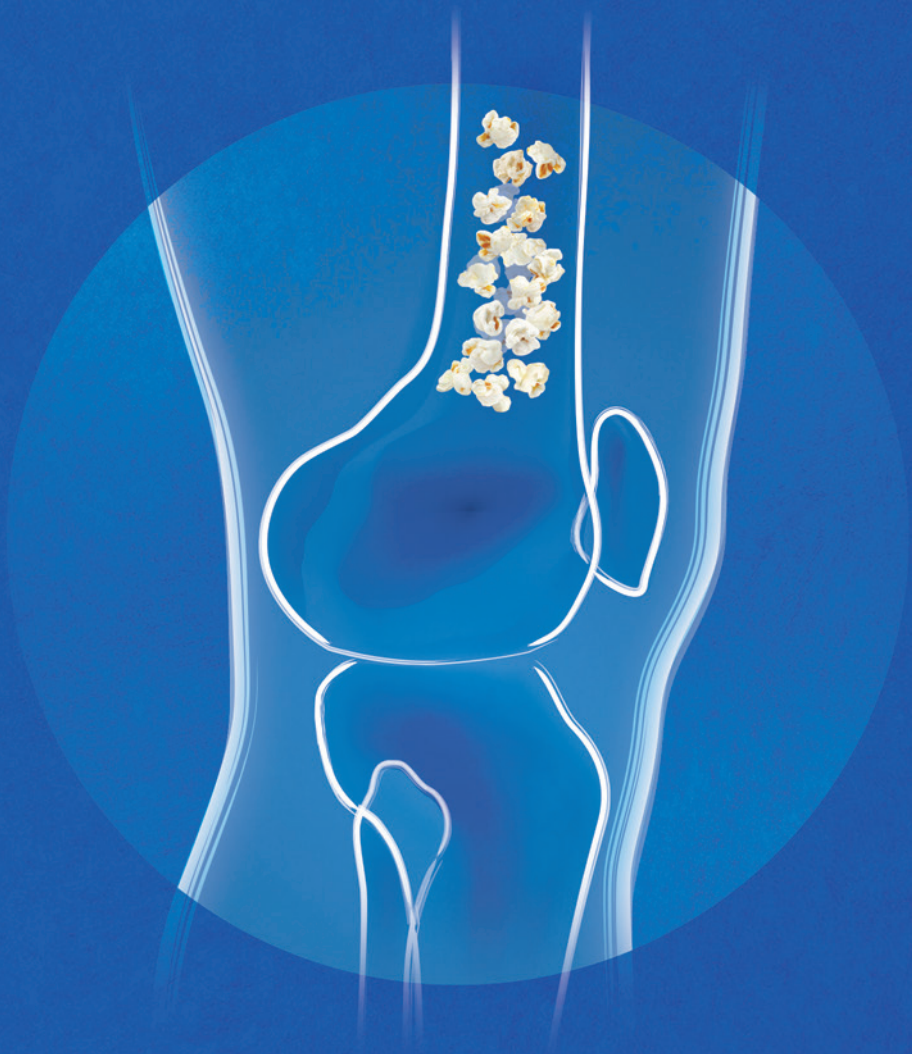
CARTILAGINOUS BONE TUMOURS

NEW PERSPECTIVES ON TREATMENT OF ATYPICAL CARTILAGINOUS TUMOURS



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Cartilaginous bone tumours

New perspectives on treatment of Atypical Cartilaginous Tumours

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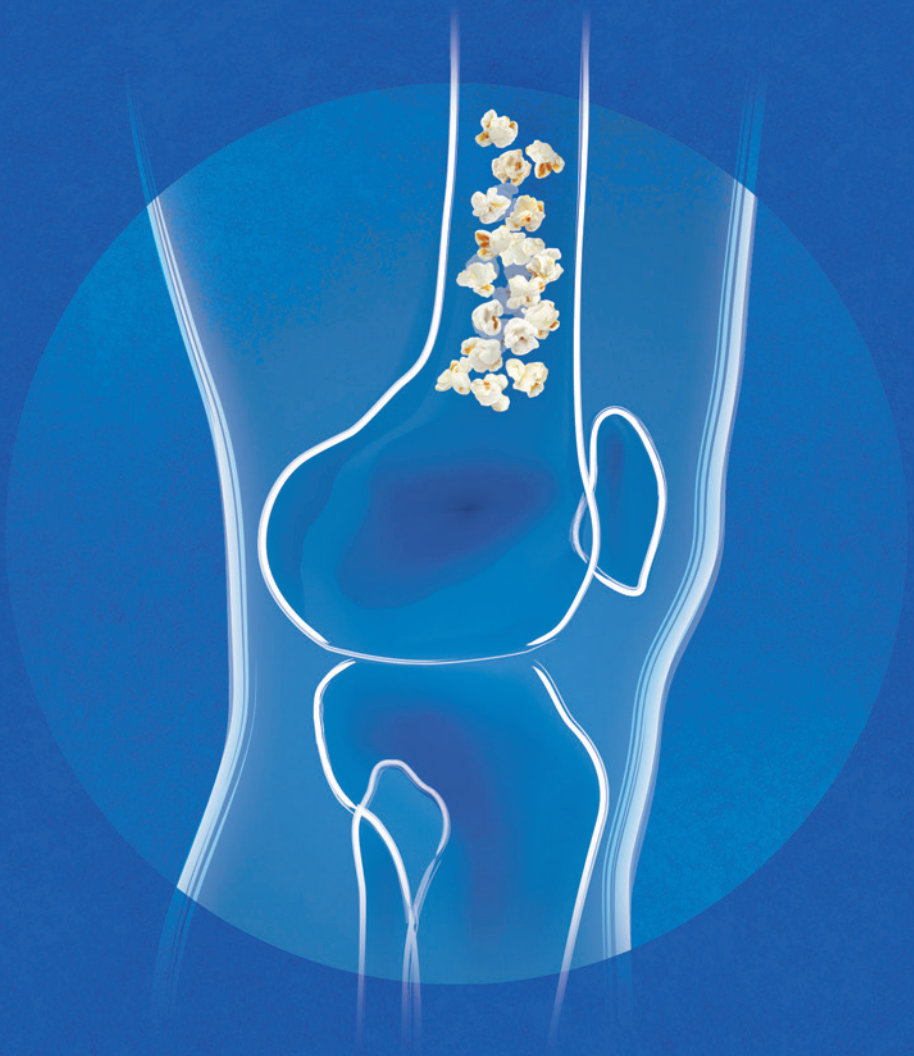

CHAPTER 1

General introduction

Cartilaginous tumours

Cartilaginous tumours are bone tumours characterized by cells producing cartilaginous matrix[1]. The term cartilaginous tumour contains a large group of tumours with diverse histological and radiological features as well as different clinical presentation and prognosis. This thesis will elaborate on central cartilaginous tumours, from enchondroma to high-grade conventional chondrosarcoma.

Enchondroma are benign cartilaginous tumours, representing the most frequent (27.7%) benign primary bone tumour[2]. They are predominantly found in the short tubular bones of the hand and the appendicular long tubular bones (e.g. humerus, femur)[3,4]. Whereas enchondroma in the hand may present with pathologic fractures, enchondroma in the long tubular bones are often asymptomatic. The exact incidence is therefore unknown as these tumours are mostly incidental findings on imaging performed for adjacent pathology or symptoms not related to the enchondroma.

Central conventional chondrosarcoma (CCS) are malignant cartilaginous tumours, predominantly found in the bones of the pelvis, the long tubular bones and ribs[3]. Over the last decades, a clear increase in incidence of chondrosarcoma has been observed in the Netherlands: between 1989 and 1996 the incidence of chondrosarcoma was 2.88 per million citizens compared to 8.78 per million citizens in 2005 – 2013[5]. This rise in incidence might be explained by the simultaneous increased use of MRI, resulting in more incidental findings[4,5]. CCS are classified into histological grades, ranging from 1 to 3, which correlate with aggressiveness and therefore with local recurrence rate, metastatic potential and the disease specific survival. Since chondrosarcoma grade 1 rarely metastasizes, the World Health Organization (WHO) decided in 2013 to change the classification of chondrosarcoma grade 1 (CS1) from malignant into locally aggressive[3]. In addition, to better describe its clinical behaviour the synonym atypical cartilaginous tumour (ACT) was introduced. In the latest WHO classification (2020) this terminology was defined: *"the term CS1 is reserved for tumours of the axial skeleton, including the pelvis and scapula, reflecting the poorer clinical outcome of tumours at these sites. Cartilaginous tumours located in the appendicular skeleton (long and short tubular bones) should be termed ACT"*[1]. Similar to enchondroma, ACTs in the long tubular bones are mostly asymptomatic and thus commonly found incidental. In contrast, patients with chondrosarcoma grade 2 and 3 often present with pain complaints, as these aggressive tumours cause bone destruction. Between 10% and 30% of grade 2 and about 70% of grade 3 chondrosarcoma metastasize[6]. In the Netherlands, as reported by the latest retrospective observational study[5], the 5- years overall survival was 74% for grade 2 chondrosarcoma and 31% for grade 3.

Transformation of cartilaginous tumours to high-grade chondrosarcoma is sparsely reported in the literature[7,8]. The true risk of transformation is unknown as observational studies are lacking[7]. Reported risks of 4 – 6% seem to be overestimated considering the large amount of asymptomatic cartilaginous tumours discovered recently. The rise in incidence of CCS is mainly caused by ACTs: the share of ACTs increased from 42% between 1989 and 1996 to 75% of all CCS in 2005 – 2013[5]. As a result an increased number of patients underwent surgical removal of ACT to prevent malignant transformation. A decline in incidence of high-grade chondrosarcoma would therefore be expected, whereas in fact the incidence of high-grade chondrosarcoma increased[5]. The risk of transformation of cartilaginous tumours to high-grade chondrosarcoma cannot be ruled out but the risk is currently assumed to be less than 1%[5,9].

Table 1 Classification WHO 2020.

Benign
Enchondroma
Locally aggressive
Atypical cartilaginous tumours (located in the appendicular skeleton)
Malignant
Chondrosarcoma grade 1 (located in the axial skeleton)
Chondrosarcoma grade 2
Chondrosarcoma grade 3
Related terminology
Low-grade chondrosarcoma (= grade 1 chondrosarcoma)
High-grade chondrosarcoma (= grade 2 and 3 chondrosarcoma)

Diagnosis

To correctly diagnose cartilaginous tumours the clinical, radiologic and histologic information is evaluated in a multidisciplinary team.

Pain is the most common symptom in patients with cartilaginous tumours. It is important to evaluate the source of the pain as physical and radiologic assessment might show other, non-tumoral, causes (e.g. osteoarthritis, bursitis). Cartilaginous tumours, especially enchondroma and ACTs, could be asymptomatic incidental findings. Only when pain complaints are caused by the tumour itself, pain is considered a sign of malignancy.

Radiologic imaging of cartilaginous tumours consists of multimodal assessment including at least conventional radiography and MRI. Typical for cartilaginous tumours are the popcorn-like calcifications and the lobulated contours. Due to the

numerous similarities of enchondroma and ACT/CS1 on imaging, differentiating these tumours is problematic[10-12]. High-grade chondrosarcoma are recognized by aggressive radiologic features such as bone destruction and soft tissue extension.

Histological diagnosis of chondrosarcoma is one of the most challenging areas of bone pathology. Due to the heterogeneity of cartilaginous tumours within the same tumour, a diagnostic biopsy is unreliable in assessing the definitive grade of a specific chondroid tumour[13]. Categorizing the grade of the surgically removed tumour, should be based on the highest grade found in the specimen[14].

Several studies have shown low reliability, both radiological and histological, for the grading of cartilaginous lesions in the long bones, which is worrisome[15,16]. Fortunately, the assignment of high-grade chondrosarcoma is typically not a diagnostic challenge. The problem is differentiating enchondroma from ACTs due to the clinical, radiologic and histologic similarities[10-16].

Treatment

Surgery is currently the only curative treatment option for cartilaginous tumours as they are highly resistant to both radiation and chemotherapy. Several mechanisms are responsible for chemo- and radiotherapy resistance, amongst others poor vascularity and low mitotic activity. Recent discoveries in molecularly targeted therapies (e.g. isocitrate dehydrogenase 1 and 2 (IDH1/2) and angiogenesis inhibitors), show promising preclinical results[17]. Further research is necessary but is awaited with great interest as these new therapies might achieve better clinical outcome for unresectable chondrosarcoma. Recently, a phase 2 clinical trial has started (NCT04950075), testing a tetravalent death receptor 5 (DR5) agonist antibody which activates the extrinsic apoptotic pathway to induce cell death in cancer cells[18]. These new therapies are beyond the scope of this thesis as they are still in the clinical trial phase.

Enchondroma are benign bone tumours, and nowadays they are commonly discharged from follow-up if asymptomatic and located in the long bones. Enchondroma located in the hand are often treated with intralesional surgery with local adjuvant therapy to prevent pathological fractures[19].

Historically all types of chondrosarcoma, regardless of grade, were treated with wide resections to acquire free surgical margins. When possible, the large bone defect is reconstructed with either (special tumour) prosthesis or large allografts (Figure 1a). This invasive type of surgery often leaves the patient with functional deficiencies, despite reconstruction[20]. Nowadays wide resection is the standard treatment for chondrosarcoma grade 2 and grade 3.

In the early 90's less invasive surgical techniques were introduced for ACTs as new insights revealed low recurrence rates and low metastatic tendency. ACT is currently treated with intralesional surgery (curettage) and local adjuvant therapy.

In curettage, the tumour is removed through a small cortical window, preserving the integrity of the affected bone. Different local adjuvant therapies such as phenol and cryosurgery are used after curettage to destroy remaining tumour cells and decrease local recurrence rate. At the Radboud university medical centre cryosurgery has been used as an adjuvant therapy since 1991[21]. In cryosurgery, liquid nitrogen is sprayed into the cavity to induce surrounding cell death by repeating freeze-thaw cycles. The remaining cavity in the bone is filled with a bone graft or cement (polymethylmethacrylate, PMMA). Depending on the size of the bone defect plating is used to reduce postoperative fracture risk (Figure 1b). Curettage with local adjuvant therapy decreases the morbidity in comparison with wide resection. Still, patients need to adhere to weight bearing rules of the operated limb for several weeks postoperatively and complications such as postoperative fractures, infection, and local recurrence do occur[22].

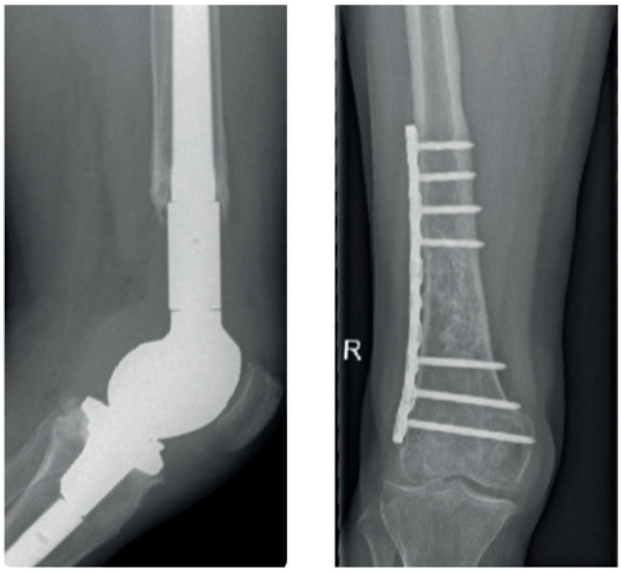

Figure 1 a, b: Different surgical treatment options of cartilaginous tumours in the distal femur. (**a**) Tumour prosthesis after wide resection. (**b**) Plate osteosynthesis after curettage and cryosurgery.

Recently, radiofrequency ablation has been introduced for ACT treatment[23]. In radiofrequency ablation (RFA) a high frequency alternating current heats the tumour till cell death takes place.

A great advantage of using RFA is that it can be applied percutaneously under computed tomography (CT) guidance. This minimal invasive treatment leaves the bony structure intact and allows early weight bearing postoperatively. Currently only short term results are available for treatment of cartilaginous tumours with a diameter less than 50mm. Furthermore, a recent study showed 30% of the tumours did not achieve complete necrosis after RFA treatment[23].

New perspective

With the current standards for treatment of cartilaginous tumours in mind, the diagnostic dilemma (enchondroma versus ACT) results in a therapeutic dilemma. Surgeons are cautious not to unnecessarily operate benign inactive lesions such as enchondroma, whereas ACTs should not be erroneously discharged. However, the necessity of surgical treatment for ACTs needs to be discussed as they are mostly incidental findings and the risk of malignant transformation seems overestimated.

For that reason, active surveillance instead of surgery has been proposed for ACTs. In active surveillance regular radiologic follow-up is performed to monitor the tumour. If the tumour shows any signs of progression (e.g. growth or pain) the tumour will be removed by performing intralesional surgery with local adjuvant therapy. The frequency and the duration of active surveillance for these tumours is unclear as knowledge of the natural course is sparse. To minimise overtreatment of ACTs, active surveillance could be a solution. The impact of this new treatment approach on patients' quality-of-life should also be considered. It could be argued that the burden of diagnosed but untreated disease outweighs the benefit of refraining from surgery.

Aims of this thesis

The objective of this thesis is to evaluate current practice regarding atypical cartilaginous tumours (ACTs), exploring its natural course and determine the feasibility of active surveillance.

The aims of this thesis are defined as follows:

1. To provide an overview of MRI characteristics used to date to differentiate ACTs and high-grade chondrosarcoma
2. To study the oncological results of the current treatment method (curettage and cryosurgery) for ACTs as well as associated complications.
3. To evaluate the natural course of ACTs and study the feasibility of active surveillance.
4. To study the impact of active surveillance of ACTs on the quality of life in patients.

Outline of this thesis

In the previous decades research mainly focused on differentiating enchondroma from ACT. Differentiating grade 2 and 3 chondrosarcoma from ACT is clinically more relevant if active surveillance is implemented. Due to the aggressiveness of high-grade chondrosarcoma these tumours should not be erroneously diagnosed as ACT and consequently radiologically followed-up. In Chapter 2, a systematic review was presented to provide an overview of MRI characteristics used to differentiate between ACT and high-grade chondrosarcoma.

Active surveillance instead of surgery has been proposed for the rapidly growing group of patients with ACTs, because the negative side-effects of treating ACTs with intralesional surgery seems to outweigh the potential benefits. However, the so called benefits and negative side effects of intralesional surgery are vague as widely varying rates of local recurrence and complications are reported. In Chapter 3, our own experience with the surgical treatment of ACTs in a large group of patients is reported, including the oncological results and the complications of curettage and cryosurgery.

In Chapter 4, the natural course of ACTs in the long bones was explored by regular radiological follow-up in a small cohort of patients, in which was refrained from surgery.

In Chapter 5, the natural course of ACTs was evaluated more thoroughly in a large group of patients, by scoring the changes of tumour characteristics on MRIs. Based on our findings schemes for follow-up for ACT in the long bones were proposed.

To support the patients in understanding and recalling all information given by the orthopaedic surgeon a digital decision aid was developed with up-to-date information on the diagnosis and treatment options of ACTs. Moreover patients' motives to opt for one or the other is of interest. In Chapter 6, our experience of developing and using the digital decision aid was described and results of patients' preference questions were reported.

Furthermore, little is known about the impact of active surveillance of bone tumours on patients' quality of life. In Chapter 7, measurements of quality of life during active surveillance were presented.

Finally, the most relevant results of these studies are reviewed and future perspectives are discussed in Chapter 8.

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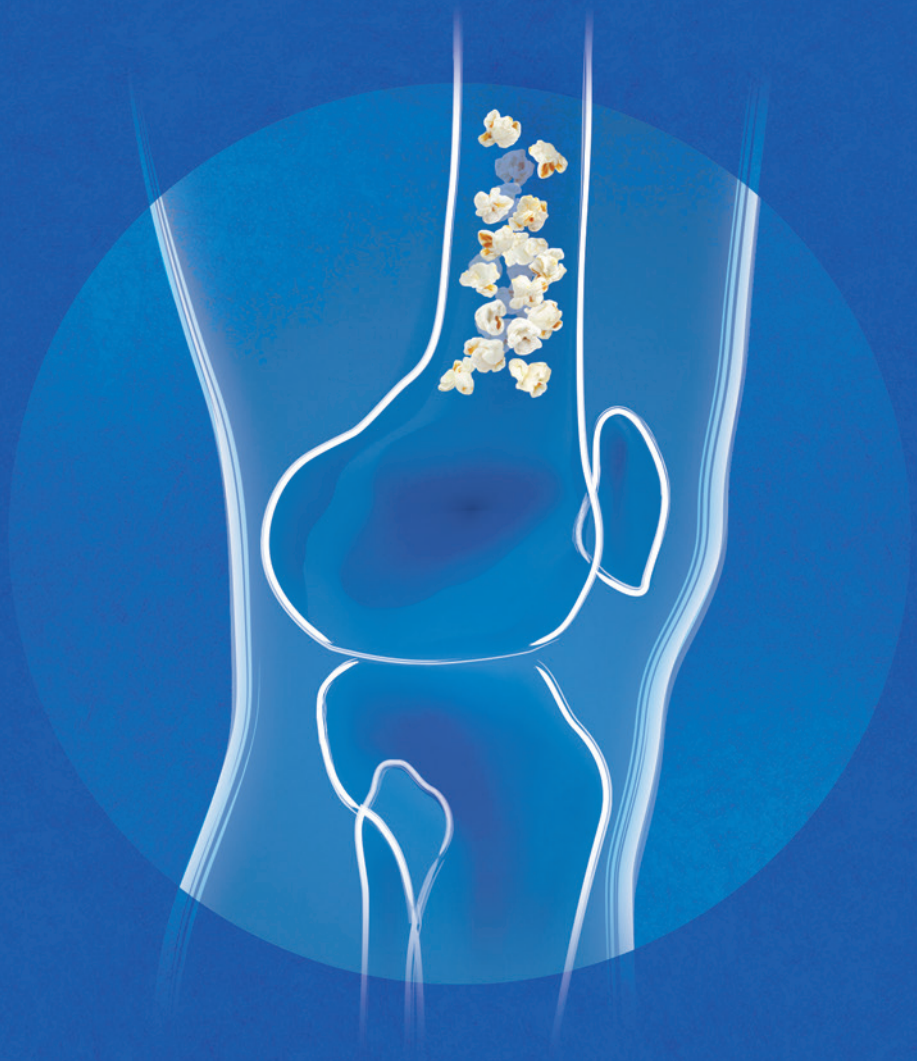

CHAPTER 2

Can MRI differentiate between atypical cartilaginous tumours and high-grade chondrosarcoma? A systematic review

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Abstract

Background and purpose: Adequate staging of chondroid tumours at diagnosis is important as it determines both treatment and outcome. This systematic review provides an overview of MRI criteria used to differentiate between atypical cartilaginous tumours (ACT) and high-grade chondrosarcoma (HGCS).

Methods: For this systematic review PubMed and Embase were searched, from inception of the databases to July 12, 2018. All original articles describing MRI characteristics of pathologically proven primary central chondrosarcoma and ACT were included. A quality appraisal of the included papers was performed. Data on MRI characteristics and histological grade were extracted by 2 reviewers. Meta-analysis were performed if possible. The study is registered with PROSPERO, CRD42018067959.

Results: Our search identified 2132 unique records, of which 14 studies were included. 239 ACT and 140 HGCS were identified. The quality assessment showed great variability in consensus criteria used for both pathologic and radiologic diagnosis. Due to substantial heterogeneity we refrained from pooling the results in a meta-analysis and reported non-statistical syntheses. Loss of entrapped fatty marrow, cortical breakthrough and extraosseous soft tissue expansion appeared to be present more often in HGCS compared to ACT

Interpretation: This systematic review provides an overview of MRI characteristics used to differentiate between ACT and HGCS. Future studies are needed to develop and assess more reliable imaging methods and/or features to differentiate ACT from HGCS.

Introduction

The incidence of chondrosarcoma of bone appears to have been increasing during the last decade and is now reported to be the most common primary malignant bone tumour in several countries[1,2]. Conventional chondrosarcoma is the most common subtype of chondrosarcoma. Other subtypes of chondrosarcoma (e.g., juxtacortical, mesenchymal, or secondary chondrosarcoma) are rare and show different radiologic appearance and clinical behaviour[3].

Conventional chondrosarcoma is classified into the histological grades 1 (currently known as atypical cartilaginous tumour (ACT)), 2, and 3. The metastatic potential, and therefore the disease specific survival, correlates with the histological grade[1,4,5]. ACTs rarely metastasize and are therefore reclassified as an intermediate type of tumour, not a malignancy[4]. Due to the increase in patients undergoing MRI examinations for joint-related complaints, the incidental detection of ACT has increased substantially[2].

With the increasing incidence of ACT, clear radiologic criteria to differentiate ACT from high-grade chondrosarcoma (i.e. grades 2 and 3) become more and more important. Adequate staging of chondroid tumours at diagnosis is important as it determines both treatment and prognosis. High-grade chondrosarcoma behave aggressively. Between 10 and 30% of grade 2 and about 70% of grade 3 chondrosarcomas metastasize[6]. Hence, high-grade chondrosarcoma (HGCS) requires wide en bloc resection with free surgical margins. In contrast, ACTs are intermediate tumours and can be treated either with intralesional curettage and local adjuvant or nonoperatively with regular follow-up when located in the long bones[7].

Due to the heterogenous composition of chondroid tumours, diagnostic biopsy is unreliable in assessing the genuine histological grade and malignant potential of chondrosarcomas[5]. Therefore, physicians need to rely on imaging and clinical findings (e.g., pain is more common in HGCS) to differentiate ACT from HGCS. Imaging evaluation of cartilaginous and other bone tumours is generally based on multimodal assessment including at least conventional radiography and MRI[8].

During the most recent decades research has focused mainly on differentiating enchondroma from chondrosarcoma[9-12]. New insights have shown that both enchondroma and ACT located in the long bones can be observed without treatment[7,13,14]. These insights make the differentiation between ACT and HGCS clinically relevant. Currently, literature on differentiating ACT from HGCS is sparse and clear radiologic criteria are lacking. Therefore, we performed a systematic review to provide an overview of MRI characteristics used to date to differentiate between ACT and HGCS.

Methods

The aim of this systematic review is to provide an overview of MRI characteristics used to differentiate between atypical cartilaginous tumours (ACT) and high-grade chondrosarcoma (HGCS). The inclusion criteria and method of analysis were specified in advance and documented in a PROSPERO protocol (CRD42018067959). This study was conducted and reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE guidelines.

Search strategy and selection of studies

The search strategy, composed of 3 elements (histology, MRI, and chondrosarcoma), was developed in collaboration with information specialists from the medical library of the Radboud university medical centre Nijmegen, the Netherlands. The detailed search strategy can be found in the Supplementary data (Table 1). No limits (e.g., language or publication date) were used.

The search strategy was carried out in Pubmed and Embase (last search performed July 12, 2018). Additionally, reference lists of the included studies and of relevant reviews were screened for potentially relevant papers.

After removal of duplicates, all unique records were imported in EROS (Early Review Organizing Software, Buenos Aires, Argentina) to allocate references randomly to two independent reviewers (CD, MS) responsible for screening and selection. Discrepancies were solved by discussion.

During the first screening phase, original studies (i.e. no case reports, conference proceedings, systematic reviews) were included if they mentioned the combination of chondrosarcoma, histology/pathology, and imaging in title and/or abstract. If not enough information was provided to make a valid judgment, the full-text was evaluated. Full-text versions of all selected studies were screened and included if they met the pre-specified eligibility criteria: (1) preoperative MRI grading; (2) histopathological grading; (3) presence of MRI characteristics per chondrosarcoma grade; (4) primary central chondrosarcoma of bone; (5) adult patients.

Types other than primary central chondrosarcoma of bone (e.g., juxtacortical, mesenchymal, or secondary chondrosarcoma) were excluded as these different types of tumour show different radiologic appearance and clinical behaviour[3].

Data extraction

Two independent reviewers (CD, MS) performed data extraction from each included study in a pre-piloted form. Information was extracted related to: study design, studied population, tumour location and size, tumour grade based on postoperative histology/pathology, pathology criteria used for diagnosis, type of MRI used, and MRI characteristics described per grade of chondrosarcoma (e.g., cortical breakthrough, soft tissue expansion).

If studies included other types of chondrosarcoma (e.g., juxtacortical, mesenchymal or secondary chondrosarcoma), only data related to central ACT and HGCS were extracted.

If outcome data were presented incompletely, we tried to contact the authors to obtain the original data. A reminder was sent to those who did not reply within two weeks. When attempts to obtain original data failed, the article was excluded.

According to the WHO classification, ACT (i.e., chondrosarcoma grade 1) were categorized as low-grade chondrosarcoma (LGCS). Grade 2, grade 3 and dedifferentiated chondrosarcoma were categorized as HGCS[4].

Quality appraisal

The quality of the included studies was assessed using STROBE for the assessment of observational studies (Supplementary data, Table 2). We are aware of the fact that the authors of STROBE did not develop their tool for methodological quality assessment. However, due to the lack of validated and accepted tools for such assessments of observational studies, STROBE is often used for this purpose[15]. In accordance with other studies, only 10 of the 22 items of the STROBE checklist were used for methodological assessment[15,16]. The other 12 of the 22 items, were found not to contribute to the methodological assessment.

In addition, we analysed the quality of histopathology and MRI assessments. We checked whether there was (1) a description of the criteria used for diagnosis, (2) cited reference to consensus criteria used for diagnosis, and (3) if the diagnosis was established by an experienced musculoskeletal pathologist/radiologist[16]. In addition, we added whether the pathologist and/or radiologist was blinded. If the level of experience of the pathologist/radiologist was not specified in the article, the authors were contacted.

Two reviewers (CD, MS) independently scored each item as: well described (+), partly described (±), or poorly/not described (-). Discrepancies were solved by discussion.

No overall score was calculated, as we felt different study characteristics that are related to study quality cannot be judged as if they are of equal importance or interchangeable[17].

Data analysis

Heterogeneity was assessed by visual inspection of forest plots and quantified using the I^2 and τ^2. The latter were calculated even when the judgment was been made that calculating a pooled estimate was not justifiable[18]. Before undertaking a meta-analysis, we first checked whether the studies were similar enough to justify combining their results. If the features of studies were deemed not sufficiently similar to combine in a meta-analysis, we displayed the results of included studies

in a forest plot but suppressed the summary estimate[19-21]. If possible, pooled estimates of proportions with their corresponding 95% confidence intervals were calculated using the logit transformation using inverse-variance weighting within a random effects model framework. Between-study variance was quantified using the τ^2 statistic, estimated using the Sidik-Jonkman estimator. Data were analysed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using the meta package.

Publication bias was assessed only if more than 10 studies were included in the meta-analysis.

Data for different MR modalities (conventional MRI, diffusion weighted imaging, dynamic contrast enhancement and quantitative texture analysis) were reported separately, as these outcome measures were found not to be comparable to pool.

MRI signal intensity, such as high signal on T1, can be related to several histopathological findings (e.g., haemorrhage, entrapped fat) and therefore does not necessarily indicate grade of chondrosarcoma. Therefore, we have chosen to exclude these MRI characteristics from our analysis.

Results

Conducting our search strategy in PubMed and Embase retrieved 2132 unique records. Five additional relevant articles were found via cross-referencing. 2123 articles were excluded because they did not meet our eligibility criteria (Figure 1). Errani et al. provided additional data upon request[22]. Consequently 14 articles were included in our systematic review (See Table 1)[10-12,22-32]. 239 ACT and 140 HGCS were included in this systematic review. The following conventional MRI characteristics were reported by the included studies and analysed: entrapped fat, perilesional bone marrow oedema, internal lobular architecture, lobular outer margin, bone expansion, cortical thickening, scalloping, cortical breakthrough, periosteal oedema, soft tissue oedema, extra-osseous soft tissue expansion, ring and arc enhancement, solid enhancement and central non-enhancing region. Due to substantial heterogeneity (I^2 50 – 90%) and insufficient information to further investigate this heterogeneity we decided to refrain from pooling the results and only provide non-statistical syntheses. The reported presence of conventional MRI characteristics in both ACT and HGCS is displayed in separate forest plots but we suppressed the summary estimates (Figure 2). Only the most commonly reported MRI characteristics are shown in Figure 2; all other MRI characteristics can be found in Supplemental Figure 1.

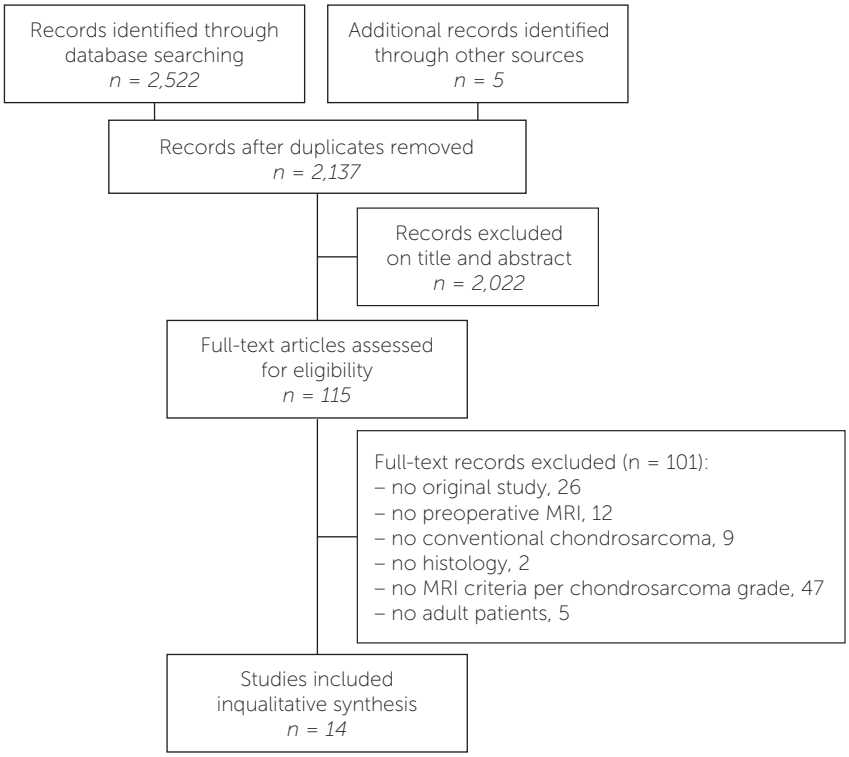

Figure 1: PRISMA flow diagram.

Both Kang et al. and Douis et al. compared maximum tumour size between ACT and HGCS. Kang et al. found a significant difference in tumour length between ACT (3.0 cm, SD 0.7 cm) and HGCS (7.4 cm, SD 2.7 cm), whereas Douis et al. did not find a difference in tumour length between ACT (11 cm, range 2.1-26 cm) and HGCS (13 cm, range 4.3-30 cm)[24,26].

Three DWI studies were included describing apparent diffusion coefficient (ADC). Douis et al. found no statistical significant difference in both mean apparent diffusion coefficient (ADC) and minimum ADC between ACT and HGCS[23].

Welzel et al. found in their subgroup analyses that chondrosarcoma grade 1 had statistically significantly higher, mean, minimum, maximum and normalized ADC values than grade 2 chondrosarcoma in the skull base[30].

Müller et al. measured the following ADC values in eight chondrosarcoma grade 1 tumours of the skull base: mean ADC 2017 (+/- 140) x 10-6 mm^2/s. No ADC values of HGCS were measured[29].

Table 1 Study characteristics.

Study	Study setting	Patients (n)	Tumor location (n)	MRI field strength (T)
Conventional MRI				
Crim et al. 2015	Retrospective	12 CS 1	Humerus (5), radius (1), femur (4), fibula (2)	*
Douis et al. 2014	Retrospective	28 ACT 79 CS 1 36 CS 2 13 CS 3 23 Dediff†	Humerus (58), femur (98), tibia (24)	*
Douis et al. 2018¥	Retrospective	15 CS 1 3 CS 2 1 CS 3 4 Dediff	Humerus (10), femur (9), tibia (3), fibula (1)	3T
Errani et al. 2017	Retrospective 1986-2015	17 ACT	Humerus (5), femur (9), tibia (3)	1.5T
Fayad et al. 2015	Retrospective 1991-2014	6 CS 2 1 CS 3	Hands and Feet (7)	1.5T
Kang et al. 2016	Retrospective 1993-2016	6 CS 1 15 HGCS	Para-acetabular (21)	1.5T
Liu et al. 2017	Retrospective 2008-2015	17 Dediff	*	3T
MacSweeney et al 2003	Retrospective 1995-2005	8 Dediff	Humerus (2), femur (6)	1.0 or 1.5T
Yoo et al. 2009	Retrospective 1999-2008	28 LG 14 HG	Humerus (16), scapula (1), pelvic bone (9), femur (15), fibula (1)	1.0T or 1.5T
Yoshimura et al. 2013	Retrospective 1996-2011	6 CS1 10 CS2 1 CS3	Humerus (4), ulna (1), phalange (2), femur (7), tibia (1), calcaneus (1), rib(1)	*
Diffusion weighted imaging				
Douis et al. 2015	Retrospective 2012-2013	5 ACT 15 CS 1 3 CS 2 2 CS 3 3 Dediff	Humerus (19), rib (2), hand (3), spine (1), pelvis (5), femur (17), tibia (5)**	3T
Muller et al. 2016	Retrospective 2007-2012	8 CS 1	Skull base	
Welzel et al. 2018	Retrospective	24 CS1 10 CS2 1 CS3	Skull base	3T

	Intravenous contrast	MRI characteristics assessed
	+	Length, deep endosteal scalloping, cortical breakthrough, soft tissue mass, gadolinium enhancement
	-	Bone marrow edema, soft tissue edema, bone expansion, cortical thickening, cortical destruction, active periostitis, soft tissue mass, tumour length
	+	Tumour length, endosteal scalloping, bone marrow edema, soft tissue edema, cortical destruction, periosteal reaction, bone expansion, macroscopic fat, calcification, soft tissue mass, hemorrhage
	*	Scalloping, soft tissue mass
	+	T1 signal, T1 heterogeneity, T2 hyperintense, T2 heterogeneity, bone marrow edema, soft tissue edema, gadolinium enhancement, soft tissue mass
	+	Length, high signal foci on T1, high signal on T1-T2-STIR‡, soft-tissue mass, peritumoral edema, lobular border, acetabular cartilage destruction‡, diffuse signal changes in acetabulum‡, mass inside hip joint‡, femoral head involvement‡.
	+	Patterns of bone destruction, periosteal reaction, matrix mineralization, soft tissue mass, enhancement pattern, signal intensity
	+	Soft tissue extension
	+	T1 signal, entrapped fat within the tumor, lobular architecture preservation, cortical destruction, soft tissue mass, gadolinium enhancement
	+	Entrapped fat within the tumor, lobular architecture, ring and arc enhancement, T1 signal, soft tissue mass, gadolinium enhancement
	-	Apparent diffusion coefficient
	*	Apparent diffusion coefficient
	+	Apparent diffusion coefficient

Table 1 Continued.

Study	Study setting	Patients (n)	Tumor location (n)	MRI field strength (T)
Dynamic contrast-enhanced MRI				
Douis et al. 2018	Retrospective	15 CS 1 3 CS 2 1 CS 3 4 Dediff	Humerus (10), femur (9), tibia (3), fibula (1)	3T
Quantitative texture analysis				
Lisson et al. 2017	Retrospective	11 CS1	*	1.5 & 3T

*= not mentioned **= 24 enchondroma tumors are included in description of tumor location.
†= dedifferentiated chondrosarcoma ‡= MRI characteristic not analyzed in our systematic review
¥= study mentioned twice as different imaging modalities are used in the same study

Only one study was found that described dynamic contrast-enhanced (DCE) MRI parameters.

Douis et al. found no statistically significant difference for the various DCE-MRI parameters (angle of the DCE-MRI curve, absolute enhancement and relative enhancement on DCE MRI) between LGCS and HGCS[24].

Lisson et al. performed an MRI-based 3D texture analysis in which they compared enchondroma with low-grade chondrosarcoma[12]. No comparison with HGCS was made. The most promising texture parameters for differentiation were, among others, kurtosis (the magnitude of pixel distribution) in the contrast-enhanced T1-weighted images and entropy in non-contrast T1-weighted images.

The quality appraisal of diagnosis are presented in the supplementary data, Table 3. The individual scored items on the STROBE checklist of each study can be found in the supplementary data, Table 2. Our assessment of the reporting quality shows great variability in consensus criteria used for diagnosis for both pathologic and radiologic diagnosis. Only in 7 of 14 studies did an experienced pathologist in musculoskeletal oncology perform pathologic assessment. In the other 7 studies level of expertise was not mentioned. In 10 out of 14 studies MRI assessment was performed by experienced musculoskeletal radiologists.

	Intravenous contrast	MRI characteristics assessed
	+	Dynamic contrast-enhanced (DCE) MRI parameters; angle of DCE-MRI curve, absolute enhancement and relative enhancement
	+	Quantitative texture analysis to assess tumor heterogeneity

Discussion

Correct diagnosis of chondrosarcoma grade is crucial in determining both treatment and prognosis. Therefore, we performed a systematic review to provide an overview of MRI characteristics used to differentiate between ACT and high-grade chondrosarcoma (HGCS).

Although we did not pool the overall results due to the considerable amount of heterogeneity, it appears that, HGCS may present more often with the following MRI characteristics: loss of entrapped fatty marrow, cortical breakthrough and extraosseous soft tissue expansion compared to ACT.

These MRI findings are in line with the histopathological findings described by several authors[31,33,34].

In cartilaginous tumours production of chondroid matrix results in the typical lobulated growth pattern and the so called ring and arc appearance[34]. In HGCS these typical chondroid features become lost due to poor differentiation of cells. Chondrosarcoma cells actively infiltrate between individual fat cells compressing and eventually replacing them[33]. Absence of areas of entrapped fat is therefore highly indicative of HGCS. In addition, invasion of Haversian systems leads to periosteal reaction. Eventually there is destruction of the cortex and invasion of soft tissue[33]. Yoo et al. found that on gross pathological evaluation, a central non-enhancing region corresponded to an area of haemorrhagic cyst, necrosis, and/or yellow-brown soft tissue mass reflecting a myxoid change, all characteristics of malignant tumours[31].

Due to the heterogeneity of cartilage tumours, areas of ACT can be seen in HGCS lesions. Therefore, the presence of MRI characteristics indicating ACT must

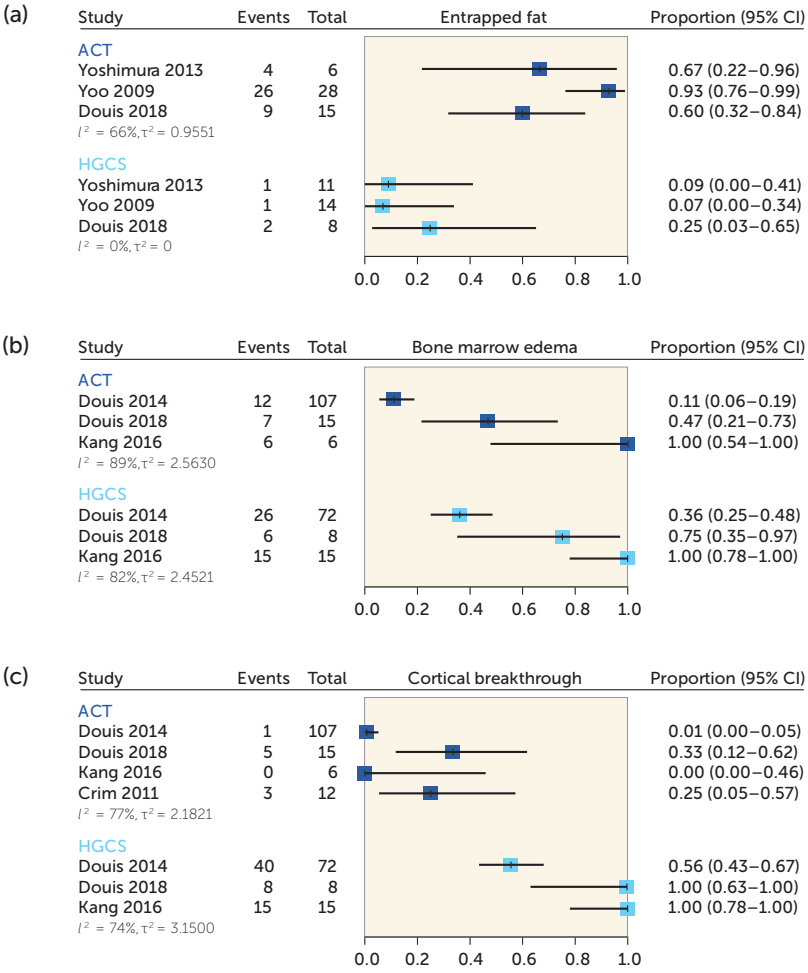

Figure 2: Forest plots of proportions of the reported presence of **(a)** entrapped fat, **(b)** bone marrow oedema, **(c)** cortical breakthrough, **(d)** extra-osseous soft tissue expansion, and **(e)** ring and arc enhancement on conventional MRI in atypical cartilaginous tumours (ACT) and high-grade chondrosarcoma (HGCS).

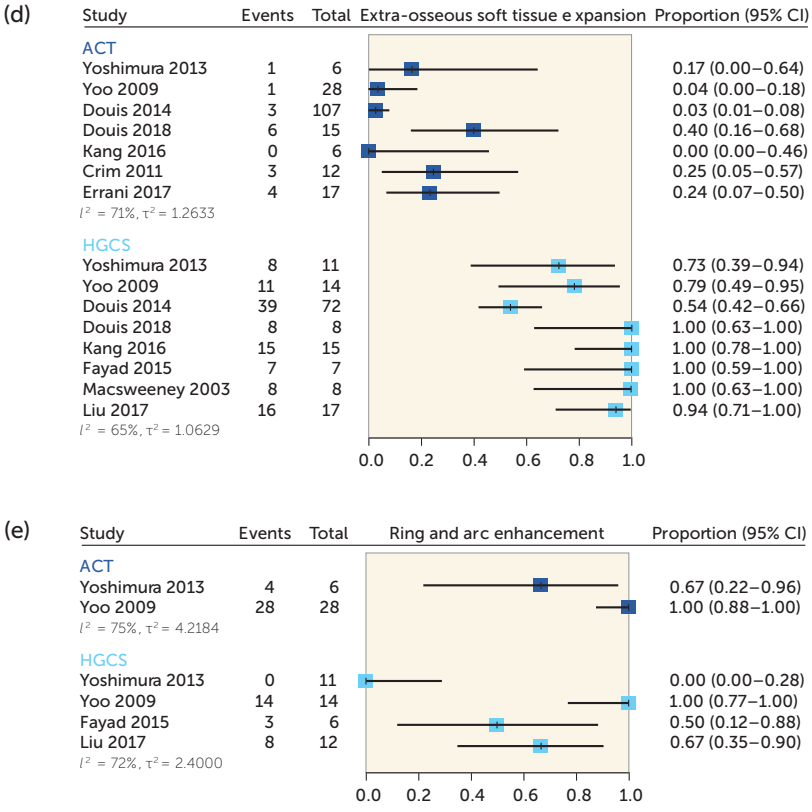

Figure 2: Continued.

be viewed in context and clinical findings must be taken into account. In addition, single MRI characteristics alone cannot differentiate between ACT and HGCS.

The assessment of the clinical relevance of our findings is not straightforward. Heterogeneity was substantial (I^2 50 – 90%) in majority of the analyses. Due to the considerable heterogeneity we decided not to perform a meta-analysis. Heterogeneity may be explained by either clinical and/or methodological diversity between included studies. Included studies showed great variability in tumour location within and between studies. Different bones (e.g., phalanges, femur) as well as types of bone (e.g., flat, long bones) were included in most studies which might show different clinical behaviour and radiologic appearance[3]. We were unable to perform a sensitivity analysis on tumour location. In addition, heterogeneity might be caused by poor reliability between radiologist. The SLICED study group showed poor to slight reliability between radiologists for the subgroup of outcome-

determined high-risk patients[35]. However, the imaging modalities available for radiologists varied and different criteria were used. In those cases where MRI scans were available the reliability increased substantially. Zamora et al. showed fair interobserver agreement between orthopaedic oncologists for diagnosis and grading of cartilaginous neoplasms[36]. Nevertheless, no evaluator proposed observation or follow-up for lesions considered as malignant neoplasm.

Limitations

To reduce bias we excluded tumours other than primary central chondrosarcoma from our systematic review. Several studies were excluded as they included e.g., secondary or periosteal chondrosarcoma as well and we were not able to extract data of the primary central chondrosarcoma[37-41]. Excluding studies to reduce bias resulted in a limited number of tumours included in this systematic review.

Several studies have shown that both radiological and histopathological diagnosis of chondrosarcoma is subject to low reproducibility, which may be caused by difficult and ambiguous definitions[35,36]. Different terminology has been used in chondrosarcoma literature during the past years, for example CLUMP (cartilaginous lesion of unknown malignant potential), borderline chondrosarcoma or grade 0.5 CS, compromising comparability of studies. As can be seen in Supplementary data Table 3, several different grading methods have been used to assess the level of malignancy of chondrosarcoma. In addition, other imaging methods used (e.g., radiographs, CT) could have influenced radiologist during MRI interpretation. Only Crim et al. and Fayad et al. stated that both radiographs and MRI were available for the radiologist[10,25]. Other articles included did not report information on other imaging methods used but this could have been the case as combining different imaging methods is common practice.

Possible inter-reader variability of chondrosarcoma grading may have resulted in misclassification bias in our systematic review. We would recommend a standardized grading method and terminology for chondroid tumours to improve comparability between studies and decrease the amount of bias.

Third, we are aware of the fact that the authors of STROBE did not develop their tool for methodological quality assessment. Due to the lack of validated and accepted tools for such assessments for observational studies, STROBE is often used for this purpose[15]. We have used relevant items of the STROBE tool to give an overview of the methodology by the included papers. As shown by Mueller et al. there is considerable disagreement on how systematic reviews of observational studies should be done[20]. We agree that there is a need for a comprehensive source of methodological guidance, in particular for quality assessment of observational studies.

This systematic review provides an overview of currently used MRI characteristics. Future studies are needed to develop and assess a reliable method for differentiating chondrosarcoma based on radiologic and clinical findings. Reliability could be increased by protocol driven image acquisition for cartilaginous lesions and an easy to use grading system that could be reliably quantified.

From this systematic review it appears that MRI may possibly be helpful to differentiate ACT from HGCS. Extraosseous soft tissue expansion and cortical breakthrough appear to be present more often in HGCS and entrapped fat presents more often in ACT

As a correct differentiation of ACT and HGCS is important, we recommend future studies to develop and assess more reliable imaging methods and/or features to differentiate ACT from HGCS.

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Chapter 2 Supplemental material

Table 1: Search strategy.

	PubMed Search July 12, 2018	Results
#1	("Histology"[Mesh] OR Histology[tiab] OR Histological[tiab] OR histopathology*[tiab] OR "pathology"[MeSH Terms] OR pathology[tiab] OR pathological[tiab])	1227694
#2	("Magnetic Resonance Imaging"[Mesh] OR imaging[tiab] OR diagnostic imaging [Subheading] OR mri[tiab] OR DWI[tiab] OR MR scan*[tiab])	1749265
#3	("Chondrosarcoma"[Mesh]) OR Chondrosarcom*[tiab] OR (cartilag*[tiab] AND (tumor*[tiab] OR tumour*[tiab] OR sarcom*[tiab]))	14424
#4	#1 AND #2 AND #3	824

	Embase Search July 12, 2018	Results
#1	histology/ or pathology/ or histopathology/ or (histology or histological or histopathology or pathology or pathological).ti,ab,kw.	2549953
#2	nuclear magnetic resonance imaging/ or (imaging or mri or dwi or MR scan*).ti,ab,kw.	1354712
#3	Chondrosarcoma/ or Cartilage tumor/ or (chondrosarcom* or (cartilag* AND (tumor* OR tumour*OR sarcom*)).ti,ab,kw.	18163
#4	#1 AND #2 AND #3	1698

Table 2: Quality assessment.

Study	Corresponding items on STROBE checklist									
	Study Design (4)*	Setting (5)	Participants (6)	Variables (7)	Data sources/ measurement (8)	Bias (9)	Statistics (12)	Participants (13)	Descriptive data (14)	Outcome data (15)
Crim et al. 2015	+	+	+	+	+	+	+	+	+	+
Douis et al. 2014	+	+	+	+	+	+	+	+	+	+
Douis et al. 2015	+	+	+	+	+	+	+	+	+	+
Douis et al. 2018	+	+	+	+	+	+	+	+	+	+
Errani et al. 2017	+	+	+	+	+	+	+	+	+	+
Fayad et al. 2016	+	+	+	+	+	-	+	+	+	+
Kang et al. 2016	+	+	+	+	+	+	+	+	+	+
Lisson et al. 2017	-	-	+	+	+	-	+	+	+	+
Liu et al. 2017	+	+	+	+	+	+	+	+	+	+
Macsweeney et al.	+	+	-	+	+	+	-	+	+	+
Muller et al. 2015	+	+	+	+	+	-	+	+	+	+
Welzel et al. 2018	+	+	+	+	+	+	+	+	+	+
Yoo et al. 2009	+	+	+	+	+	+	+	+	+	+
Yoshimura et al. 2013	+	+	+	+	+	-	-	+	+	+

*(numbers) correspond with item numbers of the STROBE checklist.

Table 3: Quality appraisal of pathological and MRI assessment.

Study	A	B
Crim et al. 2015	Brien et al. 1997[33], Henderson et al. 1963[42], Mirra et al. 1985[43], Dahlin et al. 1956[44], Mirra et al. 1989[45]	+ (blinded)
Douis et al. 2014	Evans et al. 1977[6], Dahlin et al. 1971[51], Enneking et al. 1986[52]	*
Douis et al. 2015	Hogendoorn et al. 2013[4], Inwards et al. 2013[4]	+
Douis et al. 2018	Hogendoorn et al. 2013[4]	+
Errani et al. 2017	-	+
Fayad et al. 2015	Dorfman et al. 1998[53]	+ (imaging available)
Kang et al. 2016	Pritchard et al. 1980[54], Sanerkin et al. 1980[55]	*
Lisson et al. 2018	-	*
Liu et al. 2017	-	+
MacSweeney et al. 2003	Evans et al. 1997[6]	*
Muller et al. 2016	-	*
Welzel et al. 2018	Detailed description of the pathologic criteria is specified in the article	*
Yoo et al. 2009	Welkerling et al. 1996+2003[57,58], Rozeman et al. 2006[59], Inwards et al. 1995[60]	+
Yoshimura et al. 2013	Evans et al. 1977[6]	*

A. Text includes reference to previously published or consensus criteria used for pathologic diagnosis.
B. Diagnosis established by a pathologist with expertise in musculoskeletal oncology.
C. Text includes reference to previously published or consensus criteria used for radiologic diagnosis.
D. Was the diagnosis established by a radiologist with expertise in musculoskeletal oncology.
*not mentioned in the article

C	D
Walden et al. 2008[46], Geirnaerdt et al. 1997&2000[40,47], Murphey et al. 1998&2003[48,49], Mirra et al. 1989[45], Beuckeleer et al. 1995&1996[37,50]	+ (blinded)
-	+ (blinded to pathologic information)
-	+
-	+
Murphey et al. 1998[48], Crim et al. 2015[10]	- orthopaedic oncologist
-	+
-	+ (blinded)
-	- experienced in MRI texture analysis
-	+
Mercuri et al. 1995[56]	*
-	+ (blinded to pathologic and clinical information)
-	+ (blinded to pathologic and clinical information)
Welkerling et al. 2003[57], Geirnaerdt et al. 1993&2000[39,40], De Beuckeleer et al. 1995&1996[37,50], Murphey et al. 2003[49], Aoki et al. 1991[61]	+ (blinded to pathologic information)
Murphey et al. 2003[49], Yoo et al. 2009[31]	*

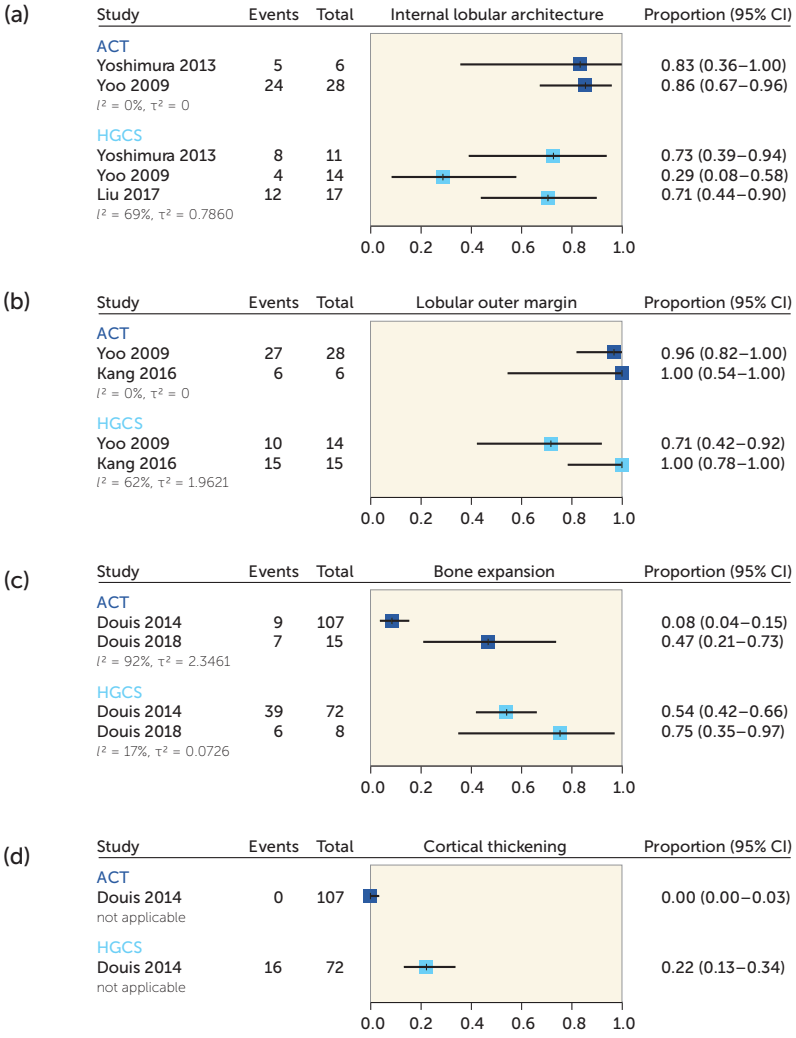


Figure 3: Forest plots of proportions of the reported presence of **(a)** internal lobular architecture, **(b)** lobular outer margin, **(c)** bone expansion, **(d)** cortical thickening, **(e)** scalloping, **(f)** periosteal edema, **(g)** soft tissue edema, **(h)** solid enhancement, and **(i)** central non-enhancing region on conventional MRI in atypical cartilaginous tumors (ACT) and high-grade chondrosarcoma (HGCS).

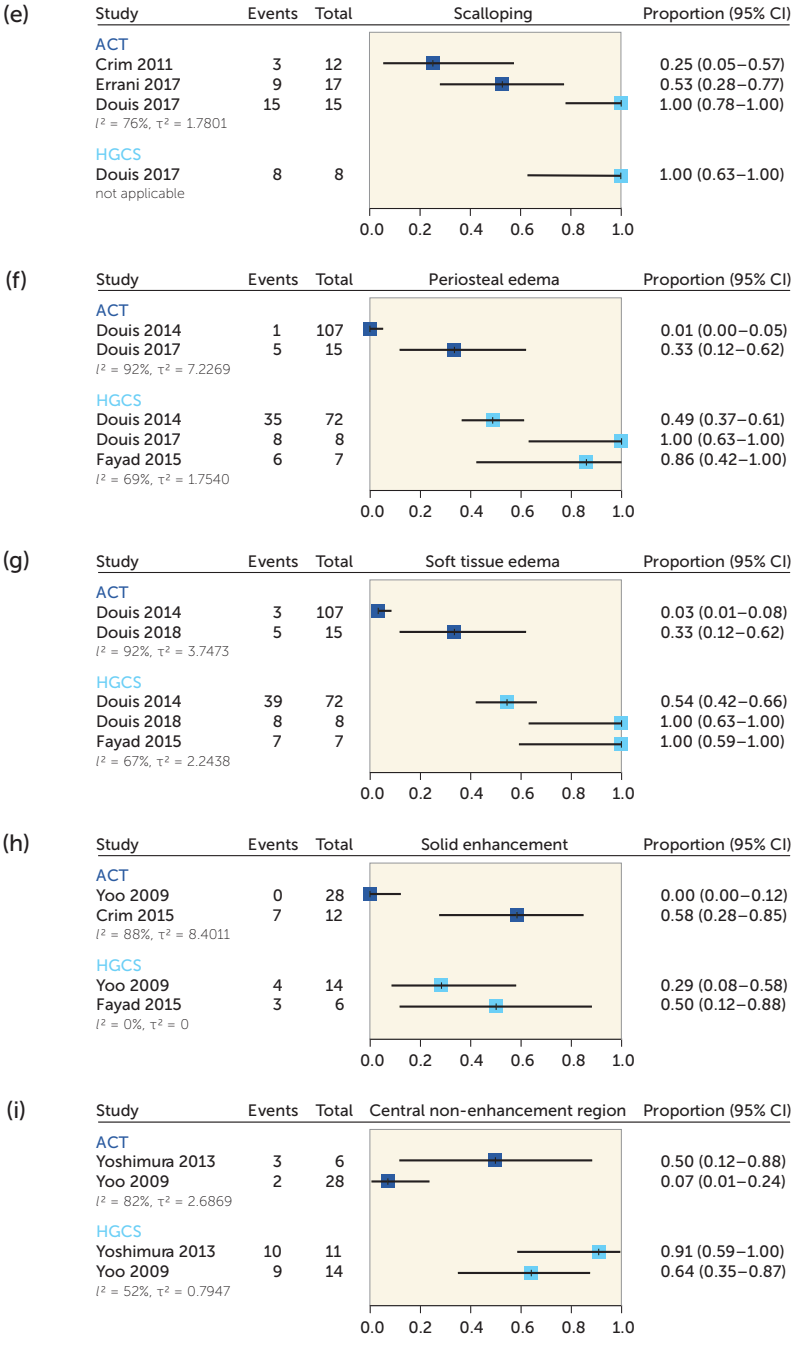
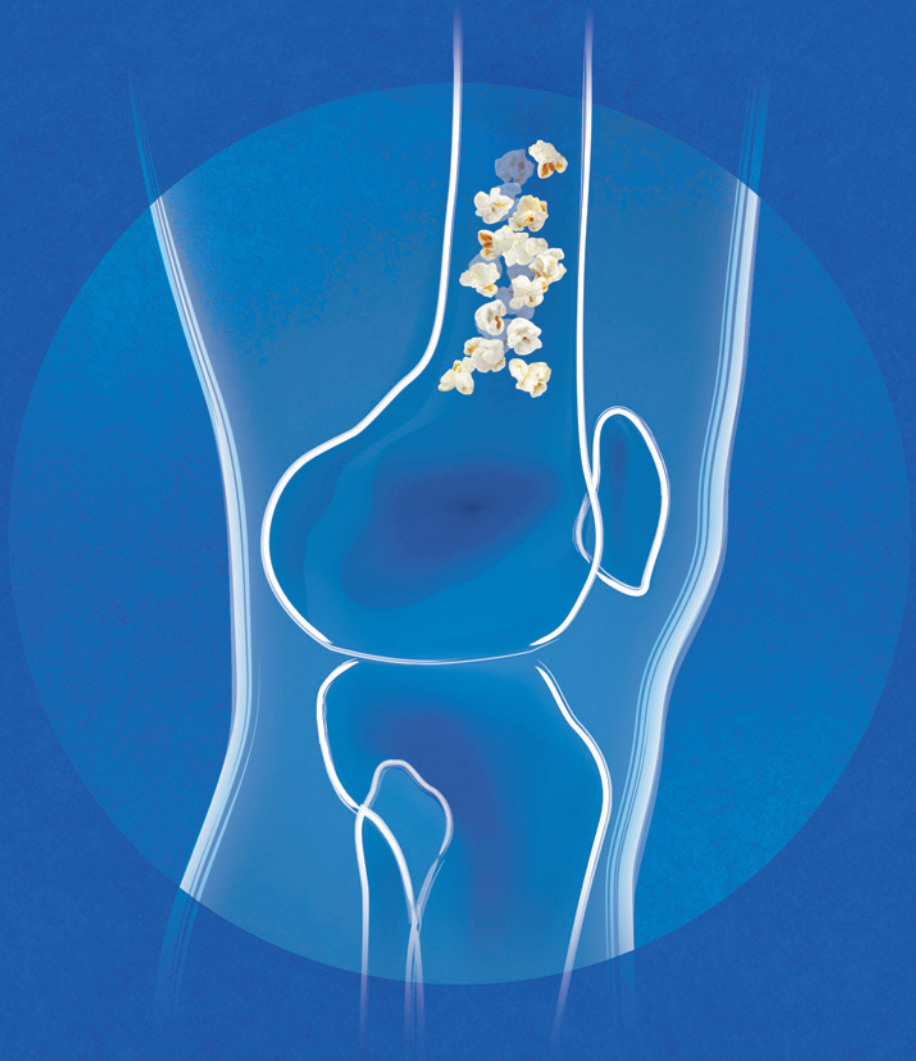


Figure 3: Continued.



CHAPTER 3

Curettage and cryosurgery for enchondroma and atypical cartilaginous tumours of the long bones, oncological results of a large series

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Abstract

Background and Objectives: Intralesional surgical treatment is the preferred therapy for atypical cartilaginous tumours (ACTs) of the long bones in many institutions. However, the literature is still controversial regarding intralesional treatment versus wide resection. Due to the relative rarity of these tumours, studies reporting on results of intralesional treatment are often small sample studies.

Methods: We retrospectively analysed the oncological results of 55 enchondromas, 119 ACTs and 5 chondrosarcomas grade 2 (CS2) treated with curettage and cryosurgery between the years 2004 and 2017 at our institution. The median follow-up period was 53 months (range 24 – 169 months).

Results: In total, seven cases (three ACTs, four CS2) recurred. Residual tumour was detected in 20 cases. Three cases underwent secondary curettage and cryosurgery due to local recurrence. Four cases underwent wide resection and reconstruction due to local recurrence with aggressive imaging characteristics. In total, 20 post-operative complications were seen.

Conclusion: Curettage and cryosurgery for enchondroma and ACTs shows very good oncological results with a low recurrence rate and acceptable complication rate. Curettage and cryosurgery is reliable as a surgical treatment for enchondroma and ACTs. Further research should define the criteria for determining which specific cartilaginous tumours necessitate surgical treatment.

Introduction

The incidence of cartilaginous tumours located centrally in the long bones increased enormously during the last decade. In the Netherlands, the incidence of chondrosarcoma was 2.88 per million citizens in 1989 – 1996 compared to 8.78 per million citizens in 2005 – 2013[1]. This might be explained by the simultaneous increased use of MRI and as a result rise in incidental findings[1-3].

Cartilaginous tumours of the central bone are classified as either benign (enchondroma), locally aggressive (atypical cartilaginous tumour/chondrosarcoma grade 1), intermediate grade malignant (chondrosarcoma grade 2) or high-grade malignant (chondrosarcoma grade 3)[4]. Prognosis and treatment differ according to their classification[1,2,4,5]. Because chondrosarcomas are resistant to radiotherapy and chemotherapy, surgery remains the only curative treatment option. The most common treatments for cartilaginous tumours are intralesional surgery (extended curettage with local adjuvant) and wide resection. Grade 2 and grade 3 chondrosarcoma behave aggressively and wide resection with free margins is mandatory[4]. Due to their slow growth and very low metastatic potential, atypical cartilaginous tumours (ACT), formerly known as chondrosarcoma grade 1, are usually treated with intralesional surgery, because functional results are superior to wide resection[6]. Taken into account the behaviour of ACTs and the difficulty in differentiating them from benign enchondromas, wide resection is considered disproportionate.

There is still controversy over the best surgical method in current literature[6-8]. In their systematic review, Dierselhuis et al. found evidence of very low certainty that recurrence-free survival is equal between intralesional treatment and wide resection[6]. They stated that there was very limited and very low-certainty evidence on how to treat central low-grade chondrosarcoma of the long bones. Accordingly, Shemesh et al. addressed the need for methodologically high quality studies on this topic in their systematic review[7]. Due to the relative rarity of these tumours, studies reporting results on intralesional treatment are often small sample studies, limited by (lack of) meaningful statistics. Local recurrence and complication rates vary widely, respectively 0% – 26.3% and 0% – 21%[6-8].

In our orthopaedic oncology centre we have been treating both enchondroma and ACT with curettage and cryosurgery since 1991. In this paper, we describe our oncological results and complications after curettage and cryosurgery of these tumours located in the long bones. In addition, we will discuss our points of view on future treatment of cartilaginous tumours. To the best of our knowledge, this is the largest study describing the results of curettage and cryosurgery for enchondroma and ACT of the long bones.

Methods

All patients who underwent curettage and cryosurgery for cartilaginous tumours at our institution between 2004 and 2017 were selected from our archives.

Patients were included in this retrospective study if they met the following eligibility criteria: (1) having central cartilaginous tumours treated with curettage and cryosurgery; (2) tumour located in the long bones; (3) at least 2 years follow-up post-operatively; (4) not diagnosed with Ollier or Maffucci disease; (5) no juxtacortical chondroid tumour; (6) no additional treatment (i.e. radiofrequency ablation); (7) no prior treatment at other institutions.

Enchondroma are benign bone tumours and we are aware that surgical treatment is not necessary[4]. Due to difficulty in differentiation enchondroma from ACT on conventional radiographs as well as MRI, especially in the long bones, overtreatment by curettage and cryosurgery is common[9].

In some early cases, a trocar biopsy was performed as a separate procedure before curettage and cryosurgery. In all patients, the same method of curettage and cryosurgery was used, three cycles of freezing below -50°Celsius and thawing were applied[10,11]. Surrounding soft tissue was protected with gauze and the temperature was monitored during cryosurgery. The cavity was filled either with a bone graft (homologous or autologous) or cement (polymethyl methacrylate [PMAA]). In several cases, prophylactic plating was applied to decrease fracture risk. The decision for prophylactic plating was not standardized during this study period. Growing insights led to more usage of prophylactic plating during ongoing years. Titanium plating was used to minimize interference on MRI studies at follow-up. Postoperative partial weight-bearing mobilization started several days after surgery and was continued for 6 – 12 weeks, depending on extent of surgery and anatomical location.

All biopsy and curettage material was reviewed by experienced pathologists and histological diagnosis was made according to established criteria[4,12].

Postoperative follow-up consisted of regular physical examination and conventional radiology, whereas additional MRI studies were performed in cases of clinical or radiological suspicion of local recurrence. Patients were discharged from follow-up after a disease-free period of at least 2 years. When discharged, patients were instructed to contact our hospital in case of (pain) complaints or other local problems at the surgical site, such as local recurrence.

Data regarding patient and tumour characteristics, operation details, complications due to curettage and cryosurgery, residual tumour, recurrence, metastasis, upgrading after recurrence, and re-operations were collected from clinical charts. To differentiate local recurrence from residual tumour, postoperative imaging was compared with preoperative imaging.

Analysis of the data was performed using IBM SPSS statistics for Windows (version 25). All continuous variables were visually inspected and tested for normality by the Shapiro-Wilk test. The Fisher exact test was used to identify differences between groups. P-value < 0.05 was considered statistically significant.

Results

In total, 179 cases were included in this study, one patient was enrolled with two separate cartilaginous tumours. In 73 cases, a trocar biopsy was performed before curettage and cryosurgery. In 11 out of 73 cases (15%), definite diagnosis after curettage and cryosurgery was higher than biopsy diagnosis (four cases ACT versus CS 2, seven cases enchondroma versus ACT). After curettage and cryosurgery, 55 cases were histopathologically diagnosed as enchondroma, 119 as ACT (i.e. chondrosarcoma grade 1), and five as chondrosarcoma grade 2.

In 113 cases, the defect was filled with cement (PMMA); in 53 cases, a bone graft was used (45 homologous, 8 autologous), and in 13 cases the defect was not filled. In 56 cases, prophylactic plating was applied for tumours located in the femur (35), humerus (17), and tibia (4). Patient demographics can be found in Table 1.

Median follow-up after curettage and cryosurgery was 53 months (IQR 33 – 64 months; range 24 – 182 months). In 54 cases, MRI was performed for the following reasons: diagnosed with CS2 (n=5), suspicion of residual tumour on radiographs (n=17), persistent pain complaints (n=22), infection (n=1), neuropraxia (n=1), and in two cases other, non-cartilaginous, tumours were reason for MRI. In six cases the exact reason to perform MRI could not be retrieved. Patients diagnosed with chondrosarcoma grade 2 after curettage and cryosurgery received intensive follow-up. Regular MRI and X thorax was performed on these patients to screen for recurrence and metastases.

Oncological results of curettage and cryosurgery for enchondroma and ACT

Residual tumour was detected in 20 cases (11.5%), with a median size of 2.5 cm (IQR 1.9 – 3.6 cm). Two out of 20 cases were re-operated and one case biopsied. No transformation of tumour grade was seen. In the remaining 17 cases, we refrained from surgery and opted for active surveillance. No tumour growth or tumour-related pain was noticed during follow-up (mean 93 months; range 32 – 165 months). Residual tumour was not related to tumour size, tumour location, or tumour grade (p-values: p=0.572, p=0.914, p=0.203).

Three cases (2%) underwent secondary curettage and cryosurgery due to local recurrence, with no transformation of tumour grade seen. Two patients were

Table 1: Patient demographics.

	N (%)
Mean age (range, years)	50 (12 – 78)
Female	116 (65)
Male	62 (35)
Location	
Proximal humerus	42 (23)
Humerus diaphysis	14 (8)
Ulna diaphysis	1 (<1)
Distal ulna	1 (<1)
Distal Radius	2 (1)
Proximal femur	9 (5)
Femur diaphysis	37 (21)
Distal femur	41 (23)
Proximal tibia	9 (5)
Tibia diaphysis	5 (3)
Distal tibia	3 (2)
Proximal fibula	12 (7)
Fibula diaphysis	2 (1)
Distal fibula	1 (<1)
Tumour size	
Enchondroma	4.5 cm (IQR 3.0 – 7.0; range 1.0 – 16.8)
ACT	4.4 cm (IQR 3.0 – 7.0; range 1.3 – 18.0)
Chondrosarcoma grade 2	5.1 cm (IQR 5.0 – 7.4; range 4.5 – 8.9)

Abbreviations: ACT, atypical cartilaginous tumor; IQR, interquartile range.

already discharged from regular follow-up but returned, as instructed, due to new pain complaints. All three patients suffered from pain related to the local recurrence. After surgery, the pain complaints were relieved. Currently, all three patients are free of disease.

Two cases (1%) underwent wide resection and reconstruction with tumour prosthesis due to local recurrence with radiologic aggressive characteristics (cortex breakthrough and soft tissue expansion). Both cases were histologically diagnosed chondrosarcoma grade 2 after resection. In retrospect, areas of grade 2 chondrosarcoma (such as bone entrapment and hypercellularity) were already visible in previous specimens graded as ACT. In addition, characteristics of high-grade chondrosarcoma had been already visible on MRI before curettage and cryosurgery.

Oncological results of curettage and cryosurgery for chondrosarcoma grade 2

In two out of the five cases diagnosed as chondrosarcoma grade 2, recurrence occurred after 12 and 28 months, respectively. Both cases underwent wide resection and reconstruction with tumour prosthesis. Pathological diagnoses remained chondrosarcoma grade 2 in both cases. In the other three cases, lesions did not recur during follow-up. No metastatic disease was seen in any of the patients nor did any patients die of disease.

Detailed information on secondary operated cases and cases of grade 2 chondrosarcoma can be found in Table 2.

Complications

In total, 20 complications (11.1%) occurred due to curettage and cryosurgery; nine fractures, four superficial wound infections, three deep vein thrombosis, two transient n. peroneus palsy, one reflex sympathetic dystrophy, and one neuroma.

Seven out of nine fractures were related to sufficient trauma. In six out of nine cases, fracture was a reason for reoperation, the other fractures consolidated without surgical intervention. None of the cases with postoperative fractures had residual tumour or recurrence of the tumour.

In total, 43 patients (24%) were re-operated during follow-up, eight of whom underwent multiple surgical interventions. The majority of the patients underwent osteosynthesis removal. Fifty-four percent of the prophylactic plating used was eventually removed due to complaints related to it. All surgical interventions are reported in Table 3.

Table 2: Detailed information of local recurrence and chondrosarcoma grade 2 cases.

Patient age	Tumour size (cm)	Location	Preoperative MRI characteristics
Residual tumour			
40	2.8	Distal femur	Scalloping
60	1.5	Distal femur	No malignant criteria
Recurrence			
17	9.8	Tibia diaphysis	Scalloping and cortical thickening
70	5.7	Proximal humerus	Not available
57	3.0	Proximal tibia	Not available
78	5.3	Proximal humerus	Extensive scalloping, cortex breakthrough, loss of ring and arc pattern, perilesional oedema.
63	4.0	Proximal tibia	Cortex breakthrough, loss of ring and arc pattern, perilesional oedema.
Chondrosarcoma grade 2			
58	4.5	Distal femur	Not available
56	8.9	Proximal humerus	Extensive scalloping, cortex breakthrough, loss of ring and arc pattern, perilesional oedema, periostitis.
36	5.1	Tibia diaphysis	Extensive scalloping, loss of ring and arc pattern.
50	7.4	Tibia diaphysis	Extensive scalloping, focal loss of ring and arc pattern.
49	5.0	Distal femur	Extensive scalloping, cortex breakthrough, focal loss of ring and arc pattern.

Abbreviations: ACT, atypical cartilaginous tumor; FU, follow-up; MRI, magnetic resonance imaging; PA, pathology

** Postoperative MRI after secondary curettage cryosurgery showed the residual tumor remained.*

***Erroneously diagnosed ACT.*

Table 3: Post-operative surgical intervention.

Surgical intervention	*N*
Biopsy	1
Secondary curettage and cryosurgery	5
Segmental resection	4
Removal of osteosynthesis material	30
Removal of neuroma	1
Fracture treatment	6

Biopsy grade	Grade after curettage and cryosurgery	Time till recurrence (months)	Surgical intervention (PA grade)	Total FU (months)
None	ACT	7	Curettage and cryosrugery (ACT)	108
None	Enchondroma	22	Curettage and cryosurgery (reactive tissue)*	100
ACT	ACT	10	Curettage and cryosurgery (ACT)	128
None	ACT	85	Curettage and cryosurgery (ACT)	107
ACT	ACT	117	Curettage and cryosurgery (ACT)	167
ACT	ACT**	12	Resection (CS2)	65
ACT	ACT**	19	Resection (CS2)	83
None	CS 2	26	Resection (CS2)	115
ACT	CS 2	28	Resection (CS2)	88
ACT	CS 2	None	None	94
ACT	CS 2	None	None	42
ACT	CS 2	None	None	39

Discussion

We presented an overview of all cartilaginous tumours in the long bones treated with curettage and cryosurgery between 2004 and 2017 at our institution.

Our oncological results after curettage and cryosurgery of enchondroma and ACT are excellent and comparable with other studies[13-15]. We found a recurrence-free survival of 97% which is in line with the literature (mean recurrence-free survival 93%; range 77% - 100%)[6].

Two cases initially diagnosed as ACT after biopsy and curettage and cryosurgery recurred with radiologic aggressive characteristics. After wide resection both lesions were diagnosed histopathologically as chondrosarcoma grade 2. We concluded

that these cases did not show tumour progression but were erroneously diagnosed as ACT and should have been initially diagnosed as grade 2 chondrosarcoma. On MRI, before curettage and cryosurgery, characteristics of high-grade chondrosarcoma (e.g., loss of ring and arc pattern, perilesional oedema, cortex breakthrough) had been already visible in both cases[2,16]. In retrospect, both cases showed focally histopathological characteristics of grade 2 chondrosarcoma (e.g., high cellularity, mitoses) in the first specimen. As shown by Laitinen et al., the prognosis should be based on the highest grade found in the specimen[17]. It is known that histopathological grading of chondrosarcoma is difficult and open to interpretation. The SLICED study estimated interobserver reliability for the grading of cartilaginous neoplasms in long bones to be 0.443 (moderate) for pathologists[9].

We noted residual tumour in 20 cases (11.5%), of which two cases underwent secondary curettage and cryosurgery. With the current knowledge of residual tumours, we nowadays would not have operated these two cases. As seen in the remaining cases in which we choose for active surveillance, residual tumour did not cause pain complaints nor showed tumour growth. The current literature remains inconclusive on the frequency and duration of active surveillance. This is a topic of great interest and we are currently working on a natural course study which will aid to answer the question on the duration and frequency of follow-up.

To lower the residual rate, navigated curettage or an intraoperative computed tomography might be used to verify complete tumour removal[18]. Clinical relevance could be questioned due to the benign nature of these residual tumors[14].

Five cases were diagnosed chondrosarcoma grade 2 after curettage and cryosurgery. Preoperative MRI already showed signs of high-grade chondrosarcoma in all five cases; however, they were graded as ACT after biopsy. Mismatch between biopsy tumour grade and definitive tumour grade is a known problem caused by tumour heterogeneity[19,20]. For this reason, biopsies are nowadays sparsely performed in our hospital to differentiate between the different grades of cartilaginous tumours. To warrant wide resection, biopsy is performed to confirm the diagnosis of high-grade chondrosarcoma in the few cases when MRI grading is not conclusive. Our oncological results of chondrosarcoma grade 2 treated with curettage and cryosurgery were poor, with a recurrence free survival rate of 60%. More importantly, no metastatic disease was seen and all five patients are currently disease free. Only a few other studies could be found to compare our oncological results of curettage and cryosurgery of chondrosarcoma grade 2 in the long bones. Ozaki et al. reported recurrences of all three cases of chondrosarcoma grade 2 in the long bones treated intralesionally[21]. No evidence of disease was reported after resection. Cho et al. reported on 15 cases of unexpectedly found chondrosarcoma grade 2 after curettage[22]. Only three cases were not re-operated and underwent radiological follow-up (total follow-up of 67, 111, 119 months). All three cases were continuously disease free.

Based on our results and the few cases described in the literature, we propose intensive follow-up by MRI and X-thorax of intralesional-treated grade 2 chondrosarcomas and only when recurrence is detected, wide resection should be performed.

Complications occurred in 11% of the cases, which is in accordance with the literature. Shemesh et al. found in their systematic review a mean event rate of 0.108 for their intralesional subgroup[7]. In our previous study on cryosurgical therapy, we had a much higher complication rate mainly due to 14% post-operative fractures[10]. Prophylactic plating was only used in 8.5% of the cases, whereas in this study prophylactic plating was used in 31% of the cases. As a result, our postoperative fractures decreased till 5%. We recommend prophylactic plating after curettage and cryosurgery for tumours located in the (meta)diaphysis. However, the high rate of secondary operations due to plate removal (n=30) needs to be mentioned.

This study is limited by its retrospective design, which is common in the sarcoma field due to the rarity of these tumours. Whereas other studies often cover long time periods (e.g., 37, 92 years)[23,24] and different case mixes to reach large study populations, we only included patients with cartilaginous tumours located in the long bones operated on between 2004 and 2017 to reduce inhomogeneity.

No control group was available to compare our results of curettage and cryosurgery with either other commonly used adjuvants or wide resection. We agree with Dierselhuis et al. that a randomized control study comparing intralesional treatment with wide resection is unwarranted as local recurrence of ACT is rare and most importantly did not have a negative effect on patient survival[6]. Another limitation of our study is the use of radiographs in most cases during follow-up. MRI was only performed for adjacent pathology or when a residual tumour or local recurrence was suspected. As shown by Verdegaal et al., radiographs overestimate the disease-free survival[25]. In this retrospective series, the residual tumour was detected on radiographs in 13 out of 20 cases and on MRI only in 7 out of 20 cases. The clinical relevance of performing MRI postoperatively to detect asymptomatic residual tumour seems to be low due to the benign behaviour of these tumours. We would therefore only perform MRI postoperatively for patients with persistent pain complaints to rule out other pathology or local recurrence. As well for patients with conventional radiologic appearance of growth of remaining tumour tissue.

In conclusion, curettage and cryosurgery is recommended as surgical treatment of enchondroma and ACT. Excellent oncological results were achieved in our large cohort of enchondroma and ACT in the long bones, no transformation to higher grade chondrosarcoma was seen.

Although several complications occurred (11%) and the secondary operation rate was high (24%), this was in the majority of cases due to complaints of plates.

With the current knowledge of behaviour of ACT in the long bones, the negative side effects of operative treatment should be considered before opting for surgery[13,26].

Further research should define criteria regarding, which specific cartilaginous tumours require surgical intervention.

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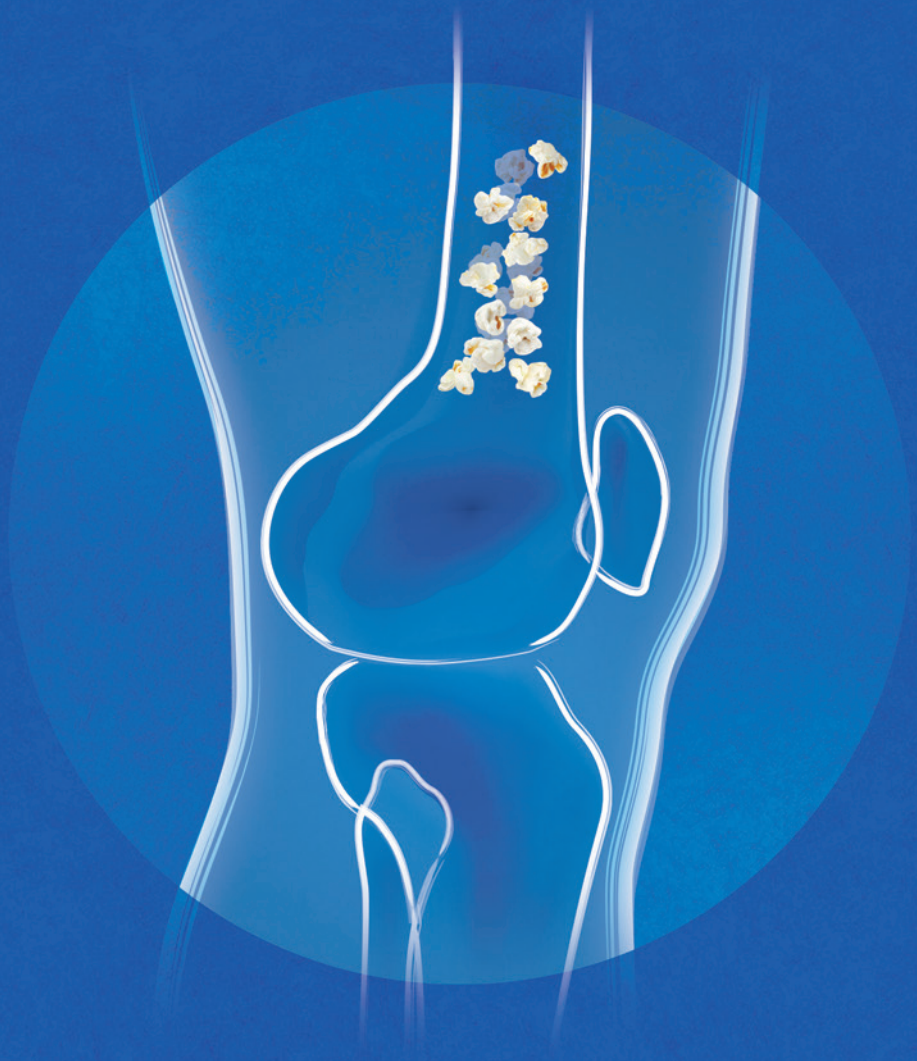

CHAPTER 4

Radiologic follow-up of untreated enchondroma and atypical cartilaginous tumours in the long bones

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Abstract

Background and Objectives: Both enchondroma and atypical cartilaginous tumours (ACTs) are not considered malignant, so inactive and asymptomatic tumours might not need surgery. To the best of our knowledge, this is the first study that has been done to evaluate the natural course of conservative treated enchondroma and ACTs in the long bones.

Methods: For this retrospective study, we analysed the results of patients in whom we refrained from surgery and only regularly performed radiological follow-up of the tumour. Minimal follow-up after initial diagnosis was 24 months.

Results: Forty-nine patients were included in this study. Eight out of forty-nine cases received surgical treatment during follow-up of the tumour. The reasons for this surgery were radiologic growth of the tumour in two cases, pain in one case, patient request in three cases, another indication for surgery in the same limb in two cases.

Conclusion: In this small series of conservatively treated enchondroma and ACTs, only 6% of the patients had a medical indication for surgery. This study shows that indication for surgery should be discussed more thoroughly. Based on our results, we would recommend annual radiologic follow-up for asymptomatic enchondroma or ACTs in the long bones, irrespective of tumour size.

Introduction

Enchondroma and chondrosarcoma are common bone tumours that typically occur central in the medullary cavity in any bone originating from enchondral ossification. They are characterized by tumour cells producing cartilaginous matrix.

In the current 2013 World Health Organization (WHO) classification system, grade 1 chondrosarcoma has been renamed as "atypical cartilaginous tumours" (ACTs) better describing its clinical behaviour[1]. ACT rarely metastasizes and therefore it is now classified as an intermediate type of tumour, not a malignancy[2,3].

Due to more frequent imaging, for example, radiographs and MRI scans, accidental findings of enchondroma and ACT have become more common[4,5]. This often leads to referral of the patient to an orthopaedic oncologic centre for further diagnostics and treatment advice.

To distinguish enchondroma from ACT on conventional radiographs and MRI is often difficult, especially when the lesion is located in the long tubular bones[6-12]. This may result in significant overtreatment of benign lesions in case of enchondroma being diagnosed as ACT. Or it results in undertreatment in case of ACT being diagnosed as enchondroma and erroneously discharged from follow-up. Histological differentiation between enchondroma and ACT depends on subtle criteria and malignant features could easily be missed by a biopsy due to the heterogeneity of cartilaginous tumours[9,13].

Terms as borderline chondrosarcoma and chondrosarcoma grade ½ have been used for lesions with some radiographic malignant characteristics, but with insufficient histological signs to confirm the diagnosis chondrosarcoma[14]. Dahlin used these terms to alert surgeons not to over treat this group of patients. Nowadays these terms have generally been abandoned.

The current surgical treatment for small, central enchondroma and ACT in long bones that are confined to the bone is intralesional curettage with local adjuvant therapy. Reported complications of curettage and local adjuvant treatment in enchondroma and ACT are postoperative fractures, infection, and local recurrence[15,16]. Enchondromas are benign lesions that do not need surgical treatment if inactive and symptomless[10,17]. It is estimated that approximately 4% of solitary enchondromas change into secondary chondrosarcoma, indicating that follow-up is needed[18].

Many authors have proposed radiographic follow-up instead of surgery for cartilaginous tumours in the long bones without signs of local aggressiveness[6,7,19,20]. Radiographic follow-up instead of surgery may prevent overtreatment of this group of patients, resulting in less morbidity and lesser costs.

However, to the best of our knowledge no study has yet been performed showing the results of radiological follow-up.

The aim of our study was to evaluate the natural course of enchondroma and ACT through active surveillance. This study is approved by the medical ethical committee. To the best of our knowledge, this is the first study that has been done to evaluate the natural course of conservatively treated enchondroma and ACT in the long bones.

Methods

To evaluate the natural course of enchondroma and ACT of the long bones, we analysed the results of conservatively treated patients in which we refrained from surgery and only did regular follow-up of the lesion.

In this study, we included conservatively treated patients with enchondroma or ACT, who were under radiologic follow-up in Radboudumc between 2008 and 2013. Conservative treated patients, with enchondroma or ACT, were retrospectively selected by using a record of all patients seen in our hospital.

Inclusion criteria were conservatively treated patients with enchondroma or ACT, at least 18 years old, with lesions in the long bones of the extremities and a follow-up time of minimal 24 months since initial diagnosis. Patients with Ollier disease, Maffucci syndrome or high-grade chondrosarcoma were excluded. Forty-nine cases met the inclusion criteria and were included in our study.

All lesions were evaluated at diagnosis using physical examination, plain radiographs, and MR-imaging. Whenever cases were referred to our hospital, all imaging was reviewed by our experienced musculoskeletal radiologist. Standardized techniques were used for plain radiographs in all cases.

In a few early cases, a trocar biopsy was performed, either in the referral hospital or in our hospital, before a treatment advice was given. Nowadays biopsies are no longer performed in our hospital for this cause since histological diagnosis is not reliable.

Due to the similarity of imaging characteristics of enchondroma and ACT on conventional radiographs and MRI, no difference could be made and all cases diagnosed based on only imaging methods were diagnosed as enchondroma/ACT.

Malignant radiologic characteristics used to indicate chondrosarcoma grade 2 or grade 3 were cortical destruction, presence of soft tissue mass, moth-eaten or permeative osteolysis, pluri-lamellar or speculated periosteal reaction[10,19,21]. Based on these malignant characteristics, differentiation between high-grade chondrosarcoma and enchondroma/ACT was made (See Figure 1 and Figure 2).

When no invalidating pain and no radiographic signs of malignancy were seen, active surveillance was advised to the patient. Patients who approved through verbal consent, with active surveillance, were followed-up with a MRI scan after

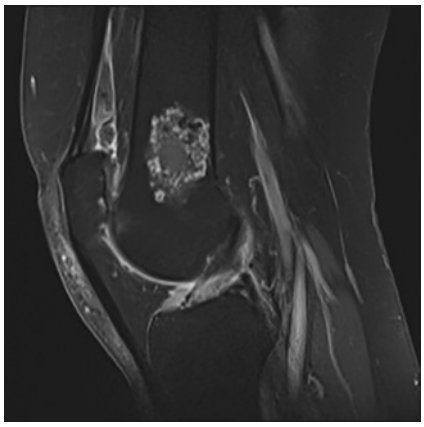

Figure 1: SE T1-weighted contrast-enhanced sagittal image with fat saturation of a 65-year old woman shows a 4cm intramedullary lobulated tumour with septal and rim enhancement abutting the posterior cortex. No surrounding oedema or periosteal reaction. Histologically proven ACT.

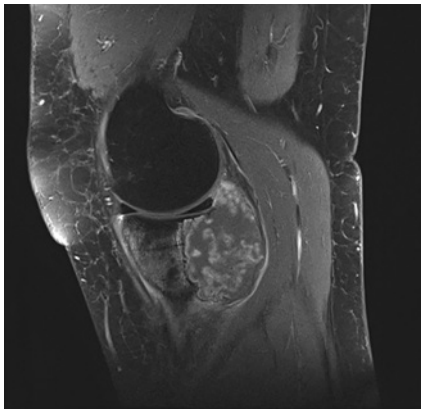

Figure 2: SE T1-weighted contrast-enhanced sagittal image with fat saturation of a 40-year old woman shows predominantly irregular rim enhancement. There is vast cortical destruction with extensive soft tissue involvement as well as intra-articular extension. Histologically proven chondrosarcoma grade 2.

6 months. If the MRI scan showed no growth of the tumour or other radiological changes, radiologic follow-up was continued every 1-2 years. Increased calcification was excluded as growth of the lesion. Radiologic follow-up consisted of conventional radiographs or MRI depending on interpretability of the tumour on conventional radiographs.

All patients who were managed by active surveillance were instructed to contact our hospital in case of new or increased pain. In case of new or increased pain complaints, physical examination and radiologic assessment were performed to rule out other sources of pain.

Whenever invalidating pain or radiographic changes occurred or the patients revised their choice for conservative therapy, patients were treated with surgery. The following operating technique was used in all cases treated with surgery. An oval-shaped cortical window was made with a high speed burr, after which the lesions were thoroughly curettaged followed by three cycles of cryosurgery with rapid freezing of at least - 50°C and slow thawing. After cryosurgery, the bony defects were filled up with either bone graft or bone cement. In diaphyseal lesions, prophylactic plating was performed to prevent postoperative fractures. All operated cases stayed under follow-up after surgery.

Results

A total of 49 cases (27 female and 22 male patients) met the inclusion criteria for this study. Mean age at diagnosis was 49 years (range: 20-76 years). See Table 1 for patient demographics.

Thirty-three of the forty-nine cases (67%) were first diagnosed in another hospital and were referred to our hospital for further analysis.

In five of the 49 cases (10%) a trocar biopsy was performed to confirm the diagnosis. After biopsy, four of these five cases were diagnosed histopathologically as enchondroma and one case was diagnosed as ACT. In 44 out of 49 cases (90%), no biopsy was performed and the diagnosis was based on clinical examination and radiographic appearance, conventional radiographs and MRI. All those 44 cases were diagnosed as enchondroma/ACT due to the similarity of those tumours on imaging methods.

Mean follow-up time since initial diagnosis was 66 months (range: 25-213 months).

All patients are current on their surveillance imaging, no patients were lost to follow-up.

Table 1: Patient demographics.

	N (%)
Median age (range, years)	49 (20-76)
Mean follow-up (range, months)	67 (25-213)
Gender	
Male	22 (45)
Female	27 (55)
Location	
Distal femur	33 (67)
Proximal femur	3 (6)
Proximal humerus	8 (16)
Proximal tibia	3 (6)
Distal tibia	1 (2)
Proximal fibula	1 (2)
Tumour size	
<2 cm	7 (14)
2-5 cm	23 (47)
5-10 cm	17 (35)
10-15 cm	1 (2)
15-20 cm	1 (2)

Clinical presentation

Forty-three of the cases (88%) were incidental findings and two (4%) presented themselves with pain complaints. Of the remaining four cases (8%), the referral indication was unknown, all these cases were diagnosed more than 10 years ago.

Radiological follow-up

In eight of the 49 cases (16%), there was a radiologic change of the lesion noticed during follow-up. All eight cases presented with growth of the lesion, none presented scalloping or cortical breakthrough. Mean time between initial diagnosis and change of the lesion was 41 months (range: 20-76 months). The only case histopathologically diagnosed as ACT showed no radiologic changes 2 years after biopsy. Both cases that presented with pain complaints showed no radiologic changes.

Secondary surgery

Eight of the 49 cases (16%) underwent surgical treatment during follow-up (Table 2). Mean time between initial diagnosis and surgical treatment was 37 months (range:

Table 2: Cases operated during follow-up.

Referral indication	Location	Initial size in cm	Reason for surgery	Time in months from diagnosis to surgery	Prophylactic plating used	Radiologic diagnosis before surgery	Pathologic diagnosis after surgery
Incidental	Distal tibia	3.2	Radiologic growth (0.6cm)	53	No	Ech/ACT	ACT
Incidental	Distal femur	4.6	Radiologic growth (1.0cm)	44	Yes	Ech/ACT	ACT
Incidental	Distal femur	20.0	Pain	10	Yes	Ech/ACT	Ech
Incidental	Proximal tibia	4.7	Choice patient	34	Yes	ACT	Ech
Incidental	Proximal tibia	6.0	Choice patient	21	Yes	Ech/ACT	Ech
Incidental	Proximal tibia	1.7	Choice patient	48	No	Ech/ACT	Heamangioma
Incidental	Distal femur	3.2	Total knee arthroplasty	57	No	Ech/ACT	Ech
Incidental	Distal femur	2.7	Total knee arthroplasty	30	No	Ech/ACT	Ech

Ech: Enchondroma; ACT: atypical cartilaginous tumour

21-57 months). The reasons for surgery were radiological change of the lesion in two cases, invalidating pain in one case, patient request in three cases and total knee arthroplasty (TKA) due to osteoarthritis combined with curettage of the lesion in two cases.

All cases operated on have been under follow-up after surgery. No recurrence of the tumour is seen in these cases. Mean time between surgery and last follow-up was 12 months (range: 1-44 months).

Four out of eight cases (50%) that showed radiological change have been operated. Two cases were operated because of radiologic change during follow-up and in two cases minimal growth (<5mm) was detected and surgery was requested by the patient.

Four out of eight cases (50%) showed radiological change but were not operated on. All four cases showed minimal growth, ranging from 3 to 8 mm.

In 37 of the 49 cases (73%), there was no change observed during follow-up, on conventional radiographs or MRI, or any other reason to perform surgery.

Discussion

The purpose of this study was to evaluate the natural courses of enchondroma and ACT in the long bones by active surveillance. To the best of our knowledge, this is the first study that evaluates the natural course of enchondroma and ACT.

Performing radiographic monitoring for both enchondroma and ACT is in accordance with Crim et al. who recommend serial follow-up rather than curettage for non-painful cartilaginous lesions of any size due to problematic imaging criteria for both enchondroma and ACT[6]. Campanacci et al. recommend that small (<5cm), asymptomatic, intraosseous cartilaginous lesions of long bones without radiological signs of local aggressiveness should be observed as benign enchondroma, and no surgery or further investigations other than serial follow-up is indicated[20].

Surgical treatment of ACT of the long bones has been a subject of debate for the last decades. In our hospital, curettage with cryosurgery has been the treatment of choice for ACT[16]. Curettage and local adjuvant treatment is also considered as adequate treatment according to the 2013 WHO standard[1]. Postoperative fractures, infection and local recurrence have been reported to be complications after curettage and local adjuvant treatment.

The low rate of transformation to higher grade of malignancy and rare metastases of enchondroma and ACT implicates that these lesions might not need surgery. A malignant transformation rate of 4% for enchondroma was reported by Altay et al[18]. In their study, six out of 143 cases of enchondroma underwent malignant transformation, five had changed into ACT and only one case transformed

into grade 2 chondrosarcoma. Schwab et al. reported a malignant transformation rate of ACT in the long bones in only four of 164 patients[22]. Andreou et al. reported a malignant transformation of ACT of 0% in the upper extremity and of 6% in the lower extremity. Only cases that transformed to grade 2 chondrosarcoma developed metastases[23]. This low malignant transformation rate is in accordance with our study were none of the included lesions transformed into high-grade chondrosarcoma.

In the present study, we found that only three of the 49 cases (6%) had a medically grounded indication for removal of the lesion, being invalidating pain or radiographic changes as described in Table 2.

The longer follow-up time before surgery had no consequences for the surgical procedure or the rehabilitation process. All cases operated on were treated with curettage and cryosurgery. None of the patients included in this study suffered from local complications, for example, pathologic fractures during follow-up.

Selection of patients for conservative therapy is important. We were careful to exclude all tumours that were not clearly enchondroma or ACT, that is, showed radiological signs of high-grade chondrosarcoma. Other studies showed that distinction between low and high-grade chondral lesions can be safely determined based on MR-imaging, without the need for pre-operative biopsy[24,25]. We also excluded lesions of the axial skeleton because of the worse prognosis compared to lesions in the long bones[2,23,26,27].

With only 6% of the studied cases needing surgery, this study shows that indication for surgery should be discussed more thoroughly. As the reported complications after curettage are considerable, surgery should be confined to tumours with substantial risk of malignant transformation or metastasis.

However, in case of conservative therapy, there is, to our knowledge, no evidence in the literature for follow-up frequency and duration of follow-up. In our study mean time between initial diagnosis and radiologic change of the lesion was 41 months with a wide range of 20 - 76 months and the mean time between initial diagnosis and surgery was 37 months (range: 10 - 57 months).

The study of Herget et al. showed that the time between the initial diagnosis of enchondroma and the diagnosis of malignancy, varied between six months and up to 30 years[28]. This indicates that enchondroma and ACT lesions might profit from a lifelong radiological follow-up. Brien et al. recommend a follow-up of at least two decades for solitary enchondroma of the long bones if detected after age 25[5]. The frequency of skeletal imaging must be outweighed against the risk of cumulative radiation exposure.

Herget et al. recommend annual clinical and annual/biennial MRI examination for the follow-up of asymptomatic enchondroma localized in the long bones, >5 to 6 cm. Annual clinical and bi-/triennial radiological examination (plain radiographs,

in any doubt MRI) follow-up is recommended for asymptomatic enchondroma lesions <5 to 6 cm[28]. Parlier-Cuau et al. recommend radiologic follow-up once a year for inactive lesions[19]. Based on our results, we would recommend conservative treatment for asymptomatic enchondroma or ACT in the long bones, irrespective of tumour size. Geinaerdt reports that only in the axial skeleton, tumours larger than 4-6 cm are generally malignant[10]. Radiologic follow-up is necessary, based on our experience we recommend annual MR-imaging. MR-Imaging is recommended because it is better in correct tumour measurement compared to radiographs[10,21]. Since growth of the tumour is one of the criteria to decide for operation, the correct measurement of tumour size is of high importance. When no changes occur during follow-up of at least two years, frequency of MR-imaging can be reduced to every 2-3 years. More research should be done to make an international protocol for optimal radiological follow-up of enchondroma an ACT.

The results of this study should be interpreted with some caution as this study had some limitations. Due to the rarity of these tumours, the size of the group studied was small and follow-up in this study was relatively short. Considering the slow biological progression of enchondroma and ACT, it is not possible to make definite conclusions about the oncological outcome.

In only five of the 49 cases, diagnosis was confirmed by biopsy, in the other cases diagnosis was made based on radiographic appearance, conventional radiographs, and MRI. In these 44 cases, no difference could be made between ACT or enchondroma. This means that the exact number of enchondroma and ACT cases included in this study is therefore not known.

Conclusion

In this small series of conservatively treated enchondroma and ACT, only 6% of the studied cases had a medically grounded indication for surgery. None of the surgically treated lesions was transformed into a high-grade chondrosarcoma. This study shows that indication for surgery should be discussed more thoroughly. Based on our results, we would recommend annual radiologic follow-up for asymptomatic enchondroma or ACT in the long bones, irrespective of tumour size.

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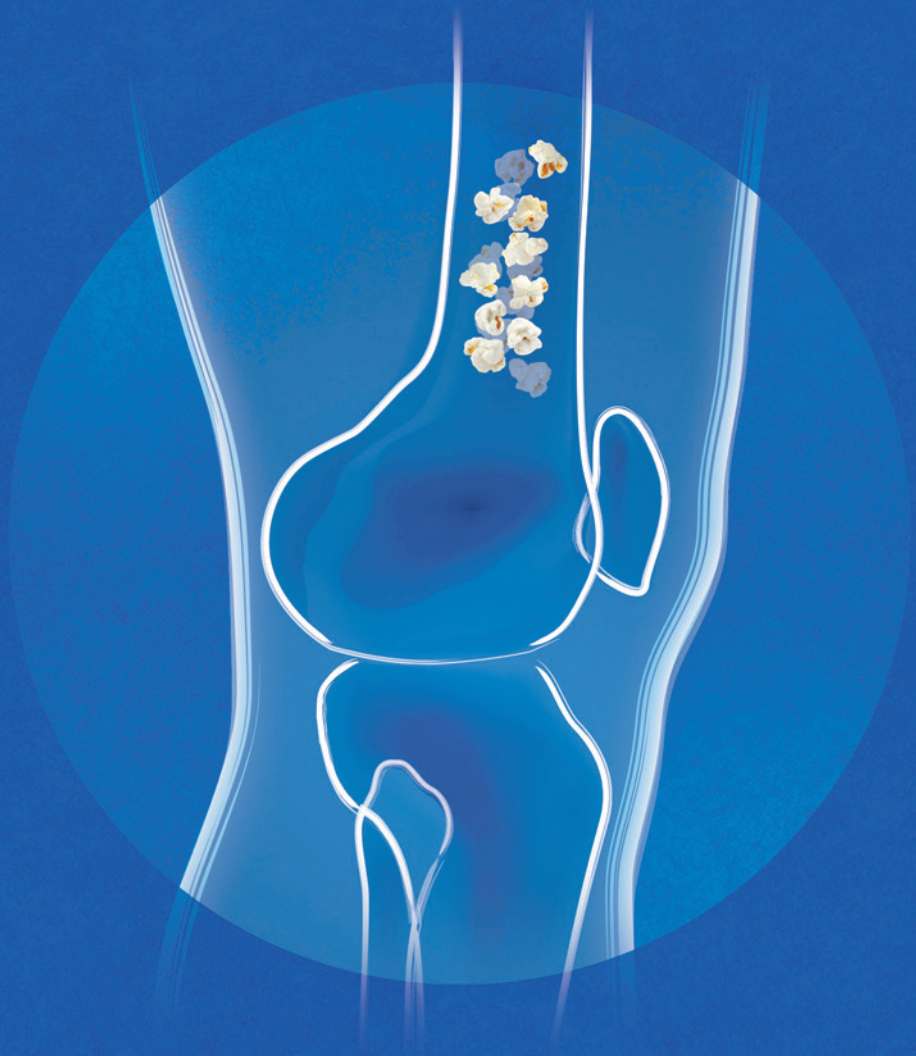

CHAPTER 5

Midterm MRI follow-up of untreated enchondroma and atypical cartilaginous tumours in the long bones

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Abstract

Management of atypical cartilaginous tumours (ACTs) in the long bones is shifting towards active surveillance to avoid unnecessary surgeries. The frequency and duration of active surveillance for these tumours is unclear as there is little knowledge of its biological behaviour. In this retrospective study, we examined the natural course of enchondroma and ACTs through active surveillance. A total of 128 central cartilaginous tumours, located in the long bones, with a minimum interval of 24 months between baseline and last MRI were included. MRI characteristics (e.g., size, scalloping, fat entrapment) were scored and tumours were classified according to the changes between MRIs. Mean follow-up of this study was 50 months, range: 25 – 138 months. The majority of the cartilaginous tumours (87%) remained stable (*n*=65) or showed regression (*n*=46) on MRI. A total of 87% of the cases that developed tumour regression presented with entrapped fat at diagnosis. Only 13% (*n*=17) showed some progression on MRI, although none of the tumours developed characteristics of high-grade chondrosarcoma. Based on our results, active surveillance is considered safe for enchondroma and ACTs of the long bones. We propose active surveillance for all asymptomatic enchondroma or ACTs in the long bones irrespective of tumour size, and follow-up schemes should be tailored on natural course.

Introduction

Nowadays central cartilaginous bone tumours are reported as the most common primary bone tumour. Enchondroma are benign cartilaginous tumours, whereas chondrosarcoma are malignant cartilaginous tumours. Chondrosarcomas are divided into grades ranging from 1 to 3 which correlate with aggressiveness and therefore with local recurrence rate, metastatic potential and the disease specific potential. Since chondrosarcoma grade 1 of the long bones rarely metastasizes and show no signs of local malignant behaviour, the WHO decided in 2013 to change the classification of chondrosarcoma grade 1 (CS1) from malignant into locally aggressive[1]. In the latest 2020 WHO classification, a clear distinction between CS1 in the axial skeleton and appendicular skeleton was made[2]. Tumours in the axial skeleton are still termed CS1, reflecting the more aggressive local behaviour and poorer clinical outcome of tumours at these sites, whereas CS1 in the appendicular skeleton are now termed atypical cartilaginous tumours (ACTs). Typical for cartilaginous tumours are the popcorn-like calcifications and the lobulated contours. Due to the numerous similarities of enchondroma and ACTs on imaging, differentiating these tumours is problematic [3-5]. High-grade chondrosarcoma are recognized by aggressive radiologic features such as bone destruction and soft tissue extension.

Several studies have shown a rise in incidence over the last decades, which is mainly caused by ACTs and might be explained by a simultaneous increase of MRI usage, resulting in more incidental findings[6,7]. Similarly, the incidence of enchondroma increased over the last decades[6]. Orthopaedic oncologists and radiologists are more frequently confronted with the diagnostic dilemma of differentiating enchondroma and ACT[3-5]. The slight increase in incidence of high-grade chondrosarcoma (grade 2, 3 and dedifferentiated chondrosarcoma) is much lower than the increase in incidence of ACTs and enchondroma[6,7]. Based on recent studies on the incidence of cartilaginous tumours, the risk of transformation of atypical cartilaginous tumours (ACTs) to high-grade chondrosarcoma (HGCS) is assumed to be <1%, instead of the previously reported risk of 2.5–6%[6,7].

Due to these new insights, the most recent literature on cartilaginous tumours shifts towards active surveillance for ACTs in the long bones to avoid unnecessary surgeries[8-11]. Several authors have studied active surveillance for central cartilaginous tumours in the long bones without aggressive imaging characteristics (e.g., cortical destruction, soft tissue expansion)[12-15]. Omlor et al. showed that active surveillance of enchondroma and ACTs has benefits in clinical and functional outcome compared to surgical treatment[15]. However, the frequency and the duration of active surveillance for these tumours is unclear, as there is little knowledge of their natural course. The few studies that describe the natural course of enchondroma

and ACTs are limited by small numbers of patients and short follow-up[12,14,16]. Important to mention is that none of these studies described transformation to HGCS. Overall, active surveillance seems appropriate for central cartilaginous tumours in the long bones without aggressive characteristics.

The aim of this study is to examine the natural course of central cartilaginous tumours located in the long bones without aggressive imaging characteristics. As magnetic resonance imaging (MRI) is the imaging method of choice for central cartilaginous tumours[17], we analysed MRI characteristics of enchondroma and ACTs, in which we refrained from surgery.

Methods

A retrospective cohort study was performed on all patients diagnosed between 2008 and 2017 with central cartilaginous tumours in the long bones without aggressive imaging characteristics. In total, 391 cartilaginous tumours without aggressive imaging characteristics were located in the long tubular bones, of which 227 tumours underwent active surveillance instead of surgical removal (See Figure 1).

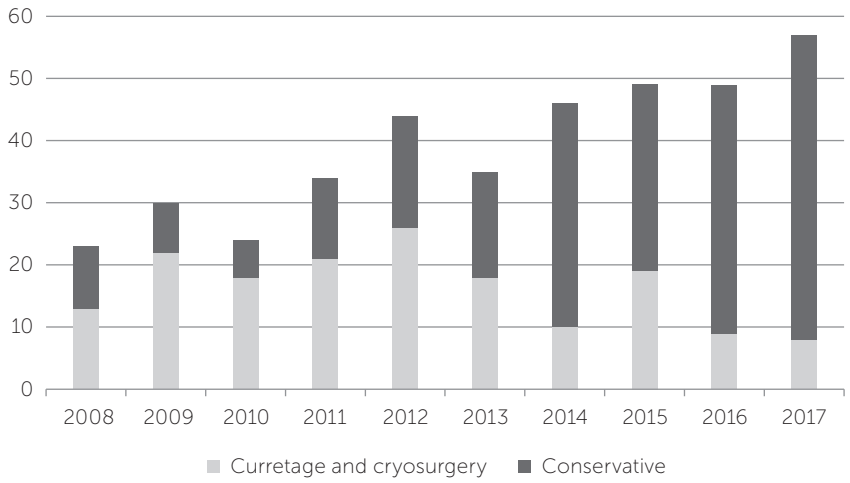
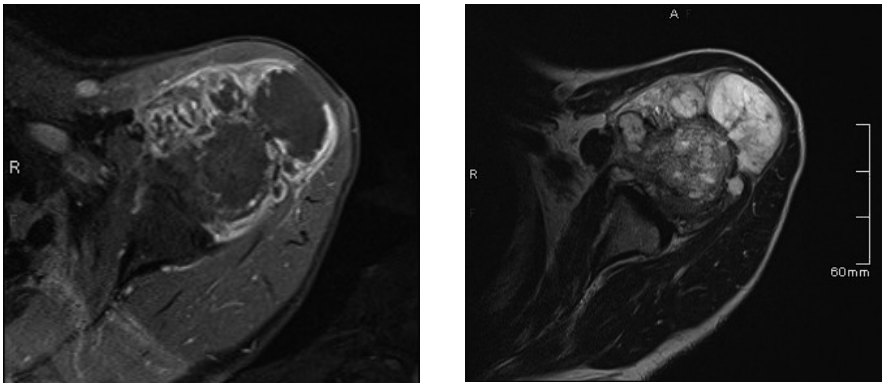


Figure 1: Number of cartilaginous tumours without aggressive characteristics located in the long bones treated at our institution between 2008 and 2017.

For the purpose of this study patients were included if they met the following criteria: (1) A central cartilaginous tumour located in the long tubular bones, (2) under active surveillance, and (3) who underwent at least two MRIs of the tumour with a minimum time interval of 24 months. Patients with Ollier's disease or Maffucci syndrome were excluded. Previously biopsied tumours were also excluded as this could interfere with MRI interpretation.

We did not differentiate between enchondroma and ACT due to the similarities of these tumours when located in the long tubular bones[3-5]. After referral to our hospital, physical examination was performed and all imaging was reviewed by experienced musculoskeletal radiologists and, if necessary, additional imaging (i.e. X-ray and/or MRI) was performed[16]. Active surveillance was advised when neither invalidating pain nor any of the following radiological signs of malignancy were seen: cortical destruction, presence of soft tissue mass, moth-eaten, permeative or extensive osteolysis, multi-lamellar or aggressive periosteal reaction[16,18,19]. Figure 2 shows an example of an excluded patient with radiological signs of malignancy. Patients who accepted the active surveillance were followed-up with MRI after 6 months. If MRI showed none of the previous described malignant characteristics or excessive tumour growth, active surveillance was continued. Patients were educated on their diagnosis and instructed to contact our hospital in case of new or increased pain. When invalidating pain or progression of the tumour on MRI (i.e. tumour growth, malignant characteristics) occurred, or when the patients revised their choice for conservative therapy, patients were surgically treated. Our surgical



(a) (b)

Figure 2 a, b: Axial CE (Contrast Enhanced) TSE T1-weighted and axial SE T2-weighted image of the proximal humerus of the same patient: extensive cortical breakthrough with soft tissue mass in a 66-year-old male with histopathologically proven dedifferentiated chondrosarcoma.

method consists of curettage and cryosurgery, filling of the void with cement or bone graft, and in some cases prophylactic plating[20,21]. Curettage material was reviewed by experienced pathologists and histological diagnosis was made according to established criteria[1,22]. All operated cases were regularly monitored after surgery, consisting of physical examination and conventional radiology. In cases of clinical or radiological suspicion of local recurrence, additional MRI was performed.

MRI analysis

At our institution all MRIs were performed on a 1.5T scanner, and intravenous gadolinium was standardly used. Most patients were referred to our tertiary centre with a baseline MRI, often performed without gadolinium in the referring hospital. All MRIs analysed in this study were performed between 2008 and 2020.

An experienced senior musculoskeletal radiologist (JdR) scored the following tumour characteristics: craniocaudal size, location, presence of endosteal scalloping, peritumoral oedema, fat entrapment, ring and arc enhancement, calcifications, and replacement of cartilaginous lobules by fatty marrow.

Tumour size was measured as the largest craniocaudal dimension on coronal or sagittal images. To account for possible measurement error, only a size difference of ≥ 3mm was considered progression or regression. Endosteal scalloping defined as loss of inner cortical bone was evaluated on axial images. The degree of scalloping was not quantified, scalloping was scored as increased/decreased when there was increased/decreased circumferential loss of inner cortical bone compared with the baseline MRI. Fat entrapment was defined as presence of intralesional foci of high signal intensity on T1-weighted images, correlating with fat within the cartilage tumour, as described by Vanel et al.[23]. Ring and arc enhancement could only be scored when contrast enhanced MRI was available. Loss of enhancement might be attributed to increased fat entrapment, increased calcification or use of different imaging techniques resulting in different contrast uptake. Fatty replacement was only scored on the last MRI and defined as replacement of cartilaginous lobules by normal fatty marrow.

After scoring of the tumour characteristics at baseline and last MRI, tumours were classified as regression(R), progression(P), or no change (NC). Tumours were classified as regression when one or more of the following changes occurred: (1) Decreased tumour size (≥3mm), (2) decreased scalloping, (3) increased calcification, (4) increased fat entrapment, or (5) replacement of cartilaginous lobules by fatty marrow. Tumours were classified as progression when one or more of the following characteristics were scored: (1) Increased tumour size (≥3mm), (2) increased scalloping, or (3) loss of calcification.

Statistics

Analysis of the data was performed using IBM SPSS statistics for Windows (version 25). All continuous variables were visually inspected and tested for normality by the Shapiro-Wilk test.

After MRI analysis, three groups were defined (R, P and NC) and the differences at first presentation between these groups were assessed. Kruskal-Wallis and Mann-Whitney U were used for continuous variables. For categorical variables Chi-squared or Fisher's exact test depending on expected frequency in cells, were used. P-value < 0.05 was considered statistically significant.

Results

In total, 128 tumours in 124 patients (47 male, 77 female) met the inclusion criteria for this retrospective study. Mean age at diagnosis was 52 years (range 20 – 76 years). Patient demographics are reported in Table 1. As our hospital is a tertiary care referral centre, 73% of the cases were first diagnosed in another hospital. Mean time of conservative follow-up since initial diagnosis is 50 months (range: 25 – 138 months).

Symptoms at presentation

The majority of the lesions were incidental findings (125 cases; 97.7%), whereas two cases (1.6%) were referred with pain that could not be explained by adjacent pathology, and for one case the referral indication could not be retrieved from the clinical charts. Most incidental findings (22.4%) were found after patients presented themselves with knee complaints not related to the tumour (e.g., osteoarthritis, meniscal tears). Some of the other reasons for imaging were trauma (14.1%), shoulder complaints not related to the tumour (14.8%), cancer staging imaging studies (8.6%) and rheumatoid arthritis screening (7.0%). Only two patients (1.6%) reported pain that could not be explained by adjacent pathology and was therefore, probably related to the tumour. In both cases pain complaints were transient and active surveillance was continued. Seven cases developed new pain complaints during follow-up. In six out of seven cases, physical examination and imaging showed other causes (e.g., bursitis, osteoarthritis) for the pain. In one case no other cause was found but the pain was transient and active surveillance was continued.

MRI analysis

A total of 65 cases showed no change (NC), 46 regression (R), and 17 progression (P). MRI characteristics are summarized in Table 2. One case presented with peritumoral oedema, which could be explained by a recent fracture and subsequently diminished

Table 1: Patient demographics.

	No change (*n*=65, 51%)	Regression (*n*=46, 36%)	Progression (*n*=17, 13%)	P-value
Mean age (range, years)	55 (21 – 73)	52 (23 – 76)	39 (20 – 56)	.000 b, c
Male : Female	25 : 40	16 : 30	9 : 8	.419
Median follow-up (months)	46 (25 – 102)	49 (26 – 116)	47 (30 – 138)	.149
Tumour location (n,%)				.078
Proximal humerus	23 (35.4)	15 (32.6)	3 (17.6)	
Humerus diaphysis	0	4 (8.7)	0	
Proximal femur	12 (18.5)	4 (8.7)	1 (5.9)	
Femur diaphysis	5 (7.7)	7 (15.2)	2 (11.8)	
Distal femur	19 (29.2)	13 (28.3)	7 (41.2)	
Proximal tibia	2 (3.1)	0	2 (11.8)	
Tibia diaphysis	1 (1.5)	1 (2.2)	0	
Distal tibia	0	0	1 (5.9)	
Proximal fibula	2 (3.1)	2 (4.3)	1 (5.9)	
Distal fibula	1 (1.5)	0	0	
Baseline MRI characteristics				
Median size (mm)	38 (13 – 158)	54 (14 – 170)	40 (12 – 64)	.000 a, c
Excentric location of the tumour	33 (51)	19 (41.3)	6 (35.3)	.413
Scalloping	34 (52.3)	20 (43.5)	7 (41.2)	.557
Fat entrapment	40 (61.5)	40 (87.0)	6 (35.3)	.000 a, c
Septa nodular enhancement	7 (10.8)	4 (8.7)	4 (23.5)	.107
Calcifications	57 (87.7)	43 (93.5)	13 (76.5)	.172

Values are displayed as mean/median (range) or n (%).
a= significant difference between NC and R, b=significant difference between NC and P, c= significant difference between R and P.

on the last MRI. Of the 46 cases in the regression group, 37 cases showed fatty replacement, 39 increased fat entrapment, 5 decreased scalloping, 11 increased calcifications, and 17 decrease of tumour size (mean tumour decrease 8mm: range 3 – 30 mm). In majority of the cases (83%), a combination of two or more MRI changes related to regression was seen. Two patients of the regression group showed tumour growth (3 and 10 mm) prior to development of signs of regression (increased fat entrapment, fatty replacement). All 17 cases with progression of the tumour showed increased tumour size over time (median tumour growth 5mm; range 3 – 23 mm). Only eight of the 17 cases showed tumour growth over time of more than 5 mm. Two cases showed loss of ring and arc enhancement in addition

Table 2: MRI characteristics.

	Baseline MRI			Last MRI			
MRI characteristics	Present *n* (%)	Absent *n* (%)	N.A.	Increased *n* (%)	Decreased *n* (%)	Unchanged *n* (%)	N.A.
Scalloping	61 (48)	67 (52)	-	0	5 (4)	123 (96)	-
Peritumoral edema	1 (1)	127 (99)	-	0	1 (1)	127 (99)	-
Fat entrapment	86 (67)	42 (33)	-	39 (30)	0	89 (70)	-
Calcifications	113 (88)	15 (12)	-	11 (8)	1 (1)	116 (91)	-
Ring and arc enhancement	116 (91)	0	12	0	20 (16)	94 (73)	14
				Present	Absent		
Fatty replacement	-	-	-	37 (29)	91 (71)		

N.A.: not assessable; no contrast enhanced MRI available.

to 6 and 23 mm tumour growth (respectively, 62 and 51 months follow-up). The tumour with 23 mm growth was removed and histopathologically diagnosed as ACT (Table 3). The other patient remains under active surveillance as tumour growth developed gradually and the patient has no pain complaints. None of the cases included in this study showed any aggressive MRI characteristics often seen in HGCS (e.g., cortical destruction or soft tissue mass extension) during follow-up.

In total, six of the 128 cases included in this study were operated (Table 3), either due to tumour growth (*n*=5) or osteoarthritis and total knee arthroplasty was combined with curettage of the lesion (*n*=1). None of the operated cases transformed into HGCS.

Table 3: Operated cases.

Referral	Age at diagnosis	Location	Initial size (mm)	Total growth (mm)	Reason for surgery	Time in months from diagnosis to surgery	Pathologic diagnosis
Incidental	49	Tibia (proximal)	30	5	Growth	40	Sample error
Incidental*	47	Femur (distal)	50	11	Growth	43	ACT
Incidental	36	Fibula (proximal)	12	4	Growth	49	ACT
Incidental	22	Femur (distal)	34	23 ×	Growth	55	ACT
Incidental*	38	Tibia (distal)	32	7	Growth	53	ACT
Incidental*	64	Femur (distal)	32	-	Prosthesis	57	Enchondroma

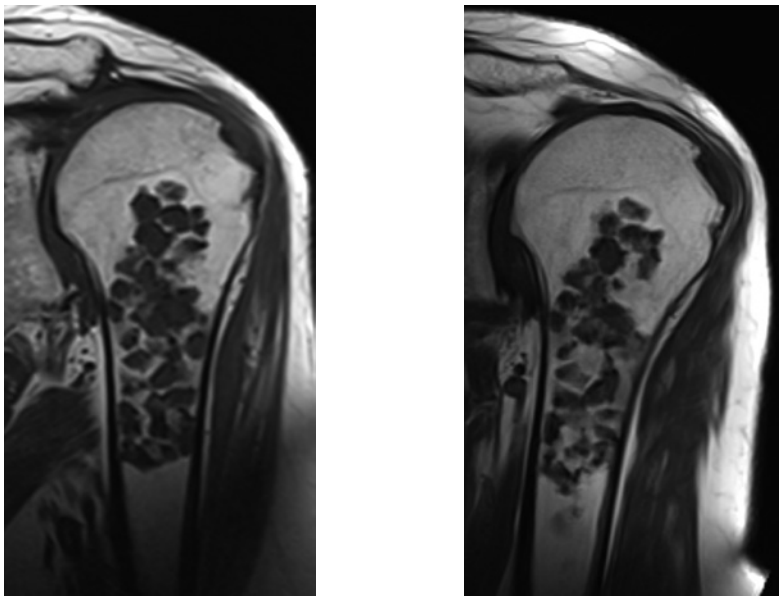
** cases also included in Deckers et al. 2016. × Growth in combination with loss of ring and arc enhancement on MRI.*

Discussion

Changes in the WHO classification from chondrosarcoma grade 1 of the long bones to atypical cartilaginous tumour (ACT), together with the recent insight of low transformation risk of ACTs (<1%), has resulted in a more conservative treatment approach of ACT in literature[1,2,6,7]. Many authors have questioned if the negative side effects of surgical treatment outweigh the potential benefits and therefore proposed active surveillance[6,8,10,12,14-16]. To support development of evidence-based guidelines for active surveillance, we studied the natural course of enchondroma and ACTs in the long bones. In this study, MRI analysis of 128 cases was performed with a minimum interval of 24 months between baseline and last MRI. The majority of the cartilaginous tumours (87%) remained stable or showed regression on MRI. Only 13% showed some progression on MRI, although none of the tumours developed characteristics of high-grade chondrosarcoma (HGCS). Based on our results, active surveillance is considered safe for enchondroma and ACTs of the long bones, and follow-up schemes should be tailored on natural course.

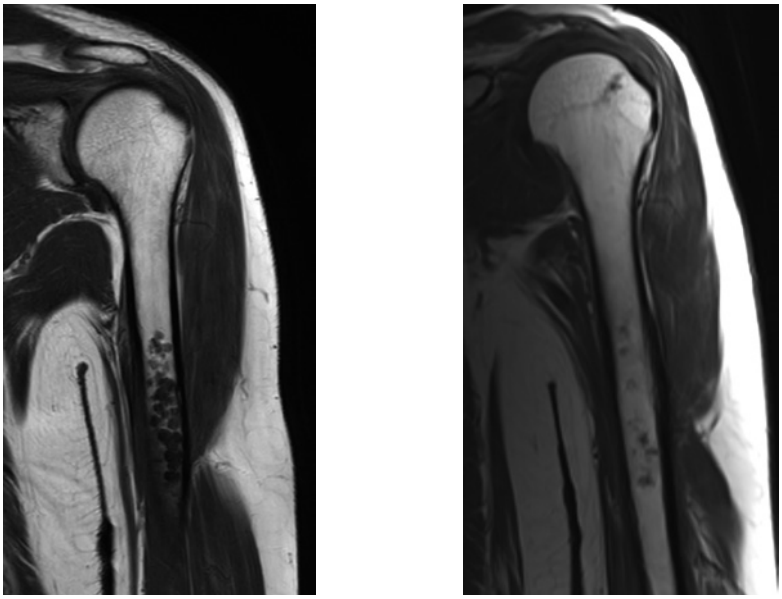
Our study provides additional evidence that cartilaginous tumours located in the long bones can be regressive. In the present study, 46 cases (36%) developed signs of regression during follow-up (52 months, range 26 – 116). In line with Chung et al. we showed a larger incidence of regression than progression during follow-up[12].

Replacement of cartilaginous lobules by normal marrow fat is only mentioned in a few studies, as most studies focus on tumour size, scalloping and development of aggressive features[12,24]. This fatty replacement was seen in 29% of our cases, predominantly in peripheral areas of the tumour (Figure 3 and 4). Sensarma et al. proposed that a process similar to endochondral ossification might explain resorption of cartilage lesions[24]. Entrapped fat was present at diagnosis in majority (87%) of cases that underwent regression and might predict biological behaviour. Entrapped fat is known as a reliable MRI characteristic to differentiate benign from malignant tumours[18,19,23,25]. A combination with fatty replacement was seen in 36 of the 90 cases (40%) that either presented with fat entrapment at diagnosis or developed fat entrapment during follow-up. None of the cases in this study showed a decrease of fat entrapment during follow-up. In those six cases of the progression group in which entrapped fat was seen at diagnosis, only minimal growth was reported (median 3.0mm). Since two cases also showed tumour growth followed by signs of regression, including fat entrapment, we hypothesize that cases with entrapped fat in the progression group might develop signs of regression later on.



(a) (b)

Figure 3 a, b: Coronal Spin Echo T1-weighted images of the same cartilaginous tumour 3 years apart. Signs of fatty replacement are seen peripheral and central in the tumour.



(a) (b)

Figure 4 a, b: Coronal Spin Echo T1-weighted images of the same cartilaginous tumour 4 years apart. Almost complete replacement of the cartilaginous tumour by normal bone marrow fat.

All cases that were scored as progressive (*n*=17; 13%) showed tumour growth, but only in eight cases (6%) tumour growth over 5mm was seen. The clinical relevance of including cases in the progression group with tumour growth ≤5mm measured over our midterm follow-up period could be questioned. Although five cases were operated due to tumour growth, surgery could have been redundant to achieve oncological safety, because none showed histopathological signs of HGCS. Besides, it is important to note that tumour progression in this study was seen in relatively small tumours (size at diagnosis ranged from 12 to 64 mm). Cartilage tumours in the long bones smaller than 5 cm are often considered to behave benign and are therefore, discharged from follow-up in some institutions[26,27]. Based on our findings of tumour growth mainly occurring in relatively small tumours we would recommend active surveillance irrespective of tumour size.

Although patients in the progression group were significantly younger (Table 1), we felt we could not conclude that progression is only seen at young age due to the wide range (20 – 56 years). Our finding implies that older patients (e.g., >65

years old) might not need frequent follow-up. Future studies are needed to investigate if active surveillance should be tailored to age difference.

Previous studies have suggested scalloping to be a distinctive feature to differentiate between enchondroma and ACT[18,28]. The results from this study have shown that presence of scalloping does not predict natural course as scalloping was reported in all three groups and there was no significant difference between these groups (Table 1). The clinical relevance of measuring scalloping could be questioned as there is also only fair observer agreement[3,29].

Active surveillance for ACTs prevents unnecessary surgery and should be the treatment of choice for asymptomatic cartilaginous tumours in the long bones. Due to sparse knowledge on the biological behaviour of these tumours, guidelines for active surveillance are lacking and follow-up strategies vary amongst institutions. The Birmingham study group developed a pragmatic imaging tool for triaging cases for referral[11]. We agree that the current rise in incidence of these tumours warrants a pragmatic approach, as a large prospective long term follow-up study would take too long to accomplish. Since we concluded that these tumours show both progression and regression, we propose tumour follow-up schemes should be tailored accordingly.

For active surveillance, we propose an MRI follow-up six months after diagnosis. If HGCS were mistakenly treated with active surveillance, radiologic change of HGCS would be expected within six months. In the study of Davies et al. only two out of 97 patients, with two or more MRI examinations, were diagnosed with HGCS showing malignant characteristics after five and seven months on MRI follow-up[13]. Furthermore, a six month follow-up would support patients' wellbeing, since anxiety may arise after the initial diagnosis, which is relieved after a follow-up MRI that shows a stable or regressed tumour.

The next steps in active surveillance are dependent on changes in tumour characteristics at the first follow-up MRI, six months after diagnosis. When the first follow-up shows no changes, a biennial MRI is recommended. This follow-up period might even be extended when the tumour remains stable after longer follow-up. When tumours show regression in asymptomatic patients, we would advise a follow-up MRI at three years after first signs of regression. If the three-year MRI shows no change or continued regression, the patient can be discharged with instructions to contact the hospital in case of new or increased pain. Due to the still limited follow-up of this study, we currently discourage discharge of the patient when first signs of regression are seen. When tumours show progression during follow-up without development of malignant characteristics (e.g., cortical destruction, soft tissue extension), next follow-up MRI is recommended within one year. When tumour growth is accompanied with persistent pain related to the tumour, intralesional surgery is advised.

Although active surveillance seems effective for ACTs in the long bones, we should be cautious for active surveillance to become a cycle of never ending follow-up and prevent overutilization of costly advanced imaging. Therefore, long-term follow-up studies are necessary and predictive nomograms should be developed. Furthermore, future studies should not only focus on aggressive characteristics (e.g., tumour growth, scalloping) but also on characteristics that might predict regression. Based on this study, fat entrapment at diagnosis seems a promising MRI characteristic to predict tumour regression.

This study is limited by its retrospective design, because the indication for surgery changed during the study period. Whereas cases with minimal tumour growth were operated at the start of the study, we currently refrain from surgery. Furthermore, the exact number of enchondroma and ACTs in this active surveillance study is not known as there was no clinical benefit for majority of the patients to perform biopsy or intralesional surgery.

Conclusion

In conclusion, the natural course of cartilaginous tumours can either show progression, stability or regression. This study shows that active surveillance for enchondroma and ACTs in the long bones is safe, as none of the included tumours developed aggressive characteristics. Follow-up schemes should be tailored according to biological behaviour to prevent overutilization of costly advanced imaging.

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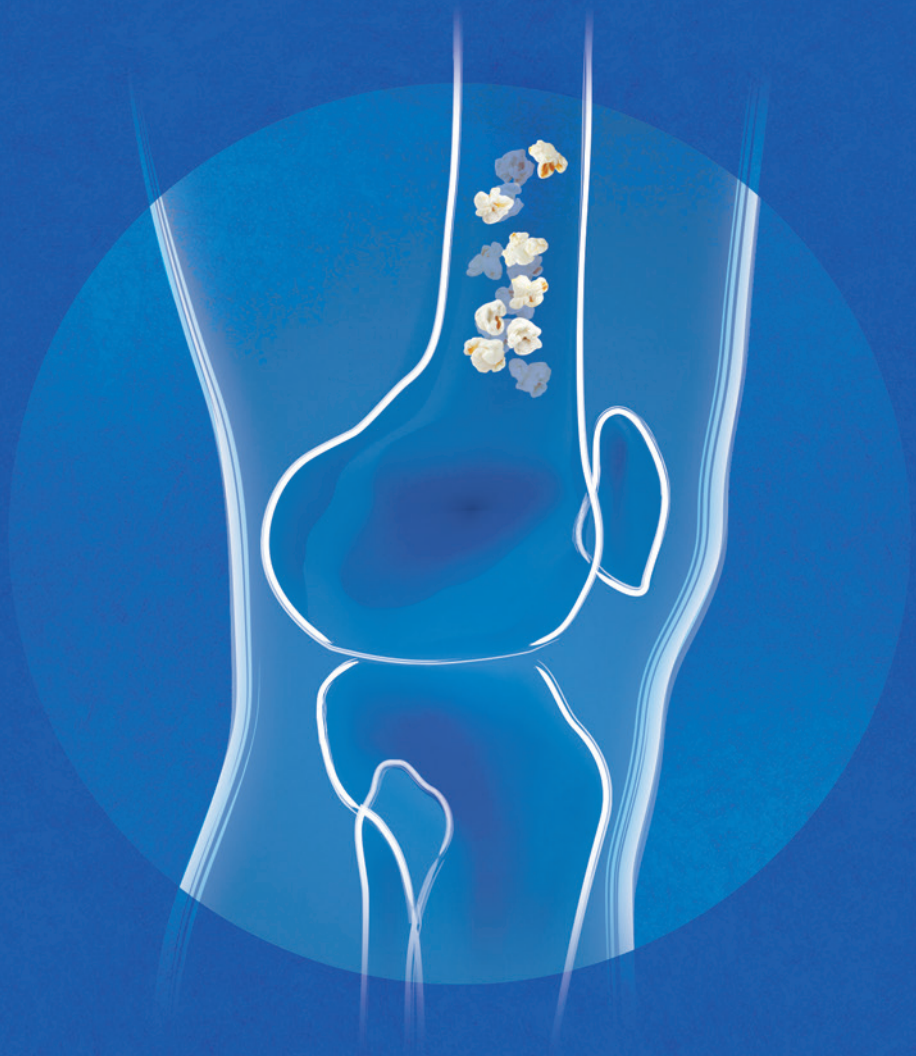

CHAPTER 6

Shared decision making: Does a decision aid support patients with an atypical cartilaginous tumour in making a decision about treatment

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Abstract

Objective: Due to new insights, atypical cartilaginous tumours (ACTs) of the long bones are no longer considered malignant and treatment is shifting from surgery to active surveillance. We developed a decision aid in order to support in shared decision making on treatment.
The aim of this study is to evaluate the treatment preferences of patients with an ACT in the long bones.
Methods: During thirty-four months, patients received a decision aid digitally with information about the disease, the treatment options, and the risks and benefits of active surveillance and surgical treatment. The given answers to patients' preference questions were evaluated qualitatively in relation to the final choice of treatment.
Results: Eighty-four patients were included. None of the patients who preferred active surveillance later underwent surgery. Only four patients underwent surgery based on patient preference.
Conclusion: In our experience the decision aid is useful for shared decision making as it provides the patient with information and the clinician with insight into patient's preferences. The preference for treatment generally corresponds to the eventual treatment.

Introduction

Cartilaginous tumours such as enchondromas and atypical cartilaginous tumours (ACTs) are often located in the long bones[1,2]. Due to more frequent imaging, in patients with joint-related symptoms, incidental detection of these tumours has increased over time[3]. This often leads to a referral of the patient to an orthopaedic oncology centre for further diagnostics and treatment advice.

Enchondromas are benign chondroid tumours. ACTs are tumours that can be locally aggressive, but metastasizing or upgrading of an ACT is extremely rare[4]. The present classification is intermediate type of tumour, not a malignancy. ACTs and enchondromas can have similar radiographic findings, which makes it very difficult to distinguish between these two diagnoses[5,6]. Until recently surgery was standard of care for these tumours. In most centres, treatment consisted of intralesional curettage with local adjuvant treatment such as phenolisation or cryosurgery[7,8]. The remaining bone cavity was filled with cement or bone graft, with or without prophylactic plating. This was followed by a 3 to 4 month rehabilitation period, with physiotherapy to rehabilitate to a presurgical functional level[9]. The post-operative follow-up period ranged from 2 to 5 years with radiographic imaging[6]. Advantage of surgery is that the tumour is removed and follow-up is limited. There are however several disadvantages, such as the associated prolonged recovery, poorer functional results and the risk of complications (e.g., wound infection and bone fracture)[9].

Due to new insights on the natural course of these tumours, active surveillance with radiographic follow-up instead of surgery is nowadays becoming more common, in order to prevent overtreatment[5]. Literature on active surveillance is promising as no malignant transformation is reported and tumour growth seems to occur only in a small group of patients[2,10,11]. A retrospective study of Deckers et al. showed that only 6% of the patients who were included for radiographic follow-up of an ACT eventually underwent surgical treatment on medical grounds, such as pain, tumour growth or radiological changes[12]. Considering the risks and benefits for a patient, this does not imply an increased health risk for the patient. The burden on the patient is posed by periodically undergoing radiographic imaging, such as an MRI.

Indications for surgery today are based on medical ground (i.e., pain and tumour growth), or on the patient's wishes[12]. If the psychological burden, due to the tumour in the bone, dominates a patient's daily life, this may be a reason for surgery.

The recent new insights on the behaviour and treatment of ACTs call for adjustment of patient information. In order to make a well-informed decision about the preferred management (active surveillance or surgical treatment) of an ACT, patients need to be well counselled with complete and updated information.

It is well known that patients immediately forget 40% to 80% of medical information provided by healthcare professionals, and that nearly half of the information is incorrectly remembered[13]. This is due to several factors, including the use of understandable language, the use of medical terminology and whether information is supported by written material. Patient related factors affecting memory include age, anxiety, level of education and specific expectations[14].

To help patients understand and remember the medical information and make a well-informed decision on treatment we have developed a decision aid for patients with an ACT in the long bones. Decision aids are designed to assist patients and clinicians in making informed decisions about possible management options, and to support the process of shared decision making[15]. Offering a choice in treatment options increases involvement in decision making and leads to better informed patients[16]. Decision aids improve knowledge, reduce indecision, and improve agreement between values and choices[17].

The health professional and the patient are able to discuss the patients' thoughts, preferences and values, and this assists shared decision making[18]. This improves patient satisfaction, and results in increased patient empowerment, and in an increased confidence in the health professional-patient relationship[19].

The aim of this study is to evaluate the preferences of patients in relation to the eventual treatment for ACT in the long bones and to share our experience with the implementation of a decision aid.

Methods

A decision aid for patients with an ACT was developed with the goal to inform patients, to support patients and healthcare professionals in the shared decision and to avoid unnecessary treatment.

Decision aid development

The content of the decision aid was based on the latest insights of the behaviour and treatment of ACTs and the Dutch guidelines for developing a decision aid[15,20]. This is in line with International Patient Decision Aid Standards (IPDAS)[21]. The content was written by physicians, a physician researcher and a nurse practitioner and it has been checked for readability by the communications department.

The first section of the decision aid consisted of information about the diagnosis and treatment. The information on treatment options, both active surveillance and surgical treatment, was supplemented with an overview of the risks and benefits of each option. In the second section, knowledge questions were formulated for the patient to check whether he or she understood the information of the decision aid.

The results and correct answers to these questions were visible only to the patient. The final section consisted of questions about patients' values and preferences. The answers to these questions formed the basis for the following conversation between the patient and the health professional about the treatment that best suited the patient's situation.

After implementation in April 2018, the decision aid was presented to and adjusted by the Dutch Patient Association[22]. After the Dutch Patient Association evaluated the content of the decision aid, one of the questions to determine patients' values (no 5) was changed, wording it more positively.

Value and preference questions:

1. I am concerned about the diagnosis cartilaginous tumour
2. I do not mind undergoing surgery
3. I do not mind having frequent MRIs
4 I do not mind being unable to put weight on my arm / leg for a short period of time

5a. Leaving / not operating on my cartilaginous tumour frightens me

6 At this moment my preference is: Follow-up / operation / I do not know yet

Changed question from 14-12-2018:

5b. Active follow-up of my cartilaginous tumour reassures me

Since the decision aid was developed as a digital tool, it was incorporated in the patient electronic health record of the hospital. All patients had access to their electronic health record, allowing them to receive the information, and answer the questions digitally. The answers to the questions to determine patients' values and preferences were saved in the electronic health record, and could be easily reviewed by the patient and the health professional.

Data collection procedure and analysis

Between April 2018 and January 2021, patients, who were diagnosed with an ACT in the long bones at our orthopaedic oncology department, received the digital decision aid in his or her electronic health record after their first physical consultation at our outpatient clinic.

One week after the consultation at the outpatient clinic, consultation by phone was performed by the physician or nurse practitioner. During this consultation, remaining questions could be answered by the clinician, and the patient was invited to discuss the values and preferences with the physician or nurse practitioner. At the end of the consultation, a final shared decision was made on the preferred management, and this was documented in the patient's health record.

For this study, all records were analysed, to determine the patients' preferences and what management had eventually been performed. The minimum follow-up, after diagnosis, was nine months. For patients with active surveillance, the follow-up consisted of MRI at six months after diagnosis, and for patients who were included in the first two years of this study, also at 18 months after diagnosis.

In addition to the analysis of the answers to the questions related to the patients' values and preferences, the data analysis also included information on patient demographics and tumour-related data.

Retrospectively, all health records were reviewed to determine how patients had experienced the information provided by the decision aid.

Results

During the inclusion period of 34 months, 84 patients (55 female and 29 male) received the decision aid and answered the preference questions. The age of the patients ranged from 20 to 78 years, with a mean of 54 years. In 39 patients the tumour was located in the femur, and in 33 patients in the humerus. Other locations included the tibia (*n*=8), fibula (*n*=2) or other long bone (*n*=2).

Sixty-nine patients (80%) were referred to our orthopaedic oncology centre based on an incidental finding on radiograph or MRI scan. Other referral indications were pain (*n*=9), referral from another orthopaedic oncology centre for second opinion (*n*=2), a palpable lesion (*n*=2), and unknown/other (*n*=4).

In total, 11 of the included patients (13%) underwent surgical treatment, because of pain (*n*=5), growth of the tumour (*n*=2) or patients' preference (*n*=4).

Outcomes of the questions to determine patients' values and preferences

As reported in figure 1, half of the patient group was concerned about the diagnosis of ACT.

One third of the patients did not mind undergoing surgery followed by restricted weightbearing for a short period of time. The majority did not mind having frequent MRIs.

Among the patients who received the question about leaving / not operating on the tumour, there were equally mixed feelings about leaving the tumour in place.

For the majority of the patients active follow-up of the ACT provided a feeling of reassurance. This was reflected in the results for the preference for treatment questions.

Sixty-eight percent of all patients preferred follow-up, 14% preferred operation, and 18% did not have a preference at the first contact moment after providing the decision aid (Figure 2).

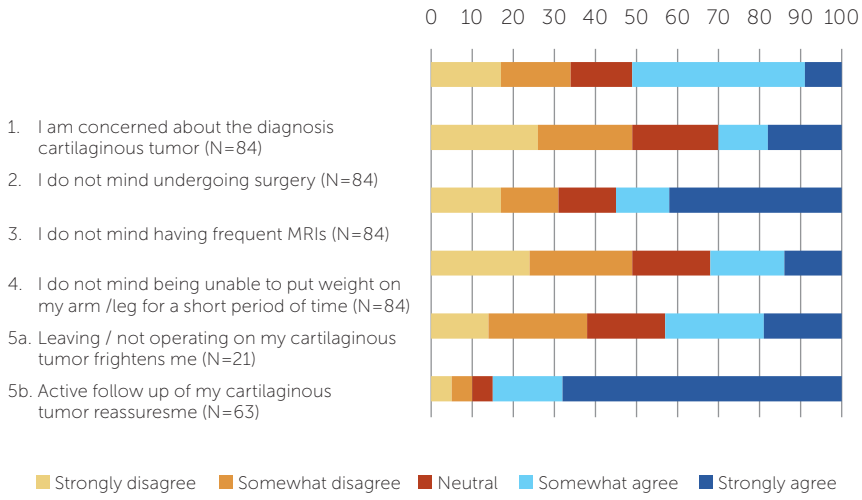

Figure 1: Answers of the patients values and preferences (in %).

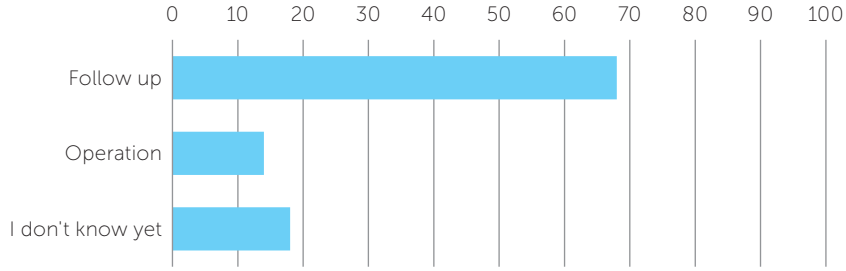

Figure 2: Patients answers of preference question 6: "At this moment my preference is:" (in %).

Outcomes of treatment

During the study period, a total of eleven (13%) patients underwent surgical treatment, seven (8%) of which based on physical symptoms/pain or tumour growth.

None of the patients who preferred active surveillance, underwent surgery during the follow-up period.

Nine of twelve patients who initially indicated a preference for surgical treatment, proceeded to surgery. Six out of these nine underwent surgical treatment based on physical symptoms/pain or tumour growth, and three of them based on patient's whish.

Three of twelve patients who initially indicated a preference for surgical treatment, proceeded to active surveillance. During the telephone consultation with the clinician, during which the patients' values and preferences were discussed, these patients, in a shared decision, changed their initial preference for treatment.

Two of fifteen patients, who initially had no specific management preference, underwent surgery, after shared decision-making. In one patient it was based on his personal wish and in the other case on physical symptoms/pain.

Outcomes related to patients experience of the decision aid content

Information on how patients experienced the content of the decision aid was documented in 36 electronic health records. The responses showed that the majority of patients felt that the information in the decision aid was found to be comprehensive and understandable, that it contributed to the verbal information provided during the hospital visit, and that it supported patients in making a management decision.

Only two patients stated that the decision aid did not offer new insights, as the information during the hospital visit had been clear enough.

Discussion

This study shows that, after receiving information provided by the decision aid, patients are able to indicate their preference and that, for most patients, this preference corresponds to the eventual management.

With the introduction of the decision aid, we have sought to comply with the principles of shared decision making[23]. Information about the diagnosis and treatment options is provided, patient values and preferences are explored and discussed with the physician or nurse practitioner, and a final decision is made. However, the decision aid is just a tool to support patients in shared decision making and is a useful supplement, but it cannot replace the consultation in clinical practice[18].

Despite the explanation of the behaviour of the tumour, most patients are concerned about the diagnosis. However, a majority finds undergoing surgery objectionable and most do not mind having frequent MRI scans. When a well-informed decision choice is made to follow the course of the tumour over time and to avoid an operation, an operation is usually not required, unless there are changes in the appearance on imaging or the patient develops symptoms. Therefore, we have been able to refrain from surgery in patients with ACTs in over 90% of the cases, where surgery had previously been the standard of care. This huge decrease in surgery rate can be contributed to both new pathophysiological insights as well as patient involvement and shared decision making. This results in a reduction of preventable surgical complication rates, avoidance of unnecessary post-operative rehabilitation, and reducing costs in healthcare[24-26].

During the study, on the advice of the Dutch Patient Association, one question of the decision aid was changed to ask the question with a more positive spin. The way a question is formulated may influence the answers of respondents[27]. A positive wording leads to a more positive representation of the patient's opinion[28]. After changing the wording of the question, the previous answers to the originally worded questions do not automatically translate to the new question. However, it does provide information on how patients perceive the possible management.

The question (5a in figure 1) whether leaving / not operating on the cartilaginous tumour is frightening was answered with equal numbers of agree and disagree. After changing the question, the majority indicated that conservative management and monitoring of the tumour was reassuring. This also corresponded to the final management choice of most patients. The sum of the provided answers gave the physician and nurse practitioner information about the patient's values and preferences, and this facilitated final decision making.

The limitation of our study is that patients were not initially involved in the development of the decision aid. During implementation, we realized this and presented the decision aid to the Dutch Patient Association for comment and review. This does not substitute for direct input from the main users/target of the decision aid and could have prevented modification of a question.

Furthermore, we did not record the patients expectations and preferences during their first consultation in our outpatient clinic, before providing the information. Although it is known that patients often do not have clear preferences at the outset, we have no insight into the possible change of mind of the patient by the provided verbal and written information[29]. As a control group of patients who received only verbal information was not available in this study, the actual impact of the additional written information on the final preferred management of the patient was not measured.

We also lack information about the impact this decision aid may have on the possible change of perception and understanding of the information given to the patients by the health professional during the initial consultation. Awareness of the content of the decision aid may lead to bias of the physician or nurse practitioner, allowing them to provide information more extensively after the implementation of the decision aid. Furthermore, the way a physician or nurse practitioner provided the information in the consultation, and whether the physician's choice or recommendation for treatment was discussed with the patient, was not recorded. Communicative behaviours of physicians have great influence on certain patient outcomes[29]. Patients are more likely to choose recommended treatments when communication is satisfactory[30]. On the other hand, we know that after an initial consultation with a physician, very little medical information is remembered, and that the amount of retained information will decrease over time[31]. Studies have

shown that written information supports verbal information and contributes to a better consideration of choices[13,32]. This is confirmed by the patients' answers to the question on how the information in the decision aid was experienced.

Evaluation of patients' experience with the decision aid was documented only in 36 files. The vast majority of those patients were positive. For the remaining patients, we have no formal data, but we experienced that the patients were very positive about it during the follow-up period. Therefore, we do not think that the experience of the 36 patients is a selection bias.

This study provided information about patients' values and preferences related to the treatment of ACT. Further studies should focus on the actual effect of the decision aid on joint decision-making. The Shared Decision Making Questionnaire (SDM-Q) is a reliable and brief instrument that can be used to assess the effectiveness of the implementation of the decision aid on shared decision making[33].

Conclusion

After implementation of the digital decision aid none of the patients who opted for active surveillance revised their choice during follow-up. We experienced that a decision aid helps to inform patients about their diagnosis and management options, and patients can make informed choices about their treatment preferences. Clinicians became more aware of patients' values and preferences so that they could reach a shared decision about treatment.

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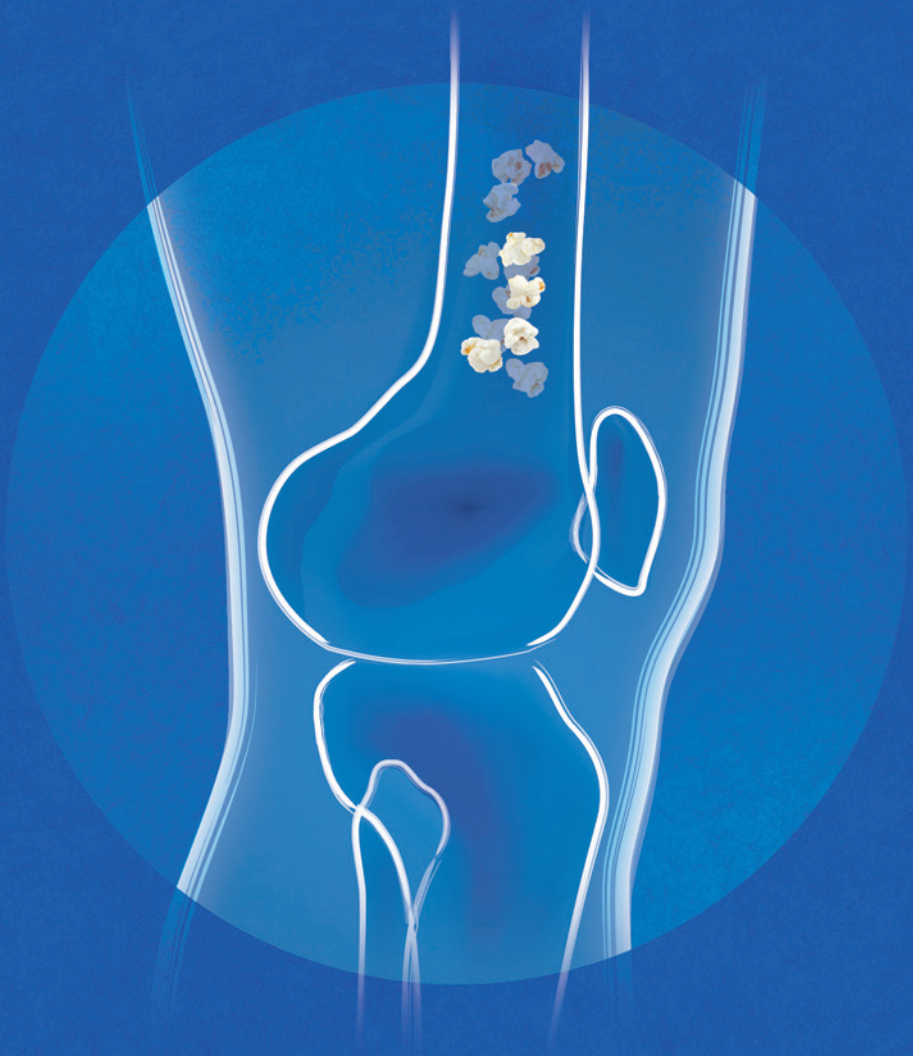

CHAPTER 7

Active surveillance of atypical cartilaginous tumours of bone: short term quality of life measurements

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Abstract

Background: In the recent years active surveillance has been introduced for atypical cartilaginous tumours(ACTs). This is the first study on the impact of this new treatment approach on patients' quality-of-life. We evaluated general health-related quality of life (HRQL) in patients diagnosed with enchondroma or ACT.

Methods: In this prospective study, patients recently diagnosed with enchondroma and ACT of the long bones were asked to participate. Health-related quality of life (HRQL) was assessed at diagnosis and at six month follow-up, using the 36-item Short Form Health Survey (SF-36) and Numeric Pain Rating Scale (NRS). HRQL of the active surveillance group was compared to the Dutch population and a Dutch sample with locoregional cancer.

Results: In total, 45 patients were included in the study, of which four patients underwent curettage and cryosurgery, 41 patients were under active surveillance. The HRQL of the active surveillance group seemed lower compared to the Dutch population, but similar to patients suffering locoregional cancers. No comparison between the surgery and the active surveillance group could be made. In the active surveillance group no statistical difference was found between baseline and six months follow-up regarding HRQL and pain during rest and activities.

Conclusion: Patients diagnosed with non-malignant chondroid tumours have lower HRQL compared to the healthy population. Active surveillance had no adverse effect on patients well-being, after six months active surveillance the HRQL remained unchanged. Interestingly, in our study no impact on mental health was seen, implicating that diagnosed but untreated chondroid tumours do not seem to influence patients anxiety.

Introduction

Enchondroma and atypical cartilaginous tumours (i.e. chondrosarcoma grade 1) are primary bone tumours consisting of cartilaginous matrix [1]. Over the last decades, an increase in incidence of enchondroma and atypical cartilaginous tumours (ACT) has been observed, probably due to the increased detection rate of asymptomatic tumours[2,3]. They are nowadays the most common primary bone tumours[2,3].

Enchondroma are benign inactive bone tumours and patients with enchondroma are commonly discharged from follow-up[1]. For patients with ACT, an intermediate grade tumour, intralesional surgery with local adjuvant therapy is recommended[1]. Morbidity of this treatment is low but complications such as postoperative fractures, infection, and local recurrence do occur[4,5]. The necessity of surgical treatment for ACT lesions has been subject of debate the last years for several reasons[6]. First, in most patients incidental found cartilaginous tumours are asymptomatic and development of clinical manifestations over time is rare[7,8]. Secondly, with the current standards for treatment of cartilaginous tumours in mind, the diagnostic challenge to differentiate enchondroma from ACT due to the numerous similarities on imaging[9], results in a therapeutic dilemma.

ACT are nowadays defined as intermediate type tumours, with non-metastatic potential, instead of malignant cartilaginous tumours[1], and refraining from surgery might be an attractive treatment strategy[3,7,10,11]. In the recent years active surveillance has been introduced for ACT to prevent over-treatment. In active surveillance regular radiologic follow-up is performed to monitor the tumour[7,11]. If the tumour shows any signs of progression (e.g. growth or pain) the tumour can still be removed by performing intralesional surgery with local adjuvant therapy. Omlor et al. showed that surgery of enchondroma and ACT did not prove superior compared to conservative clinical and radiological observation, whereas the conservative approach showed a significantly better functional outcome compared to the surgical treatment[10].

The impact of this new conservative treatment approach on the patient's quality-of-life should also be considered. It could be argued that the burden of diagnosed but untreated disease outweighs the benefit of withholding surgery. Active surveillance might be new for non-malignant cartilaginous tumours (i.e., enchondroma and ACT) but in several other fields in oncology it is already a common treatment method. Studies performed in the field of prostate cancer have shown that active surveillance has no major adverse effect on patients wellbeing[12,13].

Currently, no evidence exists on how active surveillance for patients with chondroid bone tumours impacts patients' quality of life. In this prospective study we evaluated general health-related quality of life (HRQL) in patients diagnosed with non-malignant chondroid tumours. HRQL was measured after diagnosis and during follow-up, changes over time were investigated.

Methods

This prospective study was designed as a single-centre observational study and follows the STROBE guidelines[14]. From April 2018 till July 2020, all adult patients referred to our orthopaedic oncology outpatient clinic with a recently diagnosed chondroid tumour in the long bones were asked to participate in this quality-of-life study. Patients with suspected high-grade chondrosarcoma on imaging (e.g. cortical destruction, soft tissue extension), Ollier or Maffucci disease, tumours localized juxtacortical or in the axial skeleton were excluded, because these tumours have a more aggressive biological behaviour[1]. Patients who underwent previous treatment elsewhere were also excluded. For the purpose of this study patients with enchondroma or ACT of the long bones were included in this study when they completed both the questionnaires at baseline and at six months follow-up assessment.

This study has been reviewed and approved by the ethics committee of our hospital on the basis of the Dutch Code of conduct for health research, the Dutch Code of conduct for responsible use, the Dutch Personal Data Protection Act and the Medical Treatment Agreement Act. Exemption was obtained as the Medical Research Involving Human Subjects Act does not apply for this study. Written informed consent was obtained from all patients included in this study.

During the first consultation, diagnosis and treatment options (active surveillance versus intralesional surgery with local adjuvant treatment) were discussed with the patient. A digital decision aid developed by our team was available for patients to provide them with up-to-date information on the diagnosis and current treatment options. After one week, wherein the patient could have studied the digital information, and discussed the options with relatives, the patient was called by the nurse practitioner or the orthopaedic oncologist to decide on the treatment.

If patients chose surgery, they were treated with curettage and cryosurgery (CC-group), and depending on the bone defect osteosynthesis (plating) was used[15]. Postoperative follow-up consultations were planned at six months and at 18 months after the treatment. If patients chose for active surveillance (AS-group) then radiologic follow-up, preferably magnetic resonance imaging (MRI), was performed at six months and at 18 months after diagnosis[7]. Depending on radiologic criteria and clinical manifestations, radiologic follow-up was continued every year or every two years. Patients included in the current quality of life study were sent digital questionnaires after the first consultation and at six months after diagnosis, irrespective of the chosen treatment. Demographic (age, sex), clinical (referral, tumour size, location) treatment (surgery, surveillance) and outcomes data were collected as part of routine follow-up.

Outcome measures

Patient-reported health-related quality of life (HRQL) was measured using the Dutch version of the Short Form-36 (SF-36), a general health assessment instrument[16].

The SF-36 measures consists of eight subscales that can be combined into a physical component summary (PCS) and a mental component summary (MCS) scale. The eight subscales include physical functioning (PF), body pain (BP), general health perceptions (GH), mental health (MH), social functioning (SF), vitality (VT), and role limitations due to physical (RP) and emotional problems (RE). To create the Mental Component Summary (MCS) and Physical Component Summary (PCS) answers were combined using the method as described by Ware et al.[17].

Scores of component scales and subscales range from 0 to 100, with higher scores indicating better HRQL. The SF-36 has been translated and validated to Dutch, norm values are available for the Dutch population[16].

In this study we compared the SF-36 scores of the active surveillance group with norm groups of the Dutch population and a Dutch sample with locoregional cancer[16].

In addition, the Numeric Rating Scale (NRS) for pain, ranging from zero (no pain) to 10 (worst pain imaginable), was measured. The NRS was used for two questions. Patients were asked if they experienced any pain during rest (NRSr) and if they experienced any pain during activities (NRSa) and they rated it accordingly.

Statistical analyses

Baseline patient characteristics were explored for both the study group and the group who did not respond to the follow-up questionnaires, (non-respondents) to exclude any significant differences. Patient who did not complete both questionnaires (baseline and six months) were excluded from further analyses. All continuous variables were visually inspected and tested for normality by the Shapiro-Wilk test. For both AS and CC-group continuous variables are described and presented as the mean and standard deviation (SD) or as the median and inter quartile range (IQR), depending on normality. Categorical variables were described as counts and percentages and compared using the Fisher exact test. To compare non parametric continuous variables of the AS-group between baseline and six months follow-up the Wilcoxon signed rank test was used. Since only four people were included in the CC-group their results of the baseline and six months follow-up were only described.

A sensitivity analyses was performed to analyse if having had the follow-up MRI impacted HRQL after six months. The SF-36 results at six months were compared using the Wilcoxon signed rank test of these patients that already underwent the follow-up MRI, when completing the six months questionnaire, and those patients that were awaiting there follow-up MRI.

All *p*-values were tested two-sided, and a *p*-value of <0.05 was considered statistically significant.

Despite our data being non parametric and to compare results with the Dutch norm groups the results of the current study are presented in figure 1 as mean and standard error (SE). We visually compared the results.

All data was collected from the hospital digital charts by January 2021 and stored in a secured environment by using Castor EDC (Castor electronic data capture, Amsterdam, the Netherlands). Statistical analyses were performed using SPSS 25 software (IBM SPSS Statistics for Windows, Version 25 IBM Corp., Armonk, NY, USA.) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Seventy patients were asked to participate in this study, two of whom did not receive the questionnaires. Of the 68 patients participating, 23 patients were excluded as they did not complete the SF-36 questionnaire at both measurement times. In total, 45 patients (13 male, 32 female) that reported HRQL outcomes, both at baseline as well as after six months of follow-up (response rate 66.2%), were included in the analyses. At baseline, patient characteristics and tumour characteristics for both the study group (n=45) and the non-respondents (n=23) did not differ (Table 1).

Health-related Quality of Life changes

In Table 2 the results of the SF-36 and NRS questionnaires at baseline and follow-up are shown. At both baseline and follow-up, the surgery group (n=4) seemed to have higher pain scores compared to the active surveillance group (n=41) and lower scores on the following SF-36 subscales; body pain and role limitations due to physical function. On the remaining SF-36 subscales the surgery (curettage and cryosurgery; CC) group and the active surveillance (AS) group scored similar results. HRQL changes between baseline and follow-up were tested for the active surveillance group. No comparison between the AS and CC-group was made as only four patients underwent surgery. No significant changes in any of the eight SF-36 subscales (physical functioning, physical role, emotional role, vitality, mental health, social functioning, bodily pain, general health) were seen when baseline results were compared to six months follow-up. Nor did any significant changes occur in the physical and mental health component scores over time.

Table 1: Patient characteristics.

	Study group (n=45) *n* (%)	Non-respondents (n=23) *n* (%)	*p*-value
Mean age ±SD	52 ±10.9	54 ±12.8	.32
Gender			.55
Male	13 (28.9)	7 (30.4)	
Female	32 (71.1)	16 (69.6)	
Treatment			.44
Surveillance	41 (91.1)	20 (87)	
Surgery	4 (8.9)	3 (13)	
Lesion location			.56
Upper extremities	17 (37.8)	9 (39.1)	
Lower extremities	28 (62.2)	14 (60.9)	
Lesion size			.65
0 – 2 cm	5 (11.1)	2 (8.7)	
2 – 5 cm	22 (48.9)	13 (56.5)	
5 – 10 cm	16 (35.6)	7 (30.4)	
10 – 15 cm	2 (4.4)	1 (4.3)	
Referral indication			.18
Incidental	39 (86.7)	17 (73.9)	
Pain	6 (13.3)	4 (17.4)	
Second opinion	0 (0)	1 (4.3)	
Unknown	0 (0)	1 (4.3)	

p-values were derived by a paired samples t-test for the variable age, for all the other variables fisher exact test was used.

Fourteen out of the 41 patients (34%) in the active surveillance group had their follow-up MRI before they completed the second questionnaire. To analyse if having had the follow-up MRI impacted HRQL after six months, additional Wilcoxon Signed Rank analyses were performed. No significant differences in any of the eight SF-36 subscales or component scores at six months follow-up were found when the 14 patients who already had their follow-up MRI are compared with the 27 patients still awaiting follow-up MRI.

In addition to the SF-36, NRS pain scores in rest and during activity were measured at baseline and follow-up. The surgery group reported higher pain scores (NRSr median 3.0 [2-6]; NRSa median 6.5, IQR [3-7]), interestingly they did not decrease at six months follow-up. All four patients who went for surgery had their surgery within the first six months after diagnosis. No significant changes between baseline and six month follow-up in pain scores were detected for the surveillance group.

Table 2: HRQL outcomes as measured by SF-36 and NRS compared between baseline and six months follow-up.

	Baseline		Follow-up		*p*-value
	AS (*n*=41)	CC (*n*=4)	AS (*n*=41)	CC (*n*=4)	AS
PF	70 [43-90]	67.5 [61-85]	75 [55-90]	80 [24-88]	.17
RP	75 [0-100]	0 [0-75]	75 [0-100]	0 [0-75]	.88
RE	100 [0-100]	100 [100-100]	100 [33-100]	100 [100-100]	.15
VT	70 [45-83]	65 [45-78]	65 [40-78]	65 [61-69]	.31
MH	80 [68-86]	74 [69-79]	80 [68-90]	80 [73-93]	.55
SF	75 [63-100]	75 [53-97]	87.5 [63-100]	68.8 [16-84]	.17
BP	67.5 [45-85]	50 [45-64]	67.5 [45-90]	51.3 [19-73]	.38
GH	60 [43-80]	60 [56-60]	65 [50-78]	72.5 [70-75]	.82
PCS	44.6 [32-54]	32.9 [32-44]	43.4 [36-52]	36.9 [21-46]	.67
MCS	54.8 [39-59]	56.6 [52-59]	54.2 [45-60]	56.8 [55-59]	.59
NRSr	1.0 [0-5]	3.0 [2-6]	1.0 [0-5]	2.5 [0-7]	.35
NRSa	3.0 [0-6]	6.5 [3-7]	2.0 [0-6]	6.0 [2-8]	.87

Values are presented as median [IQR]. P-values were derived by performing Wilcoxon signed rank test. AS: active surveillance, CC: curettage and cryosurgery
Physical function (PF); role limitations due to physical (RP); and emtional problems (RE); vitality (VT); mental health (MH); social functioning (SF); body pain (BP); general health (GH), physical component summary (PCS), mental component summary (MCS). NRSr: NRS score in rest, NRSa: NRS score during activity

HRQL of the Active Surveillance (AS) group compared to Dutch norms

As depicted in Figure 1, subscales of the SF-36 at baseline and follow-up of the active surveillance group were compared to data of a healthy Dutch norm group. The active surveillance group showed comparable scores in mental health but lower results on most subscales.

Visual comparison of the current study results with a Dutch sample with local regional cancer (LRC) shows similar results on most subscales (PF, RE, VT, MH, SF, GH). The LRC group scored lower on role limitations due to physical problems (mean 36, SE 2.4) but scored slightly higher on the subscale body pain (mean 73, SE 1.4).

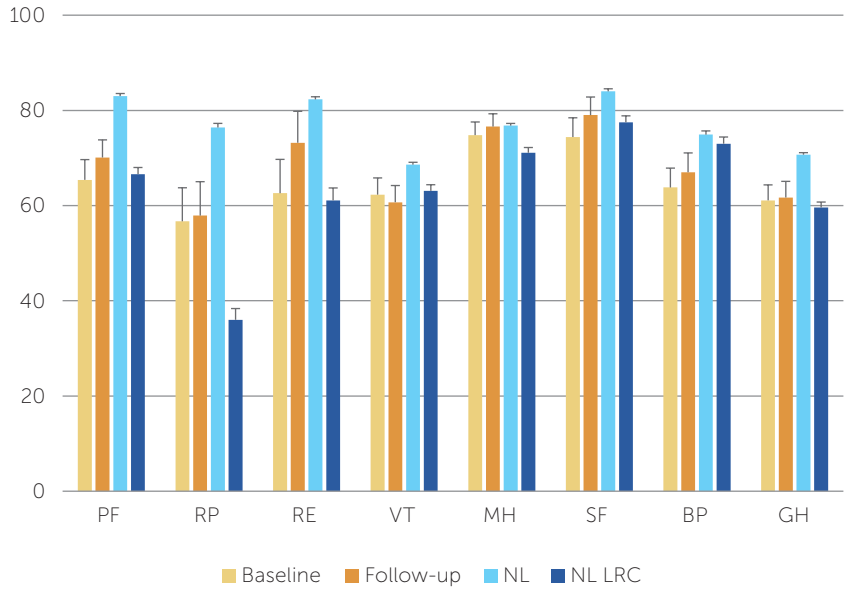

Figure 1: Comparison of SF-36 subscales.

Active surveillance group (n=41) at baseline and follow-up compared to Dutch population (NL, n=1742), Dutch population suffering local regional cancer (LRC, n=286).
Bars reflect mean SF-36 scores and standard error of the mean (SE).
Physical function (PF); role limitations due to physical (RP); and emotional problems (RE); vitality (VT); mental health (MH); social functioning (SF); body pain (BP); general health (GH).

Discussion

In this study we evaluated the health-related quality of life (HRQL) of patients with chondroid tumours, without malignant characteristics, located in the long bones. This is the first study that reports HRQL of patients with chondroid bone tumours under active surveillance. It is important to explore if the burden of diagnosed but untreated disease outweighs the benefit of refraining from surgery. HRQL was measured after diagnosis and during follow-up, no changes in HRQL over time were found. Compared to the Dutch population the active surveillance group scored lower on most SF-36 subscales, however results were similar when compared with patients suffering local regional cancers[16].

Of the 45 patients included in this study only four patients opted for surgical treatment whereas the majority, 41 patients, chose active surveillance. The high rate of patients choosing active surveillance might be caused by the available decision aid.

It is known that the use of decision aids tends to shift patients preferences towards non-surgical interventions[18]. We were unable to apply statistical methods on the surgical treatment-group (CC-group), as only few patients chose surgery. In the active surveillance-group (AS-group), no significant changes in any of the eight SF-36 subscales, SF-36 summary scores, and NRS pain scale could be observed when baseline results were compared with six months follow-up. This indicates that active surveillance has no adverse effect on patients wellbeing over time, between diagnosis and 6 months later.

Interestingly, the CC-group reported high pain scores preoperatively, which did not decrease several months after surgery (Table 2). These pain complaints might still be explained by the surgery performed due to the relative short follow-up of this study. Omlor et al. reported results after 24 months follow-up and showed that the surgically treated patients had worse results for pain compared to conservatively treated patients[10]. Surgery is often advised when patients experience pain, however it has not been proven to diminish pain complaints. It should be considered that pain might not be related to the tumour nor the operation but to adjacent pathology instead.

In this study we were not able to compare results between surgery and active surveillance, due to the small surgery group. There were no studies found in literature reporting results of all SF-36 subscales of patients with chondroid tumours treated with intralesional surgery. Van der Geest et al. reported in their study only the physical functioning subscale (mean 58; SD 29), which was significantly lower than the norm scores of the Dutch population and seems lower than our results of the AS-group[19]. Shchelkova et al. reported results of the SF-36 of 22 patients with chondrosarcoma (ACT and grade 2 chondrosarcoma) but it is not reported if these patients were operated on[20].

Since there is little knowledge on HRQL after intralesional surgery of chondroid tumours it is difficult to put our HRQL results of active surveillance in context.

We visually compared the results of the SF-36 subscales of our AS-group with the Dutch population (Figure 1). HRQL of our study group seemed lower on all subscales with the exception of the subscale mental health (MH). As there are several similarities between the SF-36 mental health subscale and typical depression and anxiety screening questionnaires we presume that diagnosed but untreated chondroid tumours do not seem to influence patients anxiety. In addition, the mental health component score (MCS) at six months follow-up assessment was 57 (IQR 52-59) whereas the threshold for mental disorder is a MCS of $\leq$38[21].

On the other subscales the AS-group seems to score lower, implicating that diagnosis and treatment of non-malignant chondroid tumours impacts HRQL negatively. Visual comparison showed the greatest difference on the subscales

physical function (PF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), body pain (BP), and general health (GH). The lower scores on the subscales PF, RP, and BP were unexpected, as 87% of the included tumours in our study are incidental findings on imaging and therefore assumed to be asymptomatic. Adjacent pathology (e.g., osteoarthritis or trauma), the initial reason for performing imaging, might be the reason for the lower HRQL scores. For example, our results on the subscales PF, RP, BP and GH are comparable to the HRQL results of patients suffering osteoarthritis[22]. The SF-36 questionnaire is a general health assessment instrument and comorbidities should have been taken into account. In this study, 87% of the patients suffered from health problems leading to having imaging performed. We did not have information on patients comorbidities. For this reason, we cannot conclude that the lower HRQL of the patients in this study was solely caused by the diagnosis and treatment of chondroid tumours.

In addition to the healthy Dutch population, we also visually compared our results with patients suffering from local regional cancer (LRC). Except from the subscale bodily pain (BP) the LRC-group scored similar or lower compared to the AS-group.

Visual comparison showed the greatest difference on the subscale role limitations due to physical problems (RP). This could be explained by the chemotherapy and/or radiotherapy treatment received by the patients in the LRC-group.

The AS-group scored lower than the Dutch population on the subscale role limitations due to emotional problems (RE). Compared to the LRC-group, results on the subscale RE were similar.

However, as shown in figure 1, an increased trend is seen in the subscale RE after six months follow-up, reporting higher results than the LRC-group. Presumably, a longer follow-up could potentially show a significant increase in the subscale RE as patients might be reassured of the non-malignant character of the tumour when the tumour remains stable during follow-up.

To our knowledge, this is the first study performed evaluating the HRQL of patients with chondroid tumours who underwent active surveillance, hence comparison with similar studies could not be made. Therefore, we broadened our view and searched for published results in related oncological fields where active surveillance is more common. Studies on chronic lymphocytic leukaemia and prostate cancer show contradictory results: in most cases those on active surveillance reported higher HRQL compared with those undergoing treatment but a few studies showed that those on active surveillance experienced greater anxiety and depression[23]. As reported in the systematic review of Kim et al., including 73 studies, patients with chronic lymphocytic leukaemia or prostate cancer were dissatisfied with the information received[23]. The experienced lack of information could be an explanation

for the increased anxiety and depression. It is known that education and communication alleviates anxiety and improves the sense of patients control of the situation[24]. We have provided the patients in this study with a digital decision aid which could explain why we did not find any impact of active surveillance on the mental health subscale. Decision aids improve people's knowledge and reduce the decisional conflict[18].

Several limitations should be discussed. First, this study lacked data on employment status, socioeconomic status, marital status, and education level, all factors that could influence HRQL. The impact of comorbidities should also have been taken into account. It is common that chondroid tumours are incidental findings on imaging performed for adjacent pathology, such as osteoarthritis. It is known that musculoskeletal disease have a substantial impact on HRQL[22]. We hypothesize that when patients suffering from musculoskeletal diseases such as osteoarthritis were excluded from our study sample, the reported HRQL of patients with chondroid tumours would have been higher.

The HRQL in this study can therefore be influenced, either positively or negatively, by different potentially influencing factors that were not measured.

Second, this study was limited by the skewedness of the data. To be able to compare the results of the SF-36 questionnaires with the Dutch population the mean and standard error were reported despite the skewed distribution of our data. As such, no statistical methods could be applied to compare the data and only visually inspection was performed. In addition, no comparison between the AS and CC-group could be made as only four people in this study opted for surgery. We don't know if surgery might have increased the patients HRQL at follow-up. Therefore we cannot fully answer the question if the burden of diagnosed but untreated disease outweighs the benefit of withholding surgery.

Third, this study reported the results of short-term HRQL and future research using long-term HRQL is recommended. Active surveillance for chondroid tumours without malignant characteristics is becoming more popular, as such report of the current first short-term HRQL results is acceptable.

In conclusion, patients diagnosed with non-malignant chondroid tumours have lower HRQL compared to the healthy population. Interestingly, in our study no impact on mental health was seen, implicating that diagnosed but untreated chondroid tumours do not seem to influence patients anxiety. Furthermore, active surveillance had no adverse effect on patients wellbeing, no statistical difference was found between baseline and six months follow-up regarding HRQL and pain during rest and activities. It is important that orthopaedic oncologist are aware of the lower HRQL of patients diagnosed with non-malignant chondroid tumours and educate their patients to alleviate anxiety.

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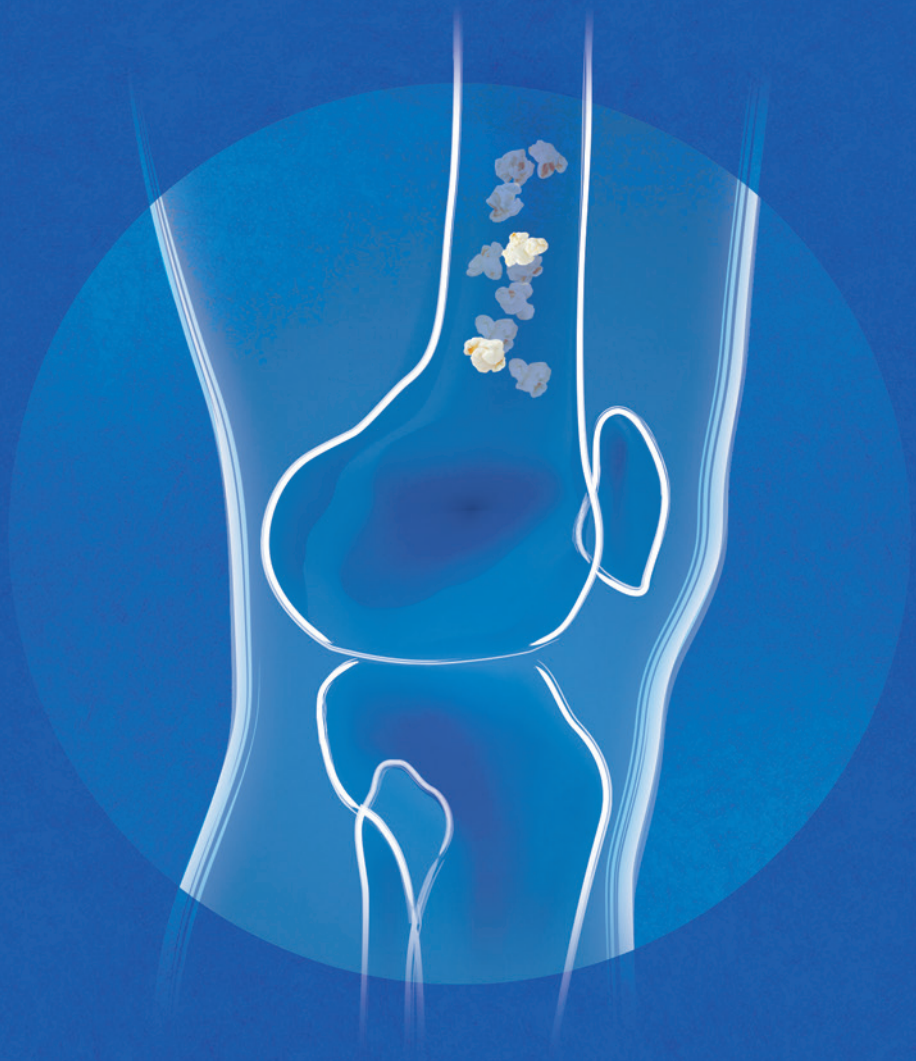

CHAPTER 8

General discussion and future perspectives

As outlined in the general introduction, due to the latest insights in the field of chondrosarcoma a new perspective on the treatment of atypical cartilaginous tumours (ACTs) is required.

The objective of this thesis is to evaluate current practice regarding atypical cartilaginous tumours (ACTs), exploring its natural course and determine the feasibility of active surveillance. Specific aims were formulated and outlined in **chapter 1**. In this chapter we will discuss the main findings of this thesis and their implications for clinical practice and future research.

Aim 1: To provide an overview of MRI characteristics used to date to differentiate atypical cartilaginous tumours and high-grade chondrosarcoma

To successfully implement active surveillance for ACTs, accurate differentiation between ACT and high-grade chondrosarcoma (i.e. chondrosarcoma grade 2 and grade 3) is of paramount importance. Due to the aggressiveness of high-grade chondrosarcoma (HGCS) these tumours should not be erroneously diagnosed as ACT and consequently radiologically followed-up. Several studies have investigated MRI characteristics to differentiate chondrosarcoma. In **chapter 2,** a systematic review is presented of MRI characteristics used to date to differentiate ACT from HGCS. We concluded that MRI may possibly be helpful to differentiate ACT from HGCS. Several MRI characteristics were analysed of which entrapped fat presents more often in ACT. Compared with ACT, HGCS may present more often with the following MRI characteristics: loss of entrapped fatty marrow, cortical breakthrough, and extraosseous soft tissue expansion (**chapter 2**, Figure 2). These findings are in line with the more aggressive behaviour of HGCS; actively infiltrating between individual fat cells and invasion of Haversian systems resulting eventually in cortex destruction and soft tissue expansion. Thorkildsen et al. reported in their prognostic observational study that presence of soft tissue expansion is an independent predictor of adverse levels of local recurrence, metastasis and disease specific survival[1]. Their findings underline that tumours with soft tissue expansion should not be radiologically followed-up but require surgical treatment.

In our systematic review we only provided non-statistical syntheses due to substantial heterogeneity (I^2 50-90%). Heterogeneity could be explained by clinical diversity between the included studies. In most studies different tumour locations (e.g. phalanges, femur) as well as types of bone (e.g. flat, long bones) were included, which might show different clinical behaviour and radiologic appearance[2]. Heterogeneity could also be explained by poor reliability for grading of cartilaginous tumours. Dr. Aboulafia stated in a commentary article which was aptly named "*If You Don't Know Where You're Starting from, You Can't Get Directions*" that the literature has been clouded by a lack of agreement as to the criteria for distinguishing

low-grade chondrosarcoma from active enchondroma and grade 2 chondrosarcoma[3]. The SLICED study group and Zamora et al., reported poor inter observer reliability for radiologist (Kappa 0.35), pathologist (Kappa 0.44) as well as orthopaedic oncologist (Kappa 0.44)[4,5]. In both studies MRI was not available in all cases, though reliability for radiologic classification increased when MRI was available (Kappa 0.44)[4]. Differentiating enchondroma from ACT in the long bones is very difficult due to the similarities on imaging. This diagnostic challenge contributes to the poor reliability for grading of cartilaginous tumours[6]. With the introduction of active surveillance of both enchondroma and ACT, differentiating these tumours has become less clinical relevant. When pre-operatively differentiating cartilaginous tumours in the long bones, one should focus on accurately differentiating HGCS from non-malignant cartilaginous tumours. A recent study differentiating ACT from HGCS on MRI reported a very good inter-observer correlation for MRI grading of these cartilaginous tumours (Kappa 0.94). Furthermore, an overall accuracy of 92% for predicting HGCS/dedifferentiated chondrosarcoma was achieved[7], which is in line with Zamora et al. Despite the low inter observer agreement found in their study, none of the evaluators proposed observation or follow-up for HGCS. This implicates that the risk of erroneous radiologic follow-up of HGCS is low if active surveillance for ACT is implemented. This is confirmed by the natural course studies in this thesis, where not a single HGCS was erroneously included.

Aim 2: To study the oncological results of the current treatment method (curettage and cryosurgery) for atypical cartilaginous tumours as well as associated complications.

Several authors questioned whether the negative side-effects of treating the rapidly growing group of patients diagnosed with ACTs with intralesional surgery outweigh the potential benefits. They have proposed active surveillance instead. However, the so called benefits and negative side effects of intralesional surgery are still vague. As shown by the systematic review of Dierselhuis et al., current literature mostly consist of small sample studies and widely varying rates of local recurrence and complications are reported[8].

At our institution curettage and cryosurgery is the current surgical treatment method for ACTs. Previously a high complication rate of 21% was reported, mainly due to a high amount of post-operative fractures[9]. As a result, more prophylactic plating has been applied and full weight bearing was postponed. In **chapter 3** the recent oncological results of cryosurgical treatment for ACTs in a large group of patients, as well as associated complications is reported.

Five tumours were diagnosed postoperatively as chondrosarcoma grade 2, and thus erroneously treated with curettage and cryosurgery. These tumours were

preoperatively graded ACTs according to the biopsy specimen, despite the characteristics of HGCS on MRI. It is known that tumour heterogeneity can result in mismatch between biopsy tumour grade and definitive tumour grade, mismatches of 22% and 18% have been reported[7,10]. For this reason biopsies are nowadays sparsely performed in our hospital, we rely on MRI to grade cartilaginous tumours.

Very good oncological results were achieved for the 174 enchondroma and ACT cases included, with a recurrence free-survival of 97% and no metastatic disease. Our oncological results are comparable with other case series in which curettage with local adjuvant treatment is applied[8]. The question is whether these good oncological results are caused by the surgical treatment or due to the very mild natural behaviour of these tumours. We know from experience that residual tumour tissue behaves benign, in this study the residual rate was 11%. As the objective of curettage and cryosurgery is complete tumour removal, the effectiveness should be questioned. Other studies performing curettage and phenolisation instead of cryosurgery reported residual rates of 5%[11] and 8%[12], suggesting that the type of adjuvant used has little to no effect on the residual rate.

No transformation of tumour grade was seen in our study despite the impression created in two cases. Both cases were erroneously diagnosed as ACT postoperatively, in retrospect grade 2 characteristics were already visible in the specimens. Literature reporting tumour transformation of ACT might as well have included underdiagnosed HGCS in their studies[13-15]. For example, Leerapun et al. reported transformation of ACTs, but included tumours with cortical disruption and soft tissue extension which, with current knowledge, would have been treated as HGCS[15].

There are several disadvantages of curettage and cryosurgery worth to mention. To prevent fractures postoperatively, full weight bearing of the affected limb is discouraged for several weeks, impacting patients daily life. Compared to our previous study our postoperative fracture rate decreased from 14% (*n*=18) to 5% (*n*=9). In total, 20 complications (11%) occurred due to curettage and cryosurgery, of which seven required surgical intervention; six fractures and one neuroma removal. Our reoperation rate was considerable, in total 24% of the patients were reoperated during follow-up, largely due to removal of osteosynthesis material (18%). On top of that, 55 tumours (31%) might have been operated on unnecessarily as they were postoperatively diagnosed as an enchondroma. Enchondroma are benign tumours and therefore can be discharged from follow-up if the tumour does not cause complaints. It is however extremely difficult to differentiate enchondroma from ACTs, which explains the high amount of enchondromas in our study. This also applies for the study of Omlor et al., comparing conservative and surgical treatment of non-malignant cartilaginous tumours in the long bones, 79% of the cases in the surgical group were enchondroma[16]. More important

however, is their finding that surgically treated patients showed worse results for functional limitations, pain, and the MSTS score compared to conservatively treated patients.

All in all, it seems that for intralesional surgery of non-malignant cartilaginous tumours of the long bones the negative side effects indeed outweigh the potential benefit. This is especially true for the large group of asymptomatic patients with incidental detection of ACT. Only when patients suffer from symptoms the balance of medical benefits and harms changes; benefits are more likely and harms more acceptable[17].

Aim 3: To evaluate the natural course of atypical cartilaginous tumours and study the feasibility of active surveillance.

Active surveillance instead of surgery for ACTs in the long bones prevents overtreatment, resulting in less morbidity and less costs. Implementation of active surveillance is hampered by the sparse knowledge of the natural course of these tumours since surgery is the standard of care. In **chapter 4** the natural course of conservatively treated enchondroma and ACTs in the long bones is evaluated. Due to the similarity of imaging characteristics of enchondroma and ACT in the long bones, all cases in this thesis diagnosed based on only imaging methods were diagnosed enchondroma/ACT. This small series of 49 cases was one of the first studies evaluating the natural course of non-malignant cartilaginous tumours in the long bones. Active surveillance seemed promising, as none of the tumours transformed to HGCS and operation rate after choosing active surveillance was low. Only 6% of the studied cases had a medically grounded indication (i.e. pain or growth) for surgery. Notable is the fact that in three cases (6%), patients revised their choice for conservative therapy. We were cautious and operated cases with only minimal tumour growth whereas we nowadays continue follow-up if tumour growth is not combined with malignant characteristics (i.e. cortical breakthrough, loss of ring and arc enhancement).

To aid in the development of evidence-based follow-up guidelines, MRI characteristics on the first and last MRI of 128 tumours were analysed in **chapter 5**. After a mean time of 50 months (range: 25 – 138 months) no change occurred in 51% of the tumours included, whereas tumour progression was seen in 13%. All 17 cases with progression of tumour showed increased size, but only eight cases (1.5%) showed growth over time of more than 5mm. Tumour growth was seen in relatively small tumours (size ranged from 12 to 64mm) and patients in the progression group were significantly younger. Implicating that small tumours and tumours in young patients might have more potential to show progression and should be followed-up.

An important finding of our study was the large group of cases (36%) that showed regression during follow-up. Entrapped fat was present at diagnosis in majority (87%) of the cases that underwent regression and might predict benign biological behaviour.

Based on the findings in this thesis we would recommend active surveillance using MRI for ACT, irrespective of tumour size and tailor follow-up according to biological behaviour.

Some studies imply that small tumours (<4cm) can be discharged from follow-up, however we found mainly small tumours showing tumour progression. One could hypothesize that larger tumours (>10cm) might be less interesting for follow-up, as they have shown no development of malignant characteristics whilst growing. Since we still do not understand if and how malignant transformation occurs we would advise not to discriminate tumours based on size.

The frequency and duration of active surveillance is up to debate. We began active surveillance with frequent follow-up as knowledge of the natural course was sparse. The six month follow-up was a built in safety to catch underdiagnosed HGCS. This might be unnecessary since we saw no HGCS in our studies or extensive growth at six months. However, a recent study by Davies et al. using the Birmingham Atypical Cartilage Tumour Imaging Protocol (BACTIP), did find excessive tumour growth in two tumours after five and seven months, and both were diagnosed as HGCS[18].

We agree with our colleagues from Birmingham that we must prevent active surveillance to become a never ending cycle of follow-up. Therefore it is important to tailor follow-up to biological behaviour. As shown in **chapter 5,** and as well by Chung et al., a rather large group of these tumours are regressive over time, hence not in need of active surveillance[19].

Ideally in the future we are able to predict which tumours will show progression or regression, and adjust our treatment accordingly.

Aim 4: To study the impact of active surveillance of atypical cartilaginous tumours on the quality of life in patients.

Due to the new insights in the biological behaviour of ACT and the negative side effects of surgical treatment we started with active surveillance at our institution. Patients were often referred from other hospitals with the intention of surgical treatment as that had been the standard of care. To inform patients on the treatment changes a digital decision aid was developed, informing patients on both active surveillance as well as surgical treatment with curettage and cryosurgery. Definitive treatment decision was based on shared decision making.

In our first active surveillance study (***chapter 4***), 6% of the patients revised their choice for conservative therapy towards surgical therapy during follow-up. After

implementation of the digital decision aid none of the patients who choose active surveillance revised their choice during follow-up. As reported in **chapter 6,** only 5% of the patients underwent surgery based on patients' preferences only.

From additional questions to determine patients' values and preferences we learned that only one third of the patients minded having frequent MRIs. We were surprised to find out that one third of the patients did not mind undergoing surgery and subsequently be restricted on weight bearing of the affected limb for several weeks. This rather high percentage might be caused by the fact that despite the information given, half of the patients were still concerned about the diagnosis cartilaginous tumour.

It could be argued that the burden of diagnosed but untreated disease outweighs the benefit of refraining from surgery. The impact of this new treatment approach on the patient's quality-of-life should also be considered. In **chapter 7** we prospectively evaluated general health-related quality of life (HRQL) in patients diagnosed with non-malignant cartilaginous tumours. Despite that half the patients' group after receiving the decision aid was still concerned about the diagnosis, no impact in the subscale mental health was measured. Implicating that diagnosed but untreated cartilaginous tumours do not seem to influence patients' anxiety. Nevertheless the overall HRQL was found to be lower than the healthy Dutch population, but active surveillance had no adverse effect on patients wellbeing. Since ACT are often asymptomatic and detected incidentally the impact of comorbidities should be taken into account. We hypothesize that the lower HRQL found in our patients is mainly caused by comorbidities such as osteoarthritis and not caused by the cartilaginous tumour itself.

Ideally we would have compared the active surveillance group with the intralesional surgery group. During the inclusion period of this study only four patients opted for surgery, which made comparison impossible. Also in literature no sufficient data on HRQL of patients treated with intralesional surgery was found to compare our data with. More research into the HRQL of patients with cartilaginous tumours is needed.

Implications for clinical practice and future research

As shown in this thesis active surveillance should be the treatment of choice for the growing group of patients diagnosed with ACT, to prevent overtreatment of cartilaginous tumours. Refraining from surgical treatment has a positive outcome for the individual patient with less morbidity, and for the society as a whole with reducing medical costs.

Selection of tumours for active surveillance is important as HGCS should not be erroneously followed-up. In chapter 2 we have shown several criteria which are more present in HGCS but we were limited in our analyses by the heterogeneity between studies. To prevent heterogeneity, future studies should be aware not to report different entities of cartilaginous tumours (e.g. appendicular, axial, juxtacortical) under the same title.

In practice cartilaginous tumours are generally not diagnosed based on single radiologic criteria but the presence and/or absence of several radiologic criteria is examined. Upcoming techniques such as Artificial Intelligence (AI) might be of help to improve radiologic differentiation of cartilaginous tumours. Gitto et al. reported their machine learning method was 92% accurate in differentiating ACT from chondrosarcoma grade 2 in the long bones[20]. It is interesting to study whether AI can predict biological behaviour.

Active surveillance consists of strict follow-up with the goal to detect early signs of tumour progression and transformation to HGCS. During the development of this thesis several papers published important findings on the incidence of ACT, as a result the risk of malignant transformation is estimated to be much lower than previously thought (<1% instead of 4-6%)[18,21]. Transformation to HGCS was not seen in any of our studies and slow growth of the tumour occurred only in a small group of patients. It seems that, with current knowledge, active surveillance for all non-malignant cartilaginous tumours is too excessive. Future research should define which cartilaginous tumours are at risk for progression, these should be admitted to active surveillance. All other tumours could be discharged from active surveillance with the instructions to contact their orthopaedic oncologist to get radiologic control on tumour growth when complaints occur. As shown in chapter 5, fat entrapment seems a promising criterium to predict regression. Future research is needed to confirm our hypothesis that tumours with fat entrapment will not show progression and subsequently can be discharged from active surveillance.

In this thesis no clear criteria were defined on when cartilaginous tumours should be operated if they show signs of progression. During the course of this thesis our perspective on when to operate these tumours has changed. In the beginning tumours with only minimal growth have been operated on, whilst today we continue active surveillance if tumour growth is not accompanied with aggressive

radiologic criteria. This thesis includes some large (>15cm) cartilaginous tumours without aggressive characteristics, indicating that tumour growth itself is not a reason for surgery as it occurs as well in benign tumours.

Pain caused by the tumour is a clear indication for surgery, when other possibly pain causing pathologies are ruled out. Radiofrequency ablation (RFA) might be the solution for these patients if the tumour size is suitable (maximum 50 mm). RFA is a minimally invasive treatment with limited effect on functional outcome and low complication rates[22]. Compared to intralesional surgery it allows early postoperative weightbearing, though posttreatment fractures are seen as well.

This thesis contributes to an increasing knowledge of the natural course of ACTs. Based on the results of this thesis we have implemented active surveillance in our institution as the standard of care for ACTs. As a consequence we; 1. decrease preventable surgical complications; 2. avoid unnecessary post-operative rehabilitation and productivity loss due to sick leave; and as a result 3. reduce healthcare costs.

Future research, ideally in a multicentre setting, is necessary to develop evidence based guidelines for active surveillance. Future researchers should be cautious for active surveillance to become a cycle of never-ending follow-up and overutilization of costly advanced imaging should be prevented.

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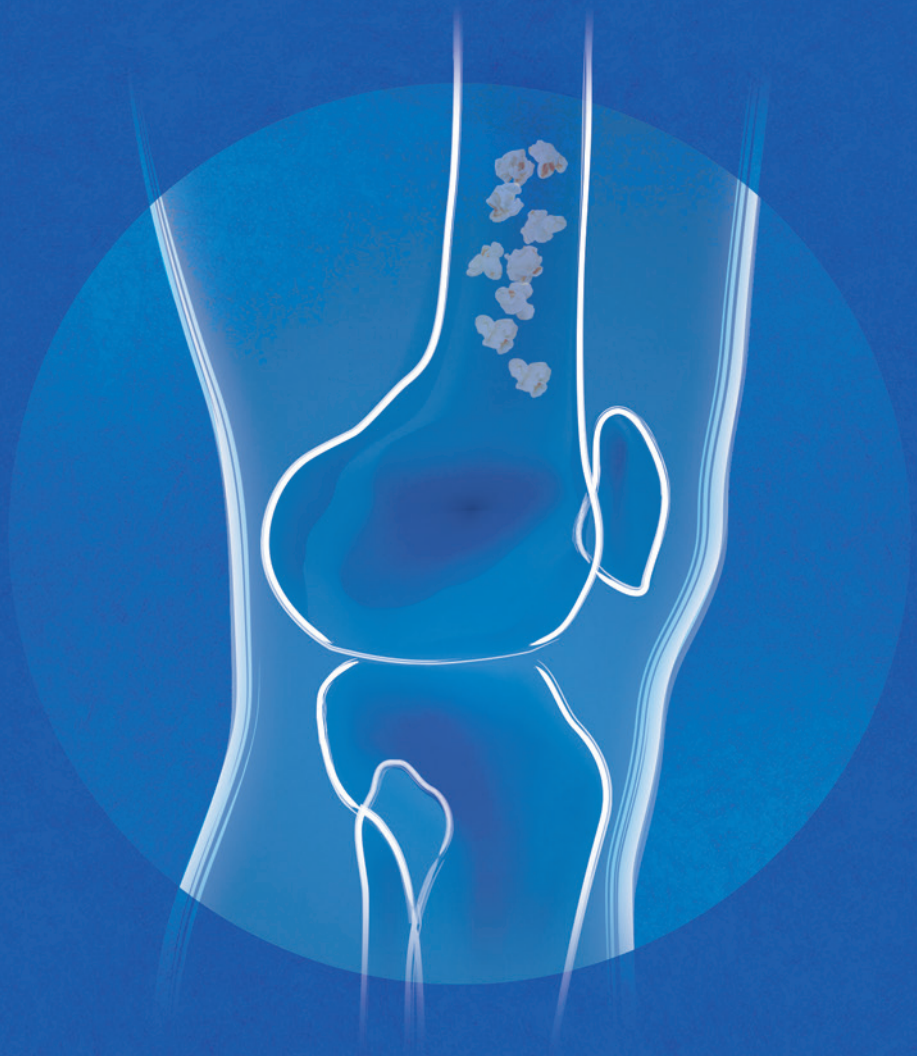


CHAPTER 9

Summary
Samenvatting

Summary

Cartilaginous bone tumours are primary bone tumours with diverse histological and radiological features, which correlate with clinical presentation and prognosis. Enchondroma are benign cartilaginous tumours, whereas chondrosarcoma are malignant cartilaginous tumours. Chondrosarcoma are divided into grades, ranging from 1 to 3, which correlate with aggressiveness. In this thesis we focus on chondrosarcoma grade 1 (CS1). Since 2013 CS1 are considered tumours of intermediate type and are renamed atypical cartilaginous tumours (ACTs) when located in the long bones. ACTs are typically discovered as coincidental finding, hence necessity of surgical treatment for ACT lesions is subject of debate and active surveillance has been proposed to prevent overtreatment.

The objective of this thesis is to evaluate current practice regarding atypical cartilaginous tumours (ACTs), exploring its natural course and determine the feasibility of active surveillance.

Chapter 1 provides an extensive introduction into cartilaginous tumours, diagnosis and treatment options and presents the outline of this thesis.

Since ACTs are nowadays defined as intermediate type tumours, instead of malignant tumours, refraining from surgery might be attractive. These insights make the differentiation between ACT and high-grade chondrosarcoma (HGCS) more clinically relevant. Due to the aggressiveness of HGCS these tumours should not be erroneously diagnosed as ACT and consequently radiologically followed-up. Several studies have investigated different MRI characteristics to differentiate chondrosarcoma, we aimed to provide an overview in **chapter 2**. Based on data from 14 studies, including a total of 239 ACTs and 140 HGCS, we concluded that MRI may possibly be helpful to differentiate ACT from HGCS. Due to the considerable amount of heterogeneity we refrained from pooling the results in a meta-analysis. The non-statistical syntheses provided, showed that extraosseous soft tissue expansion and cortical breakthrough were MRI characteristics more often present in HGCS, whereas entrapped fat was present more often in ACT compared to HGCS .

Chapter 3 presents our current oncological results and complications after curettage and cryosurgery of cartilaginous tumours located in the long bones. In this retrospective study we achieved very good oncological results for enchondroma (n=55) and ACT (n=119), with a recurrence free-survival of 97% and no metastatic disease. In five patients, a grade 2 chondrosarcoma (CS2) instead of ACT was found in the final histopathology after curettage. In these patients, there was a recurrence

free-survival of 60%, stressing the fact that intralesional surgery is not the treatment of choice for CS2, albeit no metastatic disease was reported. Due to more prophylactic plating and postponing of weight bearing, less postoperative fractures occurred (5%). However, the more frequent use of plating contributed to our considerable reoperation rate of 24%. Majority of the reoperations were performed due to removal of osteosynthesis material.

To prevent overtreatment of non-malignant cartilaginous tumours in the long bones, active surveillance has been proposed. The major restraint to implement active surveillance was the lack of knowledge on the natural course of these tumours. Therefore we evaluated the natural course of conservatively treated enchondroma and ACT of the long bones in **chapter 4**. In this small retrospective case series (*n*=49), only 6% had a medical indication for surgery (i.e. growth of the tumour or pain) during follow-up and no transformation to HGCS was seen. All operated cases were histopathologically diagnosed enchondroma or ACT, therefore in hindsight the necessity of these surgical interventions could be debated.

As promising results for active surveillance were shown, we further explored the natural course of enchondroma and ACTs to aid in the development of guidelines for active surveillance. In **chapter 5**, MRI's of 128 conservatively treated non-malignant cartilaginous tumours were analysed, with a minimum interval of 24 months between baseline and last MRI. Our data showed that 51% of the cartilaginous tumours remained stable, whereas only 13% showed some progression (i.e. minor growth) on MRI. Still, none of these progressed tumours developed characteristics of HGCS. Surprisingly, a large amount of the cartilaginous tumours (36%) showed signs of regression on MRI. Entrapped fat was present at diagnosis in majority (87%) of the cases that underwent regression, which might be indicative for the biological behaviour.

Based on these results, we consider active surveillance safe for non-malignant cartilaginous tumours of the long bones. Active surveillance follow-up schemes should be tailored on natural course as we have shown that tumours can either remain stable, show slight growth, or could even regress over time.

The shift in treatment approach from surgical removal to active surveillance calls for adjustment of patient information. To help patients understand the medical information and make a well-informed decision on treatment, we have developed a digital decision aid for patients with an ACT in the long bones. Moreover, patients' motives to opt for one or the other is of interest. In **chapter 6**, we described the development process of the digital decision aid and evaluated the patients'

values and preferences. In total, 84 patients answered the predefined values and preferences questions at the end of the digital decision aid. One third of the patients did not mind undergoing surgery followed by restricted weightbearing for a short period of time. The majority of patients (70%) did not mind having frequent MRIs and 90% found active surveillance of the tumour reassuring.

The impact of this novel conservative treatment approach on the patient's quality-of-life should also be considered, since it could be argued that the burden of diagnosed, but untreated disease outweighs the benefit of withholding surgery. Therefore, in **chapter 7** we evaluated health-related quality of life (HRQL) of 45 patients diagnosed with non-malignant cartilaginous tumours. While patients diagnosed with non-malignant cartilaginous tumours had a lower HRQL compared to the healthy population, no impact the subscale mental health was seen. The lack of change in mental health implicates that diagnosed but untreated cartilaginous tumours do not seem to influence patients' anxiety. Concluding, six months of active surveillance had no adverse effect on patients' well-being.

The content of this thesis explored the usage and (dis-)advantages of active surveillance for ACT in the long bones. We also evaluated the results of surgical treatment of these tumours, showing a considerable reoperation rate. Based on the results of this thesis, active surveillance could become treatment of choice for ACT as it prevents unnecessary surgery and does not impact the quality of life of patients. Importantly, no transformation of ACT to malignant HGCS was seen. On the contrary, we have shown in this thesis that these tumours could become regressive. This thesis contributes to the sparse knowledge of the natural course of cartilaginous tumours and predisposes further research on this topic.

Samenvatting

Kraakbeentumoren zijn primaire bottumoren met diverse histologische en radiologische karakteristieken, welke overeenkomen met de klinische presentatie en prognose. Enchondromen zijn goedaardige kraakbeentumoren, chondrosarcomen daarentegen zijn kwaadaardige kraakbeentumoren. De conventionele chondrosarcomen worden onderverdeeld in verschillende gradaties, van graad 1 tot graad 3, overeenkomend met de agressiviteit. In dit proefschrift focussen we op chondrosarcoom graad 1 (CS1). Sinds 2013 wordt CS1 niet langer beschouwd als een kwaadaardige tumor en is hernoemd tot atypische kraakbeentumor (ACT) wanneer het is gelokaliseerd in de lange beenderen (b.v. dijbeen). De noodzakelijkheid van een operatie voor ACT's staat ter discussie, aangezien ACT's vooral worden ontdekt als toevalsbevinding. Daarom is actieve vervolging van de tumor middels beeldvorming voorgesteld.

Het doel van dit proefschrift is om het huidige beleid omtrent atypische kraakbeentumoren (ACT's) te evalueren, het natuurlijke beloop van deze tumoren te exploreren en de haalbaarheid van actieve vervolging te onderzoeken.

Hoofstuk 1 bevat een uitgebreide introductie over kraakbeentumoren, de diagnose en de behandelopties. Eveneens wordt in hoofdstuk 1 het doel en de opzet van dit proefschrift uiteen gezet.

Sinds ACT's niet langer worden beschouwd als kwaadaardige kraakbeentumoren, is het een optie om deze tumoren niet meer operatief te verwijderen. Deze optie maakt de differentiatie tussen ACT's en hooggradige chondrosarcomen (HGCS) uitermate klinisch relevant. Gezien de agressiviteit van HGCS mogen deze tumoren niet ten onrechte als ACT worden gediagnosticeerd en daardoor slechts radiologisch worden opgevolgd. Meerdere studies hebben verschillende MRI karakteristieken onderzocht om het onderscheid tussen chondrosarcomen te maken. Ons doel was om een overzicht weer te geven. In **hoofdstuk 2** geven we middels een systematische review een overzicht van MRI-karakteristieken, die tot op heden zijn gebruikt om onderscheid te maken tussen ACT en HGCS. In onze systematische review zijn 239 ACT's en 140 HGCS uit 14 studies opgenomen. Gebaseerd op deze gegevens concludeerden we dat MRI waarschijnlijk behulpzaam is in het onderscheiden van ACT en HGCS. Wegens de aanzienlijke heterogeniteit konden wij de algehele resultaten niet samenvoegen voor een meta-analyse. Uit de niet statistische synthese bleek wel dat uitbreiding van de tumor in de weke delen en cortex doorbraak MRI karakteristieken zijn die vaker voorkomen bij HGCS, terwijl ingesloten vetweefsel vaker voorkomt bij ACT's dan bij HGCS.

In **hoofdstuk 3** analyseerden we onze huidige oncologische resultaten en complicaties na curettage en cryochirurgie van kraakbeentumoren gelokaliseerd in de lange beenderen. In deze retrospectieve studie werden zeer goede oncologische resultaten bereikt voor enchondromen (*n*=55) en ACT's (*n*=119), met een recidiefvrije overleving van 97% en geen gemetastaseerde ziekte. Bij vijf patiënten werd in de uiteindelijke histopathologie na curettage een graad 2 chondrosarcoom (CS2) in plaats van ACT gevonden. De recidiefvrije overleving van slechts 60% benadrukt dat intralesionale chirurgie niet de eerste keuze is voor CS 2, hoewel er geen gemetastaseerde ziekte werd gerapporteerd.

Postoperatief deden zich slechts enkele bottbreuken (5%) voor doordat we vaker profylactisch osteosynthese gebruiken en volledig belasten van het aangedane lichaamsdeel uitstellen. Het vaker gebruiken van osteosynthese droeg wel bij aan het aanzienlijke heroperatie percentage (24%). Merendeel van de heroperaties zijn uitgevoerd wegens het verwijderen van osteosynthese.

Om overbehandeling van niet-kwaadaardige kraakbeentumoren in de lange beenderen te voorkomen, is actieve vervolging van deze tumoren voorgesteld. De grootste barrière voor toepassing van actieve vervolging in de praktijk was het gebrek aan kennis over het natuurlijk beloop van deze tumoren. Daarom evalueerden wij in **hoofdstuk 4** het natuurlijk beloop van conservatief behandelde enchondromen en ACT van de lange beenderen. In deze kleine retrospectieve serie van 49 casussen, had slechts 6% een medische indicatie (d.w.z. groei van de tumor of pijn) voor chirurgie tijdens de follow-up. Belangrijk is dat er geen transformatie naar HGCS werd gezien. Alle geopereerde tumoren werden histopathologisch gediagnosticeerd enchondroom of ACT. Derhalve kan achteraf de noodzaak van deze chirurgische ingrepen worden betwist.

Aangezien veelbelovende resultaten voor actieve vervolging van deze tumoren zijn aangetoond, hebben we het natuurlijke beloop van enchondromen en ACT's verder onderzocht. Deze kennis kan de ontwikkeling van een richtlijn voor actieve vervolging van deze tumoren ondersteunen. In **hoofdstuk 5** werden de MRI's van 128 conservatief behandelde, niet-kwaadaardige kraakbeentumoren geanalyseerd, met een minimum interval van 24 maanden tussen de eerste en laatste MRI. In deze studie bleef 51% van de kraakbeentumoren stabiel. Slechts 13% toonde enige progressie (d.w.z. lichte groei) op MRI, maar geen van de tumoren ontwikkelde kenmerken van HGCS. Verrassend was dat een groot deel van de kraakbeentumoren (36%) tekenen van regressie vertoonde. In de meerderheid (87%) van de tumoren die regressie vertoonden, was ingesloten vet aanwezig bij diagnose, hetgeen biologisch gedrag zou kunnen voorspellen.

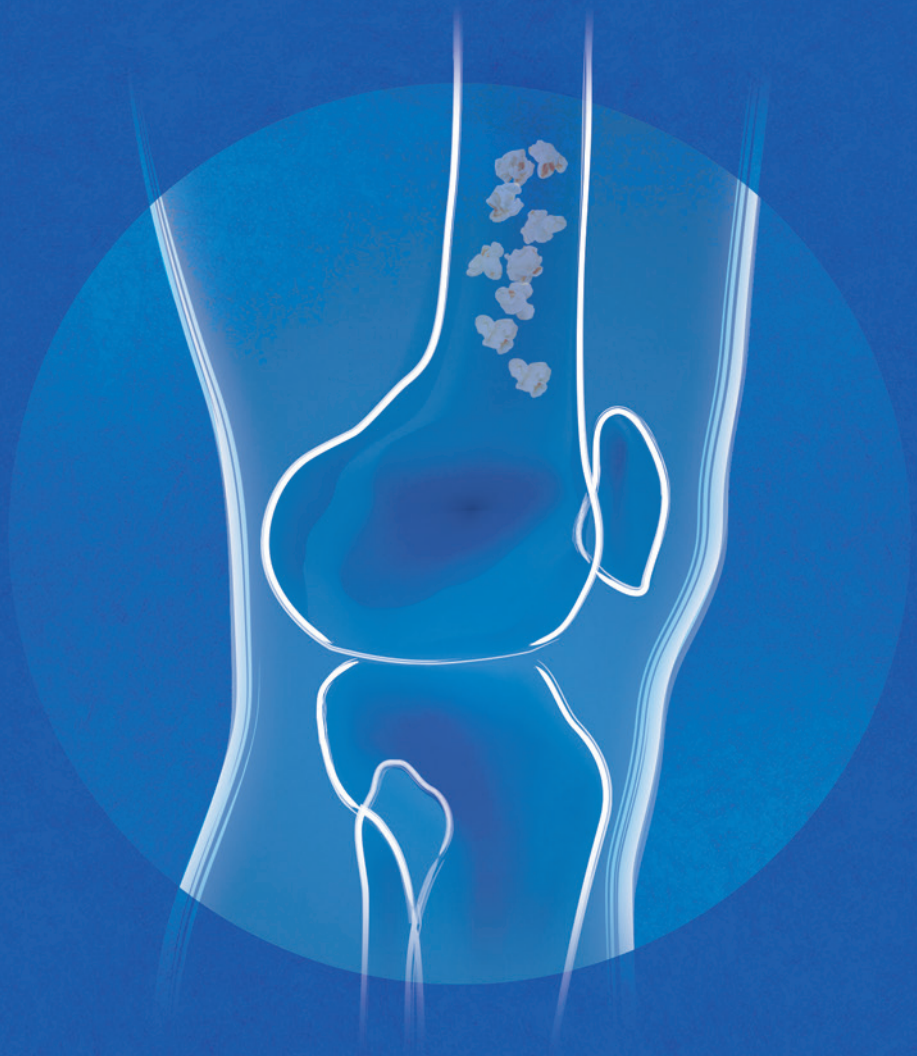
Op basis van deze resultaten achten wij actieve vervolging veilig voor niet-kwaadaardige kraakbeentumoren van de lange beenderen. Follow-up schema's voor actieve vervolging moeten worden afgestemd op het natuurlijk beloop, aangezien wij hebben aangetoond dat tumoren stabiel kunnen blijven, lichte progressie kunnen vertonen, maar ook kunnen afnemen in de loop der tijd.

De verschuiving in behandeling van chirurgische verwijdering van de tumor naar actieve vervolging, vraagt om aanpassing van de patiëntinformatie. Om patiënten te helpen de medische informatie te begrijpen en een weloverwogen beslissing over de behandeling te nemen, hebben wij een digitale keuzehulp ontwikkeld voor patiënten met een ACT in de lange beenderen. Bovendien zijn de motieven van patiënten om voor de een of de andere behandeloptie te kiezen interessant. In **hoofdstuk 6** is het ontwikkelingsproces van de digitale keuzehulp beschreven en zijn de waarden en voorkeuren van de patiënten geëvalueerd. De vooraf gedefinieerde waarden- en voorkeurs vragen werden door 84 patiënten beantwoord. Een derde van de patiënten vond het niet erg om een operatie te ondergaan, gevolgd door een periode met beperkte belastbaarheid. De meerderheid van de patiënten (70%) vond het niet erg om regelmatig MRI's te laten maken en 90% vond actieve vervolging van de tumor geruststellend.

Er moet ook rekening worden gehouden met de gevolgen van deze nieuwe conservatieve behandeling voor de kwaliteit van leven. Men zou kunnen beredeneren dat de last van de gediagnosticeerde, maar onbehandelde ziekte zwaarder weegt dan het voordeel van het voorkomen van een operatie. Daarom evalueerden wij in **hoofdstuk 7** de gezondheid gerelateerde kwaliteit van leven (HRQL) van 45 patiënten die gediagnosticeerd waren met niet-kwaadaardige kraakbeentumoren. In deze studie bleek dat patiënten gediagnosticeerd met niet-kwaadaardige kraakbeentumoren een lagere HRQL hebben vergeleken met de gezonde populatie. Er werd geen effect op de mentale gezondheid gezien, wat impliceert dat gediagnosticeerde maar onbehandelde kraakbeentumoren geen invloed lijken te hebben op de angst van patiënten. Actieve vervolging van de tumor had geen negatief effect op het welzijn van patiënten; na zes maanden actief vervolgen bleef de HRQL onveranderd.

In dit proefschrift werden de toepassing, voor- en nadelen van actieve vervolging voor ACT in de lange beenderen onderzocht. We evalueerden ook de resultaten van chirurgische behandeling van deze tumoren, waaruit bleek dat het heroperatie percentage aanzienlijk was. Gebaseerd op de resultaten van dit proefschrift zou ACT behandeld kunnen worden middels actieve vervolging, waarmee onnodige chirurgie voorkomen wordt. Belangrijk is dat geen enkele van de tumoren transformatie naar een kwaadaardig chondrosarcoom heeft ondergaan. Integendeel, we hebben in dit proefschrift aangetoond dat enchondromen en ACT's in regressie kunnen gaan.

Dit proefschrift draagt bij aan de schaarse kennis over het natuurlijk beloop van kraakbeentumoren en stimuleert verder onderzoek naar dit onderwerp.



APPENDICES

Data management
Radboudumc Graduate school portfolio
Dankwoord
Curriculum vitae

Data management

Data used within this thesis were collected and stored according to the Findable, Accessible, Interoperable and Reusable (FAIR) principles. This thesis is based on data collected from electronic patients records from the Radboudumc. The use of medical records from patients for the studies in this thesis was approved by the medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem-Nijmegen, Nijmegen, the Netherlands. The studies described in chapter 6 and chapter 7 used data from patient questionnaires. Ethical approval for these studies was obtained (file number CMO: 2017-3901) and all patients gave written informed consent. Informed consent papers are stored at the department of orthopedics. The PhD candidate had obtained a Good Clinical Practice certificate (BROK) in 2019.

Data collected from the questionnaires and electronic patients records from the Radboudumc were stored in a Castor EDC-database, which was created at the start of the project. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA). No identifying variables are included in the Castor-database. Each record entered in the database received an unique record-ID. A separate key-file was created, and stored on the server of the department of Orthopaedics. The key for identification is only available for the research team. In order to ensure that data are generally accessible and interoperable, a manual was created in order to upload new data in the Castor-database, or to download data from the Castor-database for future analyses.

Al studies are published open access. The data will be archived for 15 years after termination of the study. The datasets generated and analysed are available from the corresponding author upon reasonable request.

PhD portfolio of Claudia Deckers

Department: **Orthopaedic surgery**
PhD period: **01/06/2018 – 01/06/2022**
PhD Supervisor(s): **Prof. dr. H.W.B. Schreuder**
PhD Co-supervisor(s): **Dr. I.C.M. van der Geest, Dr. E.F. Dierselhuis**

Training activities	Hours
Courses	
- RIHS - Introduction course for PhD candidates (2018)	15.00
- RIHS PhD introduction course (2018)	21.00
- Statistiek voor promovendi met SPSS (2018)	56.00
- Introduction in using R (2018)	5.60
- Presentation Skills (2018)	42.00
- Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK) (2019)	49.00
- Radboudumc - Scientific integrity (2020)	20.00
Followed courses for orthopaedic training:	
- Advanced Trauma Life Support (2021)	28.00
- OTC II: Operatieve fractuurbehandeling – Basic (2021)	16.00
- ROGOO educational program for orthopedic residents (2022)	24.00
- Heupprothesiologie (2022)	10.00
- Stralingshygiëne voor medisch specialisten (2022)	24.00
Symposia and congresses	
- Nederlandse Orthopaedische Vereniging Najaarsvergadering (2015): oral presentation	14.00
- Spiegeluur Orthopaedic Research Lab (2019): oral presentation	12.00
- British Orthopaedic Oncology Society 30th annual meeting (2019): oral presentation	21.00
- European Musculo Skeletal Oncology Society 32nd annual meeting (2019): oral presentation and 2 poster presentations	63.00
- International Society of Limb Salvage 20th general meeting (2019): oral presentation	42.00
- Nederlandse Orthopaedische Vereniging Najaarsvergadering (2019): oral presentation	14.00
- Nederlandse Orthopaedische Vereniging jaarcongres (2020): oral presentation	21.00
- European Musculo Skeletal Oncology Society 33rd annual meeting (2021): poster presentation	24.00
- European Musculo Skeletal Oncology Society 34th annual meeting (2022): oral presentation	30.00
Total	**551.60**

Dankwoord

Dit proefschrift was er niet geweest zonder de hulp en het vertrouwen van velen. Een aantal personen wil ik in het bijzonder bedanken voor hun steun, direct dan wel indirect, tijdens dit promotietraject:

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Curriculum Vitae

Claudia Deckers was born on the 27th of April in 1993 in Breda. In 2011, she obtained her gymnasium diploma at the Katholieke Scholengemeenschap Etten-Leur. After a local selection procedure, she started her medical training at the Radboud University in Nijmegen in the same year.
During her bachelor the fascination for the musculoskeletal system grew and she became interested in orthopaedic surgery. She contacted the orthopaedic department to work on a research project and was introduced to dr. I.C.M. van der Geest. What started as a small project eventually developed into this thesis.

After obtaining her medical degree in 2018, she worked on her PhD at the Radboud University medical center, under the supervision of prof. dr. H.W.B. Schreuder, dr. I.C.M. van der Geest and dr. E.F. Dierselhuis.

In 2019 she started her clinical career at the department of orthopaedic surgery at Rijnstate Hospital (Arnhem) under the supervision of dr. J.L.C. van Susante and dr. M.L. Wagener.

In 2020 she successfully applied for the orthopaedic surgery residency program of the Radboud university medical center (Nijmegen), Sint Maartenskliniek (Nijmegen) and Rijnstate Hospital (Arnhem). Currently, Claudia is in her third year of residency at the Radboud university medical center.

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