Diplomarbeit

MRI long-term follow-up of incidentally detected enchondromas of the long bones

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Graz, am 18.05.2021

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Graz, am 18.05.2021 *Moritz Dreier eh.*

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Abbreviations and definitions

ACT	Central atypical cartilaginous tumor
AP	Anterior-posterior
CB	Cortical breach
CE	Contrast enhancement
CS	Chondrosarcoma
CS1	Chondrosarcoma grade 1
CCS	Conventional high-grade chondrosarcoma
CT	Computed tomography
3D	Three dimensional
EC	Enchondroma
ED	Peritumoral bone edema
ES	Endosteal scalloping
FS	Fat-suppression
FSE	Fast spin-echo
FU	Follow-up
G1	Grade 1
G2	Grade 2
G3	Grade 3
GE	Gradient echo-sequence
IND	Initial diagnose
MRI	Magnetic resonance imaging
n	Numbers
NOS	Non-other-specified
Pat.-ID	Patient identification number
PET-CT	Positron emission tomography – computed tomography
PR	Periosteal reaction
SDS	Sumo of differences in size
SE	Sequences
Std. Dev.	Standard deviation
SPSS	Statistical Package for Social Science
SUV	standardized uptake values
SWI	Susceptibility-weighted images
T1	Longitudinal relaxation time
T1W	T1 weighted sequence
T2	transversal relaxation time
T2W	T2 weighted sequence
TSE	Turbo spin echo
WHO	World Health Organization

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Abstract

Introduction: The incidental finding of an enchondroma (EC) within a long bone is a common reason for referral to a bone tumor unit, and the population prevalence of incidental cartilage tumors on MRI scans is increasing due to the higher number of MRI scans performed. The reported risk of malignant transformation varies between 0 and 6% and there are no valid data on the long-term growth behavior of EC. There is no consensus or recommendation on follow-up for EC. The aim of this study was to analyze the long-term changes of incidentally detected ECs of the long tubular bones on MRI.

Materials and Methods: This retrospective study included 110 patients with EC of the long bones suggestive of an EC diagnosed between 2006 and 2009. A follow-up period of at least 10 years after the initial diagnosis was the main inclusion criterion. To investigate the growth behavior, the change in size was analyzed. Malignant transformation was assessed using radiological criteria including cortical breach, endosteal scalloping, peritumoral edema, and soft tissue component. In addition, the rate of secondary surgeries was analyzed during the observation period.

Results: 77/110 (70%) patients were reached by phone and 24/77 (31%) agreed to a follow-up MRI examination. The mean follow-up time for the MRI-group (n=24) was 140 months (range 120-172 months). The localization of EC was: 17 femur (71%), 3 tibia (13%), 2 humerus (8%), 1 fibula (4%), 1 ulna (4%). The mean age of the patients at initial diagnosis was 49 years (range, 27-67). 11 ECs (46%) increased in size, 10 ECs (42%) remained stable, and 3 ECs decreased in size. The mean increase in EC size was 3 mm (range -2 mm - +18 mm) between the initial and subsequent MRI. Two patients developed endosteal scalloping, one patient showed new peritumoral edema, in one patient cortical breach with periosteal reaction was found. Overall, 6/77 (8%) patients underwent secondary surgery, all lesions were histologically confirmed as EC.

Conclusion: This study has shown that imaging follow-up is justified for all EC, irrespective of initial lesion size, as EC have shown unpredictable growth patterns. As progression is slow, it seems reasonable to extend follow-up intervals to several years. The newly occurrence of solitary features of biological aggressiveness, such

as endosteal scalloping, without clinical symptoms, does not require surgery but follow–up.

Zusammenfassung

Einleitung: Der zufällige Befund eines Enchondroms (EC) in einem langen Röhrenknochen ist ein häufiger Grund für die Überweisung an ein Sarkomzentrum. Aufgrund der zunehmenden Anzahl an durchgeführten MRT-Untersuchungen steigt auch die Inzidenz von EC. Es gibt keine Daten zum Langzeitverlauf von nicht operierten EC und das Entartungsrisiko wird mit 0 bis 6 % angegeben. Es besteht kein Konsens über die Nachbeobachtung von EC. Ziel dieser Studie war es, die Veränderungen von EC im MRT über einen Mindestzeitraum von 10 Jahren zu analysieren.

Materialien und Methoden: In einer retrospektiven Datenbankanalyse wurden 110 Patientinnen und Patienten identifiziert, welche zwischen 2006 und 2009 wegen eines zufällig diagnostizierten EC am Sarkomzentrum der Universitätsklinik für Orthopädie und Traumatologie, Medizinische Universität Graz, konservativ behandelt wurden. Einschlusskriterien für die Teilnahme waren die Lokalisation des EC in den langen Röhrenknochen, eine MRT-Untersuchung zum Zeitpunkt der Erstdiagnose sowie ein Nachbeobachtungszeitraum von mindestens 10 Jahren. Um das Wachstumsverhalten zu untersuchen, wurde die Größenveränderung analysiert. Das Entartungsrisiko wurde mit folgenden radiologischen Parametern untersucht: kortikale Destruktion, endosteal scalloping, peritumorales Ödem und Weichgewebsanteil. Zusätzlich wurde die Rate an sekundär operierten Patientinnen und Patienten im Beobachtungszeitraum analysiert.

Ergebnisse: 77/110 (70%) Patientinnen und Patienten konnten telefonisch kontaktiert werden und 24/77 (31%) stimmten zusätzlich einer MRT-Nachuntersuchung zu. Die mittlere Nachbeobachtungszeit der 24 Patientinnen und Patienten (8 Männer, 16 Frauen) betrug 140 Monate (Bereich 120-172 Monate). Die Lokalisation der EC in den langen Röhrenknochen war folgende: 17 Femur (71%), 3 Tibia (13%), 2 Humerus (8%), 1 Fibula (4%), 1 Ulna (4%). Das Durchschnittsalter der Patientinnen und Patienten bei der Erstdiagnose betrug 49 Jahre (Bereich 27 – 67 Jahre). Insgesamt nahmen 11 ECs (46%) an Größe zu, 10 ECs (42%) blieben stabil und 3 (13%) ECs verringerten die Größe. Die mittlere Zunahme der EC-Größe betrug 3 mm (Bereich -2 mm - +18 mm). Zwei Patientinnen und Patienten entwickelten ein endosteal scalloping, ein Patient zeigte ein neu aufgetretenes

peritumorales Ödem und bei einer Patientin konnte eine kortikale Destruktion mit periostaler Reaktion festgestellt werden. Im gesamten Beobachtungszeitraum wurden 6/77 (8%) EC im Verlauf operiert, wobei alle Läsionen histologisch als EC klassifiziert wurden.

Diskussion: Die Ergebnisse diese Studie zeigen, dass bei jedem EC eine MRT Nachuntersuchung gerechtfertigt ist, da das Wachstumsverhalten von EC, unabhängig von ihrer Ausgangsgröße, nicht vorhersehbar ist. Da die Größenprogredienz sehr langsam ist, sollten die Nachkontrollen in Abständen von mehreren Jahren stattfinden. Das Neuauftreten von singulären malignitätsverdächtigen Merkmalen, wie zum Beispiel endosteal scalloping, ohne klinische Symptomatik rechtfertigt regelmäßige, engmaschige Nachkontrollen, jedoch nicht unmittelbar die intraläsionale Resektion des EC.

1 Introduction

1.1 Enchondroma

Benign cartilaginous bone tumors (Table 1), including enchondromas (EC), are the most frequent group of primary benign bone tumors. Overall, EC accounts for 3% of all bone tumors and 13% of benign bone tumors with equal sex distribution and a wide age range. The incidence of clinically noticeable EC is highest in the 3rd and 4th decade of life (1–3).

The average size of the tumor is less than 3 cm, but they can enlarge over time (1). ECs grow preferentially intramedullary and mainly occur in the short tubular bones of the hand. Another common localization are the long tubular bones, often affecting the femur and humerus. Flat bones are in less than 1% of the cases affected. EC usually occurs more often uni- than multifocally. Multifocal appearance is typical for enchondromatosis, (i.e., Maffucci syndrome, Ollier's disease), which shows a higher risk of malignant transformation than conventional EC (1, 4). In patient with enchondromatosis, the overall incidence of development of chondrosarcoma is 40%. The highest risk, in the case of enchondromatosis, are in EC, localized in the long tubular bones or in the axial skeleton (especially pelvis) (5).

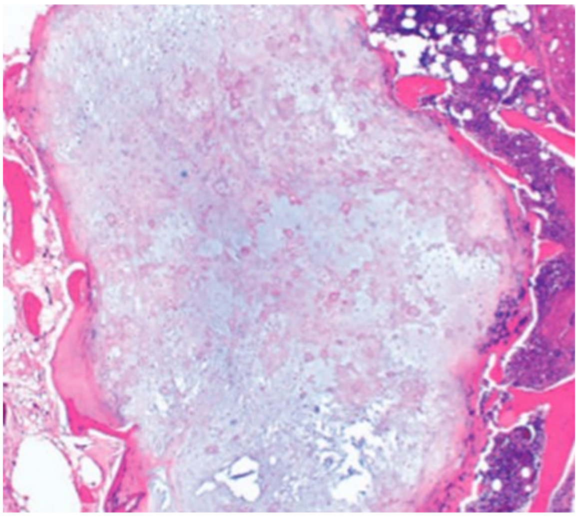

Figure 1: Microscopic image of an EC
Microscopic image of an EC showing a variable number of benign-appearing chondrocytes, with focal areas of scattered calcifications and bone deposition on the periphery of the nodule (Figure reproduced from Suter et al. (6) with permission of publisher (College of American Pathologists Publications)).

Furthermore, contrary to EC of the short tubular bones, which are often associated with swelling, pain, and pathological fractures, EC of the long bones usually do not cause pain or have a propensity to fracture (1, 6).

Histologically, ECs show hypocellularity with an abundance of hyaline cartilage matrix which displaces, rather than destroy the bone tissue (Figure 1). In addition, signs of degeneration, including focal necrosis or calcification can be detected, cytological atypia and mitosis are always absent (1, 7).

The risk of malignant transformation has been reported to vary between 0-6%, although it is presumed that the true rate is much lower (8–12).

Moreover, there is missing or inconsistent data about the growth patterns of EC. It is assumed that ECs are of constant size and do not grow, strongly indicative of their benign behavior (2, 11, 13).

WHO classification of bone tumors: Chondrogenic tumors	
Benign	- Subungual exostosis - Bizarre parosteal osteochondromatous proliferation - Periosteal chondroma - Enchondroma - Osteochondroma - Chondroblastoma NOS - Chondromyxoid fibroma - Osteochondromyxoma
Intermediate (locally aggressive)	- Chondromatosis NOS - Atypical cartilaginous tumor
Malignant	- Chondrosarcoma, grade 1 - Chondrosarcoma, grade 2 - Chondrosarcoma, grade 3 - Periosteal chondrosarcoma - Clear cell chondrosarcoma - Mesenchymal chondrosarcoma - Dedifferentiated chondrosarcoma

Table 1: WHO classification of chondrogenic bone tumors (1)

1.2 Central atypical cartilaginous tumor/ Chondrosarcoma grade 1

A central atypical cartilaginous tumor (ACT)/ chondrosarcoma grade 1 (CS1) is a hyaline cartilage-producing tumor in the bone marrow with a locally aggressive growth pattern (1).

In the latest WHO classification, CS1 was renamed and defined more specifically due to the different aggressive growth behavior at various locations. CS1 of the appendicular skeleton show a less aggressive growth pattern and have been renamed to ACT, while the lesions in the axial skeleton are more aggressive and termed as CS1. In addition, a distinction can be made between ACT/ CS1 that developed primarily without a precursor lesion and those that have developed secondarily from a precursor lesion. The highest incidence of central ACT/ CS1 is in the 3rd to 6th decades of life and with no gender difference (1).

In contrast to EC, central ACT/ CS1 are rarely found in the hands and feet. ACT/ CS1 occur most frequently in the long bones, with 31% affecting the femur. Other frequently affected long bones are the humerus (11%) and tibia (8%). About 50% of the ACT/ CS1 in the long tubular bones occur in the metaphysis. The diaphysis (about 33%) and epiphysis (17%) are less frequently affected. The second most common location are the pelvic bones (22%).

Clinical presentation of patients with ACT/ CS1 can be very heterogeneous, ranging from an asymptomatic course, through the pain with or without swelling, to neurological deficits (1).

Histologically, central ACT/ CS1 show a large amount of hyaline cartilage matrix with a characteristic lobulated growth pattern, configured irregularly and of different sizes. This lobular growth pattern leads to cortical thinning, which is visible radiologically as endosteal scalloping. The envelope pattern (deposition of bone surrounding the tumor lobules) as in EC, which is typical of slow growth, is hardly visible in ACT/ CS1. Instead, the tumor lobules destroy the lamellar cones, which is a sign of rapid growth (Figure 2). The cellularity is higher than in the EC, but still low in contrast to high-grade chondrosarcoma, and local necrosis can be present (1, 7).

On radiography and computed tomography, EC shows a typical well-defined geographic pattern of bone destruction. Due to the histological similarity to ECs, the radiological differentiation between EC and ACT/ CS1 is very difficult. This is described in more detail in chapter 1.5.

For the staging of ACT/ CS1, the bone sarcoma protocols (TNM staging system of bone tumors) are used (1). Due to the locally aggressive behavior, ACT/ CS1 have a higher recurrence rate than EC. Local recurrences occur in 7.5-11% (14–16) of the cases and 10% of these locally recurrent ACT/ CS1 dedifferentiation into a higher-grade CS is detected (17–19). In literature, the 5-year overall survival rates of ACT/CS1 are reported as 87-99%, the 10-year overall survival rates 88-95%, respectively (8, 16, 19–23). Recurring ACT lesions anatomically demanding locations such as the skull base or pelvis are the leading cause of mortality among these patients (19, 22–25).

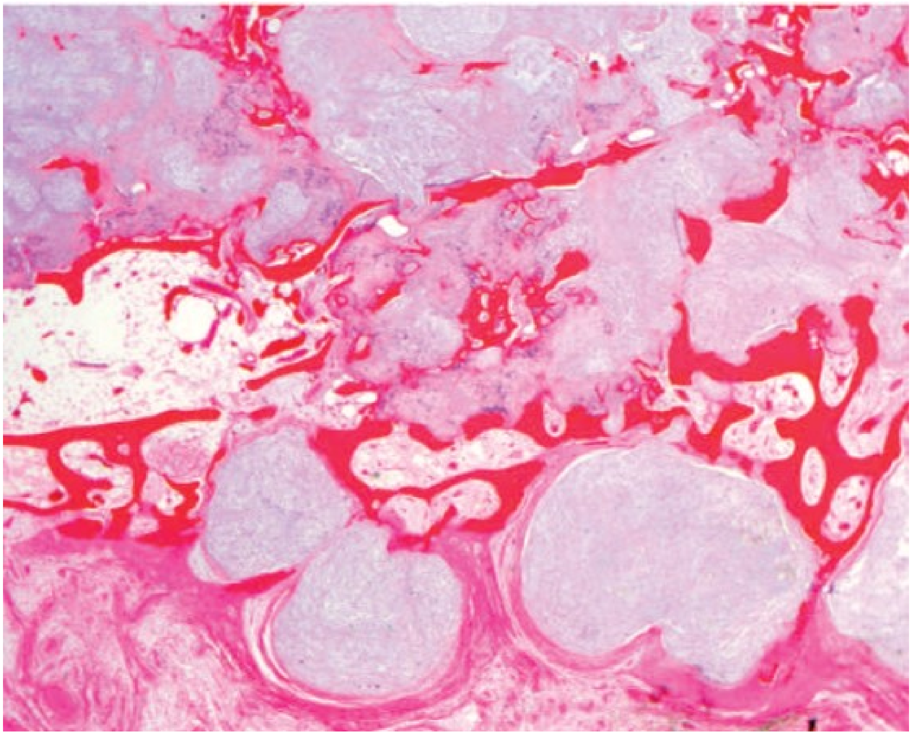

Figure 2: Microscopic image of an ACT/ CS1
This microscopic image shows the infiltrative appearance of a low-grade chondrosarcoma with encasement of pre-existing bony trabeculae and focal extension through the cortex into the surrounding soft tissue (bottom of image) (Figure reproduced from Suter et al. (6) with permission of publisher (College of American Pathologists Publications)).

1.3 Chondrosarcoma

Chondrosarcoma (CS) is a locally aggressive bone tumor characterized by the formation of a cartilaginous matrix. Accounting for up to 20% of all malignant bone tumors, it is the second most common primary malignant bone tumor after osteosarcoma. The etiology of primary CS is unknown. Patients with CS present clinically with pain and local swelling. If the skull base is affected, neurological symptoms can occur (1, 26–30).

1.3.1 Subtypes of CS

CS are either primary, arising de novo, or secondary neoplasms, which arise from a pre-existent cartilaginous mass (Table 2). The secondary CS with central location, arise from an existing EC, while peripheral CS arise from an existing cartilaginous cap of an osteochondroma. The periosteal (formerly called juxtacortical) CS arises from the surface of the bone with a connection to the periosteum (1, 31, 32).

Primary	Secondary
○ conventional intramedullary chondrosarcoma (or central chondrosarcoma): → low, intermediate or high-grade ○ periosteal chondrosarcoma: → low, intermediate or high-grade ○ clear cell chondrosarcoma ○ myxoid chondrosarcoma: → usually intermediate grade ○ mesenchymal chondrosarcoma: → usually high-grade ○ extraskeletal chondrosarcoma ○ dedifferentiated chondrosarcoma	○ osteochondroma ○ solitary osteochondroma ○ hereditary multiple exostoses ○ enchondroma ○ solitary enchondroma ○ Ollier´s disease

Table 2: Subtypes of CS (1)

1.3.2 Grading of CS

Histologically, the grading of CS is based on nucleus size, nuclear hyperchromatism and cellularity, and the lesions are divided into three grades (G1, G2, G3) (Table 3) (1).

Grade	Histological characterization	Examples
Grade 1 - low grade	• low cellularity • mostly chondroid matrix • little if any myxoid • difficult to distinguish from enchondroma	• conventional chondrosarcoma • juxtacortical chondrosarcoma
Grade 2 - intermediate grade	• increased cellularity • little chondroid matrix • necrosis and more common prominent myxoid	• conventional chondrosarcoma • juxtacortical chondrosarcoma • myxoid chondrosarcoma
Grade 3 - high grade	• highly cellular • nuclear pleomorphism • absent chondroid matrix • stroma present is myxoid	• conventional chondrosarcoma • juxtacortical chondrosarcoma • mesenchymal chondrosarcoma • dedifferentiated chondrosarcoma

Table 3: Grading of CS (1)

1.3.3 Conventional intramedullary Chondrosarcoma

The frequency peak of conventional intramedullary chondrosarcoma (CCS) is in the 6th decade of life with male predominance (33, 34). CCS can arise from endochondral ossification in any bone of the skeleton, and most are found in the long tubular bones (45%). The femur is most often affected (20-30% of all cases), followed by the tibia (5%). Nevertheless, the flat bones like the pelvis (25%), ribs (8%), spine (7%), and sternum (2%) are also affected. The skull base, upper jaw and the short tubular bones are less commonly involved (1-4%) (1, 34)

There is an abundance of extracellular matrix material in cytology, which is best appreciated on air-dried, Giemsa based stained material. There are also recognizable lacunae, often containing binucleated or multinucleated chondrocytes. ACT/ CS1 is cytomorphologically indistinguishable from an EC. In contrast, grade 2 and grade 3 CS are more cellular, more atypical, and with more myxoid matrix (35). Histological CCS show an abundant cartilaginous matrix with chondrocytes embedded in lacunae and show lobular or diffuse growth pattern (depending on grade). Furthermore, CCS show the permeation of intertrabecular spaces (Figure 3). Varying degrees of increased cellularity, nuclear atypia and mitotic activity can be distinguished. Grade I is characterized by minimally increased cellularity, nodular growth, and occasional binucleate nuclei, Grade II by moderate cellularity and diffuse growth, and Grade III with high cellularity, marked atypical cells, pleomorphic appearance, and easily identifiable mitotic figures (1, 7).

Genetic analysis reveals IDH1 and IDH2 mutations in approximately 50% of cases. In addition, aneuploidy is seen with increasing histologic grade and TP53 mutations, and affected active signaling pathways (RB1, CDKN2A, CDK) are identified particularly in high-grade CS. Stains are not necessary in the majority of cases and S100 is uniformly strongly positive but in grade III it can be focally negative in less differentiated areas. (35–40). Associates of the BCL2 family seem to play a significant part in the chemoresistance of CS (1, 31, 41, 42).

The prognosis depends on the grade of the tumor and the therapy carried out. For CS grade 2 the reported local recurrence rate is 19% and 26% for grade 3 (16). Distant metastasis, mainly intrapulmonal, occurs in 10-30 % of grade 2 CS and 32-71 % of grade 3 CS (16, 19, 22, 43).

The overall 5-year survival rates for high-grade CS are 74%–99% (grade 2), and 31%–77% (grade 3), while the 10-year survival rates are 58%–86% (grade 2), and 26%–55% (grade 3) (16, 19–23, 44).

In addition, high-grade CS have a lower survival rate when they are located in the axial skeleton than located in the extremities (20, 22, 23, 25).

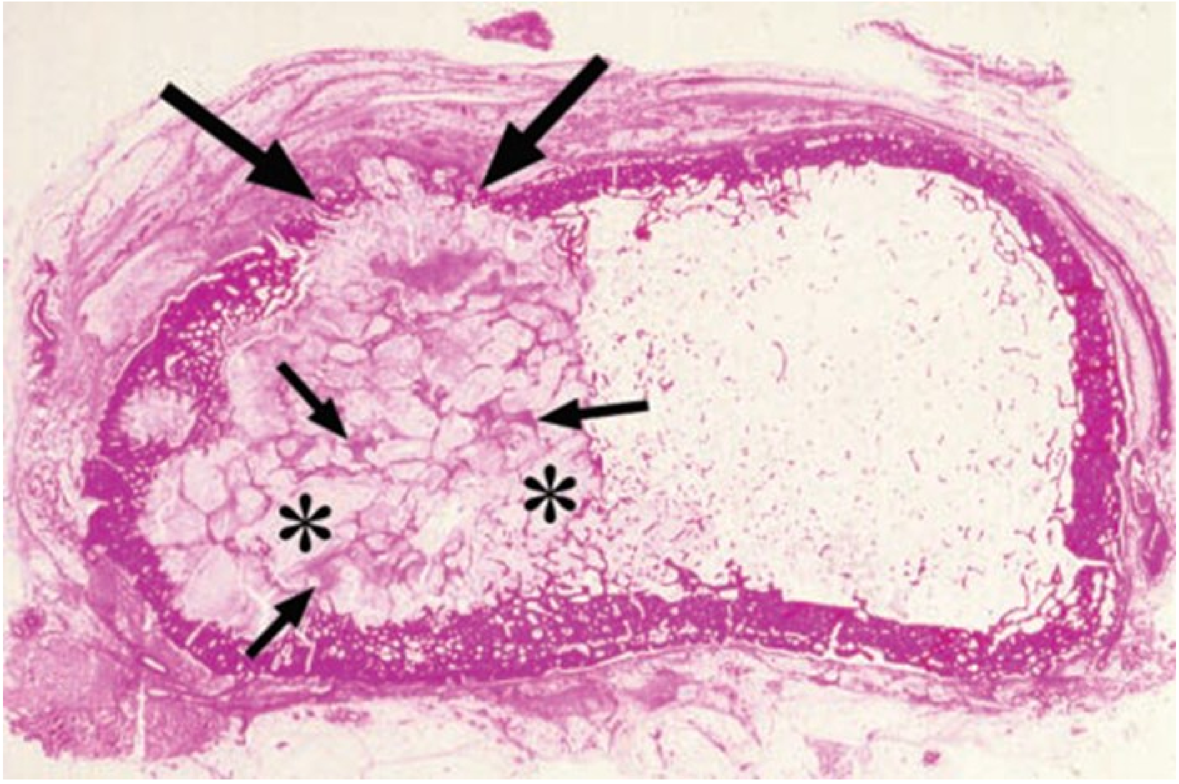

Figure 3: Microscopic image of an CS.

This microscopic image shows multiple cartilaginous lobules (star) replacing the femoral marrow with deep endosteal scalloping anteriorly, cortical penetration, and a small focus of soft-tissue extension (large arrows), findings that represent conventional intramedullary chondrosarcoma. Enchondral ossification at the periphery of the chondroid lobules causing a ring-and-arc appearance is also seen (small arrows) (Figure reproduced from Murphey et al. (34) with permission of publisher (RSNA journals Publications)).

1.4 Imaging criteria

1.4.1 Imaging criteria of EC

EC have a somewhat variable appearance by imaging, thus the exclusion of suspicious radiological features is a key in diagnosis. Since most EC are asymptomatic incidental findings, the lesions in a typical location and with pathognomonic imaging characteristics are not usually further investigated. Imaging is generally less helpful in corroborating the benignity of lesions in the hands and feet and in enchondromatosis or skeletally immature patients (2, 45, 46).

In the plain radiography EC are lytic lesions with a geographic pattern of bone destruction and typically smaller than 5 cm (Table 4).

Non-aggressive features	Pertinent negatives
○ narrow zone of transition ○ sharply defined margins ○ +/- chondroid calcification (rings and arcs calcification) ○ often no matrix mineralization (purely lytic) in the hands/feet ○ +/- expansile ○ more commonly in hands/feet ○ may have mild endosteal scalloping ○ should not "grow" through cortex (unless pathologic fracture)	○ no gross bone destruction ○ no periosteal reaction ○ no soft tissue mass

Table 4: Imaging characteristics of EC(1, 2, 13)

The majority of EC more frequently arise in the metaphyseal region, owing presumably to their origin from the growth plate, although they are commonly seen in the diaphysis, assumably due to bone growth. They are rarely seen in the epiphysis, and a cartilaginous lesion in an epiphysis is more likely to be a CS grade 3 (47–49).

MRI is helpful in evaluating soft tissue extension and for confirming the diagnosis. EC appear as well-circumscribed somewhat lobulated masses. In the T1 weighted sequence (T1W), EC show intermediate to low signal. In T2 weighted sequence

(T2W), a high signal of the cartilaginous matrix is depicted with an internal foci of low signal characteristic of calcification. After Gadolinium-contrast application, there is a variable enhancement of the lesion and may be seen both peripherally or translesional septae. A contrast enhancement pattern (CE) is not a differentiating factor to CS (Figure 4). In addition, the position in the bone, which can be either central or peripheral, and the presence and amount of endosteal scalloping can be assessed in the MRI (1, 2, 13) (Table 4).

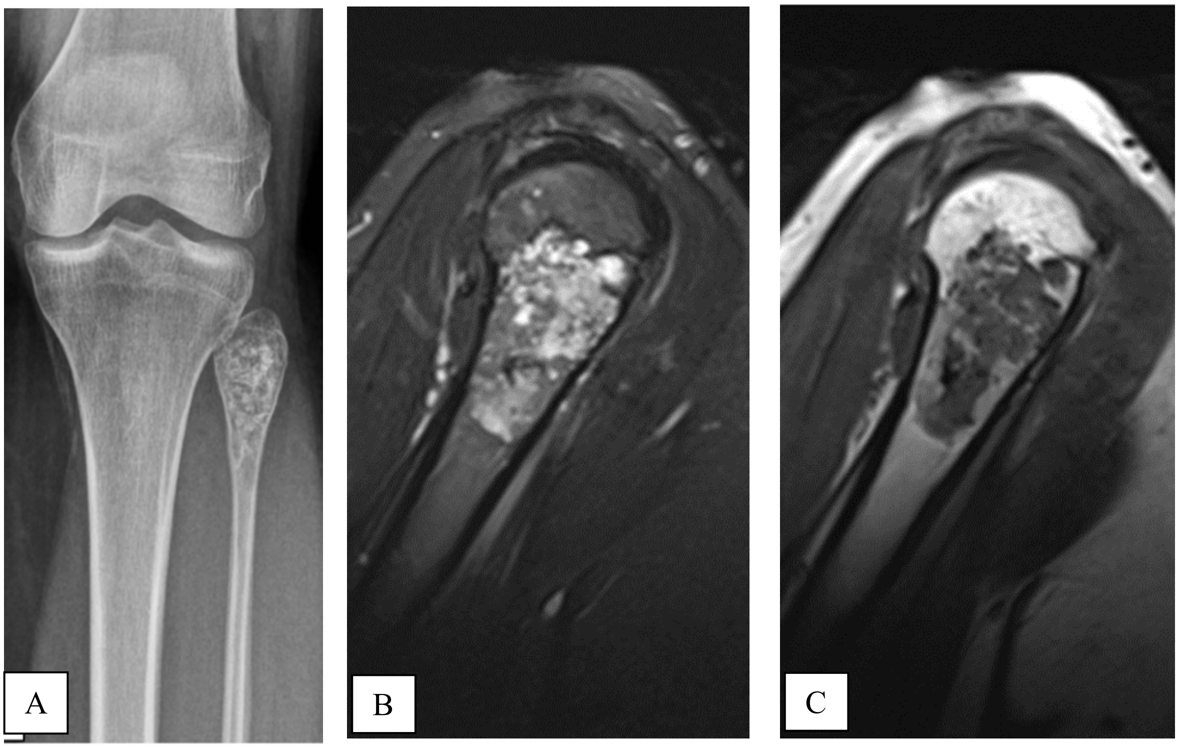

Figure 4: AP radiography and MRI images of an EC

A: Popcorn-like calcification of EC in the proximal Fibula (2)

B/C: Oblique sagittal T1W (B) and fat-saturated T2W (C) images of the shoulders show findings typical of EC with low signal intensity on T1W and high signal intensity on the fat-saturated T2W image (Figures reproduced from Mulligan et al. (2) with permission of publisher (Elsevier Publications)).

1.4.2 Imaging criteria of central ACT/ CS1

Although the ACT/ CS1 share the same radiological characteristics as EC, and cannot be distinguished clearly from one other using only radiological diagnostics, subtle imaging characteristics make the diagnosis of ACT/ CS1 more likely (1, 47, 48).

In plain radiography and computed tomography, lytic lesions with local destruction and endosteal scalloping more than 2/3 of the cortical thickness without breakthrough are typical for central ACT/ CS1. In addition, popcorn-like cartilaginous matrix calcifications can often be seen as well. In MRI, ACT/ CS1 shows low signal intensity in the T1W sequence and high signal intensity in the (fat-saturated) T2W image similar to EC (1). Lesions larger than 5 cm in size and located in the proximal metaphysis are also more likely to be classified as ACT/ CS1 (34, 47, 50).

1.4.3 Imaging criteria of CS

Imaging findings vary somewhat between different subtypes but do have some general features. In this section, the typical imaging appearances are best demonstrated in CCS.

In general, CS are large masses at the time of diagnosis, usually >10 cm in 50% of cases. In plain radiograph, lytic lesions are found in 50% and intralesional calcifications (ring and arcs calcification or popcorn-like calcification) in approximately 70% of the cases. Endosteal scalloping, which affects more than 2/3 of the cortical thickness, may also be present. In advanced cases, moth-eaten appearance or permeative appearance, cortical remodeling, thickening and periosteal reaction are observed (Figure 5) (2, 34).

CT has the advantage of depicting the lesion located in anatomically demanding locations, like pelvis or spine, compared to plain radiography. In the CT, 94% of the cases demonstrate matrix calcification, and 90% of the CS in the long bones show cortical breach. Endosteal scalloping is also common. If soft tissue mass is present, it should be noted that the tumor cellularity, and therefore density, increases with the increased grade of the tumor (34).

Although MRI is the method of choice for diagnosing high-grade CS, a comparison with plain radiography (or CT) is crucial (2). In T1W-sequence, CCS show a low to an intermediate signal, and in T2W-sequence, very high signal intensity in non-mineralized / calcified portions. A “blooming artifact” of mineralized/ calcified portions can be seen in gradient-echo (GE) / SWI-sequence. After Gd contrast administration, most CCS demonstrate septal and peripheral rim-like heterogeneous moderate to intense CE corresponding to fibrovascular septation between lobules of hyaline cartilage (Figure 6) (2, 51).

Figure 5: Plain radiography of high-grade CS.

AP radiographs of the femur show lytic lesion extending from the intertrochanteric area to the proximal femoral shaft with expanded cortex. Focal area of endosteal scalloping at the level of the lesser trochanter (arrow) but no obvious matrix mineralization (Figure reproduced from Mulligan et al. (2) with permission of publisher (Elsevier Publications)).

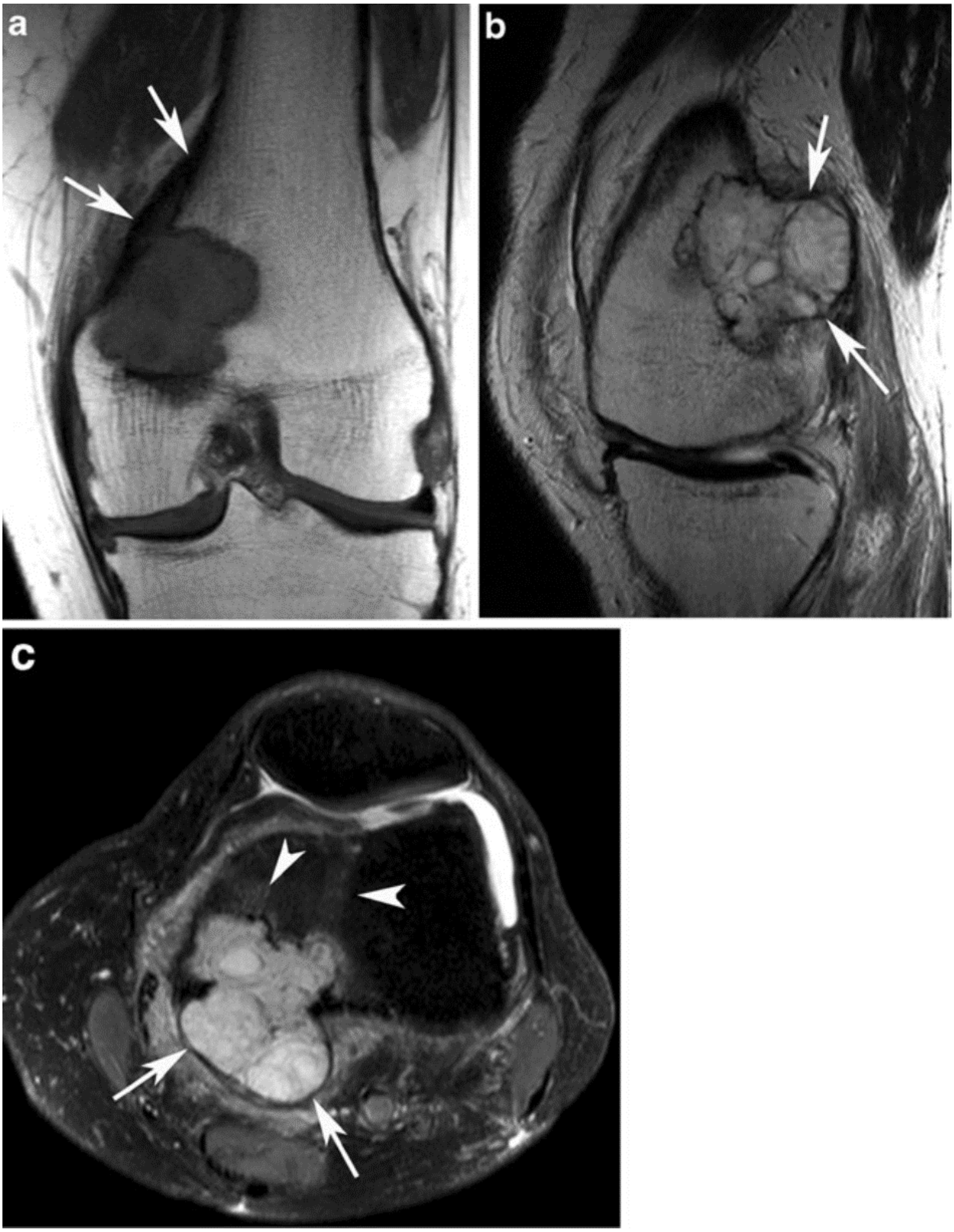

Figure 6: MRI-characteristics of grade 2 CS of the distal femur.

In (a), a coronal T1W image shows thickening of the femoral cortex (arrows) adjacent to the lesion. In (b), a sagittal T2W FSE image shows cortical destruction and extra-osseous tumor extension (arrows). In (c), an axial fat suppressed (FS) T2W FSE image shows mild tumor related reactive marrow oedema-like signal intensity (arrowheads) and extra-osseous tumor extension (arrows) (Figures reproduced from Douis et al. (56) with permission of publisher (European Radiology Publications)).

1.5 Distinction between EC, ACT/ CS1 and high-grade CS

Due to the clinical and radiological similarities between EC and ACT/ CS1, a distinction between the two entities is challenging. Reasonable distinguishing features can be detected clinically, radiologically, and histologically (7, 52). Radiological and histological differentiation between ACT/ CS1 and high-grade CS, which is more relevant regarding treatment, has been proven to be more reliable (6, 27, 49, 53).

1.5.1 Clinical presentation

Clinically, EC is less frequently associated with pain than ACT/ CS1. In the latter pain being is progressive and persisting over a longer period (months to years) (1, 34, 54). In EC, pathological fractures (except in the short tubular bones of the hand) and soft tissue swelling is also less common (1, 2). In addition, from an epidemiological point of view, ECs occur around one to two decades earlier than ACT/ CS1 (1, 33). The localization can also be used to help distinguish between these two entities, as EC occurs mainly in the short tubular bones (hand) while ACT/ CS1 is often found in the long tubular bones (femur, tibia) (1, 26, 34). CCS is more likely when pain persists, the hands or feet are not affected, and the patient is middle-aged (1, 5, 32, 55).

1.5.2 Imaging criteria

The distinction between EC and ACT/ CS1 poses a major challenge for radiologists in everyday clinical practice (56).

On plain radiography, imaging criteria, such as cartilaginous lesion smaller than 5 cm, and metaphyseal lesions favors EC. However, these features can also occur in ACT/ CS1 (49). Lesions larger than 5 cm are indicative of CCS. The most important criterion on plain radiography is the absence of worrisome features, such as deep endosteal scalloping (10% EC vs. 90% CCS), cortical destruction (8% EC vs. 88% CCS in the long bone), or periosteal reaction (2, 34, 54), with deep endosteal scalloping (more than 2/3 of the cortex) being the most significant, but only visible at an advanced stage (49).

Like most other bone tumors, for the distinction between EC and ACT/ CS1, an MRI combined with plain radiography or CT plays a key role in the diagnosis and differentiation between the two entities. No distinction can be made based solely on

MR-signal properties, since both entities show lobular growth pattern with low or intermediate T1W signal, high T2W signal, and for chondroid matrix typical CE pattern (2, 48).

Dynamic MRI can provide further support for differentiation since ACT/ CS1 and high-grade CS show a faster enhance (57, 58).

Diffusion-weighted sequences of MRI do not provide any further information for differentiation (59, 60).

The literature states that the most important distinguishing imaging features are cortical breach, endosteal scalloping, permeative or moth-eaten bone appearance, periosteal reaction or microfracture, loss of calcifications, soft tissue component beyond bone, peritumoral edema, and the length of the tumor (11, 47, 50, 54, 56, 61). These criteria are usually not seen in EC and show a high probability for a high-grade CS. Unfortunately, these imaging criteria in a certain percent of the cases can be lacking or only be isolated present (2, 34). Among these summarized characteristics, the highest significance for the differentiation have probably the deep endosteal scalloping and peritumoral edema, since this suggests a growth of the lesion (2, 34). Soft tissue mass is never found in an EC and is therefore, a clear sign of a CS (49, 61, 62).

When endosteal scalloping or a cortical breakthrough is found in plain radiography, computed tomography can be performed to further discriminate the lesion or further evaluate the spinal, skull base, or pelvic lesions. In addition, CT helps in differentiating EC from bone infarct. The latter is characterized by shell-like sclerosis with a serpiginous border and usually lacks central mineralization (2, 49).

In positron emission tomography – computed tomography (PET-CT), no further distinction can be made between EC and ACT/ CS1, since the entities do not differ in their maximum standardized uptake values (SUV) (63, 64). If the maximum SUV exceeds 4.4, the probability of a high-grade CS is high and a diagnosis of ACT/ CS1 becomes less likely (64).

Recently, a MRI-based texture analysis had the potential to be served as a feasible method in discriminating low-grade chondrosarcoma from enchondroma (65).

1.5.3 Histology

Diagnosis of EC and ACT is usually based on radiology and clinical findings, while the diagnosis of high-grade CS is based on radiology and histology (66). The biopsy is usually obtained through of curettage or fine-needle aspiration (67).

Five parameters (high cellularity, host bone entrapment, open chromatin, mucoid matrix degeneration >20%, and patient age >45 years) are used to distinguish between EC and ACT/ CS1, with mucoid matrix degeneration >20% and host bone entrapment being the most significant ones (1, 68).

Despite these possible distinguishing features, it is a challenge to differentiate between EC and ACT/ CS1 only based on the histology, since ACT/ CS1 and high-grade CS also have features of an EC and not all parts of the ACT/ CS1 are mapped in a small biopsy (1, 68). Therefore, a biopsy is no longer recommended if the possible suspected diagnosis is either EC or ACT/ CS1 because of the possibility of sampling errors and histological overlay (62). Ferrer-Santacreu et al. (48) summarized the differential features between EC and ACT/ CS1 (Table 5).

Features	EC	ACT/ CS1
Clinical	Younger patients Pain is rare Typical in appendicular skeleton Usually <5 cm	Patients > 25 years Inflammatory pain Axial skeleton Lager size
Radiological	Intramedullary No periosteal reaction No endosteal scalloping No changes over time No soft tissue mass	Intramedullary Periosteal reaction and microfractures Endosteal scalloping Loss of calcification, Increasing size Soft tissue mass in some cases
Pathology	Encasement pattern No endosteal scalloping Multinodular Surrounded by lamellar bone No bone marrow infiltration	Haversian system invasion Periosteal reaction and endosteal scalloping Single mass Occasional sites of necrosis and haemorrhage Bone marrow invasion

Table 5: Differential clinical and imaging features between EC and ACT/ CS1 (48)

1.6 Treatment options

Treatment options depend on histological grade and anatomical localization of cartilage lesion (69).

1.6.1 EC

According to the current knowledge, EC have a low risk of malignant transformation and show no local aggressiveness or risk of distant metastases (8, 10, 11). Hence conservative treatment regimen is advised. The standard orthopedic treatment includes radiological follow-up over several years, and the lesion remains unchanged, some authors state, that further radiological follow-up can be omitted (70). Nevertheless, due to the lack of data for the risk of malignant transformation and growth behavior, there are no guidelines regarding the time intervals for follow-up examinations and follow-up modality (71). If due to the clinical and radiological similarity between EC and ACT/ CS1, no definitive differentiation is possible at the time of initial diagnosis, different treatment options exist (69). On the one hand, it is possible to advise radiological follow-up at short intervals (47, 72). On the other hand, some authors suggest intralesional resection with or without local adjuvants of the lesion including histological workup (72, 73).

1.6.2 ACT/ CS1

The current recommendation for the treatment of ACT/ CS1 is an intralesional resection with local adjuvant therapy or watchful waiting with regular follow-up examinations with MRI (72, 73). Compared to the conservative approach, superiority of the surgical approach could not be proven in large studies. Therefore, better therapy options are the subject of current research (23, 69, 74).

1.6.3 CS grade 2 and grade 3

If a high-grade CS is suspected clinically and radiologically, a biopsy must be performed to confirm the diagnosis histologically. Definitive therapy requires a wide resection with R0 margins to reduce local recurrences and distant metastasis. If a lesion can be removed with wide free resection margins, amputation offers no advantage over limb salvage in terms of overall prognosis. After the surgical treatment, regular follow-up examinations should include local staging with MRI and a CT scan of the chest, abdomen and pelvis (47, 67, 75).

Due to known chemotherapy-resistance in high-grade CS patients have no benefit of the treatment. Radiation therapy, with its limited effect, should only be used in the palliative setting for unresectable lesions (47, 76).

1.7 Aim of this study

Most studies reporting on EC have only a short follow-up period and report either the risk of malignant transformation or growth behavior (8, 10, 11, 77). Evidence-based guidelines are currently not available for the follow-up of ECs as the behavior of EC has not been investigated on a long-term basis (9, 11, 78). In a time of defensive medicine, due to uncertainty about progression or possible malignant transformation of EC, a large number of follow-up MRIs are ordered by treating orthopedic surgeons, which leads to high costs and retention of resources. (79, 80). To the best of my knowledge, this is the first study that has investigated the long-term MRI follow-up of EC over more than one decade. The aim of this study was: (i) to analyze the long-term changes in size of incidentally detected ECs of the long tubular bones, (ii) to analyze the change of MRI findings, in particular risk of malignant transformation in patients with a minimum follow-up of 10 years after initial radiological diagnosis, and (iii) to analyze the rate of secondary surgeries of EC.

2 Materials and methods

2.1 Study design and population

For this study, a retrospective database review of all patients diagnosed with EC of the long bones between 2006 - 2009 at the Medical University of Graz Department of Orthopedics and Trauma was conducted. A total of 165 patients with incidentally diagnosed EC of the long bones have been identified. 47 (28%) patients underwent primary surgery while the remainder (n=118, 72%) was planned for conservative treatment. Criteria for conservative treatment were asymptomatic patients diagnosed with EC that had no signs of malignant transformation on initial MRI scans. At that time, a relative indication for primary surgery was EC size, i.e. in lesions larger than 5 cm either surgery or regular MRI follow-up was offered to patients. Patients planned for conservative treatment, were usually discharged from follow-up at our department after the initial diagnosis and transferred to local orthopedic surgeons or district hospitals and annual MRI scans were advised. Patients were instructed to contact sarcoma service in case of new onset of localized symptoms or signs of progression or malignant transformation on MRI scans. For the purpose of this study one follow-up visit including a clinical and MRI examination was re-scheduled at our department. Inclusion criteria of the study were: 1.) Minimum follow-up of 10 years and 2.) conservative treatment intention at initial diagnose of EC of long bones, 3.) available MRI images from initial diagnosis and last follow-up. Patients with EC of the short tubular bones and patients with type I and type II enchondromatosis (Ollier's disease and Maffucci syndrome) were excluded from this study (Table 6).

Inclusion criteria	Exclusion criteria
Patient age > 18 years at initial diagnosis	EC of the flat bones, vertebra, foot, hand
Diagnosis of EC clinically	Skeletally immature patients
Conservative treatment intention	Syndromatic patients (Ollier's disease/ Mafucci Syndrome)
MRI scan at initial diagnosis at last follow-up when no surgery was performed during follow-up	Incomplete data, in particular lack of MRI
Minimum follow-up of 10 years	

Table 6: Eligibility criteria

Within the group of untreated ECs, 8/118 (7%) patients had died of other diseases. The remaining 110 patients were contacted both by mail and phone and invited to participate in the study. 33/110 (30%) were lost to follow- up, 6/110 (5%) patients had undergone secondary surgery, 47 (43%) patients refused to undergo follow- up MRI but agreed to a phone interview and none of them has had surgery for the EC or clinical symptoms at the site of EC. 24/110 (22%) patients agreed to have a follow-up MRI and physical examination at our institution (Figure 7).
Patient demographics and increase in size of EC was calculated with descriptive methods. All analyses were completed using the Statistical Package for Social Science (SPSS Statistics for Windows, Version 26.0; IBM Corporation, Armonk, NY, USA). Ethic's board approval was obtained prior to this study (EK-Number: 31-236 ex 18/19).

Cortical breach
Endosteal scalloping
Permeative or moth-eaten bone appearance
Periosteal reaction or microfracture
Loss of calcifications
Soft tissue component
Peritumoral edema

Table 7: MRI characteristics of a possible malignant transformation

2.2 Radiological and clinical assessment

All MRIs, including postcontrast T1W-sequences after application of Gd-based intravenous contrast material (except in one patient who refused the application), were analyzed by an experienced radiologist specialized in musculoskeletal tumor imaging. If patients had MRI scans from other facilities, imaging was obtained and also reviewed by our radiologist. Radiological criteria for malignant transformation to high-grade CS were defined as a cortical breach, deep endosteal scalloping involving > 2/3 of cortical thickness, permeative or moth-eaten bone appearance, periosteal reaction or microfractures, loss of calcifications, soft tissue mass beyond bone and bone edema (Table 7). The total growth of EC was calculated as the sum of the differences in size (=SDS) in all three planes (mediolateral, craniocaudal, anteroposterior) measured in the initial and latest MRI as shown previously (77). A measurement error of two millimeters was accepted, i.e. increase in size was present if the SDS was > 2 mm.

Clinical presentation was classified as asymptomatic, pain complaints due to other reasons or pain related to EC.

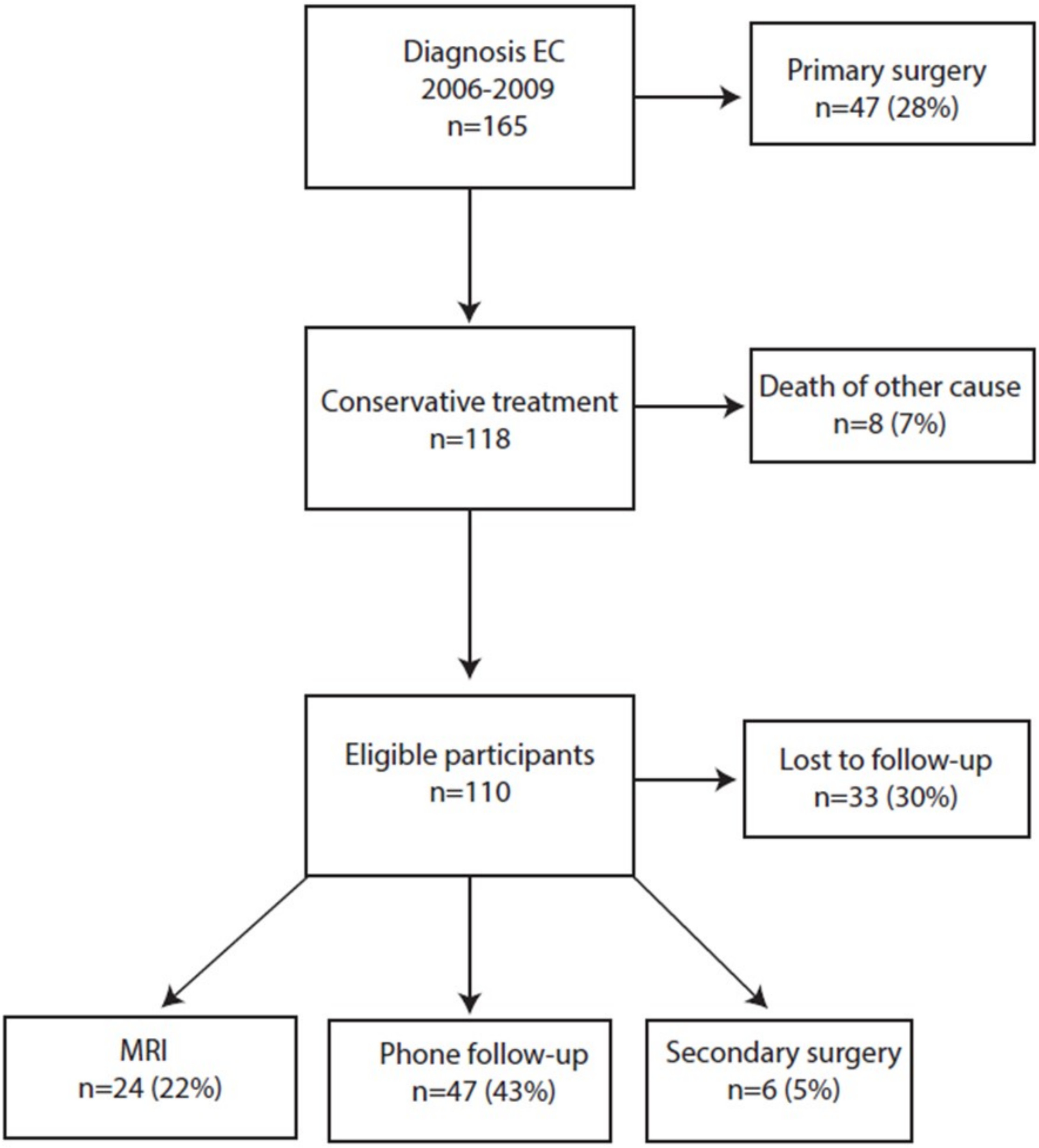

Figure 7: Flow chart of patient requirement

3 Results

3.1 Description of study population

77 patients (43 women, 34 men) met the inclusion criteria. Mean age at initial diagnosis was 50 years (median: 51; range: 25-75 years) and the mean follow-up was 141 months (median: 140; range: 120-235 months). 59/77 (77%) of the EC were located in the lower extremities, the majority (47/59, 80%) of them in the femur. All patients were diagnosed in our center and six out of 78 (8%) patients underwent secondary surgery (Table 8). None of the patients have had surgeries in other hospitals.

	All patients (n=77)	**MRI** (n=24)	**Interview** (n=47)	**Secondary surgery** (n=6)
Sex female male	 43 (56%) 34 (44%)	 16/24 (67%) 8/24 (33%)	 25/47 (53%) 22/47 (47%)	 2/6 (33%) 4/6 (67%)
Age initial diagnosis (years)	Mean: 50±12 (median: 51; range: 25-75)	Mean: 49±10 (median: 52; range: 27-67)	Mean: 51±12 (median: 51; range: 25-75)	Mean: 45±17 (median: 43.5; range: 27-68)
Follow-up (months)	Mean: 141±18 (median: 140; range: 120-235)	Mean: 140±15 (median: 139,5; range, 120-172)	Mean: 138±14 (median: 140; range: 120-165	Mean: 167±38 (median: 163; range: 128-235)
Anatomical site femur ○ proximal ○ distal tibia humerus fibula ulna	 47/77 (61%) 9/47 (19%) 38/47 (81%) 8/77 (10%) 17/77 (22%) 4/77 (5%) 1/77 (1%)	 17/24 (71%) 6/17 (35%) 11/17 (65%) 3/24 (13%) 2/24 (8%) 1/24 (4%) 1/24 (4%)	 26/47 (55%) 2/26 (8%) 24/26 (92%) 5/47 (11%) 13/47 (28%) 3/47 (6%) 0/47 (0%)	 4/6 (67%) 1/4 (25%) 3/4 (75%) 0/4 (0%) 2/4 (50%) 0/4 (0%) 0/4 (0%)

Table 8: Summary of patient's demographics

3.1.1 Gender distribution

In our dataset (n=77) the proportion of women was 56% (n=43) and that of men 44% (n=34). A similar distribution (53% female (n=25)) was seen in the group of phone interviews (n=47). In the group of MRI participants (n=24), the proportion of women was greatest among all subgroups 67% (n=16).

In contrast the male proportion of the study participants was 67% (n=4) in the secondary surgery group (Figure 8-11).

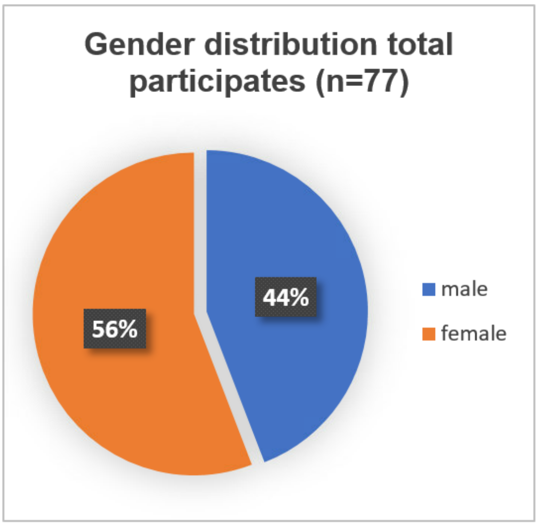

Figure 8: Gender distribution of the entire study population

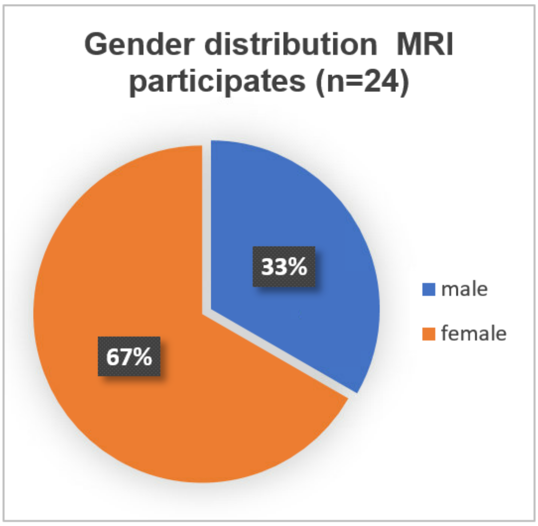

Figure 9: Gender distribution of subgroup "MRI"

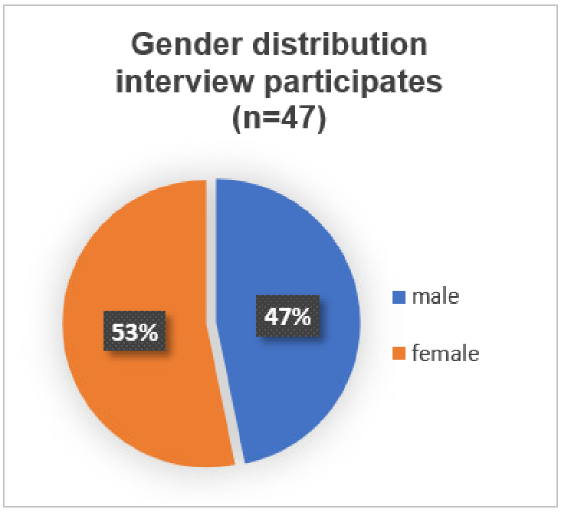

Figure 10: Gender distribution of subgroup "interview"

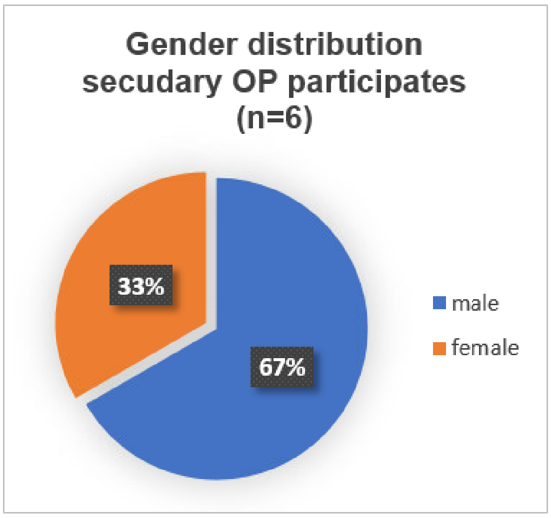

Figure 11: Gender distribution of subgroup "secondary surgery"

3.1.2 Age distribution

At the initial diagnosis, the mean age in the entire sample was 50±12 years (median: 51 years, range: 25-75 years). In the sample of MRI participants, the mean age was 49±10 years (median: 52 years, range: 27-67 years), in the sample of phone interview participants 51±12 years (median: 51 years, range: 25-75 years) and in the group of secondary operated participants 45±17 years (median: 43,5 years; range: 27-68).

At the time of last follow-up examination, the mean age of the entire sample was 62±12 years (median: 63 years, range: 36-85 years), the mean age of the MRI participants was 61±11 years (median: 63 years, range: 37-80 years), in the group of phone interview participants 63±12 years (median: 63 years, range: 36-85 years) and in the group of participants who underwent secondary surgery, the mean age was 59±15 years (median: 56,5 years; range: 39-82 years) (Table 9).

	All patients (n=77)	**MRI (n=24)**	**Phone Interview (n=47)**	**Secondary surgery (n=6)**
Age initial diagnosis (years)	Mean: 50±12 (median: 51; range: 25-75)	Mean: 49±10 (median: 52; range: 27-67)	Mean: 51±12 (median: 51; range: 25-75)	Mean: 45±17 (median: 43.5; range: 27-68)
Age at last follow-up (years)	Mean: 62±12 (median: 63; range: 36-85)	Mean: 61±11 (median: 63; range: 37-80)	Mean: 63±12 (median: 63; range: 36-85)	Mean: 59±15 (median: 56,5; range: 39-82)

Table 9: Age distribution

3.1.3 Follow-up time

The mean follow-up time in the entire study population was 141±18 months (median: 140 months, range: 120-235 months), in the group of MRI participants 140 ± 15 months (median: 139.5 months, range: 120-172 months), the group of phone interview participants 138 months (median: 140 months, range: 120-165 months) and in the group of participants with secondary surgery 167±38 months (median: 163 months, range: 128-235 Months).

3.1.4 Anatomical location of the lesions

In this study, ECs were distributed over five bones: femur, tibia, fibula, humerus and ulna, with the femur and tibia still subdivided into proximal and distal portion. In the remaining bones, only the proximal portion of the bone was affected.

In the entire study sample (n=77), the most frequently affected bone was the femur with 61% (n=47), followed by the humerus with 22% (n=17). Overall, the distal femur was most frequently affected (49%, n=38).

In the group of MRI participants (n=24), the femur in general (71%, n=17) and particularly distal part of the femur (46%, n=11) was also the most frequently affected bone followed by the tibia (13%, n=3), with EC only in the proximal part. The ulna was only affected in one patient in this subgroup (1%).

In the group of phone interview participants (n=47), as in the other groups, the femur in general (55%, n=26) was most frequently affected, particularly the distal part (92%, n=24), followed by the humerus with 28% (n=13).

In the subgroup of participants with secondary surgery (n = 6), only the femur (67%, n=4) and the humerus (33%, n=2) were affected. In the femur, 75% (n=3) of the ECs were located in the distal part and 25% (n=1) in the proximal part of the bone, respectively. The exact distribution of the localization of the lesions in the various subgroups and the entire sample is shown in Figures 12-15.

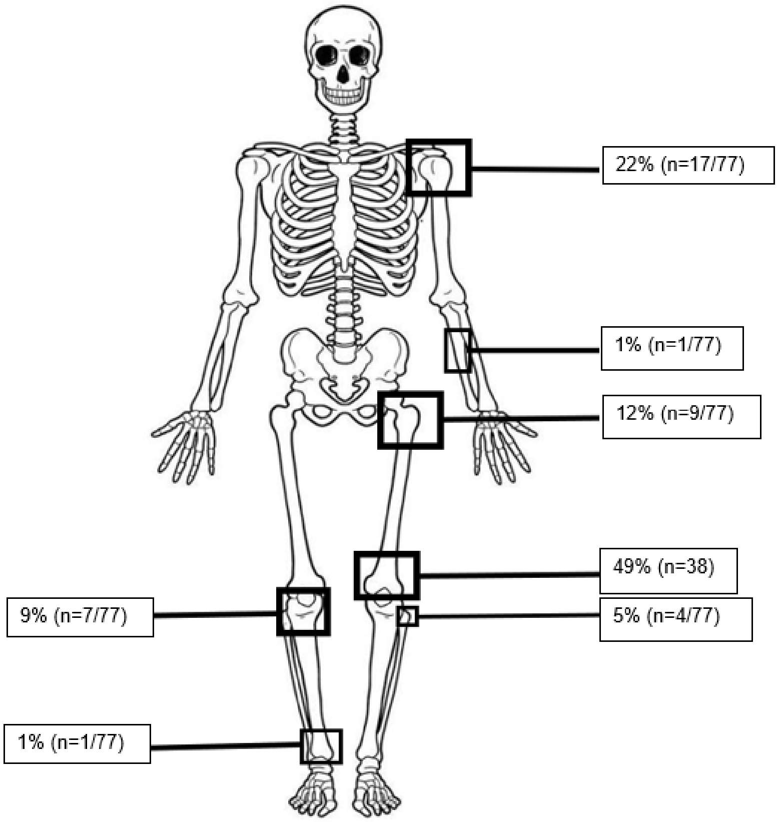

Figure 12: Localization of EC in the entire sample (n=77)

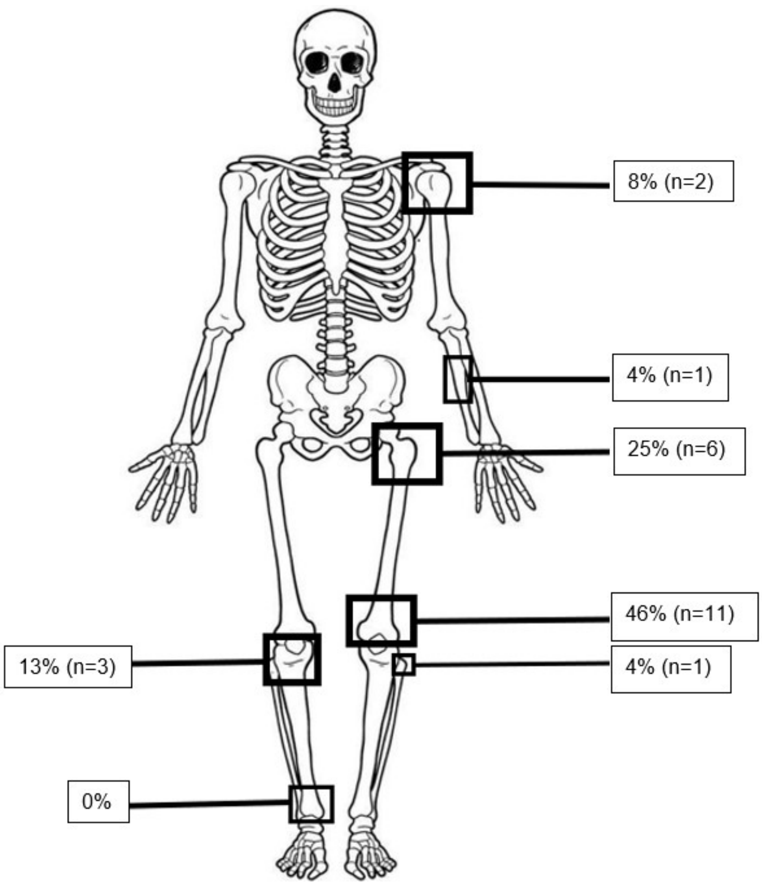

Figure 13: Localization of the EC in MRI subgroup (n=24)

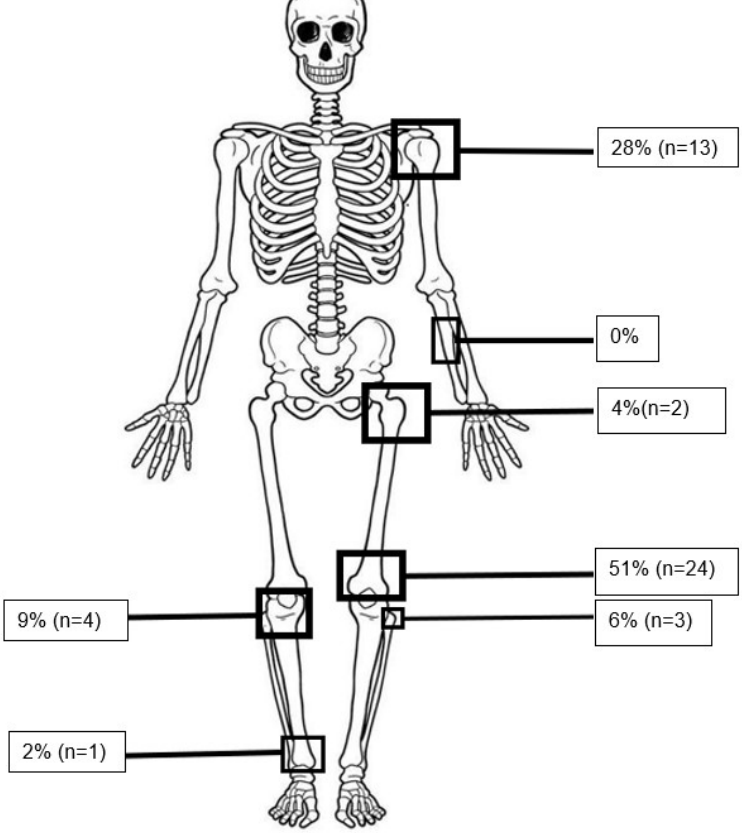

Figure 14: Localization of EC in phone interview subgroup (n=47)

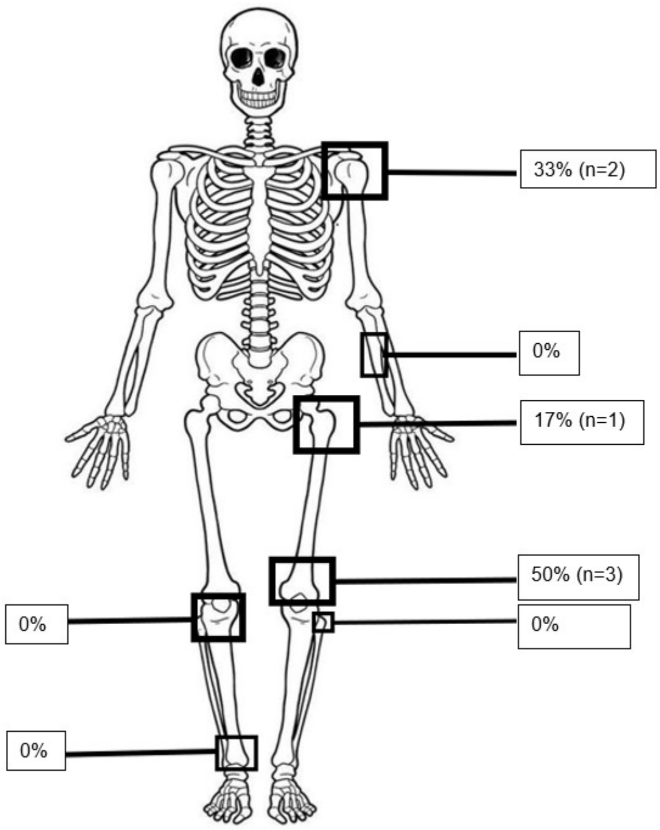

Figure 15: Localization of EC in secondary surgery (n=6)

3.1.5 Size of EC

Due to the partially incomplete MRI data in the subgroups "Phone Interview" and "Secondary Surgery", only the subgroup "MRI" (n=24) was considered for further analysis.

At the time of the initial diagnosis, the mean size of the ECs in the longest extension was 2.3 cm±1.4 cm (median: 2.1 cm, range: 0.6-5.7 cm) (Figure 17). At the last follow-up, the average size in the longest extension was 2.5 cm±1.4 cm (median: 2.3 cm, range: 0.7-6.2 cm) (Figure 18).

The raw data of the individual lesions at the two measurement times are shown comparatively by means of a stem-leaf plot in Figure 16.

Size at initial diagnosis		Size at last follow-up	
Frequency	Stem & Leaf	Frequency	Stem & Leaf
4,00	0. 6678	4,00	0. 7789
7,00	1. 0066688	6,00	1. 067999
7,00	2. 0123578	7,00	2. 1155678
3,00	3. 069	4,00	3. 0146
1,00	4. 4	1,00	4. 1
1,00	5. 0	2,00 Extremes (>=5,2)	
1,00 Extremes (>=5,7)			
Stem width:	1,0 (cm)	Stem width:	1,0 (cm)
Each leaf:	1 case(s)	Each leaf:	1 case(s)

Figure 16: Stem-leaf-plot containing the raw data of the size of EC

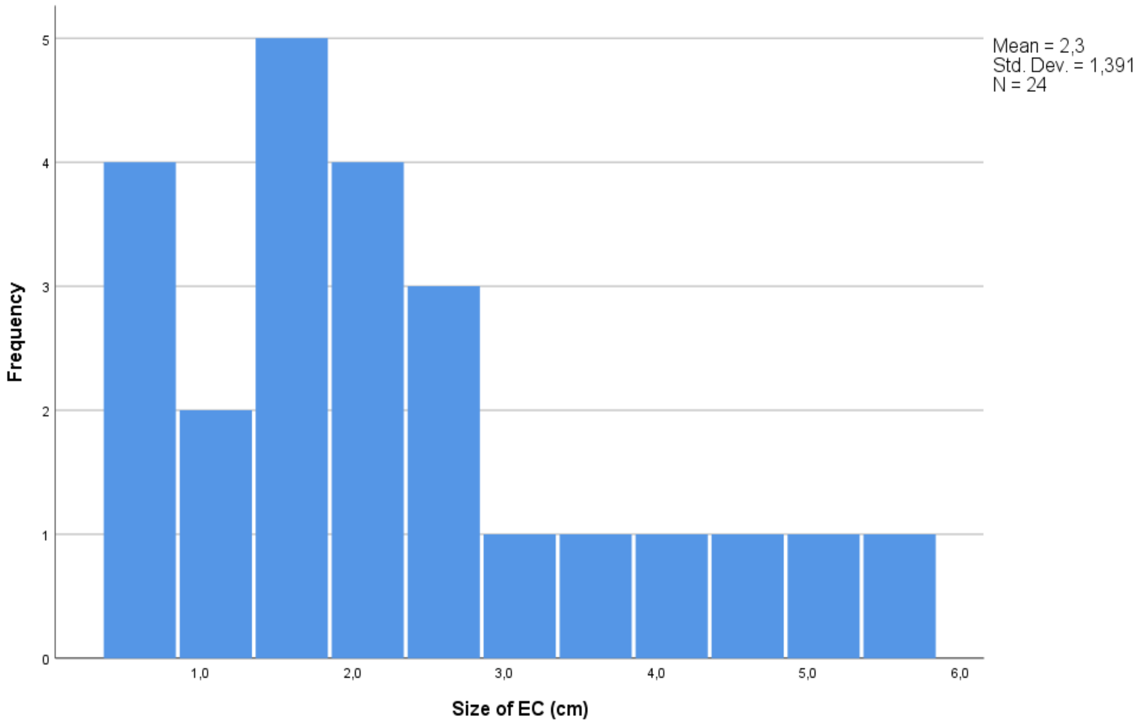

Figure 17: Distribution of size of EC at initial diagnosis

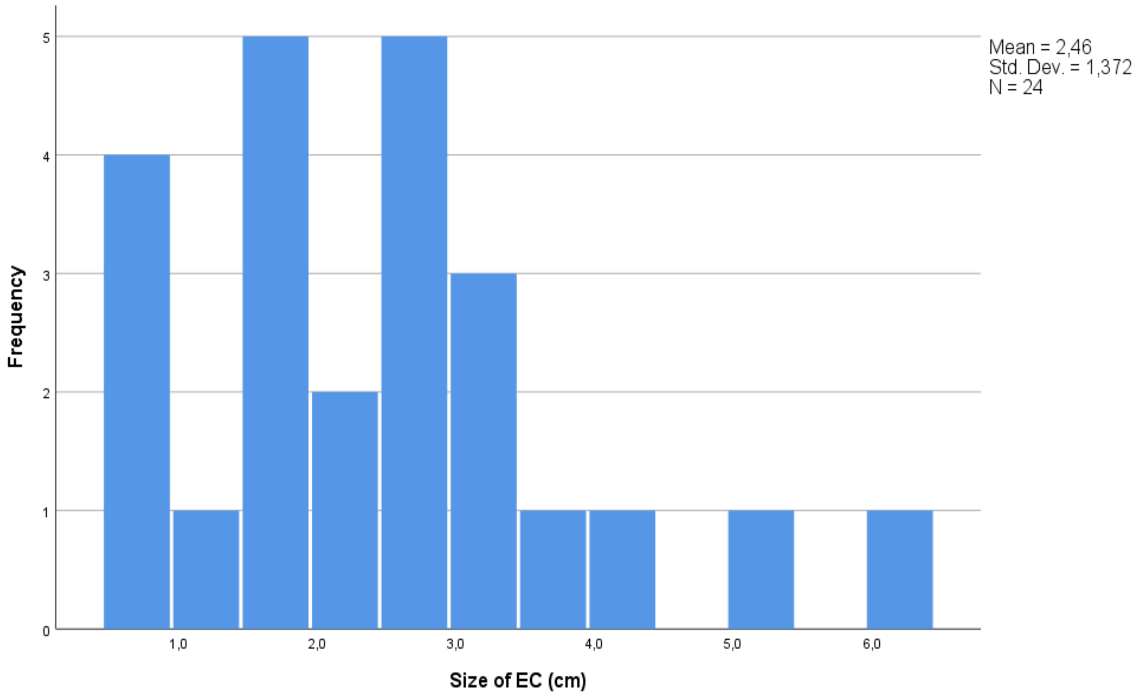

Figure 18: Distribution of size of EC at the last follow-up

3.2 What is the change in the size of untreated incidentally detected EC over a minimum follow-up of 10 years?

When measuring the sizes, a measurement inaccuracy of 2 mm was accepted. Therefore, only lesions with SDS> 2 mm in all three planes were classified as growing lesions. Lesions between -2 mm and +2 mm were classified as stable EC and lesions that had decreased by more than 2 mm have been counted as decreasing EC.

Three EC (12%) regressed in size while the remainder increased (n=11, 46%) or showed no change (n=10, 42%) (Figure 19).

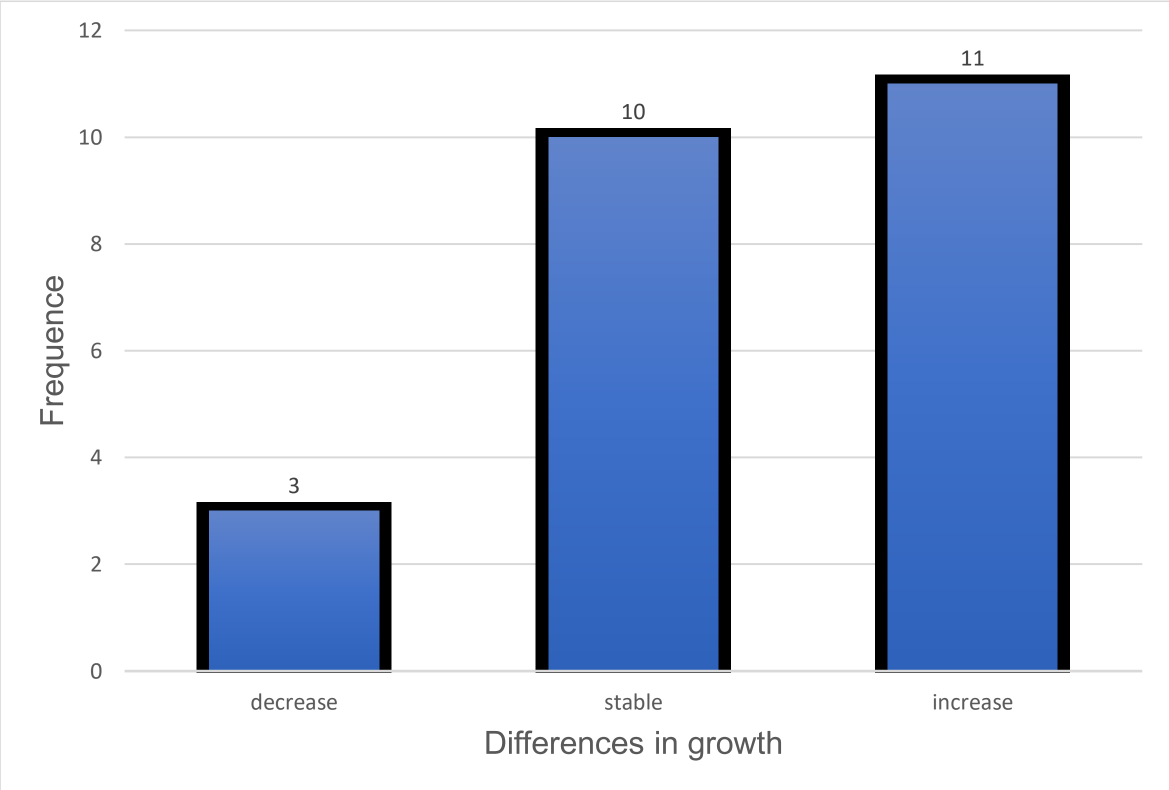

Figure 19: Change in size of untreated EC

Including only those EC that have not decreased (n=21), the mean absolute difference in the largest diameter was 0.3 cm (median 0.1 cm, range -0.2-1.8 cm) between initial and follow-up MRI.

The absolute mean difference in SDS in all three planes was 0.3 cm (median 0.2 cm, range -1.9 - +1.8 cm, Figure 20). The relative increase ranged between 0 and 50 % (mean 12%, median 6%) with respect to initial EC SDS in all three planes (Figure 21). Overall, the mean change of SDS in all three planes per EC per year was 0.04 cm (range 0-0.14 cm/year). Using SDS in all three planes and the ≤ 0.2

mm absolute margin of error 13/24 (54%) of EC did not increase over a minimum follow-up of 10 years. 42% of EC (n=10) had increased more than 5 % of their initial size (SDS in three planes) during follow-up.

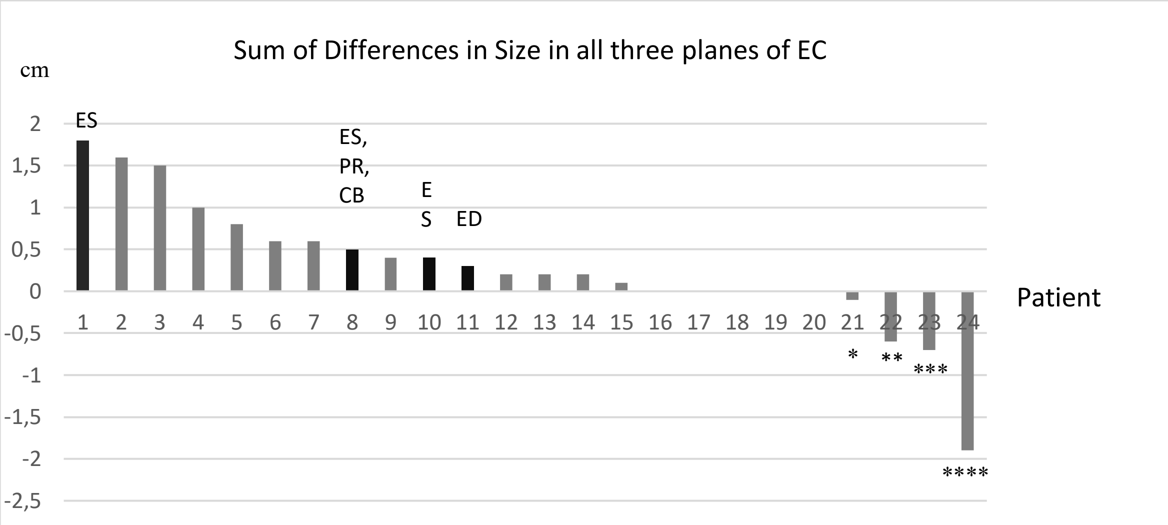

Figure 20: Total growth of EC

ES= endosteal scalloping, CB= cortical breach, PR= periosteal reaction; ED= peritumoral bone edema; *Pat. 21: largest diameter: 0,7 cm initial diagnosis (IND), 0,6 cm last follow-up (FU); SDS in three planes: 1,7cm IND, 1,6 cm last FU ** Pat. 22: largest diameter 5.0 cm IND, 5.2 cm last FU, SDS in three planes: 9.7 cm IND, 9.1 cm FU; *** Pat. 23: largest diameter 4.4 cm IND, 3.6 cm last FU, SDS in three planes: 5.4 cm IND, 4.7 cm FU; ****Pat. 24: largest diameter: 2.8 cm IND, 1.9 cm last FU; SDS in three planes: 6.9 cm IND, 5.0 cm FU;

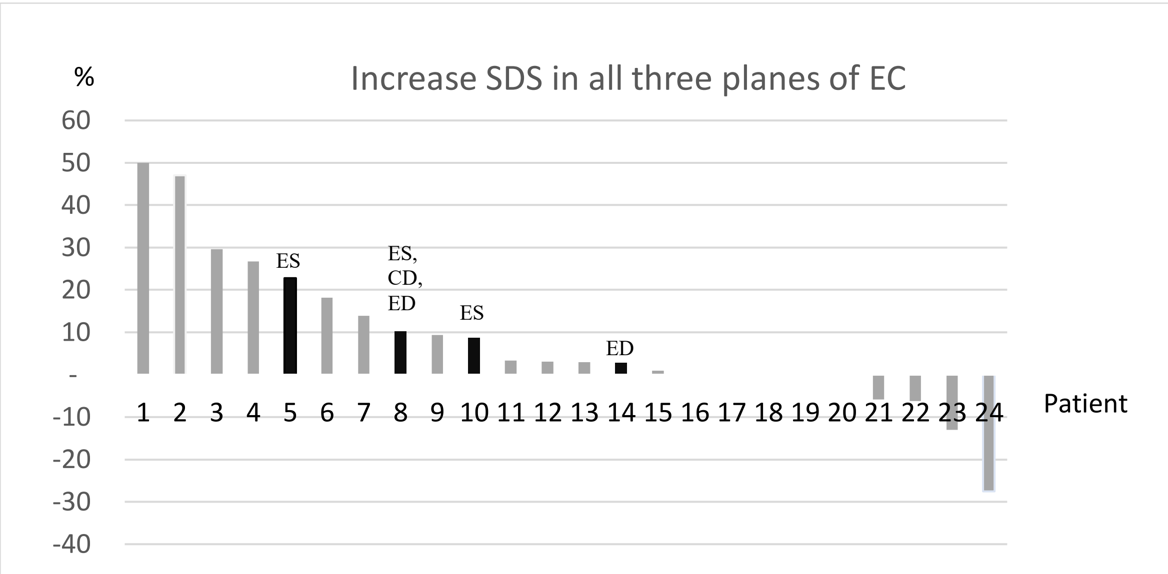

Figure 21: Relative growth of EC

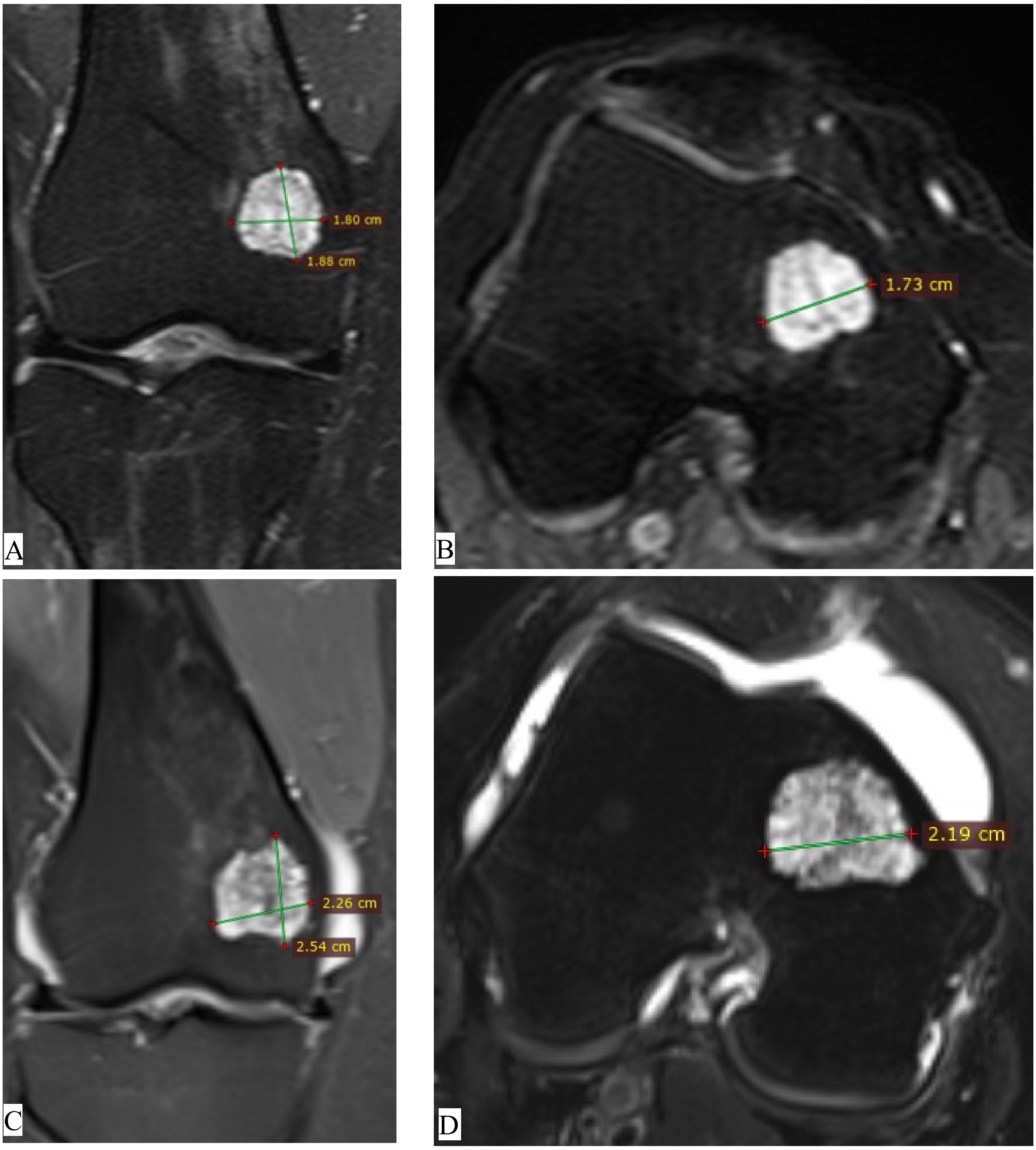

Figure 22: 55-year-old study participant with an increase in the size of the EC (Department of Radiology, Medical University of Graz)

The MRI images (A) and (B) were taken at the initial diagnosis in 2007; the study participant was 43 years old at that time. (A) shows the geographic lesion in the medial condyle of the right femur in a coronal T2W TSE sequence with heterogenous high signal of cartilage matrix corresponding to EC. The image (B) shows the expansion of the EC in the same sequence in the axial plane. The MRI images (C) and (D) show the extent of the EC at the last follow-up. (C) shows the EC in a PD TSE sequence in the coronal plane and (D) shows the EC in a T2W TSE sequence. The SDS in all three levels was +1.7 and in the largest diameter + 0.7 cm.

3.3 What is the percentage of untreated incidentally detected EC of the long bones undergoing malignant transformation?

20/24 (83.3%) patients have shown none of the features indicative of malignant transformation on follow-up MRI. Two patients (8.3%) have newly developed deep endosteal scalloping, and another patient has developed perilesional bone edema on follow-up MRI, all three patients were clinically asymptomatic on the last follow-up. A follow-up MRI examination in 6 months was recommended for these three patients. A patient with known endosteal scalloping showed progression with additional peritumoral edema and periosteal reaction (Table 10). The patient was recommended to have a follow-up MRI examination in 3 months.

Patient ID	Anatomical site	Largest diameter (initial MRI vs last MRI) (cm)	Total sum in size (cm) initial diagnosis	Difference SDS last follow-up (cm) (% increase)	Follow-up (months)	Follow-up MRI
1	Proximal femur, eccentric	1.6 vs 1.9	4.6	+0.4 (9%)	151	**New:** deep endosteal scalloping, clinically asymptomatic
2	Distal femur, central	5.7 vs 6.2	10.7	+0.3 (3%)	141	**New:** perilesional edema, clinically asymptomatic
3	Proximal fibula, eccentric	1.8 vs 1.9	4.9	+0.5 (10%)	144	**New:** cortical breach, periosteal reaction, **Persistent:** deep endosteal scalloping; clinically asymptomatic
4	Proximal humerus, eccentric	3.9 vs 4.1	7.9	+1.8 (23%)	158	**New:** deep endosteal scalloping, clinically asymptomatic

Table 10: Patients with radiological features suggestive for malignant transformation on follow-up MRI

Figure 23: MRI of an EC in the proximal fibula at initial diagnosis (A), (B) with homogenous growth pattern and at the last follow-up (C), (D) with heterogeneous growth pattern and (Department of Radiology, Medical University of Graz)

The 71-year-old female patient had newly developed cortical breach and periosteal reaction but was symptom-free at last follow-up. There is also a change in the structure of the lesion. (A) shows the baseline sagittal MRI images in a T1W TSE sequence with fat-suppression after contrast application with a poly-lobulated geographic lesion in the proximal fibula with peripheral and septal enhancement typical for cartilaginous matrix. At this point the patient was 58 years old and symptom-free. (B) shows a PD TSE FS sequence in the transversal plane. Images (C) and (D) show the corresponding MRI images of the lesion at the time of the last follow-up control. There was a change in tumor morphology with an intensive CE of the tumor lobules. (C) shows the EC in the MRI image in a T1W TSE FS sequence with contrast agent in the sagittal plane, (D) the MRI image in a T2W FS in the transversal plane. When analyzing the change in size in the greatest extent, no increase could be found, but the SDS in all three levels showed a growth of approximately 10%.

3.4 What is the percentage of untreated incidentally detected EC undergoing secondary surgery?

Six out of 110 (8 %) patients underwent secondary surgery during follow-up (Table 11). Only half of them 4% (3/110), had a medically grounded reason for secondary surgery as EC had shown relevant growth between follow-up MRIs. Two further patients insisted on surgical treatment due to anxiety of malignant transformation. Another patient underwent curettage of EC due to persistent pain following 2 months after the initial diagnosis of EC. In this case the diagnosis of EC was confirmed histologically, but the pain persisted due to concomitant cervical degeneration. All patients underwent curettage, and histology confirmed EC.

Anatomical site	Initial size (cm)	Reason for surgery	Time initial diagnosis to surgery (months)	Histology	Surgical procedure	Clinical outcome
Proximal humerus	13.5	Pain	2	EC	Curettage, ORIF and bone cement	persistent pain
Distal femur	11.0	Patient wish	11	EC	Curettage, ORIF and bone cement	asymptomatic
Distal femur	3.0	Patient wish	2	EC	Curettage, bone cement	asymptomatic
Proximal femur	2.0	Radiological growth (15mm)	104	EC	Curettage, bone cement	asymptomatic
Distal femur	1.3	Radiological growth (12mm)	105	EC	Curettage, ORIF and bone cement	asymptomatic
Proximal humerus	4.3	Radiological growth (2.5 cm)	6	EC	Curettage, ORIF and bone cement	asymptomatic

Table 11: Secondary surgery during follow-up

4 Discussion

4.1 Summary

In our study, 14 EC increased in size, showing prolonged growth rate, while the remainder showed no change or regressed in size over a mean follow-up of 11.6 years. In the subgroup of patients in which follow-up MRI was available, there was no consistent growth behavior detectable for EC.

None of the participants in the study showed histologically a malignant transformation into a high-grade CS or undergone surgery for dedifferentiation into high-grade CS. In the MRI subgroup, solitary features of malignant transformation (Table 7) have newly developed in about 17% of EC, however, no clear malignant transformation into a CCS could be determined, it was decided to perform a radiological follow-up in 6-month intervals in these cases. Interestingly, not all EC that developed features of malignant transformation on MRI increased in size during follow-up.

Five percent of conservatively planned EC underwent secondary surgery due to an increase in the size of EC or patient wish during follow-up. All of them were EC upon histological workup.

4.2 EC growth

In the literature, there have been reports of regressions of EC as well as progression and size increase. In their study, Kumar et al. (77) examined a total of 98 patients with intramedullary cartilage neoplasms and 46 patients had a follow-up period of three years. They have concluded that there are both active and latent cartilaginous lesions and that ECs can increase in size. Regarding EC growth, spontaneous regression as seen in our dataset was also observed by Chung et al. (9), who investigated MRI findings of 19 chondroid tumors (either EC or ACT) with a minimal follow-up of 12 months. Currently, reasons for regression are not known, and there are no criteria that reliably help distinguish growing lesions from regressing ones at initial diagnosis. Nevertheless, orthopedic surgeons must decide on further management, i.e., discharge from follow-up, follow-up intervals, or surgery, once EC has been incidentally detected.

A mean EC growth rate of less than half mm per year, as seen in this dataset, is unlikely to be detected on MRI s and in particular not on x-rays when having 6 or 12 months follow-up intervals as recommended by some groups (11, 71, 81, 82). To account for rapidly growing lesions, Kumar et al. (77) suggested a follow-up MRI one year and three years following initial diagnosis to detect so-called active ECs, which they defined as EC that increase more than 6 mm in the first three years following diagnosis. However, the authors' inclusion criteria were "cartilage tumor" and it is unclear how many of them were ACTs. Of note, in this dataset, all EC showing features of malignant transformation at last follow-up have increased less than 6 mm in one plane.

Patel et al. (70) defined an increase of more than one cm in one plane on MRI as a relevant change in central cartilage lesions of the proximal humerus and knee warranting a specialist consultation. Further, this group has suggested an algorithm based on the authors' clinical experience. Patients were discharged from follow-up if central EC is < 4 cm and there is no endosteal scalloping. While this pragmatic approach aims to reduce the number of unnecessary specialist referrals, we have shown that also initially, small eccentric EC can develop endosteal scalloping, which should be followed up. Based on the findings of this study, we recommend follow-up MRI irrespective of initial EC size.

The pragmatic approach of measuring only in one plain must also be critically discussed. Akoh et al. (45) measured the change in growth in only one plane in their retrospective EC study with 55 participants, but only analyzed plain radiograph images. Therefore, they did not have an imaging method in which a measurement was possible in all three planes. Deckers et al. (11) also used the one dimensional method in their follow-up study on EC and ACT/ CS1 with 49 study participants, but they examined the lesions with MRI. However, it should be noted, that their study did not focus precisely on the change in size of the lesion, but on the risk of malignant transformation. The difference in size was only one of several factors, and it has not been described in detail how the lesions changed in size. In studies in which a precise analysis of the change in size was examined, the measurement method with the change in size in all three planes (SDS) was used. In their follow-up study on progression and regression, Chung et al. (9) examined 21 patients with EC or ACT with a minimum follow up of one year and measured the change in size in both the longest spread and in three planes. As already described, Kumar et al. (77) also used the measuring method with the size change in three planes.

This study showed that almost 50% of the EC has increased by more than 5% when measured in all three plains, regardless of the initial size. This cannot be verified with a measurement in one plane. Thus, measuring EC in only one plane underestimate the growth of a lesion.

Absolute threshold values of size, used to enable a possible differentiation between EC and ACT/ CS1, have been long a matter of debate. In an earlier work by Campanacci et al. (78), the authors recommended that lesions smaller than 5 cm can be classified as EC and lesions larger than 5 cm as CS. Patel et al. (70) tried to implement a limit value of 4 cm for daily work with their pragmatic approach. Van der Sande et al. (47) summarized recent results from the literature in a brief commentary. The authors concluded that EC can be assumed if the lesion is smaller than 2 cm and located in the small tubular bones or in the distal metaphysis (48, 50, 52, 83). They also summarized that lesions larger than 5 cm and located in the proximal metaphysis with signs of malignancy in the MRI (e.g. cortical remodeling, deep endosteal scalloping) suggest ACT/ CS1 diagnosis (50, 56). However, they reported on the problem of classifying lesions between 2 - 5 cm as EC or ACT/ CS1 (9, 47). Our study shows that distinction between EC and ACT/ CS 1 cannot only be based on lesion size. The most extensive lesion (5.7 cm at initial diagnosis) in our study showed no signs of malignancy and no change in size after 141 months. In contrast, a lesion that was smaller than 2 cm at the initial diagnosis shows an increase in size and individual characteristics of a malignant transformation after 144 months, which would more likely mean ACT/CS1 diagnosis.

In addition, absolute thresholds in size do not account for the 3-dimensional growth (3D) of ECs. Patel et al. (70) argue that measurement in one plane is practicable and sufficient, as cartilage lesions either extend along the bone marrow cavity or present with endosteal scalloping if they extend in the transverse plane. Nevertheless, EC included in this study regularly showed progressive growth or regressed in all three dimensions. Therefore, an SDS in three planes, the method previously described by Kumar et al. (77), seems more accurate when specifically assessing the growth of a cartilage lesion.

When comparing this 3D to one-dimensional measurements of EC, it is noticeable that only 66% (16/24) of EC were classified in the same category (regression, stable, growing lesion). In 8% (2/24) cases, EC were classified as regressing measuring in one plane while it was increasing in size when using the 3D-method and 4 % (1/24) were classified as increasing measured in one plane while it was regressing in size when using the 3D-method.

In our study, measurement in one plane was less precise and can lead to an incorrect conclusion about the growth behavior, which might directly affect the patient's treatment. Thus, measurement in three planes is relevant for academic projects and should also be applied in daily practice.

4.3 Malignant transformation of EC

While EC/ ACT and high-grade CCS are relatively easy to differentiate on MRI, as the latter often present with overt aggressive features such as cortical breach and soft tissue masses, malignant transformation of EC into ACT is not well defined (70, 84). Three patients have newly developed deep endosteal scalloping on follow-up MRI in our study, which has been described as a worrisome feature suggestive of lesions' growth (61, 71). However, other studies in the literature did not support these findings. The rational is, that correlation between endosteal scalloping and malignant transformation into ACT by assessing the extent of scalloping is limited, and the interobserver agreement is shown to be only fair (50, 77). Furthermore, bone cortex and endosteal scalloping cannot be precisely assessed on the MRI images due to technical conditions regarding the slice thickness and orientation of the cortex in relation to the imaging plane. The fibula, as seen in one patient in this study (Pat. ID 3), with its small diameter, is a frequent pitfall, due to the described technical restrictions in radiological diagnostics (2).

In this patient endosteal scalloping was present in initial MRI, but due to location, difficult to analyze. Additional plain radiographs failed to depict the osteolytic lesion in the fibula. After 144 months of follow-up, the patient had newly developed cortical breach and periosteal reaction. Following multidisciplinary case discussion and despite the medical advice, the patient refused further surgical treatment, and only clinical and radiological follow-up was performed. At the last follow-up three months later, no change in the lesion was noted. This example shows that endosteal scalloping is an important imaging feature that can in early follow-up suggest a possible malignant transformation of the EC. Still, in the fibula, this observation cannot always be applied (2, 85). In our experience, in equivocal cases, additional evaluation using CT should be performed, to provide more diagnostic information.

Patients with incidentally detected EC must be informed about the likelihood of malignant transformation of EC. However, it is difficult to give evidence-based advice on the exact rates as literature is scarce and data are difficult to compare. In this study, histologically the rate of malignant transformation was 0%, radiological 17% of EC showed solitary features of malignant transformation and the decision was made to perform regular MRI follow-up. Other studies showed dedifferentiation rates as high as 4-6 %, depending on anatomical sites. Furthermore, the cited studies' results can be influenced by selection bias, as the unclear and more complicated cases are more likely treated at large tumor centers: Thus the rate of malignant transformation could be overestimated (8, 10, 82). Given the increasing number of MRI examinations performed and the growing incidence for ECs, it seems reasonable that the actual rates of malignant transformation from EC to ACT / CS1 should be significantly lower (70).

Another issue of previous studies analyzing malignant transformation is whether allocation bias was present, i.e., whether the included ECs were truly EC and not ACT at initial diagnosis. (11, 80, 86). Therefore, rates of malignant transformation are difficult to compare. Ahmed et al. (86) recently investigated 73 cartilage lesions with two months minimum radiological follow-up (mean 48 months) and detected a 1.4% dedifferentiation rate. The authors retrospectively analyzed cartilage lesions from their institutional database and allocated lesions, mainly based on plain radiographic findings into EC or ACT/CS groups. Due to the very short follow-up, the results regarding the long-term behavior and the risk of malignant transformation must be viewed critically, since in this short time hardly any changes are to be expected in a tumor that, due to its biology, is avascular and has a slow metabolism (75).

Although the study population is smaller in our study, the data are conclusive because the minimum follow-up period was 10 years. According to state-of-the-art imaging guidelines, all ECs should be assessed using MRI as well as CT/ plain radiograph. However, the EC analysis using plain radiographs is less sensitive in detecting the features suggestive of malignant transformation such as cortical destruction or the extent of soft tissue masses (50, 77).

4.4 Secondary surgery

Either development of features suggestive for malignant transformation or significant tumor growth are objective reasons for secondary surgery of EC (11). In this study two patients have requested surgery due to anxiety of possible malignant transformation of EC. Another issue is subjectivity of the patients and false relating of the symptoms with EC, albeit an alternative condition might be the reason for pain. Whether the presence of pain is helpful to detect progression of EC is discussed controversially (70, 77) as an alternative explanation of symptoms is often possible. Patients with conservatively treated EC who show solitary signs of malignant transformation in the radiological follow-up, such as endosteal scalloping without other features of aggressiveness, but do not report any clinical symptoms relating to EC, should not undergo surgery (27). Finally, indicating surgery for EC should be carefully considered, as complication rates, particular for larger EC, are relatively high. Campanacci et al. (78) reported in their retrospective review study on 85 patients with diagnosed CS1 the complication rates for segmental resection and intralesional curettage of 28.6% and 1.6% respectively. In their retrospective study, Omlor et al. (87) examined 228 patients with EC or ACT / CS1 and analyzed the outcome between conservative and surgical therapies. The outcome parameters were pain, satisfaction, functional limitations, and the musculoskeletal tumor society (MSTS) score. The group with conservative therapy had significantly less pain and fewer functional limitations. Our study also confirms the recommendation to choose surgical therapy with a very strict indication. All secondary operated lesions in our study were confirmed as EC after the histological assessment, regardless of whether the lesion showed growth, or the patient reported pain. Our research also indicates that surgically treated ECs do not have a better outcome than conservatively treated ECs. The patient with Pat.-ID 1 in the secondary surgery study population (Table 11) associated his chronic cervical spine pain with the relatively large tumor in his humerus and after a short time wished to undergo a surgery. After the operation, the pain persisted, and therefore no benefit occurred from the operation. On the contrary, no patients of the study reported pain in the EC area on long-term follow-up.

4.5 Limitations of the study

The results of this study must be interpreted with caution, as there are certain limitations. First, due to the retrospective study design this study might be subject to selection bias. In particular, about 30% of patients were lost to follow-up, i.e., phone contact or follow-up MRI was not possible. Further selection bias might be present, as included ECs were relatively small in size with a mean largest diameter at initial diagnosis of 23 mm. Larger EC were more likely to undergo primary resection since at the time of EC diagnosis, indication for surgical treatment was often made when EC was > 5 cm. Although the results might not be generalizable to larger ECs, the mean initial size of EC in this study is representative of the majority of all EC (1, 77, 83).

Another limitation arises from the small number of study participants, making it difficult to detailed statistical analyses about EC growth and the risk of malignant transformation. However, this sample has analyzed the longest average follow-up for EC reported so far and a very accurate measurement of change in EC size.

A further limitation of the study is that in some patients, the initial diagnostic imaging was performed on a 1.5T device, whereas the follow-up was performed on a 3T MRI device which influences the image quality and consequently an image analysis.

Finally, concerning secondary surgeries the pressure that the patient exerts on the orthopedic surgeon and vice versa concerning their subjective feeling (e.g., fear of malignant transformation, pain association with the tumor) might influence treatment decisions.

5 Conclusion

This study has shown that long-term imaging follow-up is justified for all EC, irrespective of initial lesion size, as suggested in the past. EC have shown unpredictable growth patterns, and if they increase in size, they progress slowly. Thus, it seems reasonable to extend follow-up intervals to several years instead of annual or biannual follow-up. The absolute threshold values of size should also be critically assessed and redefined when deciding whether a lesion should be subjected to a follow-up check or not.

Secondary operations in EC are rare and, in our study, patients did not benefit from the operation. All lesions undergoing secondary surgeries were histologically confirmed as EC and if pain was indicated for surgery, the pain persisted after the operation. Therefore, a decision about secondary surgery should always be questioned critically and a conservative approach should be preferred.

MRI is the preferred imaging modality as it reliably detects features of progression of EC. The presence of solitary features of biological aggressiveness, such as endosteal scalloping, without clinical symptoms, does not require surgery but follow–up. This difficult distinction between EC and ACT/ CS1 results in a possible field of research. In this work, it was not always possible to conclusively clarify whether it is an EC or an ACT/ CS1. A further examination of this entity and the elaboration of additional reliable differentiation criteria would be worthwhile in clinical work.

When assessing EC, it is important to consider individual criteria such as anatomical localization, growth direction, and growth rate, which underlines the importance of multidisciplinary work.

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7 Attachment

Case Report Form

Observational study on conservatively managed cartilage tumors of unknown malignant potential of the long bones

Patient ID:		
Datum der		Nachkontrolle:
UntersucherIn:		

Einwilligung des/der PatientIn Ja ☐ Nein ☐ vorhanden:

Labor: Hausarzt ☐ LKH ☐

Serum-Kreatinin (mg/dl)	GFR > 30 (ml/min)	Datum der Untersuchung
	Ja ☐ Nein ☐	

Kontrastmittel Allergie? Ja ☐ Nein ☐

Metallimplantate Ja ☐ Nein ☐ vorhanden?

wenn ja, welche (Prothesen (Knie/Hüfte), Schrittmacher, Z.n. Verletzung mit Metallsplittern, etc.):

Telekonsil: Ja ☐ Nein ☐

ERSTDIAGNOSE

Datum der Erstdiagnose:	
Therapie: operativ / konservativ	Konservativ ☐ operativ ☐
Datum/ Ort erstes MRT:	
Erstes MRT vorhanden:	Ja ☐ Nein ☐
Wie wurde die Erstdiagnose gestellt:	Zufallsbefund ☐ lokale Beschwerden ☐

Wurden seit der Erstdiagnose weitere Kontrollen durchgeführt: Ja ☐ Nein ☐

Wenn ja, wo und in welchen Abständen:

Wenn ja, mit welchen Methoden:
klinisch ☐
nativradiologisch ☐
MRT (ohne KM) ☐ (mit KM) ☐
CT (ohne KM) ☐ (mit KM) ☐

Wurde eine Knochenszintigraphie durchgeführt: Ja ☐ Nein ☐

wenn ja, wo und Tracer Uptake Ort:	Tracer Uptake:
Ort:	Tracer Uptake:

MRT Kontrolle

MRT Gerät (Tesla):	LKH ☐ Tesla:	Auswärts ☐ Tesla:
MR Protokoll:		
Verwendetes Kontrastmittel		
Kontrastmittelreaktion:		

Nachbesprechung an der Orthopädie stattgefunden: Ja ☐ Nein ☐

Andere Komplikationen Ja ☐ Nein ☐

Wenn ja, Meldung erfolgt/notwendig?

Fragebogen (Brief Ilness Perception Questionnaire) Ja ☐ Nein ☐ ausgefüllt:

Nachuntersuchung Orthopädie Ja ☐ Nein ☐

Klinische Symptomatik an der betroffenen Region: Ja ☐ Nein ☐

Lokalstatus:

Wurden an der betroffenen Region Operationen durchgeführt (K-TEP, ASK, etc.)

Ja ☐ Welche:
Nein ☐

Fazit Nachkontrolle: Befundprogredienz	Ja ☐ Nein ☐
Vereinbarung Nachsorgetermin mit Patienten:	Ja ☐ Nein ☐

Wenn ja -> Ort:	Datum:	Intervall:
Wenn nein -> Ursache: Ablehnung durch Patienten ☐		
Anderer Ursache für Ablehnung:		

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Unterschrift