Diploma thesis

ENCHONDROMA VS. CHONDROSARCOMA G1: WHICH FEATURES INDICATE MALIGNANCY?

submitted by

Sabrina Galsterer

to attain the academic degree

Doctor medicinae universae

(Dr. med. univ.)

at the

Medical University of Graz

conducted at the

Department of Orthopaedics and Trauma

under the supervision of

Dr. med. univ. Dr. scient. med. Maria Smolle

and

Univ.-Prof. Dr. med. univ. Andreas Leithner

Graz, 17.02.2022

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 17.02.2022 *Sabrina Galsterer eh*

Danksagungen

Mein besonderer Dank gilt meiner Betreuerin DDr. Maria Smolle, die mir jederzeit mit Rat und Tat zur Seite stand und bei etwaigen Fragen, von denen es im Laufe der Zeit genug gab, sofort eine Antwort parat hatte. Auch möchte ich meinem zweiten Betreuer Univ.-Prof. Dr. Andreas Leithner danken, der mich ebenfalls mit Ideen und seiner Expertise unterstützt hat. Besonderer Dank gilt auch unseren Reviewern der *Universitätsklinik für Orthopädie und Traumatologie, Medizinische Universität Graz*, OA Priv. Doz. DDr. Jörg Friesenbichler und OA DDr. Marko Bergovec sowie den Reviewern von der *Universitätsklinik für Radiologie, Medizinische Universität Graz*, OA DDr. Jasminka Igrec und Ass. Dr. Jakob Steiner.

Ich möchte auch meinen Eltern danken, die mir dieses Studium erst ermöglicht haben und mir immer mit Rat und Tat zur Seite gestanden sind. Danke auch an meine Schwester und meine Tante, die mich auf diesem Weg unterstützt haben und jederzeit ein offenes Ohr für mich hatten. Dank meiner Familie war es mir erst möglich, meine Ziele zu erreichen und mir den Traum vom Medizinstudium zu erfüllen.

Abschließend möchte ich noch meinen Freundinnen und Freunden danken, sowie ganz besonders meinem Partner Stefan, von dem ich sehr viel Unterstützung und Geduld, auch in stressigeren Zeiten, erfahren habe.

Index

Abbreviations

111In	Indium-111
^{201}Tl	Thallium-201
67Ga	Gallium-67
99mTc	Technetium-99m
ACT	Atypical Cartilaginous Tumour
AIC	Anterior Iliac Crest
CD	Cluster of Differentiation
CS	Chondrosarcoma
CT	Computed Tomography
EC	Enchondroma
F^{18}FDG	2-Fluoro-2-Deoxy-D-Glucose
FCM	Flow Cytometry
FISH	Fluorescent in Situ Hybridization
G1	Low Grade, Grade 1
G2	Intermediate Grade, Grade 2
G3	High Grade, Grade 3
Gd-DTPA	Gadolinium Diethylenetriamine-Penta-Acetic Acid
H&E	Haematoxylin and Eosin
IDH	Isocitrate Dehydrogenase
MRI	Magnetic Resonance Imaging
MRT	Magnetresonanztomographie
NA	No Answer given
PAS	Periodic Acid-Schiff
PET	Positron Emission Tomography
SE	Spin Echo
SPECT	Single Photon Emission Computed Tomography
STIR	Short Tau Inversion Recovery
WHO	World Health Organization

Index of figures

Index of tables

Zusammenfassung

Einleitung

Die radiologische Unterscheidung zwischen Enchondromen und atypischen chondrogenen Tumoren (ehemals Chondrosarkome G1) ist eine Herausforderung. Oft ist es anhand der Radiologie allein schwierig zu beurteilen, ob der Tumor benigne oder maligne ist, wovon jedoch das weitere Vorgehen – „Watch and Wait“, Biopsie oder entsprechende operative Versorgung – abhängt. Unser Ziel ist es sowohl klinische als auch radiologische Merkmale herauszuarbeiten, die auf eine etwaige Malignität der Läsion schließen lassen.

Methoden

Patient*innen, die die histologisch verifizierte Diagnose “Enchondrom“ oder „atypischer chondrogener Tumor“ bzw. ehemals „Chondrosarkom G1“ der langen Röhrenknochen zwischen 2006 und 2018 erhalten haben, wurden in die retrospektive Studie inkludiert. Von MEDOCS wurden verschiedene Daten zu den Patient*innen gesammelt, wie Alter, Geschlecht, Symptome, Befunde (klinisch, histologisch, radiologisch), Diagnosen, Röntgenbilder, Magnetresonanztomographie (MRT) und Computertomographie, Szintigraphie, Kontrolluntersuchungen und etwaige Rezidive. 103 Röntgenbilder und 25 MRT-Bilder wurden von vier Reviewer*innen bezüglich vorher festgelegter Merkmale, wie Cortex-Arrosion und peritumorales Ödem, evaluiert, ohne die Histologie oder Klinik zu kennen. Anschließend wurde von ihnen eine Diagnose abgegeben, getrennt nach Röntgen und MRT. Darüber hinaus gab ein fünfter Reviewer eine Verdachtsdiagnose der Läsionen basierend auf Röntgenbildern ab. Es fand eine Nachbesprechung statt, bei welcher die definitiven Diagnosen nach aktuellen Richtlinien noch einmal geprüft und gegebenenfalls abgeändert wurden.

Ergebnisse

Als signifikantes, zwischen Enchondromen und atypischen chondrogenen Tumoren unterscheidendes radiologisches Merkmal, wurde „Cortex-Arrosion“ identifiziert. Ebenso zeigte sich bei der Größe ein signifikanter Unterschied zwischen den beiden Tumorarten. Die Intraklassenkorrelation, welche die Übereinstimmung der vier Reviewer*innen aufzeigt, war für die meisten radiologischen Merkmale eher gering, was auf eine hohe Interobserver-Variabilität schließen lässt. Nur die Merkmale „Lokalisation“ (Röntgen und MRT) sowie „Cortex-Arrosion“ (Röntgen) zeigten eine gute bis exzellente

Übereinstimmung. Die korrekte Diagnose wurde von den Reviewer*innen anhand von Röntgen und MRT im Schnitt in 65.9% (5 Reviewer*innen) und 66.7% (4 Reviewer*innen) abgegeben, entsprechend einer Sensitivität von 83.1% bzw. 89.3% und einer Spezifität von 29.7% bzw. 28.0%.

Schlussfolgerungen

Die rein radiologische Unterscheidung zwischen Enchondromen und atypischen chondrogenen Tumoren bleibt weiterhin schwierig. Ein großes Problem stellt die hohe Interobserver-Variabilität dar, woraus sich schließen lässt, dass die Radiologie alleine zur Diagnosefindung von Enchondromen bzw. atypischen chondrogenen Tumoren möglicherweise nicht geeignet ist. Daher sollte die Diagnosefindung von kartilaginären Tumoren immer unter Einbezug von Klinik, Radiologie und Histopathologie erfolgen. Dies zeigt erneut die große Bedeutung eines multidisziplinären Vorgehens bei der Diagnostik von muskuloskelettalen Tumoren.

Abstract English

Objective

Differentiating between enchondroma (EC) and atypical cartilaginous tumour (ACT) on a radiologic basis can be very challenging. It is often not clear if the tumour is benign or malignant, but if known, surgery or biopsy may not be required. Our aim is to identify specific features which indicate malignancy both radiologically and clinically to get an overall impression.

Materials and methods

All patients with histologically verified diagnosis "enchondroma" or "atypical cartilaginous tumour" – former chondrosarcoma (CS) G1 – of the long bones between 2006 and 2018 at one institution were retrospectively included. Data was collected from MEDOCS, included personal data, symptoms, diagnostic findings, x-ray, magnetic resonance imaging (MRI) and computed tomography (CT) images, scintigraphy, histological results, follow-up and relapses. 103 x-rays and 25 MRIs were subsequently blindly re-evaluated by two radiologists and two orthopaedic surgeons from the *Medical University of Graz*, regarding radiological features like cortex-arrosion and peritumoral oedema. Afterwards a diagnosis based on these features was made, separately for x-ray and MRI. A fifth reviewer diagnosed lesions on x-rays only. Afterwards, a debriefing was performed to check the final diagnosis. Some diagnoses were subsequently changed adhering to current guidelines.

Results

Cortex-arrosion was the only significant radiological feature to differentiate between EC and ACT/CS G1. There was also a significant difference regarding size between the two tumour entities. The intraclass correlation coefficient was rather poor for most of the features, indicating a high interobserver variability. Only the features "tumour location" (x-ray and MRI) and "cortex-arrosion" (x-ray) showed a good or excellent agreement. The diagnosis made by the reviewers based on x-ray and MRI correlated with the histopathological one in 65.9% (5 reviewers) and 66.7% (4 reviewers). Sensitivity on x-ray and on MRI was 83.1% and 89.3%, respectively, and the specificity 29.7% (x-ray) and 28.0% (MRI).

Conclusion

Distinguishing between ECs and ACTs/CSs G1 still remains challenging in case only imaging is used. One of the major problems is the high interobserver variability, wherefore radiology only may not lead to the correct diagnosis of EC and ACT/CS G1. Consequently, the importance of a multidisciplinary approach involving clinical presentation, radiology and histology is highlighted.

1 Introduction

1.1 Bone tumours

"Primary" bone tumours are neoplasms that develop from the skeleton-forming mesenchyme (1). They can be divided into osteo-, chondro- and fibrogenic lesions, fibrohistiocytic lesions and round cell lesions. They account for 0.5 – 1% of malignant tumours, whereas skeletal metastases are 2.5 times more common, and therefore the most common malignant bone lesions (1, 2). "Secondary" bone tumours can further be divided into metastatic ones or malignant transformation of benign lesions (2). Malignant ones – like osteosarcoma, multiple myeloma, chondrosarcoma (CS) and Ewing sarcoma – are less common than benign ones – like enchondroma (EC) and osteochondroma – and 50% of primary malignant bone tumours occur in children and adolescents (1, 2). Over 70 entities exist according to the World Health Organization (WHO) (3). For diagnosis, both histology as well as radiology should be used. When it comes to differentiating between various tumours, the age and exact location within the bone can be of help, as well as the knowledge whether the lesion is solitary or multiple (1, 2). Different age groups are more commonly affected by certain bone tumours. Outside the usual age group, a specific tumour may not provide the characteristic features, both regarding location and radiology (2).

1.1.1 Cartilaginous tumours

The most commonly benign cartilaginous tumours are osteochondromas (40% of benign bone tumours) and ECs, while chondroblastomas and chondromyxoid fibromas are less frequent (1). CS (15% of all malignant bone tumours) is the second most common malignant bone tumour, after osteosarcoma (1).

Radiology

The lesion is radiolucent with areas of calcification, with variable appearance like comma-shaped, annular or punctate (2). There may also be a sign of so-called scalloping of the cortex, reflecting the lobular growth of the lesion. Small arrosions are due to slow growth, which is common in EC, deep scalloping on the other hand is characteristic for ACT/CS G1 and higher graded CS, with the latter feature also being associated with cortical

thickening (2, 4-6). Furthermore, periosteal reaction and a soft-tissue mass is possible, connected to CS (2).

Histology

The matrix of cartilaginous tumours contains less collagen, compared to osteoblastic, i.e. bone-forming tumours. The cells are located in so-called lacunae. Cartilaginous tumours are frequently positive for S-100 protein. Benign lesions like EC are sparsely cellular, comprising cells with small nuclei, have scarce or no vascularization and contain areas of calcification, whereas CSs are more pleomorphic with larger nuclei and mitoses. (2).

Molecular pathology

There is evidence that mutation of isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*) plays a role in the development of intraosseous cartilaginous tumours like EC and CS (1).

Beside ECs, other benign entities exist: juxtacortical chondroma (beneath or in the periosteum), soft-tissue chondroma (soft-tissue mass with chondroid portion, including calcification), synovial chondromatosis (occurring in the synovium, bursae and tendon sheaths), osteochondroma (osseous formation with a cartilage cap), multiple hereditary osteochondromata, chondroblastoma (usually in long bone epiphysis of younger ones) and chondromyxoid fibroma (stellate or spindle-shaped cells, fibromyxoid or chondroid matrix) (2).

1.2 Imaging of bone tumours

Bone tumours are usually first suspected on conventional x-rays. Radiology provides the most useful data when it comes to location und morphology of the lesions, whereas other techniques – like scintigraphy, ultrasound or arteriography – can be useful in some cases to provide extra information, like vascular supply (2).

CT and MRI are important for staging of the tumour. Whilst CT shows the exact location (including expansion in the cortex, trabecular bone and marrow cavity), size and configuration of the lesion as well as its relation to the cortex, MRI is more useful in assessing the intra- and extramedullary extent and relation to nearby structures (2). In case of malignancy, the standard imaging tool used for staging is CT, allowing for detection of any metastatic foci in lungs, abdomen, or pelvic region. Further, less frequently used techniques for staging the tumour are single photon emission computed tomography

(SPECT) – where white blood cells are labelled by technetium-99m (99mTc), gallium-67 (67Ga) citrate and indium-111 (111In), scintigraphy, and positron emission tomography (PET), either alone, or combined with CT or MRI. PET shows the metabolism of the lesion in form of accumulation of 2-fluoro-2-deoxy-D-glucose ($F^{18}FDG$), with a higher rate correlating with an higher glucose uptake, enhanced metabolism, and thus higher degree of malignancy (2, 7). However, it has to be noted that for strongly sclerotic lesions, PET is not useful (7).

1.2.1 X-ray

X-ray is the most important method to primarily identify bone tumours. Furthermore, their growth rate and dignity can already be estimated based on plain x-rays (7). Topography and borders of the lesion, the sort of bone destruction, periosteal reaction, soft-tissue involvement (mirrored by a soft-tissue shadow visible on the x-ray) and the lesions' type of matrix are important features that can be observed on conventional radiographs (2). Bone tumours can be divided into 3 grades according to Lodwick, including bone destruction, periosteal reaction, penetration of cortex, expanded shell, sclerotic rim and mineralization. Lodwick grade IA to IB lesions are slowly growing tumours, and mainly considered benign. Lodwick grade IC lesions can be either benign or malignant, whereas grade II to III tumours show an intermediate to fast growth, indicative of a likely malignant behaviour (7-10).

Location

Many tumours show a typical localization concerning a specific bone or site. For example, ECs are often found in the short tubular bones of hands and feet and are located centrally (2). For more examples, see *Figure 1 Location, adapted from Jundt and Breitenseher et al. (1, 7)*.

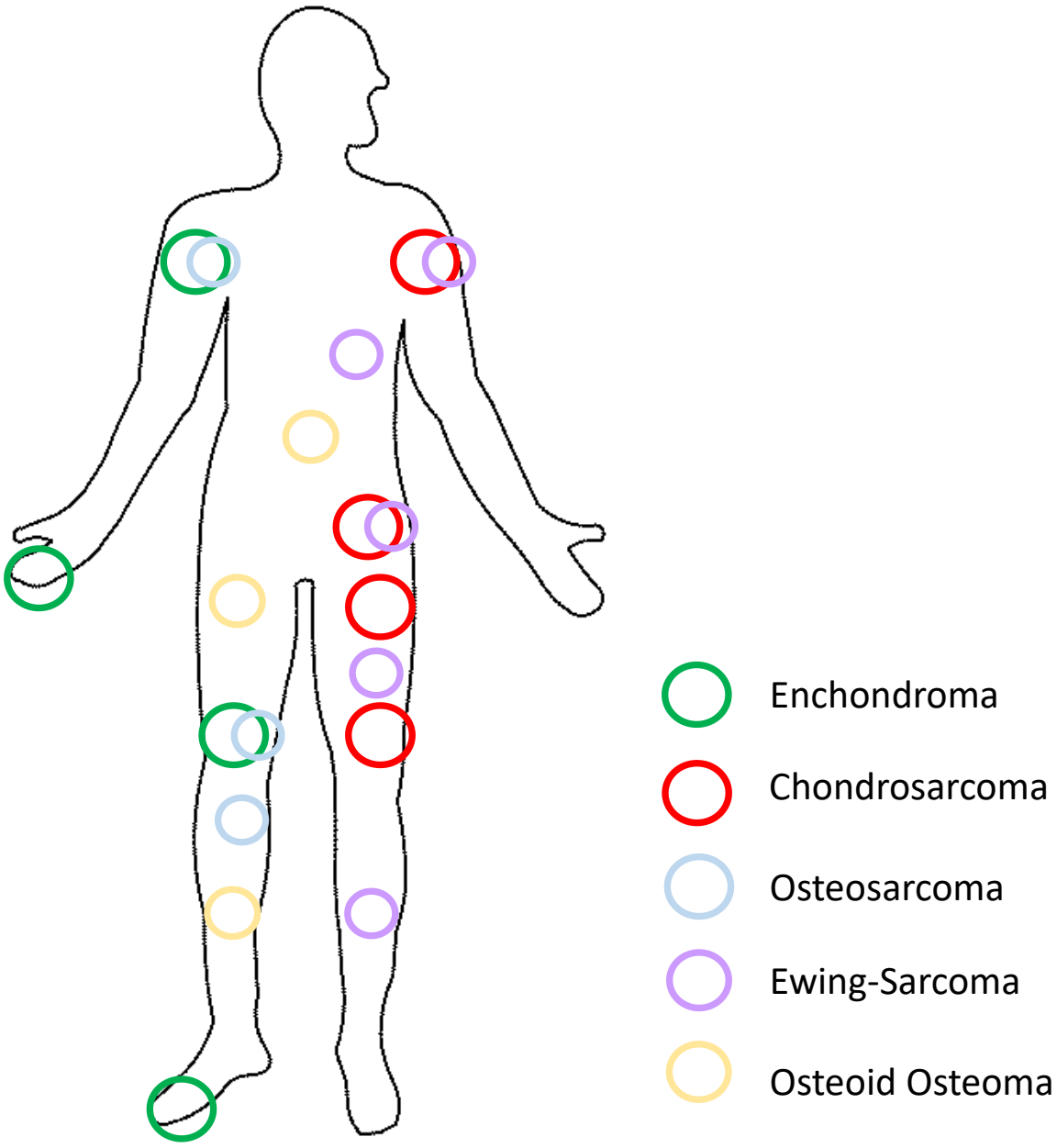


Figure 1 Location, adapted from Jundt and Breitenseher et al. (1, 7)

Zone of transition

The border of the lesion refers to the zone where the peripheral part of the tumour and the healthy bone meet. It can either be well-defined – with a narrow zone of transition – or ill-defined, with a wide zone of transition (2). The former can be divided into two types: sharp-sclerotic and sharp-lytic with no sclerosis. The well-defined ones reflect a slower growth and therefore a more likely benign lesion whereas ill-defined borders are associated with a faster growth, often affect the whole circumference of the bone, and are more likely to be malignant (2).

Well-defined: sharp demarcation (2)

Sclerotic: the osteolysis is well-defined with a sclerotic border (2, 7).

Lytic: well-defined but no sclerosis (2)

Ill-defined: there is a wide zone of transition and no clear border to the adjacent bone (7).

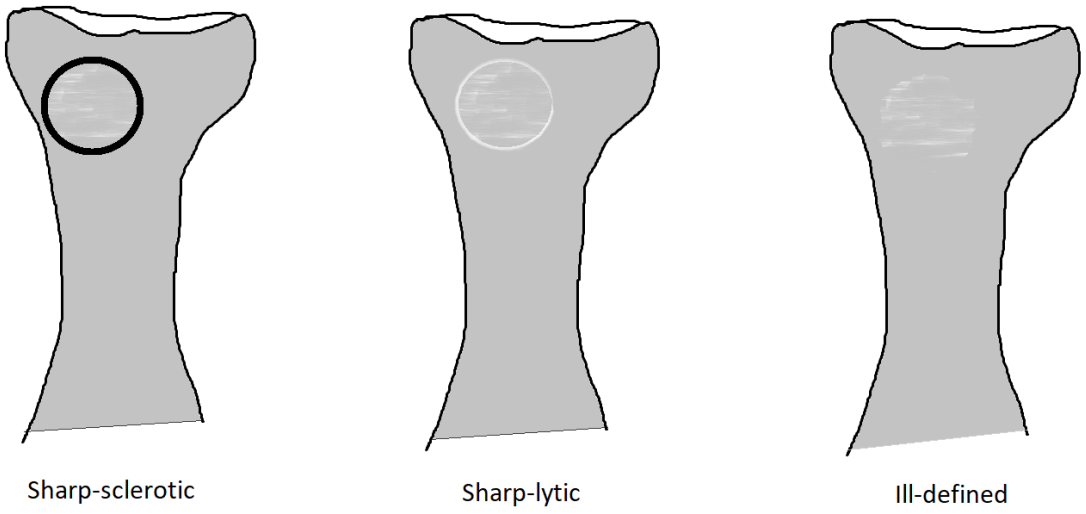


Figure 2 Zone of Transition, adapted from Greenspan et al. (2)

Bone destruction

The bone destruction occurs due to the tumour cells themselves or the growing pressure of the lesion and hyperaemia caused by the tumour (2). On radiographs, the destruction of the cortex appears earlier, because of its higher homogeneity and density compared to trabecular bone. In the trabecular bone, there has to be a loss of about 70% of the healthy bone to be visible as "disease" in the radiograph, even though it is destroyed faster than the cortex (2). The type of osteolysis can be divided into 3 groups: geographic, moth-eaten and

permeative (2, 7). Benign bone lesions like EC usually cause a geographic destruction of the bone, while malignant ones show a permeative or moth-eaten pattern. However, it has to be taken into account, that also benign lesions may show aggressive patterns, and the other way round (2).

Geographic (Lodwick IA-IC): the osteolysis is circumscribed, the zone of transition is regular or lobulated and sharply demarcated (2, 7).

Moth-eaten (Lodwick II-III): there are multiple osteolytic lesions in different sizes, often clustered (2). They can appear in cancellous bone as well as in compact bone (7).

Permeative (Lodwick III): multiple small osteolytic lesions which are sized similarly, oval-shaped or streaky and ill-defined (2, 7). They appear almost exclusively in the compact bone (7).

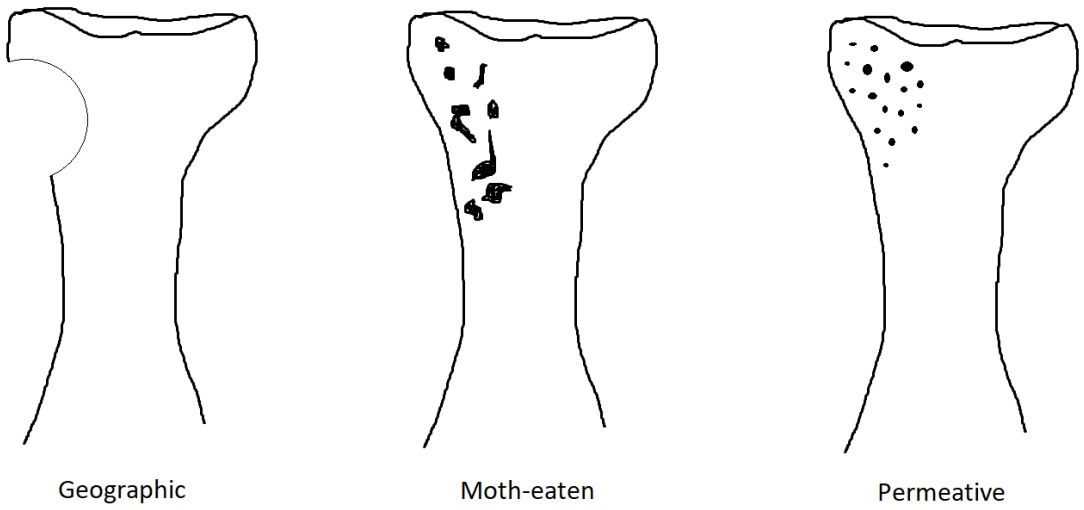


Figure 3 Bone Destruction, adapted from Breitenseher et al. and Greenspan et al. (2, 7)

Periosteal reaction

Periosteal reaction can appear as any alteration of the outer bone contour, like broadening or irregularities (2). A periosteal reaction can occur in benign lesions like inflammation as well as in malignant lesions of the bone. In the latter case, it is often characteristic (7). Two types of reactions can be differentiated based on their coherence: Continuous (uninterrupted) ones, which are well circumscribed and associated with benign alterations, and discontinuous (interrupted) ones. Single lamellar reaction, undulating shape, solid buttress and solid elliptical or smooth layers are examples for continuous reactions, whilst sunburst (radial spiculae) and onion-skin pattern (parallel lamelliform) as well as the

Codman triangle are classified as discontinuous periosteal reactions (2, 7). The latter periosteal reaction is formed by the remnants of lamellar bones which is destroyed by the tumour invading through the cortex (2).

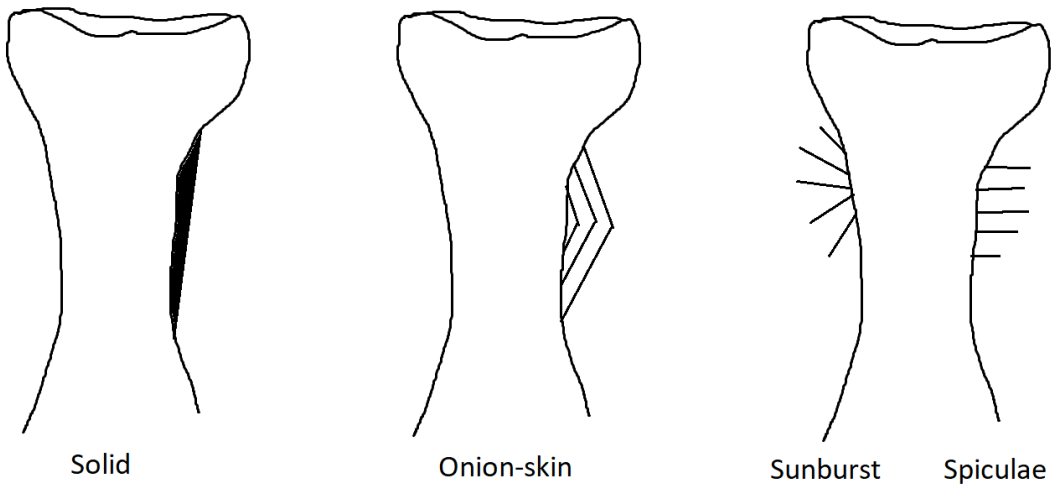


Figure 4 Periosteal Reaction, examples, adapted from Breitenseher et al. (7)

Soft-tissue mass

The soft-tissue mass associated with bone tumours usually consists of tumour mass outside the bone contours (7). It is associated with aggressive and malignant processes. In these cases, the mass is usually well demarcated and the tissue planes are intact (2). Also, some benign lesions may create a soft-tissue mass, as well as some nonneoplastic processes like osteomyelitis. In these, the mass may not be sharply demarcated and the fatty tissue may be obliterated (2). It is also not always clear if the soft-tissue mass is part of a bone tumour or if it is the other way round and the soft-tissue mass is constituting the primary tumour that has secondarily invaded the bone. In the latter case, the bone lesion is often smaller than the soft-tissue mass and there is no periosteal reaction due to destruction of the periosteum by the tumour (2).

Tumour matrix – Calcification

Matrix is the material between the cells. It is produced by mesenchymal cells and includes different elements (chondroid, osteoid, bone, collagen and myxoid) (2). The tumour matrix is often osteolytic (7). In chondrogenic lesions like EC and ACT/CS G1, there are typically calcifications within the matrix, which can be stippled or punctate, flocculent or irregularly shaped, or have a “rings and arcs” (annular or comma-shaped) or “popcorn like” appearance. The calcification may occur due to endochondral ossification, as typically seen

in benign or well differentiated malignant tumours. In tumours with an osteogenic origin, the calcifications are more solid, dense and cloudy (2, 7). Radiolucent lesions are typically of fibrous or chondrogenic matrix (2).

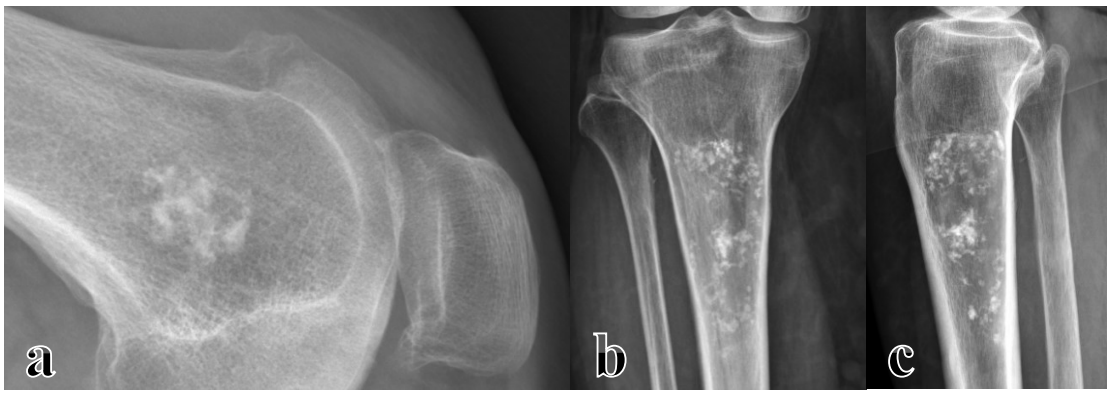


Figure 5 Tumour Matrix
a) Popcorn like calcification, b) + c) stippled calcification

Potential features of bone tumours in general (2):

- Zone of transition: sharp sclerotic, sharp lytic, ill-defined
- Bone destruction: geographic, moth-eaten, permeative
- Periosteal reaction: continuous (single lamellar, undulating shape, solid buttress, solid elliptical/smooth layer), discontinuous (sunburst, onionskin, Codman triangle)
- Soft-tissue mass: yes, no
- Tumour matrix: osseous, cartilaginous
- Calcification: stippled or punctate, flocculent or irregularly, annular or comma-shaped rings and arcs (curvilinear)

In summary, lesions with ill-defined borders, moth-eaten or permeative destruction, a discontinuous periosteal reaction and soft-tissue mass are highly indicative of malignancy, whilst well-defined borders, geographic destruction and a continuous periosteal reaction is more likely pointing towards a benign lesion (2).

Endosteal scalloping

Deep endosteal scalloping is a sign frequently found in ACTs/CS G1 as well as higher-graded CSs, reflecting the lobular – and locally aggressive – growth of these lesions (4-6). Benign chondrogenic lesions tend to no or only superficial (shallow) scalloping (1, 2).

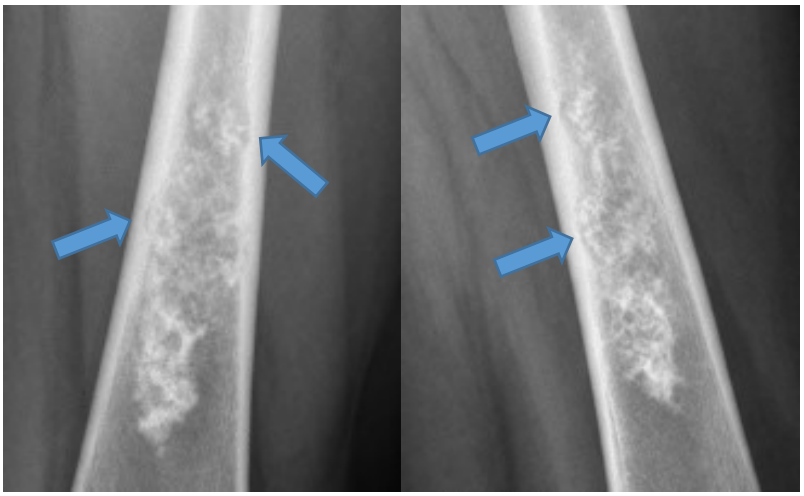


Figure 6 Endosteal Scalloping in the distal diaphysis of femur.

1.2.2 Magnetic resonance imaging

MRI is important for staging the tumour. This includes the extent of the tumour within the bone und bone marrow, as well as infiltration of joints, blood vessels, nerves and soft-tissue involvement in general (7). Especially for evaluation of the degree of bone marrow involvement, MRI is considered the best modality (6). If radiography shows cortical destruction and a soft-tissue mass, MRI is the method of choice (2). There are different sequences suitable for identifying the tumour, with spin echo (SE) sequence being the preferred one in bone tumour radiology (2). On T1 weighted SE sequences, bone tumours show an intermediate or low signal intensity and the contrast between tumour and bone, bone marrow and fat is increased. On T2 weighted images, the tumour displays high signal intensity, there is a better contrast between tumour and muscle. Furthermore, peritumoral oedema is visible (2). Also intravenous administration of gadolinium diethylenetriamine-penta-acetic acid (Gd-DTPA) to receive a contrast-enhanced MRI can be useful. More vascularized areas show contrast enhancement whilst necrotic ones show none on T1 weighted images. Also, chemical shift or fat suppressed sequences may be used, improving the interface between tumour and adjacent structures like the reactive zone, oedema and muscle (2). There are some limitations in using MRI to elucidate whether a lesion is benign or malignant, as both dignities may imitate the other one on MRI or show both benign and malignant features at the same time. Furthermore, signal intensity may vary in tumours which are histologically identical and – the other way round – may be similar in histologically different types of tumour, wherefore a certain diagnosis based on MRI scans only without histopathological evaluation is still not recommended (2).

1.2.3 Computed tomography

CT can be used for focal staging of the tumour, in addition to MRI or as an alternative (7). The representation of soft-tissue is inferior to MRI, but it is a good technique to assess periosteal reaction (2, 7). Its strengths lies not necessarily in gaining a specific diagnosis but in providing additional information like extend and invasion of cortex. Moreover, CT allows good visualization of surface-located lesions like osteoid osteoma, juxtacortical CS and periosteal chondroma (2). CT is also the better technique – compared to MRI – when it comes to detecting calcifications within the tumour (2). An important indication for CT, for example, is diagnosing osteoid osteoma because of the characteristic appearance of the nidus (7).

1.2.4 Bone scintigraphy

Bone scintigraphy uses radionuclides to show the mineral turnover within the bone which is related to its processes of change and repair. There are different agents in use, like ^{99m}TC-methylene diphosphonate, ^{67}Ga and Thallium-201 (^{201}Tl) chloride. (2). It is used to identify small lesions, which may not be visible on conventional radiographs, metastases and multifocal lesions like enchondromatosis, multiple myeloma and Ewing sarcoma (2, 7). This technique is also superior to plain radiography, when it comes to the lesion's spread beyond the point of origin and intramedullary involvement, but not for cartilaginous lesions (2, 7). However, it has to be considered that also in hyperaemic and oedematous areas a higher uptake of the isotope is present (2). Bone scintigraphy has its limitations, particularly regarding the identification of a benign vs. malignant bone lesion, as both dignities usually show a greater deposition of isotopes and activity of osteoblasts. The degree of the radionuclide uptake correlates with the aggressiveness of the tumour, but not necessarily with the histological grade of the tumour. Bone scintigraphy also lacks specificity concerning the type of tumour, as any process leading to new bone formation (reactive or tumour associated), bone turnover or an increased blood flow within the tumour, leads to an increased uptake (2). Notably, Tc-scintigraphy is only useful for osteoblastic tumours. On the other hand, in osteolytic bone lesions, Tc-scintigraphy will not be positive (7).

1.2.5 Positron emission tomography

In PET, radioactive substances like $F^{18}FDG$ are used to create images based on detection of emitted gamma rays. It can show organ perfusion, metabolic activity and biochemical changes within the body (2). Compared to CT and MRI, PET has a greater sensitivity in detecting primary, secondary and recurring tumours, but it is limited in showing involvement of the bone marrow, due to the physiological accumulation of radioactive substances within. Also, specificity is low, aggressive but benign lesions as well as inflammatory ones can show radioactive substance uptake (2). There is also the option of combining PET and CT (called PET-CT), allowing for combination of both types of information – biochemical and metabolic activity and anatomical details – in one image. PET-CT is used for tumour staging, detecting metastases and recurrence of tumour as well as evaluating therapeutic response rates (2). It is also possible to combine PET and MRI (PET-MRI), it is similar to PET-CT but with the strengths of MRI, which also includes that there is no ionizing radiation, compared to CT (2).

1.3 Pathology of bone tumours

According to the World Health Organisation's (WHO) Classification of Soft Tissue and Bone Tumours, about 70 different bone tumour entities exist (2, 3).

1.3.1 Immunohistochemical staining

The gold standard in histopathology of bone tumours is staining with haematoxylin and eosin (H&E) after decalcification of the specimen. Sometimes, histochemical and immunohistochemical stains are needed to identify the tumour's origin. Different antibodies against specific structures – like vimentin (some epithelial cells, mesenchymal cells), cytokeratins (most epithelial cells), desmin (muscles), S100 protein, Melan A (melanocytic differentiation), antigens on the cell surface (assigned to a cluster of differentiation number [CD]) – may be used to further differentiate between histological subtypes (2). Also, other special stains may be needed for a more specific information about the tumour entity, like van Gieson stain (presence of collagen), Giemsa stain (small round cell tumours), Gomori stain (reticulin fibres), Novotny stain, periodic acid-Schiff (PAS) stain (intracytoplasmic glycogen), mucin stain (metastatic adenocarcinoma) and trichrome stain (extracellular substances like collagen) (2). Ki-67 staining is used to show cellular proliferation, as Ki-67 is a protein only synthetized during replication and

therefore being indicative for a lesion's growth, even if only a small number of cells are positive (11).

1.3.2 Genetics

Gaining information about chromosomal changes may be useful for diagnosing the tumour or choosing a targeted therapy. There are different techniques for detecting such changes, like flow cytometry (FCM) as well as molecular and digital cytogenetics (2).

FCM

FCM is used to obtain information about the DNA content and the proliferation rate, using fluorescence. Cells with differing amount of DNA (more or less), compared to normal control cells, are called "DNA aneuploid". Cells are also split depending on their phases of the cell cycle. The proliferating cell fraction is represented by the number of cells in the phase of DNA synthesis, the S phase. In cartilaginous tumours both increased proliferation cell fraction as well as DNA aneuploidy, has been described (2).

Cytogenetics

Detecting abnormalities concerning the chromosomes, like deletion, translocation or numerical change, is useful for diagnosis of bone tumours, in particular Ewing sarcoma. (2). Previously, the chromosomes were stained and analysed microscopically, after stopping the cells during the metaphase of the mitosis (2). Nowadays, the molecular cytogenetic method fluorescent in situ hybridization (FISH) is used, allowing for analysis of chromosomal aberrations, translocations and fusions, during the interphases (2).

1.4 Enchondroma

ECs grow within the medullary cavity and have a hyaline cartilage origin (1, 2). They are the most common benign tumour of the hand-forming bones, accounting for 10 – 25% of all benign bone tumours (2, 7). Taking all bone tumours together – benign and malignant - they account for about 3% (12). An incidence peak is seen before the 4th decade, most frequently in the 2nd – 4th decade (2, 7). There is no gender preference (2). The main localizations of ECs are the small tubular bones and flat bones of the hands and feet, accounting for 60% of all EC sites, as well as the femur (proximal and distal) and humerus (proximal) (1, 2, 7). They are mainly located in the metaphysis or diaphysis and rarely in the epiphysis (representing only 2 to 5%) (2, 7, 13). Usually, the tumour is smaller than 3 cm and it is uncommon that the lesion is greater than 5 cm (2). However, it has to be taken into account, that especially in long bones, the lesion may be greater and nevertheless still benign (6, 14).

ECs are often found incidentally on imaging performed due to other reasons (11). For example, on MRI performed for other pathologies of the knee, ECs are present in 2.9% of the cases (most commonly found in the femur, followed by the tibia and less frequently in the fibula) (15).

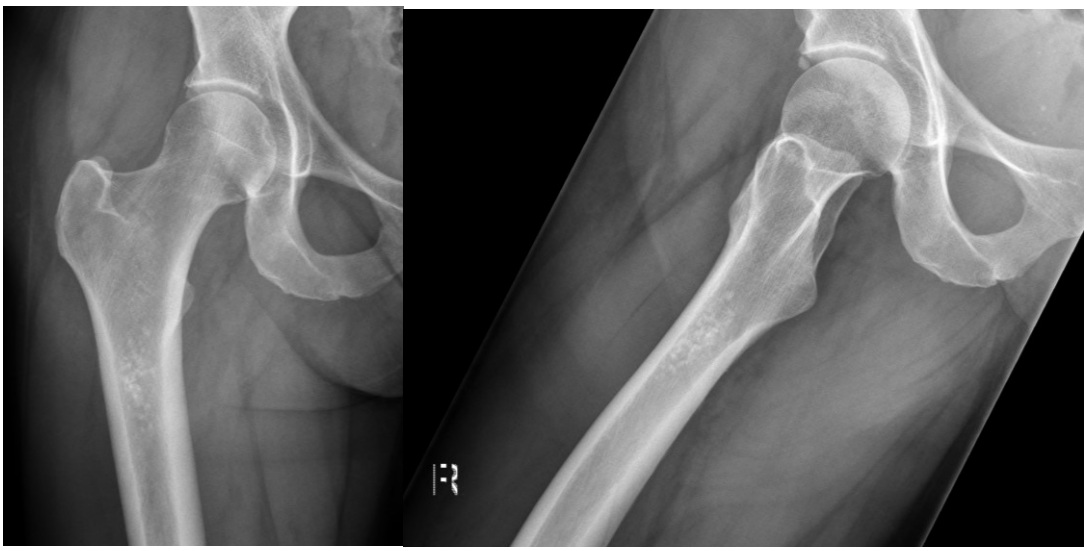


Figure 7 Enchondroma of the proximal femur

Chondrogenic lesion with a maximum diameter of 5.5 cm at right subtrochanteric region in 44-year old female patient incidentally diagnosed during examination for sciatica. Fine, irregular calcifications centered within the medullary canal. No cortical arrosion, scalloping or periosteal reaction present. Histological diagnosis: enchondroma. Patient underwent curettage. No recurrence has developed after 4.1 years of follow-up.

1.4.1 Symptoms

Most of the time ECs are not associated with pain and grow – if even – very slowly (1). Symptoms involve swelling, optionally pain and pathologic fractures in small bones. In case long bones are affected, the lesion is often asymptomatic and found accidentally on plain radiographs performed for other reasons (2).

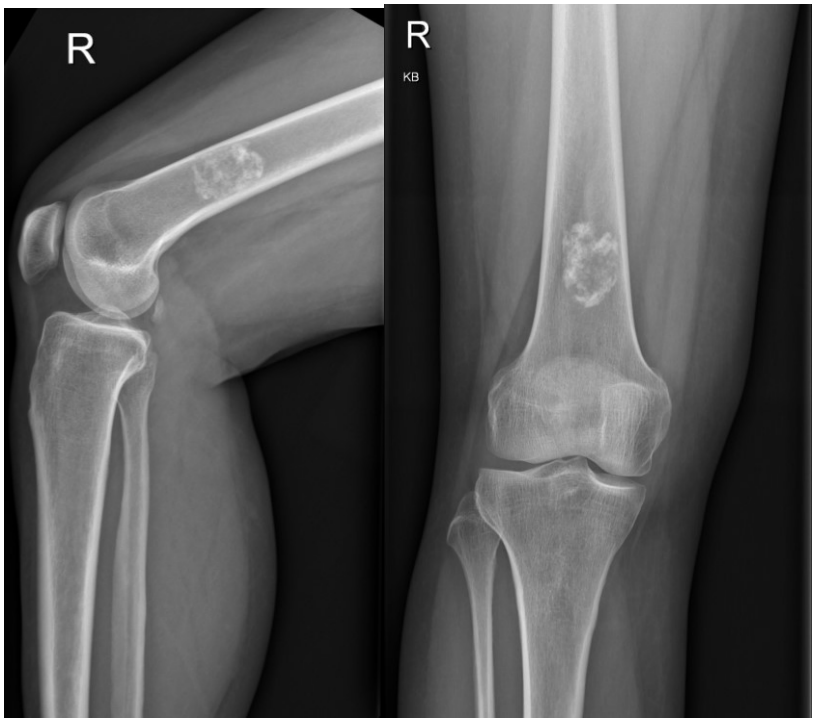


Figure 8 Enchondroma of the distal femur
Chondrogenic lesion, with a maximum diameter of 4.0 cm, at distal right femur in 50-year-old female patient diagnosed following trauma to the right lower limb. Mixed stippled and popcorn-like calcification within the medullary canal without scalloping, cortical thickening or periosteal reaction. Histological diagnosis: enchondroma. Treatment with curettage. No recurrence at 1.2 years of follow-up.

1.4.2 Imaging

An osteolytic appearance with calcifications is typical – often popcorn-like, rings-and-arc-like, punctuate or flocculent (1, 2, 7). The calcification of the radiolucent lesion increases as patients get older (11). Type of bone destruction is described as geographic (16). The border of the lesion is usually well defined, with a smooth contour (2, 14). In case of epiphyseal location, a thin sclerotic rim may be present, with the reason for this feature being largely unknown (17). Regarding cortex arrosion, there is no clear consensus. According to one source, there is either no cortex arrosion or slightly endosteal scalloping (1). Others state that a thinned-out cortex is often present, as well as shallow endosteal

scalloping (2, 7). Usually, periosteal reaction is not present in ECs, but it may occur due to pathologic fracture with delayed presentation. In small bones, a central or eccentric location or even a complete replacement of the medullary cavity by cartilaginous tissue is possible (2). In comparison to CS, there is usually no soft-tissue mass, periosteal reaction, cortical destruction or remodelling or periosteal reaction (2, 6).

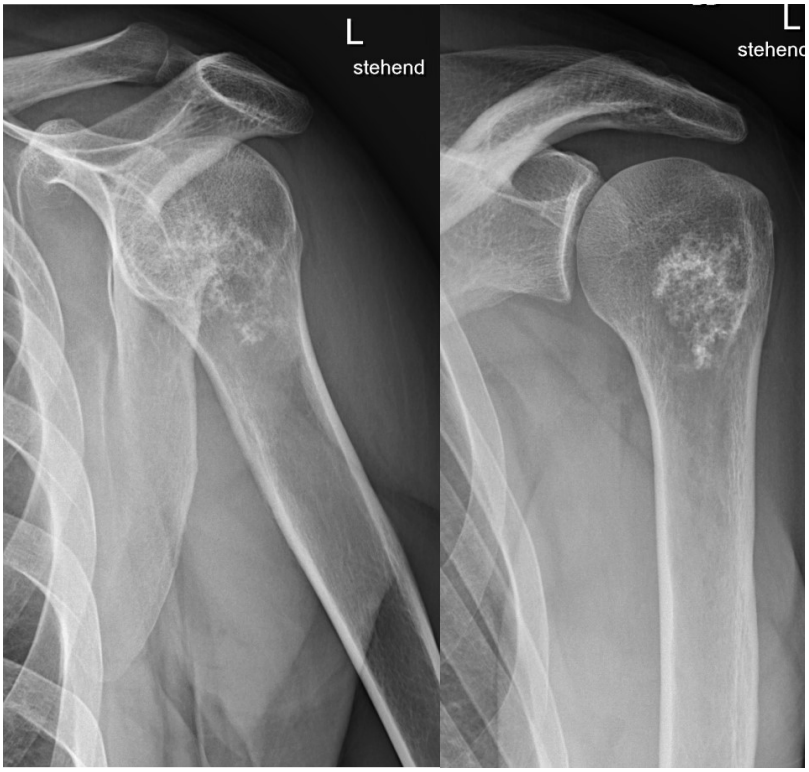


Figure 9 Enchondroma of the proximal humerus

Chondrogenic lesion in left proximal humerus of 42-year-old male patient, with a maximum diameter of 3.2 cm. Lesion was accidentally diagnosed during examination for shoulder pain eventually verified as subacromial bursitis. Popcorn-like, well-defined calcification within the medullary canal visible. Superficial scalloping of the posterior cortex. No cortical thickening or periosteal reaction. Histological diagnosis: enchondroma. The patient underwent bioptic verification of the lesion. As he was free of complaints, he refused further therapy with curettage.

MRI

On T1-weighted sequences, the lesion exhibits a low-to-intermediate signal. On T2 weighted ones, the tumour displays a high signal intensity, whereas the calcified matrix shows low signal intensity. Gadolinium-enhancement can be present (2). T1-weighted small high signal foci within the lesion are frequently found (6). Usually, there is no abnormal peritumoral marrow signal or soft-tissue oedema seen in ECs on short tau inversion recovery (STIR) sequences (18).

CT

Calcification and scalloping is better visible in comparison to plain radiography (2, 19).

Bone scintigraphy

There is a mild uptake of radioactive agent. Higher uptake may be seen in lesions with pathologic fracture or when malignant transformation has occurred (2). The uptake within the lesion, compared to the anterior iliac crest (AIC), is equal or less (6). According to Ferrer-Santacreu et al., only an uptake lower than that of the AIC is indicative of EC, whilst equal and higher uptake makes the diagnosis of ACT/CS G1 more likely (20).

1.4.3 Macroscopy

The tissue of ECs is lobulated and white, whilst focally calcification is shown as yellow white material (1, 17). In long bones, there is often a multinodular architecture of the tumour, separated by the marrow, whereas in small tubular bones, a confluent growth is visible (2).

1.4.4 Histology

Histologically, there is no destruction of existing bone tissue by the mature chondrogenic tissue present (1). There may be a slight arrosion of the cortex, but never an invasion (2). A well-defined border between the cartilage nodules and the bone and surrounding marrow is seen, with multiple nodules separated by bone marrow (2, 21). Calcification may occur. Also, endochondral ossification is possible, especially in heavily calcified ECs, shown as rim of bone around the cartilage tissue (2, 22). The tumour is not vascularized and there is a lot of hyaline cartilage (22). Usually, there is low-to-moderate cellularity with variable sized chondrocytes and hyperchromatic small and round nuclei. Single binucleated cells may occur (2). A higher amount of cells and binuclear cells as well as cellular atypia may particularly occur in lesions deriving from short tubular bones, but these lesions still remain benign (1, 22). If this appearance is seen in tumours originally located in long tubular bones, it correlates with ACT/CS G1 (1).

Immunohistochemical staining

Weinstein et al. showed in their study that after using Ki-67 staining (a proliferation marker), all cases of ECs located in long bones and flat bones were negative, whilst ECs of the hand tended to be positive (three out of four cases), correlating with the higher cellularity and atypia (aggressive histologic features) of the lesion in short tubular bones, as mentioned earlier (23).

1.4.5 Genetics

There may be structural abnormalities on different chromosomes, e.g. 16q22-q24 and 12q12-q15" (2). *IDH1* and *IDH2* may be detected in solitary ECs, as well as in case of hereditary conditions with occurrence of several ECs (see "1.4.10 Multiple enchondromas") (24).

1.4.6 Complications

Complications of ECs involve transformation to a malignant lesion and pathological fracture. In particular, malignant transformation may be seen in Ollier's disease with multiple ECs (2). According to Altay et al. malignant transformation occurs in about 4.2% of solitary ECs (25).

1.4.7 Therapy

ECs may be treated by watch-and-wait if there are no symptoms present, no growth of the lesion is seen, and there is no risk of fracture. In this case, frequent follow-up appointments should be scheduled at distinct time-points, e.g. one after 3 months, one after 6 months and annually thereafter (26). The therapy of choice in ECs is curettage (1).

1.4.8 Prognosis

In most cases the tumour, if solitary, can be observed or treated using intralesional curettage (2). Local recurrence after curettage of ECs is rarely seen, with a 10-year local recurrence rate of 4 % (2, 27). Especially in long bones recurrence may develop (22).

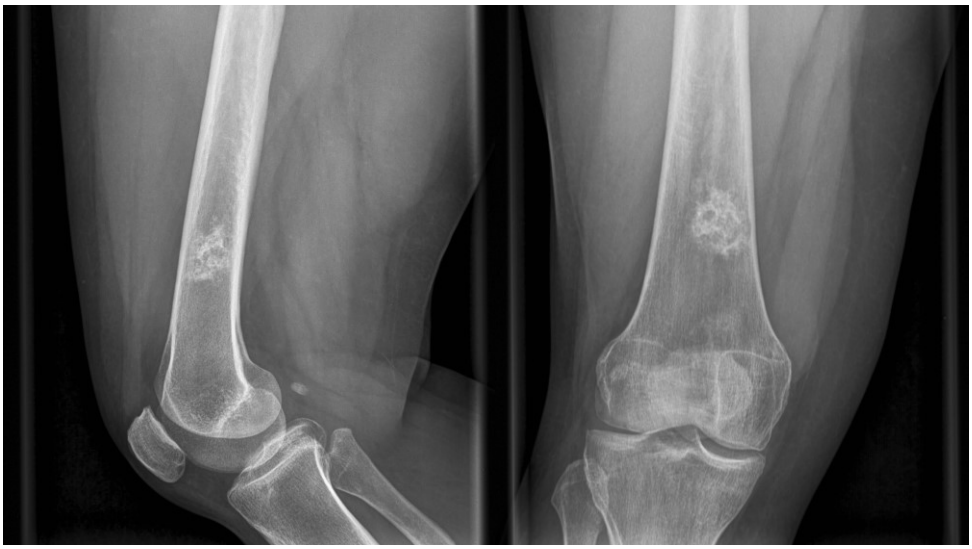


Figure 10 Enchondroma of the distal femur

Calcified lesion at distal right femur in 46-year-old female patient accidentally diagnosed on x-ray performed for unspecific knee pain. A lesion with popcorn-like calcification within the medullary canal is visible, together with superficial scalloping at the medial cortex. No cortical thickening or periosteal reaction is present. Histological diagnosis: enchondroma. The patient underwent curettage of the lesion with no recurrence having developed at 1.1 years of follow-up.

1.4.9 Differential diagnosis

Medullary bone infarct is a differential diagnosis of EC. The border is also well-defined, but there is no endosteal scalloping, compared to EC. Furthermore, a so-called double-line signal on MRI is typical for bone infarct (2). Around the knee joint, an intraosseous ganglion is a possible differential diagnosis (28). Another one is ACT or, rarely, CS G2/3 (2) (see below: "1.7 Comparison enchondroma, atypical cartilaginous tumour and chondrosarcoma").

1.4.10 Multiple enchondromas

There are some genetic conditions associated with multiple ECs like Ollier's disease (multiple ECs) and Maffucci Syndrome (multiple ECs combined with lymphangioma and haemangioma) (2).

Genetics: Presumably, somatic mutations of *IDH1* or *IDH2* play a role in development of ECs. These mutations lead to high levels of the oncometabolite D-2-hydroxyglutarate – which can be found in up to 87% of ECs (solitary or multiple) (29, 30). This leads to a block of osteogenic differentiation, whilst a stimulation of mesenchymal stem cells to a chondrogenic differentiation occurs, due to that block (29).

Enchondromatosis

Enchondromatosis is a heterogeneous disorder of the skeleton, manifesting in the early childhood without a gender preference. It is the umbrella term for different diseases, whereof Ollier's disease and Maffucci syndrome are the most common ones, whilst other subtypes, like genochondromatosis, metachondromatosis, spondyloenchondrodysplasia, cheirospondyloenchondromatosis and dysspondyloenchondromatosis are rarely found (31).

Ollier's disease

Multiple ECs with a monomelic distribution are present. Growth disturbance may occur (2). This is seen as a bone deformation in the frontal or axial plane, as well as bone shortening due to bending and curving. Also, the articular movement may be limited due to deformities adjacent to joints (32). The risk of malignant transformation ranges between 10% and 40% (2, 13, 33). Verdegaal et al. divided patients into three groups, with the first group (group I) containing patients in whom only short tubular bones of hands and feet were affected by enchondromatous lesions, group II with patients in whom only long tubular bones and flat bones were affected and group III including patients in whom all three types of bones (short tubular, long tubular and flat bones) were affected. In group I, malignant transformation occurred at a lower rate (15%) than in group II (45%) and group III (46%). Notably, in their study, more than 50% of CSs were G1 CSs (ACTs), 32% G2, 6% G3 and 10% of unknown grade (33).

Maffucci syndrome

This syndrome is similar to the Ollier's disease but with additional soft-tissue haemangiomas and lymphangiomas, with a risk of an EC undergoing a malignant transformation being > 50% (2, 33).

Both Ollier's disease and Maffucci syndrome – are nonhereditary syndromes and show symptoms like swelling of digits and length discrepancies in (fore)arms and legs (2). It is not predictable how these conditions will behave in an individual patient over time. No specific treatment exists, wherefore a lifetime monitoring in order not to oversee secondary malignant transformation is necessary (2). Histologically, Ollier's disease and Maffucci syndrome are similar to solitary tumours, but there is a chance of higher cellularity, cell atypia and myxoid stroma in comparison to solitary ECs (2).

1.5 Atypical cartilaginous tumour – Chondrosarcoma G1

In recent years, knowledge has evolved that low-grade CSs G1 appear to behave more like ECs than CSs G2, wherefore they have been re-named as "atypical cartilaginous tumours/ACTs". According to the WHO, these ACTs are an intermediate, locally aggressive neoplasm with virtually no metastatic potential (34). Even though ACTs/CSs G1 tend to be larger than ECs, there is a considerable overlap between these two entities, as long as small bones are excluded (14).

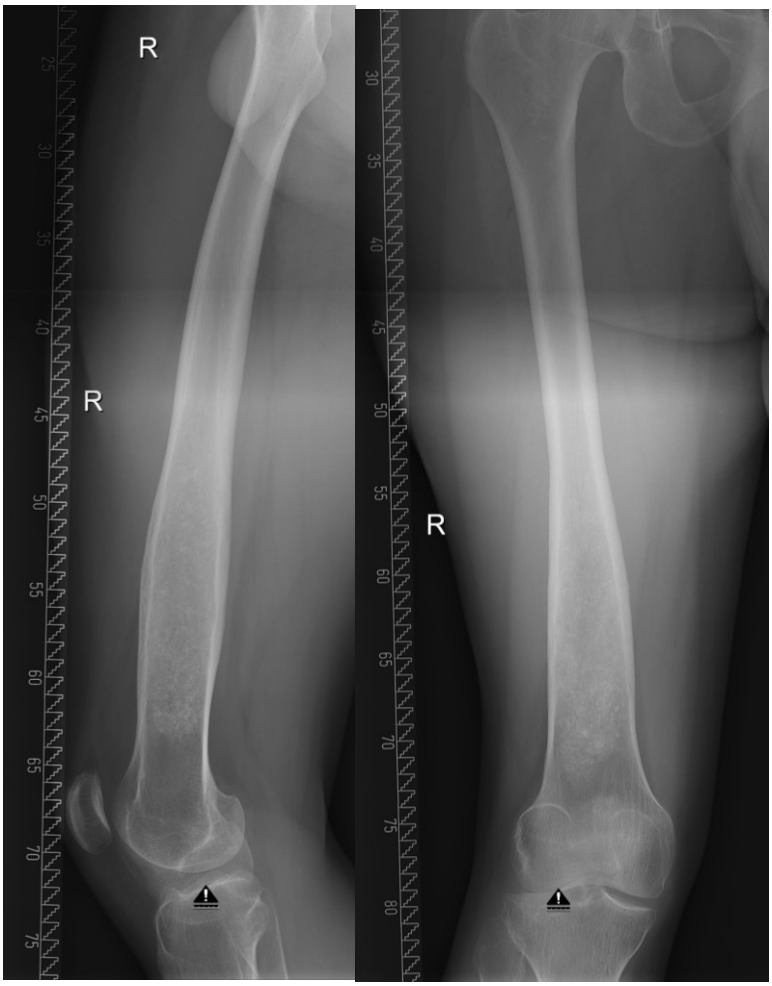


Figure 11 Atypical Cartilaginous Tumour of the distal femur
Large, chondrogenic lesion with a maximum diameter of 20.0 cm (cranio-caudal) in right distal femur of 26-year-old male patient. The lesion was accidentally diagnosed following traumatic dislocation of the patella. Shallow, stippled and partially ring-and-arc-shaped calcification visible. Pronounced enlargement of distal femoral shaft and metaphysical area. Scalloping at dorsal aspect of lesion. Reaction at ventral cortex visible. No soft-tissue shadow indicative of extra osseous tumour mass present. Histological diagnosis: ACT. The patient underwent curettage of the lesion. At 1.3 years of follow-up, no recurrence has developed and the patient is free of complaints.

1.5.1 Symptoms

Usually little to no pain is present in ACTs/CSs G1. However, if pain is present and caused by the lesion itself, this may be an important criterion for distinguishing between ACT/CS G1 and EC, with the latter lesion hardly ever causing pain (1, 4). Yet, according to Geirnaerdt et al., clinical presentation is no distinguishing feature (14).

1.5.2 Imaging

As EC and CS in general, ACTs/CSs G1 show an osteolysis with different patterns of calcification possible (1, 2, 7). In contrary to high grade CSs, low grade ones tend to present with a ring and arc-like calcification pattern and a higher mineralization (5, 17, 19, 35). The zone of transition tends to be ill-defined in more than 25% of the entire circumference, and the contour is lobulated rather than smooth (14). Also deep endosteal scalloping is seen (4). Even though a soft-tissue mass may be present, it remains a rarely seen feature (14, 19, 20).

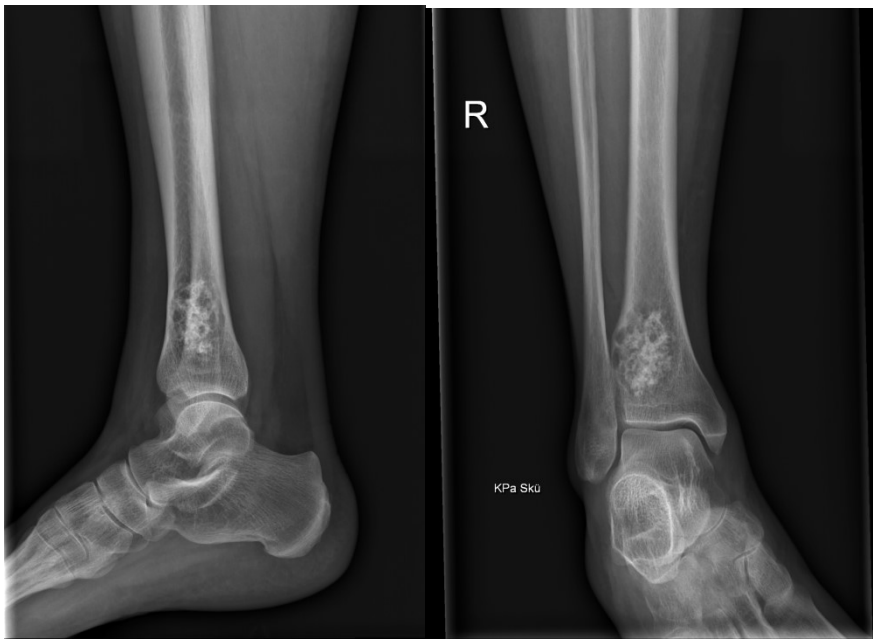


Figure 12 Atypical Cartilaginous Tumour of the distal tibia
Chondrogenic lesion at distal right tibia, with a maximum diameter of 5.0 cm, in 67-year-old female patient diagnosed during scintigraphy for preceding breast cancer. The patient herself was free of complaints. Ring-and-arc shaped calcifications present. Partially sclerotic, partially ill-defined borders. Scalloping at lateral and dorsal aspect. Enlargement of lateral metaphyseal area. No periosteal reaction or soft tissue shadow (indicative of extra osseous soft-tissue component) visible. Histological diagnosis: ACT. The patient underwent curettage. No recurrence has been diagnosed at 5.5 years of follow-up.

MRI

Similar to EC and CS in general, an intermediate signal intensity is exhibited by ACTs/CSs G1 on T1-weighted images, whilst on T2-weighted images a high signal intensity is shown (19). According to Choi et al., a predominantly intermediate signal on T1-weighted MRI and a multilocular appearance on contrast-enhanced T1-weighted MRI are indicative of ATCs/CSs G1. Furthermore, cortical destruction, soft-tissue mass, as well is abnormal signals of soft tissue and surrounding bone marrow are found in some ACTs/CSs G1, but no ECs (36).

Bone scintigraphy

Ferrer-Santacreu et al. reported an uptake equal or higher than the AIC on bone scintigraphy being a feature indicative of ACT/CS G1 (20).

1.5.3 Macroscopy

As in CSs in general, there is no significant difference between EC and ACT/CS G1 on a macroscopic basis, except for the lesion's size (2).

1.5.4 Histology

Whilst it is not difficult to detect malignant features in G2 and G3 CSs, ACTs/G1 CSs tend to show histologic characteristic similar to ECs (17). Compared to higher grade CSs (G2 and G3), upon histopathological examination ACTs/CSs G1 show only slightly increased cellularity, atypia and hyperchromasia of the nucleoli. Binucleated cells may be found to some extend and stromal myxoid change can be present (see also *Table 1 Histological Grading)* (2).

Immunohistochemical staining

On immunohistochemical staining, periostin is a biomarker expressed in ACTs/CSs G1 (37). ACTs/CSs G1 are positive for collagenase-3 with variable percentage of positive cells (ranging from 4.3% - 21.9%) and intensity (38). In the study by Weinstein et al., Ki-67 staining showed four out of six ACTs/CSs G1 being positive in 1 to 10% of their chondrocytes nuclei, even though they assumed the two negative ACTs/CSs to being either over-diagnosed ECs or the sample having been taken from an area of a pre-existing EC, missing the areas of the secondary CS (23).

1.5.5 Therapy

ACT/CS G1 may be treated by curettage and local adjuvants, if there is no aggressive pattern like relevant cortical destruction, thinning or thickening, due to a low recurrence rate of about 3.1%. In case signs of aggressive behaviour are present on imaging, wide resection may be performed. According to Campanacci et al., this therapy is associated with an extremely low recurrence rate (0% in their series), but correlates with a higher complication rate (28.6%) compared to curettage (1.6%) (39). On the other hand, Gunay et al. reported a higher rate of recurrence for both types of surgery, with a recurrence rate of 23.0% in patients undergoing intralesional curettage compared to 17.6% in case wide resection had been performed. However, it has to be taken into account that the number of patients in this study was very small (n=30) (40). De Camargo et al. reported an even higher recurrence rate of 26.3% in patients treated with intralesional curettage, even though their study population was also rather small (n=23) and included patients with lesions in small and flat bones as well as bones of the axial skeleton (41), whereas the other studies previously mentioned analysed patients with only long bones affected (39, 40).

1.5.6 Prognosis

The five-year survival for ACT/CS G1 patients is 90%, and the 10-year survival rate 83% (2, 42). Evans et al. reported on no metastases following diagnosis of ACTs/CSs G1 (42). Also according to Jundt (1), metastases of ACTs/CSs G1 are extremely rare. On the other hand, Andreou et al. reported that there is in fact a risk of up to 6% for ACTs/CSs G1 to metastasise (34). In the study by Fromm et al. likewise 16% of ACT/CS G1 patients had metastases (one already presented at the initial assessment, the other five patients developed metastases during follow-up). The authors concluded that their findings may differ from literature due to a longer follow-up (43). Bauer et al. discovered a local recurrence rate of 9% (27), even though higher rates have been reported (see “1.5.5 Therapy”) (40, 41). In 10% of cases, recurring tumours may have differentiated into higher grade CSs (2). The study by Camargo et al. suggests that this may be the case even more frequently than previously assumed, with 5 out of 6 (83%) ACT/CS G1 patients having a G2 CS as the recurrent tumour (41).

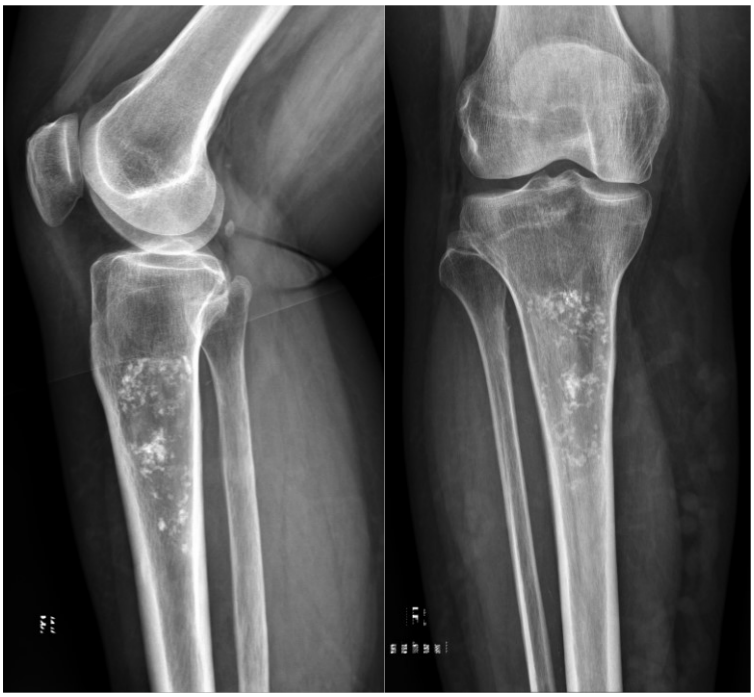


Figure 13 Atypical Cartilaginous Tumour of the proximal tibia

Chondrogenic lesion with a maximum diameter of 8.5 cm at right proximal tibia of 64-year-old female patient. The lesion was diagnosed due to pungent pain reported by the patient that led to further investigation with x-ray. Stippled, partially ring-and-arc shaped calcifications within the medullary canal. Discreet enlargement of the metaphyseal area. Shallow scalloping visible. No periosteal reaction or peritumoral soft-tissue shadow indicative of extraosseous mass present. Histological diagnosis: ACT. She underwent biopsy and curettage of the lesion. At 5.0 years of follow-up, no recurrence has emerged.

1.6 Chondrosarcoma

There are different types of the malignant cartilage-forming lesions, so-called CS (2, 3):

- Chondrosarcoma G1
- Chondrosarcoma G2
- Chondrosarcoma G3
- Periosteal chondrosarcoma
- Dedifferentiated chondrosarcoma
- Mesenchymal chondrosarcoma
- Clear cell chondrosarcoma

According to Brien et al., primary CSs are more frequently found than secondary CSs arising from solitary ECs, with an estimated ratio of 2:1 (13). However, the study by Mirra et al. showed higher rates, with 50% of CSs having EC or enchondromatosis remnants, indicative of the lesion being a secondary CS on the basis of benign precursors (21). In this context it has to be taken into account that the rate for malignant transformation is naturally higher in enchondromatosis (like Ollier's disease and Maffucci syndrome; see "1.4.10 Multiple enchondromas" and "1.6.9 Secondary chondrosarcomas") than in solitary lesions (2, 13, 33). In solitary EC, there is a chance of about 4.2% to develop a secondary CS. However, it is difficult to estimate the exact rate of malignant transformation, as ECs are often asymptomatic and therefore remain undiagnosed (25, 44). CSs are classified into 3 grades: low-grade (G1), which accounts for 60% of all CSs and are today regarded as "atypical cartilaginous tumours/ACTs" (see above), intermediate-grade (G2, 35%) and high-grade (G3, 5%) (1, 2). The grading of CSs is based on structural characteristics (cellularity, matrix, myxoid change), cytology (size, forms, nuclei, atypia), cell division rate (mitosis, bi-/multinucleated cells) as well as invasion and infiltration of pre-existing bony structures. It is important because of a correlation with the clinical behaviour of the tumour (2). On the other hand, especially in older studies, like the one by Janzen et al. (18) and Sanerkin et al. (45), G1 and G2 CSs were considered as "low-grade" and G3 CSs at "high-grade", making the sub-differentiation into ACT/G1 CS vs. G2 CS rather difficult.

Table 1 Histological Grading

	Cellularity	**Cytological atypia – nuclei**	**Binucleation**	**Stromal myxoid change**	**Further features**
G1 (low-grade) = ACT	+	Size and discrepancy in shape ↑	Few present	May be present	
G2 (intermediate-grade)	++	Size and discrepancy in shape ↑↑	Large number (double- and trinucleated)	Focally present	
G3 (high-grade)	+++	Size and discrepancy in shape ↑↑↑	Large number (double and multinucleated cells)	Commonly present	Foci of spindling and necrosis

Adapted from Greenspan et al. (2)

CSs account for 15% of all malignant bone tumours. Men are more often affected than women (1). The age peak lies between the 4th and 6th decade (1, 7). They are mainly located in the long tubular bones like femur and humerus as well as the pelvic region (1, 7). In long bones, CSs mainly develop in the metaphysis (7). Unlike ECs, CSs infiltrate the bone marrow and Haversian system, entrap bone trabeculae and destroy surrounding bone (2).

The following information (including, symptoms, imaging, macroscopy, histology, genetics, therapy and prognosis) refers especially to the conventional – or medullary – CS.

Conventional chondrosarcoma, also known as central CS or medullary CS (2).

This subtype, which represents 80% of all CSs, has mainly a hyaline cartilage differentiation. However, also calcifications and ossifications as well as myxoid components may be possible (2). Like CS in general, conventional CS has a male predominance and is more frequently found in patients over the age of 50 years, with a peak age between the 5th and 7th decade. When developing in younger patients, which is rather uncommon, conventional CSs are usually high-grade (2). As mentioned earlier, the pelvic region and long bones (especially proximal and distal femur and proximal humerus) are most commonly affected, as well as the ribs. Small bones, craniofacial bones and bones

of the hand are less commonly affected (2). CSs are usually greater than 5 cm. However, size is not a decisive factor for ECs vs. CSs (2, 6, 14).

1.6.1 Symptoms

Symptoms include swelling and pain (caused by the lesion's growth), with symptoms often being present for several months or even years (2, 11). The pain is usually worse at night and does not improve by rest, contrary to joint-related pain (11). Pathologic fractures may occur (2). In well differentiated CSs (as mentioned earlier) there is only little pain, wherefore they are often diagnosed at later stages when they are already considerably large (1). However, pain caused by the lesion is an important sign to different between ECs and ACTs/CSs G1 as well as CSs G2/G3 (4, 6). In case the skull base is affected, the tumour may even cause neurological symptoms (46).

1.6.2 Imaging

The lesion is mainly found to originate in the medullary canal. Osteolytic lesions with an irregular and sclerotic border are typical (1). The bone destruction pattern is of a geographic type, but also more aggressive patterns like moth-eaten and permeative osteolysis may be seen in CSs G3 (5, 6). Also, calcifications are common, typically popcorn-like (7). They may also vary between ring and arc-like and punctate (2). The differentiation of tumour affects the calcification pattern, with low grade CSs displaying ring and arc-like mineralization, whilst high grade lesions may show an amorphous or stippled pattern and tend to be less mineralized with large nonmineralized areas (5, 17, 19, 35). The lesion's border is rather ill-defined (17). Cortical thickening and an arrosion of the cortex can be seen because of the tumour's infiltrative growth pattern. At some point, deep endosteal scalloping with more than two thirds of the cortical thickness affected can be present (1, 2, 6). Moreover, periosteal reaction may be rarely seen (2, 7). Pathologic fracture may occur because of the cortical destruction and arrosion (2). A soft-tissue mass is also possible in CSs and an important feature to distinguish them from ECs (6), as in ACTs/CSs G1, a soft-tissue mass is rarely found, whilst it is more common in high-grade CSs (14, 19, 20, 47).

MRI

On T1-weighted images, the lesion shows a low to intermediate signal intensity, while on T2, a predominantly high and heterogeneous appearance is typical (2, 19). MRI is inferior to CT in displaying calcification, with small amounts of mineralization eventually being visible on x-ray and CT but not on MRI (19). Similar to ECs, CSs show contrast enhancement (2). In case a soft-tissue mass is present, the characteristics found on T1- and T2-weighted images resemble the intraosseous tumour parts (5). Compared to ECs, small high signal foci are less frequently found in CSs, but may still be present (6). On STIR sequences, an abnormal peritumoral marrow signal is typically seen in CSs G2 and G3. Moreover, a soft-tissue oedema can be present even in case no extraosseous component is present, most likely because of dispersion of the intramedullary oedema (18).

CT

CT scan shows calcification of the matrix very well and allows assessment of cortical involvement (2). The soft-tissue component of the tumour itself shows typical patterns like ring-and-arc or punctate calcification as well as a lobular growth. Higher attenuation is present in higher-graded lesions, corresponding to higher cellularity and therefore reduced water content (5).

Bone scintigraphy

On bone scintigraphy, increased uptake in comparison to the AIC is present (2, 6).

1.6.3 Macroscopy

The only gross macroscopic difference between EC and CS is that CSs can also show cortical involvement. Apart from that, both tumours contain white cartilaginous tissue. There is no synthesis of osteoid (1). The growth pattern is lobular. Cystic areas are also possible, as well as mucoid and myxoid parts (2). Haemorrhage and necrosis may likewise be present (17). In high-grade CSs (G3) haemorrhagic fleshy tissue of grey colour may be found (17). Regarding the cortex, a thickening can be seen and there may be arrosion, destruction and a soft-tissue involvement (particularly in flat bones) (2). Mineralization is present, shown as chalky and gritty areas of yellow-white colour (5, 46). Non-mineralized areas appear translucent, due to the high content of water within cartilaginous tissue (5).

1.6.4 Histology

Histologically, CSs are of higher cellularity than ECs and rather show atypical cells and several mitoses. They have a destructive growth, including infiltration of the Haversian systems (causing cortical thickening, remodelling and scalloping) and bone marrow. Moreover, entrapment of bone trabeculae, caused by replacement of marrow fat with cartilage, is pathognomonic for CSs and is – according to Mirra et al. – known as "CS permeation pattern" (1, 2, 17, 21). The tumour lobules are of different sizes and shapes, fibrous septae may separate them from each other (2). According to Mirra et al., there is a single confluent cartilaginous mass, with fibrous bands between the confluent lobules of peripheral cartilage (21). Furthermore, areas of fibrosis may appear (11). As in macroscopy, myxoid matrix may be seen, as well as matrix liquefaction. Especially in high-grade tumours, large areas of necrosis can be present (2). Another feature of high grade CSs (G3) is the arrangement of chondrocytes in cords and clumps (5).

Immunohistochemical staining

There are 1 – 20% Ki-67 positive chondrocytes found in CSs G2 and G3 (23). In about 20% of CSs, IDH1 mutations are present and can be identified using IDH1 R132H antibody (46). Uria et al. reported that the metalloproteinase collagenase-3 can be found in all CSs, regardless of their grading (13 G1, 2 G2 and 1 G3 CS), whereas only one out of six ECs was positive for this staining (38).

For further differentiation between ACT/CS G1 and CS G2/G3, see *Table 1 Histological Grading*.

1.6.5 Genetics

Chromosomal numerical anomalies can be present, e.g. chromosome 1, 10, 14 and 22. Rearrangements of bands e.g. 5q13, and 20q11 are possible (2). Aberrations localized at 6q13-21 correlate with an aggressive behaviour of the tumour (48). As in ECs, mutations of *IDH1* and *IDH2* may be found in conventional central CSs as well as in dedifferentiated CSs but not in peripheral CSs (24).

1.6.6 Therapy

The therapy of choice is wide resection including the biopsy tract in order to remove any tissue contaminated with tumour cells (1). This procedure applies especially to G2 and G3

CSs, but also to ACTs/CSs G1 located in the spine, pelvis or intra-articular as well as to large sized ACTs/CSs G1 and soft-tissue involvement (49, 50). Notably, ACTs/CSs G1 are nowadays treated by curettage rather than wide resection (39) (see "1.5 Atypical cartilaginous tumour – Chondrosarcoma G1" - "1.5.5 Therapy"). Due to their slow growth, CSs are rather resistant against radiotherapy. This form of therapy may thus only be considered to improve local control after incomplete resection or within a palliative setting, when resection is not possible (50). Chemotherapy is, similarly to radiotherapy, also not effective in treatment of CSs (50).

1.6.7 Prognosis

Five-year survival is 90% for ACT/G1 CS, 53% for G2 and G3 CS combined (G2 81%, G3 43%), whilst 10-year survival rate is 83% in ACT/CS G1, 64% in CS G2 and 29% in CS G3, with expectedly lower survival rates with ongoing de-differentiation (2, 42).According to Ozaki et al., there is a higher chance of metastases in intermediate- (G2) and high-grade (G3) CS (21% vs. 60%) (51). Another interesting finding in the study of Ozaki et al. was the absence of metastases in patients with secondary CS, whilst an overall metastasis rate of 42% was observed in primary CSs. Furthermore, a lower rate of metastases in patients without local recurrence (19%) in comparison to patients developing local recurrence (86%) was reported (51). Evans et al. observed metastasis rates of 10% in G2 CSs and 71% in G3 CSs. On the other hand, no correlation between grading and local recurrence was present (42). According to de Camargo et al., local recurrence rate of CSs G2 is about 43% (41). In case tumours recur, there is a 10% chance of the tumour to be of higher grade than the original lesion (2).

1.6.8 Differential diagnosis

Osteosarcoma is a potential differential diagnosis for CS. However, compared with CS, osteosarcoma appears in younger patients, formation of osteoid or bone can be observed, and periosteal reactions like sunburst or onion-skin phenomena are present (2). Also, especially in older patients metastatic disease is a differential diagnosis for any primary malignant bone tumour, including CS. Another differential diagnosis is EC or ACT/CS G1 (see below: "1.7 Comparison enchondroma, atypical cartilaginous tumour and chondrosarcoma").

1.6.9 Secondary chondrosarcomas

Malignant transformation of ECs, synovial chondromatosis or osteochondromas can lead to development of secondary CSs. Furthermore, secondary CSs may arise in primary enchondromatosis and Paget's disease of bone (2).

Enchondroma

While primary CSs are usually found in older patients, secondary CSs, due to transformation of preceding ECs having developed at early ages, are found in rather young patients. In patients with Maffucci syndrome or Ollier's disease, this transformation is far more likely than in patients with solitary ECs. In case patients develop pain in vicinity of the existing lesions, further investigation should be initiated, as pain is a worrying feature for malignant transformation (2).

Osteochondroma

There is a risk of 1% in solitary and 5% in multiple lesions of osteochondroma to undergo malignant transformation into CS (originating from the cartilage "cap" of the tumour). Pain and sudden growth are clinical features that should prompt further investigation. CSs develop in the cap of osteochondromas and are often low-grade upon initial diagnosis (2).

Synovial chondromatosis

It is extremely rare that CS arises from synovial chondromatosis or osteochondromatosis. According to Greenspan, there are less than 50 cases reported in literature. In this case, the distinction between secondarily developed CS and primary synovial CS is difficult (2).

Paget's disease

Also in case of pagetic bone, it is very uncommon for a CS to arise. Malignancies that develop more often within pagetic bone are osteosarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma (2).

1.7 Comparison enchondroma, atypical cartilaginous tumour and chondrosarcoma

Table 2 Comparison Enchondroma, Atypical Cartilaginous Tumour and Chondrosarcoma

	EC	**ACT/CS G1**	**CS**
Demographic features			
Age peak	2^{nd} – 4^{th} decade	*	4^{th} – 6^{th} decade (CS in general) 5^{th} – 7^{th} decade (conventional CS)
Gender preference	Both equally	*	Male (slightly)
Localization and size			
Most common location (ordered by frequency)	Short tubular bones of hands and feet, long tubular bones (proximal humerus, proximal and distal femur)	Comparable to EC	Pelvis, femur (proximal), humerus (proximal), femur (distal), ribs
Epi-/Meta-/Diaphysis (most frequently)	Diaphysis (and metaphysis)	Comparable to EC	Metaphysis (long bones)
Size	< 3 cm, rarely > 5 cm	Tend to be larger than EC	> 5 cm
Clinical findings			
Symptoms	Usually asymptomatic In case of pathologic fracture (small bones) palpable swelling, pain	Asymptomatic, sometimes pain	Swelling and pain (combined or alone), duration of months or years Pathologic fracture
Type of pain	*	Pain with palpation	Worse at night No improvement by

			rest
Radiology			
Zone of transition	Well-defined	Ill-defined (≥ 25% of circumference)	Ill-defined Irregular and sclerotic
Bone destruction	Geographic	Geographic	Geographic G3 even moth-eaten or permeative
Contour	Smooth	Lobulated	**
Cortex	Thinning of the cortex	Thickening of the cortex	Thickening of the cortex
	No or shallow endosteal scalloping	Deep endosteal scalloping	Deep endosteal scalloping
	No cortical destruction	*	Cortical destruction
	Hardly any cortical remodelling	*	Cortical remodelling
Periosteal reaction	No (except in pathologic fracture)	*	Scant or absent In higher graded CS more pronounced
Soft-tissue mass	No	Rarely	Possible
Tumour matrix	Osteolytic Calcifications (popcorn-like, rings and arcs, punctuate)	Osteolytic Calcifications (popcorn-like, rings and arcs, punctuate) *Tending to a ring and arc-pattern, more mineralized than higher graded CS****	Osteolytic Calcifications (popcorn-like, rings and arcs, punctuate) *Higher graded: less mineralized, amorphous and stippled****

Magnetic resonance imaging			
MRI T1-weighted	Low-to-intermediate signal intensity	(Predominantly) intermediate signal intensity	Low-to-intermediate signal intensity
MRI T2-weighted	High signal intensity, calcifications low signal intensity	High signal intensity	(Predominantly) high signal intensity heterogeneous
Small high signal foci (T1-weighted)	Yes	*	Less common
Contrast enhancement	Yes	Yes	Yes
Pattern in contrast enhanced lesions	Multilocular appearance/septal/ring and arc enhancement**** Rarely confluent enhancement	Multilocular appearance/septal/ring and arc enhancement**** Confluent enhancement possible	Multilocular appearance/septal/ring and arc enhancement*** No septal enhancement on CS G3
Abnormal peritumoral marrow signal	No	Maybe	Maybe
Soft-tissue oedema	No	Maybe	Maybe
Abnormal peritumoral marrow signal (STIR)	No	*****	Yes
Soft-tissue oedema (STIR)	No	*****	Yes

Dynamic contrast-enhanced MRI			
Start of enhancement	No early enhancement	*	Early enhancement
Start of enhancement combined with enhancement progression		*	Early and exponential enhancement
Computed tomography			
CT	Lower attenuation (compared to higher graded CS)	Lower attenuation (compared to higher graded CS)	Higher attenuation in higher graded lesions
Bone scintigraphy			
Uptake	Mild uptake (maybe higher uptake in pathologic fracture)	*	Increased uptake
Uptake compared to AIC	(Equal or) less	Higher or equal uptake	Higher
Homo-/heterogeneity	Homogenous	*	Heterogeneous
Macroscopy			
Growth pattern	Lobulated Multinodular and separated by marrow (long bones) Confluent growth (small bones)	*	Lobular Cystic, mucoid, myxoid, haemorrhagic and necrotic areas possible May develop within cortex

Tissue	White Yellow-white gritty (mineralization)	White Yellow-white gritty (mineralization)	White Yellow-white gritty (mineralization) G3: maybe haemorrhagic fleshy greyish tissue
Histology			
Pattern	Multiple nodules separated by bone marrow	*	(Confluent) lobules maybe separated by fibrous septae
Cellularity	Low-to-intermediate Higher amount possible (particularly short tubular bones)******	Slightly increased	Increased: G2 moderately G3 markedly
Atypia	May occur in short tubular bones	Yes (slightly)	Yes: G2 moderately G3 markedly
Binuclear cells	Single cells may occur Possible in short tubular bones******	Yes (few binucleated cells)	Yes (large number): G2 double-/trinucleated cells G3 double- and multinucleated cells
Stromal myxoid change	*	Focally present	Commonly present
Destructive growth	No	*	Yes (infiltration of Haversian system and bone marrow)
Entrapment of bone trabeculae	No	*	Yes

Additional features	Slightly arrosion of cortex may be present, but never invasion	/	Necrosis (especially in high-grade CS possible) Small foci of spindling at periphery (G3) Chondrocytes in cords and clumps (G3)
Immunohistochemical staining			
Periostin	Negative	Positive	**
IDH 1	*	*	Positive in 20% (R132H antibody)
Collagenase-3	Less common	Positive	Positive
Ki67	Long bones and flat bones negative Short tubular bones mostly positive	Mostly positive	G2 and G3 positive

* ECs or ACTs/G1 CSs not mentioned in particular

** only ACTs/CSs G1 included in corresponding study

*** not mentioned if G2 is included in "higher-grade" or "lower-grade"

**** disagreement if indicative of EC or ACT/CS G1 and low-grade (G1 and G2 CS)

***** ACTs/G1 CSs not included in corresponding study

****** correlation with ACT/CS G1 in long bones

Adapted from Jundt, Greenspan et al., Breitenseher et al., Murphey et al. (1998), McCarthy et al., Geirnaerdt et al. (1997), Manaster et al., Flemming et al., Janzen et al., Varma et al., Ferrer-Santacreu et al., Mirra et al. (1985), Biondi et al., Weinstein et al., Douis et al., Murphey et al. (2003), Rosenthal et al., Choi et al., Lai et al., Uria et al., Limaiem et al., de Beuckeleer et al., Crim et al., Geirnaerdt et al. (1993), Geirnaerdt et al. (2000), Jeong et al., Mirra (1989), Unni (1996, p. 25-47), Unni (1996, p.71-109) and Mulder et al. (1, 2, 4-7, 11, 14, 16-23, 35-38, 46, 52-60)

1.7.1 Demographic features

Concerning demographic features, there is a significant difference in terms of gender and age. CSs are more frequently found in men, also the patients are about one decade older than patients with ECs (2, 6). According to Jundt, Greenspan et al. and Breitenseher et al., there is a great difference regarding age peak, with the 2nd to 4th decade in ECs and 4th to 7th decade in CSs (1, 2, 7).

1.7.2 Localization and size

ECs, ACTs/CSs G1 and CSs G2/3, are often found in long tubular bones, most frequently in the humerus and femur. Over 60% of all ECs are found in the small bones of the hands and feet, whereas CSs G2/G3 are less commonly seen in these locations. ACTs/CSs G1 have a comparable location-distribution as ECs, albeit the more peripheral tumours are located, the more likely they are benign. CSs G2/3 on the other hand, are also frequently located in the pelvis and rib, which is not typical for ECs (1, 2, 7, 14, 57-60). In long bones, ECs are found more often in the diaphysis, and CSs in the metaphysis. The epiphysis is less commonly affected in any case, but if, the lesion is much more likely to be a CS (6). ECs tend to be smaller than 3 cm, whilst lesions > 5 cm size are uncommon. If the tumour is sized over 5 cm, this would be indicative for a CS, albeit size alone should not be a decisive feature (2). Even though CSs are usually larger than ECs, their extent is not very helpful in distinguishing between these entities. Apart from lesions of small bones of feet and hand, ECs and ACTs/CSs G1 as well as higher graded CSs, show a great overlap when it comes to tumour **size** (6, 14). Ferrer-Santacreu et al. reported on no significant difference between ECs and ACTs/CSs G1in long bones in case a size cut-off of ± 5 cm (20).

1.7.3 Symptoms

Pain, swelling and pathologic fracture are three clinical signs that can appear in any of the three lesions (EC, ACT/CS G1, CS G2/G3). Most of, ECs are not painful, whilst in ACTs/CSs G1, and higher-grade CSs, this feature is found more often. However, it has to be taken into account that in ACTs/CSs G1, there is often only very modest pain. In ECs, the symptoms also depend on the localization, with short tubular bones more likely being more symptomatic and long tubular bones rather being asymptomatic (1, 2). In CSs symptoms are often present for a longer time period (2). According to Geirnaerdt et al.,

there is no significant correlation between clinical symptoms, including pain, a soft-tissue mass or fracture, and the presence of EC vs. ACT/CS G1 (14). Also, unwanted weight loss, restricted motion of adjacent joints and duration of symptoms are not indicative (6). On the other hand, as mentioned above, pain related to the lesion is of relevance, occurring more often in ACTs/CSs G1 and CSs in general than in ECs (4, 6). To identify if the pain is caused by the bone tumour itself, an anaesthetic, like lidocaine, may be injected intraarticular. If the symptoms get better thereafter, the lesion is unlikely to be the cause of the pain, and joint-specific pathologies as osteoarthritis should be considered (6, 17). According to Ferrer-Santacreu et al., another distinguishing criterion regarding pain is the presence of pain upon palpation, which is found more often in ACTs/CSs G1 (20). On the other hand, pain worsening at night is rather indicative of CS (11).

1.7.4 Imaging

The type of **bone destruction** tends to be geographic in EC, ACT/CS G1 and CS G2, whilst in CS G3 a more aggressive pattern like moth-eaten and permeative osteolysis may be present (5, 6, 16).

In all three types, **calcification** is common. The calcification pattern may be popcorn-like, ring-and-arc like or punctate (1, 2, 7).

Concerning the **mineralization**, the presence or absence provides no helpful information to distinguish ECs or CSs on MRI and CT. Also, the type of mineralization, including rings and arcs and a flocculent pattern, may not be of additional help. In contrast, radiographic images allow for differentiation between ECs and CSs based on presence and amount of mineralization, with ECs being more commonly mineralized. Yet, it has to be taken into account that there is an significant overlap of this feature between the entities (6). With ongoing dedifferentiation of CS, the calcification tends to be less mineralized, with its pattern changing to an amorphous or stippled one, rather than a ring and arc-like one (5, 17, 19, 35).

The **tumour border** is a significant feature to distinguish between the two entities. In ECs, the margins are more often well-defined, whilst in ACTs/CSs G1, the border is rather ill-defined in ≥25% of its entire circumference (14). Crim et al., on the other hand, could not confirm the significance of ill-defined borders towards differentiation of tumour types. According to them, ECs located in the diaphysis may also show an ill-defined border, due to the lack of adjacent trabeculae, which are responsible for a well-defined, non-sclerotic

border due to their vicinity to the tumour's margin (53). Another useful feature is the **contour** of the lesion. A smooth contour is indicative of EC. In case the contour is lobulated (partly or entirely), the tumour tends to be an ACT/CSs G1 (14). On the other hand, Choi et al. could not show a significant difference between ACTs/CSs G1 and ECs concerning these two features (36).

Regarding the **cortex**, ECs tend to have a **thinned-out cortex**, whilst CSs more frequently show **cortical thickening** (1, 2, 7). Notably, cortical thickening is also a significant feature to distinguish between ECs and ACTs/CS G1 specifically (53). The most sensitive radiographic sign of ACT/CS G1 in comparison to EC is deep **endosteal scalloping**, which reflects the growth of the lobular lesion and may result in cortical penetration. Naturally, this feature is also more frequently seen in CSs in general (4-6). ECs show either no or shallow endosteal scalloping (1, 2). In CSs, however, the scalloping is deeper and more pronounced, involving more than two thirds of the cortex' depth and occurring at more than two-thirds of the lesion's circumferences (see *Table 7 X-ray, MRI, CT Endosteal Scalloping*) (6). According to Crim et al., the differentiation between moderate (one to two-thirds of the cortical thickness) and severe (more than two-thirds of the cortical thickness) scalloping is clinically irrelevant (53). Notably, deep endosteal scalloping may also be seen in ECs located eccentrically as well as in centrally located large ones without being a sign of malignancy. Therefore, endosteal scalloping should always be interpreted in light of the lesion's size and location (53, 61). Nevertheless, on x-ray, this feature may be invisible, in case the beam path of the radiograph is not oriented directly normal to the region of endosteal scalloping (17). **Cortical destruction** occurs in CSs, but not in ECs (2). Parlier-Cuau et al. noted that cortical destruction at the diaphyseal cortex of long bones may not be interpreted the same way as cortical destruction seen in the metaphyseal cortex, due to their different structure, with the metaphyseal cortex being thinner and slightly irregular (62).

Periosteal reaction is not found in ECs. It may appear in CSs. Also in these cases, it is rather scant or absent, whereas in higher-grade CSs, pronounced periosteal reaction may be present (2, 7).

According to Murphey et al., a response of the cortex occurs due to the slow growth of the lesions, resulting in cortical remodelling and thickening as well as in periosteal reaction. These features are less frequently found in ECs and – if they occur – are most likely found in lesions of long bones (5).

There usually is no **soft-tissue mass** in case of EC, whilst this feature is possible in CS (2, 6). Even in ACT/CS G1, it is rather rarely seen, with Ferrer-Santacreu (20) reporting no case of ACT/CS G1 in there study with a soft-tissue mass. In line with this, according to Varma et al., soft-tissue extent is a feature found in higher-grade CSs, but absent in lower grade ones, even though it is not mentioned if "lower-grade" includes G2 or not (19). On the other hand, in the study by Geirnaerdt et al. (14) a soft-tissue mass was present in 16% of ACTs/CSs G1 (and even in 11% of ECs). Nevertheless, due to the mild biologic behaviour of ACTs/CSs G1, this feature remains extremely uncommon. When including CSs G2 and G3, soft-tissue masses are seen in 30% to 76%, depending on imaging modality (plain radiography vs. MRI). In comparison, only 1% (upon x-ray) to 3% (upon MRI) of ECs present this feature (6, 14, 47).

Geirnaerdt et al. reported a likelihood of > 90% for a lesion being an ACT/CS G1, when combination of four distinct features was present, i.e. partially/completely ill-defined margins, partially/entirely lobulated contour, calcifications of popcorn-like pattern and scalloping. Nevertheless, this combination was only present in 6% of their cases and was also found in ECs (14).

On radiography, according to Murphey et al., **cortical remodelling** (shown by an expansion of the bone contour), **destruction** and **thickening** is a relevant feature in distinguishing EC from CS, as well as **periosteal reaction**, **pathologic fracture** and a **soft-tissue mass** (6).

Table 3 Features X-ray

Feature	**EC**	**CS**	**P Value**
Cortical remodelling	15%	47%	< .0005
Cortical destruction	5%	57%	< .0005
Cortical thickening	17%	47%	< .0005
Pathologic fracture	5%	27%	.0040
Periosteal reaction	3%	51%	< .0005
Soft-tissue extension	1%	46%	< .0005

Adapted from Murphey at al. (6)

According to Parlier-Cuau et al. radiological and clinical findings can be classified into two groups: aggressive features and active features (see *Table 4 Classification of clinical*

and radiological Findings). Aggressive features, disrupting anatomical planes, are indicative of CSs G2/G3. Active features, on the other hand, represent the effect of the lesion on adjacent tissue and may be found both, in EC and ACTs/CSs G1. Besides aggressive and active lesions, there are also quiescent lesions, showing none of the features stated below (62). Parlier-Cuau et al. suggest this classification being the basis for further management decisions (62).

Table 4 Classification of clinical and radiological Findings

Active	**Aggressive**
Pain related to the lesion	Pathologic fracture
Endosteal scalloping (> 2/3 depth, > 2/3 extent)	Periosteal reaction (pluri-lamellar or speculated)
Cortical thickening or hyperostosis	Moth-eaten or permeative bone destruction
Cortical remodelling	Cortical destruction
Delayed bone scintigram, uptake greater than the AIC in absence of fracture	Soft-tissue mass
Early and exponential enhancement on dynamic gadolinium-enhanced MRI-sequences	

Adapted from Parlier-Cuau et al. (62)

MRI

Choi et al. discovered that there are different features in MRI that are significantly more often seen in ACT/CS G1 than in EC, including a predominantly **intermediate** signal (T1-weighted), **multilocular** appearance (T1, contrast-enhanced), **cortical destruction**, **soft-tissue** mass and **abnormal signal** of the adjacent bone marrow and soft-tissue. According to Choi et al., the latter three features were not found at all in ECs, with a positive predictive value of 100%. The features “predominantly intermediate signal” and “multilocular appearance”, on the other hand, had a higher sensitivity (72% and 83%) than the other three features “cortical destruction”, “soft-tissue mass” and “abnormal signal of the adjacent bone marrow/soft-tissue” (33%, 28% and 22%), presumably because of the representation of aggressiveness of the latter features (36). No statistically significant

difference between ECs and ACTs/CSs G1 was found for high signals (T1-weighted), low-to-intermediate and heterogeneous signals (T2-weighted) and multiseptation (T2-weighted) (36).

In the study by Janzen et al., there was no **abnormal peritumoral marrow signal** – shown as high signal intensity – present in ECs (13 patients), but in all cases of CS (8 G2 and 5 G3 CSs) on STIR images. Histologically, the abnormal signal correlates with chronic inflammatory changes and fibrillary fibrosis (18). A soft-tissue oedema – represented as abnormal signal of high intensity – was found in 8 of 13 CSs and in none of the ECs. It is assumed that the oedema occurs due to intramedullary oedema spreading into the soft-tissue, because in all cases of soft-tissue oedema, there was also an abnormal signal within the bone marrow (18). On T2-weighted images, not all of the cases showed abnormal signs within bone marrow or soft-tissues. Moreover, abnormal signs were less frequent on T2 than on STIR sequences (18). Also Choi et al. reported on abnormal signals of bone marrow or soft-tissues in 22% of ACTs/CSs G1, but no ECs (36).

According to Murphey et al., on MRI **cortical remodelling** and **destruction** are distinguishing features for ECs vs. CSs, as well as pathologic **fracture** and a **soft-tissue mass** (see *Table 5 Features MRI*, for endosteal scalloping see *Table 7 X-ray, MRI, CT Endosteal Scalloping*). MRI is the best modality for detecting a soft-tissue expansion. Contrary to CT and plain radiography, there is no statistically significant difference between tumour types concerning the features cortical thickening and periosteal reaction (6).

The nonmineralized part of the lesion exhibits a low-to-intermediate signal on T1-weighted MRI and intermediate-to-high signal on T2-weighted MRI in EC as well as in CS. Also, low-signal-intensity septations, homogeneity and heterogeneity and a lobulated margin are no features of relevance in distinguishing between the two tumours (6).

Also according Murphey et al., **small high signal foci within the lesion** (T1-weighted) are significantly more common in ECs, compared to CSs. The foci are believed to correlate with residuals of normal bone marrow between the lobular tumour pattern of EC seen histologically. This sign is rare in CSs and an important feature for pathologists. They authors postulate that the reason for the foci shown on MRI also in 35% of CSs (in contrary to histological appearance), may be that some EC-like areas are still present in

secondary CSs (6). Choi et al., otherwise, could not confirm this in their study, when differentiating between ECs and ACTs/CSs G1 (36).

According to Murphey et al. administration of **gadolinium**, does not add any useful information, particularly concerning the pattern and degree of enhancement (6). Both EC and CS lesions show contrast enhancement (2). Also in the study by Aoki et al., every EC and CS showed the so-called ring-and-arc enhancement (63). Choi et al., on the other hand, demonstrated in their study that a multilocular appearance on T1-weighted contrast-enhanced images is in fact a feature indicative of ACTs/CSs G1 (36). This is similar to a ring-like contrast enhancement, with the so-called rings and arcs reflecting the lobular growth of the lesion, which is histopathologically mirrored by septa of fibrovascular tissue bordering the nonehancing lobules of hyaline cartilage as well as possibly nonehancing areas of necrosis and cystic mucoid tissue (19, 36, 54, 63). De Beuckeleer et al. reported on similar results, with septal/ring and arc enhancement (T1-weighted, gadolinium injected) combined with septa of low signal intensity on T2-weighted images being indicative for low-grade CSs, although it was not clearly stated in that study whether G2 was regarded as "low-grade" or "high-grade" (52). On the contrary, Crim et al. described septal enhancement to be a feature more often found in ECs than in ACTs/CSs G1. They also demonstrated that confluent enhancement may be of value in differentiating between EC and ACT/CS G1, representing a sign of malignancy (53). Geirnaerdt et al. described septal enhancement being useful in identifying low-grade CS (G1 and G2) from osteochondromas and high-grade CSs (G3), whereat the latter two entities did not show this feature (54).

Table 5 Features MRI

Feature	**EC**	**CS**	**P Value**
Cortical remodelling	11%	45%	.0080
Cortical destruction	3%	73%	< .0005
Pathologic fracture	0%	15%	.0290
Soft-tissue extension	3%	76%	< .0005

Adapted from Murphey et al. (6)

Dynamic contrast-enhanced MRI

It is not clear if dynamic contrast-enhanced MRI is suitable to differentiate between ECs and ACTs/CSs G1. According to Douis et al., this may not be the case (4). Similarly, as stated by De Coninck et al., the accuracy in distinguishing between EC and CS is the same for dynamic contrast-enhanced MRI and standard MRI (64). On the other hand, Geirnaerdt et al. found significant differences regarding onset of enhancement, with an early lesion's enhancement within 10 seconds after arterial enhancement being present in CSs but not in ECs. Furthermore, they discovered that exponential enhancement (fast enhancement, following early maximum plateau or slight increase) is more frequently found in CSs (55).

CT

Higher grade CSs tend to a higher cellularity and therefore contain less water, displaying as higher density on CT compared to lower-grade lesions and ECs (2, 5). Like on plain radiography, there are significant differences on CT between ECs and CSs in general concerning cortical remodelling, destruction and thickening, periosteal reaction, pathologic fracture and soft-tissue extension (6). Regarding endosteal scalloping – similar to MRI and x-ray – especially the depth is an important discriminating feature, with CSs showing deeper (> 2/3 of depth) scalloping than ECs (see *Table 7 X-ray, MRI, CT Endosteal Scalloping*) (6). Ferrer-Santacreu et al. also reported cortical involvement irrespective of its extent being a distinguishing feature for EC and CS (20).

Table 6 Features CT

Feature	**EC**	**CS**	**P Value**
Cortical remodelling	21%	53%	.0210
Cortical destruction	8%	88%	< .0005
Cortical thickening	10%	47%	.0130
Pathologic fracture	3%	20%	.0050
Periosteal reaction	21%	47%	.0007
Soft-tissue extension	3%	59%	< .0005

Adapted from Murphey et al. (6)

Table 7 X-ray, MRI, CT Endosteal Scalloping

Scalloping depth	**EC** **(X-ray – CT – MRI)**	**CS** **(X-ray – CT – MRI)**
None	35% - 18% - 46%	8% - 4% - 9%
< 1/3 of thickness	39% - 62% - 40%	9% - 4% - 3%
1/3 – 2/3 of thickness	17% - 10% - 9%	7% - 2% - 3%
> 2/3 of thickness	7% - 8% - 3%	21% - 14% - 12%
Cortical penetration	2% - 3% - 3%	54% - 76% - 73%
Scalloping extent	**EC** **(X-ray – CT – MRI)**	**CS** **(X-ray – CT – MRI)**
< 1/3 of extent	42% - 25% - 89%	16% - 11% - 13%
1/3 – 2/3 of extent	27% - 41% - 0%	13% - 11% - 20%
> 2/3 of extent	32% - 34% - 11%	71% - 79% - 67%

Adapted from Murphey et al. (6)

Bone scintigraphy

In ECs, there is a mild uptake of radioactive agent. In CSs, the uptake is even more pronounced. However, also in ECs, a higher uptake is possible in cases of pathologic fracture (2). Compared to the AIC, on bone scintigraphy, CSs show a higher uptake of radionuclide, whereas ECs tend to have an equal or reduced uptake (6). Ferrer-Santacreu et al., on the other hand, reported that higher *or equal* uptake of the lesion in comparison to the AIC points towards an ACT/CS G1 and *only* a reduced uptake would be indicative of ECs (20). The discrepancy could be due to the fact that Murphey et al. (6) included all grades of CSs in their study, whilst in the study by Ferrer-Santacreu (20) only ACTs/CSs G1 were evaluated. Of note, the pattern of the uptake is more often heterogeneous in CSs and homogenous in ECs (6).

1.7.5 Macroscopy

ECs and CSs have a pretty similar appearance upon macroscopy. Both are lobulated and white. A difference is that CSs may also appear within the cortex, whilst this does not apply to ECs. In ECs of small tubular bones, the growth pattern is rather confluent than lobular (2). In both EC and CS, calcification represented by yellow-white chalky and gritty

tissue is seen (5, 46). In CSs G3, additionally haemorrhagic fleshy grey tissue may be found (17).

1.7.6 Histology

The major histological difference between EC and CS is the lack of destruction of pre-existing bone structures in ECs, whilst in CSs, entrapment of bone trabeculae and infiltration of bone marrow and the Haversian system is seen (2). Whilst fibrous bands are found between the cartilaginous tissue in CSs, the lobules found in ECs are separated by marrow or coated by bone (11, 21). Only low-to-moderate cellularity is present and single binucleated cells are present in ECs, even though a higher cellularity and higher number of binucleated cells may be seen in short tubular bones (but the lesion still remains benign) (1, 2, 22). Especially in long bones, the higher amount of cells and binucleated cells is indicative of ACT/CSs G1. These features are even more prevalent in higher grade CSs, in whom also the atypia is more pronounced (see *Table 1 Histological Grading*) (1, 2). Discrimination between EC and ACT/CS G1 is believed to be pretty difficult based on histology only (14), due to a not insignificant chance of a CS having emerged from an EC (see "1.6 Chondrosarcoma"), with benign histologic features being found adjacent or within the CS itself (13, 17, 21).

Immunohistochemical staining

Chondrocytes are Ki67 positive in CS G2 and G3. Furthermore, the majority of ACTs/CSs G1 as well as ECs of the short tubular bones contain Ki-67 positive chondrocytes. In ECs of long and flat bones, on the other hand, no Ki-67 reactive cells are present (11, 23). According to Lai et al., the biomarker periostin is the most reliable one out of 17 proteins, in order to distinguish between EC and ACT/CS G1, with a specificity of 87% and a sensitivity of 70% (37). This marker is positive in ACTs/CSs G1 but neither in ECs nor in healthy cartilage (37, 56). Furthermore, Uria et al. reported collagenase-3 being a marker to distinguish between EC and CS (ACT/G1 as well as G2 and G3), with collagenase-3 being positive in all CSs but only in 17% (one out of six) of ECs (38). However, as a specificity and sensitivity of > 90% should be reached to consider a marker as reliable, there is still no histological marker reliably differentiating between EC and ACT/CS G1 (56).

2 Materials and methods

2.1 Patients

For the current diploma thesis, all patients who had been diagnosed at the *Department of Orthopaedics and Trauma, Medical University of Graz, Austria* with "Enchondroma" or "Atypical Cartilaginous Tumour (ACT)" or "Chondrosarcoma G1" of the long bones (humerus, radius, ulna, femur, tibia and fibula) between 2006 and 2018 were retrospectively included. The diagnoses had to be histologically confirmed, either by biopsy or definite surgery.

Reasons for exclusion were: non-long-bones (short tubular bones, flat bones), primary extraskeletal tumours (lymph node, soft-tissue), CS G2 and G3, wrong diagnosis, no data available for the analysis (missing histology, missing diagnostic findings), biopsy or surgery performed in other institutes (in case the diagnosis was not histologically confirmed in our institute), other tumour entities (like osteochondroma, osteosarcoma, metastases), exostosis and multifocal fibrous dysplasia.

Data was retrospectively collected using MEDOCS, reviewing medical charts, fever charts, as well as radiology, pathology, and surgery reports. The following variables were obtained: demographic features (gender, age), symptoms (pain due to the lesion, pain in the affected region in general, type of pain), incidental finding no/yes, time period for which the lesion was known, if there were multiple lesions, lesion's size and localization, date of x-ray, if MRI and/or CT images had been performed, if a bone scintigraphy had been performed, definite histological diagnosis, whether biopsy only or definite surgery was performed, information on follow-up, relapse status and final status.

Epi-/Meta-/Diaphysis: This data could not be collected completely from medical charts as in 27 (52.9%) cases of ECs and 22 (42.3%) cases of ACTs/CSs G1, this feature was not clearly stated. Therefore, the exact location within the bone was evaluated by the reviewers on x-ray and MRI, see "3.2.1 X-ray" and "3.2.2 MRI".

Size: As size the largest diameter of the lesion on MRI was used. If not available, the size as defined on CT-scans, or – if again not available – the lesion's dimension as visible on x-ray was used. If different sizes of the same lesion were reported, the description of size nearest to the date of biopsy or surgery was used.

Incidental finding no/yes: The lesion was declared as incidental finding, if it was stated as incidental finding in the clinical findings, or if it was found during an examination performed due to another cause (for example like scintigraphy because of a breast cancer or x-ray due to pain caused by arthrosis). The definite reasons for the other examinations are stated below (see *Table 13 Other Symptoms/Diseases of Patients included (n=86)*).

Time period for which the lesion is known: The lesion was stated as "longer known", if it was written in the clinical findings, or if there were follow ups after the first consultation and the biopsy and/or surgery was performed later. For all lesions known for a longer time period – according to the conditions stated before – it was assessed how long they were known, from the first finding until the biopsy or surgery. Sometimes the first finding was not always clear, as it was just stated as "known since x years" or "known since last winter". Therefore, the exact date had to be estimated. In case of "x years", the years were counted back and the middle of the year (1st July) was taken as date.

Relapse status: Only in case surgery had been performed and at least one radiological follow-up was available it could be assessed whether there was a residual or recurrent tumour. Therefore, seven EC patients and two ACT/CS G1 patient could not be analysed for this specific feature. It was not always clear if a lesion shown on the image comprised a residual tumour or a recurrent one. It was decided that any lesion visible on the first follow-up x-ray was a residual lesion. In case a lesion was detected on x-rays taken after the first follow-up x-ray, it was considered as recurrent tumour.

Duration of follow-up: For the duration of follow-up, only patients who underwent at least one radiologic follow-up were taken into account.

2.2 X-ray and MRI

2.2.1 X-ray

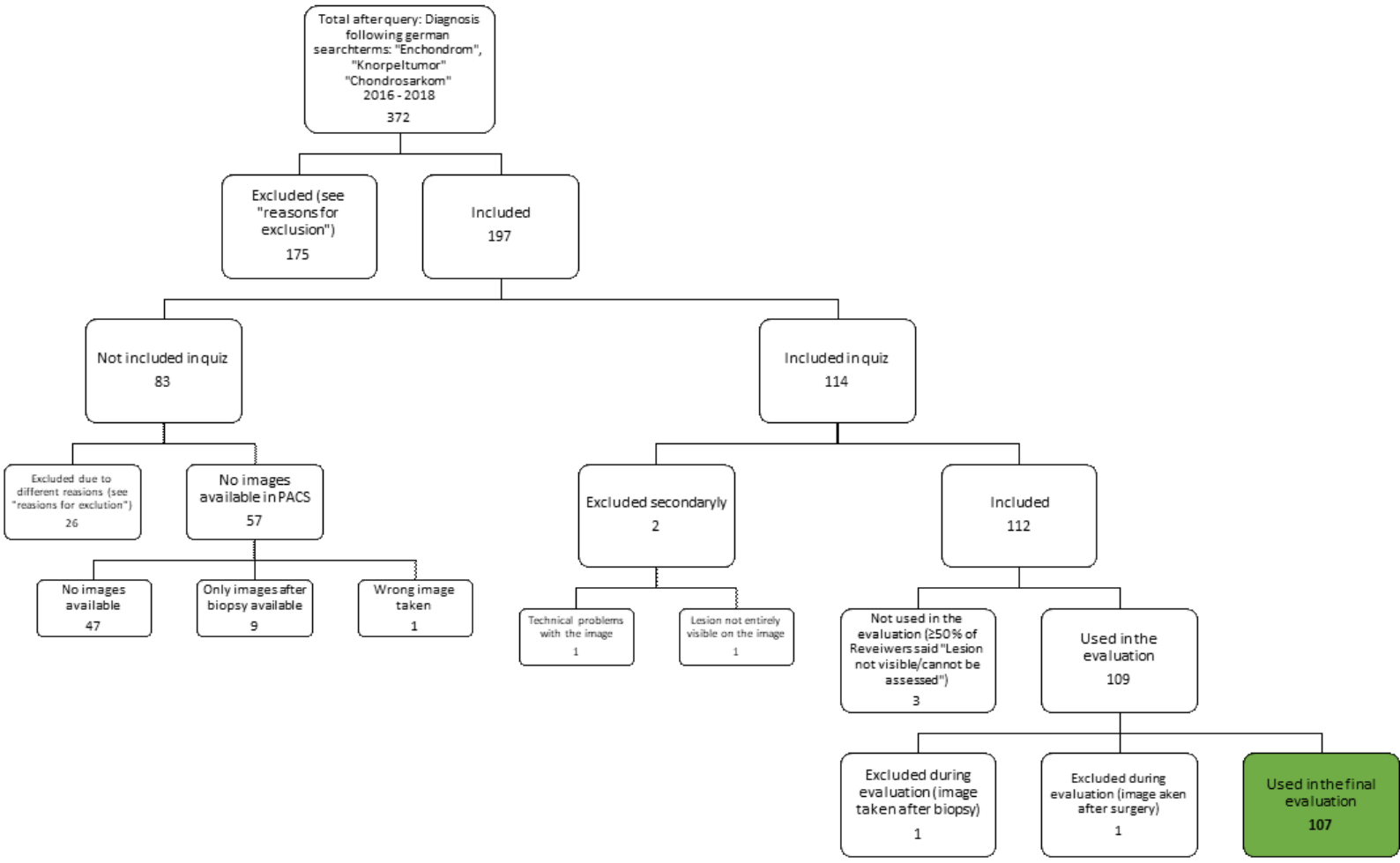
The next step was to collect all plain radiographs. We included radiographs made before biopsy and/or surgery and excluded the ones which were made after biopsy and/or surgery as well as images in whom the lesion was not entirely visible. Four independent reviewers, blinded to the definite diagnosis, were asked to analyse a.p. and lateral x-rays of patients included, each depicting the enchondroma or AC/CS G1. The reviewers comprised two radiologists and two experienced orthopaedic tumour surgeons at the *Department of Radiology* as well as the *Department of Orthopaedics and Trauma, Medical University of Graz*. Furthermore, another orthopaedic tumour surgeon evaluated all x-rays regarding definite diagnosis, but not for radiographic features mentioned further.

Features assessed by the four reviewers (apart from presumed diagnosis) were:

- Epi-/Meta-/Diaphysis (epiphysis, metaphysis, diaphysis)
- Zone of transition (defined border, diffuse, sclerotic, lytic)
- Bone destruction (none, geographic, moth-eaten, permeative)
- Cortex-arrosion (none, focal, continuous)
- Periosteal reaction (none, continuous, discontinuous)
- Soft-tissue shadow (no, yes)
- Calcification (none, stipples, popcorn-like, irregular)
- Diagnosis the reviewer would reach based on the image (EC, ACT/CS G1).

From 372 cases potentially eligible, 107 cases were used for final evaluation before debriefing, after a careful selection process, see *Figure 14 Flow Chart* as well as *2.3 Debriefing*.

Figure 14 Flow Chart



Epi-/Meta-/Diaphysis: “Epiphysis”, “metaphysis” and “diaphysis” could be chosen by the reviewers. More than one option was possible. The “main feature” contains all locations seen in one case, irrespective of how often it was observed. For example: One reviewer chose “epiphysis”, two chose “metaphysis” and the fourth one chose “epiphysis AND metaphysis”, the main feature “epi-/metaphysis” was taken for the final evaluation.

Zone of transition: For describing the lesions’ border, the features “diffuse”, “lytic”, “sclerotic” and “defined border” could be selected. Also in this case, the reviewers were able to select more than one feature per case. The answers of the reviewers were summarized as main feature, either “well-defined” or “ill-defined”. If > 50% of the reviewers chose either sclerotic, lytic or defined border, the main feature was “well-defined”. If < 50% chose diffuse, the main feature was stated as “ill-defined” (see also “2.2.1 X-ray”). In case 50% of reviewers chose one of the well-defined and 50% one of the ill-defined features, the result was interpreted as “disagreement”. As subcategory, we also evaluated the feature that was chosen most frequently, i.e. the feature(s) chosen in ≥ 50% of 4 answers or in ≥ 40% of five answers (in case some reviewers selected two answers per sample). Of note, this method applies to most of the following “main features” assessed and is therefore not stated for every subsequent one. If other methods to define features were used, this is specifically mentioned.

Bone destruction: The reviewer could choose whether the type of bone destruction is “geographic”, “moth-eaten”, “permeative” or if there is “no” destruction. In case a reviewer chose “no” AND one of the other options, the answer was not included in the final evaluation.

Cortex-arrosion: The features regarding cortex-arrosion were “no”, “focal” and “continuous”. If a reviewer chose “no” AND “focal” or “continuous”, the answer was not included in the final evaluation.

Periosteal reaction: For evaluating the periosteal reaction, the options were “no”, “continuous” and “discontinuous”. If a reviewer chose “no” AND “continuous” or “discontinuous”, the answer was not included in the final evaluation.

Soft-tissue shadow: The reviewer chose whether there was a soft-tissue shadow (“yes”) or not (“no”).

Calcification: The features were “popcorn-like”, “stipples”, “irregular” and “no”. If a reviewer chose “no” AND one of the types of calcification, the answer was not included in the final evaluation.

Diagnosis: Based on their preceding evaluation of the x-rays, the reviewer could choose between the two differential diagnoses “EC” or “ACT/CS G1”.

2.2.2 MRI

For MRIs, the same inclusion and exclusion criteria applied as for the x-ray images. MRI scans had to be taken before any biopsy and/or surgery and the whole lesion has to be visible on the scan itself. Of the 107 patients included for x-ray evaluation, the MRI scans of 26 patients could be ascertained. These were then evaluated by the four reviewers, again blinded to the definite histological diagnosis, similar to the x-ray evaluation.

Features assessed were the same as in the x-ray evaluations and some in addition:

- Epi-/Meta-/Diaphysis (epiphysis, metaphysis, diaphysis)
- Bone destruction (no, geographic, moth-eaten, permeative)
- Cortex-arrosion (no, focal, continuous)
- Cortical thickening (no, yes)
- Periosteal reaction (no, continuous, discontinuous)
- Soft-tissue shadow (no, yes)
- Diagnosis based on the image (EC, ACT/CS G1).
- Signal intensity T1-weighted (low signal intensity, high signal intensity)
- Signal intensity T2-weighted (low signal intensity, high signal intensity)
- Contrast enhancement (no, yes, no contrast agent used)
- Peritumoral oedema (no, yes)
- Soft-tissue oedema (no, yes)

Epi-Meta-Diaphysis: See “2.2.1 X-ray”

Bone destruction: See “2.2.1 X-ray”

Cortex-arrosion: See “2.2.1 X-ray”

Cortical thickening: The reviewer chose whether they could see a cortical thickening (yes) or not (no).

Periosteal reaction: See “2.2.1 X-ray”

Soft-tissue shadow: See “2.2.1 X-ray”

Diagnosis: See “2.2.1 X-ray”

Signal intensity T1-weighted and signal intensity T2-weighted: It was evaluated, if the signal intensity of the lesion was rather of low or high signal intensity. The feature >50% chosen was stated as “main feature”. If ≥50% answered “not applicable”, the feature was “not assessable”.

Contrast enhancement: The reviewer assessed the contrast enhancement, if there was any (“yes”) or not (“no”), or if there was no contrast agent used. If ≥50% answered “not applicable”, the feature was “not assessable”.

Peritumoral oedema and soft-tissue oedema: It was evaluated whether there was a peritumoral and/or soft-tissue oedema seen (“yes”) on MRIs or not (“no”).

2.2.3 X-ray and MRI

Statistical Analysis

Intraclass correlation coefficient

To assess interobserver reliability on different x-ray and MRI-based radiologic features between the four reviewers, the intraclass correlation coefficient (ICC) of absolute agreement based on two-way random effects models was used. For this, the average consistency between the four reviewers for a defined feature is regarded poor with a value less than 0.5, moderate for a value between 0.5 and 0.75, good for a value between 0.75 and 0.9, and excellent for a value above 0.9 (65). Notably, the ICC of x-ray-based diagnosis was calculated for five reviewers.

Overall accuracy of the different features

To evaluate the overall accuracy of all features, in cases where a reviewer chose conflicting features (like “no” AND “focal” in case of cortex-arrosion), his answer was excluded from overall accuracy. The same applies for the cases, where a reviewer gave no answer.

Diagnosis overall accuracy

For assessing the overall accuracy of the diagnosis, the number of diagnoses of each reviewer consistent to the final diagnosis were counted and divided by all given answers (No answer given [NA] excluded).

Reviewer sensitivity and specificity

Regarding the diagnosis EC or ACT/CS G1, sensitivity and specificity was evaluated for each reviewer as well as an overall sensitivity and specificity.

2.3 Debriefing

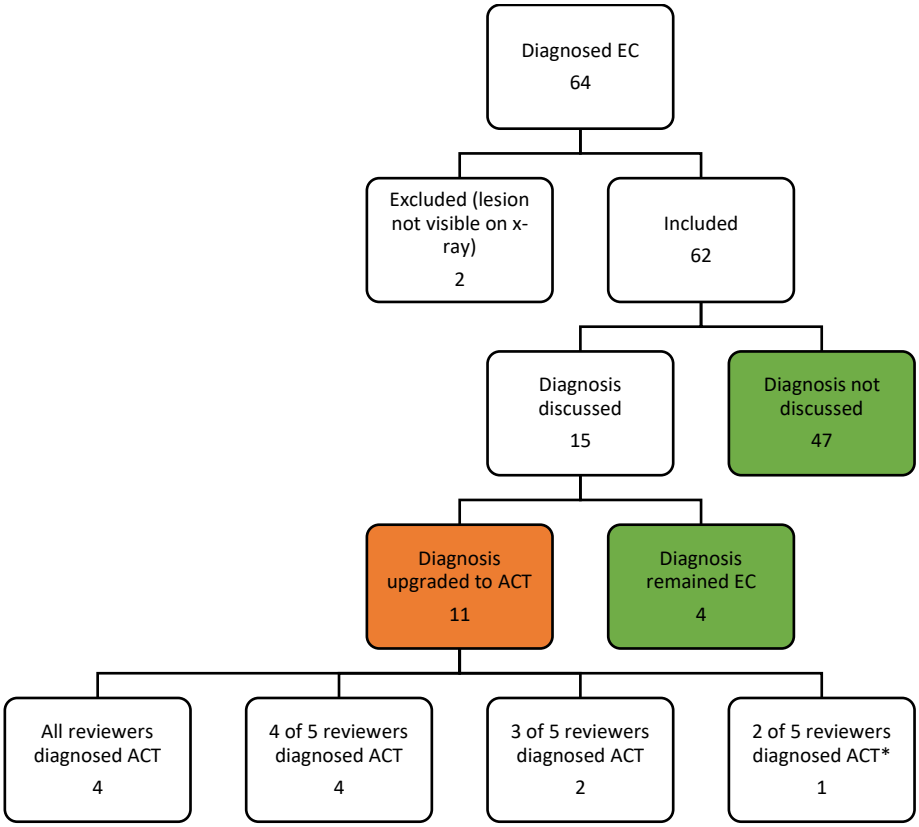
After collecting all the data and after all features had been evaluated by the reviewers, a debriefing was performed by one reviewer of the *Department of Radiology* at the *Medical University of Graz*, who is specialised in musculoskeletal radiology, as well as another orthopaedic consultant from the *Department of Orthopaedics and Trauma* at the *Medical University of Graz*. The latter one also provided a diagnosis based on the x-rays, without knowing the definite diagnosis. After that, the diagnoses were reviewed and the same x-rays as shown to the reviewers were correlated with histologically findings. Some diagnoses were upgraded from ECs to ACTs following current standards, as radiology may overrule histopathological findings, if there are signs of malignancy. On the other hand, some cases had no signs of malignancy on radiographs, but some were found in the histopathologically diagnosis, such as entrapment of bone trabeculae. In these cases, it was not possible to downgrade the lesion from ACT to EC as radiology cannot overrule pathology if there are definite signs of malignancy, e.g. entrapment of the host bone.

During the debriefing, 4 cases were excluded, as the lesions were not clearly visible on x-ray. Notably, one of these lesions had also been evaluated on MRI, wherefore the final cases of MRIs analysed was reduced to 25 instead of 26. Four cases were discussed, as some reviewers diagnosed the lesions on the corresponding x-rays as ACTs, yet the final diagnosis remained EC because there were no clear signs of malignancy either on x-ray nor histopathology. In 11 cases, the diagnosis was upgraded from EC to ACT due to radiological signs of malignancy. In 15 cases, definite diagnosis of ACT remained unchanged as histopathology revealed signs of malignancy, although at least 4 out of 5 reviewers assumed the diagnosis of enchondroma upon x-ray. For further details regarding

the cases discussed, see *Figure 18 Histology ACT, 100% on X-Ray (n=8)* – *Figure 26 Histology Enchondroma, 60% ACT on X-Ray, remained EC (n=2)*.

In summary, 51 ECs and 52 ACTs were used in final evaluation. For details see *Figure 15 Flow Chart, Debriefing, Enchondromas* and *Figure 16 Flow Chart, Debriefing, Atypical Cartilaginous Tumours*.

Figure 15 Flow Chart, Debriefing, Enchondromas

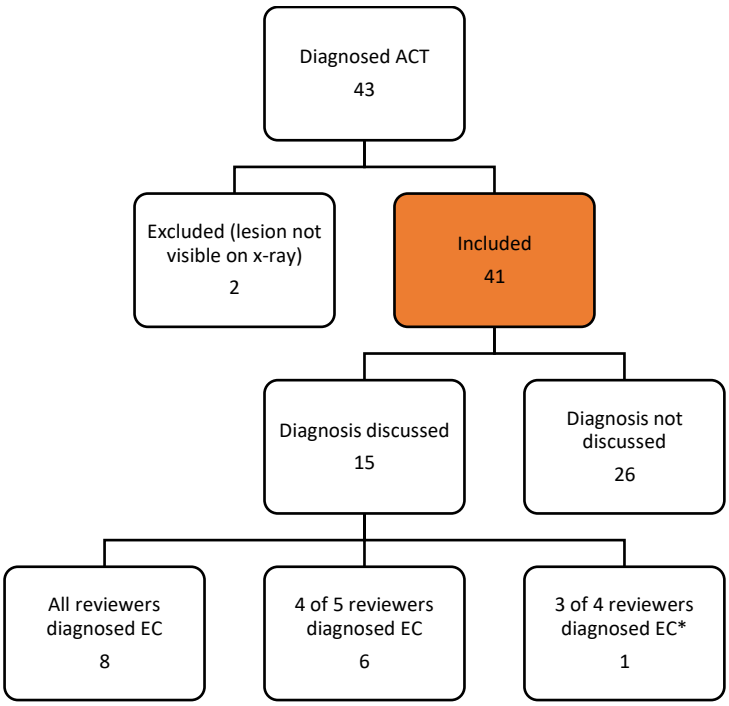


* Both reviewers of the debriefing

Green: EC-diagnoses used for final evaluation

Orange: ACD-diagnoses used for final evaluation

Figure 16 Flow Chart, Debriefing, Atypical Cartilaginous Tumours



* for one reviewer, the lesion was not visible

Orange: ACT-diagnoses used in the final evaluation.

Twenty-nine cases were clear on x-ray, as all 5 reviewers' diagnoses were consistent with the final diagnosis. Furthermore, in 2 cases that had only been evaluated by 4 reviewers, all agreed on the final diagnosis, resulting in 31 cases with 100% agreement rate (30.1%). In 24 cases, 4 of 5 reviewer had reached the same diagnosis as the final diagnosis. Three of 5 reviewer agreed with the final diagnoses in 17 cases. In other words, there were 41 cases (39.7%) in whom more than half but not all reviewers had chosen the right diagnosis. Half of the reviewers, in cases 4 reviewer evaluated the x-ray, were right in 1 case (1.0%). Less than 50 % but at least one of the reviewer diagnosed the lesion correctly in 22 cases (21.4%). In 8 cases (7.8%), none of the reviewers reached the right diagnosis. Notably, all these cases had been histologically confirmed ACTs/CS G1, whilst no signs of malignancy had been present on x-rays.

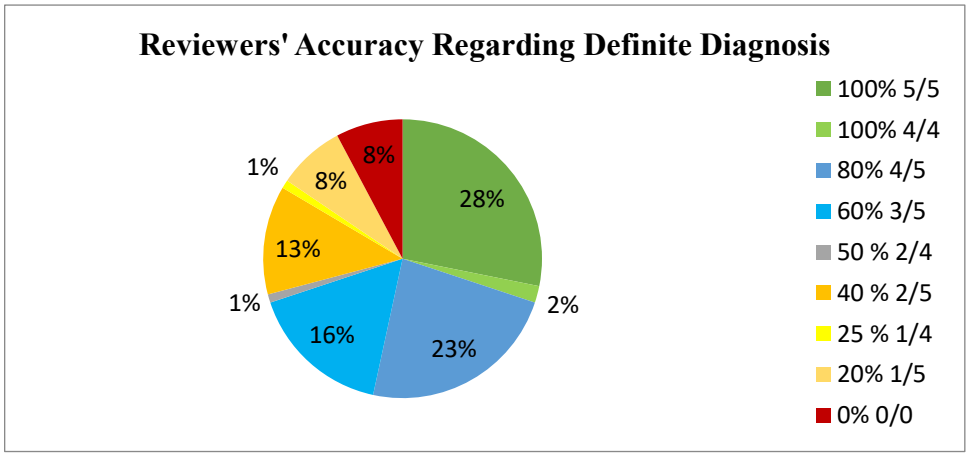
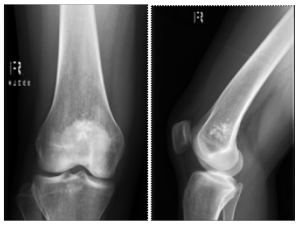
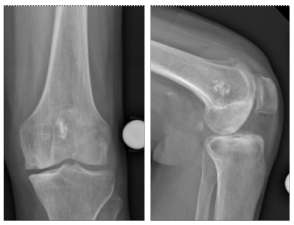
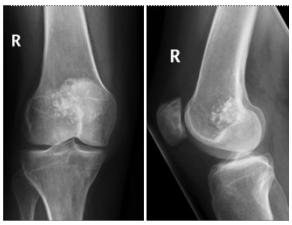
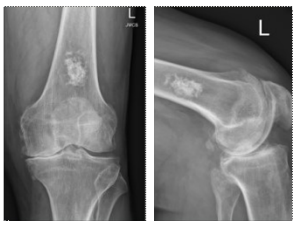
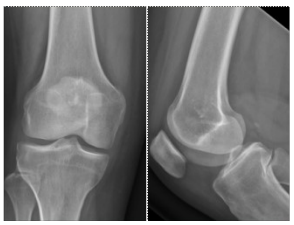
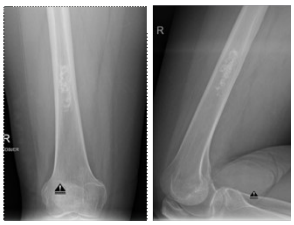


Figure 17 Reviewers' Accuracy Regarding Definite Diagnosis

	Case 1	Case 16	Case 31
			
Reviewer's Diagnosis	100% Enchondroma	100% Enchondroma	100% Enchondroma
Histology	ACT	ACT	ACT
Definite Diagnosis	**ACT**	**ACT**	**ACT**

	Case 46	Case 48	Case 75
			
Reviewer's Diagnosis	100% Enchondroma	100% Enchondroma	100% Enchondroma
Histology	ACT	ACT	ACT
Definite Diagnosis	**ACT**	**ACT**	**ACT**

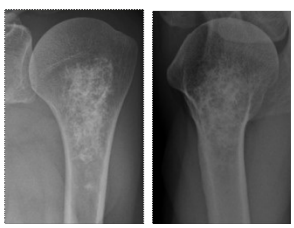
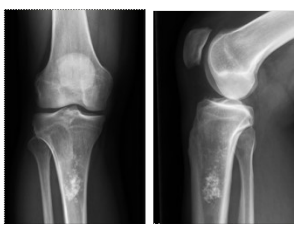
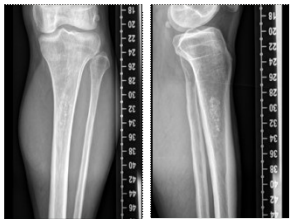
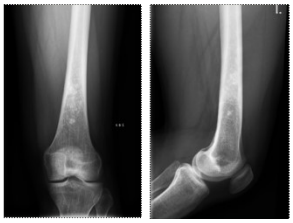
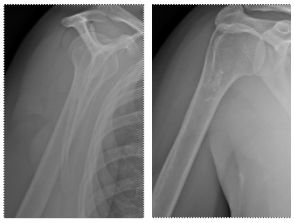
	Case 89	Case 97
		
Reviewer's Diagnosis	100% Enchondroma	100% Enchondroma
Histology	ACT	ACT
Definite Diagnosis	**ACT**	**ACT**

Figure 18 Histology ACT, 100% on X-Ray (n=8)

Eight cases of histopathologically verified ACTs/CSs G1. All reviewers (5/5=100%) diagnosed EC based on x-ray. The final diagnosis remained ACT, as entrapment of preexistent bone trabeculae was seen upon histopathological analysis.

	Case 4	Case 28	Case 54
			
Reviewer's Diagnosis	80% Enchondroma, 20% ACT	80% Enchondroma, 20% ACT	80% Enchondroma, 20% ACT
Histology	ACT	ACT	ACT
Definite Diagnosis	**ACT**	**ACT**	**ACT**

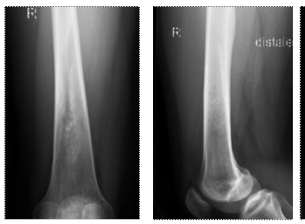
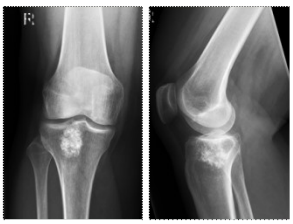
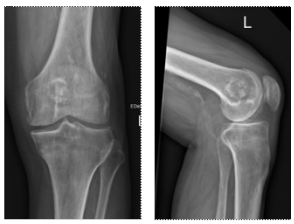
	Case 67	Case 82	Case 85
			
Reviewer's Diagnosis	80% Enchondroma, 20% ACT	80% Enchondroma, 20% ACT	80% Enchondroma, 20% ACT
Histology	ACT	ACT	ACT
Definite Diagnosis	**ACT**	**ACT**	**ACT**

Figure 19 Histology ACT, 80% Enchondroma on X-Ray (n=6)

Six cases of histopathologically verified ACTs/CSs G1. Four of five reviewers (4/5=80%) diagnosed EC based on x-ray. The final diagnosis remained ACT, as histopathology revealed entrapment of preexistent bone trabeculae.

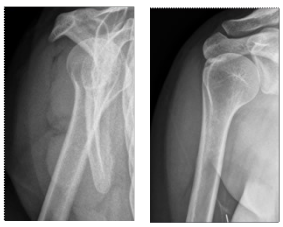
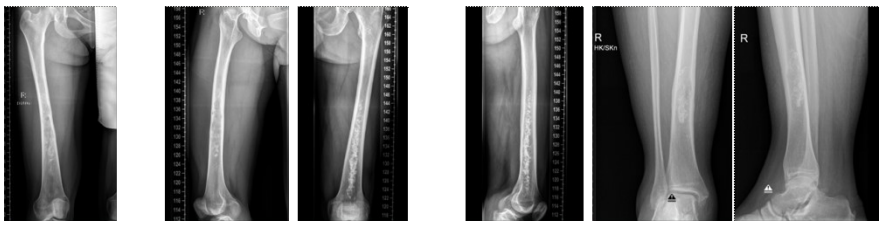
	Case 78
	
Reviewer's Diagnosis	75% Enchondroma, 25% ACT
Histology	ACT
Definite Diagnosis	**ACT**

Figure 20 Histology ACT, 75% Enchondroma on X-Ray (n=1)

One case of histopathologically verified ACT/CS G1. Three of four reviewers (3/4=75%) diagnosed EC based on x-ray. The final diagnosis remained ACT, as there was entrapment of preexistent bone trabeculae visible upon histopathological examination.

	Case 13	Case 20	Case 51
			
Reviewer's Diagnosis	100% ACT	100% ACT	100% ACT
Histology	Enchondroma	Enchondroma	Enchondroma
Definite Diagnosis	**ACT**	**ACT**	**ACT**

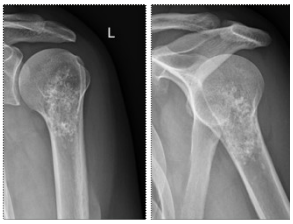
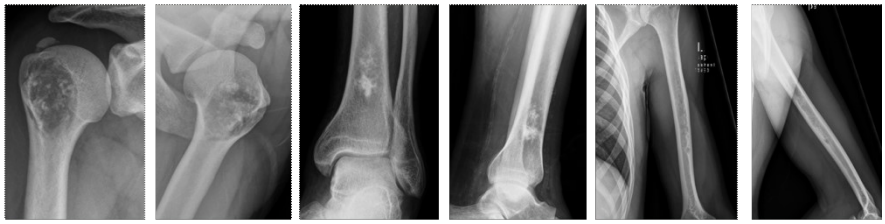
	Case 105
	
Reviewer's Diagnosis	100% ACT
Histology	Enchondroma
Definite Diagnosis	**ACT**

Figure 21 Histology Enchondroma, 100% ACT on X-Ray (n=4)

Four cases of chondrogenic lesions diagnosed as EC histopathologically, but showed signs of malignancy on x-ray. Therefore the final diagnosis was changed from EC to ACT/CS G1, as it was diagnosed by all reviewers (5/5=100%).

	Case 26	Case 35	Case 70
			
Reviewer's Diagnosis	80% ACT, 20% Enchondroma	80% ACT, 20% Enchondroma	80% ACT, 20% Enchondroma
Histology	Enchondroma	Enchondroma	Enchondroma
Definite Diagnosis	**ACT**	**ACT**	**ACT**

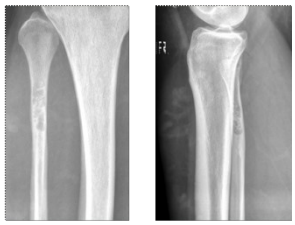
	Case 84
	
Reviewer's Diagnosis	80% ACT, 20% Enchondroma
Histology	Enchondroma
Definite Diagnosis	**ACT**

Figure 22 Histology Enchondroma, 80% ACT on X-Ray (n=4)

Four cases of chondrogenic lesions diagnosed as EC based on histopathological findings, but showed signs of malignancy on x-ray. Therefore the final diagnosis was changed from EC to ACT/CS G1, as it was diagnosed by four of five reviewers (4/5=80%).

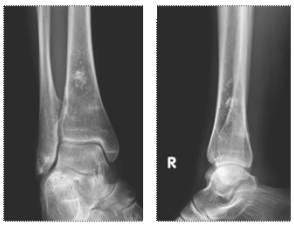
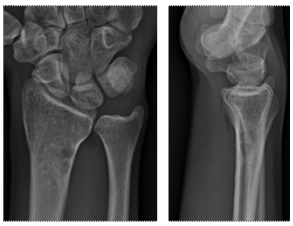
	Case 36	Case 95
		
Reviewer's Diagnosis	60% ACT, 40% Enchondroma	60% ACT, 40% Enchondroma
Histology	Enchondroma	Enchondroma
Definite Diagnosis	**ACT**	**ACT**

Figure 23 Histology Enchondroma, 60% ACT on X-Ray (n=2)

Two cases of chondrogenic lesions diagnosed as EC based on histopathological findings, but showed signs of malignancy on x-ray. Therefore the final diagnosis was changed from EC to ACT/CS G1, as it was diagnosed by three of five reviewers (3/5=60%).

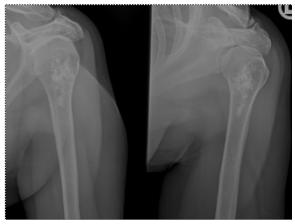
	Case 104
	
Reviewer's Diagnosis	40% ACT, 60% Enchondroma
Histology	Enchondroma
Definite Diagnosis	**ACT**

Figure 24 Histology Enchondroma, 40% ACT on X-Ray (n=1)

One chondrogenic lesion diagnosed as EC based on histopathological results, but showed signs of malignancy on x-ray. Therefore, the final diagnosis was changed from EC to ACT/CS G1.

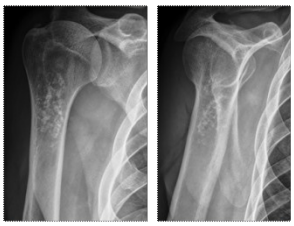
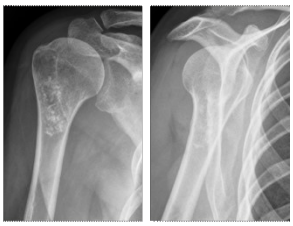
	Case 14	Case 56
		
Reviewer's Diagnosis	80% ACT, 20% Enchondroma	80% ACT, 20% Enchondroma
Histology	Enchondroma	Enchondroma
Definite Diagnosis	**Enchondroma**	**Enchondroma**

Figure 25 Histology Enchondroma, 80% ACT on X-Ray, remained EC (n=2)

In two cases of EC, four of five reviewer (4/5=80%) diagnosed ACT on x-ray. During the debriefing, no clear signs of malignancy were detected on imaging, wherefore the diagnosis remained EC, in line with histopathological results.

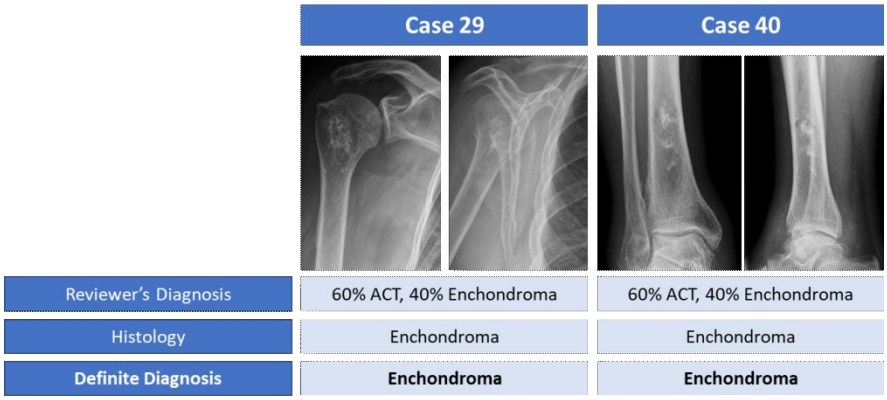


Figure 26 Histology Enchondroma, 60% ACT on X-Ray, remained EC (n=2)

In two cases of EC, three of five reviewer (3/5=60%) diagnosed ACT on x-ray. During the debriefing, no clear signs of malignancy were visible on imaging, wherefore the diagnosis remained EC, in line with histopathological results.

3 Results

3.1 Data

3.1.1 Demographic data

Gender

In total 39 (37.9%), male and 64 (62.1%) female patients were included. From the male patients, 22 (56.4%) were diagnosed with EC and 17 (43.6%) with ACT/CS G1. Out of the 64 female patients, 29 (45.3%) were diagnosed with EC and 35 (54.7%) with ACT/CS G1.

Age

The mean age in the whole study population was 48.4 ± 13.8 years. The youngest patient was 21 years old, the oldest one 83 years. The mean age of patients diagnosed with EC was 47.8 ± 12.6 years, while patients with ACTs/CSs G1 were 49.0 ± 15.0 years old on average. The youngest and oldest patients of the EC group were 22 and 83 years of age. In the ACT/CS G1 group, the youngest one was 21 years and the oldest one 78 years old.

Table 8 Patient Age (n=103)

	P25*	**P50***	**P75***	**Mean**	**SD****
EC	40.0	47.0	54.0	47.8	12.6
ATC/CS G1	40.0	47.5	58.0	49.0	15.0
Total	40.0	47.0	56.0	48.4	13.8

Age of patients in years

* $25^{th}/50^{th}/75^{th}$ percentile, ** Standard deviation

3.1.2 Localization and size

Affected bone

Concerning the 51 ECs, the most common location was the proximal humerus in 22 patients (43.1%), followed by the distal femur in 15 patients (29.4%) and the proximal fibula in 6 patients (11.8%). The most common location of the 52 ACTs/CSs G1 was the distal femur in 17 patients (32.7%), followed by the proximal humerus in 14 cases (26.9%)

and the proximal fibula as third most common location, found in 10 patients (19.2%). For less common locations see *Table 9 Affected Bone (n=103)*.

Table 9 Affected Bone (n=103)

		EC (n=51)	**ACT/CS G1 (n=52)**
Femur		16 (31.4%)	17 (32.7%)
	Proximal	*1*	*0*
	Distal	*15*	*17*
Tibia		7 (13.7%)	8 (15.4%)
	Proximal	*5*	*4*
	Distal	*2*	*4*
Fibula		6 (11.8%)	10 (19.2%)
Humerus		22 (43.1%)	16 (30.8%)
	Proximal	*22*	*14*
	Middle	*0*	*2*
Radius		0 (0.0%)	1 (1.9%)
Total		51 (100%)	52 (100%)

Lesion site

Altogether 29 (56.9%) ECs and 29 (55.8%) ACTs/CSs G1 were located on the right site, 22 (43.1%) ECs and 23 (44.2%) ACTs/CSs G1 on the left.

Lesion size

The size of the lesion was available in 102 cases (all cases of EC and 51 cases of ACT/CS G1), whilst in one case, evaluation of size was not possible due to a pathological fracture upon initial diagnosis. The smallest EC was sized 0.9 cm and the largest one 13.8 cm. Within the group of ACTs/CSs G1 1.2 cm was the smallest diameter and 20.0 cm the largest one. The mean size of all lesions was 5.7 ± 3.8 cm, with ECs being 4.9 ± 2.6 cm on average and ACTs/CSs G1 6.5 ± 4.5 cm.

Table 10 Lesion Size (n=102)

	P25*	P50*	P75*	Mean	SD**
EC	3.0	4.6	6.1	4.9	2.6
ATC/CS G1	3.5	5.0	7.9	6.5	4.5
Total	3.3	4.9	7.0	5.7	3.8

Lesion size in cm

* 25th/50th/75th percentile, ** Standard deviation

3.1.3 Clinical findings

Symptoms

Symptoms most likely caused by the lesion itself were described by 6 (11.8%) of the EC patients. No (0.0%) pathologic fractures of ECs were observed. Notably, 45 (88.2%) of the EC patients had no symptoms associated to the lesion itself. Fourteen ACT/CS G1 patients (26.9%) had lesions causing symptoms, with 12 (23.1%) reporting on pain and two (3.8%) presenting with a pathologic fracture. Of note, 29 ATC/CS G1 patients (73.1%) had no symptoms associated with the tumour itself upon presentation. ACTs/CSs G1 were per tendency more frequently associated with pain due to the lesion and pathologic fracture (p=0.101).

Table 11 Symptoms of Patients caused by the Lesion prior to Consultation (n=103)

	EC (n=51)	ACT/CS G1 (n=52)
None	45 (88.2%)	38 (73.1%)
Pain	6 (11.8%)	12 (23.1%)
Pathologic fracture	0 (0.0%)	2 (3.8%)
Total	51 (100%)	52 (100%)

Pain in the affected region

Pain in the region affected of the tumour, irrespective of its cause, was found in 37 (72.6%) of the 51 EC patients and in 39 (75.0%) of the 52 ACT/CS G1 patients (further information see below *Table 12 Patients' Symptoms (n=103)*).

Type of Pain

The type of pain and other symptoms reported by patients were assessed. For detailed evaluation see *Table 12 Patients' Symptoms (n=103)*.

Table 12 Patients' Symptoms (n=103)

Symptoms associated with the tumour (n=20)				
Symptom type	**Total Frequency**	**Percent**	**EC (n=6)**	**ACT/CS G1 (n=14)**
Load-dependent/movement-dependent pain	3	15.0%	1	2
Load-dependent/movement-dependent pain and load-independent pain	0	0.0%	0	0
Pressure pain	3	15.0%	2	1
Pressure pain and load-dependent/movement-dependent pain	3	15.0%	1	2
Night pain	1	5.0%	0	1
Night pain and load-dependent/movement-dependent pain	1	5.0%	0	1
Rest pain	1	5.0%	1	0
Constant pain	1	5.0%	1	0
Pulling pain	1	5.0%	0	1
Pulling pain and load-dependent/movement-dependent pain	0	0.0%	0	0
Diffuse stabbing pain	1	5.0%	0	1
Traumatic pain	0	0.0%	0	0
Lumboischialgia	0	0.0%	0	0
N. peroneus compression syndrome	0	0.0%	0	0

Not specified pain	3	15.0%	0	3
Pathologic fracture	2	10.0%	0	2
Total	20	100%	6	14
Symptoms due to other causes (n=56)				
Symptom type	**Total Frequency**	Percent	**EC (n=31)**	**ACT/CS G1 (n=25)**
Load-dependent/movement-dependent pain	19	33.9%	9	10
Load-dependent/movement-dependent pain and load-independent pain	1	1.8%	1	0
Pressure pain	0	0.0%	0	0
Pressure pain and load-dependent pain	1	1.8%	1	0
Night pain	0	0.0%	0	0
Night pain and load-dependent pain	3	5.4%	1	2
Rest pain	0	0.0%	0	0
Constant pain	1	1.8%	1	0
Pulling pain	1	1.8%	1	0
Pulling pain and load-dependent/movement-dependent pain	1	1.8%	1	0
Diffuse stabbing pain	0	0.0%	0	0
Traumatic pain	5	8.9%	3	2
Lumboischialgia	1	1.8%	1	0
N. peroneus compression syndrome	1	1.8%	1	0
Not specified pain	22	39.2%	11	11
Pathologic fracture	0	0.0%	0	0
Total	58	100%	37	21

Asymptomatic patients (n=27)				
	Total Frequency	**Percent**	**EC (n=14)**	**ACT/CS G1 (n=13)**
Asymptomatic	27	100%	14	13

Incidental finding

Forty-four (86.3%) cases of ECs and 42 (80.8%) ACTs/CSs G1 were incidental findings, whilst 5 (9.8%) vs. 10 (19.2%) were not. In 2 (3.9%) cases of ECs it was not clear whether the diagnosis was made on an incidental basis.

Other symptoms/diseases

In case tumours had been detected incidentally it was investigated which other symptoms or diseases led to the diagnosis. For exact symptoms or diseases see *Table 13 Other Symptoms/Diseases of Patients included (n=86)* below.

Table 13 Other Symptoms/Diseases of Patients included (n=86)

	EC (n=44)	**ATC/CS G1 (n=42)**	**Total (n=86)**
Degenerative change	4 (9.1%)	3 (7.1%)	7 (8.1%)
Arthrosis	*2*	*3*	*5*
Suspected periarthropathia subscapularis	*1*	*0*	*1*
Other degenerative changes	*1*	*0*	*1*
Inflammatory changes	2 (4.6%)	1 (2.4%)	3 (3.5%)
Bursitis	*2*	*0*	*2*
Peritendinitis	*0*	*1*	*1*
In the context of surgery	3 (6.8%)	2 (4.8%)	5 (5.8%)
Total Knee Arthroplasty	*1*	*1*	*2*
Medial patellofemoral ligament (MPFL) reconstruction	*1*	*0*	*1*
Planning of knee replacement surgery	*0*	*1*	*1*
Pre-surgical examination in case of biceps tendon	*1*	*0*	*1*

rupture			
Impingement syndrome	3 (6.8%)	2 (4.8%)	5 (5.8%)
Luxation	0 (0.0%)	2 (4.8%)	2 (2.3%)
Patellar luxation	*0*	*1*	*1*
Shoulder luxation	*0*	*1*	*1*
Meniscus symptoms	2 (4.6%)	3 (7.1%)	5 (5.8%)
Neurologic symptoms	3 (6.8%)	0 (0.0%)	3 (3.5%)
Ischialgia	*1*	*0*	*1*
N. peroneus compression syndrome	*1*	*0*	*1*
Suspected N. peroneus lesion	*1*	*0*	*1*
Trauma	10 (22.7%)	7 (16.7%)	17 (19.8%)
Examination due to other diseases, not primary musculoskeletal	2 (4.6%)	3 (7.1%)	5 (5.8%)
Scintigraphy due to mamma carcinoma	*2*	*2*	*4*
Thrombosis	*0*	*1*	*1*
Unspecific pain	6 (13.6%)	13 (31.0%)	19 (22.1%)
Joint complains	*0*	*1*	*1*
Knee joint pain	*3*	*6*	*9*
Lower leg pain and intraosseous lipoma	*0*	*1*	*1*
Shoulder and neck pain	*0*	*1*	*1*
Shoulder pain	*3*	*3*	*6*
Ankle joint pain other leg	*0*	*1*	*1*
Others	9 (20.4%)	3 (7.1%)	12 (14.0%)
Chondropathia	*1*	*0*	*1*
Ganglion	*0*	*1*	*1*
Calcifying tendinitis of the shoulder	*1*	*0*	*1*
Check-up due to leg length difference	*0*	*1*	*1*
Rehabilitation	*1*	*0*	*1*

Lipoma	*1*	*0*	*1*
Rip fracture without trauma	*1*	*0*	*1*
Rotator cuff rupture	*1*	*0*	*1*
Lesion of the supraspinatus tendon	*2*	*0*	*2*
Orthopaedic shoe supply	*0*	*1*	*1*
Spine complaints	*1*	*0*	*1*
Incidental finding (not specified)	0 (0.0%)	3 (7.1%)	3 (3.5%)
Total	44 (100%)	42 (100%)	86 (100%)

Lesion known longer

Thirty-two of all lesions were known longer – 21 (41.2%) ECs vs. 11 (21.2%) ACTs/CSs. On the other hand, 71 lesions had been recently diagnosed, compromising 30 (58.8%) ECs and 41 (78.8%) CSs.

Time since diagnosis

The mean time from diagnosis to biopsy/surgery of ECs was 39.1 ± 49.2 months and the one for ACTs/CSs G1 was 33.0 ± 25.4 months on average. Overall, both ECs and ACTs/CSs G1 were known for 37.0 ± 42.1 months on average, respectively, prior intervention. The shortest time period between diagnosis and biopsy/surgery was 5.0 months for ECs and 6.0 months for ACTs/CSs, whereas the longest time period was 167.0 and 69.0 months.

Multiple lesions

Multiple lesions were not present in any patient diagnosed with EC. In three (5.8%) patients diagnosed with ACTs/CSs G1, one more lesion was found during examination. Another ACT/CS G1 patient (1.9 %) was diagnosed with Mb. Ollier, prior to the diagnosis of the ACT/CS G1.

3.1.4 Biopsy and therapy

Biopsy only was performed in 4 (7.8%) cases of ECs and none (0.0%) of the ACTs/CSs G1. Thirty-seven (72.6%) EC patients and 28 (53.8%) ACT/CS G1 patients underwent surgery and 10 (19.6%) vs. 24 (46.2%) patients underwent biopsy followed by definite surgery.

Table 14 Biopsy/Surgery (n=103)

	EC (n=51)	ACT/CS G1 (n=52)
Biopsy	4 (7.8%)	0 (0.0%)
Surgery	37 (72.6%)	28 (53.8%)
Biopsy and surgery	10 (19.6%)	24 (46.2%)
Total	51 (100%)	52 (100%)

Type of surgery

Within the 47 EC patients who underwent surgery, 46 (97.9%) were treated by curettage and one (2.1%) received a total knee arthroplasty. From 52 ACT/CS patients, 47 (90.3%) underwent curettage, two (3.9%) received a total knee arthroplasty after curettage of the lesion, two (3.9%) underwent marginal resection and one patient (1.9%) had a wide resection followed by reconstruction with a proximal humerus tumour-endoprosthesis.

Table 15 Type of Surgery (n=99)

	EC (n=47)	ACT/CS G1 (n=52)
Curettage	46 (97.9%)	47 (90.3%)
Total knee arthroplasty	1 (2.1%)	2 (3.9%)
Resection	0 (0.0%)	2 (3.9%)
Wide resection and tumour-endoprosthesis	0 (0.0%)	1 (1.9%)
Total	47 (100%)	52 (100%)

Re-biopsy/Re-surgery

One (2.0%) EC and one (1.9%) ACT/CS G1 patient underwent a re-biopsy. Moreover, one (2.0%) EC patients and one (1.9%) ACT/CS G1 patient had a second surgery.

Table 16 Re-biopsy/Re-surgery and Type of Re-surgery of Patients included (n=103)

	EC (n=51)	ACT/CS G1 (n=52)
None	49 (96.0%)	50 (96.2%)
Re-biopsy	1 (2.0%)	1 (1.9%)
Re-surgery	1 (2.0%)	1 (1.9%)
Infection-related	*1*	*0*
Resection	*0*	*1*
Total	51 (100%)	52 (100%)

Type of re-surgery

One patient with EC underwent a second surgery due to an infection developing 12 month after primary surgery (where he received a total knee arthroplasty). The one ACT/CS G1 patient undergoing another surgery was treated by resection 4 months after curettage because of a residual tumour.

3.1.5 Imaging

MRI

MRI was performed in 50 (98.0%) EC cases and in all 52 (100%) ACT/CS G1 cases.

CT

Ten (19.6%) EC patients and 12 (23.1%) ACT/CS G1 patients had undergone CT-scan.

Bone scintigraphy

Altogether, 30 (58.8%) patients diagnosed with EC and 31 (59.6%) patients with ACT/CS G1 had undergone scintigraphy.

Table 17 MRI, CT, Scintigraphy (n=103)

	EC (n=51)	**ACT/CS G1 (n=52)**
MRI	50 (98.0%)	52 (100%)
CT	10 (19.6%)	12 (23.1%)
Bone scintigraphy	30 (58.8%)	31 (59.6%)

3.1.6 Follow-Up

Residual/Recurrent tumour

In one (2.3%) out of 44 cases of EC, a recurrent tumour was detected. In three (6.0%) out of 50 ACT/CS G1 cases a recurrent (n=1) or residual (n=2) tumour was found. Taking all lesions together, 2 (2.1 %) out of 94 patients experienced local recurrence and in 2 (2.1 %) cases a residual tumour was found.

Duration until the residual/recurrent lesion was detected

The mean time until recurrent or residual tumours were detected was 10.0 ± 10.6 months. For residual tumours, the time between surgery and detection was 0 month and 4 months (ACT/CS G1). The two recurrent tumours were detected after 12 (EC) and 24 months (CS).

Table 18 Duration until residual/recurrent Lesion was detected (n=4)

	EC (n=1)	**ACT/CS (n=3)**	**Mean time**
Residual tumour	/	2 (0 months, 4 months)	2.0 ± 2.8 months
Recurrent tumour	1 (12 months)	1 (24 months)	18.0 ± 8.5 months
Mean time	12.0 months	9.3 ± 12.9 months	10.0 ± 10.6 months

Type of follow-up

Forty-seven (92.1%) EC patients underwent radiological follow-ups, as did 50 (96.2%) ACT/CS G1 patients. Three (5.9%) patients with EC vs. one (1.9%) of the patients with ACT/CS G1 had a clinical follow-up only, whilst one patient in each group (2.0 % and 1.9%) had no follow up at all.

Duration of follow-up

The mean duration time was 40.2 ± 35.6 months, the shortest follow-up time was 1 month, the longest 134 months. For the 47 EC patients the mean duration time was 29.3 ± 30.9 months, with 1 month shortest and 120 months longest time period, whilst 50 ACT patients wear followed-up 50.5 ± 36.9 months on average, with also 1 month shortest and 134 months longest time period.

Table 19 Duration of Follow-up

	P25*	P50*	P75*	Mean	SD**
EC	6.0	16.0	49.0	29.3	30.9
ATC/CS G1	15.0	42.5	86.0	50.5	36.9
Total	13.0	30.0	59.0	40.2	35.6

Duration of follow-up in months

* $25^{th}/50^{th}/75^{th}$ percentile, ** Standard deviation

3.1.7 Final Status

Fifty (98.0%) patients with EC and all 52 (100%) patients with ACT/CS G1 were still alive. At latest follow-up, 90 patients had not experienced any recurrence (87.4%), 4 patients had developed recurrence or had a residual tumour (3.9%) and 9 patients either had no adequate follow-up or had not undergone surgery (biopsy only; 8.7%). The death of one patient (without recurrence during follow-up) was not associated to the EC or its treatment.

3.2 X-ray and MRI

Intraclass correlation coefficient

Overall, interobserver reliability for individual features was rather poor (see *Table 20 Intraclass Correlation Coefficient for X-ray and MRI-features for the four Reviewers (X-ray n=103, MRI n=25)*). The highest interobserver reliability between reviewers was observed for assessment of tumour location on MRI scans (ICC: 0.95). Interobserver reliability was still good for tumour location as assessed on x-rays (ICC: 0.79). Concerning cortex-arrosion there was good agreement between reviewers both regarding several features and yes/no (0.83 vs 0.80). Good agreement between reviewers was also present for final diagnosis based on x-ray (ICC: 0.75), whilst it was even poor when diagnosis was made on MRI-scans (ICC: 0.43).

Table 20 Intraclass Correlation Coefficient for X-ray and MRI-features for the four Reviewers (X-ray n=103, MRI n=25)

	Intraclass Correlation Coefficient (based on **t**wo-way random effects models)
X-ray	
Tumour location (Epi-/Meta-/Diaphysis)	0.79
Zone of transition	0.26
Bone destruction (several features)	0.14
Bone destruction (no/yes)	0.01
Cortex-arrosion (several features)	0.83
Cortex-arrosion (no/yes)	0.80
Periosteal reaction (several features)	0.16
Periosteal reaction (no/yes)	0.31
Soft-tissue shadow (no/yes)	N/A
Calcification (several features)	0.30
Calcification (no/yes)	0.57
Diagnosis (EC vs. ACT/CS G1)	0.75
MRI	
Tumour location (Epi-/Meta-/Diaphysis)	0.95
Bone destruction (several features)	N/A
Bone destruction (no/yes)	N/A
Cortex-arrosion (no/yes)	0.55
Cortical thickening	N/A
Periosteal reaction (several features)	0.48
Periosteal reaction (no/yes)	0.49
Soft-tissue shadow (no/yes)	0.65
Signal intensity T1 (low signal intensity vs. high signal intensity)	N/A
Signal intensity T2 (low signal intensity vs. low signal intensity)	N/A
Contrast enhancement	N/A
Peritumoral oedema (no/yes	0.50

Soft-tissue oedema (no/yes)	0.57
Diagnosis (EC vs. ACT/CS G1)	0.43
Legend N/A – ICC not calculated as too few cases assessed by reviewers Colours: green – excellent agreement; yellow – good agreement; red – moderate agreement; grey – poor agreement	

Overall accuracy of the different features

For overall accuracy of the different features, see *Table 21 Overall Accuracy of Features analysed by Reviewers (x-ray n=103, MRI n=25)*.

Table 21 Overall Accuracy of Features analysed by Reviewers (x-ray n=103, MRI n=25)

Feature	**X-ray**	**MRI**
Tumour location		
Epiphysis	4.9%	3.1%
Epi-/Metaphysis	0.0%	4.1%
Metaphysis	55.6%	42.8%
Meta-/Diaphysis	1.0%	16.3%
Diaphysis	38.5%	33.7%
Zone of transition		
Defined border	9.5%	-
Defined border and Diffuse	0.3%	-
Diffuse	41.4%	-
Sclerotic	8.1%	-
Lytic	40.7%	-
Bone destruction		
No	34.4%	33.3%
Yes	65.6%	66.7%
Geographic	35.3%	59.6%
Geographic and Moth-eaten	0.0%	1.0%
Permeative	14.5%	0.0%
Permeative and Moth-eaten	0.3%	0.0%
Moth-eaten	15.5%	6.1%

Cortex-arrosion		
No	55.2%	28.3%
Yes	44.8%	71.7%
Focal	35.3%	61.6%
Focal and Continuously	0.8%	0.0%
Continuously	8.7%	10.1%
Periosteal reaction		
No	98.5%	87.9%
Yes	1.5%	12.1%
Continuously	1.0%	11.1%
Discontinuously	0.5%	1.0%
Soft-tissue shadow		
No	98.5%	93.9%
Yes	1.5%	6.1%
Calcification		
No	4.9%	-
Yes	95.1%	-
Popcorn-like	36.5%	-
Popcorn-like and Irregular	1.0%	-
Popcorn-like and Stipples	2.2%	-
Irregular	37.5%	-
Stipples and Irregular	1.7%	-
Stipples	16.2%	-
Cortical thickening		
No	-	97.0%
Yes	-	3.0%
Signal intensity T1		
Low	-	98.9%
High	-	1.1%
Signal intensity T2		
Low	-	2.0%
High	-	98.0%

Contrast enhancement		
No	-	4.7% (4.8%*)
Yes	-	94.1% (95.2%*)
No contrast agent used	-	1.2%
Peritumoral oedema		
No	-	79.8%
Yes	-	20.2%
Soft-tissue oedema		
No	-	91.9%
Yes	-	8.1%
Diagnosis		
EC	57.7%	45.5%
ACT/CS G1	42.3%	54.5%

* "No contrast agent used" excluded

Diagnosis overall accuracy

Of all diagnoses made based on x-ray, on average 65.9% corresponded with the final diagnosis, with the accuracy of different reviewers ranging between 59.8% and 72.8%. Regarding the diagnosis EC, the overall accuracy was 73.9% and regarding the diagnosis ACT/CS G1 58.1%. On MRI, 66.7% of the diagnoses were in accord with the final diagnosis, with the lowest percentage of correct diagnosis by a single reviewer being 54.0% and the highest one 80.0%. The overall accuracy regarding EC diagnoses was 60.7% and regarding ACT/CS G1 diagnoses 74.4%.

Table 22 Diagnosis Accuracy by Reviewers based on X-ray and MRI (x-ray n=103, MRI n=25)

X-ray				
	Consistent with final diagnosis	**Inconsistent with final diagnosis**	**NA**	**% Correct***
Reviewer A	68	32	3	68.0%
Reviewer B	62	41	0	60.2%
Reviewer C	71	32	0	68.9%
Reviewer D	61	41	1	59.8%
Reviewer E	75	28	0	72.8%
Overall Accuracy	337	174	4	65.9%
MRI				
	Consistent with final diagnosis	**Inconsistent with final diagnosis**	**NA**	**% Correct***
Reviewer A	13	12	0	52.0%
Reviewer B	18	7	0	72.0%
Reviewer C	15	9	1	62.5%
Reviewer D	20	5	0	80.0%
Overall Accuracy	66	33	1	66.7%

* Correct / (Correct + Wrong); “NA” excluded

Reviewer sensitivity and specificity

On x-ray the sensitivity ranged from 79.6% to 85.4% with an overall sensitivity of 83.1%, whilst on MRI the sensitivity lied between 86.2% and 92.9% with an overall sensitivity of 89.3%. Specificity was low with an overall specificity of 29.7% on x-ray (23.9% lowest, 33.6% highest) and 28.0% on MRI (21.7% lowest, 37.7% highest).

Table 23 Reviewer Sensitivity and Specificity, X-ray and MRI (x-ray n=103, MRI n=25)

Sensitivity		
Reviewer	**X-ray**	**MRI**
Reviewer A	85.4%	86.2%
Reviewer B	81.8%	86.9%
Reviewer C	83.6%	92.9%
Reviewer D	79.6%	91.3%
Reviewer E	85.1%	-
Overall	83.1%	89.3%
Specificity		
Reviewer	**X-ray**	**MRI**
Reviewer A	23.9%	21.7%
Reviewer B	30.2%	22.3%
Reviewer C	31.2%	30.4%
Reviewer D	29.5%	37.7%
Reviewer E	33.6%	
Overall	29.7%	28.0%

3.2.1 X-ray

Epi-/Meta-/Diaphysis

The main localization of ECs within the bone was the meta-/diaphysis, with 24 cases (47.1%), followed by the metaphysis in 13 cases (25.5%). ACTs/CSs G1 were also most frequently found in the meta-/diaphysis in 23 (44.2%) cases. The second most common location was the diaphysis in 11 cases (21.2%). For further details see *Table 24 X-ray Epi-/Meta-/Diaphysis (n=103)*.

Table 24 X-ray Epi-/Meta-/Diaphysis (n=103)

	EC (n=51)	ACT/CS G1 (n=52)
Epiphysis	0 (0.0%)	0 (0.0%)
Epi-/Metaphysis	7 (13.7%)	7 (13.5%)
Metaphysis	13 (25.5%)	10 (19.2%)
Meta-/Diaphysis	24 (47.1%)	23 (44.2%)
Diaphysis	6 (11.8%)	11 (21.2%)
Epi-/Meta-/Diaphysis	1 (2.0%)	1 (1.9%)
Total	51 (100%)	52 (100%)

Zone of transition

In 18 (35.3%) EC cases and 16 (30.8%) ACT/CS G1 cases there was no agreement between the reviewers whether the lesions' border was well- or ill-defined. A well-defined zone of transition was seen in 23 (45.1%) ECs and 23 (44.2%) ACTs/CSs G1, whilst it was ill-defined in 10 (19.6%) ECs and 13 (25.0%) ACTs/CSs G1.

Table 25 X-ray Zone of Transition (n=103)

	EC (n=51)	ACT/CS G1 (n=52)
Diffuse	16 (31.4%)	21 (40.4%)
Diffuse and Lytic	12 (23.5%)	8 (15.4%)
Lytic	11 (21.6%)	15 (28.8%)
Sclerotic	6 (11.7%)	2 (3.9%)
Sclerotic and Lytic	0 (0.0%)	1 (1.9%)
Defined border	3 (5.9%)	1 (1.9%)
Multiple features assessed*	3 (5.9%)	4 (7.7%)
Total	51 (100%)	52 (100%)

* in case every reviewer chose a different feature

Bone destruction

This feature was seen in 26 (50.9%) cases of EC and 36 (69.2%) cases of ACT/CS G1. In 1 (2.0%) cases of EC and in 3 (5.8%) cases of ACT/CS G1 there was no bone destruction at

all. In the remaining cases – 24 (47.1%) ECs vs. 13 (25.0%) ACTs/CS G1 – there was no agreement between the reviewers. Further features below.

Table 26 X-ray Bone Destruction (n=103)

	EC (n=51)	**ACT/CS G1 (n=52)**
None	1 (2.0%)	3 (5.8%)
No agreement	24 (47.1%)	13 (25.0%)
Yes (no agreement)*	4 (7.8%)	7 (13.5%)
Geographic	17 (33.3%)	13 (25.0%)
Geographic and Permeative	0 (0.0%)	2 (3.8%)
Geographic and Moth-eaten	0 (0.0%)	2 (3.8%)
Permeative	1 (2.0%)	3 (5.8%)
Moth-eaten	4 (7.8%)	9 (17.3%)
Total	51 (100%)	52 (100%)

* in case > 50% of the reviewer chose a type of bone destruction, but all types equal.

Cortex-arrosion

No cortex arrosion was seen in 34 (66.6%) of all ECs and 19 (36.6%) ACTs/CSs G1, whilst it was present in 9 (17.7%) EC cases and 27 (51.9%) ACT/CS G1 cases. In 14 cases – 8 (15.7%) ECs and 6 (11.5%) ACTs/CSs G1 – no agreement could be made. The exact main features are listed below.

Table 27 X-ray Cortex-Arrosion (n=103)

	EC (n=51)	**ACT/CS G1 (n=52)**
None	34 (66.7%)	19 (36.6%)
No agreement	8 (15.7%)	6 (11.5%)
Yes (no agreement)*	1 (2.0%)	4 (7.7%)
Focal	8 (15.7%)	19 (36.5%)
Continuous	0 (0.0%)	4 (7.7%)
Total	51 (100%)	52 (100%)

* in case > 50% of the reviewer chose a type of bone destruction, but all types equal.

Periosteal reaction

Regarding this feature, most of the time there was no periosteal reaction seen by the reviewers. This applies to all (100%) cases of ECs and nearly all (98.1%) cases of ACTs/CSs G1, where in one (1.9%) case a reaction of the periosteum was seen, but the reviewer could not decide whether it was a continuous or discontinuous periosteal reaction.

Soft-tissue shadow

No soft-tissue shadow in any EC or ACT/CS G1 cases was seen.

Calcification

Calcification was present in nearly all lesions, with 48 (94.1%) cases of EC and 49 (94.3%) cases of ACT/CS G1. Only in two (3.8%) ACT/CS G1 patients, no calcification was seen. In three (5.9%) cases of EC and one (1.9%) case of ACT/CS G1, there was no agreement between the reviewers.

Table 28 X-ray Calcification (n=103)

	EC (n=51)	**ACT/CS G1 (n=52)**
None	0 (0.0%)	2 (3.8%)
No agreement	3 (5.9%)	1 (1.9%)
Yes (no agreement)*	1 (2.0%)	0 (0.0%)
Popcorn-like	22 (43.2%)	17 (32.7%)
Popcorn-like and Irregular	5 (9.8%)	6 (11.5%)
Popcorn-like and Stipples	2 (3.9%)	2 (3.9%)
Irregular	9 (17.6%)	18 (34.6%)
Stipples and Irregular	2 (3.9%)	4 (7.7%)
Stipples	7 (13.7%)	2 (3.79%)
Total	51 (100%)	52 (100%)

* in case > 50% of the reviewer chose a type of bone destruction, but all types equal.

3.2.2 MRI

Epi-/Meta-/Diaphysis

Similar to the x-ray findings, meta-/diaphysis was the most frequent localization for EC (n=7; 50.0%) and ACT/CS G1 (n=5; 45.4%). For further locations, see Table below.

Table 29 MRI Epi-/Meta-/Diaphysis (n=25)

	EC (n=14)	ACT/CS G1 (n=11)
Epiphysis	0 (0.0%)	0 (0.0%)
Epi-/Metaphysis	1 (7.2%)	2 (18.2%)
Metaphysis	3 (21.4%)	1 (9.1%)
Meta-/Diaphysis	7 (50.0%)	5 (45.4%)
Diaphysis	3 (21.4%)	2 (18.2%)
Epi-/Meta-/Diaphysis	0 (0.0%)	1 (9.1%)
Total	14 (100%)	11 (100%)

Bone destruction

In 8 (57.1%) cases of EC and 9 (81.8%) cases of ACT/CS G1, a destruction of the bone was noticed. In all 8 EC cases, the destruction was geographic, whilst in the ACTs/CSs G1, 8 lesions showed a geographic destruction and one a geographic and moth-eaten type of destruction. In the remaining 8 cases – 6 (42.9%) ECs and two (18.2%) ACT/CS G1 – there was no agreement between the reviewers regarding presence or absence of bone destruction.

Cortex-arrosion

The majority of tumours showed a cortex-arrosion on MRI, with 8 (57.2%) cases of EC and 9 (81.8%) cases of ACT/CSs G1. On the other hand, three (21.4%) EC cases and two (18.2.0%) ACT/CS G1 cases did not show any cortical arrosion, whilst in three (21.4%) vs. none (0.0%) EC vs. ACT/CS G1 cases, there was no agreement about that feature between the reviewers. See *Table 30 MRI Cortex-Arrosion (n=25)* below.

Table 30 MRI Cortex-Arrosion (n=25)

	EC (n=14)	ACT/CS G1 (n=11)
None	3 (21.4%)	2 (18.2%)
No agreement	3 (21.4%)	0 (0.0%)
Yes (no agreement)*	0 (0.0%)	1 (9.1%)
Focal	8 (57.2%)	7 (63.6%)
Continuous	0 (0.0%)	1 (9.1%)
Total	14 (100%)	11 (100%)

* in case > 50% of the reviewer chose a type of bone destruction, but all types equal.

Cortical thickening

There was no cortical thickening present on MRI in any EC or ACT/CS G1.

Periosteal reaction

Regarding ACTs/CSs G1, a continuous periosteal reaction was found in one (9.1%) case. In 7 (63.6%) cases, there was no reaction of the periosteum seen and in three (27.3%) case, there was no agreement about this feature. On the MRIs of EC patients no periosteal reaction was seen in 13 (92.9%) cases and in the remaining (7.1%) case, the reviewer did not agree about presence or absence of periosteal reaction.

Soft-tissue shadow

This feature was seen in one (9.1%) case of ACT/CS G1. In two (18.2%) cases of ACT/CS G1, there was no agreement whether a soft-tissue is seen or not. In the other cases – 14 (100%) vs. 8 (72.7%) – the feature was not present on MRI.

Signal intensity T1-weighted

On T1-weighted MRIs, 13 (92.9%) out of 14 ECs and 10 (90.9%) out of 11 ACTs/CSs G1 showed a high signal intensity. In the other two cases (one EC and one ACT/CS G1) this feature was not assessable.

Signal intensity T2-weighted

All 14 (100%) ECs and all 11 (100%) ACTs/CSs G1 showed a low signal intensity on T2-weighted MRIs.

Contrast enhancement

12 (85.8%) of all ECs and 10 (90.9%) ACTs/CSs G1 showed contrast enhancement. In one (7.1%) case of EC and one (9.1%) case of ACT/CS G1, the feature was not assessable. The reviewer could not agree in one (7.1%) case of EC whether contrast enhancement was present or not.

Peritumoral oedema

In one EC (7.1%) and one ACT/CS G1 (9.1%) case, a peritumoral oedema was detected. In 3 (27.3%) ACTs/CSs G1, the reviewer did not agree upon presence or absence of peritumoral oedema. In the remaining 13 (92.9%) ECs and 7 (63.6%) ACTs/CSs G1, no oedema surrounding the tumour was seen.

Soft-tissue oedema

Only in one (9.1%) case of ACT/CS G1 a soft-tissue oedema could be seen on MRI. Two reviewers noted that this feature was most likely seen because of a concomitant pathologic fracture.

4 Discussion

Apart from clinical features, radiological parameters to distinguish between EC and ACT on x-ray and MRI were evaluated in this diploma thesis by four independent reviewers. Furthermore, lesions were diagnosed on x-ray by five independent reviewers. Over all radiographic features, the interobserver reliability between the reviewers was rather poor. Other studies reported on a high interobserver variability than herein observed (14, 53), even though in the study by Crim et al. examples of the features had been reviewed together by the reviewers beforehand, which may have increased the overall accuracy (53). In our study, on the other hand, reviewers were both blinded to the diagnosis and had to independently assess each x-ray and MRI scan, thus not allowing reviewers to reach an agreement in advance. The overall accuracy between reviewers regarding the final diagnosis was good with 65.9% on x-ray and only slightly better for MRI (66.7%). This is a surprising finding, as MRI is generally assumed to be of greater value for distinguishing between the two tumour entities. In general, the overall accuracy was better when it comes to diagnosing ECs on x-ray, amounting to 73.9%. On the other hand, for ACTs/CSs G1, an accuracy of 58.1% was reached based on x-ray only. In other words, a greater chance of misdiagnosing histopathological confirmed ACT/CS G1s as ECs was present when using x-ray only. On MRI it was the other way round, with ECs being diagnosed correctly in 60.7% and ACTs/CS G1 in 74.2%. This difference between x-ray and MRI can be explained due to the fact that signs of malignancy are more easily detected in MRI than on two-dimensional x-ray images, where, for example, scalloping could be missed. Therefore it is easier to identify an ACT/CS G1 on MRI, but this imaging also leads to a higher rate of overdiagnosed ECs, compared to x-ray.

Regarding the pre-defined radiographic features that could be evaluated by the reviewers on x-ray and MRI, cortex-arrosion as assessed on x-ray was of statistically significance to distinguish between EC and ACT/CS G1 ($p=0.001$). Regarding the lesion's size in long bones, a significant overlap between ECs and ACTs/CS G1 has been reported (14). This corresponds to our findings of ACTs/CSs G1 being only slightly greater in size on average than ECs (6.5 ± 4.5 cm vs. 4.9 ± 2.6 cm). Nevertheless, the difference between EC and ACT/CS G1 regarding size shows significance ($p=0.0282$). But it has to be considered, that a greater size may lead to over-diagnosing of an EC as ACT/CS G1, especially if no other features of malignancy are present. For example, Kendell et al (66) discovered that 20% of ECs had a size greater than 4 cm as only a sign of malignancy, even though it has to be

taken into account that in their study only lesions of the fibula were included. The difference in size was, nevertheless, also statistically significant in their study.

The other features did not reach statistical significance to distinguish between EC and ACT/CS G1, primary due to the high interobserver variability mentioned earlier and therefore frequent disagreement between the reviewers regarding the type of particular features (e.g. “geographic” or “permeative” or “moth-eaten bone destruction) as well as whether the feature was present or not (e.g. bone destruction “yes” or “no”).

Regarding ACT/CS G1, no soft-tissue shadow was seen on x-ray and only in one case on MRI. Similar results have been shown by Ferrer-Santacreu et al. with no soft-tissue mass being present on CT or MRI in their study involving both EC and ACT/CS G1(20). Even though different authors report on a soft-tissue mass being a distinguishing feature for ECs and CSs (2, 6), this may not apply to ACTs/CSs G1, as it seems to be a feature presenting only very rarely in this well differentiated tumour. Varma et al., for example, reported on soft-tissue mass to be a feature not found in low-grade lesions (not stated if G2 CS was included in “low-grade”), but being present in higher-grade ones (19). Geirnaerdt et al. (14) showed slightly higher rates for this feature on radiographs, with 11% of ECs and 16% of ACTs/CSs G1 displaying it causing a non-significant difference between EC and ACT/CS G1 in their study.

According to Janzen et al. abnormal peritumoral and soft-tissue signals on MRI on STIR sequences are an important feature for distinguishing between EC and CS. Regarding abnormal peritumoral signals, all CSs – G2 and G3 – presented this feature, while none of the ECs did (18). On T2-weighted MRI, only some of the CSs showed abnormal peritumoral signals (18). In our study, as assessed by the reviewers, one (7.1%) EC and only one (9.1%) ACT/CS G1 depicted peritumoral oedema. Consequently, on conventional T1-weighted and T2-weighted MRIs, peritumoral oedema may not be a reliable feature to distinguish between ECs and ACTs/CSs G1, whilst on STIR-sequences – like on the study of Janzen et al. – it may as well be, even though it has to be taken into account that only CS G2 and G3 were included in Janzen’s study (18).

In our study, 56.9% of ECs and 67.3% of ACTs/CSs G1 were found in females, 43.1% vs. 32.7% in males, which contradicts literature, since both gender should be equally affected when it comes to EC, and a male gender slightly preferred in case of CSs (1, 2). Crim et al. reported even a higher preference of female gender in ECs (F:M ratio 13:3), whilst on the

other hand males and females are equally affected by ACTs/CSs G1 (53). However, Ferrer-Santacreu et al. showed higher rates for female patients in both ECs (74.7%) and ACTs/CSs G1 (76.5%) (20). Notably, this finding – similar to the one reported by Crim et al. and Ferrer-Santacreu et al. – has low validity, as the study population herein analysed is a selected one treated at a single tumour centre, thus not necessarily depicting the entire population.

The mean age in our study was almost similar between ECs and ACTs/CSs G1 (47.8 vs. 49.0 years), with similar data collected by Crim et al. (49.9 vs. 50.0 years) (53). This is an interesting finding, considering that according to literature, there should be a larger gap, with about 1 decade difference, between the EC and CS patients (6). The fact that the mean age between EC and ACT/CS G1 is similar in our study, may be due to the natural exclusion of higher-grade CSs (G2/3). According to Breitenseher et al. and Greenspan et al., ECs are often found before the 4^{th} decade, with a peak between the 2^{nd} and 4^{th} decade (2, 7). EC patients in our study are per tendency older than the typical age for this group. This could be due to the fact that some patients were diagnosed very late due to asymptomatic lesions. Another reason for the discrepancy in age may be statistical outliers; for example, the oldest patient diagnosed with EC was 83 years old. Furthermore our study only included ECs of long bones. On the other hand, ECs in short tubular bones (which is the most common affected location) tend to be symptomatic more often and therefore may be diagnosed earlier (2).

In our study, neither demographic data nor location of the tumour or tumour size were statistically relevant features for differentiating between EC and ACT/CS G1.

There was no significant difference regarding clinical presentation, with EC patients presenting with pain related to the lesion itself in 11.8% compared to 23.1% of the ACT/CS G1 patients, and 3.9% of the ACT/CS G1 patients showing pathological fracture. Previous studies, on the other hand, noted, that pain related to the lesion is in fact a significant feature for distinguishing between EC and ACT/CS G1. Douis et al. (4) (11.1% ECs vs. 60% ACTs/CS G1 vs. 87.5% higher grade CSs) and Murphey et al. (6) reported on more painful tumours (75% EC vs. 95% CSs) than found in our study. The different percentage may be due to the fact that it is rather difficult to evaluate if the pain is due to the lesion or caused by other pathologies. Furthermore, it has to be taken into account that not all studies differentiated between ACTs/CSs G1 and higher-grade CSs.

Reported results concerning follow-up and relapsed/residual tumours may be of low value, due to an often rather short time period of follow-up. In our study, the mean follow-up amounted to 40.2 ± 35.6 months. During that period, 2.1% of patients experienced a local recurrence.

4.1 Limitations

The greatest weakness of the present study was its retrospective nature. Some findings were incomplete and data could not be collected entirely. For example, type or exact region of pain was often not stated in the clinical finding. Also some images, x-ray and MRI, were not optimised, as noted by some reviewers.

Regarding symptoms, it was difficult to identify whether the pain was caused by the tumour itself or by other diseases. The fact that there was often no accurate documentation and no diagnostic findings from other institutions, made it even more complicated. Herein, we decided to rate pain that could be explained by presence of other radiological or clinical signs (e.g. preceding trauma, impingement syndrome or osteoarthritis) as not related to the chondromatous lesion itself. The problem thereby is, however, that pain without another cause identified – even if just because there is no further documentation – was accounted for symptoms caused by the tumour.

The different approach in patients, biopsy only or definite surgery may be a limiting factor concerning the validity of the histologic diagnoses. When biopsy only is performed, rather a small part of the tumour is used for histopathological examination. However, the tumour may be heterogeneous and contain areas with differing signs of malignancy and thus varying grading. Thus, it is possible for some ACTs/CSs G1 to be misdiagnosed as ECs, as the biopsy did not catch the parts with the malignant transformation. De Camargo et al. reported an agreement between grading of the biopsied specimen and grading of the resected specimen in 60% of ACTs/CSs G1 and CSs G2 (41).

5 Conclusion

Differentiation between EC and ACT/CS G1 based on radiographs is difficult, especially if no other data like clinical or histological findings are given. Nevertheless, there are some potential features to identify ACTs/CSs G1 out of ECs, like cortex-arrosion, a soft-tissue mass or peripheral oedema, although the absence of these features does not exclude an ACT/CS G1.

In our study, there was a considerable interobserver variability between the five reviewers regarding x-ray based diagnosis of the lesions, as well as between the four reviewers regarding lesions' radiological features evaluated on x-rays and MRIs and MRI based diagnosis. In many cases, there was no or poor agreement between the reviewers. Therefore, reliable and reproducible parameters could herein not be identified. This low interobserver agreement may be eliminated by discussing features of interest prior to having them assessed by each reviewer individually.

We suggest further – potentially prospective – studies, to gain complete data of clinical features, like type of pain and whether the pain is caused by the lesion, which could be identified by using intraarticular injection of anaesthetics. Furthermore, different imaging modalities should be used as well as different sequences like STIR.

Eventually, this study again highlights the importance of multidisciplinary approaches to manage chondrogenic tumours, with evaluation of distinct radiographic features being prone to significant bias caused by reviewers' subjective assessment.

6 References

1. Jundt G. Knochen. In: Böcker W, Denk H, Heitz PU, Höfler G, Kreipe H, Moch H, editors. Pathologie. 5th ed. München: Urban & Fisher Verlag/Elsevier GmbH; 2012.

2. Greenspan A, Borys D. Radiology and Pathology Correlation of Bone Tumors: A Quick Reference and Review. Philadelphia: Lippincott Williams & Wilkins; 2015.

3. Choi JH, Ro JY. The 2020 WHO Classification of Tumors of Bone: An Updated Review. Adv Anat Pathol. 2021;28(3):119-38.

4. Douis H, Parry M, Vaiyapuri S, Davies AM. What are the differentiating clinical and MRI-features of enchondromas from low-grade chondrosarcomas? Eur Radiol. 2018;28(1):398-409.

5. 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.

6. Murphey MD, Flemming DJ, Boyea SR, Bojescul JA, Sweet DE, Temple HT. Enchondroma versus chondrosarcoma in the appendicular skeleton: differentiating features. Radiographics. 1998;18(5):1213-37; quiz 44-5.

7. Breitenseher A, Nöbauer-Huhmann I. Primäre und sekundäre Knochentumore (Metastasen). In: Breitenseher M, Pokieser P, Lechner G, editors. Lehrbuch der radiologisch-klinischen Diagnostik. 2nd ed. Horn: University Publisher 3.0; 2012.

8. Lodwick G. The bones and joints. Chicago, IL: Year Book Medical Publishers; 1971.

9. Lodwick GS, Wilson AJ, Farrell C, Virtama P, Dittrich F. Determining growth rates of focal lesions of bone from radiographs. Radiology. 1980;134(3):577-83.

10. Benndorf M, Bamberg F, Jungmann PM. The Lodwick classification for grading growth rate of lytic bone tumors: a decision tree approach. Skeletal Radiol. 2021.

11. McCarthy EF, W.K. T. Distinguishing enchondroma from low-grade central chondrosarcoma. Pathology Case Reviews. 2001;6(1):8-13.

12. Unni K. Chondroma. Dahlin's Bone Tumors, General Aspects and Data on 11,087 Cases. Philadelphia: Lippincott-Raven; 1996.

13. Brien EW, Mirra JM, Kerr R. Benign and malignant cartilage tumors of bone and joint: their anatomic and theoretical basis with an emphasis on radiology, pathology and clinical biology. I. The intramedullary cartilage tumors. Skeletal Radiol. 1997;26(6):325-53.

14. Geirnaerdt MJ, Hermans J, Bloem JL, Kroon HM, Pope TL, Taminiau AH, et al. Usefulness of radiography in differentiating enchondroma from central grade 1 chondrosarcoma. AJR Am J Roentgenol. 1997;169(4):1097-104.

15. Walden MJ, Murphey MD, Vidal JA. Incidental enchondromas of the knee. AJR Am J Roentgenol. 2008;190(6):1611-5.

16. Manaster BJ, May DA, Disler DG. Chapter 32 - Cartilage-Forming Tumors. In: Manaster BJ, May DA, Disler DG, editors. Musculoskeletal Imaging (Fourth Edition). Philadelphia: W.B. Saunders; 2013. p. 383-98.

17. Flemming DJ, Murphey MD. Enchondroma and chondrosarcoma. Semin Musculoskelet Radiol. 2000;4(1):59-71.

18. Janzen L, Logan PM, O'Connell JX, Connell DG, Munk PL. Intramedullary chondroid tumors of bone: correlation of abnormal peritumoral marrow and soft-tissue MRI signal with tumor type. Skeletal Radiol. 1997;26(2):100-6.

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

20. Ferrer-Santacreu EM, Ortiz-Cruz EJ, Diaz-Almiron M, Pozo Kreilinger JJ. Enchondroma versus Chondrosarcoma in Long Bones of Appendicular Skeleton: Clinical and Radiological Criteria-A Follow-Up. J Oncol. 2016;2016:8262079.

21. Mirra JM, Gold R, Downs J, Eckardt JJ. A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orthop Relat Res. 1985(201):214-37.

22. Biondi NL, Varacallo M. Enchondroma. StatPearls. Treasure Island (FL)2021.

23. Weinstein LJ, McCarthy EF. Ki-67 immunostaining as a tool in the diagnosis of central cartilage lesions. Iowa Orthop J. 1996;16:39-45.

24. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334-43.

25. Altay M, Bayrakci K, Yildiz Y, Erekul S, Saglik Y. Secondary chondrosarcoma in cartilage bone tumors: report of 32 patients. J Orthop Sci. 2007;12(5):415-23.

26. Marco RA, Gitelis S, Brebach GT, Healey JH. Cartilage tumors: evaluation and treatment. J Am Acad Orthop Surg. 2000;8(5):292-304.

27. Bauer HC, Brosjo O, Kreicbergs A, Lindholm J. Low risk of recurrence of enchondroma and low-grade chondrosarcoma in extremities. 80 patients followed for 2-25 years. Acta Orthop Scand. 1995;66(3):283-8.

28. Scheitza P, Uhl M, Hauschild O, Zwingmann J, Bannasch H, Kayser C, et al. Interobserver Variability in the Differential Diagnosis of Benign Bone Tumors and Tumor-like Lesions. Rofo. 2016;188(5):479-87.

29. Suijker J, Baelde HJ, Roelofs H, Cleton-Jansen AM, Bovee JV. The oncometabolite D-2-hydroxyglutarate induced by mutant IDH1 or -2 blocks osteoblast differentiation in vitro and in vivo. Oncotarget. 2015;6(17):14832-42.

30. Pansuriya TC, van Eijk R, d'Adamo P, van Ruler MA, Kuijjer ML, Oosting J, et al. Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. Nat Genet. 2011;43(12):1256-61.

31. Pansuriya TC, Kroon HM, Bovee JV. Enchondromatosis: insights on the different subtypes. Int J Clin Exp Pathol. 2010;3(6):557-69.

32. Silve C, Juppner H. Ollier disease. Orphanet J Rare Dis. 2006;1:37.

33. Verdegaal SH, Bovee JV, Pansuriya TC, Grimer RJ, Ozger H, Jutte PC, et al. Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: an international multicenter study of 161 patients. Oncologist. 2011;16(12):1771-9.

34. Andreou D, Gilg MM, Gosheger G, Werner M, Hardes J, Pink D, et al. Metastatic Potential of Grade I Chondrosarcoma of Bone: Results of a Multi-institutional Study. Ann Surg Oncol. 2016;23(1):120-5.

35. Rosenthal DI, Schiller AL, Mankin HJ. Chondrosarcoma: correlation of radiological and histological grade. Radiology. 1984;150(1):21-6.

36. Choi BB, Jee WH, Sunwoo HJ, Cho JH, Kim JY, Chun KA, et al. MR differentiation of low-grade chondrosarcoma from enchondroma. Clin Imaging. 2013;37(3):542-7.

37. Lai X, Chen S. Identification of novel biomarker candidates for immunohistochemical diagnosis to distinguish low-grade chondrosarcoma from enchondroma. Proteomics. 2015;15(13):2358-68.

38. Uria JA, Balbin M, Lopez JM, Alvarez J, Vizoso F, Takigawa M, et al. Collagenase-3 (MMP-13) expression in chondrosarcoma cells and its regulation by basic fibroblast growth factor. Am J Pathol. 1998;153(1):91-101.

39. Campanacci DA, Scoccianti G, Franchi A, Roselli G, Beltrami G, Ippolito M, et al. Surgical treatment of central grade 1 chondrosarcoma of the appendicular skeleton. J Orthop Traumatol. 2013;14(2):101-7.

40. Gunay C, Atalar H, Hapa O, Basarir K, Yildiz Y, Saglik Y. Surgical management of grade I chondrosarcoma of the long bones. Acta Orthop Belg. 2013;79(3):331-7.

41. de Camargo OP, Baptista AM, Atanasio MJ, Waisberg DR. Chondrosarcoma of bone: lessons from 46 operated cases in a single institution. Clin Orthop Relat Res. 2010;468(11):2969-75.

42. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818-31.

43. Fromm J, Klein A, Baur-Melnyk A, Knosel T, Lindner L, Birkenmaier C, et al. Survival and prognostic factors in conventional G1 chondrosarcoma. World J Surg Oncol. 2019;17(1):155.

44. Herget GW, Strohm P, Rottenburger C, Kontny U, Krauss T, Bohm J, et al. Insights into Enchondroma, Enchondromatosis and the risk of secondary Chondrosarcoma. Review of the literature with an emphasis on the clinical behaviour, radiology, malignant transformation and the follow up. Neoplasma. 2014;61(4):365-78.

45. Sanerkin NG. The diagnosis and grading of chondrosarcoma of bone: a combined cytologic and histologic approach. Cancer. 1980;45(3):582-94.

46. Limaiem F, Davis DD, Sticco KL. Chondrosarcoma. StatPearls. Treasure Island (FL)2021.

47. West OC, Reinus WR, Wilson AJ. Quantitative analysis of the plain radiographic appearance of central chondrosarcoma of bone. Invest Radiol. 1995;30(7):440-7.

48. Sawyer JR, Swanson CM, Lukacs JL, Nicholas RW, North PE, Thomas JR. Evidence of an association between 6q13-21 chromosome aberrations and locally aggressive behavior in patients with cartilage tumors. Cancer. 1998;82(3):474-83.

49. Zoccali C, Baldi J, Attala D, Rossi B, Anelli V, Annovazzi A, et al. Intralesional vs. extralesional procedures for low-grade central chondrosarcoma: a systematic review of the literature. Arch Orthop Trauma Surg. 2018;138(7):929-37.

50. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320-9.

51. Ozaki T, Hillmann A, Lindner N, Blasius S, Winkelmann W. Metastasis of chondrosarcoma. J Cancer Res Clin Oncol. 1996;122(10):625-8.

52. De Beuckeleer LH, De Schepper AM, Ramon F, Somville J. Magnetic resonance imaging of cartilaginous tumors: a retrospective study of 79 patients. Eur J Radiol. 1995;21(1):34-40.

53. Crim J, Schmidt R, Layfield L, Hanrahan C, Manaster BJ. Can imaging criteria distinguish enchondroma from grade 1 chondrosarcoma? Eur J Radiol. 2015;84(11):2222-30.

54. Geirnaerdt MJ, Bloem JL, Eulderink F, Hogendoorn PC, Taminiau AH. Cartilaginous tumors: correlation of gadolinium-enhanced MR imaging and histopathologic findings. Radiology. 1993;186(3):813-7.

55. Geirnaerdt MJ, Hogendoorn PC, Bloem JL, Taminiau AH, van der Woude HJ. Cartilaginous tumors: fast contrast-enhanced MR imaging. Radiology. 2000;214(2):539-46.

56. Jeong W, Kim HJ. Biomarkers of chondrosarcoma. J Clin Pathol. 2018;71(7):579-83.

57. Mirra JM. Intramedullary cartilage- and chondroid-producing tumors. In: Mirra JM, editor. Bone tumors: clinical, radiological and pathologic correlations. Philadelphia: Lea & Febiger; 1989. p. 439-535.

58. Unni K. Enchondroma and chondrosarcoma. In: Unni KK, editor. Dahlin's bone tumors: general aspects and data on 11,087 cases. 5th ed. Philadelphia: Lippincott-Raven; 1996. p. 25-47.

59. Unni K. Enchondroma and chondrosarcoma. In: Unni KK, editor. Dahlin's bone tumors: general aspects and data on 11,087 cases. 5th ed. Philadelphia: Lippincott-Raven; 1996. p. 71-109.

60. Mulder JD, Kroon HM, Schütte HE, Tacinos WK. Radiologic atlas of bone tumors. Amsterdam: Elsevier; 1993.

61. Bui KL, Ilaslan H, Bauer TW, Lietman SA, Joyce MJ, Sundaram M. Cortical scalloping and cortical penetration by small eccentric chondroid lesions in the long tubular bones: not a sign of malignancy? Skeletal Radiol. 2009;38(8):791-6.

62. Parlier-Cuau C, Bousson V, Ogilvie CM, Lackman RD, Laredo JD. When should we biopsy a solitary central cartilaginous tumor of long bones? Literature review and management proposal. Eur J Radiol. 2011;77(1):6-12.

63. Aoki J, Sone S, Fujioka F, Terayama K, Ishii K, Karakida O, et al. MR of enchondroma and chondrosarcoma: rings and arcs of Gd-DTPA enhancement. J Comput Assist Tomogr. 1991;15(6):1011-6.

64. De Coninck T, Jans L, Sys G, Huysse W, Verstraeten T, Forsyth R, et al. Dynamic contrast-enhanced MR imaging for differentiation between enchondroma and chondrosarcoma. Eur Radiol. 2013;23(11):3140-52.

65. Portney LG, Walkins MP. Founations of clinical research: applications to practice. Prentice Hall: New Jersey; 2000.

66. Kendell SD, Collins MS, Adkins MC, Sundaram M, Unni KK. Radiographic differentiation of enchondroma from low-grade chondrosarcoma in the fibula. Skeletal Radiol. 2004;33(8):458-66.