Diplomarbeit

Do we need bone scans for cartilage tumors?

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Abstract

INTRODUCTION: Cartilage tumors represent the largest bone sarcoma group and the differentiation between enchondromas (EC) and low-grade chondrosarcomas (CS) remains a diagnostic challenge. It has been described that bone scans provide further information about the malignant potential of cartilage tumors. We aimed to identify the diagnostic benefit of bone scans in cartilage tumors.

MATERIAL AND METHODS: We retrospectively analyzed 461 patients with a cartilage tumor (321 EC, 54 CS, 74 osteochondromas (OC), 4 chondromyxoidfibromas (CMF), 4 chondroblastomas (CB), 3 Ollier disease) diagnosed at a mean age of 45.8 years (range 6 – 84) in whom a Tc99m bone scan (3 phasic) was performed. Bone scan data, x-rays, magnetic resonance imaging (MRI) and histopathological records were evaluated. For EC and CS diagnostic accuracy of bone scans was assessed with receiver operator characteristic curves (ROC) to evaluate the area under the curve (AUC).

RESULTS: Of 375 patients suffering from EC or CS, 65 (17%) underwent biopsy and 176 (46%) surgery, while in 134 cases (35%) a conservative treatment and observation in regular intervals was chosen. The most common localization of tumors were the long bones (n=245, 65%), followed by hand and foot (n=99, 26%) and trunk (n=20, 5%). The mean tracer uptake for EC was 3.8 (range 0.5 – 68.0), for CS grade 1 4.47 (range 0,5 – 12,3), grade 2 8.2 (range 3,3 – 13,5) and grade 3 7.5 (range 6,3 – 8,9). The mean tracer uptake of EC was significantly lower than for all CS ($p< 0.001$), for low- grade CS ($p< 0.001$) respectively. In 153/321 lesions (48%) the radiologist identified EC correctly, whereas 3/54 CS (6%) were correctly identified with the bone scan compared to the definitive diagnosis. In 145 patients (39%) the bone scan was inconclusive and in 54 (14%) patients the bone scan did not show any pathological finding. On multivariate analysis tracer uptake was significantly increased with pathological fracture (OR 3.9, 95% CI 3-5.2, $p<0.001$) and peripheral localization of tumors (OR 2.8, 95% CI 1.5-5-2, $p<0.001$). The AUC for all cartilage tumors increased from 0.70 (Sp 80%, Sen. 50%) to 0.80 (Sp. 80%, Sen. 64%) when adding bone scan information. The AUC for EC and CS grade 1 increased from 0.67 (Sp 80%, Sen 46%) to 0.73 (Sp 80%, Sen 52%).

DISCUSSION: We could see a statistically significant increase of tracer uptake in CS (all CS vs. EC; Grade 1 vs. EC) compared to EC. Localization and the presence of pathological fracture were significant independent predictors for higher tracer uptake. However, assessment of diagnostic performance showed, that bone scans only provide minimal additional information to select between EC and CS, low-grade CS respectively. Taking into account costs and resources to perform a bone scan as well as radiation

exposure for patients, its use in the group of cartilage tumors should be reconsidered in the future.

Zusammenfassung

EINLEITUNG: Knorpeltumore repräsentieren die größte Gruppe der Knochentumore, wobei die Unterscheidung zwischen Enchondrom (EC) und (niedrig malignem) Chondrosarkom (CS) eine diagnostische Herausforderung darstellt. Ziel dieser Studie war es, den diagnostischen Benefit der Szintigraphie im Hinblick auf Knorpeltumore zu evaluieren.

MATERIAL UND METHODEN: Wir analysierten retrospektiv 461 PatientInnen mit Knorpeltumoren (321 EC, 54 CS, 74 OC, 4 CMF, 4 CB, 3 Mb. Ollier). Das mittlere Alter bei Diagnosestellung war 45.8 Jahre (Spannweite 6 – 84). Die Daten von Szintigraphie (3-Phasen Szintigraphie mit Tc99m), Röntgen, Magnetrasonanztomographie (MRT) und die histopathologischen Ergebnisse wurden ausgewertet. Die diagnostische Treffsicherheit der Szintigraphie wurde mittels receiver operator characteristic curves (ROC) ermittelt und durch area under the curve (AUC) ausgewertet.

ERGEBNISSE: Von 375 Patienten, die an EC oder CS litten, hatten 65 (17%) eine Biopsie und 176 (46%) eine Operation, wobei man sich in 134 Fällen (35%) für ein konservatives Vorgehen entschied. Die häufigste Lokalisation waren die langen Röhrenknochen (n=245, 65%), gefolgt von Hand und Fuß (n=99, 26%) und Stamm (n=20, 5%). Der mittlere Tracer uptake für EC war 3.8 (Spannweite 0.5 – 68.0), für CS Grad 1 4.47 (Spannweite 0,5 – 12,3), Grad 2 8.2 (Spannweite 3,3 – 13,5) und Grad 3 7.5 (Spannweite 6,3 – 8,9). Der mittlere Tracer uptake für EC war significant niedriger als für alle CS ($p< 0.001$), ebenso für niedrig maligne CS ($p< 0.001$). Bei 145 Patienten (39%) war die Szintigraphie inkonclusiv und bei 54 (14%) Patienten zeigte sie keinen pathologischen Befund. Bei der multivariaten Analyse war der Tracer uptake bei pathologischen Frakturen (OR 3.9, 95% CI 3-5.2, $p<0.001$) und peripherer Lokalisation der Tumore (OR 2.8, 95% CI 1.5-5-2, $p<0.001$) signifikant erhöht. Die AUC für alle Knorpeltumore stieg von 0.70 (Sp 80%, Sen. 50%) auf 0.80 (Sp. 80%, Sen. 64%), wenn die Ergebnisse der Szintigraphie hinzugezogen wurden. Die AUC für EC und CS Grad 1 stieg von 0.67 (Sp 80%, Sens 46%) auf 0.73 (Sp 80%, Sen. 52%).

DISKUSSION: Es bestand ein statistisch signifikanter Unterschied des Tracer uptakes bei CS (alle CS vs. EC; G1 vs. EC) verglichen mit EC. Lokalisation und der Nachweis pathologischer Frakturen waren signifikante, unabhängige Parameter für erhöhten Tracer uptake. Jedoch zeigte die Beurteilung des diagnostischen Potenzials, dass die Szintigraphie lediglich minimale diagnostische Zusatzinformation liefert, um zwischen EC und CS beziehungsweise EC und niedrig malignem CS zu unterscheiden. Berücksichtigt man Kosten und Aufwand bei der Durchführung einer Szintigraphie sowie die

Strahlenbelastung für die PatientInnen, sollte die Verwendung der Szintigraphie in der Gruppe der Knorpeltumore zukünftig überdacht werden.

Abbreviations

AUC	area under the curve
CI	confidence Interval
CMF	chondromyxoidfibroma
coef	coefficient
CS	chondrosarcoma
EANM	european association of nuclear medicine
EC	enchondroma
EXT1	exostosis (multiple)-1
EXT2	exostosis (multiple)-2
Fig.	figure
G1 (2, 3)	grade 1 (2, 3)
HSPG	heparin sulfate proteoglycane
ID	initial diagnosis
logTr	logarithmic tracer uptake
MBq	mega-becquerel
OC	osteochondroma
PET	positron emission tomography
PET-CT	positron emission tomography–computed tomography
ROC	receiver operating characteristic curve
SUV	standardized uptake value
Tab.	table

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1 Introduction

1.1 Cartilage tumours

1.1.1 Enchondroma

According to the definition of the WHO, an „[e]nchondroma is a benign hyaline cartilage neoplasm of medullar bone.“(1) A synonym for EC is central chondroma. They normally occur solitarily, but also multiple lesions can be found either in one bone or distributed in the skeleton. Two syndromes are associated with those multiple ECs: Ollier disease and Maffucci syndrome (see paragraph 1.1.5).(1-4)
Within the group of bone tumors, ECs occur frequently compromising 10–25 % of all benign tumors of the bone.(5) Within the group of benign cartilage tumors, EC is the most frequent one. It has to be taken into consideration, that the number of unreported cases is much higher, since many ECs are not detected because of their clinical inconspicuousness.(5) They occur at any age, starting at 5 years up to 80 years, but most patients are affected in their 2nd to 5th decade of life.(1, 4, 6) The frequency in male and female is equal.
In approximately 40% EC involves the short tubular bones of the hands, followed by the long tubular bones such as humerus and femur. Mostly they are located in the medullar part of the metaphysis. Regarding the humerus, they are often found in the proximal part. The tibia is often affected in the distal part and the femur in both, proximally and distally. In some cases they are detected in flat bones, like the ribs and even more unlikely in craniofacial bones.(1, 4)

1.1.2 Chondrosarcoma

CSs are “a locally aggressive or malignant group of cartilaginous matrix-producing neoplasms with diverse morphological features and clinical behavior”(1) with an incidence of about 3/100.000 inhabitants per year.(4) Histologically, they are divided in three grades with increasing malignancy (grade 1, 2, 3). It can be distinguished between a primary central CS, a secondary central CS, secondary peripheral CS and a periosteal CS. Furthermore, dedifferentiated chondrosarcoma

is described, which did not occur in our study group and therefore won´t be part of this thesis.

Primary central CS is the most common type (85%) and with 20% of all malignant bone tumors the third most frequent malignancy in bones. Its origin is the medullary space of the bone and it mostly appears in patients over 50 up to 70 years, while men are slightly more affected.(1, 4)

About 75% of primary central CSs arise in the trunk, femur or humerus. The ilium is the most affected bone, followed by the other osseous parts of the pelvis, femur, shoulder girdle (proximal humerus and scapula) and ribs. In contrast to EC, it occurs rarely in the small bones of the hands or feet. Craniofacial bones as well as the spine are rarely involved.(1, 4)

While EC - apart from pathological fractures - usually is clinically inapparent, CS commonly presents with local pain with or without swelling. Almost 80% of patients with grade 2 and 3 CS coincide with pain. Pathological fractures can occur in up to 8%.(6-8)

Prognosis depends on the histological grade. Grade 1 CS - also known as atypical cartilaginous tumors - show a 5-year survival rate of 83%, while the 5-year survival of grade 2 and 3 CS is only about 50%.(1) Accordingly, treatment depends on grading: Atypical cartilaginous lesions are treated with curettage and locally applied adjuvants due to their low risk of local recurrence with exception of pelvic lesions. They should be treated aggressively with wide resection margins. Higher malignant tumors should be resected en-bloc.(1, 4, 6, 9)

“[S]econdary [central] chondrosarcoma frequently develops in solitary enchondroma, although there are no data available detailing the associated risk”(1) but always grows from pre-existing EC. Notable higher risk of secondary CS has been described for patients with Ollier disease (40%) and Maffucci syndrome (53%). A growing preexisting EC is a possible indicator of malignant potential and suspicious of a recently developed secondary CS. The prognosis corresponds to primary CS. Secondary CS usually affects younger patients compared to primary CS.(1)

Secondary peripheral CS arises from preexisting OCs and is located next to the cartilaginous cap of OCs. The lifetime risk of developing this malignancy increases from 1% for single lesions to 5% for multiple OC.(1)

In case of hereditary multiple OCs this risk seems to be increased, with reported risks between 5 to 25%.(1, 4, 10) In nearly every case this tumor degenerates into a low-grade CS and affects with a median age of 34.9 years younger patients than classical CS. Sites of involvement are frequently the pelvis and the shoulder girdle, but generally every bone can be affected. Clinically, pain or swelling is suspicious to malignant transformation.(1, 4)

Periosteal CS has its origin from the periosteum of bones. It is also known as juxtacortical CS. It mostly occurs in patients in the 2nd to 4th decade of life, while men are slightly more often affected. Periosteal CS frequently involves the metaphysis of long bones, especially the distal femur as well as the humerus. Accordingly, to the other types of CS, presence of pain or swelling might be an indicator for malignancy.(1)

1.1.3 Osteochondroma

OC is defined as "[a] benign cartilage neoplasm consisting of a cartilage-capped bony projection on the surface of bone, containing a marrow cavity that is continuous with that of the underlying bone."(1) The bony part grows either sessile or pediculated out of the medullary space. A synonym is cartilaginous or osteocartilaginous exostosis. Like EC, OC often are asymptomatic and therefore in many cases neither detected nor treated. Thus, the incidence of 35% among all benign bone tumors and 8% of the surgically removed lesions in bone is possibly underestimated. Some tumors become symptomatic due to their size causing permanent pain or activity related pain. Also, nerve- and spinal cord compression can occur. It mostly affects patients in their 1st to 3rd decade of life, while men are slightly more often affected. About 15% of OC patients present with multiple tumors as they have the autosomal dominant hereditary multiple osteochondromas syndrome (HMO).(1, 11-14) Two genes are associated with growth of OC: EXT1 (exostosis (multiple)-1) and EXT2 (exostosis (multiple)-2). They modulate the function of proteins, which are involved in the biosynthesis of HSPG (heparin sulfate proteoglycane). These HSPGs are responsible for a normal growth of the epiphyseal growth plate. Biallelic inactivation of one of these two genes leads to mutated chondrocytes caused by non-functional HSPGs. This

leads to abnormal endochondral ossification, which is estimated to be part of the development of OC. It only appears in bones formed from endochondral ossification. This fact is partly a reason for the localization: OC most commonly appears in the metaphysis of the distal femur, the proximal humerus, tibia and fibula. Flat bones are rarely involved. It is described, that OC can arise after traumatic events like fractures or radiation. Only symptomatic lesions should be resected. OC must be completely excised due to the risk of local recurrence if the tumor is not removed in total.(1, 4, 11, 13, 15, 16)

1.1.4 Chondromyxoid fibroma

According to the definition of the WHO, CMF is a " benign cartilaginous neoplasm" that consists of lobules forming "spindle-shaped cells with myofibroblastic features at the periphery".(1) The center of the lobules consists of chondrocytes. Regarding the extracellular matrix, there is a myxoid and chondroid center and a fibrous periphery. This rare tumor represents less than 1% of all primary bone tumors.(17) CMF can arise at almost any age and any bone, while it mostly occurs in the second to third decade of life and in the long bones, especially tibia and femur. Men are slightly more often affected than women. Usually it is a little painful with or without swelling. Radiologically, it appears well margined, often ovally formed, with lobules and trabecula. Cortical destruction is a common sign, as well as ballooning or expansion of one cortical side. Only a few cases with malignant transformation into CS are reported since this tumor normally stays benign.(1, 17-20)

1.1.5 Enchondromatosis

Enchondromatoses are "a group of rare, skeletal disorders in which patients have multiple enchondromas."(1) The most frequent types are Maffucci syndrome and Ollier disease. "Ollier disease is a non-hereditary developmental disorder characterized by the occurrence of multiple cartilaginous masses, particularly affecting the short and long tubular bones of the limbs. When cutaneous, soft tissue or visceral hemangiomas are also present, the disorder is referred to as Maffucci syndrome."(1)

Ollier disease shows a prevalence with one in 100.000.(3) There are several synonyms for Ollier disease, such as dyschondroplasia, enchondromatosis Spranger type I, multiple cartilaginous enchondromatosis, dyschondroplasia and multiple ECs. Usually the manifestation is in the early childhood. Ollier disease tends to occur asymmetrically, affecting one side or extremity of the skeleton more than the other. ECs mainly occur in tubular bones, but also the pelvis and ribs can be involved. As typical for the growth pattern of EC, craniofacial bones are rarely involved. Frequent complications are deformities of the extremities and leg-length discrepancies. Occasionally also pathological fractures are a possible complication, that requires surgical treatment. Furthermore, the risk for malignant degradation is up to 40%.(1, 3, 21-24)

Maffucci syndrome is typically diagnosed in childhood or already at birth as it presents with cutaneous, soft tissue or internal cavernous hemangiomas. Chondrogenic tumors occur according to the scheme of Ollier disease. However, the risk of developing secondary CS, which has been described with 53%, is even higher than in patients with Ollier disease.(1, 3, 25) Increased risk of developing further malignancies – such as adenocarcinoma of the pancreas or liver, tumors located in the brain (glioma, astrocytoma) and other sarcomatypes – have been described as well.(1, 3, 24, 26)

1.2 Diagnosis of a cartilage tumor

1.2.1 Radiology

When clinical presentation suggests a cartilage lesion a conventional x-ray is performed first. ECs are well circumscribed lesions with different grades of mineralization. The pattern of mineralization is very characteristic and varies from forming rings and arcs over popcorn-like lesions to a flocculent or punctuate pattern. Rings and arcs can form star-shaped patterns when projected over each other on x-rays. Compacta thickening can occur. An example of the presentation of EC in x-ray is shown in Fig. 1. Further methods of investigation are MRI and CT as these methods contain additional information about soft tissue extension or

tumor infiltration. In addition, tomographic imaging and can be helpful regarding the planning of biopsy or surgery. Signs of benign as well as malignant tumors can be the scalloping-phenomenon. Generally, destruction of the corticalis is suggestive for malignancy and infiltration of soft tissue, respectively. Osteolytic components and formation of spiculae are typically seen in high grade CS. In general, it is very difficult to draw conclusions from the mineralization pattern of the tumors dignity since EC and low-grade CS can impress with similar calcifications of their matrix.(1, 2, 4, 27, 28)

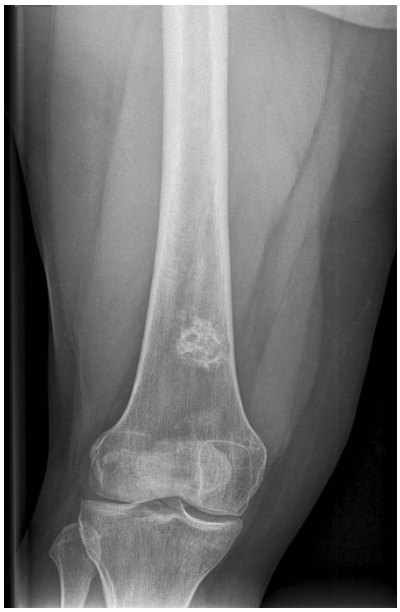

Fig. 1:

Conventional x-ray ap of a 47-year old woman with an EC of the distal femur, size 3 x 2.5 x 3 cm. The tumor is well circumscribed and presents with typical calcifications.

1.2.2 Histology

Cartilage tumors are made of hyaline cartilage, which is lobular structured and frequently covered by a thin layer of bone. This lobular structure is the histological equivalent to the popcorn-like lesions in x-rays. Regarding EC, necrosis or infiltrative growth is absent. Stroma consists of cancellous bone with fat in between. Cellularity of EC is highly variable. There are some with a very low number of cells while others contain more chondrocytes. They are small with a round dark nucleus and located in lacunar spaces. The involvement of the corticalis can only be found in combination with the so-called scalloping, which is limited to the inner two thirds of the compacta. A benign hyaline tumor is sharply circumscribed in its marginal areas. Binuclear chondrocytes are suspected to be

malignant and therefore used for the differentiation between EC and low-grade CS, as well as the lobular pattern. Lobules of CS are more irregular than lobules of EC and the tumor is surrounded by fibrous tissue.(1, 2, 28-30)
Histological differentiation between EC and high differentiated CS is a well-known difficulty. Especially in case of biopsy, i.e. only a tumor fragment can be histologically investigated – the risk is high, that the critical focal mutated part isn´t captured by biopsy. For this reason the definitive diagnosis is often made during the tumor board meeting.(1, 2, 29)

1.2.3 Bone scan

The scintigraphy of bone is one method to evaluate bone metabolism. It is based on the distribution and pathophysiological behavior of radiopharmaceuticals like 99m technetium (99m-Tc). 99m-Tc binds on hydroxyapatite crystals of bone dependent on blood flow and the activity of the bone forming osteoblasts. Osteoblasts build new boney matrix while bone is a constantly changing organism, reabsorbed by osteoclasts and newly formed by osteoblasts. Since metabolism of tumor cells is increased, osteoblast´s activity is increased and therefore more radiopharmaceuticals accumulate in the bone. They degenerate according to their specific half-life period - e.g. 6 hours regarding 99m-Tc – while releasing gamma quants. This radiation can be measured with gamma cameras. During the three-phase bone imaging not only the behavior of the radiotracer in bone but also in blood vessels as well as the extravascular distribution is examined. After the injection of the tracer the “perfusion phase” begins, measuring arterial blood flow. The “blood pool phase” represents as the second phase the venous blood flow, which is most active two to five minutes after injection. The third phase is measured three hours after injection and represents as the “delayed bone phase” the osteogenic activity.(31-36) An example of bone scan imaging can be seen in Fig. 2. The light spots represent the areas with accumulated radiopharmaceuticals.

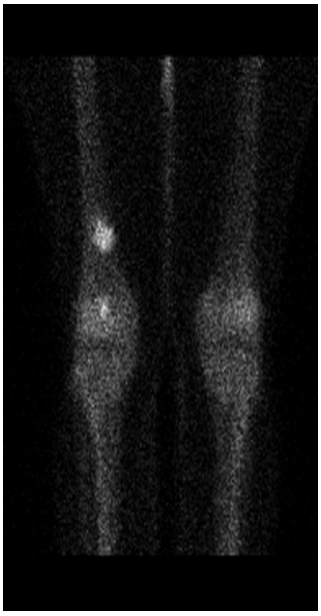

Fig. 2:

3-phasic bone scan of the legs showing a cartilage tumor of the right distal femur. Tracer uptake was 6, according to an average metabolic process.
Histology and bone scan report were inconclusive. The decision to consider the lesion as EC was finally made in the interdisciplinary tumor meeting. Therapy: curettage

2 Aim

Since there are no studies available investigating the diagnostic benefit of bone scans regarding its use in the diagnosis of cartilage tumors, we aimed to identify whether scintigraphy is a useful tool to make a distinction between different cartilage tumors. Particular attention was paid to the fact, that the differentiation between EC and CS G1 can be very difficult and bone scans have been reported to help making a distinction.

3 Material and Methods

3.1 Patients

We conducted a retrospective database analysis to identify all patients, who were diagnosed with a cartilage tumor and underwent a bone scan between 2006 and

2015 at the Department of Orthopedics and Trauma, Medical University of Graz, Austria.

750 patients were identified through a systematic database review of “AURAWEB” using the search terms *cartilage tumor* („Enchondrom, Enchondromatose, Chondrom, Osteochondrom, Exostose, Chondrosarkom, Chondroblastom, Chondromyxoidfibrom“) and *bone scan* („Szintigraphie/Knochenszintigraphie“). Patients of every age were included (0-99 years). Inclusion criterion was the diagnosis of a cartilage tumor, either by distinct radiological findings or by histology. 188 patients turned out not to suffer from a cartilage lesion after detailed review of their medical history or were duplicates. Difficult cases were discussed in the multidisciplinary team meeting, consisting of expert radiologists, pathologists and orthopedic oncologists, to obtain the definitive diagnosis. To be included in the study imaging of the lesion had to be available, either as plain radiograph, CT or MRI scan. Patients without numerical declaration of tracer uptake, i.e. relative description of the tracer uptake (focal enhancement, much uptake, etc.) or no description of the tracer uptake at all were excluded (n=101). As a result, 461 patients were remaining and listed in an excel spread sheet.

3.2 Data collection

For the included 461 patients a detailed search of their clinical history via Medocs was performed.

3.2.1 Clinical data:

Name, sex, date of birth, and date of death were collected in an excel sheet. Pre- and surname were deleted before statistics were conducted. Furthermore, date and age of initial diagnosis as well as clinical suspected diagnosis were included. The clinical suspected diagnosis was the first documented diagnosis after the first time visiting an orthopedic specialist and could either be EC, CS, OC,

chondrogenic tumor of unknown malignant potential, multiple exostosis, chondroma, chondroblastoma, CMF, Mb. Ollier, osteosarcoma, osteoma, cyst, or unclear. If histology was inconclusive or no histology was taken, the definitive diagnosis was defined as the diagnosis made in the multidisciplinary tumor board meeting. The definitive diagnosis in this collective was either EC, OC, CS, CMF, chondroblastoma, Mb. Ollier or no definitive diagnosis possible. If histology was conclusive, the pathological diagnosis was considered as the definitive diagnosis.
In addition, the localization (trunk, humerus, radius, ulna, hand, fingers, femur, patella, tibia, fibula, feet, toes, multiple), presence of metastases, information about pathological fractures of the affected bone, date and status (alive with disease, no evidence of disease, death of disease) of last follow up were included. Treatment options (conservative treatment, biopsy or operation) were analyzed. If a biopsy was performed, the date and the number of biopsies were collected. If an operation was performed, the type (curettage, removal of exostosis, wide resection, surgery discontinued, no information), date, resection margins (marginal, intralesional, wide) or conservative treatment with observations were documented.

3.2.2 Radiology

3.2.2.1 X-Ray, MRI, CT

The interpretation of a cartilage tumor in x-ray, MRI and CT was retrieved of the radiological reports and classified as EC, OC, CS, inconclusive or not available, no tumor, other, and EC OR CS. The reports were either evaluated by radiologists of the Department of Radiology, Medical University of Graz or external radiologists specialized in musculoskeletal imaging. No reevaluation of the images was performed. We classified diagnoses as shown above. Furthermore, the tumor size and the maximal diameter in centimeter were documented. As a general rule, all MRI scans were performed with contrast medium.

3.2.2.2 Bone scan

All bone scans were performed at the Department of Radiology, Division of Nuclear Medicine, Medical University of Graz. A three-phasic planar whole-body bone scan was performed. Static images were taken five minutes and three to four hours after the injection of the radiopharmaceutical. Our department used a Siemens camera, type Siemens Symbia (Siemens Medical Solution USA, Knoxville, TN, USA). As radiopharmaceutical either 99m-Technechium labelled methylene diphosphonate (99m-Tc-MDP) or 99m-Technechium labelled dicarboxypropane diphosphonate (99m-Tc-DPD) were used. The activity ranged from about 530 to 790 MBq depending on body weight.

The date of the scintigraphy, tracer uptake in numbers and a detailed categorization of the diagnosis taken from the nuclear medicine radiologists' reports were included. The evaluation and interpretation of bone scans was conducted by two radiologists specialized in bone scans and nuclear medicine. No reevaluation of the imaging for the purpose of this thesis was performed.

In our dataset, the diagnoses of the nuclear medicine radiologists' report were classified as EC, OC, no specific diagnosis, CS, negative findings, or osteoid-osteoma. Furthermore, the three scintigraphy phases (perfusion, blood pool and delayed bone phase) were categorized separately. The delayed bone phase was measured by the amount of the tracer uptake. The perfusion phase was subdivided in "without pathological findings", "slight hyper perfusion", "hyperperfusion" and "no information available". The blood pool phase was categorized accordingly as follows: without pathological findings, slight premature soft tissue extraction, and premature soft tissue extraction. If a second bone scan was performed, the date, the clinical report and the tracer uptake were collected.

3.2.3 Histology

240/461 (52%) patients underwent histological examination. Of those 35% had biopsy (83/240 patients) and/or resection/curretage (227/240 patients, 95%) of a cartilage tumor.

All histological reports were evaluated by pathologists specialized in bone tumors of the Institute of Pathology Medical University of Graz. Routinely H&E staining

was used after decalcification. Immunohistochemistry was used in selected cases, e.g. when a secondary tumor was suspected. No reevaluation of the clinical reports was conducted for the purpose of this thesis. Molecular diagnosis was not routinely conducted in our center.

We retrieved the diagnoses from the histological reports, which were either EC, CS grade 1, 2 or 3, OC, CMF, chondroblastoma, Mb. Ollier or inconclusive. If no histological examination was performed, we documented this as “not available”. Furthermore, the malignant potential (benign, grade 1, 2 or 3) was included in the excel sheet. Overall histology was categorized as “conclusive”, “not available”, or “inconclusive”.

3.3 Statistical Analyses

All data were collected retrospectively and included within a database. Categorical variables are presented as absolute and relative frequencies, numerical variables as means and ranges, as well as medians.

Detailed statistical analyses were conducted for EC and CS to address the clinical dilemma of distinguishing between these histological entities.

For categorical variables, Kappa statistics was used to measure the agreement of the diagnoses. Generally, Kappa values over 0.75 are considered as excellent, 0.40 to 0.75 as fair to good, below 0.40 as poor and <0.1 as no agreement at all.(37)

Since the main part of the thesis aims to evaluate the benefit of bone scans, tracer uptake of the different tumors was measured and influencing factors to the tracer uptake were investigated. These factors are age, sex, grading, diameter, fracture, presentation in vascular and soft tissue phase, and localization in trunk-extremities vs. finger/foot. They were measured with linear regression/variance analysis and quantified with the regression coefficient (including 95% confidence intervals). The regression coefficient indicates the alteration of the tracer uptake when the x-coordinate changes for 1 unit. 1 unit corresponds to one year regarding the age, one centimeter regarding the diameter and plus one regarding the grading. In view

of the sex it is the other one and of the fracture the presence or the absence. Results are depicted on a logarithmic scale and were analyzed in two groups (inclusion or exclusion of pathological fractures).

A further factor to differentiate between the tumors was the grading. Prediction of grading was measured with linear regression/analysis of variance (ANOVA) and quantified with the regression coefficient (including 95% confidence intervals). Factors investigated to influence the grading were age, sex, log tracer uptake, diameter, presence of a fracture, presentation in vascular and soft tissue phase, and localization trunk-extremities vs. finger/foot.

A machine learning algorithm (random forest model) was used to construct a prediction model about the capacity of the bone scan to correctly classify cartilage lesions. The differentiation was made in two groups (including and excluding pathological fractures) between EC vs. CS G1. The model was then assessed with receiver operating characteristics (ROC) and area under curve (AUC) analysis to describe the probability of the investigated factors (age, sex, logTr, presentation in vascular and soft tissue phase, and localization (trunk-extremities vs. finger/foot) to correctly differentiate between EC and CS. Furthermore, percentages of sensitivity (Sen) and specificity (Sp) were reported. In addition to single factors, combinations of different factors were investigated. The factors “age” and “sex” were excluded since they didn´t provide further information. The combination “all” included the following factors: grading, diameter, fracture, presentation in vascular and soft tissue phase, localization trunk-extremities vs. finger/foot. The combination “no scan” excluded all factors from bone scan (tracer uptake, soft tissue phase, vascular phase, diagnosis from bone scan) and included only the factors “diameter”, “fracture”, “localization”, and “diagnosis from radiology”.

An AUC-value of 0.5 means, that there is no increase of information, which would lead to a correct diagnosis, i.e. the diagnostic tool under investigation has no ability to separate the tested groups. AUC value of 0.5 corresponds to a sensitivity (Se.80) of 0.2 and specificity (Sp.80) of 0.2.

All statistical calculations were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel version 2010.

4 Results

4.1 Enchondroma, Chondrosarcoma

4.1.1 Clinical Data

Tab. 1: Synoptic table of EC and CS				
		EC	**CS**	**total**
n		321 (86%)	54 (14%)	375
Sex	male	128 (40%)	20 (37%)	148
	female	193 (60%)	34 (63%)	227
Age		48.6 (range 17-79)	48.3 (range 14-84)	48.5
Local.	Trunk/Ex	5/234	3/40	
	F/F	82	11	
Fracture		34 (11%)	5 (9%)	39
Biopsy		35 (11%)	30 (56%)	65
Surgery		125 (39%)	53 (98%)	178
B+S		30 (9%)	29 (54%)	59

Tab. 1:

frequency, sex and age, as well as the further evaluated parameters "localization" (Local.), "fracture", "biopsy", "surgery" and "both" (biopsy AND surgery, B+S) of the two tumor entities.

In this dataset, 375/461 (81%) patients presented with the diagnoses of EC (n=321, 86%) or CS (n=54, 14%). Overall, 148/375 (40%) patients were male and 227/375 (61%) female. Slightly more women were affected by EC (193 female vs.128 male patients) and CS (34 female vs. 20 male patients) in our dataset (Fig. 4). EC and CS were most common in the 5th decade of life but ranged between the third to 8th decade of life. The average age at presentation was similar (median 49, range 14 – 84) (Tab. 1) (Fig. 3).

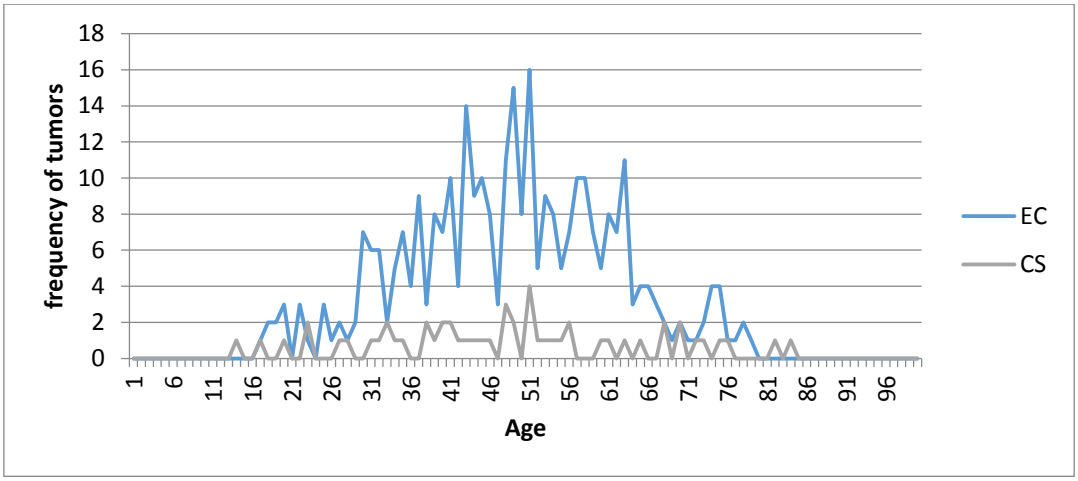

Fig. 3: Age distribution of EC and CS

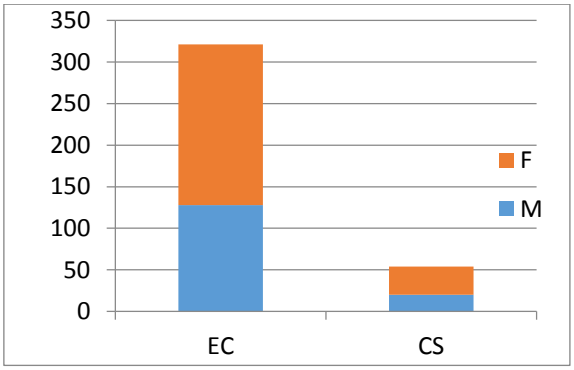

Fig. 4: frequency of EC and CS including the sex

Most tumors were located in the extremities (n=274, 73%), followed by fingers/feet (n=93, 24.8%) and trunk (n=8, 2%). 39/375 patients (10%) presented with pathological fracture. 65/375 (17%) underwent biopsy alone, 178/375 had surgery (48%) and 59/375 (16%) had both (Tab. 1). 134/375 (36%) patients neither underwent biopsy nor surgery.

Regarding EC (n=321), 128/321 (40%) patients were male and 193/32 (60%) female. The average age was 48.6 years (median 49.0, range 17 – 79). 234/321 (73%) were located at the extremities, followed by finger/feet (n=82, 26%), and trunk (n=5, 2%). 34/321 EC (11%) presented with fracture. 35/321 (11%) EC underwent biopsy, 125/321 (39%) surgery and 30/321 (9%) both. (Tab. 1)

Regarding CS (n=54), 20/54 (37%) men and 34/54 (63%) women suffered from the tumor. The average age was 48.3 years (median 48.0, range 14 – 84). CS was mostly located in the extremities (n=40, 74%), followed by finger/feet

(n=11, 20%) and trunk (n=4%). 5/54 (9%) patients presented with pathological fracture, 30/54 (56%) underwent biopsy, 53/54 (98%) had surgery and 29/54 (54%) had both (Tab. 1).

4.1.2 Radiology

Apart from bone scan further radiological examination contained x-ray, MRI or CT or combinations of the mentioned diagnostic modalities. These radiological examinations brought the following results:

Radiology suspected 250/375 (67%) tumors to be an EC, 6/375 (2%) to be a CS, in 87/375 tumors (23%) no specific tumor-diagnosis was made, and in 32/375 (9%) radiologists couldn't distinguish between EC and CS. Of the 250 tumors, which radiology suspected to be an EC, 231 tumors were correctly identified and really have been an EC. Of the remaining 19 tumors, that radiology suspected to be ECs, 14 tumors turned out to be CSs (definitive diagnosis), 2 to be an OC (definitive diagnosis) and in 3 cases the radiologically suspected diagnosis could not be evaluated. Regarding CS, 6 (11%) tumors out of 54 (100%) were suspected to be a CS. Of these 54 CS, radiology identified 2 (4%) correctly. (Fig. 5)

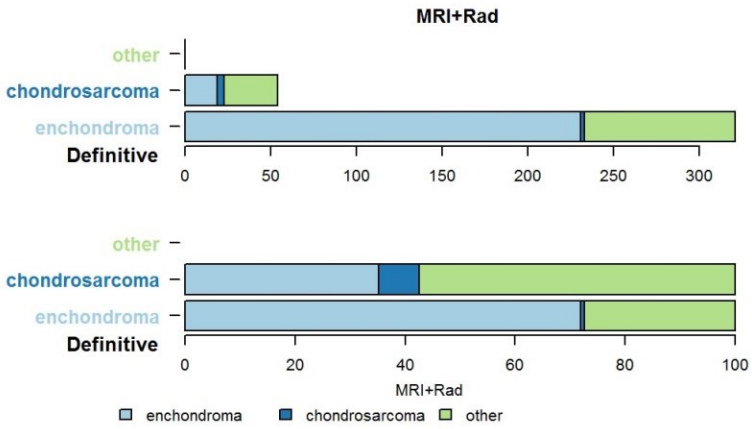

Fig. 5: Tumors detected by radiology. ECs are pictured in light blue, CSs in dark blue. The bar shows how many of the tumors verified by the definitive diagnosis were correctly identified by radiology – in absolute numbers (upper diagram) and in percent (lower diagram). Tumors, which were not detected by radiology are shown in green

4.1.3 Histology

Overall, 185/375 (49%) tumors had histological work-up. While all CS (n=54) underwent histological examination, only 131/321 (41%) EC had histology. The remainder (n=190, 59%) of EC was diagnosed radiologically. Overall, histological diagnosis was conclusive in 131/185 cases (71%), inconclusive in 54/185 (29%) and not performed in 190/375 (51%) cases. “Inconclusive” means, that histological examination was conducted but didn´t lead to a clear diagnosis and “not available (NA)” means, that histological examination wasn´t performed at all.
321 tumors were ultimately defined as EC by definitive diagnosis. Of these 321 EC, histology identified 94/131 (72%) tumors correctly as EC. Accordingly, 54 chondrosarcomas were ultimately defined as CS by definitive diagnosis. Of these 54 CS, histology identified 37 (69%) of the tumors correctly. The remainder were inconclusive: Out of these tumors, in 17 cases the tumor turned out to be a CS, regarding EC in 37 cases. (Tab. 2 and 3, Fig. 6)

Tab. 2: Histological Diagnosis

	EC	**CS**	**No def. diag.**	**Total**
EC	94	0	227	321
CS	0	37	17	54
Total	94	37	244	375

Tab. 2:
number of tumors, that underwent histological examination and the outcome: EC, CS or no definitive diagnosis possible (includes inconclusive results and the tumors, that didn´t undergo histological examination)

Tab. 3: Histology conclusive

	No	**Yes**	**NA**	**Total**
EC	37	94	190	321
CS	17	37	0	54
Total	54	131	190	375

Tab. 3:
number of tumors, when histological report was conclusive (Yes), inconclusive (No) or not available (NA)

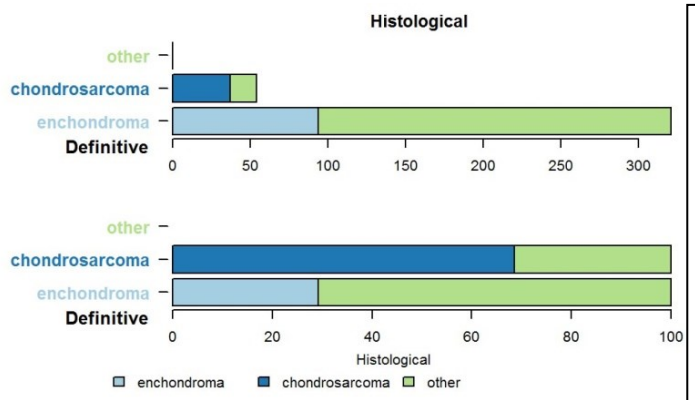

Fig. 6:
Tumors detected by histology. Enchondromas are pictured in light blue, chondrosarcomas in dark blue. The bar shows how many of the tumors verified by the definitive diagnosis were correctly identified by histology – in absolute numbers (upper diagram) and in percent (lower diagram). Tumors, which were not detected by histology are shown in

4.1.4 Bone scan

Of the 375 tumors with the definitive diagnosis of EC and CS, scintigraphy suspected the lesion to be an EC in 168/375 cases (45%), an OC in 1/375 cases (0.3%) and a CS in 7/375 cases (2%). 54/375 tumors (14%) didn´t show any tracer uptake and in 145/375 cases (39%) no specific diagnosis was suspected by bone scan.

Of the 168 suspected ECs (bone scan diagnosis), 153 tumors (definitive diagnosis) were correctly diagnosed as EC. The total number of ECs was 321 (definitive diagnosis) in this study collective. Of these 321 tumors, scintigraphy identified 153 (48%) enchondromas correctly (Fig. 7).

Of the 7 suspected CSs (bone scan diagnosis), 3 (definitive diagnosis) were correctly diagnosed as CS. The total number of CS was 54 (definitive diagnosis) in this study collective. Of these 54 CS, scintigraphy identified 3 (5.5%) correctly (Fig. 7).

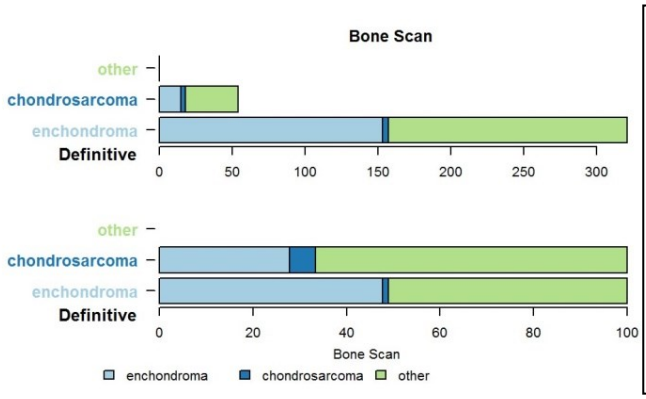

Fig. 7
Tumors detected by bone scan. Enchondromas are pictured in light blue, chondrosarcomas in dark blue. The bar shows how many of the tumors verified by the definitive diagnosis were correctly identified by scintigraphy – in absolute numbers (upper diagram) and in percent (lower diagram). Tumors, which were not detected by bone scan are shown in green.

The mean tracer uptake of EC was 3.7 (median 2.4, range 0.0–68.0), of CS 5.0 (median 4.3, range 0.0–13.5) and of OC 3.0 (median 2.5, range 0.0–20.1).

Furthermore, we evaluated the perfusion and blood pool phases of the bone scans separately and classified into categories:
The perfusion phase didn´t show any pathological findings in 320 tumors (85%), slight hyperperfusion in 26 (7%) and hyperperfusion in 28 tumors (7%). In 1 case (0.3%) no information was available (Tab. 4).
Regarding EC the perfusion phase did not show any pathological findings in 287/321 (89%) cases, slight hyperperfusion in 19/321 (6%) and hyperperfusion in 14/321 (4%) cases. In 1/321 (0.3%) case the vascular phase was not available (Tab.4)
In case of CS, no pathological findings were found in 33 CS cases (61%, p<0.001). In 7 patients (13%) the bone scan showed slight hyperperfusion in the perfusion phase, and in 14 patients (26%) hyperperfusion. CS had significantly more often hyperperfusion (n=14/54, 26%, p<0.001) than EC patients.

Tab. 4: Perfusion phase and tumors

	Overall	**EC**	**CS**	**p-value***
No path. find.	320 (85.3%)	287 (89.4%)	33 (61.1%)	p<0.001
Slight hyperperfu.	26 (6.9%)	19 (5.9%)	7 (12.9%)	p=0.08
Hyperperfu.	28 (7.5%)	14 (4.4%)	14 (25.9%)	p<0.001
NA	1 (0.3%)	1 (0.3%)	0 (0.0%)	
Frequency	375 (100%)	321 (100%)	54 (100%)	

Tab. 4:
*Tumor entities related to their perfusion phases in bone scan; * Fisher's exact test, NA= not applicable*

Overall, the blood pool phase didn´t show any pathological findings in 235 cases (63%), minimal early soft tissue extraction in 73 (19%) and soft tissue extraction in 67 cases (18%). Regarding EC no pathological findings were found in 214 (67%, p<0.001), while CS showed no pathological findings in 21 (39%) cases. Minimal soft tissue extraction was found in 63 (20%, p=1) cases regarding EC and soft tissue extraction in 44 (14%) cases. In contrast, CS showed significantly more soft tissue extraction than EC (n=23, 43%, p<0.001). Minimal soft tissue extraction appeared in 10 (19%, p=1) patients regarding CS. (Tab. 5)

Tab. 5: Blood pool phase and tumors

	Overall	**EC**	**CS**	
No path. find.	235 (62.7%)	214 (66.7%)	21 (38.9%)	*p<0.001
Minimal early s. t. extr.	73 (19.5%)	63 (19.6%)	10 (18.5%)	p=1
Soft tissue extraction	67 (17.9%)	44 (13.7%)	23 (42.6%)	p<0.001
Frequency	375 (100%)	321 (100%)	54 (100%)	

Tab. 5:
*Tumor entities related to their blood pool phase in bone scan; *Fisher's exact test*

4.2 Osteochondroma

Overall, 74/461 (16%) patients suffered from OC in this dataset. 49/74 patients were male (66%) and 25/74 female (34%). The tumor mainly appeared in younger patients between 18 and 25 years. Only one OC patient was younger than 10

years (median 28.0, mean 31,7 range 6-77). Fig. 8 depicts the age distribution of OC.

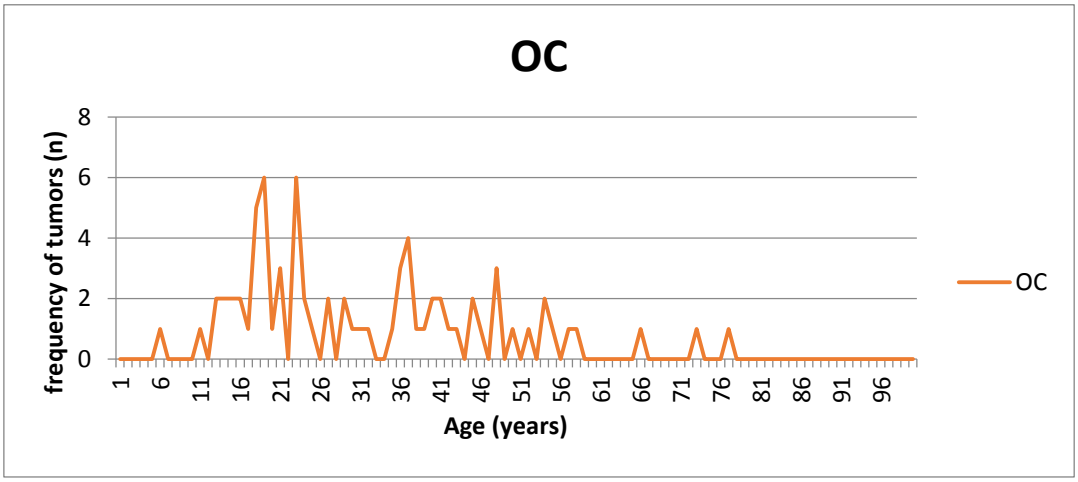

Fig. 8:
Age distribution of OC

13/74 (18%) tumors were located in the trunk, 55/74 (74%) in the extremities and 6 (8%) tumors in fingers or feet. In our dataset, no patient presented with pathological fracture. 10/74 (14%) patients underwent biopsy, 42/74 (57%) surgery and 7 (10%) patients had biopsy AND surgery. In 3/10 (30%) patients a biopsy but no consecutive surgery was performed. Radiology suspected the tumor to be an OC in 55/74 (74%) cases. In 2 (3%) cases, the OC (definitive diagnosis) was suspected to be an EC (radiological diagnosis), in 1 (1%) case to be a CS. In 2 (3%) cases the OC impressed radiologically as a non-tumorous lesion. In 14 (19%) patients, radiological diagnosis was inconclusive or NA and in 1 (1%) case radiology suspected the tumor to be either an EC OR a CS.

Histology determined 41/45 (91%) tumors as OC. Histological workup of the remaining 4 tumors was inconclusive.

Bone scan suspected an OC in 27 (37%) cases. 26 of these 27 tumors were really defined as OC by the definitive diagnosis. In scintigraphy, the remaining 47 (64%) OC (definitive diagnosis) were suspected to be EC (n=2, 3%), CS (n=1, 1%), or osteoid-osteoma (n=1, 1%). In 30 (41%) cases no specific diagnosis was determined and in 14 (19%) cases tracer uptake was 0. Mean tracer uptake was 3.0 (median 2.5, range 0.0 – 20.1). In the perfusion phase 58 (78%) OC showed no pathological findings, 7 (10%) slight hyperperfusion and 9 (12%)

hyperperfusion. In the blood pool phase 46 (62%) tumors presented without pathological findings, 11 (15%) with minimal soft tissue extraction and 17 (23%) with tissue extraction.

4.3 Chondromyxoidfibroma

Four patients (1%) suffered from CMF. After first examination and basic radiological work-up, three out of four were already suspected to be CMF, one as EC. Two were males, and two females. Mean age at diagnosis was 40.0 years (median 43.5; range 17 – 56 years). One tumor was located in the trunk and three in the extremities. None presented with pathological fracture. All underwent biopsy and surgery (three curettages and one wide resection). Radiology couldn´t find a certain tumor entity in three cases and in one a bone cyst was suspected. Histology determined all clearly as CMFs. In scintigraphy the average tracer uptake was 3.1 (median 3.0, range 2.4 – 3.9). In the perfusion phase, two fell into the category “no pathological findings” and two in “hyperperfusion”. In the blood pool phase two showed minimal soft tissue extraction and two soft tissue extraction.

4.4 Chondroblastoma

Four patients (1%) presented with CB, two males and two females. The average age was 18.3 years (median 19.0; range 12 – 23 years). After first examination and basic radiological work-up, three out of four were already suspected to be chondroblastoma, one to be CMF. One tumor was located in the trunk and three in the extremities. None presented with pathological fracture. Three patients underwent biopsy, and all underwent curettages. Radiology couldn´t find a certain tumor entity in three cases and in one a ganglion was suspected. Histology determined three clearly as CB, the histological examination of one tumor was inconclusive. In scintigraphy the average tracer uptake was 4.03 (median 3.88,

range 2.20 – 6.16). In the perfusion phase, one tumor fell into the category “no pathological findings” and three in “hyperperfusion”. In the blood pool phase one showed minimal soft tissue extraction and three soft tissue extraction.

4.5 Ollier Disease

In our patient group, three patients (0.7%) suffered from Mb. Ollier. One was male, two were females. Two patients had multiple lesions at different anatomical sites, in one patient the multiple lesions were only located in the femur. Neither biopsy nor surgery were performed since the patients already have had the diagnosis of Mb. Ollier in 2010. Radiology detected the tumors to be EC in two cases, in one radiology was inconclusive. Average tracer uptake was 1.96 (median 1.98; range 1.40 – 2.47). Only one tumor showed minimal soft tissue extraction in the blood pool phase, all other phases were inconspicuous.

4.6 Detailed statistical analysis of Enchondroma and Chondrosarcoma

Further statistical evaluation was only performed in the subset (n=375) of EC and CS reflecting the clinical dilemma of distinguishing these entities.
Tab. 6 shows frequency, sex, age, localization, fracture, and all forms of operations (biopsy, surgery and both) of EC and CS:

Tab. 6: Synoptic table of EC and CS				
		EC	**CS**	**total**
n		321 (86%)	54 (14%)	375
Sex	male	128 (40%)	20 (37%)	148
	female	193 (60%)	34 (63%)	227
Age		48.6 (range 17-79)	48.3 (range 14-84)	48.5
Local.	Trunk/Ex	5/234	3/40	
	F/F	82	11	
Fracture		34 (11%)	5 (9%)	39
Biopsy		35 (11%)	30 (56%)	65
Surgery		125 (39%)	53 (98%)	
B+S		30 (9%)	29 (54%)	59

4.5.1 Comparison of diagnostic modalities - Kappa Statistics

Kappa Statistics was used to investigate the agreement among diagnostic modalities to correctly distinguish CS (all grades) from EC: The definitive diagnosis was compared to the diagnoses obtained by histology, radiology and bone scan. Two analyses were carried out: one group including fractures and a second group excluding fractures.

Differentiation between chondrosarcoma vs. enchondroma including fractures:

	Definitive	**Histology**	**Radiology**	**Bone Scan**
Definitive	NA	0.7884	0.1076	0.006754
Histology	0.7884	NA	0.1152	0.06144
Radiology	0.1076	0.1152	NA	0.139
Bone Scan	0.06754	0.06144	0.139	NA

Tab. 7: agreement of diagnoses in finding a CS using kappa statistics incl. fractures

Most agreement existed between the definitive diagnosis and the histological diagnosis (κ 0.7884). This corresponds to an excellent conformity.
Bone scan and definitive diagnosis had no agreement (κ=0.06754). MRI and definitive diagnosis showed a very poor agreement (κ 0.1076). Also, the comparison of the radiological, histological and bone scan diagnosis among one another only indicates poor or no agreement (these k values range between 0.2 and < 0.1). (Tab. 7)

Differentiation between chondrosarcoma and enchondroma excluding fractures:

	Definitive	**Histology**	**Radiology**	**BoneScan**
Definitive	NA	0.8103	0.08644	0.07981
Histology	0.8103	NA	0.1273	0.06918
Radiology	0.08644	0.1273	NA	0.1683
Bone Scan	0.07981	0.06918	0.1683	NA

Tab. 8: agreement of diagnoses in finding a CS using kappa statistics excl fractures

Most agreement existed between the definitive diagnosis and the histological diagnosis (κ 0.8103). This is in accordance with an excellent conformity and for 0.1 higher than in the group with fractures.
Bone scan and definitive diagnosis agreed least (κ 0.07981), which indicates no agreement at all. MRI and definitive diagnosis showed no agreement (κ 0.08644), which is even less than in the group with fractures. Also, the comparison of the radiological, histological and bone scan diagnosis among one another only indicated poor or no agreement (all κ between 0.2 and < 0.1). (Tab. 8)

4.5.5 Grading and Tracer uptake

Two groups with and without pathological (fractures) were analyzed. The grading was depicted as a function of the tracer uptake.

Including fractures:

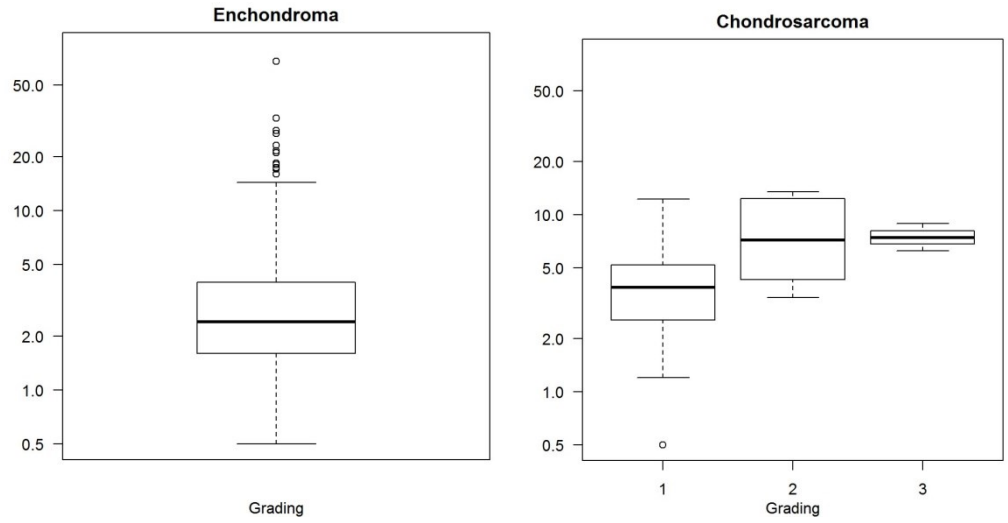

Fig. 9:
Box plots comparing tracer uptake between EC (left) and CS G 1, 2, 3 (right) including pathological fractures

There was a statistically significant difference of the tracer uptake between enchondromas (mean 3.68, median 2.4, range 0.0-68.0) and chondrosarcomas (mean 5.04, median 4.25, range 0.0-13.5) ($p < 0.001$, Tab. 9) as well as between low, intermediate and high-grade chondrosarcoma ($p < 0.001$, Tab. 9): Regarding CS G1, the mean tracer uptake was 4.41 (median 3.8, range 0.0 – 12.3), CS G2 ranged between 3.4 and 13.5 (mean 8.2, median 7.9) and for CS G3 the tracer uptake ranged from 6.3 to 20.1 (mean 10.7, median 8.2). (Fig. 9)

Excluding fractures:

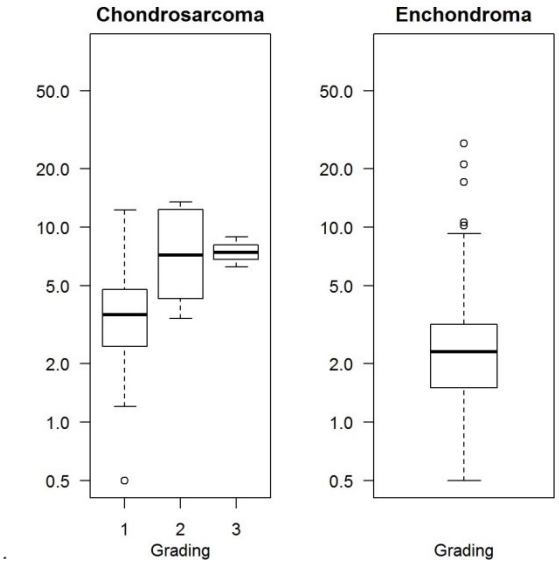

Fig. 10
Box plots comparing the tracer uptake between EC (right) and CS G 1, 2, 3 (left) excluding pathological fractures.

Regarding the group without pathological fractures, there was a statistically significant difference of the tracer uptake between ECs (mean 2.7, median 2.3, range 0.0-26.9) and CSs (mean 5.2, median 4.2, range 0.0-20.1) ($p < 0.001$, Tab. 10) as well as between low, intermediate and high-grade CS ($p < 0.001$, Tab. 10): Regarding CS G1, the mean tracer uptake was 4.2 (median 3.8, range 0.0 – 12.3), CS G2 ranged between 3.4 and 13.5 (mean 7.9, median 8.2) and for CS G3 the tracer uptake ranged from 6.3 to 20.1 (mean 10.7, median 8.1).
Overall the mean tracer uptake decreased from 3.88 in the group with fractures to 2.98 in the group without fractures. The mean tracer uptake of EC decreases from 3.68 including fractures to 2.67 in the group excluding fractures. Notably, the range of tracer uptake values narrowed: In the group with fractures the tracer uptake ranged up to 68 while in the group excluding them the maximum tracer was 26.9.

4.5.6 Factors of influence to the amount of tracer uptake

Factors investigated to influence the tracer uptake were age, sex, histological grading, diameter, presence of fracture, presentation in perfusion and blood pool phase, and anatomical localization (trunk-extremities vs. finger/foot). The

influencing potential of these factors was measured by linear regression/analysis of variance (ANOVA) and quantified by the regression coefficient (coef). Two analyses were carried out: one group including fractures and a second group excluding fractures.

Parameter	Coef	2.5% CI	97.5% CI	p ANOVA
Age at ID	0.98	0.98	0.99	**8.4e-07**
Sex	1.1	0.89	1.3	0.46
Grading	1.6	1.3	1.9	**6.6e-06**
Diameter	1.0	1.0	1.1	**0.012**
Fracture	3.9	3	5.2	**1.6e-20**
Perfusion phase	1.9	1.66	2.2	**6.6e-16**
Blood pool phase	2.0	1.8	**2.2**	**1.8e-37**
Trunk-extremities	1.2	0.65	2.1	**7.6e-16**
Trunk-hand/foot	2.8	1.5	5.2	NA

Tab. 9:
The table summarizes the regression coefficient (coef), confidence interval (CI) and p-value of the influencing factors of the tracer uptake including fractures, ID= initial diagnosis, NA= not applicable.

In the group of patients, who presented with fractures, age, grading, diameter, presence of fracture, perfusion phase, blood pool phase and localization in fingers or foot were statistically significant predictors for increased tracer uptake. The highest regression coefficient (3.9) was seen, when pathological fracture was present, followed by anatomical localization of the tumor. Tumors with localization in the hand/foot (coef 2.8) showed a significantly higher tracer uptake than a tumor in the extremities (coef 1.2). In addition, the biological activity in the perfusion (coef 1.9) and the blood pool phase (coef 2) were significant influencing factors to the tracer uptake. Increase in one histological grade corresponded to a 1.6 increase in tracer uptake. Age was a negative predictor (coefficient =0.98) for tracer uptake, i.e. the younger the patient the higher the tracer uptake. (Tab. 9, Fig. 10)

Parameter	Coef	2.5%CI	97.5%CI	p ANOVA
Age at ID	0.99	0.98	1.0	**0.0018**
Sex	1.1	0.92	1.3	0.29
Grading	1.7	1.4	2.0	**6.1e-09**
Diameter	1.1	1.0	1.1	**8.8e-05**
Perfusion phase	1.9	1.6	2.2	**2.1e-15**
Blood pool phase	1.8	1.7	2.0	**5e-27**
Trunk-extremities	1.2	0.66	2.1	**8.6e-05**
Trunk-finger/foot	1.9	1.1	3.5	NA

Tab. 10:
The table summarizes the regression coefficient (coef), confidence interval (CI) and p-value of the influencing factors excluding fractures, ID = initial diagnosis, NA = not applicable.

In the group without pathological fractures age, grading, diameter, perfusion phase, blood pool phase and localization in the extremities were statistically significant predictors for increased tracer uptake. The perfusion phase of the bone scan showed the highest coefficient (coef 1.9), followed by blood pool phase (coef 1.8) and grading (coef 1.7). The coefficient of the age remains with 0.99 almost the same (Tab. 10). Fig. 11 depicts all factors influencing the tracer uptake, including p- value on logarithmic scale.

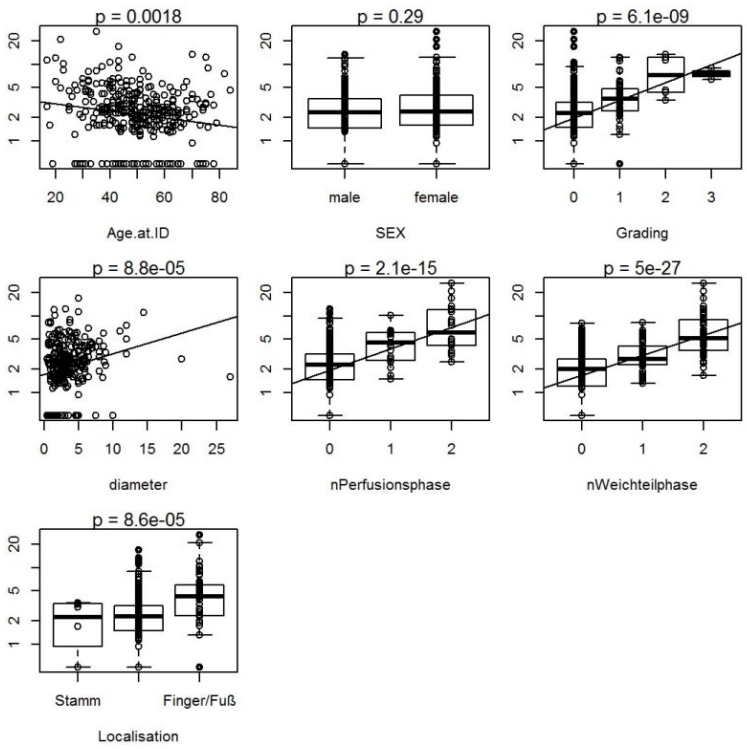

Fig. 11:
significant factors of influence to the tracer uptake depicted on logarithmic scale: age, grading, diameter, perfusion and blood pool phase, localization
ID = initial diagnosis

4.5.7 Factors of influence to obtain a correct diagnosis (EC versus all CS)

Random forest models and ROC/AUC analysis were used to quantify the potential of the bone scan to make the correct diagnosis out of the single factors (age, sex, logTr, diameter, fracture, perfusion and blood pool phase, localization) and specific combinations of these factors (Tab. 11, 12) as well as the different diagnostic methods (bone scan, radiology, histology).
Two analyses were carried out: one group including fractures and a second group excluding fractures.

Including fractures:

Findings of ROC/AUC analysis are summarized in Tab. 11. “Age” (p = 0.871) and “Sex” (p= 0.694) did not provide any further information and did not lead to an improvement of the definitive diagnosis as well as the factors anatomical “localization” and the presence of a pathological “fracture”. Statistical relevant factors of influence were tracer uptake (p = 4.02e-05, Sp 28.7%, Se 29.3%), diameter (p = 5.79e-06, Sp 31.5%, Se 27.6%), perfusion phase (p = 7.86e-10, Sp 40.9, Se 27.7) and blood pool phase (p = 5.12e-07, Sp 36,6%, Se 25.8%).

The diagnostic modalities “Radiology” and “Bone scan” were significant (p = 1.16e-07, Sp 36.6%, Se 25.8 % and p = 0.000101, Sp 23.6%, Se 21.2%).

Two combination patterns (“No scan” and “All”) consisting of different combinations of the factors were built. They showed the capacity of predicting the diagnosis while in- or excluding the bone scan. Group „All“ included all factors besides age and sex. Group „No scan“ excluded all information collected from bone scans (perfusion and blood pool phase, diagnosis from bone scan) as well as age and sex.

Regarding the single factors, AUC was highest for the factor “perfusion phase” (AUC = 0.622, Sp = 0.409, Se = 0.277) followed by the factor “radiological diagnosis (x-ray/CT/MR)” (AUC = 0.596, Sp = 0.366, Se = 0.258) and the factor “tracer uptake” (AUC = 0.588, Sp = 0.287, Se = 0.293) (Tab. 11). Regarding the combinations, the AUC was highest (0.796, Sp = 0.637, Se = 0.653) for the combination “all”. The combination “no scan” leads to a decrease of the AUC (0.7, Sp = 0.504, Se = 0.454).

	p	AUC	Sp 80	Se 80
Age at ID	0.871	0.552	0.259	0.246
Sex	0.694	0.500	0.200	0.200
logTr	**4.02e-05**	0.588	0.287	0.293
Diameter	**5.79e-06**	0.582	0.315	0.276
Fracture	0.767	0.501	0.200	0.201
Perfusion phase	**7.86e-10**	0.622	0.409	0.277
Blood pool phase	**5.12e-07**	0.577	0.366	0.258
Localization	0.137	0.520	0.230	0.212
Radiological diag.	**1.16e-07**	0.596	0.366	0.258
Bone scan diag.	**0.000101**	0.523	0.236	0.212
No scan	NA	0.700	0.504	0.454
All	NA	0.796	0.637	0.653

Tab. 11:
including fractures: The chart depicts the p-value, AUC, sensitivity (Se) and specificity (Sp) of the factors of influence and diagnostic modalities of finding a diagnosis.
ID = log Tr = tracer uptake calculated in logarithm, NA = not applicable

Excluding fractures (EC versus all CS):

In a next step, fractures were excluded, and AUC/ ROC analysis performed as shown above. Regarding the single factors the AUC was again highest for the factor “perfusion phase” (AUC = 0.66, Sp = 0.47, Se = 0.31) followed by the factor “blood pool phase” (AUC = 0.64, Sp = 0.45, Se = 0.3) and the factors “tracer uptake” (AUC = 0.61, Sp = 0.36, Se = 0.3) and “radiological diagnoses” (AUC = 0.61, Sp = 0.39, Se = 0.28) (Table 15). Regarding the combination “all” the AUC was highest (0.8, Sp = 0.65, Se = 0.65). The combination “no scan” leads to a decrease of the AUC (0.72, Sp = 0.52, Se = 0.49). (Tab. 12)

	p	AUC	Sp 80	Se 80
Age at ID	0.98	0.55	0.25	0.26
Sex	0.45	0.5	0.2	0.2
logTr	**7.7e-08**	0.61	0.36	0.3
Diameter	**1.1e-05**	0.58	0.31	0.27
Perfusion phase	**8.3e-14**	0.66	0.47	0.31
Blood pool phase	**5.3e-08**	0.64	0.45	0.3
Localization	0.17	0.52	0.24	0.21
Radiological diag.	**1.9e-07**	0.61	0.39	0.28
Bone scan diag.	**4.4e-05**	0.53	0.24	0.21
No scan	NA	0.72	0.52	0.49
All	NA	0.8	0.65	0.65

Tab. 12:
excluding fractures: The chart depicts the p-value, AUC, sensitivity(Se) and specificity (Sp) of the factors of influence and diagnostic modalities of finding a diagnosis. ID = initial diagnosis, logTr = tracer uptake calculated in logarithm, NA = not applicable

4.5.8 Prediction of the definitive diagnosis (EC versus CS G1)

	p	AUC	Sp 80	Se 80
logTr	**0.000596**	0.584	0.313	0.284
Perfusion phase	**6.88e-05**	0.579	0.333	0.245
Blood pool phase	**0.00043**	0.576	0.334	0.249
diameter	**0.000424**	0.555	0.254	0.262
sex	0.198	0.500	0.200	0.200
Fracture	0.668	0.510	0.207	0.214
Localization	0.822	0.505	0.202	0.208
Radiological diag.	**9.23e-07**	0.583	0.337	0.251
Bone scan diag.	**0.00379**	0.500	0.200	0.20
No scan	NA	0.673	0.459	0.411
All	NA	0.725	0.516	0.517

Tab. 13:
The chart depicts the p-values, AUC, sensitivity (Se) and specificity (Sp) of the factors of influence and diagnostic modalities to make the correct diagnosis for EC and CS G1 (including fractures). ID = initial diagnosis, logTr = tracer uptake calculated in logarithm, NA = not applicable

Further, the AUC was analyzed for EC and CS G1: Regarding the single factors the AUC was highest for the factor “tracer uptake” (0.584) followed by the factor “radiological diagnosis” (0.583) and the factors “perfusion phase” (0.579). When taking all factors together (combination “all”) AUC was highest (0.725, Sp 51.6%, Sen 51.7%). The combination “no scan” lead to a decrease of the AUC (0.673; Sp 45.9%, Se 41.1). (Tab. 13)

5 Discussion

This study reported about patients with a cartilage tumor in whom a bone scan was performed. In total, 461 patients were analyzed. Overall EC was the most common diagnosis (n=321), followed by OC (n=74) and CS (n=54). Included were also three patients with Ollier disease, four with CB and four with diagnosis of CMF.

Out of our three most frequent tumor entities most tumors (73.2%) were located in the extremities. One half of cartilage lesions affected the femur, about one third hands or feet. One out of ten patients approximately presented a pathological fracture, but the presence of fracture had no influence on finding a correct diagnosis in AUC/ROC analysis. Though showing statistical significance regarding the single phases and the tracer uptake of the bone scan, scintigraphy is characterized by a low potential in distinguishing between benign and malignant cartilage tumors, in particular between EC and CS grade 1. In Kappa statistics scintigraphy and definitive diagnosis had absolutely no conformity while the histological and definitive diagnosis were marked by excellent conformity. In AUC/ROC analysis only minimal improvement was seen when adding the bone scan as a diagnostic modality and insufficient values regarding sensitivity and specificity were revealed.

5.1 Strengths and limitations

Strengths:

This large cohort enabled us to perform extensive statistical evaluation including Kappa statistics, random forest and ROC/AUC analysis. Furthermore, statistical evaluations with such a high number of patients is representative for all patients suffering from a chondrogenic tumor and can therefore be transferred to the future treatment of this patient group.

There are only two major centers specialized in bone tumors in Austria. The present study covered patients in southern Austria. The Department of Orthopedic Surgery and Trauma is the only referral center in this region and for this reason patients from both rural and urban regions with cartilage tumors were usually referred to our department. In addition, all bone scans were performed at the Division of Nuclear medicine and diagnosed by nuclear medicine physicians specialized in the diagnosis auf cartilage tumors. Thus, the interobserver variation is reduced.

Limitations:

First, we performed a retrospective database review, which could possibly have led to bias regarding the medical reports: No reevaluation of the reports from histology, pathology, radiology and bone scan was performed. We used the written reports since a reevaluation of the reports wouldn´t have been feasible with the high number of patients.

Second, not all cartilage tumors might be referred to a bone scan although it was common practice at our institution to refer patients for a bone scan when a cartilage tumor was detected.

Third, due to the retrospective study design, drug interactions might have altered the quality of bone scans as we did not check each patient's specific medication. As a last point it must be remarked, that radiologists interpreting the bone scan data might be biased by previous radiological work up, such as x-ray and MRI.

5.2 Chondromyxoid fibromas, Chondroblastoma, Ollier disease and Osteochondroma

In this dataset, only 2% of cartilage tumors were CMF, CB or Mb. Ollier patients. Therefore, further statistical analysis could not be carried out. It seems, however, as 75% of CMF and CB were already diagnosed with basic radiological work-up and all these tumors were diagnosed correctly,

that bone scan is of little diagnostical relevance for CMF and CB. In case of CB, literature is scarce regarding the use of bone scan in the diagnostic process. Nickel et al.(38) published a case report of a 16-year-old girl with the diagnosis of CB and discussed imaging and therapy of the tumor. They proclaim the uselessness of scintigraphy in the diagnosis of CB in their paper. Ge(39) reviewed the diagnostic modalities of CB. He emphasized, that conventional radiology is the medium of choice in the diagnosis of CB and bone scan is as a non-specific tool not relevant in the diagnosis of CB.(39)

There is no literature regarding the use of bone scintigraphy in CMF. However, European Association of Nuclear Medicine (EANM) practice guidelines do not recommend conducting a bone scan if lesions are already "properly characterized by radiological imaging".(40)

In our dataset patients suffering from Ollier disease had already been diagnosed when this study was performed. Therefore, a statement for the diagnostical process of these lesions is not feasible. Generally, the correct diagnosis of Ollier disease is based on the clinical appearance and basic radiological work-up. Bone scan should only be conducted when observing and controlling symptomatic lesions, that increase in size or become painful.(23, 41, 42) In our dataset, bone scan in these patients was performed to evaluate the tumor size and detect potentially malignant lesions.

Regarding OC, basic radiological work-up led to the correct diagnosis in more than two third of the cases, histological examination in over 90%. In contrast, scintigraphy was not helpful to identify OC correctly in our dataset. Accordingly, it is described not to conduct a bone scan for OCs (43) and bone scan is a unspecific examination, which may lead to false positive results.(44, 45) Especially the cartilaginous cap is vulnerable for the growth of a secondary malignancy and can be examined very well using T2-weighted MRI. Thickness of the cartilaginous cap is taken as measurement for the risk of developing a secondary CS.(1, 4, 28, 46, 47) Likewise, ultrasound is a proven method to evaluate the cartilaginous cap and dignity

of OC. It is described to be comparable to MRI and an even better tool than CT.(48, 49) Since the risk of a secondary malignancy is increased in case of multiple OC, especially in these cases regular follow-up should be conducted to precocious detect malignant transformation.(50) MRI as recommended method should be performed annually.(51-53) However, some authors (4, 54, 55) recommend bone scans to exclude malignant transformation, especially when patients suffer from multiple exostosis. It is described, that radionuclide uptake correlates directly with the amount of enchondral ossification, though scintigraphy was not able to differentiate benign from malignant growth. However, it seems, that non-suspicious amount of tracer uptake excludes secondary CS.(44, 56) Kobayashi et al.(57) claimed based on their results, that low tracer uptake was a clear indicator for the benignity of the tumor. In contrast, Hudson et al.(58) disconfirmed this theory by reference to their patient group: They found malignant transformation also in lesions with normal tracer uptake and the uptake did not correlate with the cartilage metabolism.

There are no official guidelines clarifying this discrepancy. But there are studies – as stated above – which show good results by using MRI for assessing the dignity of the tumor. However, symptomatic lesions should be surgically resected (59, 60) and in doing so histology for exclusion of malignancy can be performed. Taking into consideration, that in this dataset, bone scan brought no significant benefit in diagnosis and follow-up of OC, it should not be performed regularly in the treatment of OC.

5.3 Differentiation between EC and CS

Kappa statistics were used to measure the percentage of agreement between the different diagnostic modalities regarding diagnosis and distinction of EC and CS. It is noteworthy, that histology had a very good kappa value, though it was not a value of 1. Compared to the values of the

other diagnostical tools radiology and bone scan, histology showed by far the best agreement and therefore seems to be comparatively the best qualified examination in the distinction between benign and malignant. However, it has to be taken into account that this statistical method only investigates whether two modalities agree on a diagnosis or not, but not if the diagnosis is actually correct.

Analyzing the diagnostical correctness of the single examination tools radiology, histology and scintigraphy, in this dataset radiology and histology presented with similar numbers regarding EC. Furthermore, their diagnostical accuracy regarding EC is with about two third correctly identified tumors by far better than the results of bone scan. It must be considered, that in our dataset in about one fourth of cases radiology couldn´t name a specific tumor identity and in one out of ten tumors the distinction between benign and malignant was not possible for the radiologists. Particularly regarding CS, radiology could only diagnose 4% correctly. In contrast, Modarresi et al.(61) emphasized the role of radiology, saying that adding further radiological examinations like MRI or CT allows the differentiation between EC and CS. Also, Subhas et al.(62) underlined the merit of radiology and included clinical features such as presentation with or without pain and localization to obtain a correct diagnosis. They named a number of radiological signs, like absence of perilesional edema or periosteal reaction, which was reported to exclude the presence of low grade CS, when fulfilling all of them. In case of uncertainness they suggested to perform a biopsy.

Histology maintains at least its achievement ratio of two third correctly diagnosed tumors also in view of CS. But after radiological and histological work-up a lack of non-diagnosed tumors remains. When comparing all diagnostic modalities, bone scan ranked last in kappa statistics. Agreement between the bone scan diagnosis and the definitive diagnosis was only slight and only half of the EC and 6% of CS were correctly identified by scintigraphy.

Overall, histology showed the highest precision in the diagnosis of EC and CS but still required support from further clinical and imaging modalities.(4) These results reflect the problem and clinical dilemma in diagnosis and differentiation of these tumor entities:

In clinical practice the differentiation between EC and CS is challenging even when biopsies are taken.(4, 6, 30, 63) Beside the fact, that chondrogenic tumors display typical morphological signs in radiology, in many cases no secure conclusion about malignant potential can be drawn when viewing the calcification of the tumors. The overlap in radiological morphology between EC and CS is rather high.(4, 6, 64-66) But also the ultimate diagnostical modality for distinguishing between benign and malignant - the histological examination - is not always sufficient since a huge overlap in the cellular morphology of both tumors is common.(6, 66-68)

Histology is able to distinguish between benign and malignant respectively between EC and CS and can therefore be very helpful in obtaining a correct diagnosis – pointed out with an excellent kappa value of about 0.8. Nevertheless, the kappa value is not 1 and consequently the correct diagnosis cannot only be made based on histological examination. The reason for this might be that biopsy material is difficult to assess correctly or not representative of the whole lesion, i.e. areas of low- grade CS can be missed in small tissue samples. Laitinen et al.(69) recently showed that the agreement between the biopsy diagnosis and the definitive diagnosis in their study was less than 50% in case of CS.

5.4 EC versus CS grade 1

Especially the distinction between EC and CS 1 is challenging. Their appearance in radiographs and histology is similar, making it difficult to correctly differentiate these entities in every case.(6, 66, 70, 71) But grading is determining the treatment of the tumors.(70) EC can be followed up and surgical treatment is only necessary when fractures are present, or when

they are symptomatic, and suspicion of malignant transformation is given.(4, 6) In contrast, CS G1 in the long bones are usually treated with curettage, as they feature low recurrence rates and metastasize very rarely.(72, 73) However, clear margins are recommended for pelvic cartilage tumors, as this showed better survival rates compared to curettage.(9) Thus distinguishing between these histological entities is important since it may cause completely different treatment options with significant morbidity for the patient. In the past, several attempts to distinguish have been undertaken including analysis of radiological and clinical factors such as cortical thickening or destruction, endosteal scalloping, pain, tumor size and localization.(63, 74, 75) Special attention was payed to the role of MRI. While significant differences in MR imaging between EC and low grade CS were described by Choi et al.(75), others (63, 68) did not show any improvement by adding MRI to the diagnostical pathway. Crim et al.(76) analyzed 53 patients suffering from EC or from CS G1 in whom radiographs, contrast-enhanced MRI and histopathological workup as well as a 5-year follow up were conducted. Diagnostical potential, reliability and accuracy of these diagnostic modalities were compared to the definitive diagnosis and statistically analyzed with kappa statistics and regression analysis – analogous to our study. They found out, that regarding EC, radiographs were advantageous over MRI (67% correctly diagnosed in x-ray versus 58% in MRI), while with regard to low grade CS, MRI is superior (58% correctly diagnosed in MRI versus 21% in x-ray). The false positive rate for CS was 3% in x-rays and 14% in MRI. Combining radiographs and MRI, the diagnostic accuracy of EC could be improved to 80%. Regarding CS, the correctly diagnosed number of tumors didn´t increase compared to only one radiological modality. Since Crim et al.(76) as well as our study showed, that radiology - also in addition to histological examination - was indispensable for the diagnosis of cartilage tumors but also needs support in several cases, which method can complete effectively this diagnostical gap?

5.5 Bone scan

We evaluated the bone scan in detail, since it has been described to be helpful in solving the clinical and diagnostical dilemma of distinguishing EC from CS.(31-33) In this study we investigated, whether the information obtained by bone scan enhanced diagnostic accuracy.

Further statistical examination was undertaken to investigate the benefit of bone scan: The single phases of bone scan were analyzed separately and showed statistically significant differences between EC and CS. Perfusion and blood pool phase both demonstrated significantly more often hyperperfusion or soft tissue extraction in case of CS while EC significantly more often showed no pathological findings. Thus, bone scan seems to be more helpful in the distinction of EC and CS when taking into account all three phases and not only the tracer uptake. This assumption was supported by multivariate analysis, which investigated independent factors that influence the tracer uptake. Perfusion and blood pool phase were significant predictors for increased tracer uptake.

Further investigation of the factors was conducted using random forest models and ROC/AUC analysis. The potential of the single factors to obtain a correct diagnosis was measured. Also, in this analysis, blood pool and perfusion phase were statistically significant influencing factors to a correct diagnosis. There is not much literature being concerned with the investigation of the phases of scintigraphy and cartilage tumors. McLean et al.(77) had found similar results in exploring potential diagnostical patterns regarding bone scan and CS. Also, in their study, increased blood pool activity was deemed characteristic for CS. Wang et al.(33) only mentioned the phases regarding EC, stating, that they usually are inconspicuous. He does not explain the manner of the phases in CS. Therefore, it can be suggested, that until now the main attention was paid to the amount of tracer uptake when performing a bone scan and that the single phases were mainly left out of account though they may provide further information in terms of the malignant potential of cartilage tumors.

Further age, sex, histological grading, diameter of the tumor and anatomical localization were statistically independent factors to influence the tracer uptake on multivariate analysis. Age was a negative predicting factor, meaning that the older the patient, the lower was the tracer uptake. A possible explanation could be, that osseous metabolism is increased in younger people and therefore also the tracer

uptake is higher.(78) In our dataset, localization in finger or feet versus trunk and in the extremities versus trunk were further independent risk factors for increased tracer uptake. Additional results of our study regarding the localization of the tumors showed, that distribution of EC and CS over extremities, hands/feet and trunk were comparable and all high-grade CS were located in long bones either of hands or extremities. There was no significance showing more aggressive tumors occurring more frequently in a distinct part of the body. Additionally, ROC/AUC analysis of our dataset showed no statistical significance regarding the localization of the tumor and did not confirm the results of multivariate analysis. Review of literature brought the following results regarding localization and cartilage tumors: Geirnaerdt et al.(70) investigated factors to differentiate between EC and CS G1 analyzing 78 tumors. Their results demonstrated, that localization of the tumor in the trunk and a diameter over 5 cm were significant predictors for malignancy. Saglik et al.(79) showed, that cartilage tumors of the hands were benign in a majority of cases. This corresponds to the WHO Classification of Tumors of Soft Tissue and Bone (1), where hands are described as the most commonly affected bones by EC. Appearance of EC in the trunk is described to be very rare. In contrast, CS is more often located in bones of the trunk, but also the extremities are frequently involved.(1) Andreou et al. (72) investigated independent predictors for the outcome of CS performing a retrospective analysis of 115 patients suffering from primary central CS. They found out, that localization in trunk or pelvis is a significant predictor leading to dead caused by disease. It seems, that localization of the tumors might play a role in the tumors behavior, though our results did not confirm this when using bone scan. Unfortunately, scientific literature has not covered this issue so far and further studies investigating the behavior on bone scan at different anatomical localizations are needed.

Furthermore, we examined the amount of tracer uptake regarding the different gradings of the tumors. The tracer uptake differed significantly between all grades of CS and EC. However, the tracer uptake ranged widely, in case of EC from 0.0 to 68.0. The higher the tumor grade the tighter ranged the tracer uptake. For CS G3, for example, it ranged from 6.3 to 20.1 – in contrast to a tracer uptake up to 68 in EC. It can be seen clearly, that the tracer uptake of CS is completely included in the range of the EC´s tracer uptake and that some EC showed abnormally high tracer uptakes. We could see this huge overlap also for CS G1 and 2. Thus, the

tracer uptake alone is not suitable for reliably distinguishing between EC and CS and there is certainly no cut- off value where the tracer uptake indicates malignancy.

Regarding AUC, statistically relevant factors influencing the correct diagnosis were tracer uptake, diameter, perfusion and blood pool phase. Furthermore, radiology and bone scan provided significant influence for obtaining a correct diagnosis and adding the bone scan to the diagnostical pathway showed an improvement of AUC. Nevertheless, the AUC values of the single factors ranged barely over 0.5, with the highest value of 0.66 for the perfusion phase and the lowest significant value of 0.53 for the bone scan diagnosis. This corresponds to very poor values of sensitivity and specificity. The factor with the highest significant values, the perfusion phase, showed a sensitivity of 0.31 and a specificity of 0.47, which indicated a very poor diagnostically conclusiveness. Though including scintigraphy in the diagnostic pathway increased AUC, the increase was only 0.08 and sensitivity and specificity were only 0.65.

Regarding specifically the differentiation between CS G1 and EC, AUC showed only minimal diagnostic benefit including bone scan and very low sensitivity and specificity.

Additionally, general issues of bone scan have to be taken into consideration. Costs and radiation exposure (80) to the patients are facts, that might not justify the performance of a scintigraphy when taking into account the little diagnostic benefit. Furthermore, conducting the bone scan requires resources from the hospital, which might not be balanced by the looked-for benefit of this examination.

5.6 PET CT as an alternative option for the differentiation between EC and CS G1?

Since scintigraphy is not able to clearly differentiate between EC and CS and histology as ultimate and best diagnostical tool is invasive and needs support in at least one third of our patients suffering from CS, a further option to examine cartilage tumors is needed. Feldman et al.(81) investigated “18FDG-PET applications for cartilage neoplasms”. They examined 29 patients suffering either

from EC (n=11), OC (n=7) or CS (n=11). They underwent either x-ray, MRI or CT plus whole-body PET scan. The tracer 18FDG ([18F]fluoro-2-deoxy-d-glucose) is incorporated by tumor cells, that need glucose for their metabolism. This enhancement is measured, and its amount depicted as standard uptake value (SUV). The limit line between benign and malignant of SUV for PET scans was determined at 2.0. Lesions showing values less than 2.0 were considered as benign and over 2.0 as aggressive. All EC presented with SUV values under 2.0 (range 0.8 – 1.8) and 10/11 CS had values over 2.0 (range 1.4 – 20.0). Regarding the three grades of CS, the one tumor with SUV 1.4 was a low-grade CS. CS G1 ranged from 1.4 to 3.4. G2 and G3 presented with higher SUV values (G2: range 2.4 – 4.6, G3: range 6.0 – 20.0). Overall, their study group showed very good values of sensitivity (90.9%) and specificity (100%) regarding PET. It´s accuracy was 96.6%. The research team claims furthermore, that due to their use of PET the management of several patients changed in terms of a less aggressive treatment. However, the number of patients investigated was very low and therefore may not be representative, especially regarding EC and CS G1. Although this study found benefits regarding the diagnosis and treatment of cartilage tumors, PET scans still had limitations in distinguishing EC from low grade chondrosarcomas.(82) (83)

Jesus-Garcia et al.(83) applied their study “Is PET-CT an accurate method for the differential diagnosis between Chondroma and Chondrosarcoma?” to this problem. Unfortunately, also their study group was also very small (23 patients). They included patients with either EC or CS, who had both, MRI and PET-CT. The results of the two investigations were compared, sensitivity and specificity, as well as false positive and false negative rate of PET-CT identified. A SUV value greater than 2.0 was defined as malignant, less as benign. While MRI showed a high false negative rate (17% in the group of ECs) and could not distinguish between benign and malignant in about half of the cases, PET-CT had a sensitivity of 1 and a specificity of 0.7 (95% CI). The positive predictive value of PET-CT was 0.8 and the negative 1 (95% CI). Furthermore PET-CT showed a high concordance rate to histology or 22-month follow-up (0.7; 95% CI). Jesus-Garcia et al. did not investigate the different gradings of CS. Since the major problem is based on the differentiation of low grade CS and EC, separately listed results for the three

gradings would have been important to estimate the real potential of PET-CT to solve this problem.

5.7 The role of pathological fractures

In our dataset, we distinguished two groups when conducting statistics: Including and excluding fractures. In this chapter the role of pathological fractures regarding the differentiation of EC and CS and the influence on the statistical results will be discussed.

Overall, 45 patients presented with a pathological fracture. The proportionally distribution over EC and CS was with 11% fractured lesions in EC and 9% in CS comparable. Since EC frequently arises in the long bones of the hands, pathological fractures at this anatomical site are common due to bone fragility.(1, 84) But also CS were seen in hands and pathological fractures in cartilage tumors were described to be a sign of malignancy.(4, 85, 86)

In our dataset kappa statistics and ROC/AUC were conducted for two groups: one group contained pathological fractures while the second excluded them. The agreement between histology and definitive diagnosis as well as between bone scan and definitive diagnosis was better in the group excluding fractures. In view of scintigraphy, the improved values can be explained by the increased bone metabolism in fractures, which ultimately increases the tracer uptake.(31) Thus, fractures in EC can mimic malignancy on the bone scan.(87) Hoch et al.(88) described this problem also in view of histology, saying, that fractures as "[r]eactive of the bone […] can appear alarming on histologic examination" due to their cellular abnormity and mitotic activity. Therefore and because of production of bone and callus, mistaking fractured EC for CS is a main risk. For this reason, the pathologist has to know about the presence of a pathological fracture.

Accordingly, AUC was increased in the group without fractures as compared to the whole dataset. Apart from a slight improvement for the factors tracer uptake, blood pool and perfusion phase and radiological diagnosis, as well as diagnosis in- and excluding bone scan, no difference was seen for the remaining factors when excluding fractures. This may be a result of a more conclusive diagnostical

process when no reactive lesions are present which might increase diagnostic difficulties

5.8 Conclusion

Our study investigated the use of a bone scan in cartilage tumors including patients suffering from EC, CS, OC, CMF, CB or Ollier disease. Unfortunately, the number of patients with the diagnosis of CMF, CB, and Ollier disease, who underwent a bone scan, was low and detailed analysis was not possible. However, it seems that a bone scan is not needed for these entities as they are correctly diagnosed by conventional radiology.

In the group of EC and CS, diagnoses obtained by histology, radiology and bone scan were compared to the definitive diagnosis. Histology achieved the best results, though there was no complete agreement. Bone scan and definitive diagnosis agreed least.

The tracer uptake is influenced by age, grading, diameter, presence of fracture, perfusion and blood pool phase and localization in the group of EC and CS. Statistical relevant factors of influence to obtain a correct diagnosis were tracer uptake, tumor diameter, perfusion and blood pool phase. Though bone scan and its single phases showed significant influencing potential to obtain a correct diagnosis and to differentiate between EC and CS as well as between EC and CS G1, its values are too low to attribute a sufficient validity to the bone scan. Especially in the distinction of EC and CS G1, bone scan is a non-sufficient tool since overlap in tracer uptake is too high. Considering costs and resources to perform a bone scan as well as radiation exposure for patients, its use in the group of cartilage tumors should be reconsidered in the future.

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