CHAPTER VII

General discussion, implications and future perspectives
OVERVIEW

This thesis provided an overview of the current treatment strategies for ACT and investigated new treatment options. For that reason, it was divided in two sections. Objectives of Part I were to evaluate the current literature and our own results of intralesional surgery for ACT in long bone. A systematic review of the literature was conducted in Chapter II. In Chapter III we investigated the oncological results and complications of intralesional surgery for ACT that we performed. The influence of preoperative guidance by computer-assisted surgery (CAS) versus fluoroscopy in treatment of these tumours was assessed in Chapter IV. In Part II we focussed on a new treatment modality for ACT, radiofrequency ablation (RFA), with a prospective analysis in Chapters V and VI of clinical outcome and safety of RFA for ACT in the long bones. Follow-up by G-MRI, risk of complications and the learning curve for the application of this tool were all investigated in these chapters too. The current chapter will discuss the main findings of both sections of this thesis and their implications for clinical practice and future research.

PART I

SURGICAL TECHNIQUES AND PATIENT SURVIVAL

Wide resection was often performed for ACT until two decades ago. It used to be notoriously difficult to differentiate between low-grade and high-grade cartilaginous tumours.\textsuperscript{1} Nowadays, MRI is better at distinguishing high-grade tumours from enchondroma and ACT.\textsuperscript{25} Local recurrence was thought to precede upgrading of tumour, negatively influencing patient survival.\textsuperscript{6} For that reason, local control was best provided by extensive surgery since systemic and radiation therapy have only marginal effects.\textsuperscript{7} In the last 20 years a trend towards intralesional surgery has been observed in literature, as reviewed in 2011 by Hickey et al.,\textsuperscript{8} who concluded it could not be demonstrated that curettage greatly increased the risk of local recurrence or metastases. Several studies and case series on this matter have since been published, urging us to redo a systematic review.
and meta-analysis, this time according to Cochrane standards. The results of this study in Chapter II show that, based on data from 781 patients across 18 studies, there is very uncertain evidence of intralesional surgery being as effective as wide resection. Despite the methodological limitations of the conducted studies, we were able to reconstruct a recurrence-free survival (RFS) curve for 115 individual patients. RFS was comparable between groups, with 94% in the intralesional (curettage) group versus 96% in the wide resection group (p = NS). Thus on the one hand evidence is of very low certainty, but best available evidence suggests that oncological outcome after curettage for ACT in the long bones is excellent. This raises some concerns on the grounds to take clinical decisions on. Considering the low incidence rate of ACT and the very low incidence rate of events of local recurrence, it is not feasible to design a randomised controlled trial to solve this matter (Chapter II).

The feared upgrade of tumour was seen in only 0.5% of all study participants. They were treated with second surgery, and only two patients (0.26%) died due to disease. Leerapun et al. describes two cases of death from pulmonary metastases after a local recurrence.\(^9\) One should realise that upgrading of local recurrences could also be a misinterpretation of events. As mosaicism exists within chondroid tumour, grade-II tumours could have been falsely diagnosed as lower-grade tumours.\(^10\) As a consequence, upgrading of tumour is not a result of local recurrence, but local recurrence takes place since it was a higher-grade tumour from the beginning. This could be exactly the case in the previously mentioned paper: one patient developed a local recurrence showing dedifferentiated chondrosarcoma just four months after curettage of an ACT and died within nine months. Considering the rather benign tumour biology and slow-growing nature of nearly all other ACTs we found in literature, it is quite imaginable for the tumour to have been understaged in first place. The same is true for the other patient, who was treated by wide resection since it was a lytic lesion with soft-tissue extension. These signs are more suggestive of a higher-grade tumour rather than reassuring features of an ACT.\(^3\) The fact that local recurrences developed only in the years shortly after the index procedure (which was also seen in our own centre, as reported in Chapter III) suggests that those were in fact residual tumours. Given that MRI was not as widely available back then, the tumours could have been easily missed and only brought to light once they became visible on conventional X-rays. Considering the time frame of local recurrences in our review, one could propose limiting follow-up to five years after surgery if G-MRI remains negative for tumour activity. This
is supported by a recent paper by Verdegaal et al. that was able to classify postoperative G-MRI studies and stratify patients for re-intervention, intense follow-up or moderate follow-up.\textsuperscript{11} It should be noted that they also advise routinely scanning all patients 10 years after index surgery, which might be defensive and open for discussion.

Hence although all the evidence has very low certainty, it is defendable to say that ACT runs quite a benign course. The complication rates of more extensive surgery – as described below – are therefore not acceptable in terms of ‘life over limb’.

**SURGICAL TECHNIQUES AND ITS BURDENS**

Wide resection has high morbidity, as 23% of patients experienced major complications like nerve injury, infection, fracturing and implant loosening (Chapter II). This is reflected in the Musculoskeletal Tumour Society (MSTS) scores, which were significantly and remarkably lower in those patients treated with more extensive surgery. Although these scores could be at risk for performance bias to some extent (as they are ‘doctor’s scores’), one would think that a patient who underwent joint- and bone-preserving surgery performs better than one who did not. As most data from papers that published on wide resection are somewhat archaic, and in the light of the sound oncological outcome of patients with ACT in the long bones, this technique can be deemed obsolete in the absence of radiological signs of higher-grade malignancy. Even less invasive surgery like curettage has its own morbidity rates, and postoperative fracturing does occur. In our own centre 10\% of patients had fractures, leading to at least one additional operation. Prophylactic hardware stabilisation might lower this chance and is widely applied, but has disadvantages such as increased infection risk, limited visibility of local recurrence or residue, and hardware complaints (Chapter III). These problems were not only encountered by our group but were also seen in other studies.\textsuperscript{12-14}

**PERIOPERATIVE GUIDANCE**

If one opts for intralesional surgery, perioperative navigation should ideally be precise, able to give 3D feedback, and harmless to the patient and operating theatre employees. Fluoroscopy is traditionally used as preoperative guidance, but has the drawbacks that only 2D imaging is possible and uses ionising radiation. Computer-assisted surgery (CAS) does not have these disadvantages but is supposed to be time-consuming.\textsuperscript{15-16} However, in our retrospective study (Chapter IV) we were able to demonstrate that operating times
were equal regardless of the imaging technique used. We did not experience setup-related problems like pin-tract infections or fractures. This did not have a significant impact on patient outcome, but it should be noted that only lesions that are easy to access were treated since we were gaining experience with the CAS system. Moreover, the study was underpowered, considering the low incidence of local recurrences. Our findings support the use of computer navigation on a more structural basis in oncologic orthopaedics. Farfalli et al. studied the use of computer guidance in locally aggressive tumours. They found that CAS-guided en bloc resection showed no recurrences except for two patients in the curettage group (one ABC and one GCT), while baseline characteristics, functional outcome and complication rates were alike.\textsuperscript{17}

**PART II**

Considering the relatively mild nature of ACT in the long bones and the drawbacks of surgery, less invasive treatment might add an option for the treating physician. We reckoned radiofrequency ablation (RFA) as most suitable, since there is considerable experience with this tool in bony lesions such as osteoid osteoma. Complications are rare, it is relatively cheap, and it can be performed in day care. The use of RFA for ACT in the long bones was prospectively evaluated in Chapters V and VI. Complete eradication of tumour cells was achievable according to our first results. However, the initial efficacy rate was only 45%, which was worrisome in our opinion. After careful evaluation we hypothesised that there were three main predictors of failures: (1) number and total ablation time of cycles, (2) size of the tumour (>30 mm) and (3) the heat sink effect. For that reason, we slightly adjusted our ablating protocol by delivering more local energy. We prolonged the duration of the ablation procedure and/or placed multiple needles in tumours >30 mm. Although the main element of success could not be identified, we saw primary efficacy rates rising to 71%, and complete failures dropping from 30% to 8% (\textit{Chapter VI}). It is not feasible to relate our results to others, as only one published study used RFA to treat small (<10 mm) residues of ACT after curettage.\textsuperscript{18}

In terms of functional outcome, there was a rapid return to normal activities after RFA, as opposed to lower MSTS scores after curettages in the first 12 weeks. Additionally, all
RFA procedures could be done in day care, while curettage involved a 3-5-day hospital admission. Fractures occurred twice after curettage and once after RFA. It cannot be said that thermal ablation preceded the fractures after curettage, but the fracture rate was in correspondence with the literature. The effects of RFA on the mechanical properties of bone nonetheless remain a concern for future research.

IMPLICATIONS AND FUTURE PERSPECTIVES

As shown in Chapter II, intralesional treatment of ACT in the long bones could be considered the gold standard, with wide resection reserved for doubtful cases only. Only four cases out of 781 patients (0.5%) demonstrated evolution towards a higher-grade tumour, hardly hampering patient survival: we found that only 0.26% of patients died due to disease, and those might have been higher-grade tumours from the beginning – therefore with careful patient selection, curettage is a safe treatment option. ACT has been notorious for correct diagnosis, with the risk of overstaging or understaging. As previously pointed out, understaging seems less of a concern nowadays. However, overstaging could still be a factor to reckon with, since harmless enchondromas might have also been operated on. In our own case series of intralesional treatment (Chapter III) there was still a considerable number of serious complications. Hence the adage better safe than sorry might not be exactly true for ACT, as occasionally the cure might be worse than the disease. With this in mind, we deemed that development of other treatment strategies is needed. Although we could not demonstrate advantages of the use of CAS in terms of local control (Chapter IV), 3D planning and executing techniques might still be of relevance if more challenging sites are treated. In line with our conviction that further polishing of the treatment regime is needed, some argue that active surveillance could be the treatment of choice. Deckers et al. retrospectively analysed 49 cases of enchondroma and ACT that were treated conservatively. Only 6% of patients eventually needed surgery, underscoring that overtreatment is possible if one operates in all cases. Although these are appealing figures, this was also a retrospective study, presumably blurred by selection bias to some extent.
Considering the current absence of clear criteria, or when a patient opts for surgery at his own request, less invasive procedures might be a valuable adjunct to current practices. RFA is not a new technique, and indications of its usage have increased over time, also in the field of orthopaedic oncology. It is considered to be a safe technique, with only fracturing and burning wounds reported anecdotally. Local tumour ablation by RFA has the advantage that it can be performed in day care, improves short-term function, and can be safely monitored by MRI (Chapters V and VI). Since we have only analysed the effect on short notice, future research should focus on prospective long-term outcome and improving ablating techniques with real-time monitoring and 3D positioning techniques.

All in all, treatment of ACT remains controversial, but this thesis has added valuable data to the debate: curettage seems safe for chondroid tumours that lack signs of higher-grade malignancy on MRI. Local recurrence after surgery might be actual residue and can be detected by MRI, so follow-up can be limited if signs of residue are absent. Undertreatment does not seem to be a concern nowadays, but there is the risk of overtreatment, which unnecessarily exposes patients to the burdens of surgery. For that reason, when opting for intervention minimally invasive treatment by RFA might add a valuable adjunct to current practice. With the right execution it is an effective treatment tool that can be performed in day care with no negative effect on functional outcome and low complication rates. A conservative approach towards ACT was outside the scope of this thesis, but is an interesting strategy that needs further prospective investigation. To find definitive answers, it is a must for clear criteria to be developed: if we want to get directions, we want to know where we are starting.\textsuperscript{22,23} It is of the utmost importance that any research in this field be conducted in a multicentre, multinational setting. In this way, patients and doctors are provided with the best evidence available to balance their considerations and choose the best possible treatment strategy.
REFERENCES


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