Thesis

Prevalence of enchondromas and atypical cartilaginous tumours in the knee and shoulder region as identified on MRI.

submitted by

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Graz, 19th April 2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 19th April 2023 Johannes Nikolaus Woltsche m.p.

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Abstract in German

Titel: Prävalenz von Enchondromen und atypischen kartilaginären Tumoren im Knie- und Schulterbereich am MRT.

Einleitung: Enchondrome sind benigne, intraossäre, knorpelige Tumoren des Knochens. Atypische kartilaginäre Tumoren (ACTs) stellen ihre intermediäre Form im Bereich der Röhrenknochen dar. Der Großteil dieser Tumoren präsentiert sich asymptomatisch, weswegen sie zumeist anhand einer Bildgebung erstdiagnostiziert werden, die ursprünglich aus anderen Gründen durchgeführt wurde. Dementsprechend ist wenig zur wahren Prävalenz von Enchondromen und ACTs von Knie und Schulter bekannt. Fünf Studien haben bis jetzt die Prävalenz von kartilaginären Tumoren im Bereich des Knies in kleinen bis mittelgroßen Studienkohorten untersucht. Eine einzige Studie hat die Prävalenz von Enchondromen der Schulter in einer kleinen Untersuchungskohorte ermittelt. Das Ziel dieser Diplomarbeit war es, die bisher existierenden Zahlen zu diesem Sachverhalt zu verifizieren bzw. kritisch zu hinterfragen.

Material & Methoden: Die Magnetresonanz (MRT)-Befunde aller Patient*innen, die eine MRT des Knies (44.762 Patient*innen) oder der Schulter (21.550 Patient*innen) zwischen 01.01.2007 und 01.03.2020 an einem radiologischen Privatinstitut erhalten hatten, wurden elektronisch nach den Diagnosen Enchondrom und ACT durchsucht. Die so erhaltenen Ergebnisse wurden vom Diplomanden überprüft. Bei unschlüssigen Fällen wurden MRT-Bilder und -berichte von einem erfahrenen Radiologen sowie einem Tumororthopäden überprüft.

Resultate: Die Analyse der 44.762 Patient*innen mit einer MRT des Knies zeigte, dass 651 von diesen zumindest einen kartilaginären Tumor hatten. Manche Patient*innen wiesen mehr als eine Läsion auf. Insgesamt wurden 672 Tumoren entdeckt, von denen 22 als ACT klassifiziert wurden. Daraus resultierte eine Prävalenz von 1.45% für kartilaginäre Tumoren des Knies (Enchondrome: 1.4%; ACTs: 0.05%). Dreiundneunzig der 21.550 Patient*innen mit einer MRT der Schulter hatten zumindest ein Enchondrom/ACT. Insgesamt wurden 97 Tumoren gefunden, von denen 8 als ACT eingestuft wurden. Es ergab sich somit eine Prävalenz von 0.43% für kartilaginäre Tumoren der Schulter (Enchondrome: 0.39%; ACTs: 0.04%).

Schlussfolgerung: Aufgrund von der hohen Anzahl an MRT-Bildern kann davon ausgegangen werden, dass diese Diplomarbeit sehr exakte Zahlen bezüglich der Prävalenz kartilaginärer Läsionen von Knie und Schulter liefert. Die Resultate dieser Diplomarbeit

zeigen, dass die Prävalenz von Enchondromen und ACTs bisher in den meisten Studien überschätzt wurde, sowohl für das Knie- als auch Schultergelenk.

Abstract in English

Title: Prevalence of enchondromas and atypical cartilaginous tumours in the knee and shoulder region as identified on MRI.

Introduction: Enchondroma is a benign intraosseous cartilage tumour of the bone with atypical cartilaginous tumour (ACT) representing its intermediate counterpart in the appendicular skeleton. As most of these tumours present clinically silent, they are usually discovered as an incidental finding on imaging performed for other reasons. Therefore, little is known regarding the true prevalence of enchondromas and ACTs around the shoulder and the knee. Five studies based on small- to intermediate-sized cohorts have presented figures for the prevalence of enchondromas of the knee and only one small-sized study has examined the prevalence of benign cartilage tumours around the shoulder. The aim of this diploma thesis was to challenge/validate the results of these studies via analysis of significantly larger patient cohorts for knee and shoulder.

Material & Methods: Magnetic resonance imaging (MRI) reports of all patients who had undergone MRI of the knee (44.762 patients) or shoulder (21.550 patients) between 01.01.2007 and 01.03.2020 at a radiological institute were electronically searched for diagnosis of enchondromas and ACTs. Results obtained were reexamined by the diploma student. If cases presented inconclusive, MRI scans and reports were thoroughly checked by an experienced radiologist and an expert orthopedic oncologist.

Results: Investigation of 44.762 patients who had received a knee MRI in the study period revealed that 651 of them had a cartilage tumour. As some patients presented with two lesions, 672 tumour cases were ultimately found, with 22 of them classified as ACTs. This resulted in a prevalence of 1.45% for cartilage lesions around the knee (enchondromas: 1.4%; ACTs: 0.05%). Examination of 21.550 patients with a shoulder MRI showed that 93 patients had a cartilaginous tumour. Altogether 97 tumour cases (89 enchondromas, 8 ACTs) were revealed. Therefore, a prevalence of 0.43% can be reported for cartilaginous lesions around the shoulder (enchondromas: 0.39%; ACTs: 0.04%).

Conclusion: Due to enormous number of included MRI scans, it can be supposed that this diploma thesis has the power to provide exact figures regarding prevalence of enchondromas and ACTs around the knee and the shoulder. The findings show that prevalences of enchondromas/ACTs around the knee and shoulder have largely been overestimated.

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List of Abbreviations

ACT .... *atypical cartilaginous tumour*
a-KG .... *alpha-ketoglutarate*
CT .... *computed tomography*
D2HG........ *D-2-hydroxyglutarate*
DNA........ *deoxyribonucleic acid*
DTA .... *data transfer agreement*
EC .... *enchondroma*
FIH-1 .... *factor inhibiting HIF1a*
FS........ *fat-suppressed*
FS-PD .... *fat-suppressed proton density*
Gd-DTPA........ *gadolinium diethylene-triamine penta-acetic acid*
HIF1a .... *hypoxia-inducible factor 1 alpha*
IDH .... *isocitrate dehydrogenase*
MRI........ *magnetic resonance imaging*
NGS .... *next-generation sequencing*
PD .... *proton density*
PET-CT........ *positron emission tomography computed tomography*
Seq. .... *sequence*
SUV .... *standardized uptake value*
TSE .... *turbo spin echo*
WHO........ *World Health Organization*

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1 Introduction

1.1 Definition

Enchondroma is a benign, intraosseous, cartilaginous tumour of bone that usually occurs as a solitary lesion (1). It needs to be differentiated from another benign cartilaginous bone lesion called osteochondroma (also known as exostosis), which represents an outgrowth of cartilage and bone and can be found frequently (2). Enchondromatosis is defined as the finding of multiple enchondromas in one patient, which can be seen in Ollier's disease as well as Maffucci syndrome (3). The intermediate/malignant counterparts of enchondroma are represented by atypical cartilaginous tumour (ACT) and chondrosarcoma, with the former one being subdivided into 3 different grades (4): The majority of chondrosarcomas are grade 1 to grade 2 chondrosarcomas, only seldomly metastasizing and usually behaving indolently. As opposed to these, grade 3 chondrosarcoma shows high potential of metastasis (5). In 2020, the WHO introduced a new classification and terminology for intermediate/malignant cartilaginous tumours: Chondrosarcoma grade 1 of the appendicular skeleton was termed ACT. Consequently, the term chondrosarcoma grade 1 today only refers to malignant cartilaginous tumours of the axial skeleton (e.g. spine, pelvis) (4). This distinction of histologically indifferent tumours solely depending on the site of the lesion takes into account that ACTs (chondrosarcomas grade 1 of the appendicular skeleton) show less aggressive local behaviour and better clinical outcome (4).

1.2 Epidemiology

1.2.1 Prevalence of enchondromas

As most of enchondromas are asymptomatic, their true prevalence is unknown (6). Only a handful of studies have focused on the frequency of enchondromas up until now: Brien et al. showed that enchondroma accounted for 7.7% of all cases in a series studying 3.067 primary tumours of bone and tumour-like lesions (7). Another study stated that solitary enchondroma represents the second most common benign cartilaginous lesion (following osteochondroma) constituting approximately 3-17% of all primary tumours of bone in large biopsy series (1).

1.2.1.1 Prevalence of enchondromas around the knee joint

Up to now, five studies have focused on finding the prevalence of enchondromas around the knee. Walden et al. examined 449 routine MRIs of the knee and identified 14 enchondromas in 13 patients (2.9%). With 9 cases (2%), the distal femur was most frequently affected by incidental enchondroma. This number is 10 times higher than the distal femoral prevalence of incidental enchondromas in an autopsy series (0.2%), highlighting the MRI's high sensitivity in identifying small lesions (8, 9). In a study examining 1.285 patients, these results were confirmed with the finding of a very similar prevalence for benign cartilaginous tumours (2.8%) (10). Douis et al. also found a prevalence of 2.9 % for enchondroma, when analysing 240 MRIs of the knee and discovering seven enchondromas (11). Another research team examined MRIs of knee osteoarthritis patients (n=132) and compared them with MRIs of healthy individuals (n=601), thereby revealing that the first group showed a higher prevalence of enchondromas (1.5%) than healthy controls (0.8%) (12). Both figures, however, indicated a lower prevalence of enchondromas than the other studies (12).

1.2.1.2 Prevalence of enchondromas around the shoulder joint

Up to now, only one study has investigated MRIs of the shoulder joint regarding the prevalence of enchondromas in this region (13). Hong et al. found enchondromas of the shoulder girdle in 10 patients, when examining a cohort of 477 patients, thereby detecting a prevalence of 2.1% (13).

1.2.2 Age distribution

Patients with enchondromas most typically present between the third and the fourth decade of life (6).

1.3 Etiology and pathogenesis

1.3.1 Etiological hypothesis

It is a widely believed theory that intramedullary chondromatous tumours arise out of cartilaginous remnants that have been displaced from the growth plate (7, 11, 14). This physeal remnants are trapped in the metaphysis of long bones and remain there. If this process involves multiple growth plates, development of enchondromatosis (a condition in whom patients are affected by multiple enchondromas, e.g. Ollier's disease) can be the consequence (7). This etiological hypothesis is mainly based on the finding that most enchondromas are localized in the metaphysis of long bones (1, 11). However, there is new evidence that this theory alone cannot sufficiently explain the pathogenesis of enchondromas, as Potter et al. (15) discovered that not all enchondromas reside in the metaphysis of long bones (in their cohort of 508 patients with benign intramedullary chondromatous tumours 33 patients [6.5%] showed an enchondroma of the epiphysis). Furthermore, Douis et al. challenged this long-lasting hypothesis, when examining 240 MRIs of the knee of skeletally immature individuals and finding no signs of displaced metaphyseal cartilage in any patient (11). In case the traditional hypothesis of enchondroma's evolution were to be true – according to Douis et al. – cartilaginous remnants must be found in the metaphysis of long bones in skeletally immatures just as frequently as enchondromas are found on MRIs of the knee in adults (11).

1.3.2 Genetics

Isocitrate dehydrogenase (IDH) mutations represent a typical oncogenic driver in malignant gliomas (16). Patients suffering from Ollier's disease and Maffucci syndrome show an increased risk of gliomas. This incited Amary et al. to examine IDH mutational status in cartilaginous bone tumours. The results revealed that 56% of central and periosteal cartilage tumours show IDH1/IDH2 mutations (52% of central low-grade cartilage tumours / 58.9% of central high-grade cartilage tumours: chondrosarcomas grade 2 and grade 3 / 56.5% of central high-grade cartilage tumours: dedifferentiated chondrosarcoma / 71.43% of periosteal chondromas / 100% of periosteal chondrosarcoma). Strikingly, however, mutation-positive tumours showed a significantly higher frequency in bones of hands and feet (90% of these tumours were mutation-positive) compared to extra-acral sites (53.2% of cartilage tumours in the long bones and 35.1% of cartilage tumours in the flat bones of the appendicular skeleton harbour a IDH1/IDH2 mutation). Amary et al. stated, however, that this frequency of IDH1/IDH2 mutations may well be an underestimate due to limitations of the DNA sequencing methods applied. They predicted that the true prevalence of IDH mutations in cartilage tumours would be closer to 70%, which would still leave a significant number of tumours that do not harbour IDH1/IDH2 mutations (17). Another study primarily focusing on IDH mutational status in patients suffering from enchondromatosis showed that 88% of enchondromas in patients with Ollier's disease, 80% of enchondromas in patients with Maffucci syndrome and 56% of solitary enchondromas presented as IDH1/IDH2-mutation-positive (18). In 2019, Saiji et al. applied Next-generation sequencing (NGS) to enchondromas, which is able to detect also low-level mosaic-like mutation rates: 13 enchondromas from 8 patients were examined, and NGS identified a positive IDH mutational status in every tumour. What is more, NGS revealed identical mutations in the tumours of patients suffering from enchondromatosis, thereby confirming the concept of somatic mosaicism (19).

1.3.3 Metabolism and the role of IDH

Humans have 3 different IDHs (IDH1, IDH2, IDH3), which are encoded by 5 genes. Physiologically, IDH catalyzes the oxidation of isocitrate to alpha-ketoglutarate (a-KG), which is a very important reaction in Krebs cycle (20). Furthermore, IDH can also catalyze the reduction of a-KG to isocitrate, an essential metabolic step in tumour cells under hypoxic conditions, in order to carry out glutamine-dependent lipogenesis (21).

Hotspot mutations in the genes of IDH1 and IDH2 are followed by the production of D-2-hydroxyglutarate (D2HG) (22). D2HG is an oncometabolite inhibiting a-KG-dependent dioxygenases like TET2, playing an important role in DNA demethylation. Consequently, high levels of D2HG lead to hypermethylation of CpG dinucleotides causing alterations as far as gene transcription and genome stability are concerned, thereby affecting differentiation (23). D2HG is also considered to inhibit other a-KG-dependent oxygenases (histone demethylases) and by that inducing histone hypermethylation (23, 24).

In addition, decreased levels of a-KG due to IDH-mutation cause a reduction of intermediates of Krebs cycle (succinate, fumarate, malate). This perturbation of Krebs cycle’s function, which resembles the centerpiece of cell metabolism as it integrates several metabolic pathways, leads to an increase of many amino acids (glycine, serine, methionine, tryptophan, asparagine, phenylalanine, tyrosine, threonine), thereby enabling anabolic routes promoting tumourigenesis (23).

It remains to be resolved whether increased D2HG-levels in IDH-mutant neoplasms also stimulate tumourigenesis by activating hypoxic response pathways via HIF1a (hypoxia-inducible factor 1 alpha). The degradation of HIF1a is initiated by post-translational hydroxylation, catalyzed by a-KG-dependent prolyl hydroxylases. Von-Hippel-Lindau protein is then able to bind to this transformed HIF1a subunit, thus causing ubiquitination and subsequent proteasomal breakdown of HIF1a (25). There are some conflicting studies as far as the impact of D2HG on HIF1a is concerned. On one hand, research indicates that prolyl hydroxylases are inhibited by D2HG resulting in an increase of HIF1a (26) that has proven to be a potent driver in tumourigenesis as it upregulates the expression of angiogenic factors, glycolysis (thereby enhancing the Warburg effect) and synthesis of nucleotides, lipids and amino acids (22, 23). Xu et al. also observed that the D2HG's enantiomer L2HG is even more potent in inhibiting prolyl hydroxylases (26). Koivunen et al. confirmed the inhibition of prolyl hydroxylases via L2HG. However, they obtained different results concerning D2HG, as their data showed that D2HG enhances degradation of HIF1a via increasing prolyl hydroxylase activity (27). Xu et al. postulate that D2HG stabilizes HIF1a, whereas Koivunen et al. state that D2HG causes HIF1a degradation. In part, Reiter-Brennan et al. offer a solution to this conflicting situation: D2HG and L2HG are known to suppress FIH-1 (factor inhibiting HIF1a), which as the name says inhibits HIF1a. Upregulation of D2HG or/and L2HG could thereby cause stabilization of HIF1a and support tumourigenesis (22, 28, 29).

IDH mutations represent an early event in cartilaginous tumourigenesis, whereas HIF1a expression can only be found in high-grade chondrosarcoma (30, 31). Thus, the questions arise whether there is a causal connection between IDH mutations and increased HIF1a expression and whether increased HIF1a expression is a potent driver of tumourigenesis in cartilaginous tumours (23).

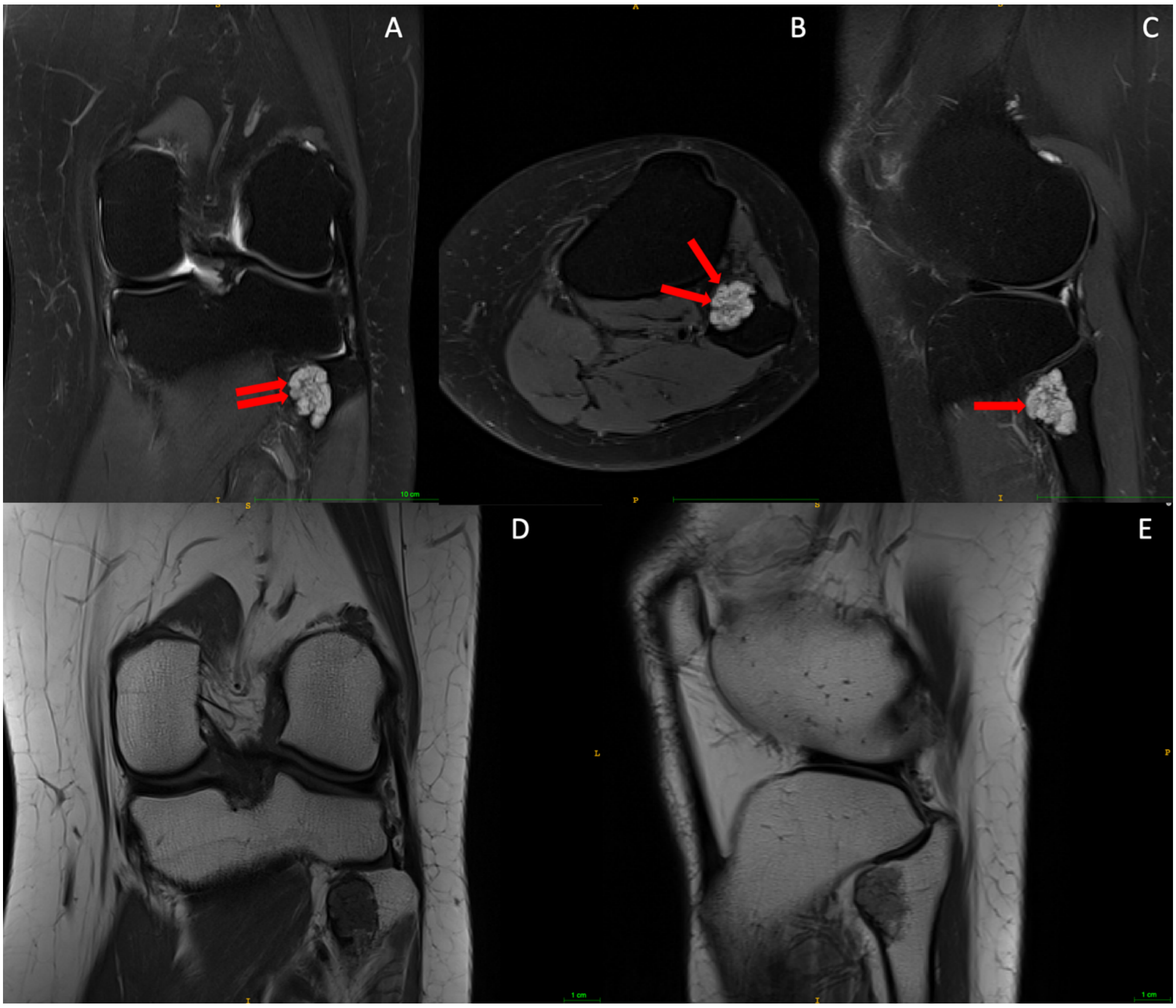

Figure 1. MRI of an ACT (deep endosteal scalloping [red arrows], no periosteal reaction, no perilesional edema, tumour size of 2.1 cm) of the left fibula (female, 48 years): (A) proton density, fat suppression, coronal, turbo spin echo; (B) proton density, fat suppression, transversal, turbo spin echo; (C) proton density, fat suppression, sagittal, turbo spin echo; (D) t1, coronal, turbo spin echo; (E) proton density, t2, sagittal.

1.4 Clinical presentation

1.4.1 Localization of enchondroma

Forty to sixty-five percent (40-65%) of enchondromas are localized in the phalanges and metacarpals of the hand, with most enchondromas residing in the proximal phalanges (40-50%), followed by enchondromas of the middle phalanges (20-30%) and enchondromas of the metacarpals (15-30%) (1). The most common finger to be involved is the little finger, whereas the thumb represents the finger least commonly affected by benign intraosseous chondromatous lesions (1, 6). Long bones as femur, humerus and tibia, come second after the small bones of the hand, with 25% of enchondromas affecting these bones around the knee and the shoulder joint (1, 6). Phalanges and metacarpals of the feet account for approximately 7% of enchondromas, whilst the remaining body sites are rarely affected by enchondroma (6).

1.4.2 Symptoms

Enchondromas most commonly present asymptomatic, they are clinically silent. Depending on lesion size and location they sometimes cause pain and in seldom cases can even lead to pathologic fractures (especially phalanges). Thus unsurprisingly, the most common risk factors for symptomatic enchondroma are large lesion size and location in small bones (10, 32).

As enchondromas most often present clinically silent, they are typically diagnosed as an incidental finding during routine clinical imaging (i.e. on radiographs, on CT [computed tomography] scans and on MRI [magnetic resonance imaging] scans) performed for other reasons (33, 34). A study performed by Levy et al. (34) analysed a cohort of patients with an enchondroma of the proximal humerus (n=57), who suffered from shoulder pain. They discovered that 47 patients (82%) reported on shoulder pain due to other pathologies than cartilaginous tumours, with rotator cuff tears presenting to be the most common origin of pain (34).

1.5 Diagnosis

1.5.1 Imaging

As the majority of enchondromas presents clinically silent, imaging plays a major role in diagnosis of intraosseous cartilaginous tumours (1, 6). Different radiological examinations can be carried out to reveal presence of an enchondroma. X-ray represents a frequently applied method in initial evaluation of patients visiting an orthopaedic or traumatological outpatient's department. Therefore, a high number of patients undergo radiographic examination, which is a sensitive method to identify calcified chondromatous tumours (7). More advanced imaging methods such as CT can be used in case radiography implies existence of an enchondroma but is not sufficient to provide a definite diagnosis (35). With the increased availability and application of MRI over the last years, the number of incidentally identified cartilaginous lesions has increased as well, thereby implying that MRI is a highly sensitive technique for the diagnosis of enchondromas (1, 36, 37). What is more, also bone scintigraphy can be applied for identification of chondromatous lesions (6).

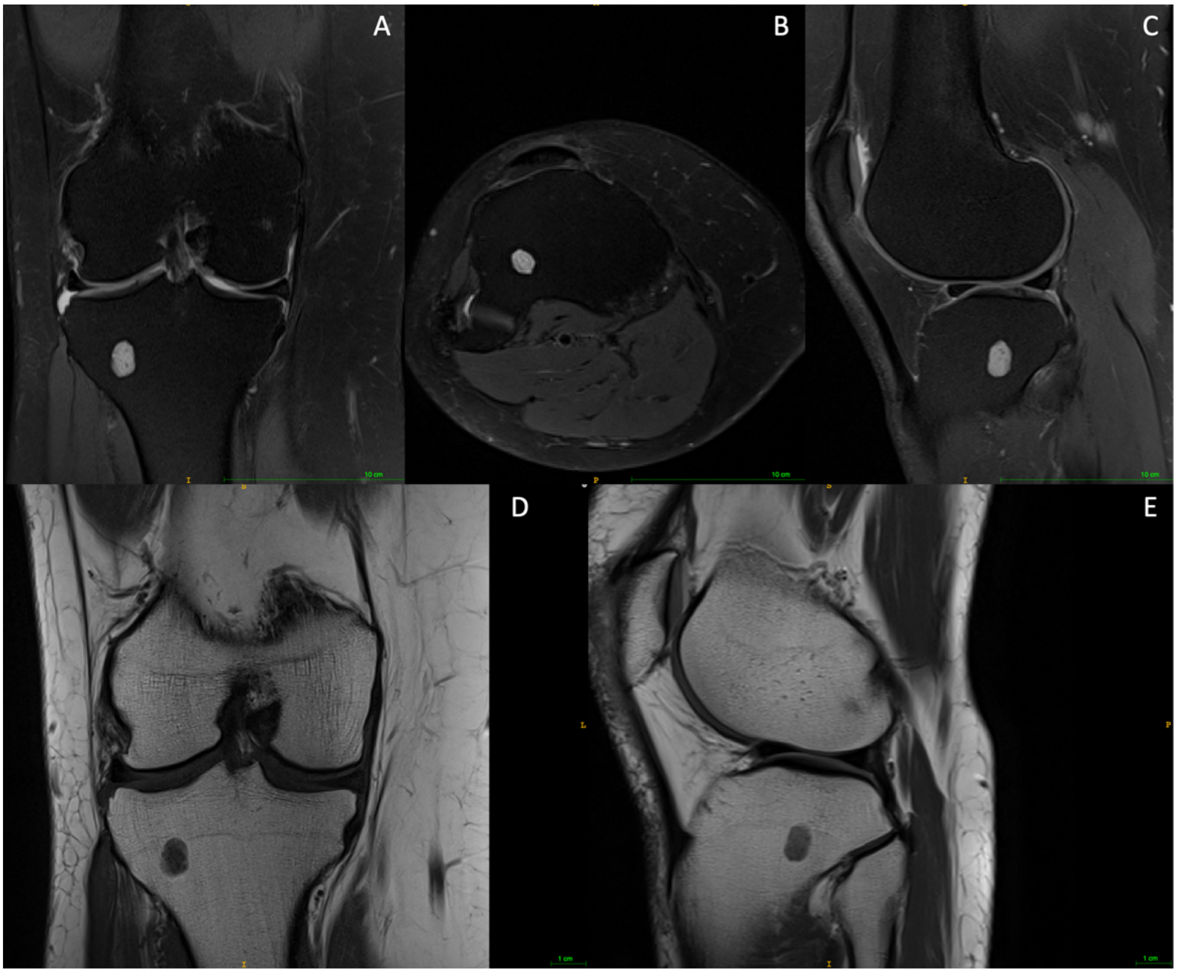

Figure 2. MRI of an enchondroma of the right tibia (female, 64 years): (A) proton density, fat suppression, coronal, turbo spin echo; (B) proton density, fat suppression, transversal, turbo spin echo; (C) proton density, fat suppression, sagittal, turbo spin echo; (D) t1, coronal, turbo spin echo; (E) proton density, t2, sagittal.

1.5.1.1 X-ray

Radiographic features of intraosseous chondromatous tumours strongly depend upon grade of calcification (6, 7), with classical enchondromas presenting as ovoid lesions that are well-circumscribed and show radio-dense areas, which can be small and punctate, or can appear as pebbles, arcs or rings (6, 7). These densities are calcifications, which are not only variable in terms of shape but also show variation as far as prominence and numbers are concerned (1, 7). Due to this mineralization of chondroid matrix and the lobular contour of enchondromas, these tumours are often referred to as popcorn-like lesions (38, 39). In case no matrix mineralization at all or solely slight calcification is present, radiography represents an inefficient method for assessment of the intramedullary extent of chondromatous tumours (6). As lesions' margins typically present non-sclerotic, this decreases the sensitivity of X-ray to diagnose chondromatous tumours even more (6). These are the main reasons why radiography might underestimate the extent of enchondromas, especially when mineralization is not prominent (1, 6).

Furthermore, radiographic appearance of enchondromas might differ depending on which bone is involved: While an enchondroma of the hand typically presents as a well-demarcated radio-lucent lesion that is located centrally in the diaphysis of tubular bones and frequently shows extension to the end of small bones, long bone enchondromas usually reside centrally or eccentrically within the diaphysis or the metaphysis of bones, occasionally depicting epiphyseal involvement (1, 7). Enchondromas of the hand frequently show deep endosteal scalloping that is typically associated with cortical thinning and can even be accompanied by a varying degree of bone expansion (1, 6). As opposed to that, benign intraosseous cartilaginous lesions of long bones are not associated with these features and deep endosteal scalloping is even considered as one differential criterion between enchondromas and ACTs of long bones (32). Some thin long bones as the fibula, however, might also present with enchondromas that are difficult to differentiate from intermediate/malign chondromatous tumours, as these lesions are often eccentric and can produce a radiographic pattern similar to that of ACTs (1, 7). Both applying to lesions of the hand as well as long bones, enchondromas are not expected to present with cortical breakthrough or periosteal reaction (6). These features may only be present when there is a pathological fracture (6).

A small percentage of chondromatous lesions are called “enchondroma protuberans”, a term describing lesions that arise in the medullary cavity but are associated with an exophytic growth pattern (40). Most of these lesions have been described to be localized in the metacarpals and phalanges, however, there are also some reports on the occurrence of an enchondroma protuberans in the humerus and ribs (6).

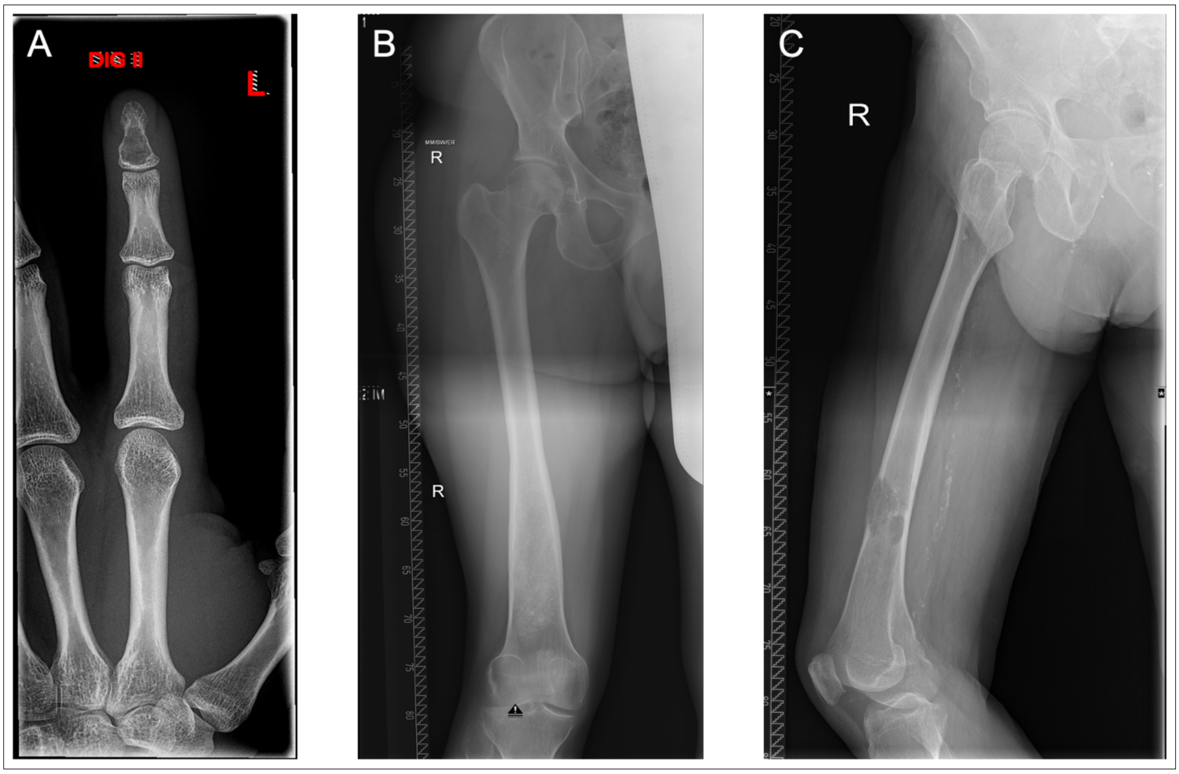

Figure 3. X-ray images of different chondromatous tumours at different locations. (A): Enchondroma of the distal phalanx of digitus II (male, 26 years). (B): ACT of the distal femur (male, 27 years). (C): Dedifferentiated chondrosarcoma of the distal femur (male, 81 years).

1.5.1.2 Computed tomography

CT is an advanced imaging technique that may not play a big role in the diagnostic work-up and evaluation of hand enchondromas, however, it has proved to be a valuable radiological method when examining chondromatous lesions in long bones or areas of complex anatomy (1). Although MRI represents the most sensitive radiological technique to identify chondromatous lesions of the bone (36), there are certain features that can be depicted more accurately on CT than with MRI: For example, CT shows a higher sensitivity for the detection of matrix mineralization and its characterization. Furthermore, CT is superior to MRI regarding diagnosis of subtle stress fractures and periosteal discontinuity (7). However, as assessment of bone marrow involvement of enchondromas via CT has shown an informative value that is comparable to that of radiography, it is clearly inferior to MRI as far as this important aspect in the diagnostic work-up of chondromatous tumours is concerned (1). Therefore, MRI represents the "gold standard" regarding imaging-based diagnosis of enchondromas. Still, there are cases of enchondromas in which it is reasonable that patients undergo a CT scan: As already outlined above, computed tomography is highly efficient in verification of radiographically diagnosed enchondromas, as CT is able to depict also extremely subtle mineralization of the matrix (1). Furthermore, assessment of the extent of endosteal scalloping of chondromatous lesions via CT is highly sufficient, as is any potential cortical breakthrough (6).

1.5.1.3 Magnetic resonance imaging

As already mentioned above, MRI represents the most sensitive radiological examination technique regarding characterization of chondromatous lesions, with the hyaline cartilage of enchondromas showing low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, as hyaline cartilage mainly consists of water (75-80%) (1, 6, 7). Enchondromas typically present as lobular lesions, with thin fibrovascular septa dividing the single lobules of cartilage. These septa are depicted hypointense on T2-weighted images (1). CT scans exceed MRI in depiction of matrix mineralization, as calcification in MRI is only represented by punctate or curvilinear areas of low signal intensity on T1- as well as T2-weighted images (6).

In daily practice, many musculoskeletal patients undergo MRI with FS-PD (fat-suppressed proton density) images, in which enchondromas show similar features to chondromatous tumours on T2-weighted magnetic resonance images (36).

Further analysis of chondromatous lesions via MRI includes administration of a contrast agent, e.g. gadolinium. Scalloping lesions' margins as well as fibrovascular septa can show enhancement after administration of gadolinium. This feature can help to differentiate between benign and intermediate/malign chondromatous tumours (41).

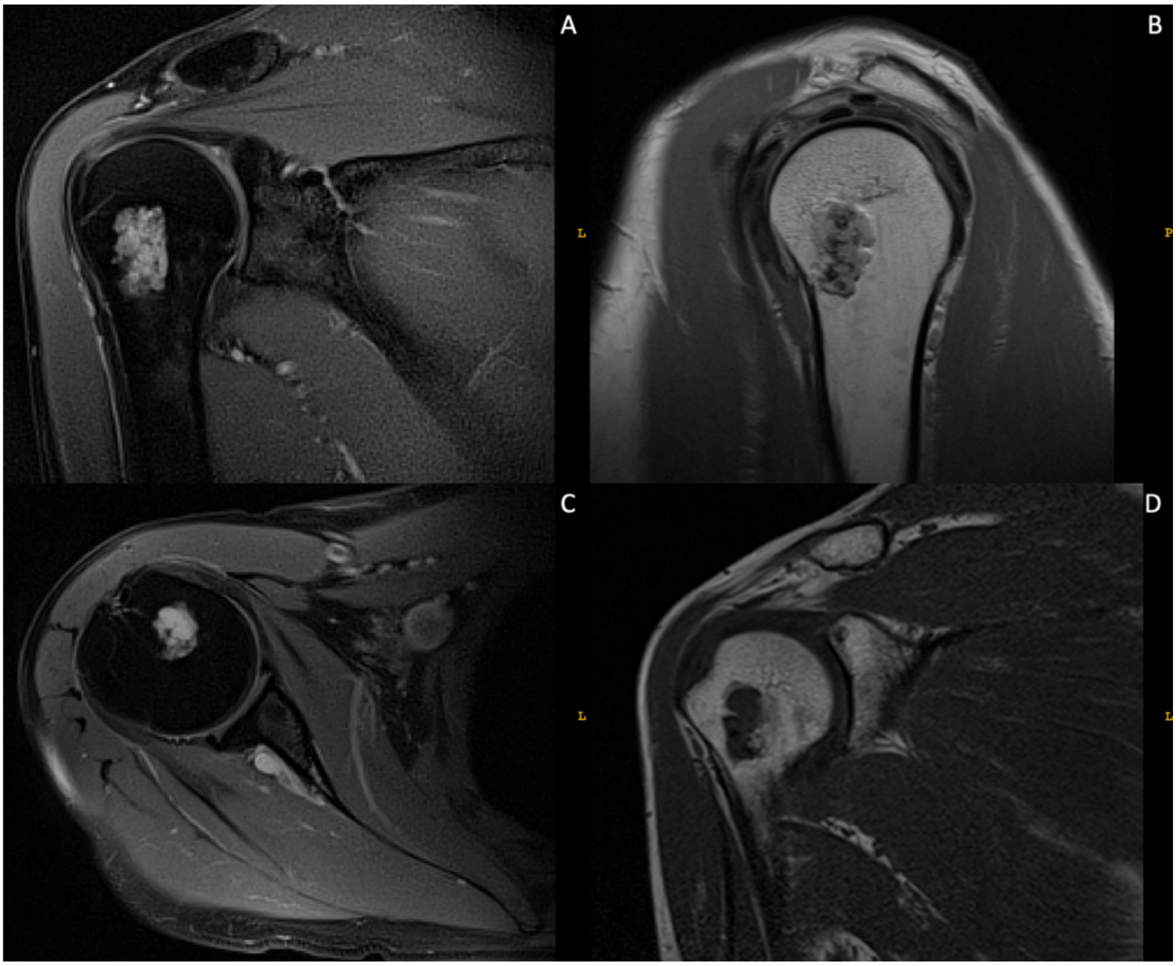

Figure 4. MRI scan of an enchondroma of the right humerus (male, 59 years): (A) proton density, blade with fat suppression, coronal; (B) proton density + t2, sagittal; (C) proton density, blade with fat suppression, transversal; (D) t1, coronal, spin echo.

1.5.2 Pathology

The impact of pathological assessment of cartilaginous lesions has been extensively discussed over the last years, as there is a high overlap in histological morphology between enchondromas and ACTs. Furthermore, cartilaginous tumours present as very heterogenous lesions, which makes biopsy sampling error a common problem (38). These are the main reasons why pathological assessment of cartilaginous tumours should primarily be undertaken in combination with imaging studies (42).

1.5.2.1 Histopathology

Histologically, enchondromas consist of hyaline-cartilage nodules of variable size, which are sharply demarcated from the adjacent bone and often encapsulated by reactive bone formation (2, 42). Numbers of typical chondrocytes within the lesions vary, binucleated chondrocytes can sometimes also be seen in enchondromas. A frequently encountered

histological feature in enchondromas is represented by scattered calcifications in the hyaline matrix. In these areas, necrotic chondrocytes can be found (42).
Similar to enchondromas, ACTs are also characterized by a neoplastic population of chondrocytes surrounded by a cartilaginous matrix. One difference – when compared to enchondromas – is that more atypical chondrocytes and a higher mitotic activity can be seen. However, as already stated before, enchondromas and ACTs often show a high overlap in histology, wherefore pathohistological differentiation can be very challenging (42).

1.5.2.2 Immunohistochemistry

Immunohistochemistry is not considered an integral tool in the differentiation of enchondromas and ACTs, as most of cartilaginous lesions are positive for the markers S100 and ERG (42). Therefore, pathological evaluation of biopsies of chondromatous tumours mainly relies on histological examination, together with radiographs, CT- and/or MR-images.

1.6 Radiological differentiation of enchondromas, ACTs and chondrosarcomas

Many different research groups have focused on the finding of imaging criteria to reliably differentiate enchondroma from its intermediate/malignant counterpart ACT/chondrosarcoma without biopsy.

1.6.1 Tumour size

Enchondromas typically present with a lesion size of less than 5 cm in long bones, whereas ACTs and higher-grade chondrosarcomas usually show a maximum diameter of more than 5 cm in the appendicular skeleton (38, 43). Increase of tumour size is very rarely seen in enchondromas, while it might be present in ACTs. Chondrosarcomas are most typically associated with tumour growth (43).

1.6.2 Tumour localization

As far as tumour localization is concerned it could be shown that benign chondromatous tumours frequently reside within the distal metaphysis, ACTs are often located in the proximal metaphysis of the affected bone and chondrosarcomas typically present in the metaphysis, epimetaphyseal transition zone or epiphysis (43). Van de Sande et al. propose that the finding of a chondromatous lesion in the diaphysis might also be consistent with the diagnosis of a benign lesion in case there are no other criteria indicating diagnosis of an intermediate/malignant lesion (38).

1.6.3 Scalloping

Besides lesion size and localization, there are many more imaging criteria that can help to differentiate enchondromas from ACTs/chondrosarcomas: Presence of scalloping and grading of scalloping might help in this process. Endosteal scalloping is defined as focal resorption of the endosteum, with deep (more than 2/3) and long-distance (more than 2/3 of the tumour size) scalloping being associated with chondrosarcoma grade 2 or grade 3, deep (more than 1/3) but short-distance (less than 2/3 of the tumour size) scalloping indicating presence of an ACT and no scalloping at all or superficial scalloping being a typical finding in enchondromas (43, 44).

1.6.4 Matrix mineralization

Regarding matrix mineralization, this can also be a parameter helping to distinguish benign cartilaginous lesions from malignant tumours, as benign enchondromas usually present as popcorn-like lesions due to calcification. While this morphological criterium can present similar in ACTs, chondrosarcomas frequently show large tumour areas without matrix mineralization. It has also been reported that a certain percentage of ACTs can show a decrease of mineralized tumour matrix during follow-up examinations (43, 45).

1.6.5 Cortical destruction

Cortical reactions, alterations and destructions due to a chondromatous tumour can be seen in chondrosarcomas. While ACTs can also lead to cortical modifications and breakthrough, these features are in general not typical for enchondromas, apart from pathological fractures of benign cartilage lesions involving the phalanges. Consequently, cortical alterations and cortical breakthrough might be indicative of diagnosis of an intermediate/malignant chondromatous bone tumour (43, 45).

1.6.6 Perilesional edema

In bony lesions, perilesional edema is a sign of growth and therefore potential malignancy. While it usually does not occur in benign lesions such as enchondromas, its presence is strongly associated with the diagnosis of a chondrosarcoma (43). For example, Yoo et al. found that perilesional edema is typically seen in high-grade chondrosarcomas (46).

1.6.7 Soft tissue mass formation

Another feature favoring diagnosis of a malignant tumour over a benign/intermediate lesion is extraosseous soft tissue mass formation. Again, presence of this morphological pattern is a sign indicating presence of a high-grade chondrosarcoma. Correspondingly, an extraosseous soft tissue component is usually not seen in enchondromas and ACTs (38, 43, 46).

1.6.8 Entrapped fat

Entrapped fat within a lesion indicates diagnosis of an enchondroma/ACT and is normally not found in malignant cartilaginous tumours (38, 43, 46).

1.6.9 Special methods

Beside these imaging criteria supporting the differentiation of benign, intermediate and malignant cartilaginous tumours of the bone via radiography, CT and MRI, there are more methods that may increase precision of diagnosis: administration of a contrast agent in dynamic MRI, use of Thallium-201 and Technetium-99 and assessment of the uptake of the lesion via scintigraphy, administration of 18-Fluorodeoxyglucose and evaluation of the lesion's standardized uptake value (SUV) via PET-CT (positron emission tomography computed tomography) (43, 47).

1.6.9.1 Dynamic contrast-enhanced MRI

Enchondromas and ACTs typically show slow and low uptake of the contrast agent in dynamic contrast-enhanced MRI. Consequently, dynamic contrast-enhanced MRI is of limited help to distinguish between benign and intermediate cartilaginous lesions (44). However, it can support the differentiation between enchondromas/ACTs and chondrosarcomas, as malignant cartilaginous tumours are associated with fast and high uptake of the contrast agent in dynamic contrast-enhanced MRI (44).

1.6.9.2 Scintigraphy and PET-CT

Bone scintigraphy evaluating the lesion's uptake of Thallium-201 and Technetium-99, is a potent method to differentiate between benign/intermediate and malignant tumours. However, again it is not an appropriate method to distinguish between enchondromas and

ACTs, as these tumour entities present similar upon bone scintigraphy (47). The same applies to PET-CT, with enchondromas and ACTs behaving alike (43). Therefore, the role of bone scintigraphy and PET-CT in the diagnostic process of benign and intermediate cartilaginous lesions has been discussed controversially over the years (38, 43).

1.7 Complications

The majority of benign cartilaginous tumours presents asymptomatic, wherefore they are usually diagnosed as incidental findings. Most of the lesions stay clinically silent and do not lead to any complications (6).

1.7.1 Malignant transformation

Due to the fact that the majority of enchondromas remains undetected, the rate of benign intraosseous cartilaginous tumours that undergo malignant transformation can only be estimated (3). For solitary enchondromas, a 4% risk of malignant transformation into chondrosarcoma has been calculated (48). Taking into account that the majority of solitary enchondromas remains undetected, though, it can be assumed that a transformation rate of 4% is most probably an overestimation, as this calculation is affected by massive selection bias (3).

Focusing on patients with Ollier's disease or Maffucci syndrome, a much higher rate of malignant transformation of enchondromas is estimated: An international multicenter study including 161 patients with enchondromatosis found that 40% of the patients endured malignant transformation (49).

1.7.2 Pathological fracture

Another potential complication of enchondromas/ACTs is represented by pathological fractures (6). A pathological fracture is defined as a broken bone due to a disease, with inadequate (i.e. minimal) force leading to the fracture. This complication is typically seen in tumours located within the small bones of the hand (6).

1.7.3 Pain

Whenever enchondromas present as painful lesions (and the pain is not provoked by mechanical influence), immediate investigation needs to be performed, as pain is the typical clinical correlative of primarily benign lesions that undergo malignant transformation (3).

Sometimes, benign enchondromas can also present as painful lesions, though. In most cases, however, enchondromas present asymptomatic (6).

1.8 Treatment

Enchondromas of the long bones usually present as clinically silent benign lesions that do not show malignant transformation or other complications such as pathological fracture in the majority of patients. Therefore, "true" enchondromas of the long bones that are asymptomatic do not need surgical treatment (50). The treatment of chondrosarcomas, however, is very different to that of enchondromas, as these malignant tumours need to be removed surgically (51). As already outlined several times, preoperative differentiation between enchondromas, ACTs and chondrosarcomas represents a diagnostic challenge (52), though, leading to the dilemma that not every tumour receives the correct diagnosis and therefore not every tumour can be treated the way it should be. In order to prevent patients with suspicious enchondromas from over-treatment (surgery) but also to prevent uncontrolled tumour growth in patients with suspected ACTs, surveillance plays an important role regarding the handling of cartilaginous tumours (53).

The therapeutic approach towards enchondromas and ACTs has undergone some changes over the last years, also due to the fact that diagnostic precision could be improved drastically: From 2010 onwards, evidence increased that ACTs had probably been overtreated with en-bloc resections, as intralesional curettage presented likewise efficient in the treatment of ACTs in terms of local recurrence rate, with less morbidity (51, 52, 54).

In 2019, ACTs were even described as "do-not-touch-lesions", requiring surveillance but no surgical treatment, except for high-risk ACTs, which should be treated via intralesional curettage (38). Even more, there is increasing evidence showing that the vast majority of asymptomatic enchondromas and ACTs of the appendicular skeleton does not undergo malignant transformation, which is why active surveillance via MRI is recommended for these tumours, in order to avoid unnecessary surgeries (4).

1.9 Aim of the diploma thesis

As most enchondromas of long bones present clinically silent and the majority of them is diagnosed as an incidental finding in the context of a medical imaging examination performed for other reasons, estimation and calculation of the true prevalence of enchondromas around the shoulder and the knee represents a difficult task (6, 34).

So far, five small to intermediate-sized studies have analysed the frequency of enchondromas/ACTs residing in the long bones around the knee joint, thereby reaching prevalence rates between 0.2% and 2.9% (8-12).

The prevalence of enchondromas around the shoulder has only been examined in one small-sized study, reporting a prevalence of 2.1% (13).

The aim of this diploma thesis was to challenge/verify these percentages via retrospective examination of a large-scale cohort using MRI scans of the knee and shoulder, containing significantly more cases than previous studies focusing on the same research question.

2 Material & Methods

2.1 Participating institutions

This study was performed with the material and patient data of a single private radiologic centre “Diagnostikum Graz”, performing – apart from numerous further imaging modalities as X-ray, CT and PET-CT – MRI scans of all body sites.

This project was initiated and planned by the Department of Orthopedics and Trauma, Medical University of Graz, Austria. A DTA (data transfer agreement) with the “Diagnostikum Graz” was set up to guarantee the lawful use of private patient data and medical images by the Medical University of Graz. The local ethics committee approved the study (33-630 ex 20/21).

2.2 Study design and study population

The present study is a retrospective analysis including patients who had received an MRI of the knee or the shoulder regardless of the indication for this medical examination.

In the time span between 01.01.2007 and 01.03.2020 (13 years and 2 months), 44.762 patients underwent an MRI scan of the knee at the “Diagnostikum Graz”. While 25.819 patients received an MRI scan of the right knee, 24.125 patients received an MRI scan of the left knee.

In the same time span between 01.01.2007 and 01.03.2020, 21.550 patients received an MRI scan of the shoulder at the “Diagnostikum Graz”. While 13.388 patients underwent an MRI scan of the right shoulder, 10.043 patients received an MRI scan of the left shoulder.

As this study’s primary focus was to find the prevalence of enchondromas and ACTs of the knee and the shoulder joint, the diploma student of this diploma thesis searched for MRI reports of the knee and the shoulder (that are stored electronically at the “Diagnostikum Graz”) containing at least one of the following search terms:

- “Enchondrom” (enchondroma)
- “kartilaginäre Läsion” (cartilaginous lesion)
- “cartilaginäre Läsion” (cartilaginous lesion)
- “kartilaginärer Tumor” (cartilaginous tumour)
- “cartilaginärer Tumor” (cartilaginous tumour)
- “chondrogene Läsion” (chondrogenic lesion)

- “chondrogener Tumor” (chondrogenic tumour)
- „chondromatöser Läsion” (chondromatous lesion)
- „chondromatöse Tumor“ (chondromatous tumour)
- “Chondrosarkom” (chondrosarcoma)
- „ACT“ (ACT)
- „atypischer chondromatöser Tumor” (atypical chondromatous tumour)
- „atypische chondromatöse Läsion“ (atypical chondromatous lesion)
- „atypischer chondrogener Tumor” (atypical chondrogenic tumour)
- „atypische chondrogene Läsion“ (atypical chondrogenic lesion)
- „atypischer cartilaginärer/kartilaginärer Tumor“ (atypical cartilaginous tumour)
- „atypischer cartilaginäre/kartilaginäre Läsion“ (atypical cartilaginous lesion)

2.3 Filtering of patients

2.3.1 MRIs of the right knee

The vast majority of patients (25.424) who had undergone an MRI scan of the right knee in the aforementioned time span did not meet the primary inclusion criteria for this study as they were negative for all search terms. **Figure 5** shows that 395 patients could be included into the further workflow.

In the next step, the diploma student looked up all MRI scan reports of these remaining 395 patients. Having conducted this step, 32 patients had to be excluded from this study due to 4 different reasons:

- Five patients had received an MRI of the right knee since they were suspected to have a cartilaginous tumour. However, MRI proved this initial tentative diagnosis wrong.
- Many patients had undergone more than one MRI of the right knee. In one patient, these follow-up examinations had led to a change of diagnosis, so that the primary suspicion (cartilaginous tumour) had to be rejected.
- In some patients, MRI reports of the right and the left knee had been saved within the same file. Therefore, 22 patients were “falsely positive” for the aforementioned search terms, as they did not have an enchondroma/ACT of the right, but rather of the left knee.

- Four patients did not have a cartilaginous tumour any more at the time point of the MRI, as their tumour had been removed surgically beforehand.

After the exclusion of these 32 patients, 363 patients were left to be eventually included. The diploma student again examined their reports together with related MRI scans and confirmed the definitive radiologic diagnosis of cartilaginous tumours for 338 patients, whereas 25 patients showed inconclusive reports and images. Therefore, the advice of an experienced radiologist was sought for these cases. Thereafter, 14 more patients were excluded, as they did not show typical features of enchondroma/ACT.

In the last step, this study aimed to ascertain the dignity of the chondrogenic tumours, as the differential diagnosis between the benign form (enchondroma) and the intermediate form (ACT) can be very challenging. Therefore, the trained diploma student searched for cases within this group of 349 patients, who had received the diagnosis of an enchondroma, but showed tumour characteristics that were suspicious of ACT. Based on the current literature (32, 35, 44) it was decided that for this study, a diagnosed enchondroma had to be rechecked by an expert if it was positive for at least one of the following characteristics:

- tumour size greater than 4.9 cm
- periosteal reaction
- perilesional edema
- deep endosteal scalloping

Twelve of the 349 patients presented with tumours showing positivity for at least one of these features. Therefore, MRIs of these tumours were thoroughly examined by an experienced orthopedic oncologist, who changed the diagnosis from enchondroma to ACT in 6 cases.

Overall, it can be stated that 349 patients presented with at least on enchondroma/ACT of the right knee, whereas 11 patients had 2 or more cartilaginous tumours of the right knee resulting in 360 cases. Of these, 11 cases showed the diagnosis of an ACT.

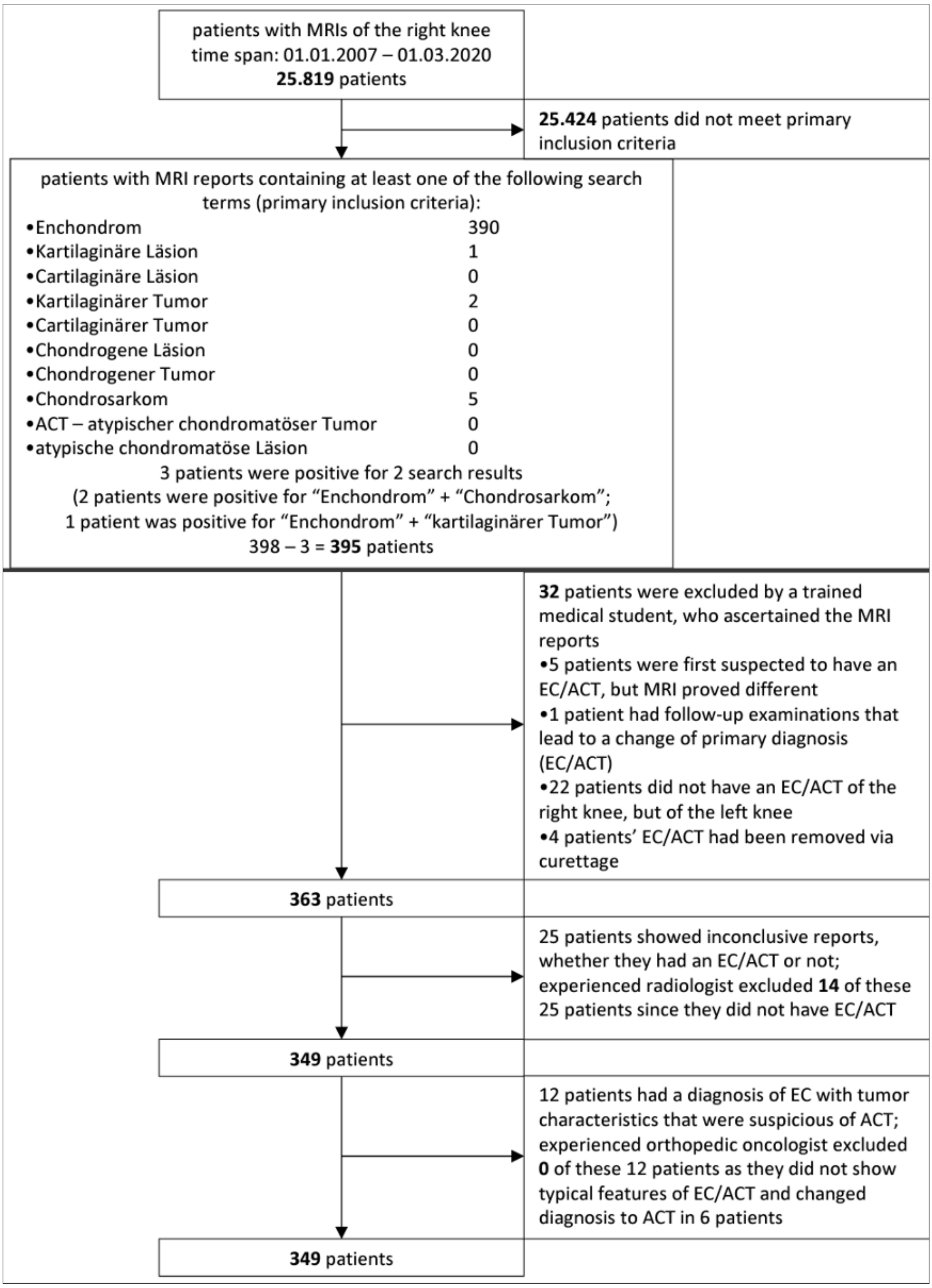

Figure 5. Flow chart representing the filtering of patients with a cartilaginous tumour of the right knee (EC = enchondroma).

2.3.2 MRIs of the left knee

Similar to the filtering of patients with MRIs of the right knee, most of patients who had received an MRI of the left knee could not be included in the further workflow (23.768), as their reports did not contain any of the above-mentioned search terms.

Of the remaining 357 patients, the diploma student had to exclude 39 more patients due to the subsequent reasons:

- In 6 patients, referral diagnosis to MRI had been a suspected cartilaginous tumour, however, MRI could not confirm this suspicion.
- Follow-up examinations revealed that the primary diagnosis of a chondromatous lesion had been wrong in 1 patient.
- Some patients had MRI reports containing not only the findings of the MRI of the left knee but also of MRIs performed at other body regions. In 31 patients, these "mixed" MRI reports revealed an enchondroma/ACT not of the left knee but of another body region. Therefore, these 31 patients had to be excluded.
- One patient had had an enchondroma/ACT before MRI examination, which could not be displayed on MRI, as it had been removed surgically beforehand.

As visible in **Figure 6,** the diploma student re-examined MRI scans of the remaining 318 patients in conjunction with the associated reports and found an inconclusive diagnosis in 17 patients. Consequently, these cases were presented to an expert radiologist, who had to exclude 7 of these patients since their MRIs did not display typical features of benign/intermediate intraosseous cartilaginous tumours.

Nineteen of the now remaining 311 patients presented with lesions exhibiting at least one of the aforementioned characteristics indicative of malignancy. Therefore, MRI scans of these tumours were thoroughly examined by an experienced orthopedic oncologist, who changed the diagnosis from enchondroma to ACT in 9 cases and excluded 5 patients as they did not fulfill the radiological criteria for diagnosis of enchondroma/ACT.

Altogether, 306 patients showed at least one enchondroma/ACT of the left knee, whereas 6 patients had two or more enchondromas/ACTs. Of altogether 312 tumour cases, 11 tumours presented as an ACT.

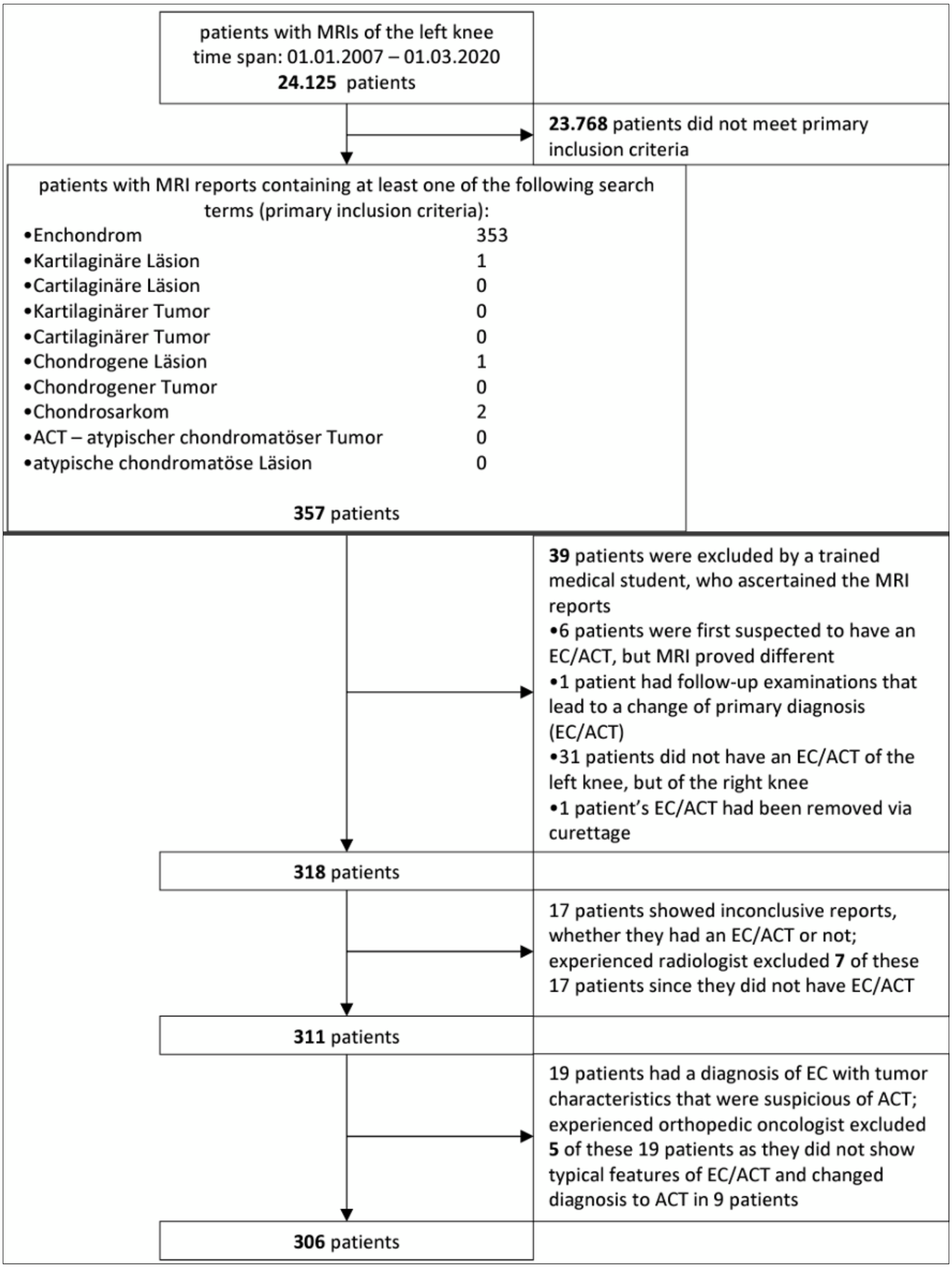

Figure 6. Flow chart representing the filtering of patients with a cartilaginous tumour of the left knee (EC = enchondroma).

2.3.3 MRIs of the right and the left knee

Figure 7 summarizes the filtering of patients who underwent an MRI of the right/left knee at the Diagnostikum Graz in the time span between 01.01.2007 and 01.03.2020.

Overall, 651 of 44.762 patients presented with a benign/intermediate intraosseous cartilaginous tumour. Twenty-one patients had multiple enchondromas at the same time (11 patients had 2 or more enchondromas of the right knee, 6 patients had 2 or more enchondromas of the left knee, 4 patients had an enchondroma of the right and the left knee), thereby leading to a total number of 672 tumour cases, with 22 of them diagnosed as ACT.

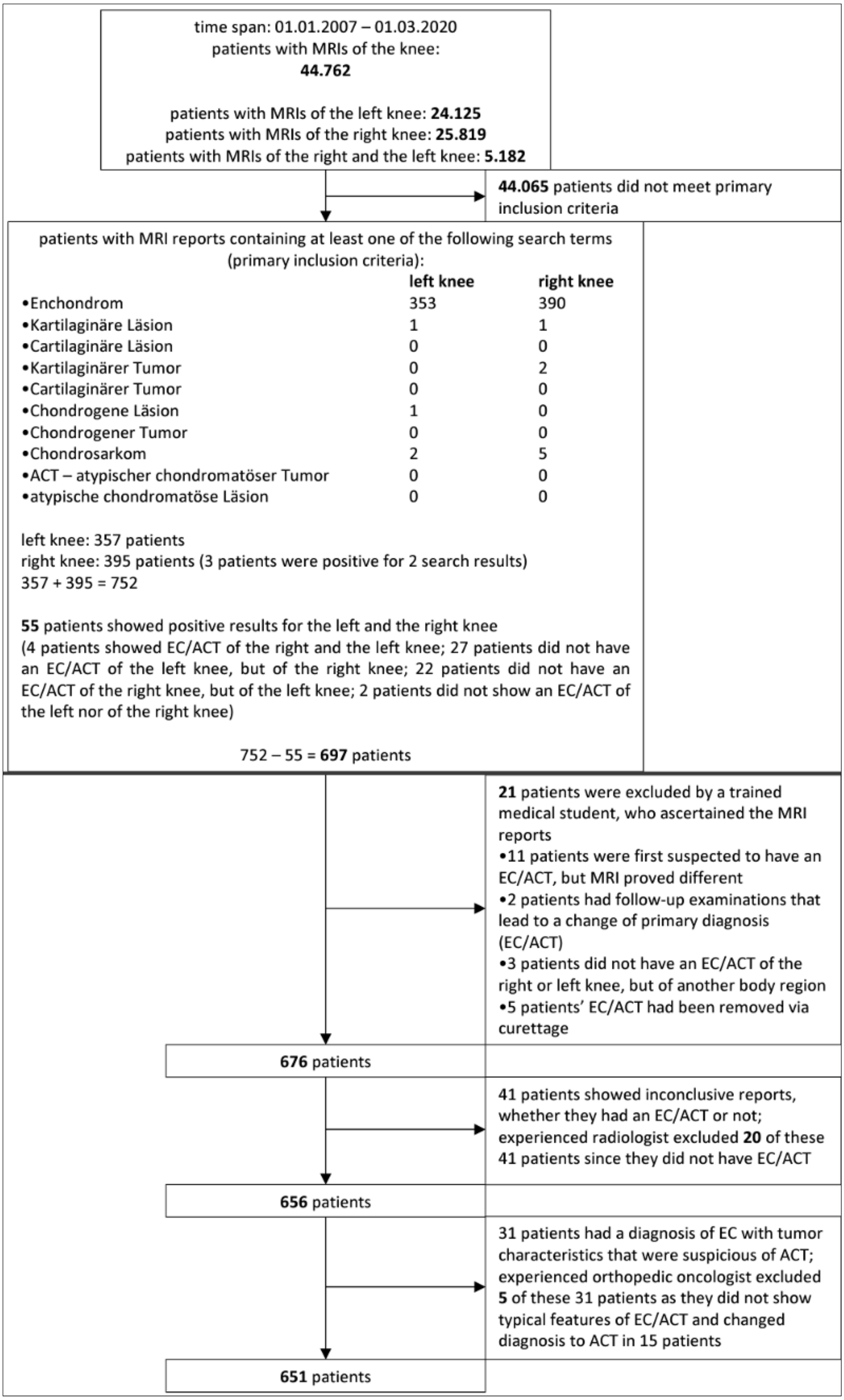

Figure 7. Flow chart representing the filtering of patients with a cartilaginous tumour of the right and the left knee (EC = enchondroma).

2.3.4 MRIs of the right shoulder

As displayed in **Figure 8,** only 62 out of 13.388 patients who had received an MRI of the right shoulder, had MRI reports that contained one of the above-mentioned search terms. After examination of these patients' MRI scan reports, the diploma student had to exclude 7 patients:

- In 2 patients, shoulder MRI had been performed as they had been suspected to have an enchondroma/ACT of the right shoulder, but this tentative diagnosis proved to be wrong.
- Five patients had to be excluded as their MRI reports also contained the findings of MRIs of other body regions containing a cartilaginous tumour. However, they did not present with an enchondroma/ACT of the right shoulder.

Seven of the remaining 55 patients had inconclusive reports, with images therefore checked by an experienced radiologist, who excluded 5 patients as their MRIs did not meet the criteria of an enchondroma/ACT.

Of the remaining 50 patients, 2 presented with lesions showing positivity for at least one of the aforementioned "ACT-like" features. Therefore, MRI scans of these tumours were re-examined by an expert orthopedic oncologist, who decided that one lesion represented an ACT rather than an enchondroma.

Altogether, 50 patients had a benign/intermediate intraosseous cartilaginous tumour of the right shoulder. As one patient had 2 cartilaginous tumours of the right shoulder at the same time, 51 tumour cases could be reported. Of these, 2 cases showed "ACT-like" features.

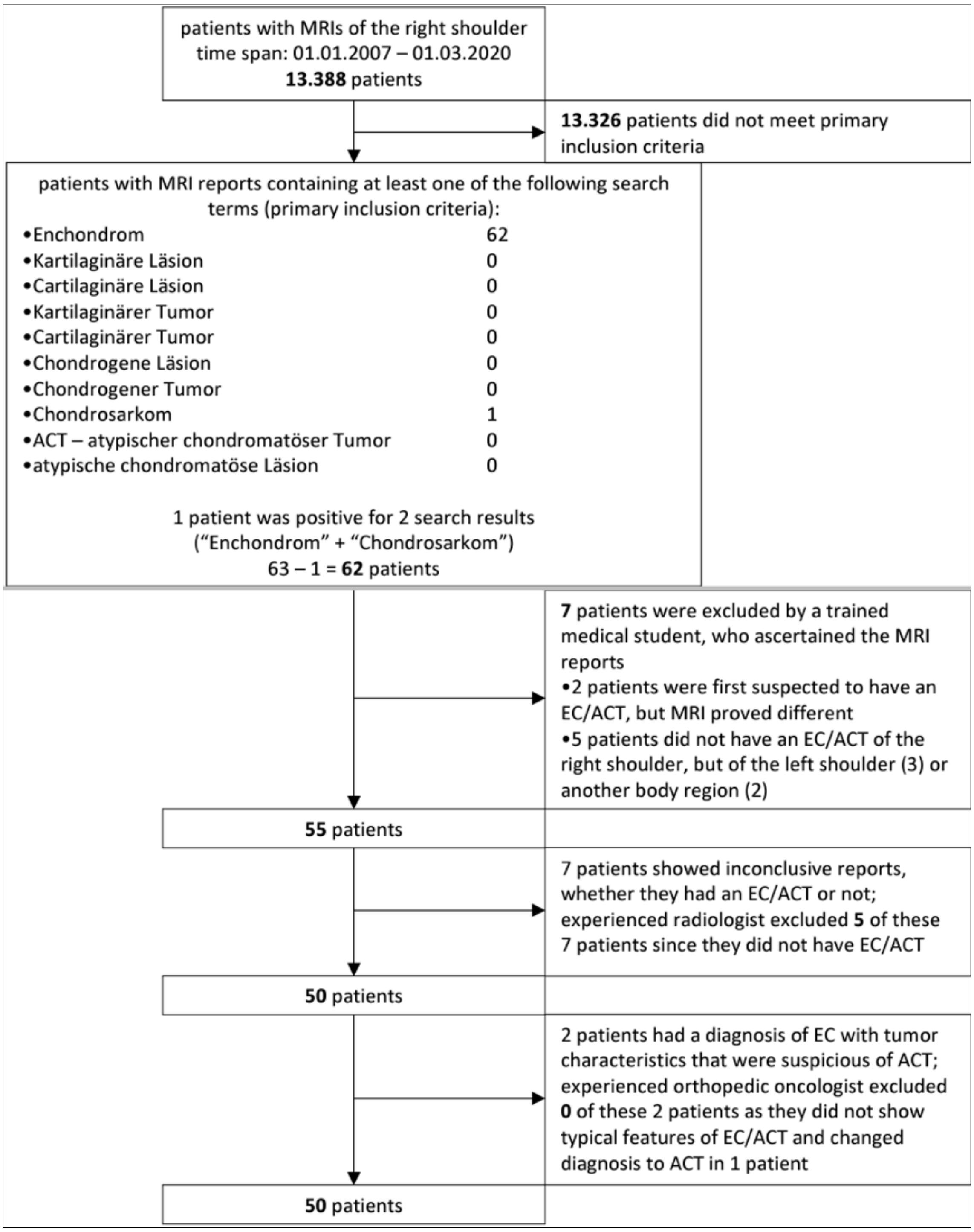

Figure 8. Flow chart representing the filtering of patients with a cartilaginous tumour of the right shoulder (EC = enchondroma).

2.3.5 MRIs of the left shoulder

Figure 9 shows that 54 of 10.043 patients' MRI scan reports of the left shoulder were positive for at least one search term, wherefore their cases were examined more closely.

The diploma student studied the MRI reports of all 54 patients and had to exclude 8 patients due to three different reasons:

- Two patients had been referred to MRI due to a suspected cartilaginous lesion. MRI had discarded this suspected diagnosis.
- Four patients had an enchondroma/ACT of another body region. MRI of the left shoulder had not revealed a cartilaginous lesion in these patients.
- Two patients had undergone surgical removal of their cartilaginous lesion before MRI.

Five of 46 patients presented with inconclusive reports and images, wherefore an expert radiologist was consulted, who decided that only 3 of the 5 patients had an enchondroma/ACT.

As with MRI scans of the knee and of the right shoulder, this diploma thesis also aimed at ascertaining the dignity of cartilaginous tumours of the left shoulder: As 6 of the remaining 44 patients presented with lesions exhibiting features indicative of ACT, these cases were reviewed by an expert orthopedic oncologist, who changed diagnosis to ACT in 5 cases.

Overall, 44 patients presented with an enchondroma /ACT of the left shoulder. Two patients had 2 cartilaginous lesions of the left shoulder concurrently. Of 46 tumours, 6 lesions were identified as an ACT.

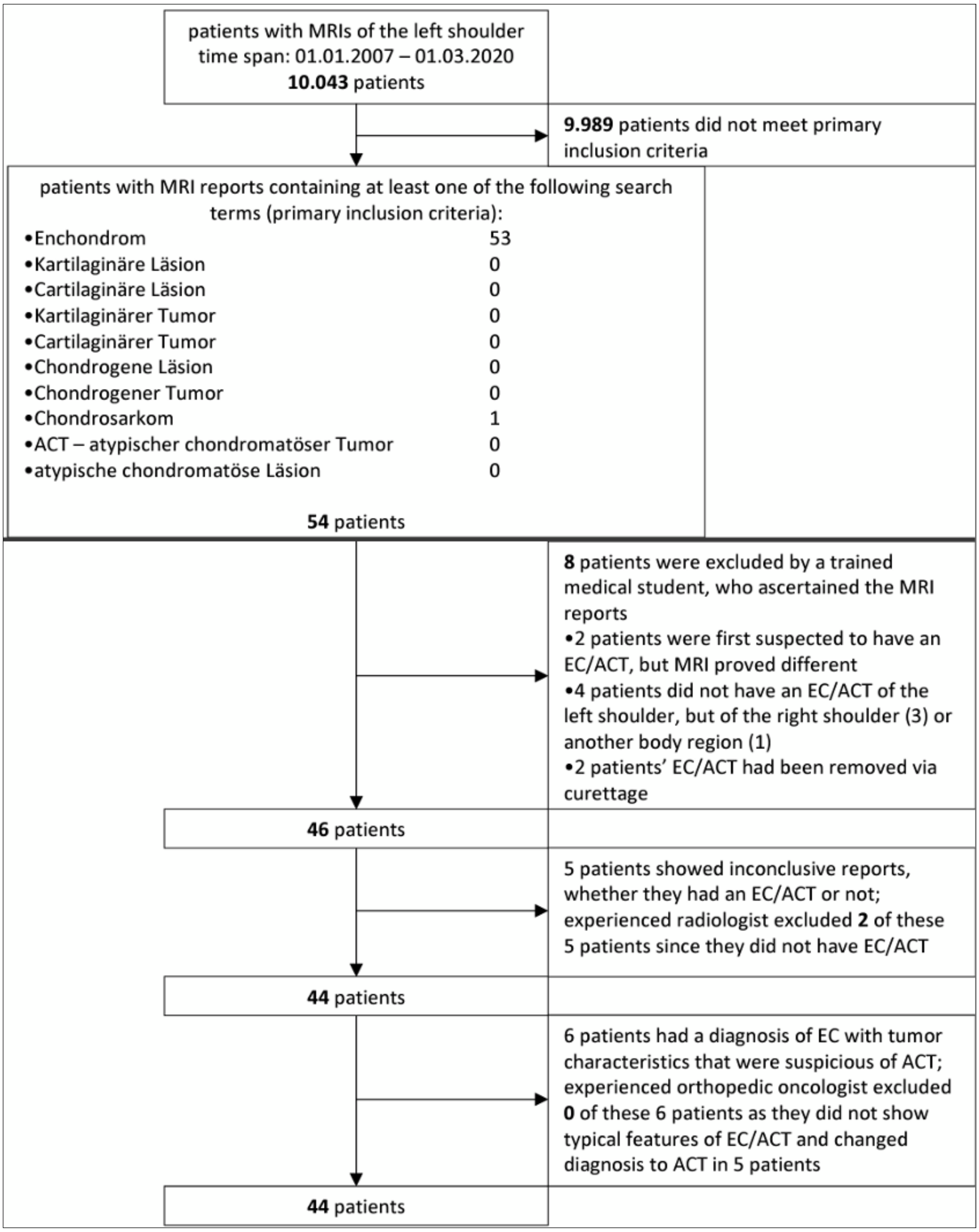

Figure 9. Flow chart representing the filtering of patients with a cartilaginous tumour of the left shoulder (EC = enchondroma).

2.3.6 MRIs of the right and the left shoulder

Figure 10 shows the summed-up counts and the merged filtering of patients, who received an MRI of the right and/or left shoulder at the same radiology center in the aforementioned time span.

Altogether, it can be stated that 93 of 21.550 patients who received an MRI of the shoulder, showed at least one enchondroma/ACT. Four patients had 2 enchondromas at the same time (1 patient had 2 enchondromas of the right shoulder, 2 patients presented with 2 enchondromas of the left shoulder, and 1 patient had an enchondroma of the right shoulder and an enchondroma of the left shoulder). This led to an overall number of 97 tumour cases, 8 of them being ACTs.

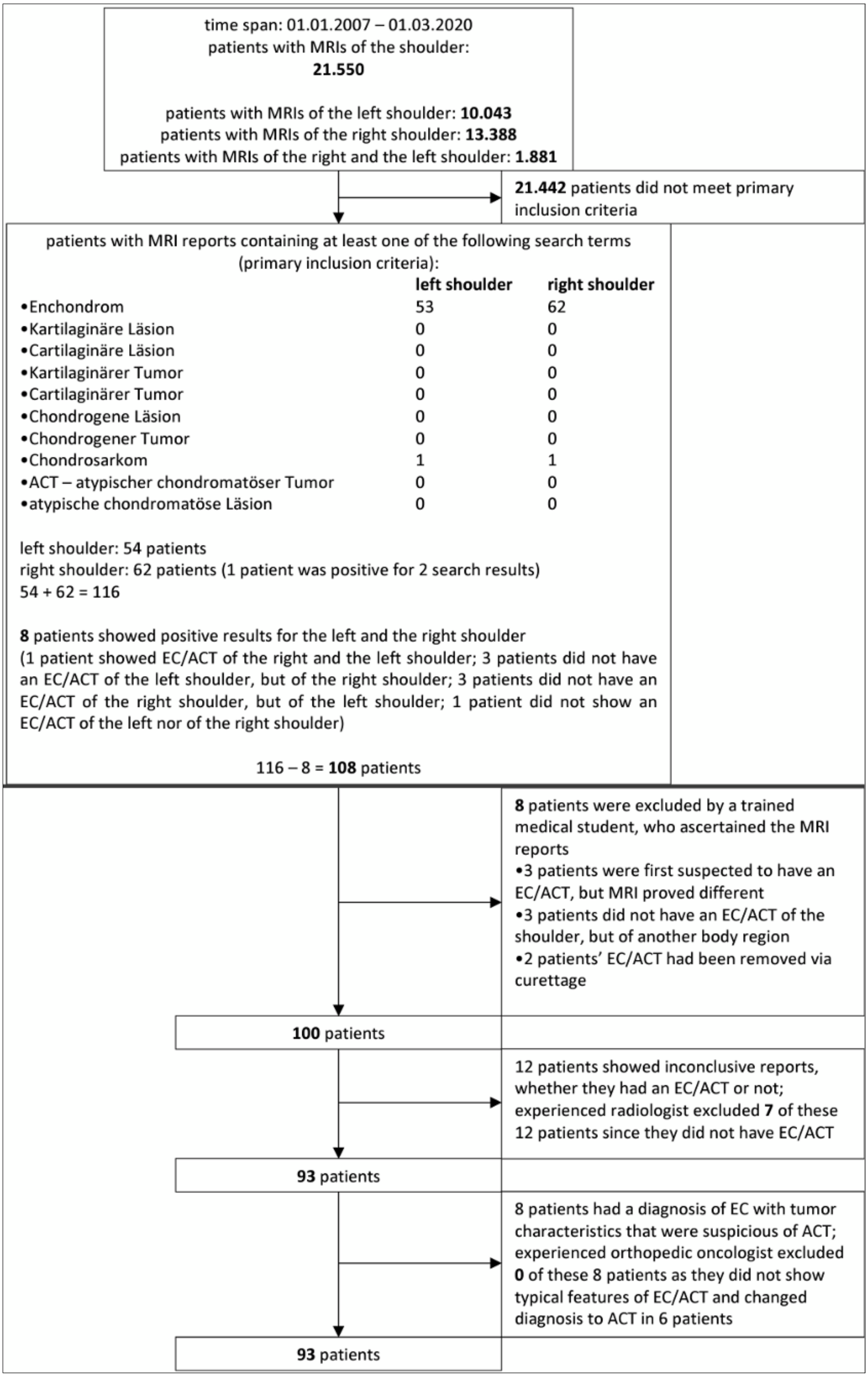

Figure 10. Flow chart representing the filtering of patients with a cartilaginous tumour of the right and the left shoulder (EC = enchondroma).

2.4 Lesion analysis

Well-defined smooth or lobulated intraosseous tumours, which showed low signal intensity on proton-density (PD) weighted MRI scans as well as on T1-weighted MRI scans and high signal intensity on PD fat-suppressed (FS) MRI scans, were identified as chondrogenic lesions. Tumours that fulfilled these criteria but were located strictly subchondral had to be excluded, as these lesions most likely represented other entities such as sclerosis, subchondral cysts/edema, contusions. **Table 1** displays all the data that was ascertained in each case.

<table>
<tr><td></td><td colspan="6">Variable description</td></tr>
<tr><td>Patient gender</td><td colspan="3">Female</td><td colspan="3">Male</td></tr>
<tr><td>Patient age</td><td colspan="6">In years</td></tr>
<tr><td>Tumour size</td><td colspan="6">Maximal diameter in cm</td></tr>
<tr><td>Tumour site (knee)</td><td>Femur</td><td colspan="2">Tibia</td><td colspan="2">Fibula</td><td>Patella</td></tr>
<tr><td>Tumour site (shoulder)</td><td colspan="3">Humerus</td><td colspan="3">Scapula</td></tr>
<tr><td>Tumour location (long bones)</td><td>Epiphysis</td><td>Epimetaphysis</td><td>Metaphysis</td><td colspan="2">Metadiaphysis</td><td>Diaphysis</td></tr>
<tr><td>Tumour location</td><td colspan="3">Central</td><td colspan="3">Marginal</td></tr>
<tr><td>Endosteal scalloping</td><td colspan="3">Yes (deep/superficial)</td><td colspan="3">No</td></tr>
<tr><td>Perilesional edema</td><td colspan="3">Yes</td><td colspan="3">No</td></tr>
<tr><td>Periosteal reaction</td><td colspan="3">Yes</td><td colspan="3">No</td></tr>
<tr><td>Indication for MRI</td><td colspan="2">Tumour-related</td><td colspan="2">Other</td><td colspan="2">Not applicable</td></tr>
</table>

Use of contrast agent	Yes	No

Table 1. Variables ascertained in each tumour case.

2.5 MRI (technical data)

2.5.1 MRI of the knee

MRI examinations of the knee were carried out on two different 3 Tesla MRI systems (*Siemens Magnetom Skyra/Siemens Magnetom Vida; both Siemens Healthcare Diagnostics GmbH, Austria*) with a 15/18-channel knee coil. **Table 2** shows a detailed description of all sequences acquired.

Regarding administration of contrast agent, 77 of 651 patients (81 of 672 tumours) received Gd-DTPA (gadolinium diethylene-triamine penta-acetic acid) (dose 2 ml/kg body weight) intravenously with a subsequent MRI examination with "sequence 4".

	Seq.* 1	**Seq. 2**	**Seq. 3**	**Seq. 4**
Section	Coronal	Transversal	Sagittal	Coronal
Weighting	PD**	PD	PD	T1 TSE***
Fat suppression	Yes	Yes	Yes	No
Field of view (mm)	160/140	160/150	160/140	160/140
Matrix	307x384/ 307x384	307x384/ 307x384	307x384/ 307x384	346x384/ 290x484
Repetition time (ms)	3000/3200	5460/4110	2920/2920	690/690
Echo time (ms)	34/25	37/35	34/34	11/19
Slice thickness (mm)	3/3	2.5-3/3	3/3	3/3
Interslice gap (mm)	0.6/0.6	0.6/0.6	0.6/0.6	0.6/0.6
*Seq. = sequence **PD = proton density ***TSE = turbo spin echo				

Table 2. Detailed technical description of the sequences used for MRI of the knee.

2.5.2 MRI of the shoulder

MRI of the shoulder was also performed on two 3 Tesla MRI systems with a 16-channel coil from Siemens Healthcare Diagnostics GmbH, Austria (*Siemens Magnetom Skyra/Siemens Magnetom Vida*). A detailed description of the five different sequences acquired is displayed in **Table 3**.

As contrast agent, Clariscan 0.5 mmol/ml (gadoterate meglumine; dose 2 ml/kg body weight) was administered via venous access in 39 of 93 patients (41 of 97 tumours). This was followed by an MRI scan with "sequence 5".

	Seq.* 1	**Seq. 2**	**Seq. 3**	**Seq. 4**	**Seq. 5**
Section	Coronal	Sagittal	Transversal	Coronal	Coronal
Weighting	PD**	PD and T2 TSE***/ PD dixon TSE	PD blade	T1 TSE	T1 TSE
Fat suppression	Yes	No	Yes	No	Yes
Field of view (mm)	160/150	160/130	160/140	150/140	150/140
Matrix	320x320/ 256x256	384x384/ 272x320	256x256/ 256x256	403x448/ 269x384	256x320/ 269x384
Repetition time (ms)	2250/2250	3520/2490	2250/3120	574/598	660/550
Echo time (ms)	46/49	28/37	43/50	12/11	11/11
Slice thickness (mm)	3/3	3/3	3/3.5	3/3	3/3
Interslice gap (mm)	0.3/0.9	0.9/0.6	0.3/1	0.3/0.9	0.9/0.9
*Seq. = sequence **PD = proton density ***TSE = turbo spin echo					

Table 3. Detailed technical description of sequences used for MRI of the shoulder.

2.6 Statistical analysis

Stata Version 16.1 for Mac (StataCorp, College Station, US) was used to carry out all statistical analyses in this study. While demographics of patients were summarized from the total number of patients with cartilaginous tumours that had been included in this study, demographics of tumours were calculated based on the total number of chondromatous lesions seen. The total number of patients with a benign/intermediate intraosseous cartilaginous lesion of the knee/shoulder was used to calculate the prevalences, and not the total number of enchondromas/ACTs detected. Therefore, patients who had received an MRI scan of the knee/shoulder during the study period but whose MRIs were negative for cartilaginous tumours were counted only once when calculating the prevalence.

Quantitative variables were provided as means with corresponding standard deviations (normally distributed variables) or as medians with corresponding interquartile ranges (non-normally distributed variables). Fisher's exact test was used for assessment of significant differences between binary/ordinary variables, whereas t-test was applied to examine differences in continuous variables. A p-value below 0.05 was considered statistically significant.

3 Results

3.1 Prevalence of enchondromas/ACTs around the knee joint

In the study period (01.01.2007 – 01.03.2020) of 13.2 years, the prevalence of enchondromas and ACTs together amounted to 1.45%. When separating the prevalence for benign and intermediate dignity, a prevalence of 1.4% was found for enchondromas, whereas the prevalence of ACTs was 0.05%.

The prevalence of benign/intermediate cartilaginous lesions around the knee joint showed a slight increase over the years of the study period. While this trend could also be seen when taking a closer look at the course of the prevalence-curve of enchondromas only, it could not be applied to the evolution of the prevalence of ACTs (**Figure 11**).

Detailed investigation of a cohort of 44.762 patients who had undergone MRI examination of at least one knee in the time period between 01.01.2007 and 01.03.2020 revealed that 651 (1.45%) of these patients had an enchondroma/ACT. In 17 of 651 patients, two lesions were discovered incidentally in the same knee. Four more patients presented with a benign/intermediate cartilaginous tumour in the left and the right knee. This led to an overall number of 672 tumour cases around the knee.

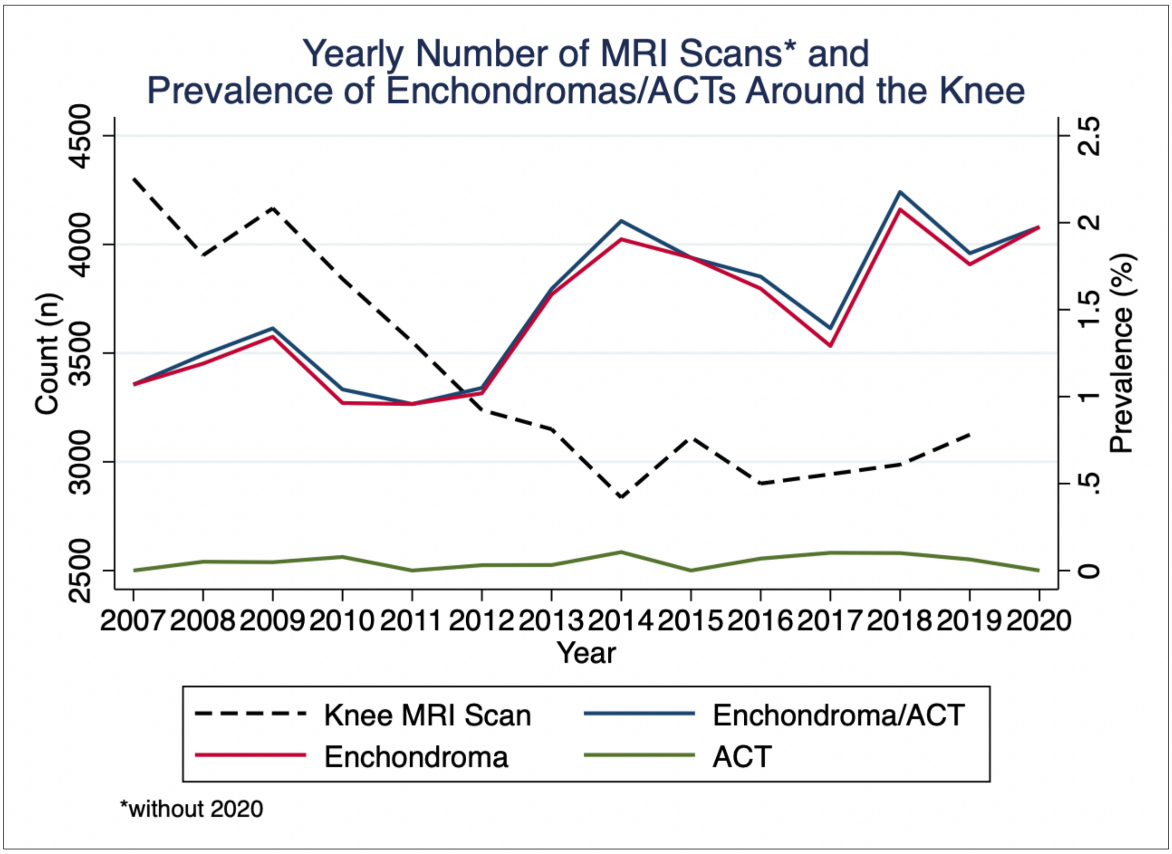

Figure 11. Numbers of patients, who received an MRI of the knee, and calculated prevalences of enchondromas and ACTs around the knee.

3.2 Characteristics of cartilaginous lesions around the knee joint

Of all 672 cases, 650 lesions (96.7%) were identified as enchondromas around the knee joint, whereas 22 lesions were diagnosed as an ACT (3.3%).

The tumour size of enchondromas was 1.5 ± 0.9 cm. ACTs presented with a statistically significantly ($p<0.001$) larger lesion size of 5.1 ± 1.9 cm, with the largest intermediate cartilaginous tumour measuring 9.0 cm (cranio-caudal) (**Table 4**).

	Enchondroma	**ACT**	**P-value**
Count	650 (96.7%)	22 (3.3%)	
Tumour size [cm]	1.5 ± 0.9	5.1 ± 1.9	<0.001*
*t-test			

Table 4. Count and size of lesions around the knee.

In 490 cases (72.9%), the cartilaginous lesions were located in the femur, thus representing the most common location of enchondromas (72.9%) and ACTs (72.7%) around the knee joint. However, a statistically significant ($p=0.011$) deviation between enchondromas and ACTs could be found when taking a closer look at the second most common bone affected: While only 6.0% of enchondromas resided in the proximal fibula, 22.7% of all ACTs were found in this location.

Enchondromas mainly resided in the metaphysis (60.2%) of the affected bone. This finding could not be reproduced for ACTs, however, that were most often found in the diaphysis (31.9%), but also in the metadiaphyseal, metaphyseal and epimetaphyseal area (all 22.7%), thereby showing statistically significant difference in comparison to enchondromas ($p<0.001$).

Most ACTs (86.4%) were located peripherally in relation to the medullary canal. Enchondromas, however, were statistically significantly ($p<0.001$) more often localized centrally (58.9%) (**Table 5**).

		Enchondroma	**ACT**	**P-value***
Bone	Distal femur	474 (72.9%)	16 (72.7%)	0.011
	Proximal tibia	136 (20.9%)	1 (4.6%)	
	Proximal fibula	39 (6.0%)	5 (22.7%)	
	Patella	1 (0.2%)	0 (0.0%)	
Location	Epiphysis	80 (12.3%)	0 (0.0%)	<0.001
	Epimetaphysis	65 (10.0%)	5 (22.7%)	
	Metaphysis	391 (60.2%)	5 (22.7%)	

	Metadiaphysis	27 (4.1%)	5 (22.7%)	
	Diaphysis	86 (13.2%)	7 (31.9%)	
	Patella	1 (0.2%)	0 (0.0%)	
Location in relation to medullary canal	Central	383 (58.9%)	3 (13.6%)	<0.001
	Peripheral	267 (41.1%)	19 (86.4%)	
*Fisher's exact test				

Table 5. Location of lesions around the knee.

Superficial scalloping could be found in one enchondroma and two ACTs, while deep endosteal scalloping was present in 12 ACTs ($p<0.001$). Medullary edema was seen in 4 benign lesions (0.62%) and in 2 intermediate tumours (9.09%) ($p=0.014$). Periosteal reaction could only be found in 2 lesions, both of them ACTs ($p<0.001$) (**Figure 12**).

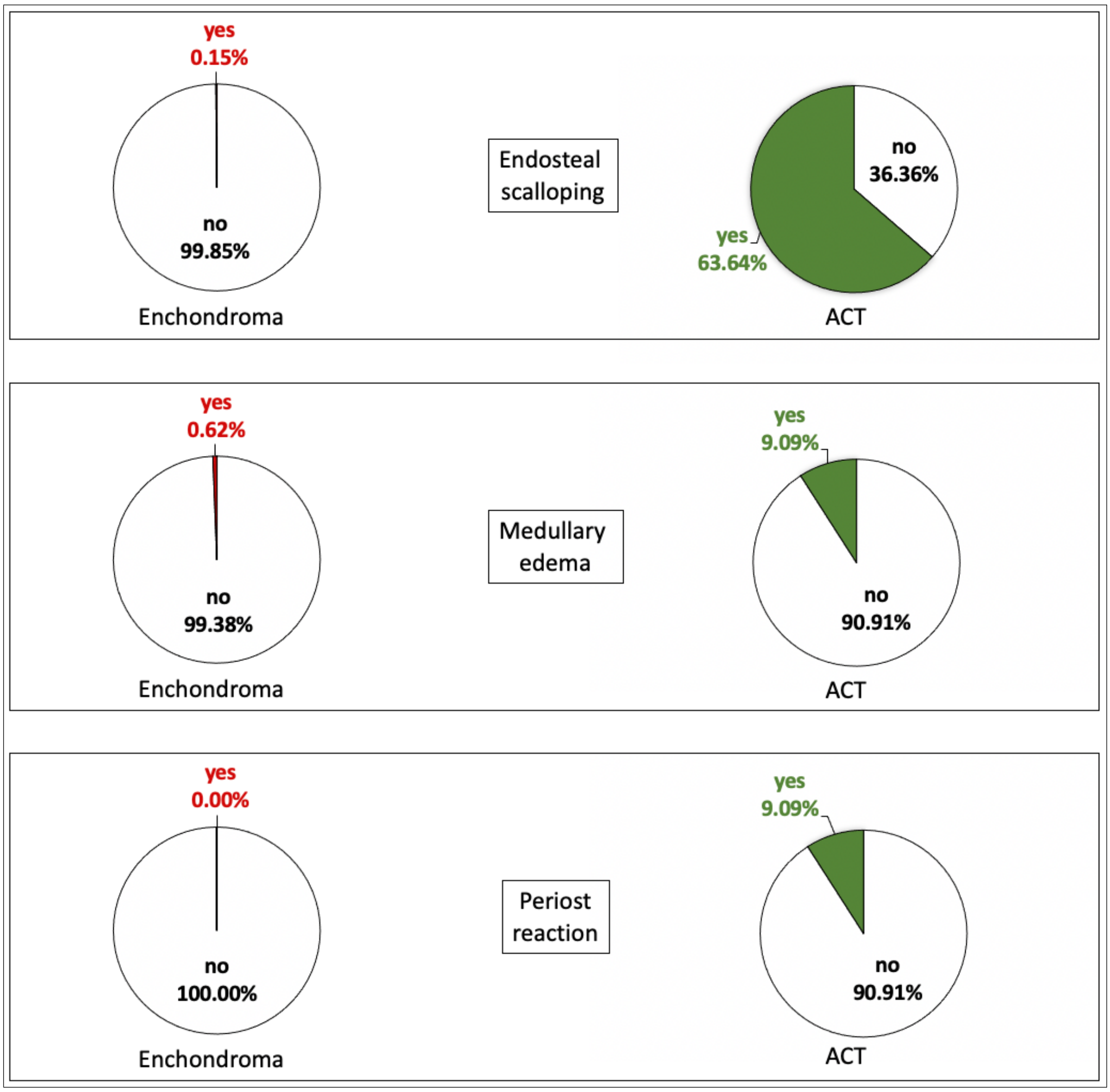

Figure 12. Radiological features for assessment of dignity for lesions around the knee.

3.3 Characteristics of patients with cartilaginous lesions around the knee

Patients receiving an MRI of the knee in the study period and showing a cartilaginous lesion, had a mean age of 52.1 ± 13.1 years. Most of patients were female (n=336; 51.6%). The majority of patients (71.1%) received an MRI of the knee due to a suspected pathology other than cartilaginous tumours. Around 16.7% of patients underwent MRI of the knee for unknown referral reason, whereas 12.2% of patients received an MRI due to a suspected cartilaginous lesion.

3.4 Prevalence of enchondromas/ACTs around the shoulder joint

Altogether, 93 patients with cartilaginous lesions of the shoulder had been identified at the aforementioned radiologic institute in the study period, thereby causing a prevalence of 0.43% for benign and intermediate chondrogenic tumours of the shoulder. When taking a closer look at enchondromas only, a prevalence of 0.39% was revealed, whereas a prevalence of 0.04% was found for ACTs.

Four of the 93 patients presented with two lesions at the same time: While three of them showed two chondrogenic lesions of the same shoulder joint, one patient presented with one enchondroma of the right and one enchondroma of the left shoulder.

Different to the course of the prevalence-curve of cartilaginous tumours of the knee (**Figure 11**), the yearly prevalence of chondromatous lesions around the shoulder joint showed an undulating course. There was no clear sign of a trend towards in- or decreasing prevalence with time (**Figure 13**).

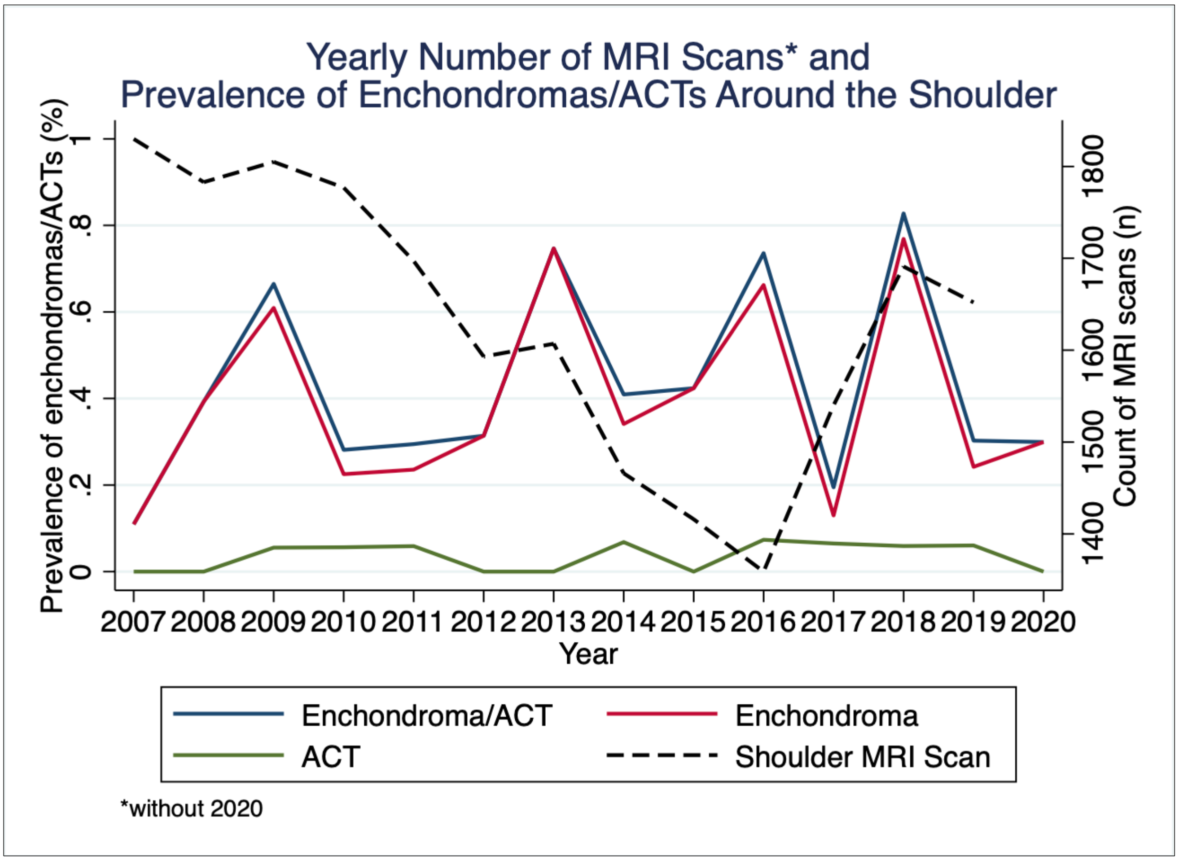

Figure 13. Numbers of patients, who received an MRI of the shoulder, and calculated prevalences of enchondromas and ACTs around the shoulder.

3.5 Characteristics of cartilaginous lesions around the shoulder joint

When separating all tumour cases (97 cases) depending on tumour dignity, the majority of cartilaginous lesions around the shoulder was represented by enchondromas (91.8%), while ACTs accounted for 8.2%.

ACTs of the shoulder showed a statistically significantly ($p<0.001$) larger tumour size (5.5 ± 1.8 cm) than shoulder enchondromas (2.0 ± 1.1) (**Table 6**).

	Enchondroma	ACT	P-value
Count	89 (91.8%)	8 (8.2%)	
Tumour size [cm]	2.0 ± 1.1	5.5 ± 1.8	<0.001*
*t-test			

Table 6. Count and size of lesions around the shoulder.

All ACTs and 96.6% of enchondromas resided in the proximal humerus. Only three lesions (all of them enchondromas) were localized in the scapula (**Table 7**).

Most of enchondromas (62.9%) were found in the metaphysis, whereas ACTs were located mostly in the metaphysis (37.5%) and the metadiaphysis (37.5%).

A statistically significant difference (p=0.009) could be revealed for location of lesions in relation to the medullary canal: While all 8 ACTs presented as peripheral lesions, enchondromas were frequently localized peripherally (52.8%) as well as centrally (47.2%).

		Enchondroma	**ACT**	**P-value***
Bone	Proximal humerus	86 (96.6%)	8 (100.0%)	0.999
	Scapula	3 (3.4%)	0 (0.0%)	
Location	Epiphysis	6 (6.7%)	0 (0.0%)	0.110
	Epimetaphysis	7 (7.9%)	0 (0.0%)	
	Metaphysis	56 (62.9%)	3 (37.5%)	
	Metadiaphysis	7 (7.9%)	3 (37.5%)	
	Diaphysis	10 (11.2%)	2 (25.0%)	
	Scapula	3 (3.4%)	0 (0.0%)	
Location in relation to medullary canal	Central	42 (47.2%)	0 (0.0%)	0.009
	Peripheral	47 (52.8%)	8 (100.0%)	
*Fisher's exact test				

Table 7. Location of lesions around the shoulder.

Regarding radiological features that can support diagnosis of the dignity of cartilaginous tumours, a statistically significant difference between enchondromas and ACTs of the shoulder joint was found for endosteal scalloping (p<0.001): 97.8% of enchondromas presented without endosteal scalloping, whilst 2 benign lesions were associated with superficial scalloping. As opposed to that, endosteal scalloping was present in 5 of 8 ACT cases (62.5%). Medullary edema was found in one enchondroma and in one ACT each (**Figure 14**).

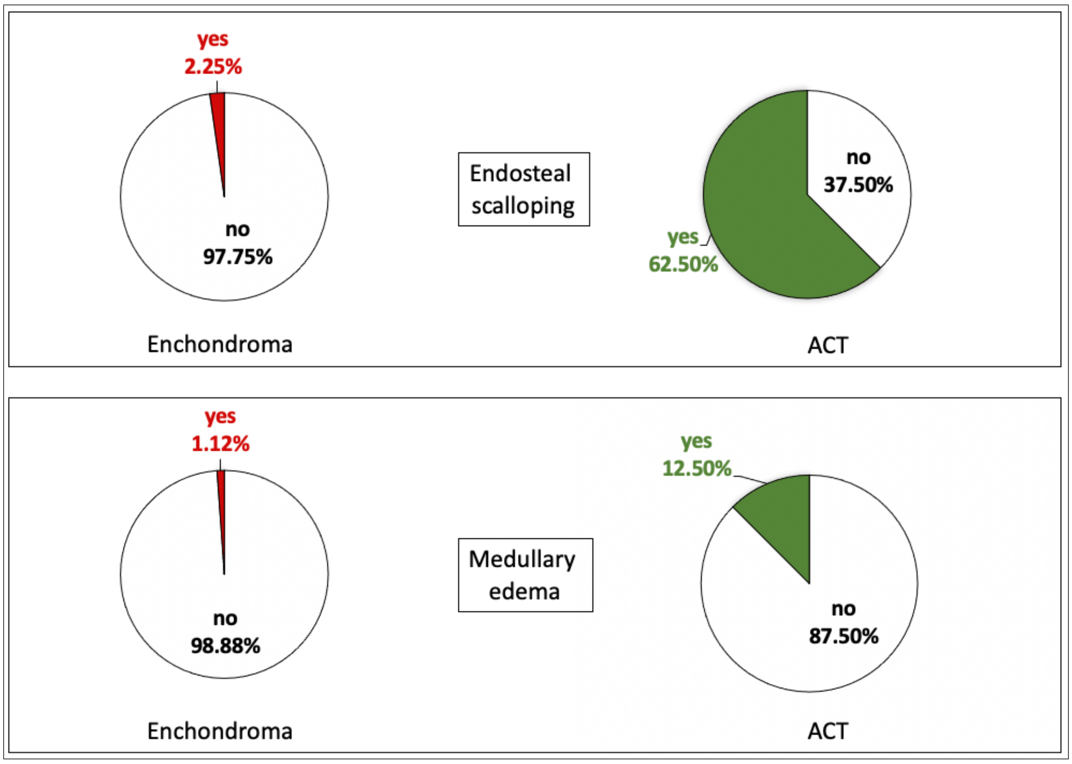

Figure 14. Radiological features for assessment of dignity for lesions around the shoulder.

3.6 Characteristics of patients with cartilaginous lesions around the shoulder

The majority of patients who had undergone an MRI of the shoulder and presented with a cartilaginous lesion was male (60.2%). Mean age at the time of MRI was 54.5 ± 11.9 years. Twenty-three patients (24.7%) were referred due to a suspected cartilaginous tumour, 61 patients (65.6%) received an MRI of the shoulder due to other reasons, and 9 patients (9.7%) underwent MRI for unknown reason.

4 Discussion

4.1 Cartilaginous tumours of the knee

This diploma thesis is based on 44.762 MRI scans of the knee, discovering a prevalence of 1.45% for benign and intermediate cartilaginous lesions. Thorough review of literature revealed that up to now, five other studies have focused on finding out the true prevalence of cartilage tumours around the knee (8-12). To the best of the author's knowledge, however, this diploma thesis is based on the largest cohort by far and might therefore have the potential to validate/challenge all figures that have been calculated with other existing cohorts.

The study of Stomp et al. (10) was based on the largest cohort when comparing previous literature on this matter: The authors examined 1.285 patients with MRI scans of the right knee and found a prevalence of 2.8% for cartilage lesions (10). Two more studies reached similar conclusions, discovering a figure of 2.9% each (8, 11): While Walden et al. (8) examined 449 MRI scans of adult patients, Douis et al. (11) analysed 240 MRIs of 209 children.

One more MRI-based study was performed by Grainger et al. (12), who evaluated knee MRIs of 601 asymptomatic healthy controls and 132 patients with knee osteoarthritis to discover whether clinical significant abnormalities are more pronounced in one group: They reported that 1.5% of patients with osteoarthritis of the knee presented with enchondromas, as compared to 0.8% of the healthy controls (12).

An autopsy study performed by Scherer et al. (9) dating back to 1928 discovered an even lower prevalence for enchondromas around the knee joint (0.2%). This figure needs to be interpreted with caution, however, as it has been proved that MRI is much more sensitive in the detection of even smallest cartilage lesions than autopsy, thereby explaining the low prevalence reported by Scherer et al (9).

Overall, it can be stated that this diploma thesis is based on a uniform study cohort that is 35 times larger than the largest study on this matter up until now (10). According to the present study, the prevalence of cartilaginous lesions around the knee might have been overestimated by Stomp et al. (10), Walden et al. (8) and Douis et al. (11), whereas findings by Grainger et al. (12) are supported by the herein discovered prevalence. Due to the large number of included MRI scans (44.762) it can be supposed that this study has the power to provide an exact figure regarding the prevalence of enchondromas around the knee.

When comparing the results for prevalence of ACTs around the knee, it becomes apparent that Stomp et al. (10) reported on a figure of 0.4%, while our study discovered a prevalence of 0.05%. This discrepancy might be explainable, considering that diagnosis of an ACT was subject to diverging criteria in the two studies: While Stomp et al. considered a lesion size of over 2 cm indicative of an ACT, this study was based on more current literature, and therefore only regarded tumours with a size exceeding 5 cm as ACTs.

A study performed by van Praag et al. (55) revealed that the frequency of diagnosed ACTs steadily grew within the time span of 1989 until 2013, other than the frequency of diagnosed higher grade chondrosarcomas that remained constant. Van Praag et al. could explain this finding by pointing out that imaging techniques and availability have improved drastically over the years, thereby increasing precision in the diagnostic process of cartilaginous tumours. Furthermore, the ageing of the population might be another factor contributing to this trend (55). The data presented in this diploma thesis cannot confirm such a trend, though, as the per year prevalence of ACTs around the knee joint did not increase from 2007 until 2020. When focusing on the course of the curve of the prevalence of enchondromas, however, a steady increase can be seen from 2007 (1.07%) until 2019 (1.8%).

4.2 Cartilaginous tumours of the shoulder

The current diploma thesis also analysed shoulder MRIs of 21.550 patients that had been performed at a single radiology institute between January 2007 and March 2020. Radiological evaluation of these MRI scans revealed a prevalence of 0.43% for benign and intermediate intraosseous cartilaginous tumours of the bone around the shoulder joint.

In-depth literature search revealed that only one study based on a small cohort of shoulder MRIs has been performed up until now, aiming at analysing prevalence of cartilage tumours in this body region (13): The study by Hong et al. examined a cohort of 477 patients with MRIs of the shoulder (13). Evaluation of these MRIs revealed a prevalence of 2.1% for benign cartilaginous lesions around the shoulder girdle. When comparing the prevalence of Hong et al. with the prevalence revealed in this diploma thesis, it becomes apparent that our study found a lower prevalence. Notably, the current prevalence is based on a 45 times larger uniform patient cohort and might thereby be represent a precise estimation of the prevalence of enchondromas/ACTs around the shoulder joint.

While the cohort of Hong et al. included 10 patients with an enchondroma and no patients with an ACT, this diploma thesis identified 93 patients with 89 enchondromas and 8 ACTs within the analysed cohort of 21.550 examined patients (13).

This thesis revealed an overall prevalence of 0.04% for ACTs around the shoulder joint, thereby presenting the first figure ever reported in literature on this matter, as no previous study has been conducted with the same research question.

Besides, van Praag et al. (55), Davies et al. (56) could also show that the number of diagnosed ACTs has increased over the last decades: This diploma thesis could not validate this finding for ACTs of the shoulder girdle, as within a time span of 13.2 years only 8 patients with ACTs of the shoulder were identified. Apparently, this number of ACTs is too low to identify a trend.

Davies et al. (56) also presented data on the per-year-frequency of diagnosed enchondromas over the last decades: Between 2009 and 2018, 85% more patients were diagnosed with a benign cartilaginous lesion of the shoulder than in the period of 1999 until 2008, thereby indicating an increase in enchondroma prevalence over the last decades. However, this diploma thesis could not confirm this trend for the time period between 2007 and 2020, with the per-year-prevalence of enchondromas showing an undulating course.

4.3 Limitations

Some limitations must be considered when interpreting the results of this diploma thesis: Due to the benign nature of enchondromas, most patients included in this diploma thesis did not undergo biopsy with consecutive histopathological examination. Therefore, diagnosis of all cartilage tumours was MRI-based only. Radiological criteria to reliably differentiate benign from intermediate cartilaginous tumours are not utterly defined, though. Despite that, it can be assumed that histological evaluation would not have significantly altered results obtained, due to the fact that histology strongly depends on quality of the biopsy and might be prone to biopsy sampling error (38).

The retrospective design represents another limitation of this diploma thesis, as MRIs had mostly been performed for other reasons than cartilaginous tumours.

4.4 Conclusions

This diploma thesis represents the largest study that focused on assessment of the prevalence of benign and intermediate cartilaginous tumours of knee and shoulder, as it included an enormous number of patients and MRI scans. Therefore, it can be supposed that this diploma thesis has the power to provide exact figures regarding prevalence of enchondromas and

ACTs around the knee (1.45%) and the shoulder (0.43%). The findings suggest that prevalences of enchondromas/ACTs around the knee and shoulder joint have largely been overestimated.

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