Chondrosarcomas (CHS)

34

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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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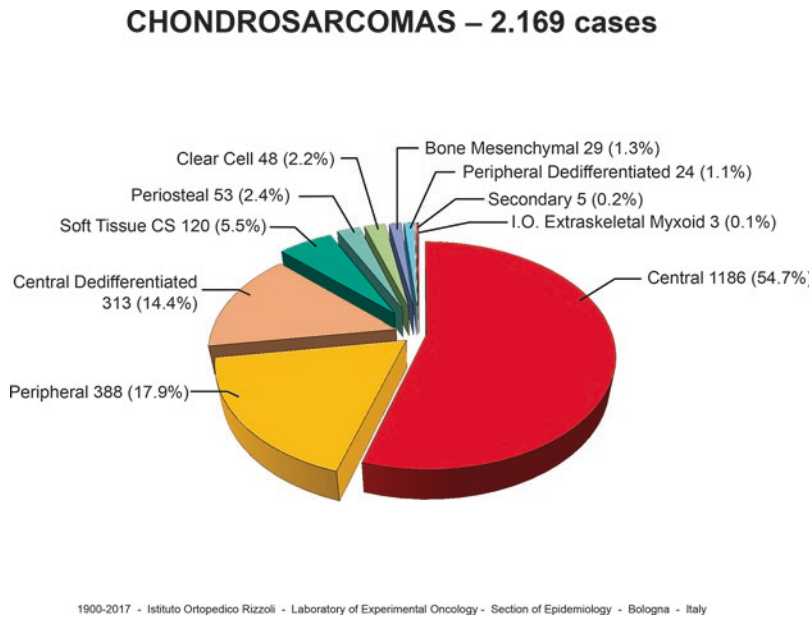
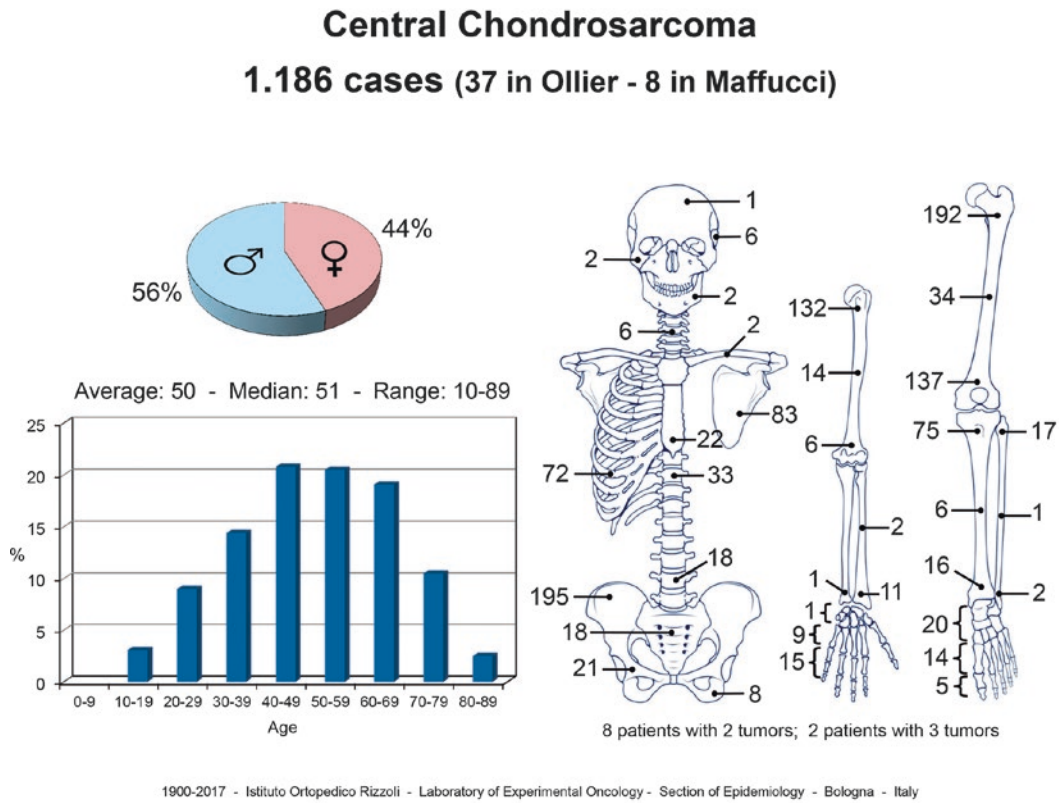


34.1 Central Chondrosarcoma

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.

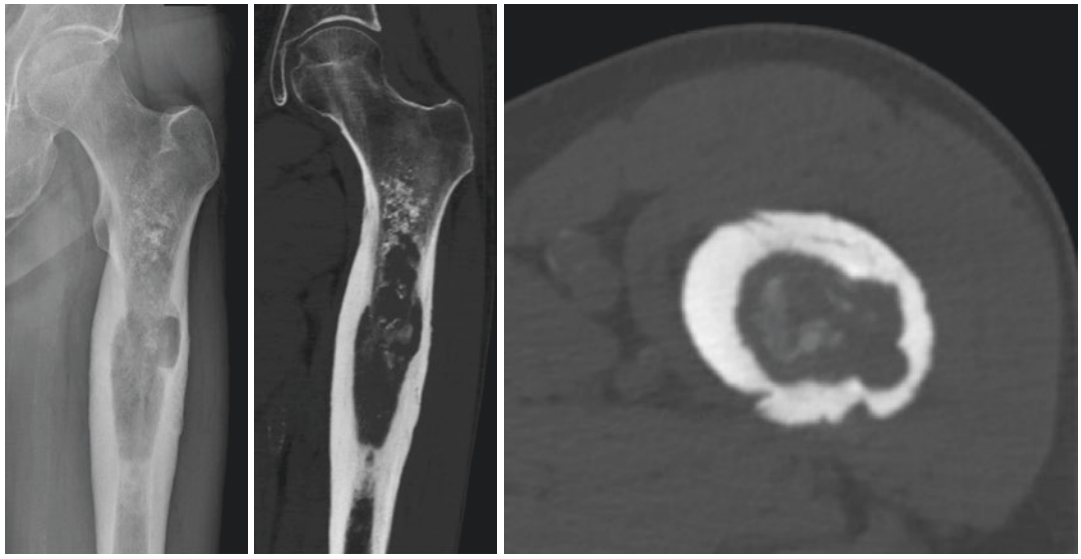
Imaging: On X-ray—intraosseous, osteolytic, geographic lesion with diffused, irregular, granules, nodules, radiopaque rings of calcifications. Sometimes, a bubbling or "honeycomb" feature, metallic or compact opacity. Cortex is scalloped, thinned, and destroyed. Often, it is thickened because the cortical 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.

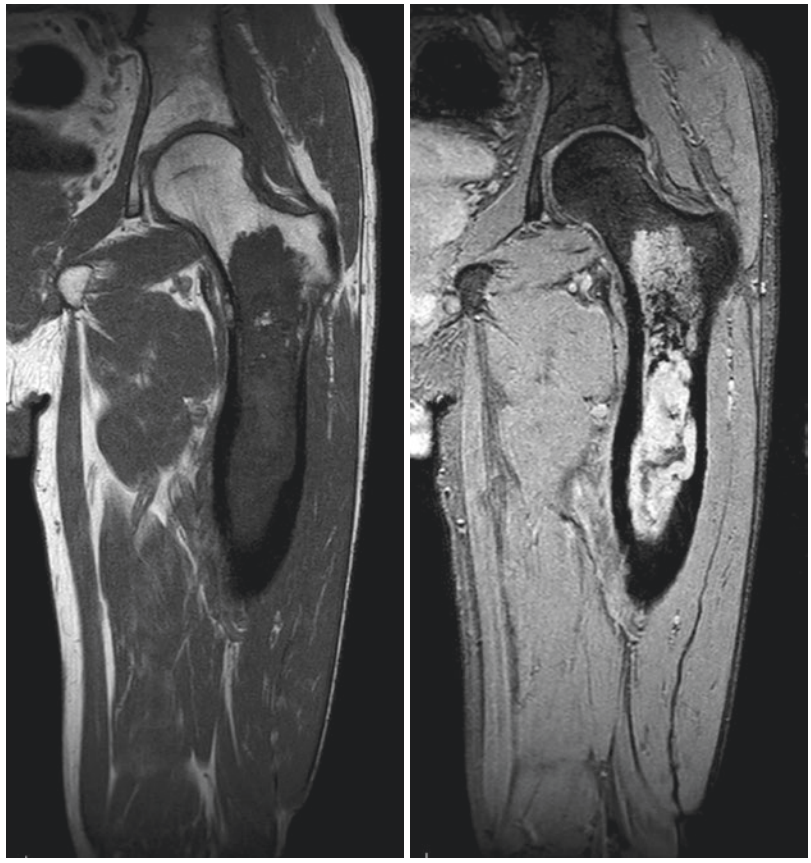
Course and Staging: Very slow growth. Typical progression in malignancy: transformation from a low to high grade or to another malignant tumor. Grade 1: very rare metastases, recurrence even after 10 years. Grade 2: frequent early or late metastases, recurrence within 5 years. Grade 3: higher rate of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

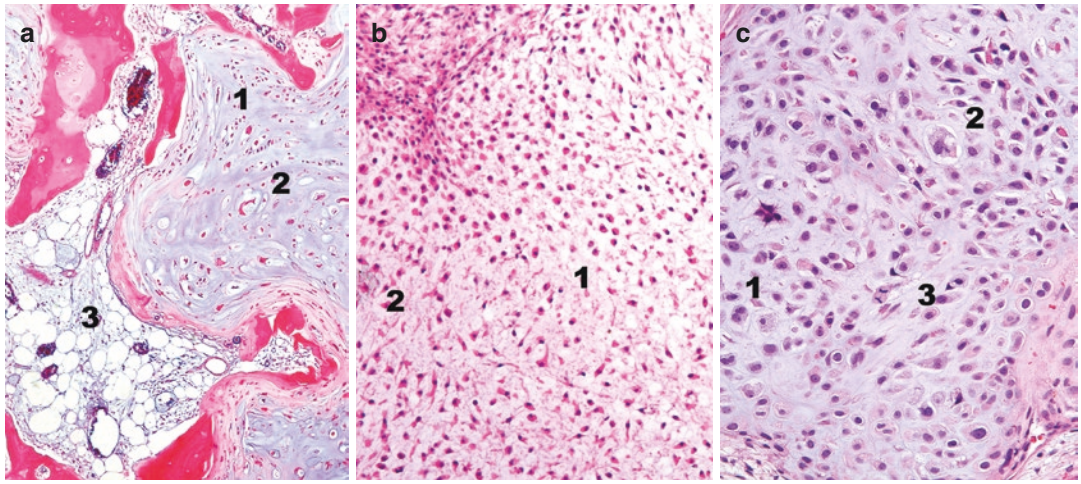
Key points	
• Clinical	Pain, adults, no children
• Radiological	Lytic lesion with granular calcifications. Expanded and invaded cortex
• Histological	Lobules of cartilage infiltrating host trabeculae
• Differential diagnosis	Chondroma, dedifferentiated chondrosarcoma



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

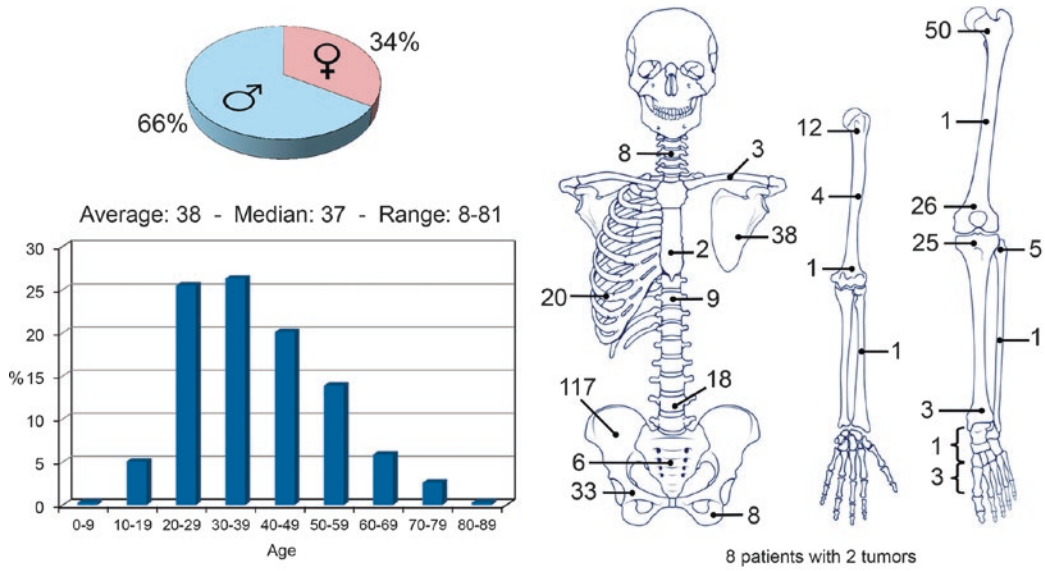
34.2 Peripheral (Secondary) Chondrosarcoma

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.

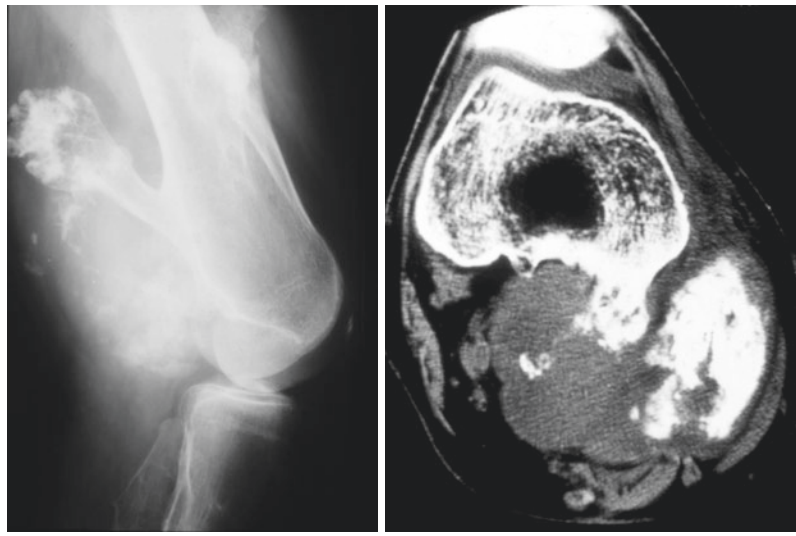
Histopathology: Large, bumpy, cauliflower-like, with a thin pseudocapsule and thick cap of cartilage, generally more than 2 cm in thickness, chalky and gritty, with hard consistency. Histologically, lobules of well-differentiated cartilage with loss of the architecture of an osteochondroma. Hypercellular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

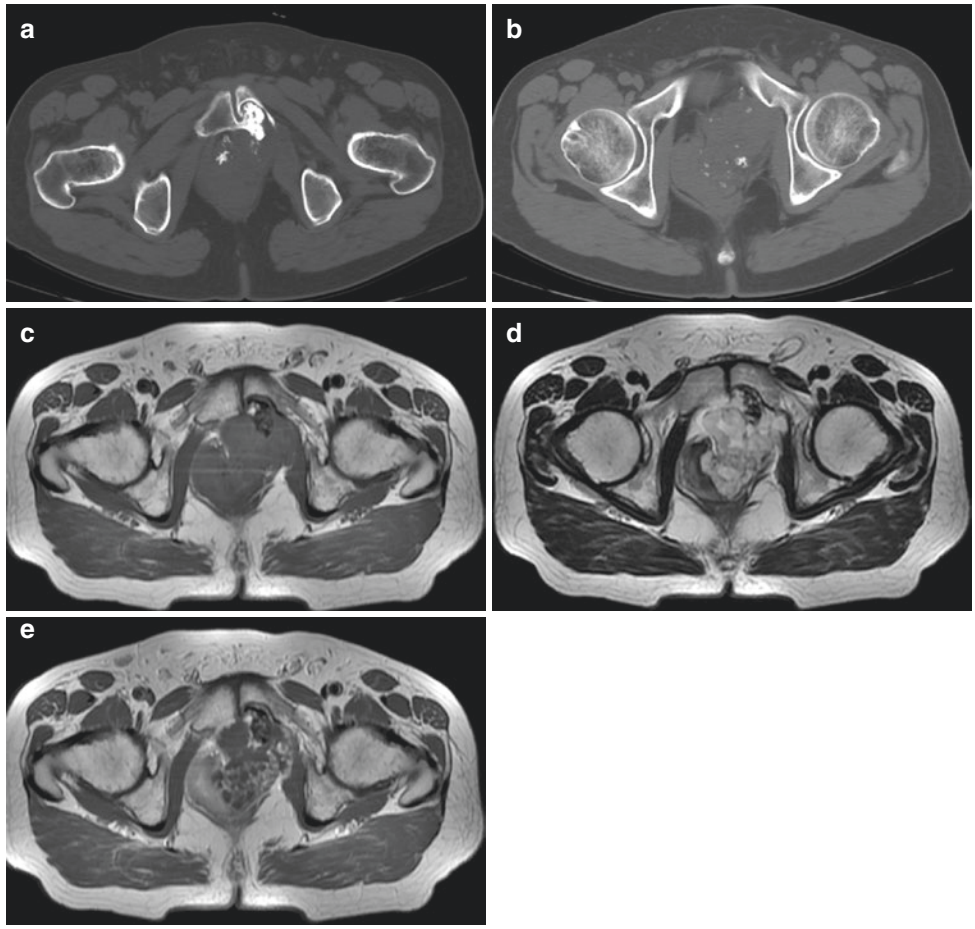
Course and Staging: It grows more slowly than central C, recurrence is observed from a few months to 10 years, <20% of cases have lung and late metastases. Dedifferentiated peripheral C is rare (4%). Usually, stage IB.

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.

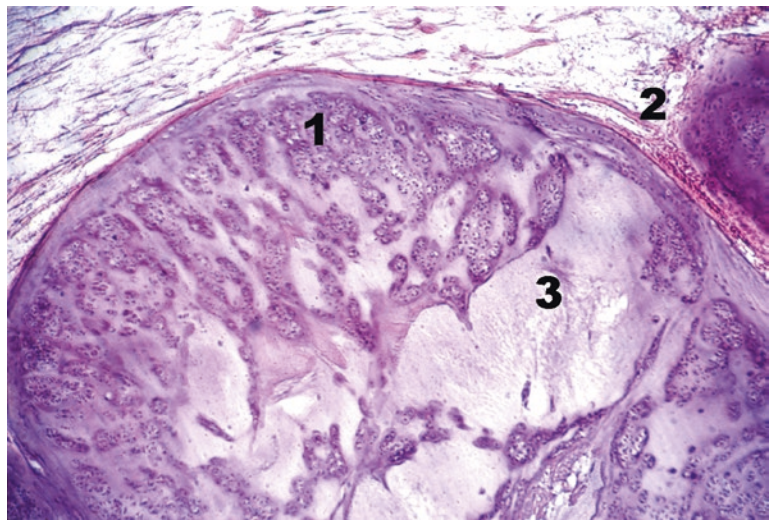
Key points	
• Clinical	Slow increasing swelling
• Radiological	Osteochondroma with lytic areas
• Histological	Thicker cap than osteochondroma with loss of the architecture of the osteochondroma
• Differential diagnosis	Osteochondroma, dedifferentiated peripheral chondrosarcoma



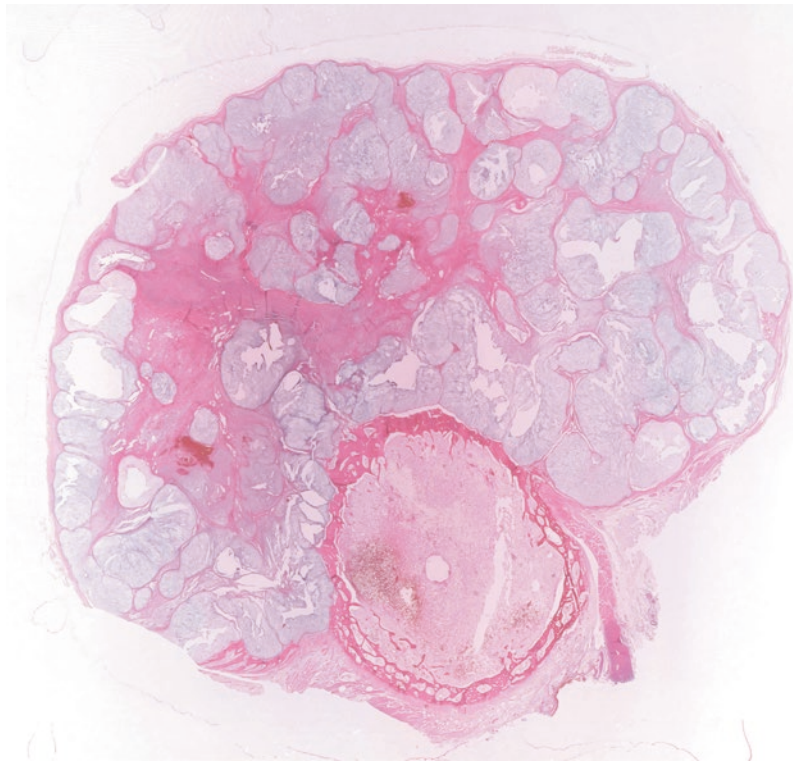
Radiograph and CT: the cortex of the osteochondroma is in continuity with the one of the normal bone. There is a large non-calcified malignant mass



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

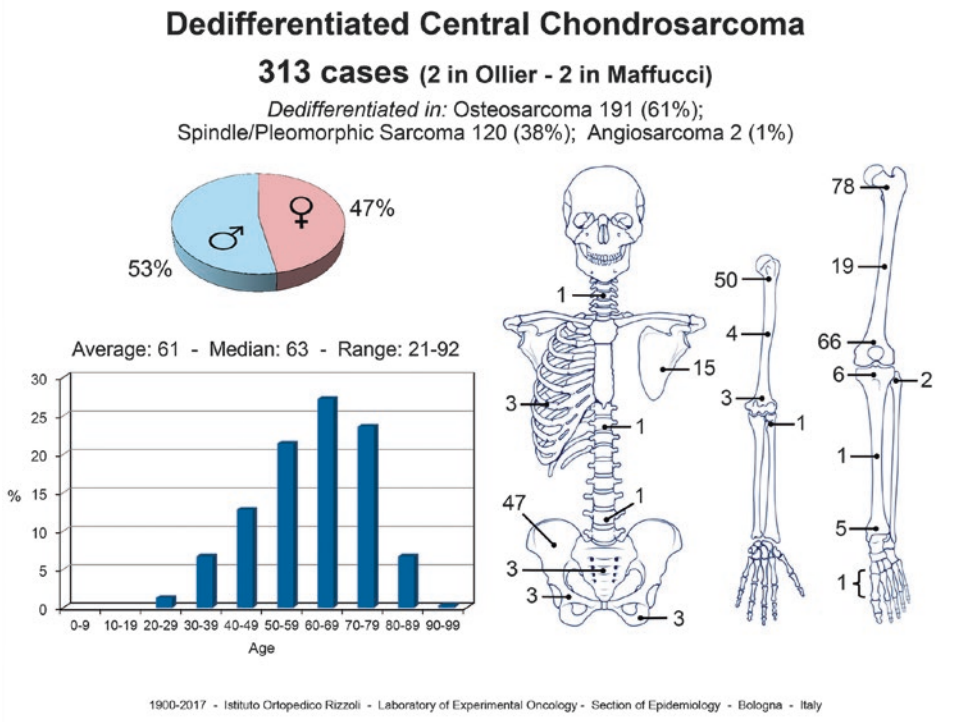


Whole macrosection with cartilaginous cup exceeding 2 cm in thickness

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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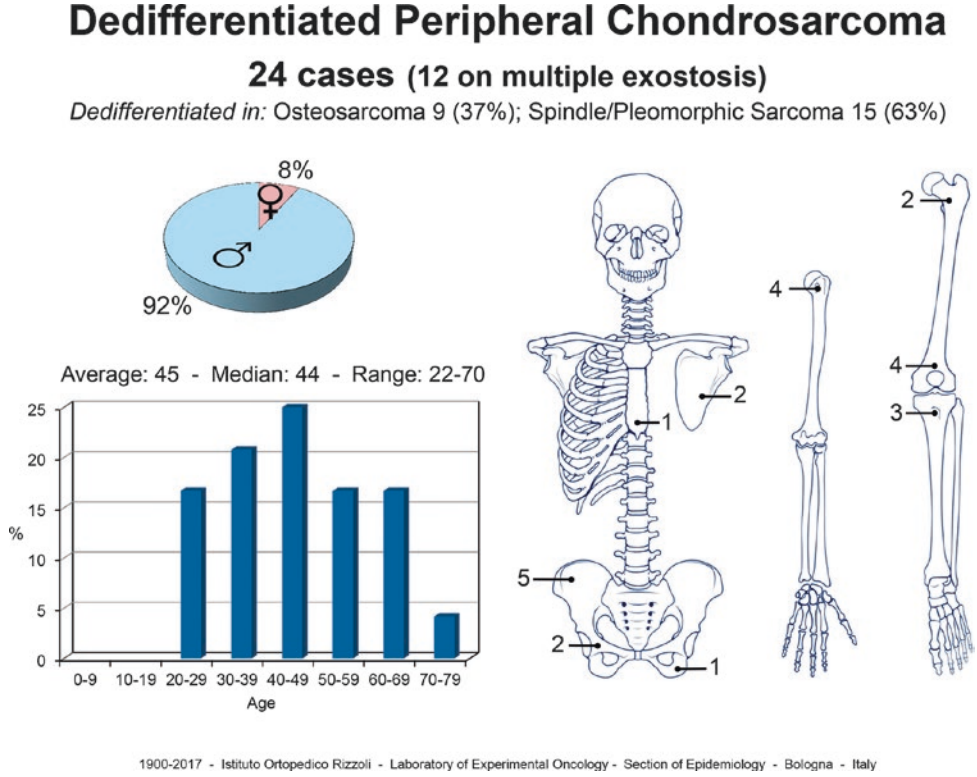
Dedifferentiated Peripheral Chondrosarcoma
24 cases (12 on multiple exostosis)
Dedifferentiated in: Osteosarcoma 9 (37%); Spindle/Pleomorphic Sarcoma 15 (63%)
♀ 8%
♂ 92%
Average: 45 - Median: 44 - Range: 22-70
% 25 20 15 10 5 0
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79
Age
2 1 5 2 1
4
2 4 3
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Location: 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.

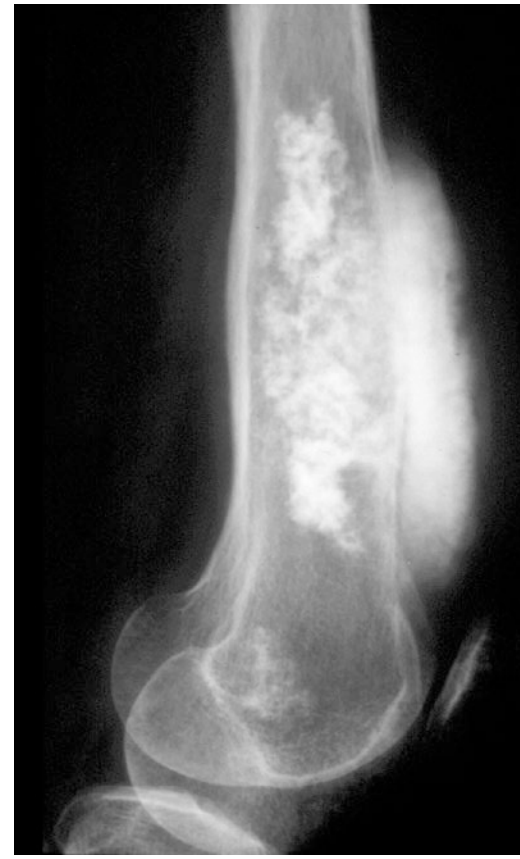
Imaging: On X-ray—(1) old cartilaginous lesion: moderate expansion of the bone with thickened, scalloped cortex, with many calcifications; (2) new lesion: destroying the cortex, involving the soft tissues, dissolving the calcifications, with ill-defined margins. Three different features: (a) pathologic 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.

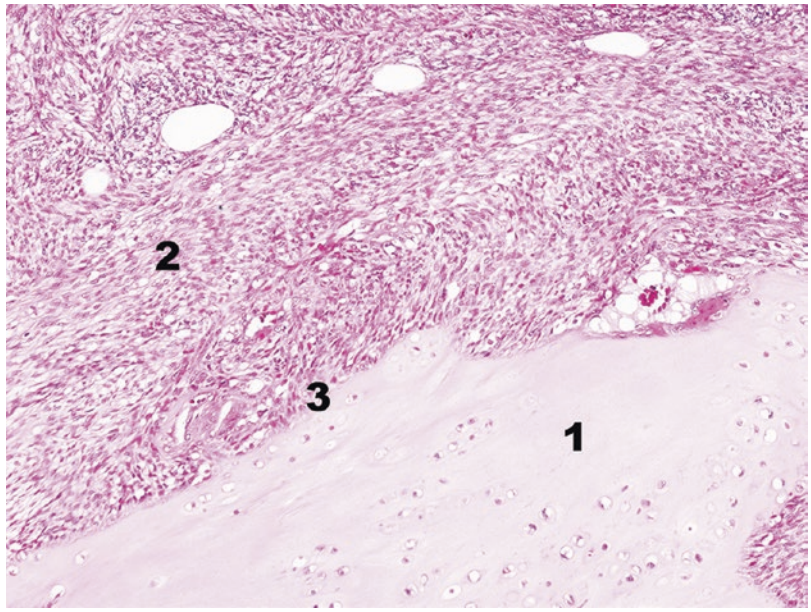
Course and staging: Fast growth, high risk of recurrence with inadequate surgery, and high rate of metastases, often observed at diagnosis. Usually, stage IIB or III.

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

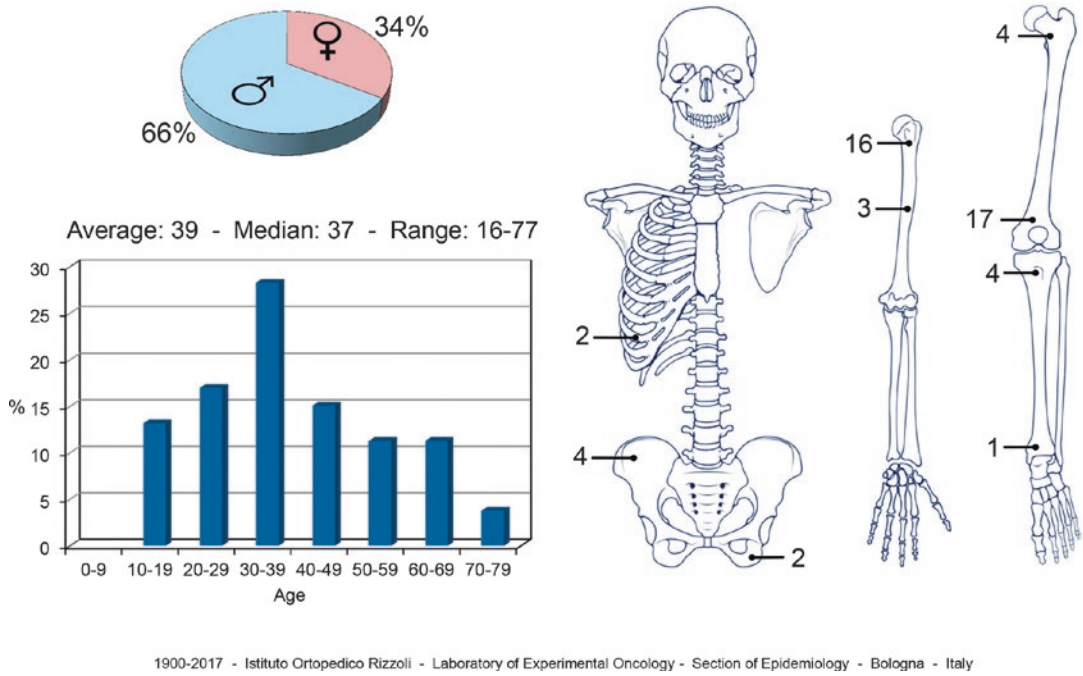


There are two clearly distinct tumor tissues. One is a well-differentiated cartilaginous tumor and the other has a different histotype, characterized by high-grade malignancy. The transition from one type of tissue to the other is abrupt. (1) Chondrosarcomatous tissue. (2) High-grade malignant tumor.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

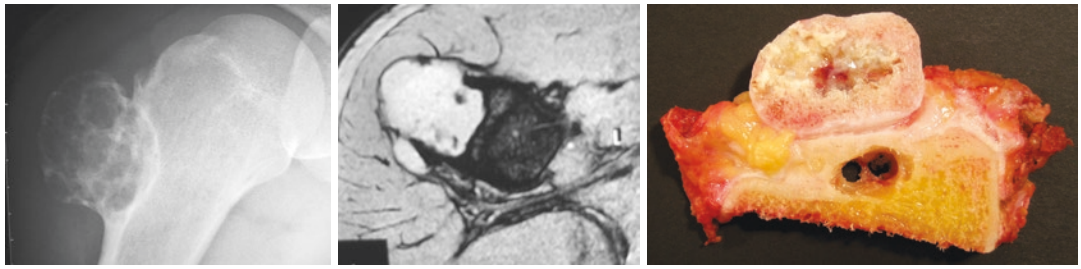
Imaging: On X-ray—globose mass lying on the outer surface of the cortex, very radiolucent or with granules, rings, spots of cartilage, rarely bunches of faded ossifications. Outer cortical erosion, saucer-like cortex, thickness of the adjacent cortex, buttress of periosteal reaction, internal sclerotic 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.

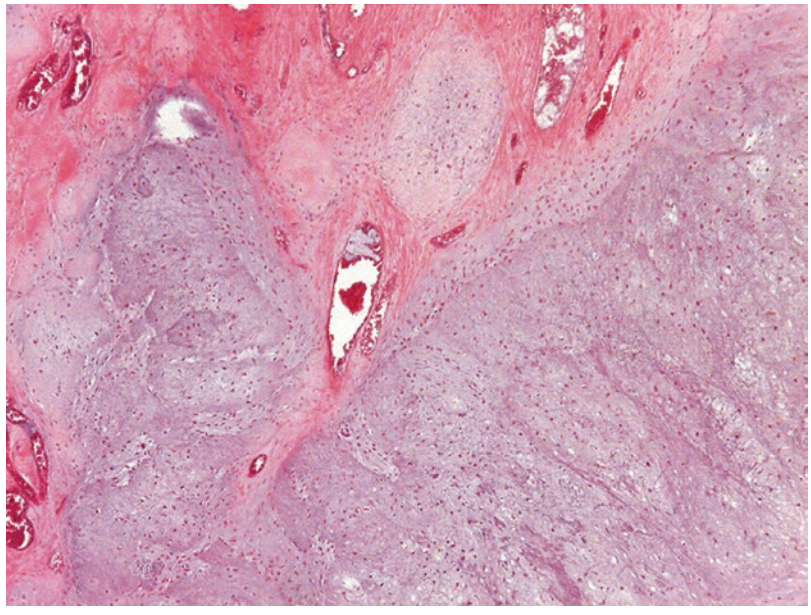
Course and staging: Rare recurrence if surgery is adequate; late, very rare mets. Usually stage IA.

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

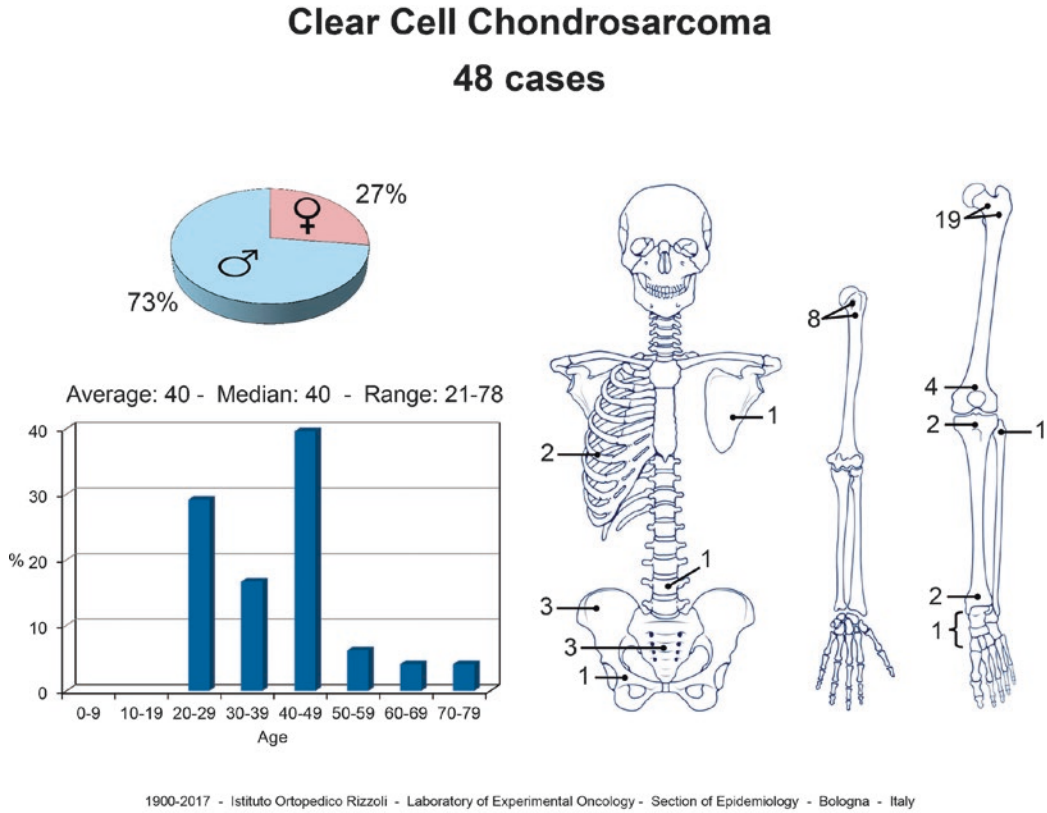


Large (usually more than 5 cm) cartilaginous tumor composed of lobules of cartilage, with myxoid change in the matrix. Permeation into the surrounding soft tissue is unequivocal evidence of malignancy

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.

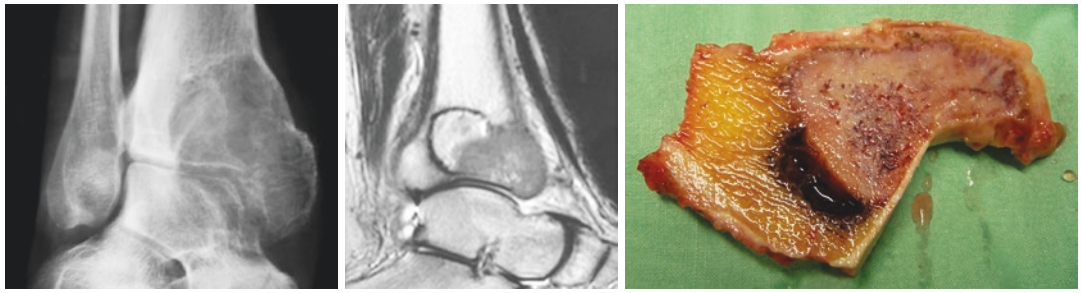
Imaging: On X-ray—like a chondroblastoma. Osteolytic lesion with small calcifications, sharp margins, irregular and ill-defined sclerotic rim. On CT—spots or small granules typical of the cartilaginous tumors.

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.

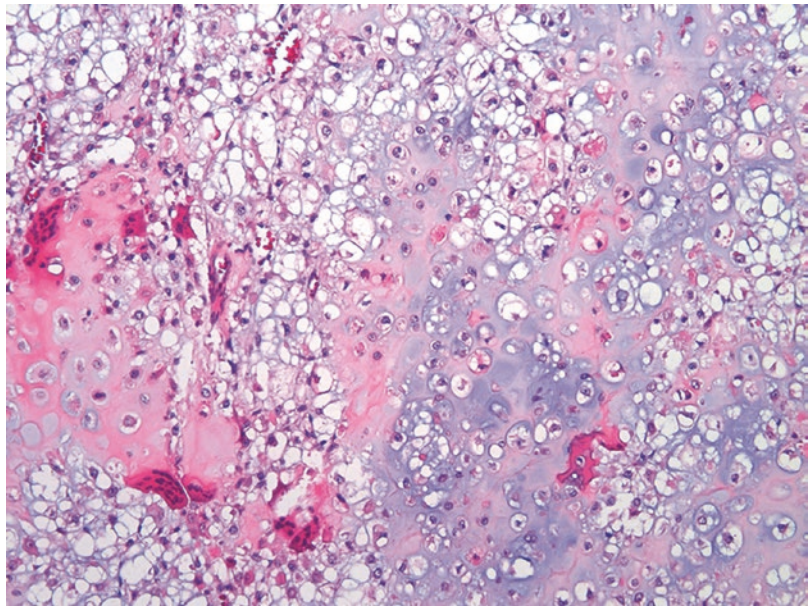
Course and staging: Slow growth, recurrence is possible when intralesional margins are obtained, metastases are exceptional. Usually, stage IA.

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

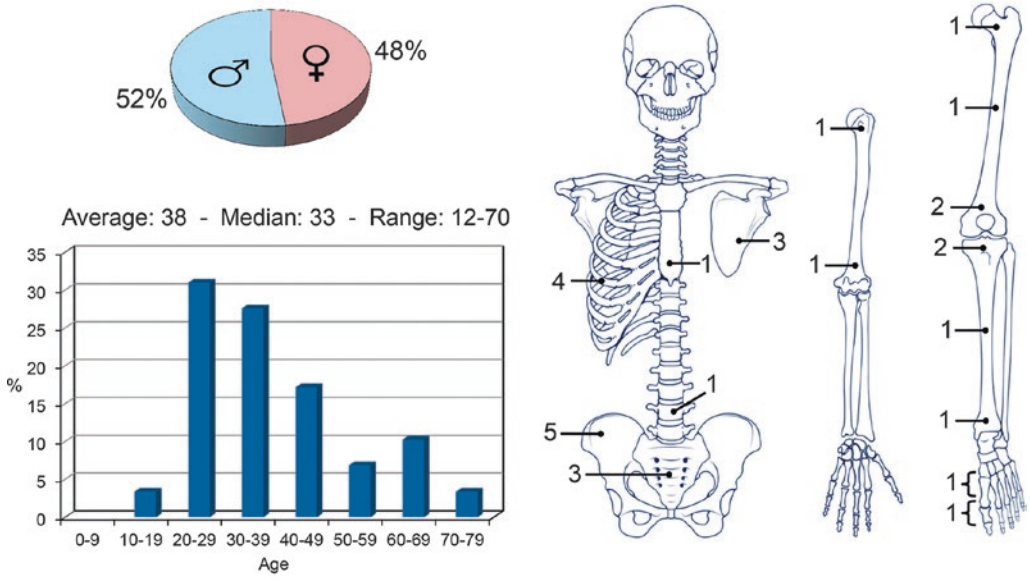
34.6 Mesenchymal Chondrosarcoma

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



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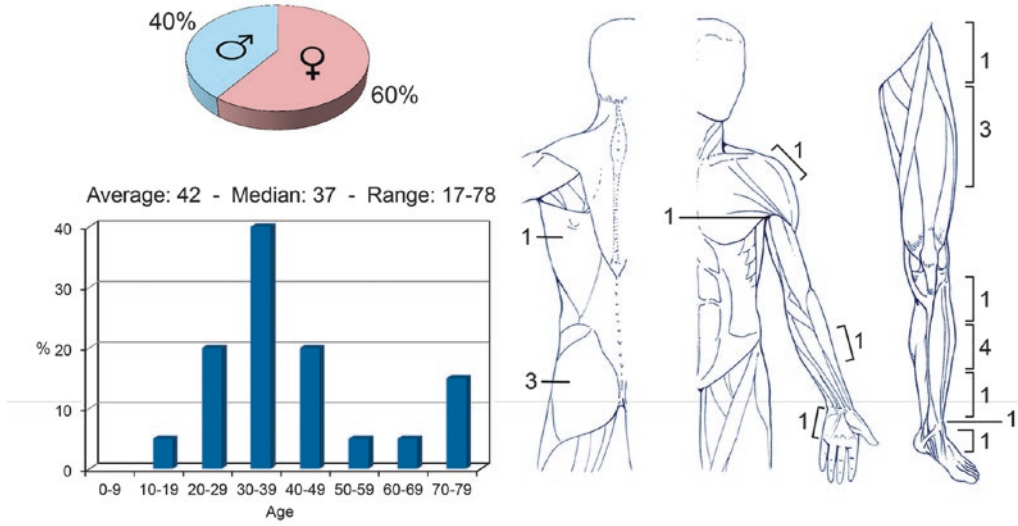
Mesenchymal Chondrosarcoma in Soft Tissue

20 cases



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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.

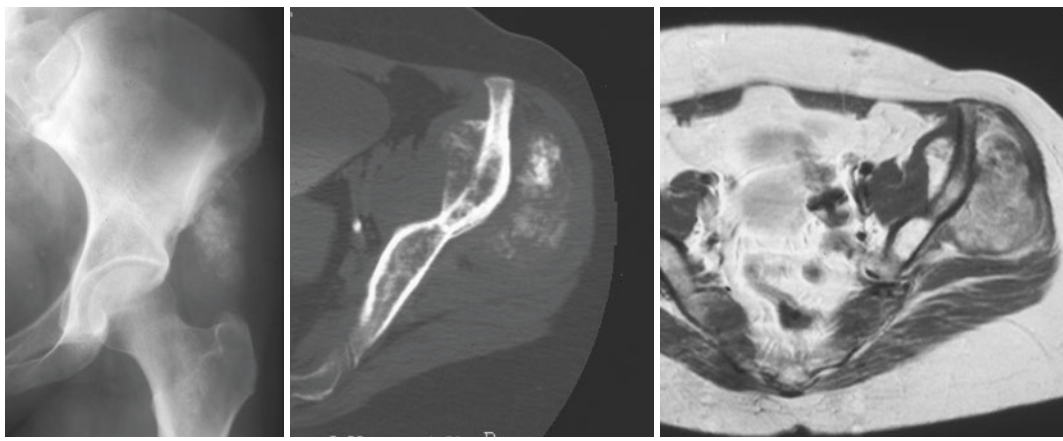
Histopathology: Dense round cells proliferation with hemangiopericytoma-like architecture. Within the tissue there are small foci or larger islands of well-differentiated hyaline cartilage. Osteoid-like matrix can be present.

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

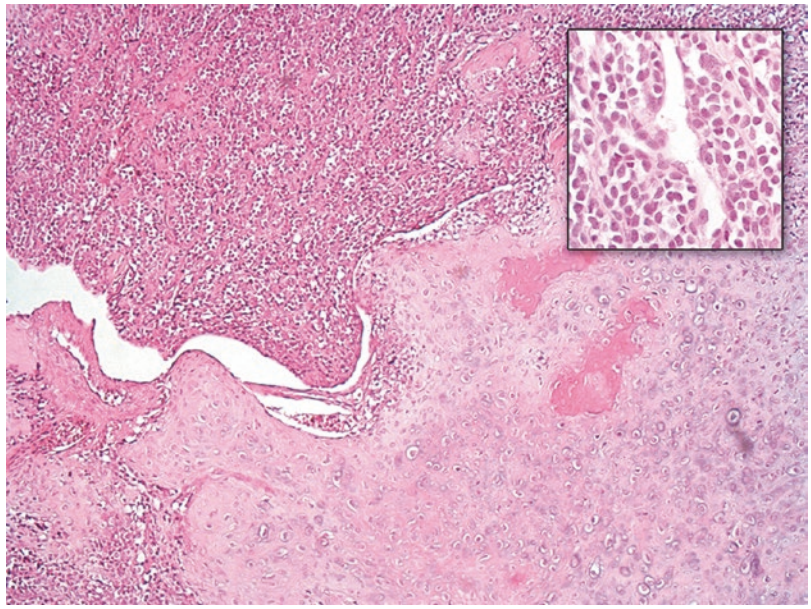
Treatment: Wide or radical resection. Chemotherapy is used but its real effectiveness is not yet known. Prognosis is poor.

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

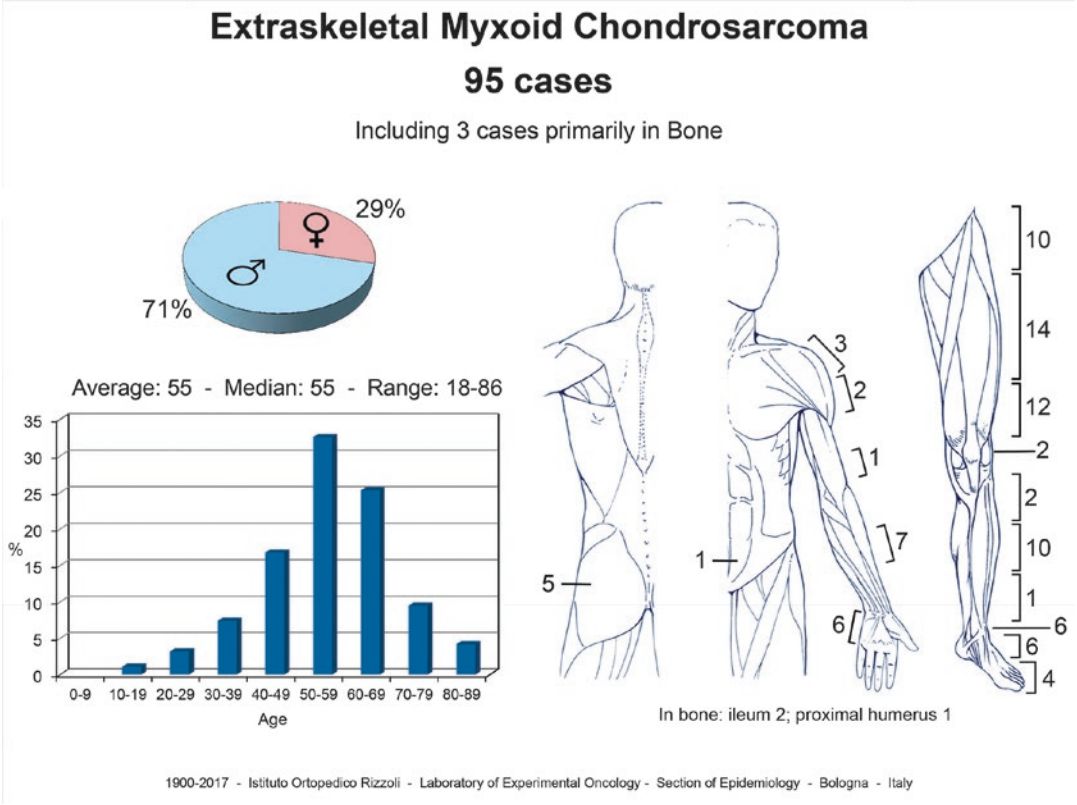


Islands of well-differentiated cartilage are surrounded by a proliferation of small round to ovoid undifferentiated cells. Hemangiopericytoma-like vessels are frequently present in the round cell component (*inset*)

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.

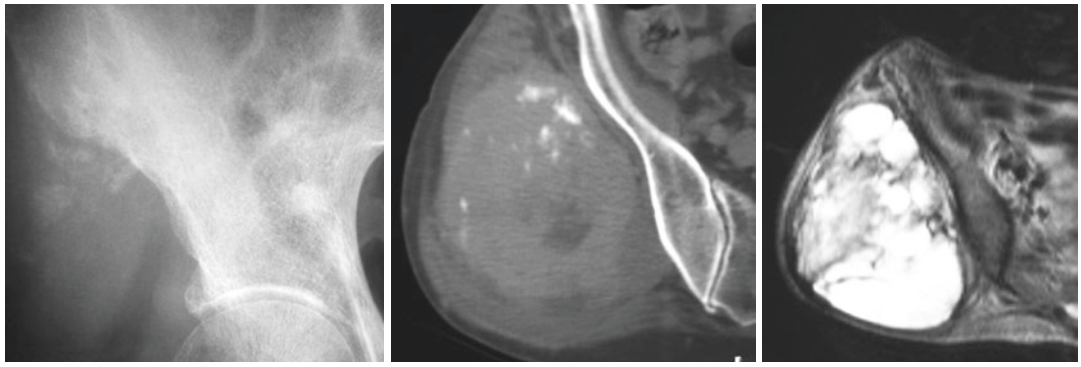
Imaging: Although imaging characteristics are nonspecific, most tumors appear lobulated, and highly myxoid tumors have a homogeneous high intensity signal on T2-weighted MRI images. Tumors with necrosis or hemorrhage have a more heterogeneous appearance.

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.

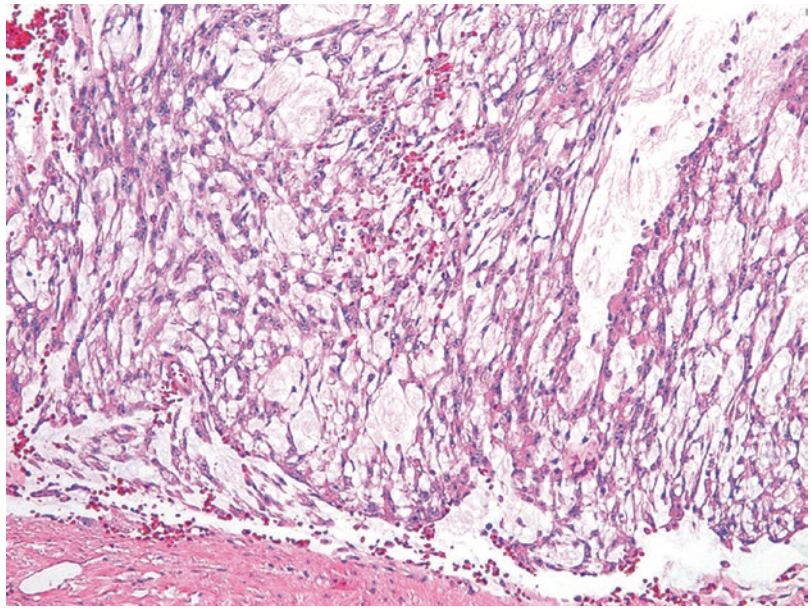
Course and Staging: Five-year survival rates are high (>80%); however, late lung metastases occur, and 10- and 15-year disease free survival rates are considerably lower.

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

Selected Bibliography

Ahmed AR, Tan TS, Unni KK, Collins MS, Wenger DE, Sim FH. Secondary chondrosarcoma in osteochondroma: report of 107 patients. Clin Orthop Relat Res. 2003;411:193–206.

Aigner T, Dertinger S, Belke J, Kirchner T. Chondrocytic cell differentiation in clear cell chondrosarcoma. Hum Pathol. 1996;27(12):1301–5.

Ali N, Vanel D, Righi A, Colangeli M, Manfrini M. Imaging features of extraskeletal mesenchymal chondrosarcoma of the hand. Diagn Interv Imaging. 2015;96(9):965–7.

Bernard SA, Murphey MD, Flemming DJ, Kransdorf MJ. Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. Radiology. 2010;255(3):857–65.

Bertoni F, Picci P, Bacchini P, Capanna R, Innao V, Bacci G, Campanacci M. Mesenchymal chondrosarcoma of bone and soft tissues. Cancer. 1983;52(3):533–41.

Bosse A, Ueda Y, Wuisman P, Jones DB, Vollmer E, Roessner A. Histogenesis of clear cell chondrosarcoma. An immunohistochemical study with osteonectin, a non-collagenous structure protein. J Cancer Res Clin Oncol. 1991;117(1):43–9.

Capanna R, Bertoni F, Bettelli G, Picci P, Bacchini P, Present D, Giunti A, Campanacci M. Dedifferentiated chondrosarcoma. J Bone Joint Surg Am. 1988;70(1):60–9.

Cesari M, Bertoni F, Bacchini P, Mercuri M, Palmerini E, Ferrari S. Mesenchymal chondrosarcoma. An analysis of patients treated at a single institution. Tumori. 2007;93(5):423–7.

Chaabane S, Bouaziz MC, Drissi C, Abid L, Ladeb MF. Periosteal chondrosarcoma. AJR Am J Roentgenol. 2009;192(1):W1–6. Review.

Corradi D, Bacchini P, Campanini N, Bertoni F. Aggressive clear cell chondrosarcomas: do distinctive characteristics exist?: a report of 4 cases. Arch Pathol Lab Med. 2006;130(11):1673–9.

Donati D, Yin JQ, Colangeli M, Colangeli S, Bella CD, Bacchini P, Bertoni F. Clear cell chondrosarcoma of bone: long time follow-up of 18 cases. Arch Orthop Trauma Surg. 2008;128(2):137–42.

El Beaino M, Roszik J, Livingston JA, Wang WL, Lazar AJ, Amini B, Subbiah V, Lewis V, Conley AP. Mesenchymal chondrosarcoma: a review with emphasis on its fusion-driven biology. Curr Oncol Rep. 2018;20(5):37.

Fanburg-Smith JC, Auerbach A, Marwaha JS, Wang Z, Rushing EJ. Reappraisal of mesenchymal chondrosarcoma: novel morphologic observations of the hyaline cartilage and endochondral ossification and beta-catenin, Sox9, and osteocalcin immunostaining of 22 cases. Hum Pathol. 2010;41(5):653–62.

Filion C, Motoi T, Olshen AB, Laé M, Emnett RJ, Gutmann DH, Perry A, Ladanyi M, Labelle Y. The EWSR1/NR4A3 fusion protein of extraskeletal myxoid chondrosarcoma activates the PPARG nuclear receptor gene. J Pathol. 2009;217(1):83–93.

Finos L, Righi A, Frisoni T, Gambarotti M, Ghinelli C, Benini S, Vanel D, Picci P. Primary extraskeletal myxoid chondrosarcoma of bone: report of three cases and review of the literature. Pathol Res Pract. 2017;213(5):461–6.

Frezza AM, Cesari M, Baumhoer D, Biau D, Bielack S, Campanacci DA, Casanova J, Esler C, Ferrari S, Funovics PT, Gerrand C, Grimer R, Gronchi A, Haffner N, Hecker-Nolting S, Höller S, Jeys L, Jutte P, Leithner A, San-Julian M, Thorkildsen J, Vincenzi B, Windhager R, Whelan J. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51(3):374–81.

Gambarotti M, Righi A, Picci P, Bertoni F, Manfrini M, Donati DM, Dei Tos AP, Vanel D. Paediatric chondrosarcomas: a retrospective review of 17 cases. Histopathology. 2016;68(7):1073–8.

Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, Bovée JV. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9. Review. Erratum in: Oncologist. 2008 May;13(5):618.

Gitelis S, Bertoni F, Picci P, Campanacci M. Chondrosarcoma of bone. The experience at the Istituto Ortopedico Rizzoli. J Bone Joint Surg Am. 1981;63(8):1248–57.

Hisaoka M, Hashimoto H. Extraskeletal myxoid chondrosarcoma: updated clinicopathological and molecular genetic characteristics. Pathol Int. 2005;55(8):453–63. Review.

Lin PP, Moussallem CD, Deavers MT. Secondary chondrosarcoma. J Am Acad Orthop Surg. 2010;18(10):608–15. Review.

Littrell LA, Wenger DE, Wold LE, Bertoni F, Unni KK, White LM, Kandel R, Sundaram M. Radiographic, CT, and MR imaging features of dedifferentiated chondrosarcomas: a retrospective review of 174 de novo cases. Radiographics. 2004;24(5):1397–409. Review.

van Maldegem AM, Gelderblom H, Palmerini E, Dijkstra SD, Gambarotti M, Ruggieri P, Nout RA, van de Sande MA, Ferrari C, Ferrari S, Bovée JV, Picci P. Outcome of advanced, unresectable conventional central chondrosarcoma. Cancer. 2014;120(20):3159-3164.

McGrory JE, Rock MG, Nascimento AG, Oliveira AM. Extraskeletal myxoid chondrosarcoma. Clin Orthop Relat Res. 2001;382:185–90.

Mercuri M, Picci P, Campanacci L, Rulli E. Dedifferentiated chondrosarcoma. Skelet Radiol. 1995;24(6):409–16.

Mitchell A, Rudan JR, Fenton PV. Juxtacortical dedifferentiated chondrosarcoma from a primary periosteal chondrosarcoma. Mod Pathol. 1996;9(3):279–83.

Murphey MD, Walker EA, Wilson AJ, Kransdorf MJ, Temple HT, Gannon FH. From the archives of the AFIP: imaging of primary chondrosarcoma: radiologic-pathologic correlation. Radiographics. 2003;23(5):1245–78. Review.

Norman A, Sissons HA. Radiographic hallmarks of peripheral chondrosarcoma. Radiology. 1984;151(3):589–96.

Nota SP, Braun Y, Schwab JH, van Dijk CN, Bramer JA. The identification of prognostic factors and survival statistics of conventional central chondrosarcoma. Sarcoma. 2015;2015:623746. https://doi.org/10.1155/2015/623746.

Nussbeck W, Neureiter D, Söder S, Inwards C, Aigner T. Mesenchymal chondrosarcoma: an immunohistochemical study of 10 cases examining prognostic significance of proliferative activity and cellular differentiation. Pathology. 2004;36(3):230–3.

Papagelopoulos PJ, Galanis EC, Mavrogenis AF, Savvidou OD, Bond JR, Unni KK, Sim FH. Survivorship analysis in patients with periosteal chondrosarcoma. Clin Orthop Relat Res. 2006;448:199–207.

Present D, Bacchini P, Pignatti G, Picci P, Bertoni F, Campanacci M. Clear cell chondrosarcoma of bone. A report of 8 cases. Skelet Radiol. 1991;20(3):187–91.

Riedel RF, Larrier N, Dodd L, Kirsch D, Martinez S, Brigman BE. The clinical management of

chondrosarcoma. Curr Treat Options in Oncol. 2009;10(1-2):94–106. Review.

Robinson P, White LM, Sundaram M, Kandel R, Wunder J, McDonald DJ, Janney C, Bell RS. Periosteal chondroid tumors: radiologic evaluation with pathologic correlation. AJR Am J Roentgenol. 2001;177(5):1183–8.

Staals EL, Bacchini P, Bertoni F. Dedifferentiated central chondrosarcoma. Cancer. 2006;106(12):2682–91.

Staals EL, Bacchini P, Mercuri M, Bertoni F. Dedifferentiated chondrosarcomas arising in pre-existing osteochondromas. J Bone Joint Surg Am. 2007;89(5):987–93.

Swanson PE. Clear cell tumors of bone. Semin Diagn Pathol. 1997;14(4):281–91. Review.

Swanson PE, Lillemoe TJ, Manivel JC, Wick MR. Mesenchymal chondrosarcoma. An immunohistochemical study. Arch Pathol Lab Med. 1990;114(9):943–8.

Tateishi U, Hasegawa T, Nojima T, Takegami T, Arai Y. MRI features of extraskeletal myxoid chondrosarcoma. Skelet Radiol. 2006;35(1):27–33.

Urbini M, Astolfi A, Pantaleo MA, Serravalle S, Dei Tos AP, Picci P, Indio V, Sbaraglia M, Benini S, Righi A, Gambarotti M, Gronchi A, Colombo C, Dagrada GP, Pilotti S, Maestro R, Polano M, Saponara M, Tarantino G, Pession A, Biasco G, Casali PG, Stacchiotti S. HSPA8 as a novel fusion partner of NR4A3 in extraskeletal myxoid chondrosarcoma. Genes Chromosomes Cancer. 2017;56(7):582–6.

Vanel D, De Paolis M, Monti C, Mercuri M, Picci P. Radiological features of 24 periosteal chondrosarcomas. Skelet Radiol. 2001;30(4):208–12.

Varma DG, Ayala AG, Carrasco CH, Guo SQ, Kumar R, Edeiken J. Chondrosarcoma: MR imaging with pathologic correlation. Radiographics. 1992;12(4):687–704.

Wang WL, Mayordomo E, Czerniak BA, Abruzzo LV, Dal Cin P, Araujo DM, Lev DC, López-Terrada D, Lazar AJ. Fluorescence in situ hybridization is a useful ancillary diagnostic tool for extraskeletal myxoid chondrosarcoma. Mod Pathol. 2008;21(11):1303–10.