CHAPTER I

General introduction
INTRODUCTION

CHONDROSARCOMA

Sarcomas are malignant tumours of mesenchymal origin that arise in soft tissue and bone. They differ from common types of cancer, such as breast cancer, which derive from epithelial cells and are called carcinomas. Sarcomas are relatively uncommon, representing about 1% of all new cancer diagnoses in the United States.\(^1\) In the Netherlands, about 150 cases of primary bone malignancies are diagnosed each year.\(^2\) Chondrosarcomas (CS) are a very heterogeneous group of cartilage matrix-producing tumours. They are most commonly seen in patients aged 40-70 and are the third most common primary bone malignancy.\(^3\) The majority of cases (85%) are de novo central tumours, inside of the bone,\(^3\) yet can also arise secondarily from the surface of the bone from an osteochondroma – peripheral CS – or in the presence of Ollier disease or Maffucci syndrome. All these tumours form a wide range of malignant potential. The benign counterpart – enchondroma – is often an asymptomatic, locally non-aggressive tumour. On the other side of the spectrum, dedifferentiated CS is a very high-grade tumour with very poor survival\(^4\) (Figure 1). In general, chondroid tumours are poorly vascularised and have a low percentage of dividing cells. This makes them relatively insensitive to radiation and/or chemotherapy, and the mainstay of treatment for malignant cartilaginous tumours is surgery.\(^3,4\)

\[\text{encondroma} \quad \text{ACT} \quad \text{CS grade II} \quad \text{CS grade III} \quad \text{dedifferentiated CS} \]

excellent prognosis \hspace{1cm} very poor prognosis

**FIGURE 1.** The spectrum of cartilaginous tumours, ranging from benign enchondroma to dedifferentiated chondrosarcoma
ATYPICAL CARTILAGINOUS TUMOUR

An atypical cartilaginous tumour (ACT) is a cartilage-producing tumour located in the bone with intermediate malignant potential – also known as low-grade or grade I chondrosarcoma (Figure 2). Most cases are incidental findings, when patients come for evaluation of other joint- or bone-related complaints. With increased usage of MRI and CT-scanning, incidence of the disease has risen in recent decades. This is why it is important for orthopaedic surgeons to be aware of this entity and its possible treatment options.

ACTs tend to be only locally aggressive, although incidental metastasising has been reported in literature. Historically a correct diagnosis has been notoriously difficult to make, since histology and imaging alone are not always conclusive and have shown high inter-observer variability. In some cases the tumour evolved to a high grade after local recurrence. This clearly has a negative impact on patient survival, and wide resection has long been advocated in order to achieve adequate surgical margins. However, nowadays

FIGURE 2. Typical MRI image of an atypical cartilaginous tumour (ACT) in the proximal humerus, showing a large lesion and wall-to-wall filling but no signs of higher-grade aggressiveness

FIGURE 3. Tumour in the diaphysis of the femur; treated by intercalary resection, and reconstructed by allograft with plate and nail fixation.
a paradigm shift has taken place in literature towards more local (intralesional) surgery.\textsuperscript{14} It may be that more aggressive tumour biology after local recurrence is the result of an undertreated high-grade tumour, rather than a direct consequence of the local recurrence in itself. With improved imaging modalities and a better understanding of the natural behaviour of these tumours, case series have been published that show excellent survival after intralesional surgery by curettage of the tumour.\textsuperscript{15-23} Given the seemingly relatively mild nature of ACT but the potential morbidity of the current surgical strategies, one can wonder whether the cure is not worse than the disease. Minimally invasive treatment might thus be a step towards an ideal treatment regime: local control leading to excellent oncological outcome, no compromise on functional results, and ideally performed in day care. This concept was developed by our group after an apparently benign lesion treated by RFA turned out to be a cartilaginous malignancy.\textsuperscript{24}

**SURGICAL TECHNIQUES AND THEIR CONSEQUENCES**

As described above, different surgical techniques have been applied for treatment of ACT, every single one with its specific characteristics and advantages/disadvantages. More details are provided below for each particular technique.

**WIDE RESECTION**

In this technique whole segments of bone (including joints) are removed in order to attain extensive surgical margins. This will sometimes lead to amputation if neurovascular bundles cannot be saved, reconstruction is not feasible, or soft-tissue coverage cannot be achieved. If limbs can be salvaged but joints are lost, endoprosthesis such as total knee arthroplasty (TKA) or total hip arthroplasty (THA) is needed. This often requires specially designed tumour prostheses rather than conventional arthroplasties. If segments of bone between joints are removed (intercalary resection), reconstruction is done with autologous bone (e.g. vascularised fibula) and/or allograft (Figure 3).

Wide resection, regardless of the reconstructive possibilities, often leads to functional deficiencies. Amputees will not be the only ones suffering from functional loss, as in reconstructive surgery too muscle function is often (temporarily) lost and weight bearing is prohibited for several months.\textsuperscript{25,26} Finally, due to the scope of the surgery, operating time and large wound bed there is a considerable risk of postoperative infection, nerve damage, fracture and thromboembolic events.\textsuperscript{26-28}
INTRALESIONAL SURGERY (CURETTAGE)

In curettage the tumour is removed while leaving the surrounding bone virtually intact. Only a small cortical window is created to have access to the tumour. The lesion is removed using a curette, traditionally under fluoroscopy guidance (Figure 4). To improve surgical margins, several local adjuvants are available. Most common are the application of phenol ($C_6H_5OH$) with ethanol washout, polymethylmethacrylate (PMMA) and the use of liquid nitrogen ($LN_2$). In an *in vitro* model, cytotoxic effects were found for concentrations of 1.5% phenol and 42.5% ethanol. Furthermore, 96% ethanol is capable of reducing phenol levels for safe washout of the cavity. PMMA is often used in orthopaedic surgery, primarily to fixate endoprostheses. It is also used to fill defects, as it enhances early weight bearing. Another possible advantage is its necrotising effect due to the exothermic chemical reaction during hardening, where temperatures over $80^\circ C$ are reached. It is estimated that the surgical margins are hereby enlarged by 2 to 5 mm in cancellous bone. Cryosurgery using liquid nitrogen is a more potent adjuvant, as 7 to 12 mm of extra bone tissue are necrotised. However, it is not widely used as it has drawbacks like temporary nerve damage and increased risk of fracturing.

Curettage preserves the integrity of the bone and joint dramatically compared to *en bloc* resection or amputation. As a result, functional outcome is significantly better after curettage than after resection in retrospective comparisons. Nevertheless, this technique also has its drawbacks, as complications such as fracturing or infection do occur. In addition, hospital admission is needed and extremities are often protected from weight bearing for several weeks to months.
RADIOFREQUENCY ABLATION (RFA)

In radiofrequency ablation (RFA) a high-frequency alternating current heats tissue to approximately 80°C. An electromagnetic field is created which results in vibration of molecules, leading to heat due to friction in about a 3-cm bony zone (Figure 5). As temperatures rise above 46°C coagulation necrosis takes place, with almost instantaneous cell death at 60°C and beyond. RFA can be applied percutaneously under computed tomography (CT) guidance under general or spinal anaesthesia (Figure 6). The technique was originally developed successfully for solid organ tumours such as hepatocellular carcinoma. Over two decades ago it was also introduced in orthopaedics and has become the gold standard for osteoid osteoma, with primary and secondary success rates of 79–96% and 97–100% respectively. It has proven to be a precise, safe and relatively inexpensive treatment tool for other bony lesions as well, such as chondroblastoma and metastases. Major advantages are that it allows early weight bearing and can be performed in day care. This technique also has potential complications, mainly burning of the skin or fracturing.
AIM AND OVERVIEW OF THE THESIS

This thesis aims to analyse in two parts the results of current practice of ACT treatment and to investigate new treatment modalities.

PART I

To date, no prospective studies have been published that could help design an adequate treatment algorithm for ACT in the long bones. There are only low-evidence retrospective studies available, with widespread publication dates, surgical indications and applied techniques. Hence in the absence of high-level evidence we first aim to review all available literature and meta-analysis data in a Cochrane Review (Chapter II). Next, we will analyse our own experience of treating ACT by intralesional surgery (Chapter III). As computer-assisted surgery (CAS) has also been introduced in the field of oncologic orthopaedics, we will also evaluate its value compared to fluoroscopy in the treatment of ACT (Chapter IV). CAS offers the surgeon real-time feedback on its whereabouts during surgery, potentially decreasing residual tumour rates and enhancing disease-free survival. Moreover, patients as well as surgeons are protected from X-rays during surgery.
PART II
Minimally invasive treatment using RFA is studied in part II of the thesis. In Chapters V and VI we provide insight into the efficacy of RFA in the treatment of ACT, together with evaluation of imaging modalities for follow-up. In Chapter V we also investigate functional outcome by means of musculoskeletal tumour society (MSTS) scores after RFA compared to intralesional surgery. In Chapter VI we analyse the learning curve of applying this new technique. A general discussion and the implications of our studies are provided in Chapter VII, and the thesis is summarised in Chapter VIII.
REFERENCES


