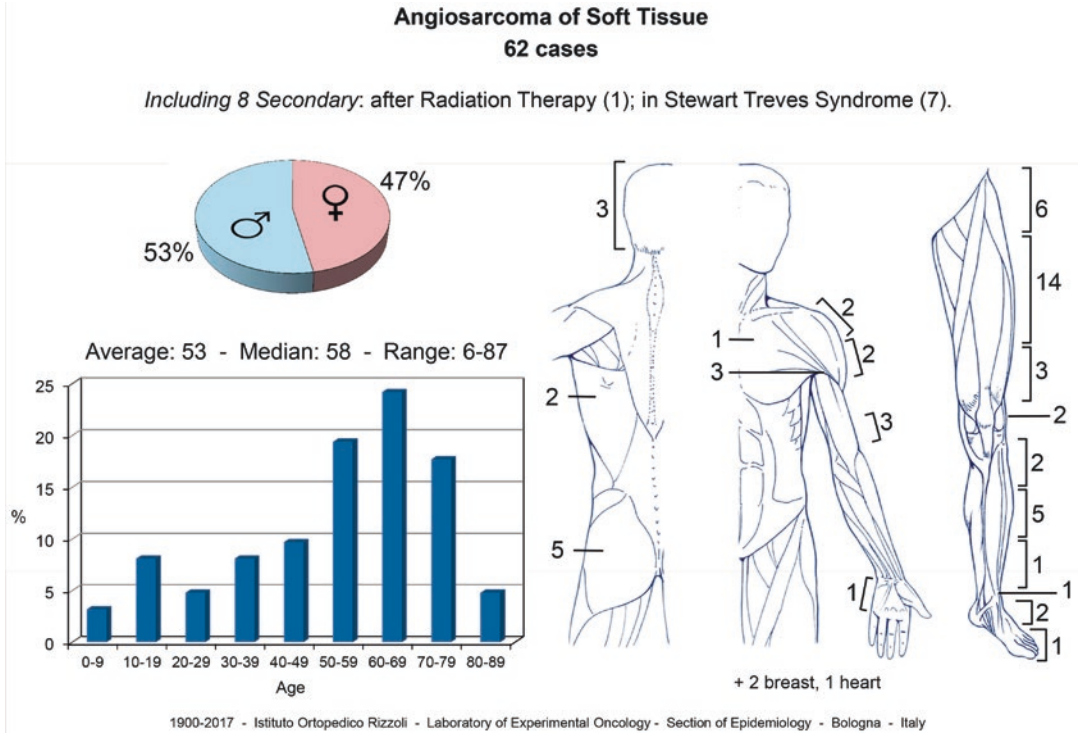


At macroscopy, angiosarcoma is usually a big mass, friable, hemorrhagic, and tan-red that destroys the cortex and extends into the soft tissue

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.

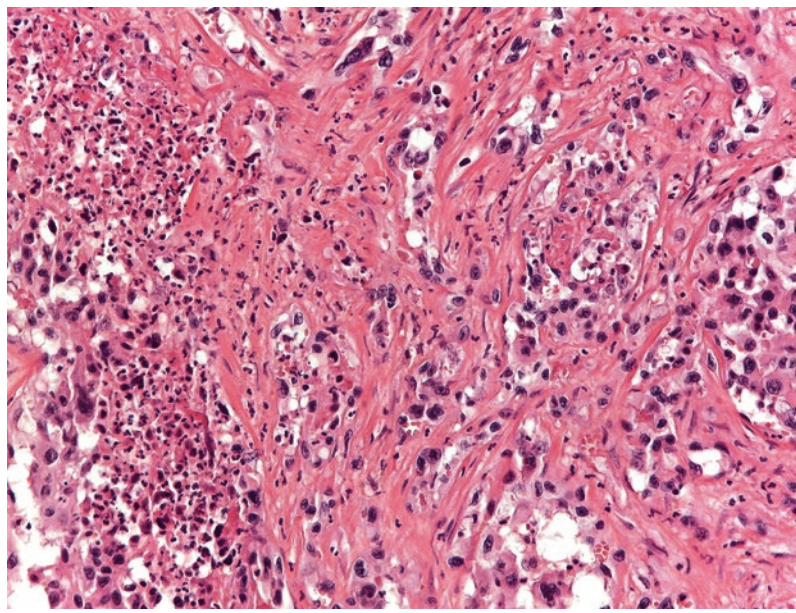
Clinical: Soft tissue angiosarcoma develops as enlarging mass, in 1/3 of patients associated with other symptoms such as coagulopathy, anemia, persistent hematoma, or bruisability.

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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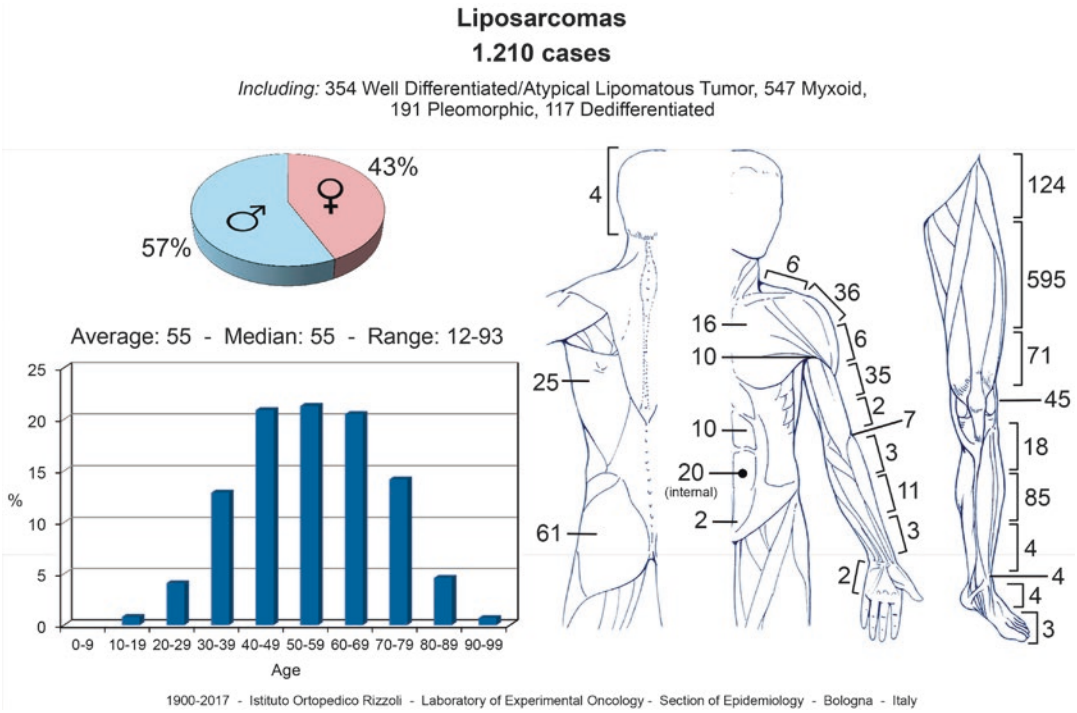
Liposarcomas

47

Angelo Paolo Dei Tos, Marco Gambarotti, and Alberto Righi

Definition: Malignant tumor featuring adipocytic differentiation.

Epidemiology: The most frequent sarcoma of the soft tissues. Prevails in males when it is localized in the limbs, but not when in retroperitoneum. Very rare prior to 20 years of age, whereas it is typical of adult and advanced age.



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Localization: Most common in thigh, retroperitoneum, inguinal region, and popliteal fossa. Rare in hands, feet, and neck.

Clinical: Insidiously growing, deep-seated, ill-defined mass that may attain a large size. Pain, tenderness, and functional disturbances occur in 10–15% of cases, but these are usually late complaints. Tumor may be painful due to compression on the nerve or cause edema of the limb due to venous occlusion. Retroperitoneal tumor may cause hydronephrosis, intestinal compression, inguinal hernia, and edema of the lower limbs.

Imaging: On X-ray: in more differentiated varieties, well-delineated radiolucency clearly distinguished from the surrounding muscles. Occasionally calcification, little vascularity. In more undifferentiated cases, less well defined masses with greater density. On CT scan: in lipoma-like type, well-marginated mass mimicking lipoma. Frequently, thickened linear, nodular septa that enhance after contrast. In myxoid type, encapsulated, septated, slightly heterogeneous mass mimicking a cyst. Density of water. On MRI, the myxoid type shows a homogeneous low signal intensity (dark) on T1 and high (white) on T2, strong enhancement, minute foci of fatty tissue, small bright streaks on T1 in an overall dark lesion are typical. Nonspecific appearances are displayed by the other varieties: heterogeneous signal intensity on T1, white and dark areas on T2, enhancement of all components. In dedifferentiated liposarcoma, a homogeneous mass of low signal intensity on T1 converts to a lesion with bright and intermediate areas on T2. Often the tumor is adherent or erodes adjacent cortical bone that responds with modest periosteal reaction. On bone scan, liposarcomas are inordinately hot in contrast to other malignant soft tissue tumors. On angiography: richly vascular with intense intra- and peritumoral neoangiogenesis.

Histopathology: Usually very large, multilobated, delimited by a thin reactive tissue (pseudocapsule) interrupted by some tumor nodules. Satellites are present.

Varieties

(a) **Well-differentiated Liposarcoma/Atypical Lipomatous Tumor (WDL/ALT)** 40% of all cases.
- Liposarcoma lipoma-like: The most common. Yellowish, soft, friable. Mature fat mixed with collagen. Variable number of lipoblasts (from many to none) and mature adipocytes. Hyperchromatic nuclei in both adipocytic and stromal cells most often within fibrous septa. Often confused with lipoma.
- Sclerosing liposarcoma: More frequent in retroperitoneum and spermatic cord. Whiter and firmer. Scattered bizarre stromal cells associated or not with multivacuolated lipoblasts set in abundant fibrillary collagen.
- Inflammatory: More frequent in retroperitoneum. Like liposarcoma lipoma-like and sclerosing liposarcoma but admixed with extensive chronic inflammation. Easily mistaken for an inflammatory process involving fat.

(b) **Myxoid Liposarcoma (ML):** Most frequent in the limbs (30–35%). Soft, pale yellow, mucoid and translucid or bright cherry red. Spindle cell proliferation set in a myxoid matrix and associated with a network of thin capillaries of uniform caliber organized in a plexiform pattern. Monovacuolated lipoblasts are most often seen at the periphery of the lesion. Mitotic activity is rare. Hypercellular areas > 5% fo the tumor, featuring ovoid-round hyperchromic cells with scanty cytoplasm and diminished intercellular myxoid matrix define the high-grade variant (formerly known as round cell liposarcoma). Genetics demonstrate characteristic chromosome translocations: t(12;16) that fuses the DDIT3 (CHOP) gene on 12q13 with the FUS gene on 16p11, and t(12;22) that fuses DDIT3 gene with EWSR1 gene on 22q12.

(c) **Pleomorphic Liposarcoma (PL):** Rare (5%). Softer, encephaloid. On high power pleomorphism is prominent. Pleomorphic lipoblasts with vacuolated cytoplasm are scattered amongst undifferentiated hyperchromatic neoplastic cells. Large atypical, multinucleated giant cells are scattered through the tissue. Myxoid change of the matrix is sometimes observed. One-third of cases features an epithelioid morphology associated with the presence of pleomorphic lipoblasts. Many atypical mitoses are observed. S-100 immunoreactivity may help highlight the presence of multivacuolated lipoblasts in those cases in whom adipocytic differentiation tends to be focal and, therefore, easily overlooked. Similar to most pleomorphic high-grade sarcomas, pleomorphic liposarcoma tends to exhibit complex karyotypes.

(d) **Dedifferentiated Liposarcoma (DL):** Relatively frequent (15%). Most cases occur in retroperitoneum. Abrupt (not always) transition for well-differentiated liposarcoma to high-grade non-lipogenic sarcoma. Sometimes dedifferentiation can show lipogenic features, with pleomorphic lipoblasts (homologous differentiation). Heterologous differentiation (myogenic, chondro-osteogenic) can be observed. On immunohistochemistry, overexpression of MDM2 and CDK4 is consistently observed in both components as a consequence of 12q13-15 chromosome region amplification.

Course and Staging: Type (a) are low-grade malignant tumors and present as stage IA. Type (b) purely myxoid liposarcomas are low-grade malignant tumors; they usually present as stage IA and seldom progress to higher stages. The presence of hypercellularity is associated with worsening of prognosis and these lesions should be considered stage II. Type (c) are high-grade malignant tumors and present as stage IIB. Type (d) are high-grade malignant tumors and present as stage IIB. Type (a and b) recur also many years after excision, whereas in type (c and d) local recurrence occurs rapidly. Metastases are exceptional in type (a), rare in type (b), frequent and early in type (c and d).

Treatment: in type (a and b) wide excision, while in type (c and d) radical removal. Radiotherapy is useful in type (c and d), and particularly effective in type (b). Conventional ifosfamide-based chemotherapy is preferred in type (c). Trabectedin (ET743) has shown to be effective in myxoid liposarcoma.

WDLPS/DDLPS (Well-differentiated liposarcoma/ Dedifferentiated liposarcoma)

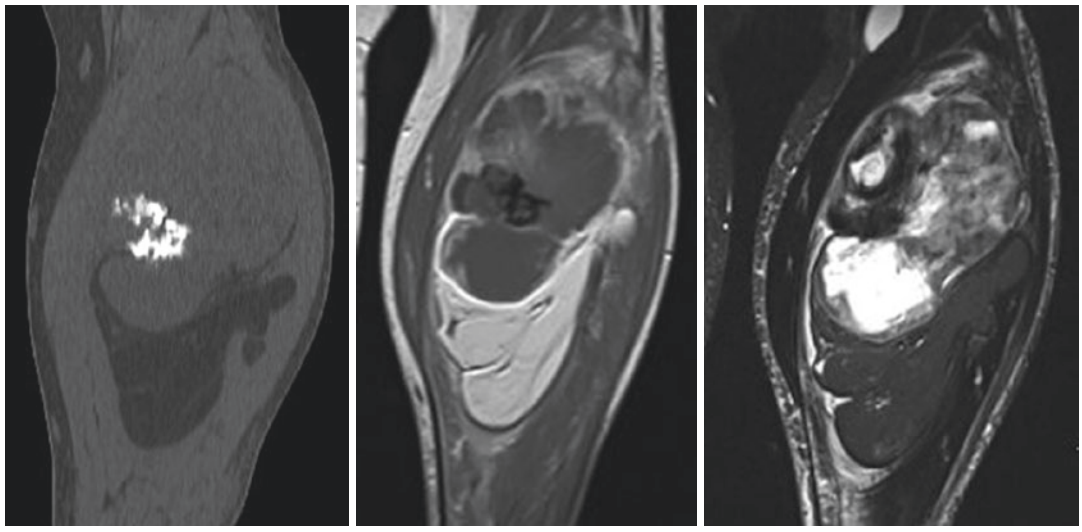
Immunohistochemical panel	
• S100	+
• MDM2	+
• CDK4	+

Atypical lipomatous tumor/well-differentiated LPS/ dedifferentiated LPS

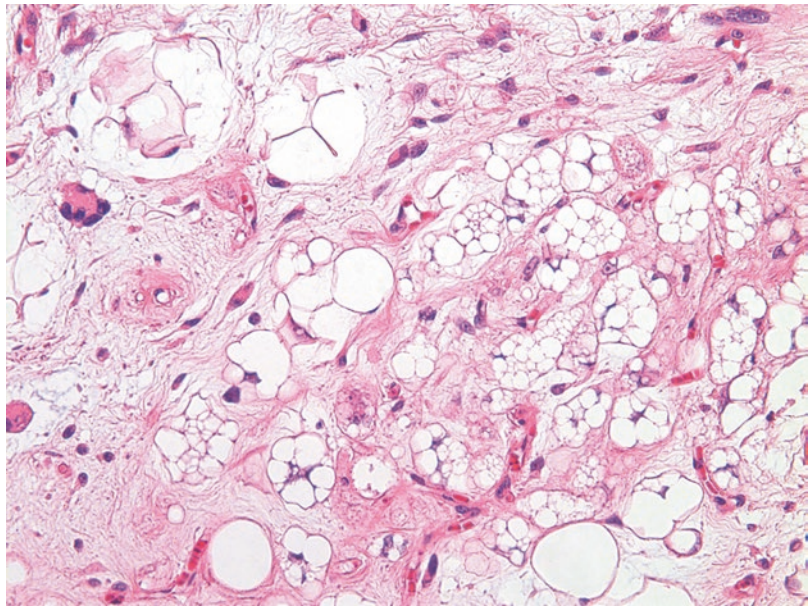
Genetic aberrations	
• MDM2	Amplification
• CDK4	Amplification

Myxoid/round cell liposarcoma

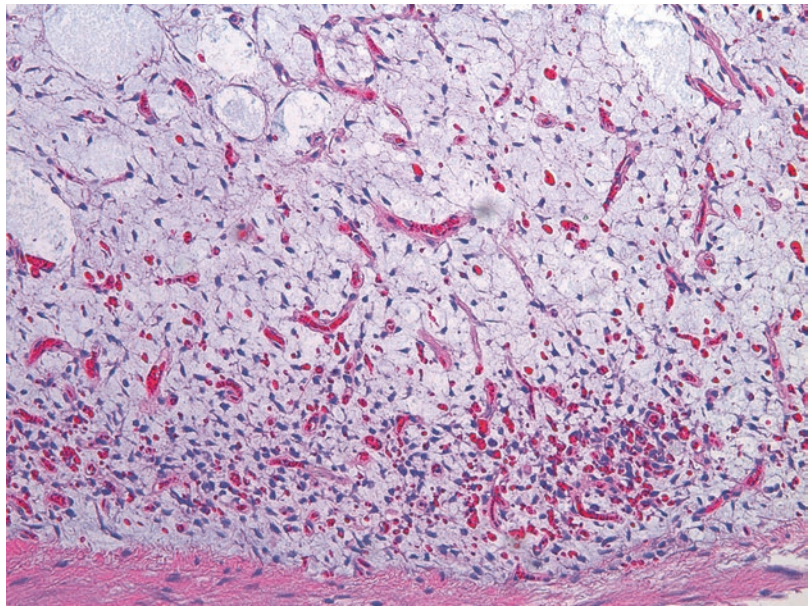
Chromosomal translocations		
• t(12;16) (q13;p11)	TLS(FUS)-DDIT3 (type 1, type 2)	95%
	TLS(FUS)-DDIT3 (type 3)	
• t(12;22) (q13;q12)	EWSR1-DDIT3 (type 1)	1–5%
	EWSR1-DDIT3 (type 2, type 3)	



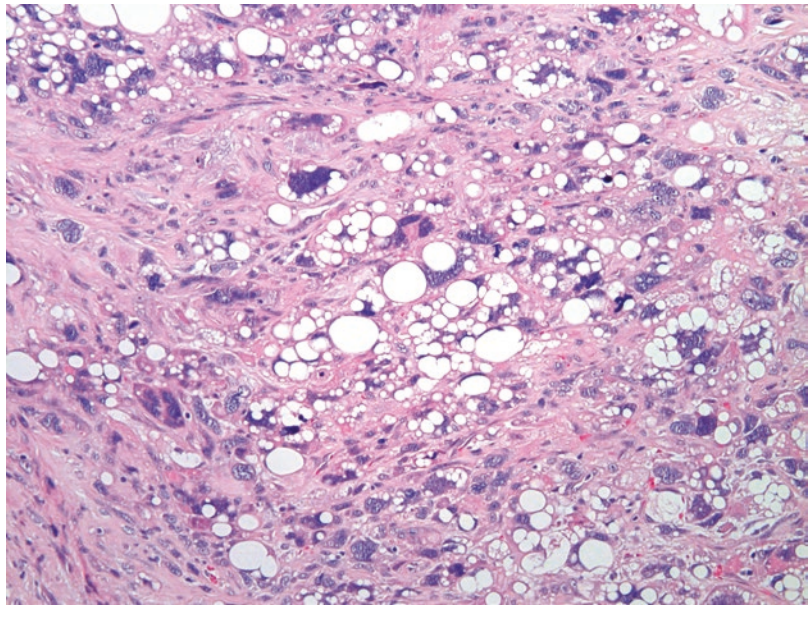
Well-limited mass of the thigh. On CT, the mass is ossified. On T1 and T2W FS coronal images, the lesion is made of two components. One is fat, corresponding to a well-differentiated liposarcoma, the second mainly fluid, is partially ossified, and corresponds to a myxoid component



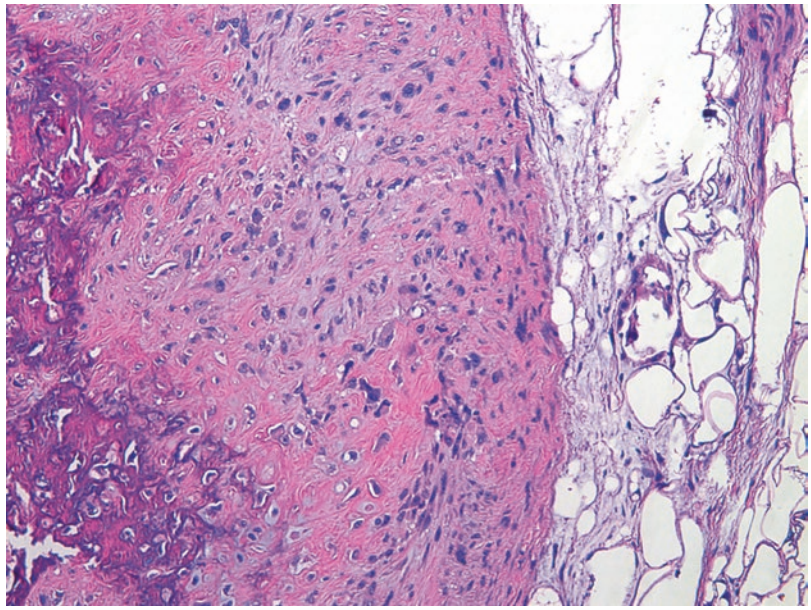
Well-differentiated liposarcoma/atypical lipomatous tumor. Mature adipocytic cells and scattered atypical adipocytes with hyperchromic nuclei and rare lipoblasts (unnecessary for diagnosis)



Myxoid liposarcoma. Oval to stellate cells embedded in a myxoid matrix with typical arborizing vascular pattern. Variable presence of an hypercellular component



Pleomorphic liposarcoma. Undifferentiated pleomorphic sarcoma-like high-grade sarcoma with scattered pleomorphic lipoblasts



Dedifferentiated liposarcoma. Lipoma-like liposarcoma that abruptly turns into a high-grade spindle cell and/or pleomorphic sarcoma; osteosarcomatous heterologous differentiation is evident in this case

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Chemotherapy of Soft Tissue Sarcomas

48

Stefano Ferrari and Emanuela Palmerini

48.1 Localized Disease

The use of chemotherapy in patients with localized high-grade soft tissue sarcoma (STS) is still under discussion in the sarcoma community. Outside clinical trials, the systemic treatment must be applied on the basis of a patient–physician shared decision [1]. Several studies have been performed with conflicting results, but in two meta-analysis an advantage from the use of chemotherapy has been showed in patients with high-grade, large (>5 cm) and deep seated STS [2, 3].

In patients with G2–3, deep, >5 cm soft tissue sarcomas (STS), regional hyperthermia in addition to systemic chemotherapy may improve the local control and the overall survival [4].

A randomized trial showed no differences between three (preoperative) and five (pre- and postoperative) courses of full-dose chemotherapy with epirubicin plus ifosfamide in high-risk STS patients [5]. Also, a recent trial compared preoperative epirubicin plus ifosfamide versus a histology-driven chemotherapy: a statistically significant benefit in terms of both disease-free survival (DFS) and overall survival (OS) in favor of epirubicin and ifosfamide was shown [6]. Since there is no obvious evidence that histology-driven chemotherapy could be detrimental, this may be viewed as providing randomized evidence of the efficacy of neo-adjuvant therapy with full-dose anthracyclines plus ifosfamide in high-risk STS, and results of final analysis are awaited.

In patients with locally advanced non-resectable tumors, or requiring mutilating surgery, chemotherapy and/or radiotherapy, isolated hyperthermic limb perfusion with tumor necrosis factor-alpha (TNFa) + melphalan in case of extremity lesions, or regional hyperthermia combined with chemotherapy are available options [7].

48.2 Advanced Disease

An EORTC randomized trial showed no survival advantage from the addition of ifosfamide to the standard doxorubicin [8]. Nonetheless the same study demonstrated a higher response rate with the combined use of ifosfamide/doxorubicin. Based on these results, chemotherapy with doxorubicin plus ifosfamide should be considered the treatment of choice in first line, when tumor shrinkage might be useful and patient performance status is good. Also, a small phase II study tested the combination of doxorubicin with an antibody directed against platelet-derived growth

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factor receptor alpha (PDGFRA), olaratumab, in the first-line setting. A statistically significant higher OS in comparison with doxorubicin alone was demonstrated, with a non-statistically significant benefit in progression-free survival (PFS) and response rate [9]. Based on a median OS gain of 11.8 months and a median PFS increase of only 2.5 months, the drug is FDA and EMA approved and results of a confirmatory phase 3 study, the ANNOUNCE (NCT02451943), will be available soon. Also, while doxorubicin monotherapy might be offered to patients with advanced solitary fibrous tumors (SFT) [10], there is retrospective evidence that doxorubicin plus dacarbazine might be a choice for multi-agent, first-line chemotherapy for SFT and leiomyosarcoma patients [11, 12].

Beyond the first line, evidence for medical treatment in STS is less robust and all the more driven by histology, since some types are more chemosensitive as compared to others and histology-specific response to different agents was demonstrated in several phase II studies.

In myxoid liposarcoma, a peculiar pattern of tumor response to trabectedin has been reported [12], which is also effective in leiomyosarcoma and synovial sarcoma [12]. Similarly, in 2016, eribulin belonging to the family of microtubule-targeting agent was approved for the treatment of liposarcoma progressing on anthracycline, with a median OS improvement of 7.2 months as compared to dacarbazine [13].

Responses have been obtained in synovial sarcoma with high-dose ifosfamide [14, 15]. Randomized evidence provided that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy and gemcitabine was shown to have antitumor activity in leiomyosarcoma also as a single agent [16]. Dacarbazine has some activity as second-line therapy, especially in leiomyosarcoma, as demonstrated in monotherapy or in combination with gemcitabine [17] and vinorelbine [18].

Angiosarcoma is sensitive to taxanes, which can be a treatment option in this histological subtype [19], with gemcitabine [20], also used in combination with docetaxel [21] and sorafenib [22] being other options.

Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans (DFSP), candidate to mutilating surgery or with metastases [23]. Similarly, imatinib [24] and nilotinib [25] were used in tenosynovial giant cell tumors (TGCT) (also known as pigmented villonodular synovitis, PVNS) based on CSF-1R expression on these tumors. Recently, the results of the first randomized phase III trial demonstrating the activity of pexidartinib in this disease were presented [26], and FDA approval is awaited.

Last, based on the results of two recent prospective and randomized studies, activity of sorafenib and pazopanib, over placebo and methotrexate/vinblastine, respectively, was shown desmoid tumors [27, 28].

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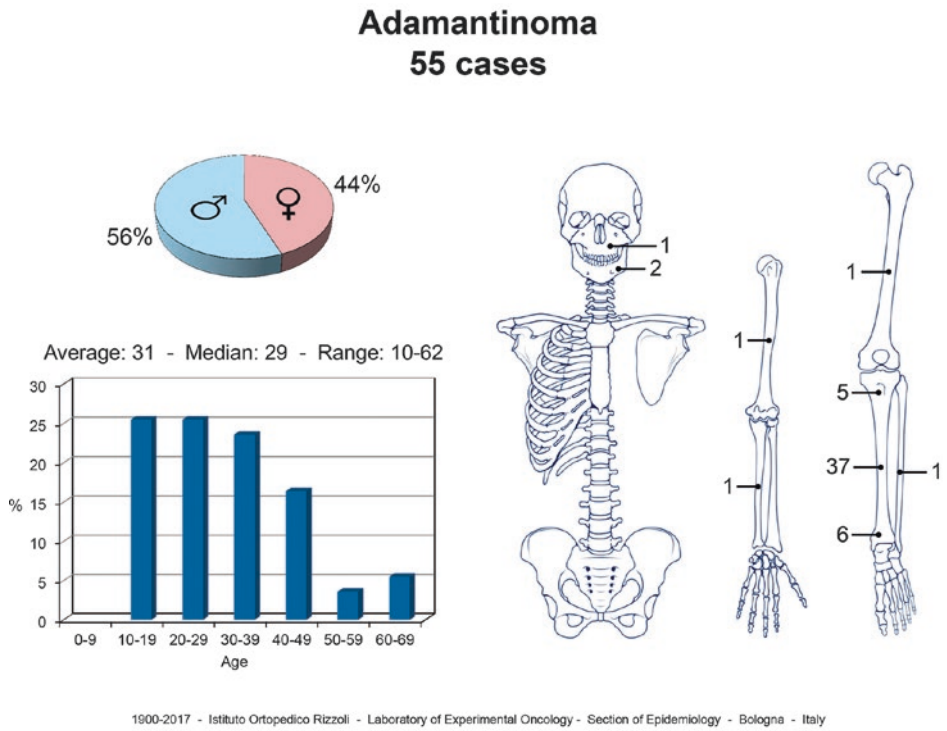
Adamantinoma

49

Alberto Righi

Definition: Low-grade malignant biphasic tumor characterized by clusters of epithelial cells in a bland spindle-cell osteofibrous component, reminiscent of the ameloblastoma of jaw bones (hence its name).

Epidemiology: Very rare (0.4% of all bone tumors). Slightly prevailing in males. It can affect all ages, but it is more common between 20 and 40. Exceptional in children below 11 years of age.



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Localization: Diaphysis of the tibia (anterior cortex) is affected in 80% of cases; often multifocal, followed by fibula. In 10% of cases combined tibia and ipsilateral fibula. Exceptional in ulna, humerus, femur, metatarsal bone, and ischium**.**

Clinical: Pain and swelling. Usually, trauma is recorded in clinical history. Symptoms are often of long duration.

Imaging: Eccentric osteolysis, mostly involving the anterior cortex of the tibia, with expansion and frequent cancellation of the cortex, with no or minimal periosteal reaction and frequent sclerotic borders. Infiltration of the soft tissues and of the medullary bone can be evident. CT and MRI indicate a solid fibrous tissue (low T1, high T2 signal), sharply demarcated from the surrounding tissues. Sometimes (mainly in younger patients), osteolysis is multifocal and extended in the diaphysis, and associated with anterior bowing of the tibia, so that the imaging is, at least initially, identical to that of osteofibrous dysplasia.

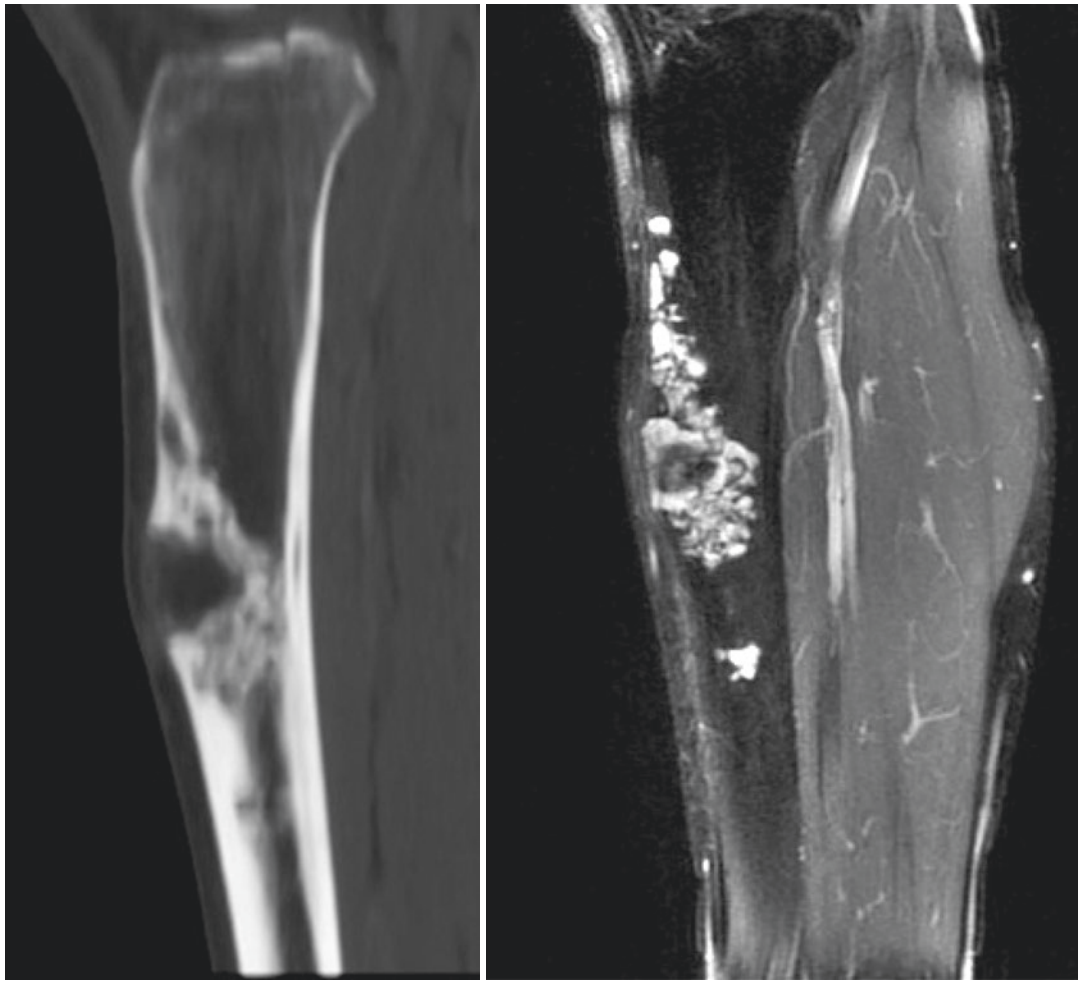
Histopathology: Grossly, the lesions range in size from less than 1 cm to more than 10 cm. The tissue is solid, whitish, and fibrous-firm, with occasional hemorrhagic or cystic areas. Histologically, it is composed by islands of malignant epithelial cells in an osteofibrous stroma. Different histological patterns can be observed in the epithelial component. The basaloid pattern is the most frequent. It is characterized by islands of epithelial cells similar to a basal cell carcinoma; tumoral cells may be dispersed and spindled in the center of the islands, cuboidal or columnar in the periphery, where they are oriented at right angles to the inner mass, forming palisading structures. Cystic spaces can be present. The spindle cells pattern is characterized by a proliferation of spindle cells with plump nuclei, arranged in intersecting fascicles, reminiscent of monophasic synovial sarcoma. The tubular pattern is characterized by gland-like cystic spaces, sometimes anastomosing, lined by one or more layers of flattened or cuboidal cells, reminiscent of a vascular tumor. The squamous pattern is the rarest; it is characterized by nests of epithelial cells showing cytoplasmic keratinization and keratin pearls. More than one pattern can be present in a single lesion. The epithelial cells of adamantinoma, whatever their shape and aggregation, are of small to medium size, with rather hyperchromatic nuclei, small or absent nucleoli, scarce pleomorphism, and rare mitosis. At the electron microscope, epithelial cells show tonofilaments, microfilaments, desmosomes, and basal membrane, thus confirming their epithelial nature. The osteofibrous component of classic adamantinoma is composed of a proliferation of bland spindle cells in a storiform pattern, intermixed with irregularly shaped woven bony trabeculae with osteoblastic rimming. A zonal architecture with more mature bony trabeculae toward the periphery and lamellar bone at the periphery of the lesion is evident. Foam cells, mast cells, and multinucleated giant cells can also be present. The so-called osteofibrous dysplasia-like adamantinoma (differentiated adamantinoma) is characterized by a predominant osteofibrous component, with only scattered small groups of epithelial cells. Very rarely, adamantinoma can show a dedifferentiation in a high-grade sarcoma (dedifferentiated adamantinoma).

Course and Staging: Adamantinoma has generally an indolent course. The interval between the first symptoms and surgical treatment may be of several years, up to 20. Metastasis to the lungs, lymph nodes, and skeleton can occur in 12–29% of cases. The stage of the tumor at presentation is I A or B.

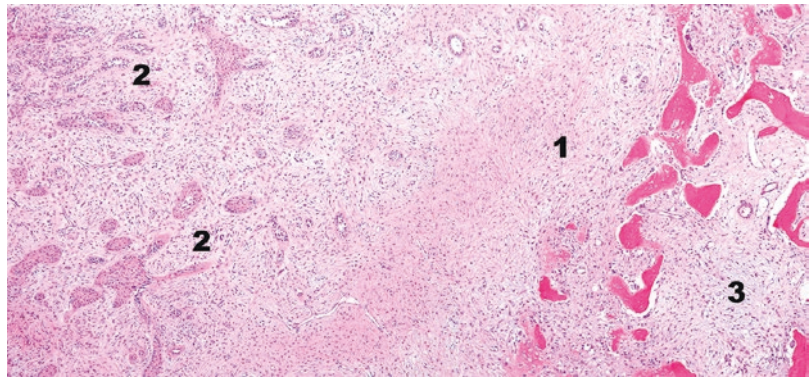
Treatment and Prognosis: Treatment is only surgical and should aim at wide margins. Regional lymph nodes should be excised when showing some enlargement. An intralesional or marginal excision is quite regularly followed by local recurrence. With an adequate treatment, the cure rate should be around 90%.

Key points	
• Clinical	Young adults, pain, and swelling
• Radiological	Eccentric pure lytic lesion in the tibia diaphysis
• Histological	Islands, nests and/or cords of epithelial cells in an osteofibrous stroma
• Differential diagnosis	Osteofibrous dysplasia of long bones

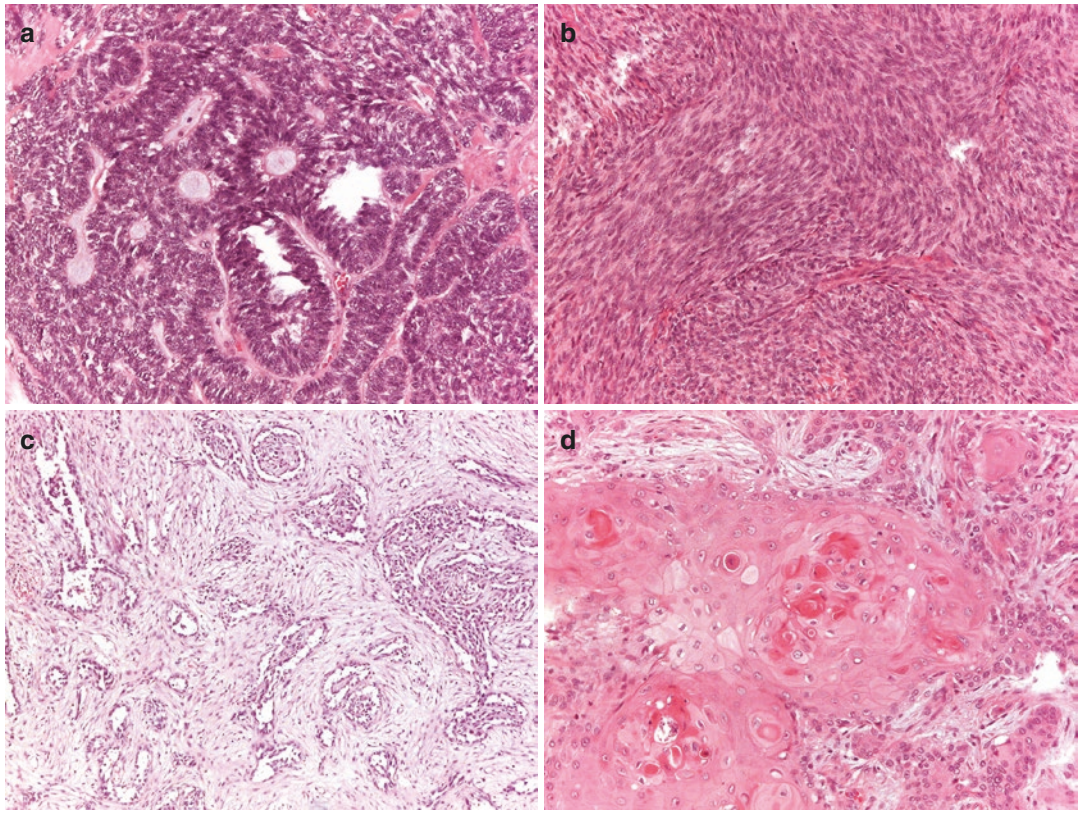
Immunohistochemical panel	
• CK	Groups of epithelial cells positive



Sagittal CT reconstruction and T2 MR images. The lesion involves the anterior cortex of the shaft of the tibia and is heterogeneous. A satellite lesion is easily detected in the cortex



Islands of malignant epithelial cells in an osteofibrous stroma: (1) nests of epithelial cells, (2) abundant fibrous stroma with bland spindle cells in a storiform pattern, (3) irregularly shaped woven bony trabeculae with osteoblastic rimming



Basaloid (**a**), spindle cell (**b**), tubular (**c**), and squamous (**d**) pattern of the epithelial component

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Notochordal Differentiation

50

Alberto Righi

50.1 Benign Notochordal Cell Tumor

Definition: A benign vertebral lesion of notochord origin (also called giant notochordal rest or ecchordosis physaliphora when localized in spheno-occipital region) recently introduced as benign counterpart of chordoma.

Epidemiology: The incidence is uncertain, although in a relatively small study an incidence of at least 20% of cadavers has been reported.

Location: Cervical and lumbar spine (clinical case); smaller lesions could also be found in the sacrum, coccyx, and clivus at autopsy.

Clinical: Most lesions are incidentally found on imaging examinations because they are usually asymptomatic. Lesions that fill the vertebral body may be symptomatic.

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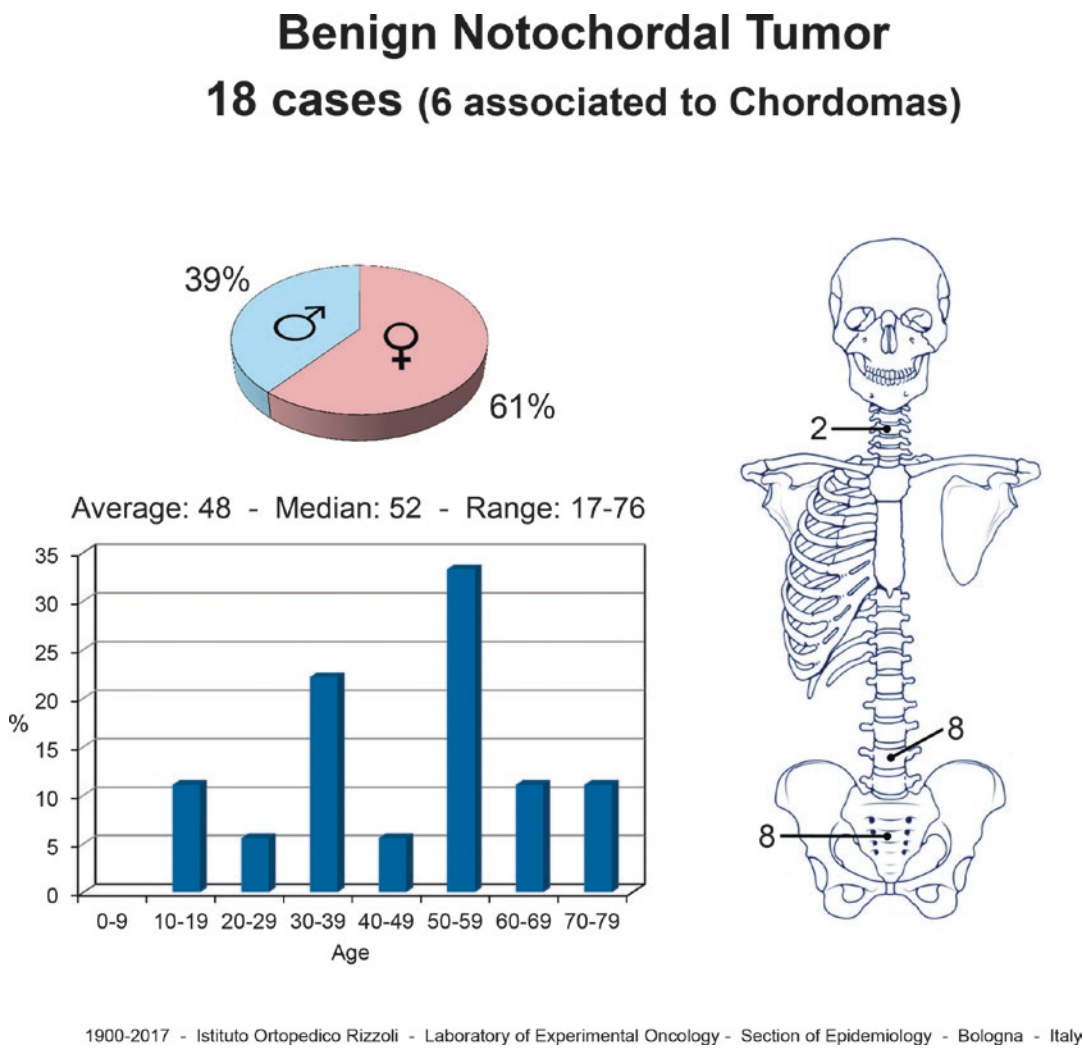
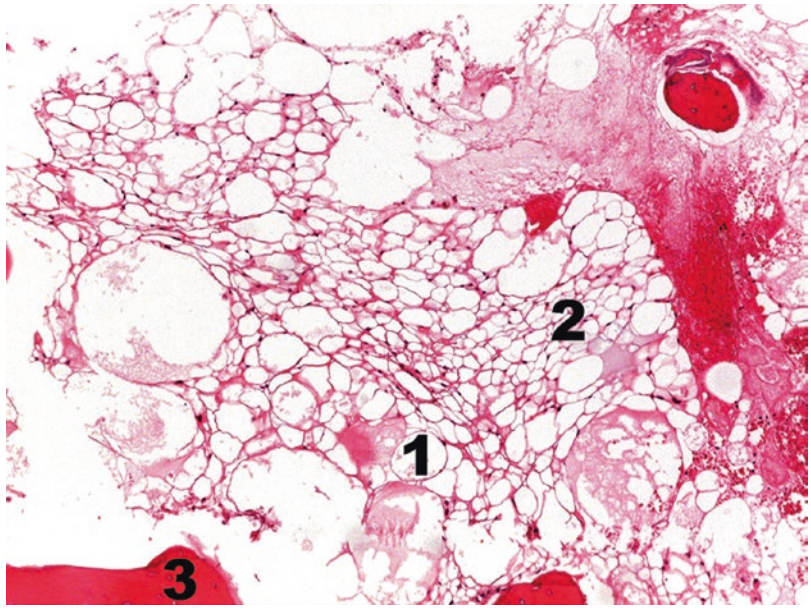


Imaging: Radiographs occasionally reveal mild osteosclerosis. Computed tomography scan shows an intraosseous sclerotic lesion without extraosseous tumor extension. Magnetic resonance imaging reveals homogeneously low signal intensity on T1-weighted imaging, homogeneously high signal intensity on T2-weighted imaging, and no contrast enhancement on gadolinium-enhanced.

Histopathology: Macroscopically, the cut-surfaces disclose an unencapsulated and well-demarcated tumor with a bright tan, glossy texture. Morphologically, the lesion consists of solid sheets of adipocyte-like vacuolated and eosinophilic tumor cells with bland nuclei without mitotic figures. Benign notochordal cell tumor lacks intercellular myxoid matrix, although some cystic spaces filled with colloid-like material can be seen. The involved bone trabeculae are mildly, occasionally markedly, sclerotic. Bone marrow islands may be seen within the lesion. A lobular configuration formation of fibrous septa are absent. The tumor cells are immunohistochemically positive for brachyury, epithelial markers, and S-100 protein.

Course and Staging: Prognosis is excellent and the clinical course is very indolent except for the very low risk of malignant transformation in chordoma.

Treatment: This lesion does not require any surgical intervention and a follow-up with imaging is necessary.

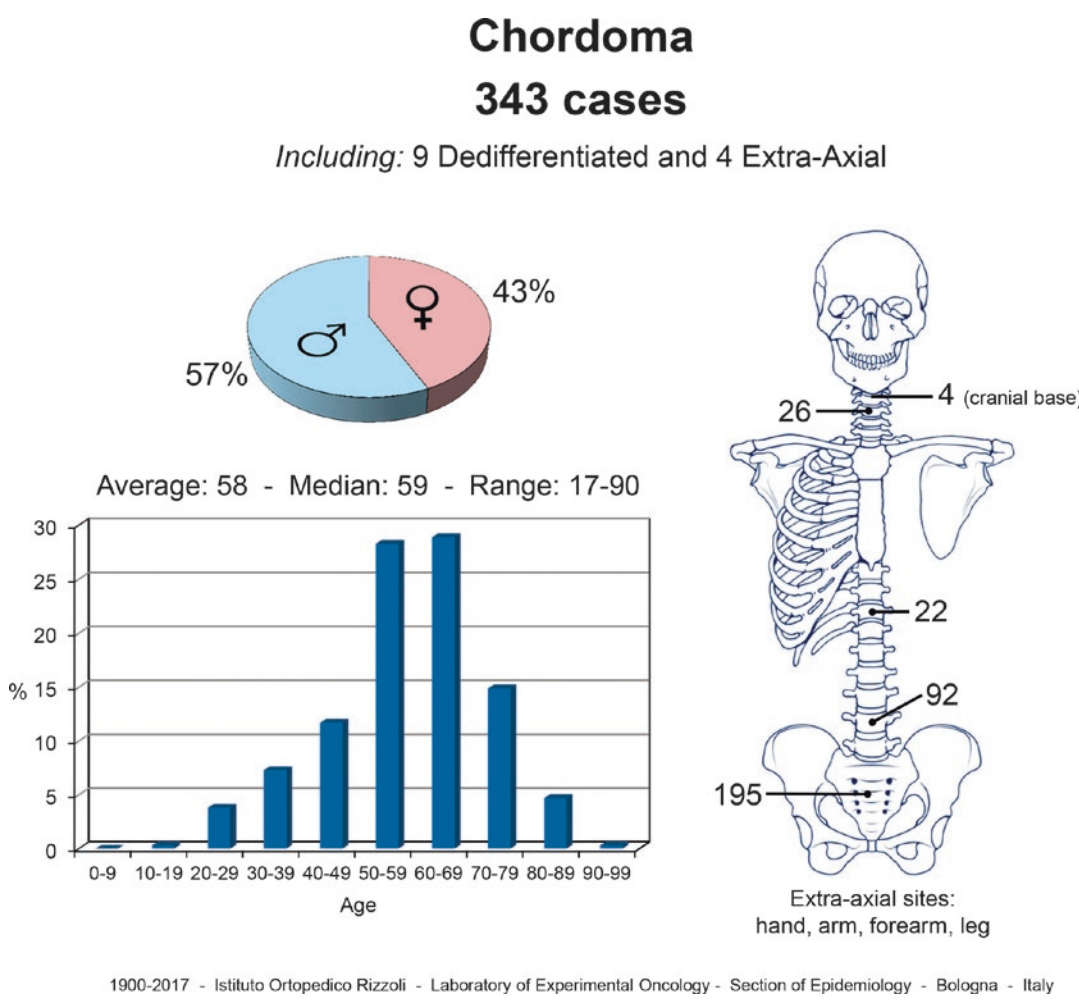


Benign notochordal cell tumor. Intraosseous tumor in the vertebral body composed of aggregates of large "adipocytes-like" cells. (1) Notochordal cells are large and show abundant clear cytoplasm. (2) The cells have well-defined cell membranes and centrally or peripherally placed nuclei with no atypia. (3) Affected bone trabeculae are often sclerotic

50.2 Chordoma

Definition: A rare, slow-growing, malignant bone tumor showing notochordal differentiation.

Epidemiology: The incidence is 0.08 per 100,000 people with a male prevalence (male to female ratio is 1.8/1). The tumor commonly develops in the fourth to seventh decades of life although all age groups are affected.



Location: 50–60% in the sacro-coccyx region, followed by skull base/spheno-occipital region (25–30%), vertebrae (15%) and with anecdotal reported extra-axial and extraosseous cases.

Clinical: Skull-based chordoma most commonly present with headache, neck pain, diplopia, or facial nerve palsy. Chordoma of the mobile spine and sacrum present with chronic low-back pain, constipation, hemorrhoids, dysuria, limping, hypoesthesia, and sphincteric paresis.

Imaging: On radiographs, osteolytic bone destruction lesion is usually evident. The outlines of bone and lines of the sacral foramina have disappeared. Faded radiopaque spots of intratumoral calcifications are frequent. The vertebral body chordomas show a relatively well-defined edge, with sclerotic rim, calcifications. CT evidences a destructive bone tumor with extraosseous tumor formation. In the sacrum, extraosseous mass protrudes more anteriorly than posteriorly with well-defined borders and infiltration of the adjacent muscles, dislocation of the viscera or of the dural sac. MRI reveals low homogeneous signal intensity on T1-WI, heterogeneously high signal intensity on T2-WI, and marginal or entire enhancement on Gd-enhanced T1-WI.

Histopathology: Most chordomas are conventional type, but there are three other rare subtypes: chondroid, poorly differentiated, and

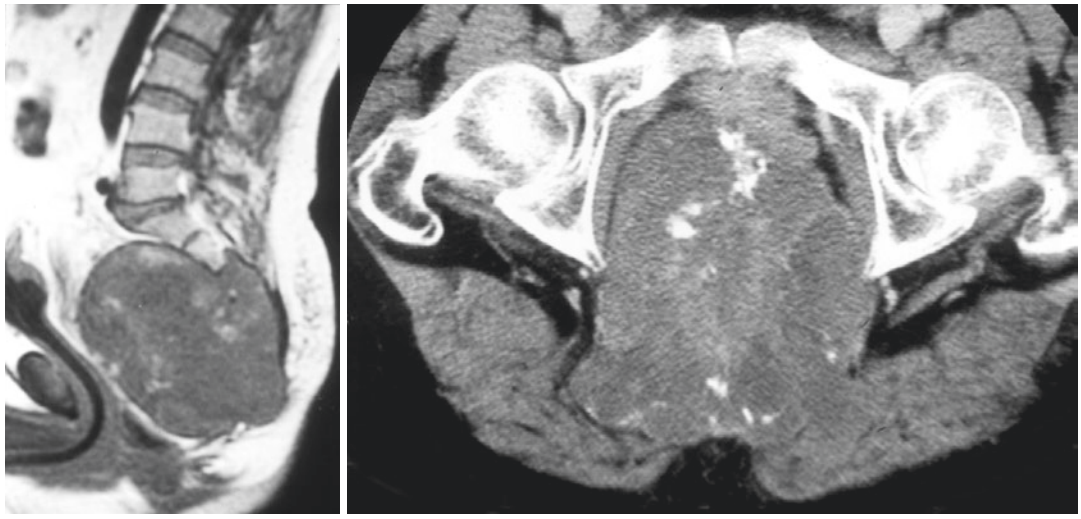
dedifferentiated chordomas. On macroscopy, the tumor, usually associated with a huge extraosseous tumor mass, is well demarcated and encapsulated with a thin fibrous capsule. Dedifferentiated chordoma is associated with a nonmyxoid tumor component with a fairly sharp margin. Morphologically, chordoma is an encapsulated lobular tumor composed of solid sheets and/or cords of epithelioid vacuolated tumor cells – so called "physaliphorous cells" – with a varying amount of intercellular myxoid matrix. Each lobule is separated by thin fibrous septa. The tumor cells show clear to eosinophilic cytoplasm. Poorly differentiated chordoma looks like pleomorphic spindle cell sarcoma but the tumor cells show signs of notochordal differentiation. Chondroid chordoma that has a predilection for the base of the skull shows chondrosarcoma-like components in addition to classic chordoma morphology. Dedifferentiated chordoma consists of two components: conventional chordoma and high-grade sarcoma, without notochordal differentiation. Immunohistochemically, all subtypes (except the dedifferentiated component in dedifferentiated chordoma) typically show positive staining for keratins, brachyury, S100, and EMA. Recently, a subset of chordoma (often poorly differentiated-subtype) shows an absence of INI1 / SMARCB1 expression.

Course and Staging: Chordoma recurrence rate is high at locations where surgical excision with sufficient tumor-free margins is not possible, which directly affects the long-term survival rate of these patients. Next to local recurrence, metastasis to the lung, bone, lymph nodes, and skin occurs in 5–43% of patients. The median overall survival is 4–7 years and the 10-year survival rate ranges from 40 to 60%. Poorly differentiated-type, that often affects children, appears to be more aggressive than conventional and chondroid chordoma in both the skull base and the spine, with a decreased mean overall survival. Dedifferentiated chordoma is lethal, with systemic spread occurring in approximately 90% of cases.

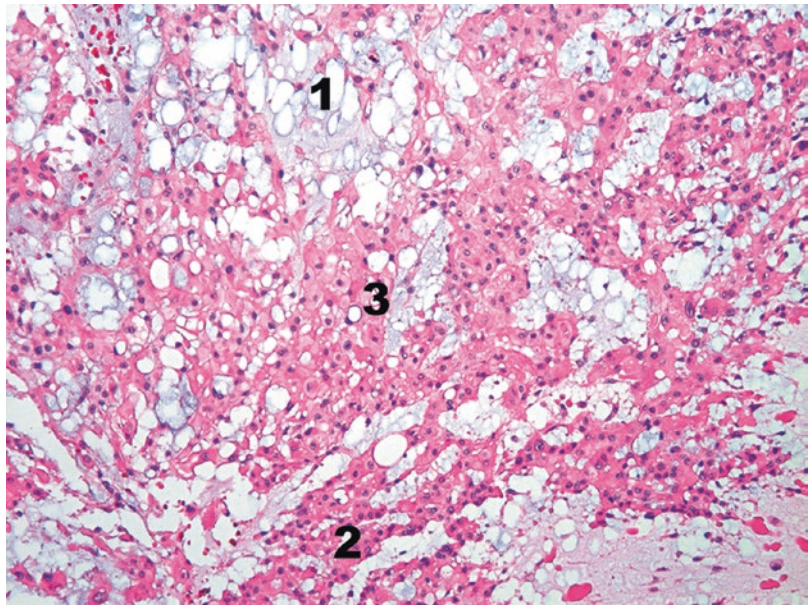
Treatment: Chordoma has been primarily managed by surgery for a long time. Wide resection is mandatory, but often impossible. Traditional chemotherapy has not been effective so far. Instead of chemotherapy, proton therapy has been primarily applied in combination with surgery. Carbon-ion radiation therapy has taken over from proton therapy to treat unresectable chordomas. The 5-year local control, overall survival, and disease-free rates of carbon-ion radiation therapy are 77%, 81%, and 50%, respectively. Despite the satisfying results, radiation therapy is not able to prevent distant metastasis even though it is effective in controlling local disease.

Key points	
• Clinical	Old patients, pain, and compression symptoms
• Radiological	Pure lytic lesion
• Histological	Lobular pattern with physaliferous cells
• Differential diagnosis	Bone metastasis, chondrosarcoma, and all other primary purely osteolytic lesions of adults—benign notochordal cell tumor

Immunohistochemical panel	
• CK	+
• EMA	+
• S-100	+/–
• INI1 (SMARCB1)	+/–
• Brachyury	+ (nuclear)



CT and sagittal T1 MR image. Huge tumor destroying the last sacral vertebrae, invading the anterior soft tissues, pushing the rectum, which remains free. On CT, remaining pieces of bone are well visible

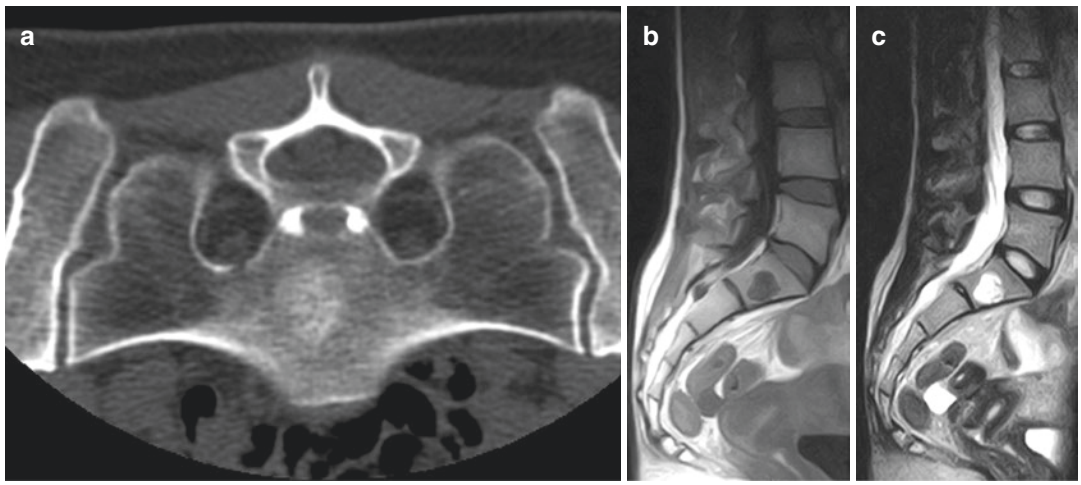


The histological picture of the tumor may vary from field to field. However, the architecture is usually characterized by cellular cords isolated and anastomized, producing mucin and contained in the mucoid substance accumulated on the outside. (1) Mucoid substance. (2) Large, deeply eosinophilic cells organized in cords. (3) Signet-ring cells and physaliphorous cells may be observed in more differentiated areas

50.3 Differential Diagnosis Between Benign Notochordal Cell Tumor and Chordoma

Differential diagnosis between chordoma and benign notochordal cell tumor is fundamental and represents a challenge for pathologist in particular on biopsy specimen because of an overlapping immunohistochemical profile. The radiograph features of benign notochordal cell tumor on CT (sclerotic lesion within bone, without lysis) and on MRI (a homogenous intraosseous lesion with a low signal on T1-weighted images and high signal on T2-weighted images, that does not take up contrast medium) allow differential diagnosis with chordoma. Morphologically, chordomas show fine fibrous capsules and/or septa with vasculature, lobular configuration, intercellular myxoid matrix, and bone destruction. The border of chordoma to bone marrow cells of host bone seems very smooth because of a thin fibrous membrane existed. In contrast, the border of benign notochordal cell tumor seems slightly zigzag along the contour of adjacent marrow adipocytes because of a lack of intervening fibrous membrane.

The distinction between benign notochordal cell tumor and chordoma applying the radiologic and histologic criteria is occasionally difficult, so recently some authors propose a designation of atypical notochordal cell tumors that should be used for the subset of notochordal-derived tumors that fail to fulfill current diagnostic criteria for either benign notochordal cell tumor or chordoma.



Incidental discovery. On TC (**a**) the lesion is medial, sclerotic. Cortex is normal and soft tissues are not involved. The lesion has a low signal on sagittal T1 (**b**) and high signal on T2 (**c**) MR images (there was no change after contrast medium injection)

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Other Rare Malignant Lesions

51

Marco Gambarotti and Alberto Righi

51.1 Synovial Chondrosarcoma

Synovial chondrosarcoma is an exceeding rare entity. It can arise de novo or as a malignant transformation of synovial chondromatosis. In the latter situation, synovial chondrosarcoma can arise on a pre-existing synovial chondromatosis or coexist with a synovial chondromatosis. The rate of malignant transformation of synovial chondromatosis is about 5% of cases, generally after several recurrences, many years after the first diagnosis. Radiologically, synovial chondrosarcomas may show aggressive features; however, the differential diagnosis between synovial chondromatosis and synovial chondrosarcoma can be challenging. Histologically, features in favor of malignancy are hypercellularity, loss of clustering of the chondrocytes, myxoid change of the matrix, necrosis, and infiltration of bone and soft tissues with permeative margins. Although the majority of synovial chondrosarcomas behave as low-grade conventional chondrosarcomas, metastasis can develop in about 29% of cases. For this reason, a wide surgical treatment is recommended and the differential diagnosis with synovial chondromatosis is very important, as the latter is generally treated with a more conservatory surgical approach.

51.2 Desmoplastic Round Cell Tumor

Desmoplastic small round cell tumor is a highly malignant, polyphenotypic mesenchymal neoplasm, that mainly affects young adults, with a peak incidence in the second decade and a male prevalence. This tumor often arises in mesothelium-lined surfaces. Histologically, it is characterized by the presence of sharply demarcated clusters of small rounded cells, separated by a hypocellular spindle cell desmoplastic stroma. Desmoplastic small round cell tumor exhibits a remarkably distinctive polyphenotypic immunohistochemical profile, which consists of immunopositivity for epithelial (cytokeratins, EMA), myogenic (desmin), and neural/neuronal (neuron-specific enolase, S100 protein, CD57) differentiation markers. Cytogenetically, desmoplastic small round cell tumor is characterized by a reciprocal translocation, t(11;22)(p13;q12), that involves the genes WT1 and EWSR1. Even if improved survival seems to be achieved by high-dose chemotherapy regimens associated with extensive surgery, most patients die either of advanced uncontrolled local disease or of distant metastases within 48 months after diagnosis.

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51.3 Kaposi Sarcoma

Kaposi sarcoma is a multifocal, virus-induced vascular proliferation associated with human HHV-8 in nearly all cases. It usually presents with cutaneous lesions in the form of multiple patches, plaques, or nodules, but may also involve different mucosal sites, lymph nodes, or visceral organs. Morphologically, Kaposi sarcoma is composed of well-formed, irregular vascular channels and spindled endothelial cells in varying proportions, depending on the stage of lesion. The lining cells of vascular structures and the spindled tumor cells are positive for endothelial markers (CD31, ERG) as well as lymphatic markers (podoplanin), and show a nuclear expression of HHV-8. The evolution of disease depends on the epidemiological-clinical type of Kaposi sarcoma and on its clinical extent.

51.4 PEComa

PEComa is a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells. The PEComa family includes angiomyolipoma, clear cell sugar tumor of the lung, lymphangioleiomyomatosis, and a group arising at a variety of soft-tissue and visceral sites, including retroperitoneum, abdominopelvic region, uterus, gastrointestinal tract, skin, and bone. PEComa is more frequent in females (female to male ratio, 6:1), with a wide age range and a peak in young to middle-aged adults (mean age, 45 years). Morphologically, PEComas are composed of large polygonal, epithelioid cells, with abundant granular eosinophilic to clear cytoplasm, often arranged in nests surrounded by delicate capillary vessels. Immunohistochemically, the neoplastic cells are reactive for both smooth muscle markers (smooth muscle actin) and melanocytic markers (HMB-45 and/or melan-A). Criteria for malignancy have not been established. Clinically malignant PEComas are typically large and usually show marked nuclear atypia, pleomorphism, mitosis, necrosis, and infiltrative margins.

51.5 Ossifying Fibrous Myxoid Tumor

Ossifying fibrous myxoid tumor is a rare mesenchymal neoplasm of uncertain lineage with cords and trabeculae of ovoid cells embedded in a fibromyxoid matrix, often surrounded by a peripheral partial shell of lamellar bone. This tumor occurs in adult of all ages with a median age around 50 years and with a slight prevalence in males. The most common sites are the thigh, head and neck, and the trunk wall. Radiologically, a well-circumscribed, lobulated mass surrounded by an incomplete ring of calcification is evident. Malignant variant has been reported in literature characterized by high nuclear grade or high cellularity and >2 mitoses per 50 HPFs. Immunohistochemically, ossifying fibrous myxoid tumor is positive for S100 protein (>90% of cases) and desmin (40–50%). This immunohistochemical phenotype is useful to distinguish ossifying fibrous myxoid tumor from myoepithelioma and extraskeletal myxoid chondrosarcoma. Surgery is the treatment of choice. The recurrent rate is approximately 10–20% for typical variant with an occurrence of distant metastases in less than 2% of cases. Malignant variant shows a 60% of rate of local recurrence and metastasis.

51.6 Malignant Granular Cell Tumor

Malignant granular cell tumor is a rare high-grade sarcoma with a Schwannian phenotype, composed of malignant granular cells with cytoplasmic lysosomal inclusions. This tumor occurs with a female predominance and age range of 3–70 years (mean of 40 years). The most common locations are the soft tissue of the thigh, proximal upper extremity, trunk, and then distal extremity. Approximately 2% of granular cell tumors are malignant. Hallmark histological features are sarcomatoid morphology, vesicular nuclei with prominent nucleoli, increased mitotic activity, geographical necrosis, marked pleomorphism, and high nuclear to cytoplasm ratio. As reported in benign counterpart, most malignant

tumors show a strong positivity for S100 protein and CD68. A rate of metastasis is of 50%. Local recurrence, metastasis, large tumor size, and older patient age are adverse prognostic factors.

51.7 Soft Tissue Giant Cell Tumor

Giant cell tumor of soft tissues is a primary soft tissue neoplasm histologically similar to giant cell tumor of bone. It mainly affects adult patients, with predominant localization in the superficial soft tissues of the distal extremities, while the trunk and the head and neck regions are less frequently affected. Histologically, giant cell tumor of soft tissues shows a multinodular architecture, and the lesion is composed of round cells and multinucleated osteoclast-like giant cells. A peripheral shell of woven bone is often detected. Recently, no mutation of the H3F3 gene was detected in different series of giant cell tumor of soft tissues, indicating that giant cell tumor of soft tissues might be genetically different from its osseous counterpart. The clinical course is characterized by local recurrence in approximately 10% of the patients, while distant metastases are very rare.

51.8 Malignant Pigmented Villonodular Synovitis

The designation malignant pigmented villonodular synovitis (also called malignant giant cell tumor of tendon sheath, diffuse-type) is used for lesions in which a typical-appearing benign pigmented villonodular synovitis coexists with overtly malignant areas, or when the typical benign pigmented villonodular synovitis recurs as a morphologically malignant mesenchymal lesion. The criteria of malignancy for pigmented villonodular synovitis were defined by Bertoni et al. who reported the presence of larger mononuclear cells, featuring round or round to oval hyperchromatic nuclei sometimes showing prominent nucleoli, and presence of atypical mitotic figures. Xanthomatous cells as well as giant cells decreased in number and sometimes absent. To our knowledge, 32 cases of malignant pigmented villonodular synovitis are reported in literature: 17 cases were primary malignant pigmented villonodular synovitis and 15 arose from a prior histologically benign lesion. Seven out of these 32 cases metastasized to regional lymph node: 4 patients died of disease with a rapid progression (mean 22 months, range 12–41 months), two were alive with disease 17 and 36 months after the first surgical treatment, respectively, and only one patient was well without disease 10 months after the first surgical treatment.

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Part V

Systemic Lesions

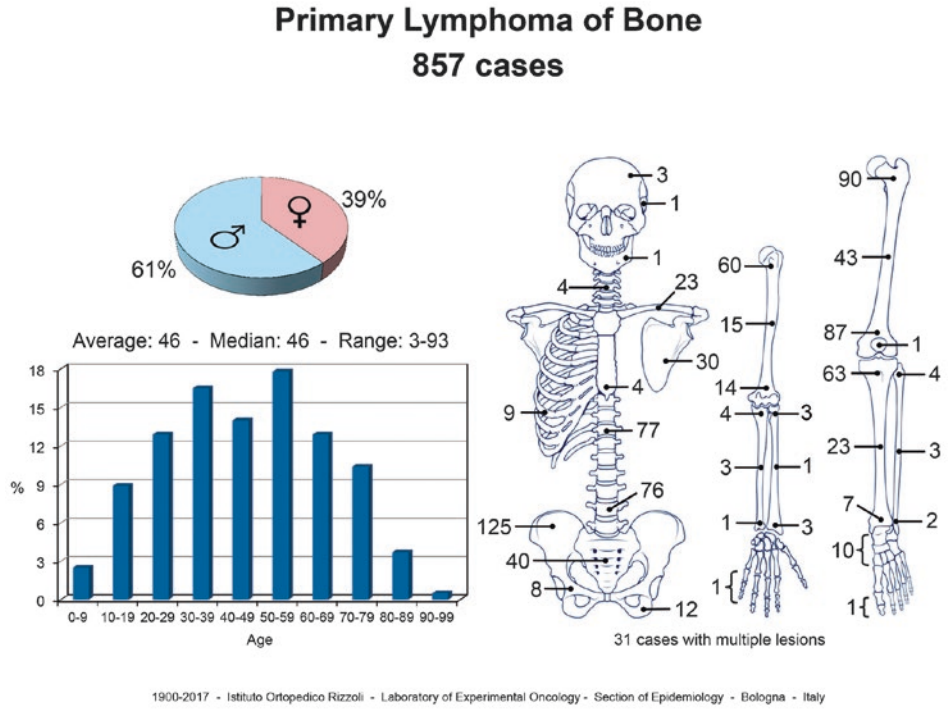
Primary Lymphoma of Bone

52

Marta Sbaraglia

Definition: Intramedullary malignant lymphoma without lymph node involvement or other extranodal site.

Epidemiology: Primary bone lymphomas (PBL) are rare, representing 7% of all malignant bone tumors and 5% of all extranodal lymphomas. Secondary involvement of bone following primary node lymphomas is the more frequent situation. Males outnumber females. Typically the tumor affects adults with a mean age at diagnosis of 45 years.



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Localization: Most cases of PBL involve the axial skeleton including the pelvis and vertebrae. Other frequently affected sites are the long bones such as humerus and femur; lesions are usually located in the meta-diaphyseal region of bone. Multifocal bone lesions may be observed often involving multiple bones.

Clinical: Clinical presentation is variable and dependent on the localization of the disease. It may include pain, swelling, pathological fracture, and neurological deficits in case of vertebral involvement. Symptoms are mild and of long duration. Systemic symptoms referred to as "B-symptoms" (fever, night sweats, and weight loss) may also be present.

Imaging: On X-ray, small diffuse ill-defined lytic lesions featuring a permeative pattern are the most frequent appearance of PBL. Often a moth-eaten radiographic pattern is also observed in PBL. The cortex may be broken or destroyed with extension in the surrounding soft tissue, mimicking a bone sarcoma. Sometimes, the cortex can be thickened mimicking osteomyelitis. Usually, a periosteal reaction is absent but in rare cases a spicular or lamellar reaction may be observed mimicking radiologic features of osteosarcoma and Ewing sarcoma. At times, PBL is represented by an eccentric aggressive lytic lesion mimicking metastatic carcinoma. More rarely, non-Hodgkin lymphoma can have a sclerotic appearance on X-ray, a feature that is more commonly encountered in Hodgkin lymphoma. Pathological fractures are a common finding in PBL. CT scan shows the typical permeative or moth-eaten radiographic features of PBL. The mottled appearance on CT scan due to reactive hyperostosis is very useful to evaluate the relationship with the neurovascular bundles, the involvement of the joint and for the staging of the disease. MRI is not as useful in PBL affecting long bones as for PBL involving the spine, where MRI imaging can highlight possible spinal cord compression. Finally, bone scans may be useful to better define the lesions.

Histopathology: Diffuse large B-cell lymphoma (DLBCL) is by far the most common histotype of newly diagnosed PBL. The remaining minority of PBL includes other histotypes such as follicular B-cell lymphoma, marginal B-cell lymphoma, Hodgkin lymphoma, and anaplastic large T-cell lymphoma. On histology, PBL shows the same morphologic features encountered in nodal lymphomas. In addition, non-neoplastic inflammatory cells are frequently spread in and around the tumor, possibly obscuring the malignant cell population. Most PBLs are composed of sheets of neoplastic cells with a striking permeative growth pattern infiltrating in between bone trabeculae and medullary fat. The most common histotype, DLBCL, shows a diffuse proliferation of medium to large lymphoid cells that rarely have a pleomorphic appearance, with prominent fibrosis and presence of reactive osteoid. Mitoses are usually frequent and sometimes atypical. Additionally, DLBCL can be subdivided immunohistochemically in germinal center B-cell type and non-germinal center using BCL2, BCL6, CD10, and MUM1 (see table "immunohistochemical panel"). Anaplastic large T-cell lymphoma arising in bone is extremely rare, but the most common among T-cell lymphomas. Classical Hodgkin lymphoma primarily arising in bone is also extremely rare. Reticulin fibers surround small groups of cells forming thick fibrous bands. Immunostains for B- and T-cell markers and common leukocyte antigens can aid in the classification of PBL as well as in differential diagnosis. Additionally, useful tools to rule out double-hit large B-cell lymphoma include molecular analysis to investigate *BCL2*, *BCL6,* and *MYC* gene status.

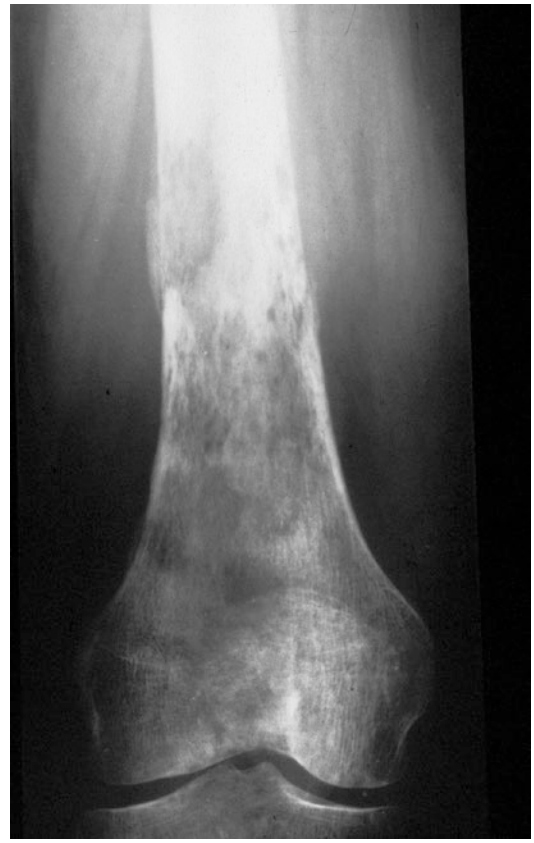
Course and Staging: When primary lymphoma of bone is diagnosed, it is necessary to stage the disease. It is important to evaluate the presence of multiple bone lesions and possible nodal and extraskeletal involvement.

Treatment and Prognosis: Combined chemo-radiotherapy is the standard treatment for PBL; however, there is no accepted consensus on therapy regimen for the localized form. Surgery may be indicated in spine localizations to decompress marrow and spinal roots or to prevent pathologic fractures in the long bones. Surgery is always combined with radio- and chemotherapy. The 5- and 10-year survival rates for PBL patients are about 65% and 53%, respectively, whereas

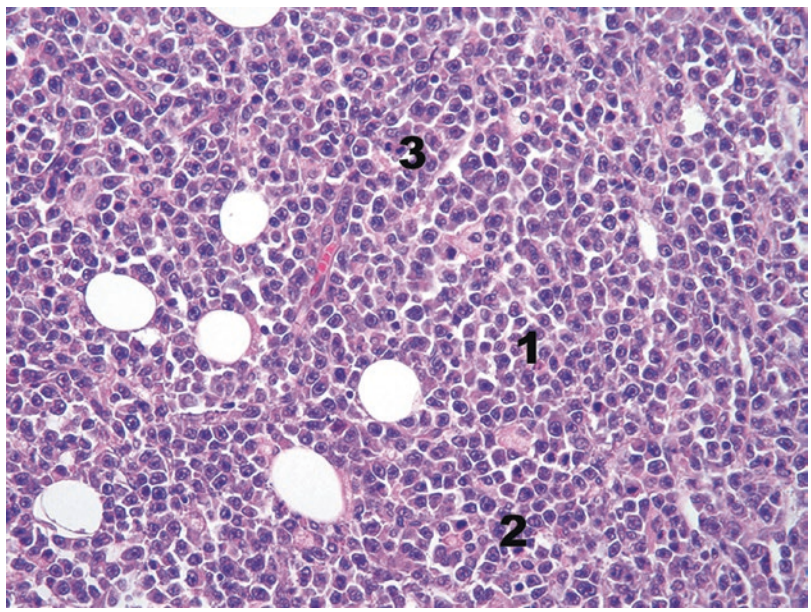
the survival rates in systemic lymphomas with bone lesion are 53% and 43%, respectively. Age less than 60 years is a favorable prognostic factor. Bulky disease, extraskeletal dissemination, and polyostotic involvement are considered unfavorable prognostic factors.

Key points	
• Clinical	Adults, pain and swelling, possible pathologic fracture
• Radiological	Large lytic destructive lesion, bone margins often moth-eaten or permeative, rare periosteal reaction
• Histological	Pleomorphic blue round cells
• Differential diagnosis	Osteomyelitis, osteosarcoma, Ewing sarcoma, langerhans cell histiocytosis, metastatic carcinoma

Immunohistochemical panel	
• DLBCL – Germinal center – Non-germinal center	CD45+; CD20+; CD79a+; PAX5+ CD10+; BCL6+ or MUM1− CD10−; BCL6− or MUM1+
• Anaplastic T-cell lymphoma	(CD3 CD2 CD4 CD5) ≥1 positive pan T-cell marker CD30+; ALK +/−
• Hodgkin lymphoma Reed–Sternberg cells	CD30+; CD15+; CD20−



Radiograph. Mixed lytic and sclerotic femoral lesion, with limited cortical destruction, and moth-eaten pattern



Primary lymphoma of bone: In this example of DLBCL, the tumor is composed of sheet of large atypical B cells, showing irregular and cleaved nuclei with prominent nucleoli (1). Nuclei are generally larger than those observed in Ewing sarcoma (2). Mitotic figures are frequent (3)

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Multiple Myeloma

53

Marta Sbaraglia

Definition: Multiple or plasma cell myeloma (PCM) is a bone marrow-based multifocal plasma cell neoplasm, usually associated with secretion of a single homogeneous monoclonal immunoglobulin called M protein. The bone marrow is the site of origin of nearly all PCMs. Multifocal bone marrow involvement is frequently observed. In advanced disease, extramedullary involvement can be appreciated.

Epidemiology: PMC accounts for about 1% of malignant tumor with an incidence of about 20 cases/million/year. Male predominance is observed. PMC is almost never found in children and extremely rare in young adults (mean age at diagnosis: ≈70 years). In elderly patients, PMC represents the most common primary bone malignant neoplasm.

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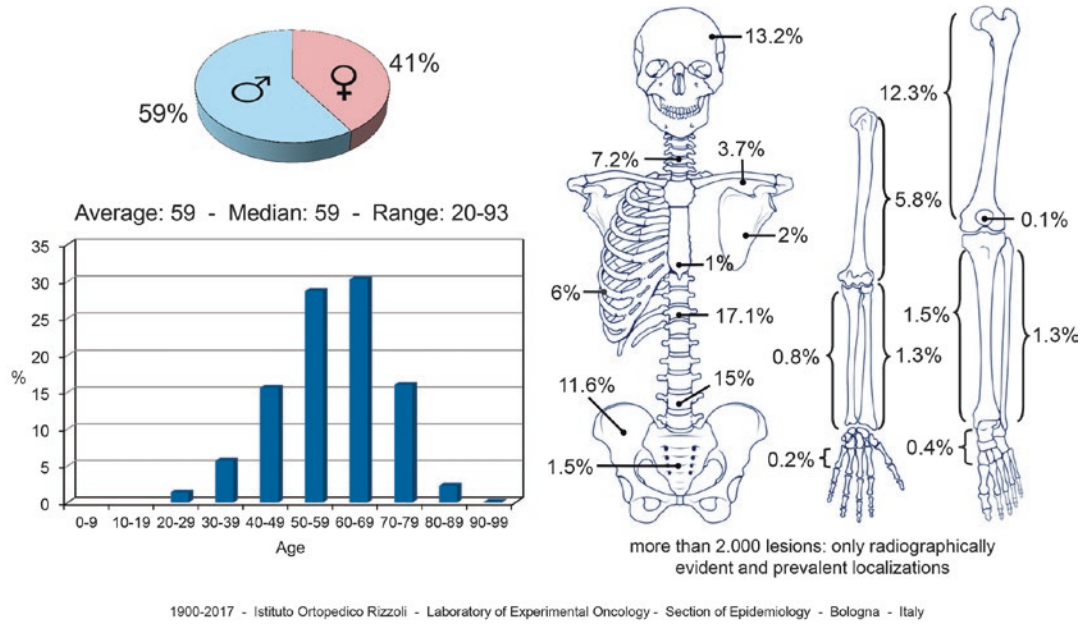


Localization: The axial skeleton is the preferred site. In the appendicular skeleton, the metaphysis is favored. It is very rare in bones of the hand and foot.

Clinical: In most patients, the symptomatology includes local pain (usually relieved by rest), hypercalcemia, and occasionally pathologic fracture (more often at a later stage) resulting from lytic lesions and/or osteoporosis. In advanced stages, there may be local swelling, weight loss, anemia, bleeding diathesis, and propensity to infections. Renal failure and hyperuricemic syndromes occur due to tubular damage resulting from monoclonal light chain proteinuria. In 90% of cases, serum and/or urinary immunoelectrophoresis shows a spike due to the excess of the monoclonal protein. Congestive heart failure, peripheral neuropathy, and carpal tunnel syndrome may be frequently observed. Erythrocytes sedimentation rate is usually elevated. Elevated serum creatinine and hyperuricemia are rather frequent. Anemia, leukopenia, and thrombocytopenia are seen due to substitution of bone marrow.

Imaging: Radiographic skeletal changes include:

- Diffused osteoporosis (osteopenia), particularly seen in the spine; (2) "punched-out" round lytic areas without associated osteoblastic changes and absence of sclerotic rim; (3) large or massive osteolytic tumors (trabeculated, honeycombed, or even bubbly).

The cortex is thinned or broken, with frequent extension of the tumor in the soft tissues, particularly in ribs and spine. Occurrence of pathologic fractures is frequent. Periosteal reaction is absent.

Rarely (1–2%), PCM generates osteosclerotic lesions. Sclerotic changes are observed in younger patient, generally associated with hypocellular tumors, lower levels of monoclonal proteins, and more elevated serum alkaline phosphatase. It reflects a less aggressive infiltrative process, which allows time for osteoblastic reaction. MRI is the most sensitive to discover diffused and nodular disease in cancellous bone. Isotope bone scan is usually negative or scarcely positive.

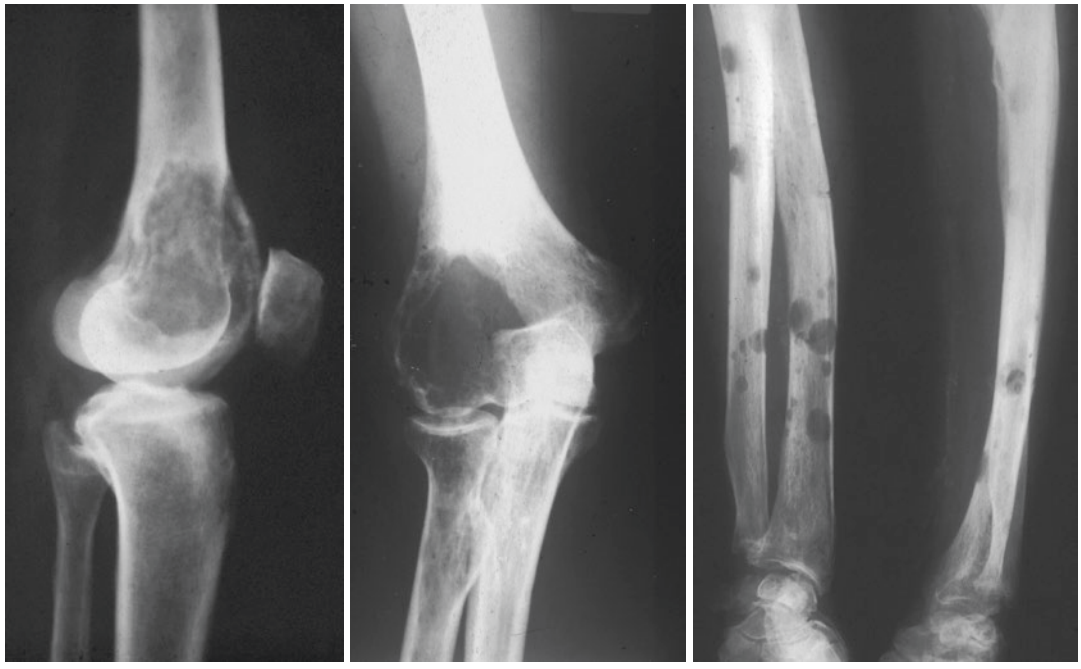
Bone marrow aspiration. If necessary, it should be repeated from multiple sites. It is diagnostic in about 90% of cases. Aspirate smears may contain a different proportion of monoclonal plasma cells that varies from bare increase to >90%.

Histopathology: Macroscopically the tumor appears as a soft, fleshy hemorrhagic tissue that replaces the affected bone marrow. Histologically the tumor is composed of either easily recognizable or highly pleomorphic malignant or blastoid-type plasma cells. The tumor cells may be organized in small clusters, focal nodules or in diffuse sheets into bone marrow. In focal patterns of involvement, foci of interposed normal hematopoiesis were observed, whereas they may be markedly decreased in advanced disease. In differentiated forms, the tumor is composed of mature plasma cells, featuring a round, eccentric nucleus showing a distinctive "cartwheel" chromatin, harbored by basophilic cytoplasm with a perinuclear hof. In contrast, immature forms have a more dispersed nuclear chromatin, a higher nuclear-cytoplasmic ratio, and prominent nucleoli. In almost 10% of cases, the plasmablastic morphology is observed. Pleomorphism is extremely rare. Intracytoplasmatic cherry-red, refractile round bodies, so-called Russell bodies, can be frequently observed. Immunohistochemically, neoplastic cells are strongly positive for CD138 and MUM1. Clonality of neoplastic plasma cells can usually be demonstrated with staining for Ig Kappa and Lambda light chains. On core biopsy, at least 30% of the bone marrow volume should be replaced by monoclonal plasma cells in order to formulate a diagnosis of myeloma. Prominent osteoclastic activity is observed in some cases.

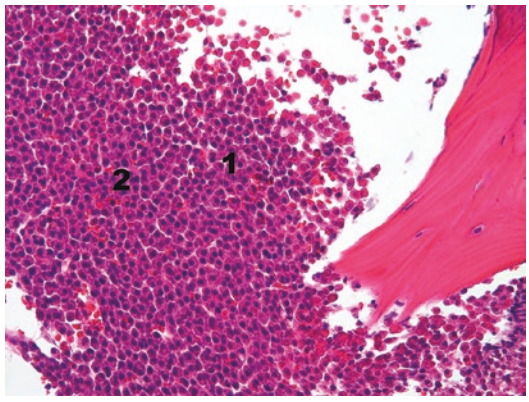
Treatment and Prognosis: Treatment is based on chemotherapy, particularly using alkylating agents (cyclophosphamide, melphalan, nitrosourea BCNU). Molecular targeted therapy with bortezomib is also currently available. Prednisone, thalidomide, and biphosphonates can also be used. In younger patients, allogenic marrow transplantation has been employed. Radiation treatment is used, to relieve pain, decrease spinal cord compression, and prevent pathologic fractures. Surgery may be indicated to decompress the spinal cord or stabilize the spine with internal fixation, to treat or prevent pathologic fractures (internal fixation) and occasionally manage destructive lesions or fractures in the long bones (resection with endoprosthesis). PMC is an incurable progressive disease, with a 5-year survival rate of 30%. Median survival is around 5.5 years. Systemic spread is very frequent, even occurring 8–12 years after the diagnosis. Adverse prognostic factors are the extent of bone involvement and the severity of anemia, hypercalcemia, impaired renal function, circulating monoclonal proteins, hyperuricemia, and alkaline phosphatase.

Key points	
Clinical	Elderly, most common primary malignant bone neoplasm
Radiological	Pure lytic lesion frequently multifocal. Bone scan usually negative
Histological	At least 30% of the bone marrow volume is composed of plasma cells secreting a monoclonal immunoglobulin
Differential diagnosis	Metastasis of carcinoma and melanoma, lymphoma primary of the bone and chronic osteomyelitis

Immunohistochemical panel	
CD138	+
MUM1	+
Kappa	±
Lambda	±



Radiograph. Multiple well-defined purely osteolytic lesions



The bone marrow is entirely constituted of a very thick mat of cells with no intercellular matrix (1). The tumor is composed of sheets of mature plasma cells with oval, eccentric nucleus showing a typical "cartwheel" chromatin (2)

53.1 Solitary Plasmacytoma of Bone

Definition: Solitary plasmacytoma of bone (SPB) is a rare localized tumor consisting of monoclonal plasma cells with no clinical features of PCM. In some cases, flow cytometry identifies minimal (<10%) clonal bone marrow plasma cell. Most often osteolytic lesions are identified in the axial skeleton.

Epidemiology: It is more common in men and median patient age at diagnosis is 55 years.

Imaging: Radiological studies show a localized and often massive homogeneous, trabeculated, or bubbling osteolysis with frequent destruction or inflation of the cortex.

Histopathology: Histologically, plasmacytoma has the same morphology described in PCM. The immunophenotype is also similar to that of PCM.

Treatment and Prognosis: It is based on radiation therapy and/or surgery and sometimes chemotherapy. Two-thirds of cases evolve to PCM, mostly in patients with minimal bone marrow involvement at diagnosis. Median overall survival is about 10 years.

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Hodgkin's Disease in Bone

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Marta Sbaraglia

Definition: Lymphoid neoplasms composed of large dysplastic mononuclear and multinucleated cells surrounded by variable mixture of non-neoplastic inflammatory cells. Hodgkin lymphoma included two different types: nodular lymphocyte predominant HL (NLPHL) and classic HL (CHL).

Epidemiology: Primary bone HLs are extremely rare with only few cases reported in literature, mostly associated with HIV infection. Males prevalence is observed. Most tumors occurred in young adult (mean 30 years).

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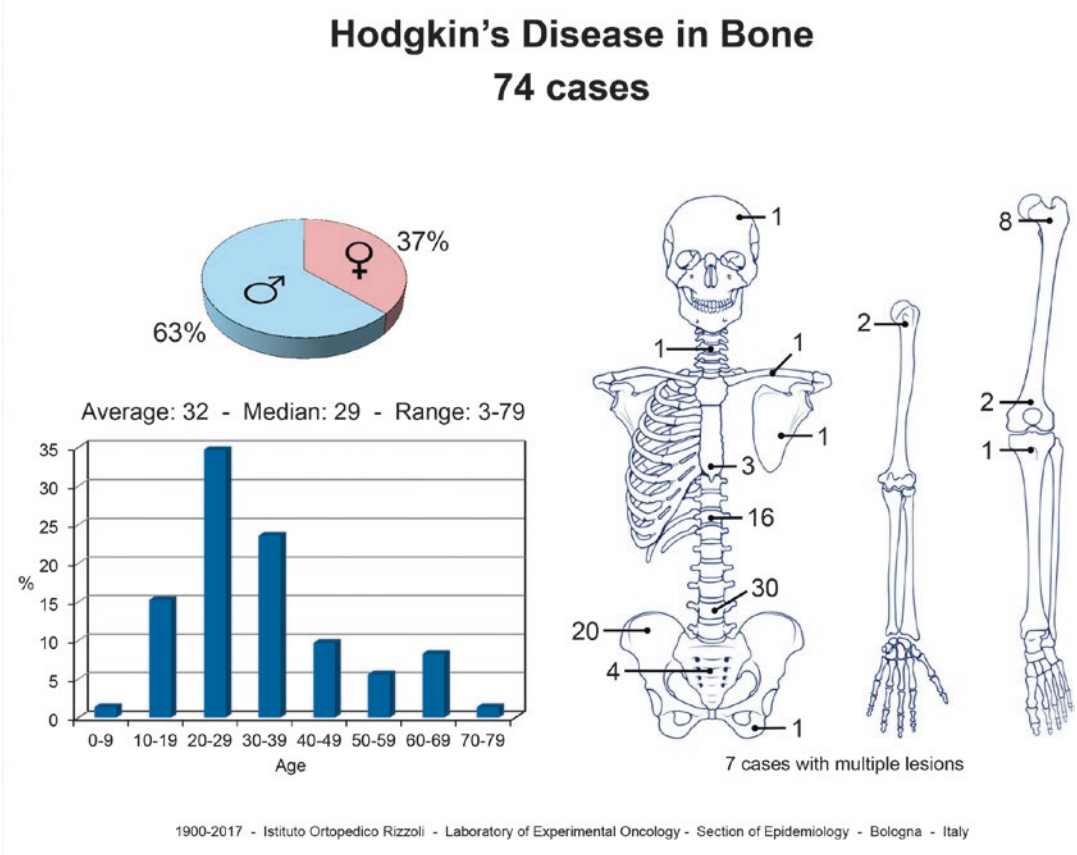

Localization: Most cases of PBL involve the axial skeleton including the pelvis and vertebrae. Less frequently the lower limbs are affected.

Clinical: Clinical presentation is variable and dependent on the localization of the disease. In about 40% of patients, "B-symptoms" consisting of fever, drenching night sweats, and weight loss may be present.

Histopathology: Tumor is composed of an admixture of reactive inflammatory infiltrate and variable numbers of distinctive Hodgkin/Reed-Sternberg (HRS) cells, the latter showing abundant basophilic cytoplasm with at least two nuclear lobes containing a prominent nucleolus with perinuclear clearing. The HRS cells typically show immunopositivity for CD30, CD15, and PAX5.

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Metastatic Lesions

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Marco Gambarotti and Marta Sbaraglia

Definition: Secondary localization in bone of malignant epithelial neoplasm.

Importance: Bone is the most common anatomic site for metastases. Lung, breast, gastrointestinal, and prostatic carcinomas frequently spread to the bone. In fact, metastases represent the most common neoplasm encountered in the skeleton.

Epidemiology: Autopsy reports, revealed bone metastases in approximately 30% of patients affected by breast, prostate, thyroid, lung, and kidney cancer. Adult and elderly patients are most often involved. However, thyroid or breast cancers may also be observed in younger patients. Male predominance is observed.

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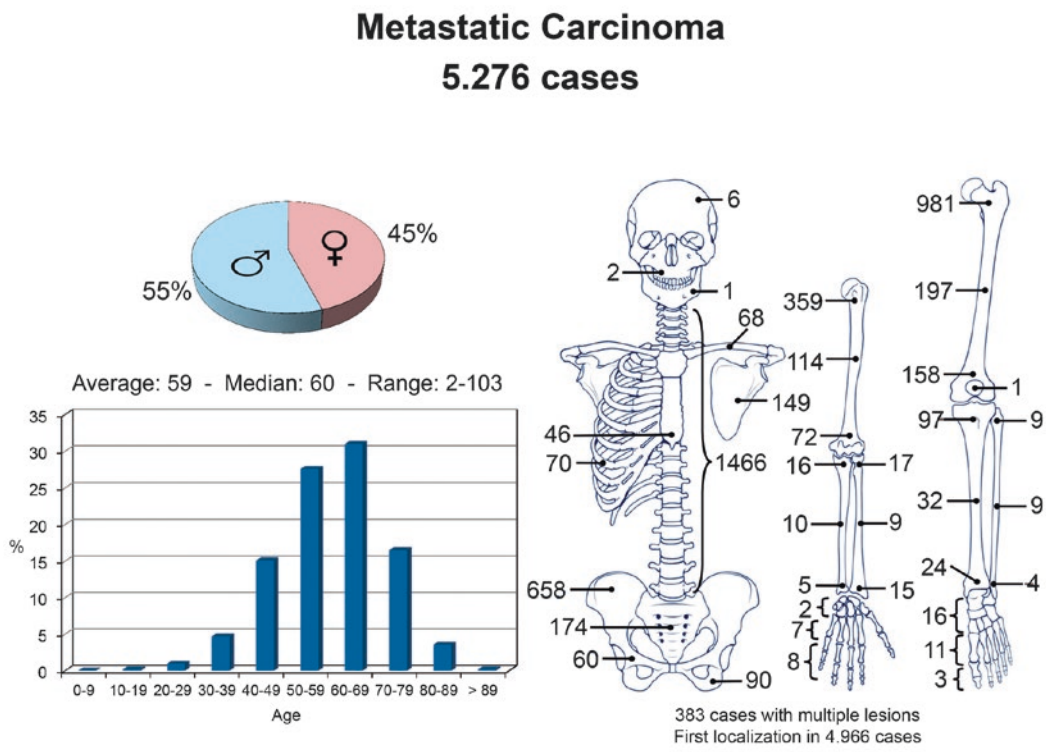


Localization: Metastases may affect any skeletal sites; however, the axial skeleton and the proximal region of the appendicular skeleton represent the most common locations. Extremities and cranial bones are rarely involved. Multiple lesions are often observed. Organs other than the skeleton can be frequently involved configuring a disseminated multisystemic disease.

Clinical: Pain, swelling, and pathological fractures are the typical presenting symptoms. In about 20% of cases, the site of the primary origin is unknown.

Imaging: Standard radiography may be negative (40% of cases). Frequently, bone metastases appear as osteolytic lesions. Isotope scan and MRI are much more sensitive than x-ray in detecting bone metastases. PET-CT is very useful to detect bone lesions and to evaluate the progression of the disease.

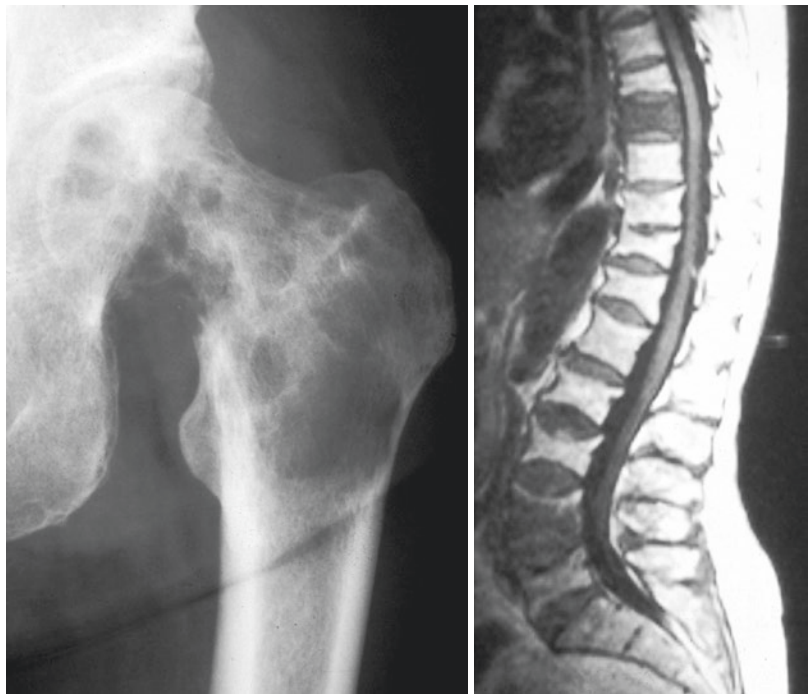
Histopathology: Histologically metastases tend most often (but not always) to reproduce the morphology of the primary lesion. Of course, immunohistochemical analysis can help identifying the site of origin in case of poorly differentiated morphology.

Treatment: In metastatic patients to improve the quality of life represents the most important aim. Palliative treatment is indicated in presence of diffused disease. An adjuvant treatment using chemotherapy, low dose radiotherapy, and surgery is useful in patients with indolent disease. In case of good prognosis chemotherapy, high dose radiotherapy and wide resection with stable reconstruction can be combined to achieve long survival.

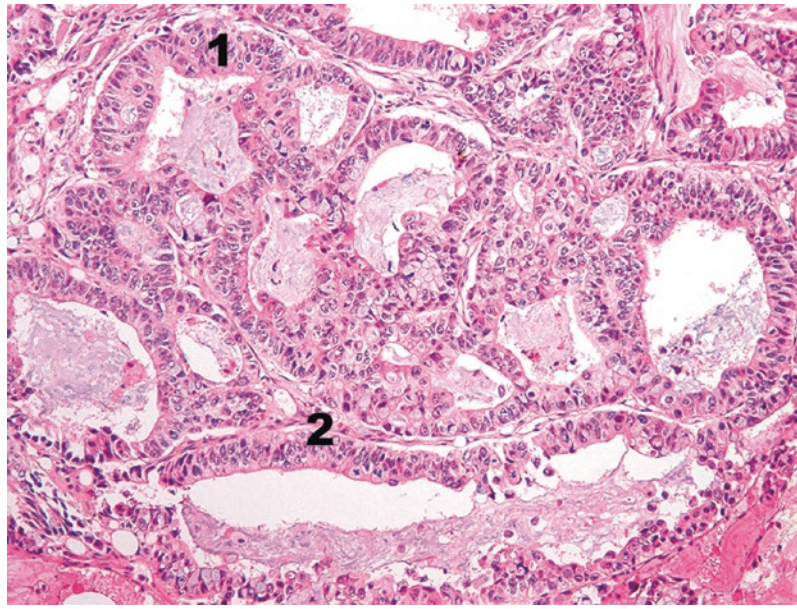
Key points	
• Clinical	Most frequent bone lesion. Adults, pain Pathologic fracture
• Radiological	Permeative or purely lytic lesions
• Histological	Epithelioid morphology, depending on primary lesion
• Differential diagnosis	Metastatic melanoma, lymphoma, epithelioid angiosarcoma

Immunohistochemical panel								
	Breast	Prostate	Lung	Thyroid	Kidney	Colon	Urothelial	Melanoma
CK AE1/AE3	+	+	+	+	+	+	+	–
CK 7	+	–/+	+	+	–	–	+	–
CK 20	–	–/+	–	–	–	+	+	–
TTF1	–	–	+ (Adcr)	+	–	–	–	–
P40	–	–	+ (Sq. cr.)	–	–	–	+	–
Thyroglobulin	–	–	–	+	–	–	–	–
CDX-2	–	–	–	–	–	+	–	–
ER	+/–	–	–	–	–	–	–	–
PRG	+/–	–	–	–	–	–	–	–
PSA	–	+	–	–	–	–	–	–
Nk3x1	–	+	–	–	–	–	–	–
AMACR	–	+	–	–	–	–	–	–
GATA3	+	–	–	–	–	–	+	–
PAX8	–	–	–	–	+	–	–	–
CD10	–	–	–	–	+	–	–	–
S-100	–	–	–	–	–	–	–	+
HMB-45	–	–	–	–	–	–	–	+
MART-1	–	–	–	–	–	–	–	+
MYTF	–	–	–	–	–	–	–	+

Adcr Adenocarcinoma, *Sq. Cr.* squamous carcinoma



Radiograph and sagittal spine T1 MR image. Heterogeneous mainly lytic lesion, destroying the femoral neck cortex. Multiple metastases of the spine



Metastatic adenocarcinoma. Malignant epithelial cells (1) forming glandular structures (2) are seen

Metastasis from non-sarcoma—origin on 2150 cases			
Breast	555	25.8	
Kidney	416	19.3	
Lung	381	17.7	62.9
Gastro-enteric	152	7.1	
Prostate	129	6.0	
Thyroid	117	5.4	18.5
Melanoma	60	2.8	
Undifferentiated	59	2.7	
Bladder urothelium	59	2.7	
Hepatic	54	2.5	
Uterus	41	1.9	
Bilio-pancreatic	27	1.3	
Ovary	16	0.7	
Other	15	0.7	
Neuroendocrine	12	0.6	
Oropharynx	12	0.6	
Sarcomatoid	11	0.5	
Brain	4	0.2	
Pheochromocytoma	4	0.2	
Larynx	4	0.2	
Paraganglioma	4	0.2	
Skin	3	0.1	
Salivary	3	0.1	
Adrenal gland	3	0.1	
Testis	3	0.1	
Mesothelioma	2	0.1	
Parotid	2	0.1	
Wilms	2	0.1	
	2150	100.0	

Rarely the origin of a metastatic lesion in bone can be from a visceral or a soft tissue sarcoma. The most represented tumor is uterine leiomyosarcoma (see table).

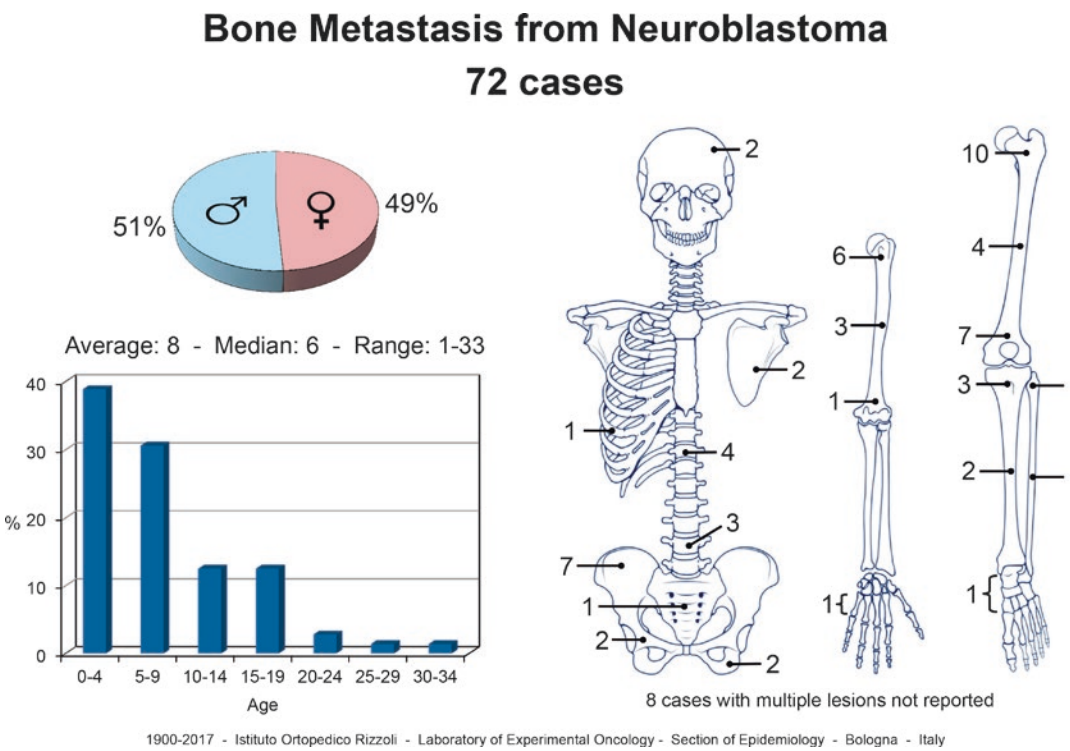
Metastasis from sarcoma—Origin on 43 Cases	N.	%
Uterine leiomyosarcoma	26	60.5
Unknown	4	9.3
Meningeal hemangiopericytoma	3	7.0
Fibrosarcoma	2	4.7
Gist	2	4.7
Myoepithelioma	2	4.7
Angiosarcoma	1	2.3
Renal pecoma	1	2.3
Rhabdomyosarcoma uterus	1	2.3
Malignant Peripheral Nerve Sheath Tumor (MPNST)	1	2.3
	43	100.0

55.1 Metastatic Neuroblastoma

Neuroblastoma is a tumor of neuroblasts affecting children usually under 5 years of age.

These lesions enter into differential diagnosis with Ewing Sarcoma of bone.

The age is lower (Ewing sarcoma is rare below 5 years of age), the skeletal lesions are frequently multiple, there is a retroperitoneal or mediastinal mass, and catecholamine metabolites are found in urine. Histologically, differentiation is more difficult, but neuroblastoma often has more evident rosettes, more large, "pear" shaped, pleomorphic and hyperchromatic nuclei with more abundant cytoplasm.



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Correction to: Synovial Chondromatosis

Eric L. Staals

Correction to: Chapter 28 in: P. Picci et al. (eds.),
***Diagnosis of Musculoskeletal Tumors and Tumor-like Conditions*,**
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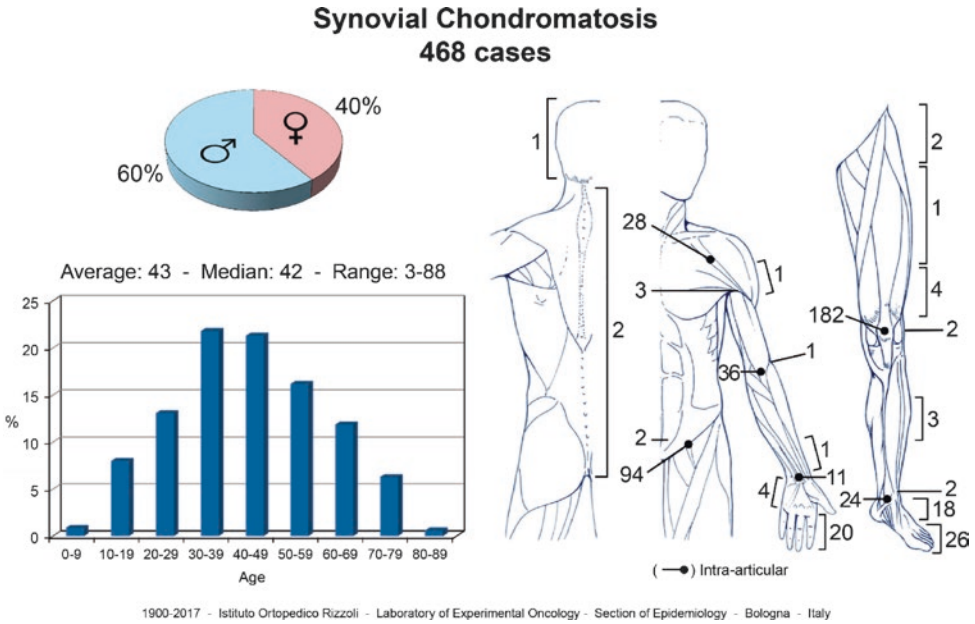
Chapter 28 was inadvertently published with the following error:

The figure on page 131 was misplaced. The correct figure has been included in this erratum. The chapter has now been updated.



The updated online version of this chapter can be found at https://doi.org/10.1007/978-3-030-29676-6_28

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