Advances of treatment in atypical cartilaginous tumours
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CHAPTER V

Radiofrequency ablation as a new treatment modality in cartilaginous lesions in the long bones; results of a pilot study

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ABSTRACT

Background: Atypical cartilaginous tumours are usually treated by curettage. The purpose of this study was to show that radiofrequency ablation was an effective alternative treatment.

Patients and methods: We enrolled 20 patients (two male, 18 female, mean age 56 years (36 to 72) in a proof-of-principle study. After inclusion, biopsy and radiofrequency ablation were performed, followed three months later by curettage and adjuvant phenolisation. The primary endpoint was the proportional necrosis in the retrieved material. Secondary endpoints were correlation with the findings on gadolinium enhanced MRI, functional outcome and complications.

Results: Our results show that 95% to 100% necrosis was obtained in 14 of the 20 patients. MRI had a 91% sensitivity and 67% specificity for detecting residual tumour after curettage. The mean functional outcome (MSTS) score six weeks after radiofrequency ablation was 27.1 (23 to 30) compared with 18.1 (12 to 25) after curettage (p < 0.001). No complications occurred after ablation, while two patients developed a pathological fracture after curettage.

Conclusion: We have shown that radiofrequency ablation is capable of completely eradicating cartilaginous tumour cells in selective cases. MRI has a 91% sensitivity for detecting any residual tumour. Radiofrequency ablation can be performed on an outpatient basis allowing a rapid return to normal activities. If it can be made more effective, it has the potential to provide better local control, while improving functional outcome.
INTRODUCTION

The mainstay of treatment for primary bone tumours is surgery. Central atypical cartilaginous tumours (ACT - formerly known as chondrosarcoma grade I) are generally treated by curettage: previously, treatment consisted of wide resection or amputation. In general, the treatment of chondroid tumours can be problematic, since they are relatively resistant to irradiation and chemotherapy. It can also be difficult to differentiate ACT from its benign counterpart (enchondroma) and grade II tumours. In contrast to higher grade chondrosarcoma, ACTs grow slowly and do not metastasise, unless upgrading or dedifferentiation occurs. Although curettage causes less morbidity than more extensive surgery, it still has a negative impact on functional outcome.

Local recurrence (LR) occurs in up to 7.7% of patients after curettage. In the event of LR, a repeat operation is often needed, exposing the patient to the additional risks of common peri-operative complications such as infection or fracture. In addition, prophylactic hardware is sometimes needed. All these measures have a negative effect on a patient’s quality of life. Although the adage ‘life before limb’ remains true for ACT, the relatively mild nature of these tumours in the long bones might justify less aggressive treatment.

Therefore, a new treatment strategy is needed that improves local control and functional outcome, while lowering the rate of complications. Moreover, follow-up must be sufficient to evaluate the effect of such treatment. A minimally-invasive approach using radiofrequency ablation (RFA), monitored by gadolinium-enhanced magnetic resonance imaging (G-MRI), might be capable of meeting these requirements.

For nearly two decades, RFA has been used as a minimally-invasive surgical technique in orthopaedics. With RFA, a high-frequency alternating current heats tissue to approximately 80°C, causing it to necrose. Initially, RFA was used to treat osteoid osteoma. With increasing clinical experience, bone metastases and chondroblastomas have also been successfully treated. Complications are rare, although local adverse events such as cellulitis or burns of the surrounding skin have been reported. When more challenging sites, such as the femoral neck, are treated, fracture is possible. Nonetheless RFA is a safe, precise and inexpensive technique which can be performed in the outpatient department.
The purpose of the study was twofold: to demonstrate the effective ablation of cartilaginous tumour cells in the long bones and to evaluate the ability of G-MRI to detect residual tumour after thermal ablation.

**TABLE 1.** Demographic data and primary outcome.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (sex)</th>
<th>Location</th>
<th>Diameter</th>
<th>Histology biopsy&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Histological response&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57 (M)</td>
<td>Femur diaphysis</td>
<td>34 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>2</td>
<td>52 (F)</td>
<td>Tibia metaphysis</td>
<td>28 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>3</td>
<td>50 (F)</td>
<td>Femur metaphysis</td>
<td>31 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>4</td>
<td>64 (F)</td>
<td>Femur metaphysis</td>
<td>23 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>5</td>
<td>70 (F)</td>
<td>Tibia metaphysis</td>
<td>31 mm</td>
<td>ACT</td>
<td>R2</td>
</tr>
<tr>
<td>6</td>
<td>49 (F)</td>
<td>Tibia diaphysis</td>
<td>31 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>7</td>
<td>63 (F)</td>
<td>Femur metaphysis</td>
<td>35 mm</td>
<td>ACT</td>
<td>R2</td>
</tr>
<tr>
<td>8</td>
<td>36 (F)</td>
<td>Humerus metaphysis</td>
<td>26 mm</td>
<td>ACT</td>
<td>R1</td>
</tr>
<tr>
<td>9</td>
<td>61 (F)</td>
<td>Humerus metaphysis</td>
<td>35 mm</td>
<td>ACT</td>
<td>R2</td>
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<tr>
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<td>ACT</td>
<td>R1</td>
</tr>
<tr>
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<td>59 (F)</td>
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<td>24 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
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<td>22 mm</td>
<td>ACT</td>
<td>R1</td>
</tr>
<tr>
<td>13</td>
<td>64 (F)</td>
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<td>29 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>14</td>
<td>72 (F)</td>
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<td>ACT</td>
<td>R2</td>
</tr>
<tr>
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<td>37 mm</td>
<td>ACT</td>
<td>R2</td>
</tr>
<tr>
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<td>ACT</td>
<td>R1</td>
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<tr>
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<td>Humerus metaphysis</td>
<td>36 mm</td>
<td>ACT</td>
<td>R1</td>
</tr>
<tr>
<td>18</td>
<td>49 (F)</td>
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<td>25 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
<tr>
<td>19</td>
<td>70 (F)</td>
<td>Femur metaphysis</td>
<td>37 mm</td>
<td>ACT</td>
<td>R2</td>
</tr>
<tr>
<td>20</td>
<td>44 (M)</td>
<td>Femur diaphysis</td>
<td>35 mm</td>
<td>ACT</td>
<td>R0</td>
</tr>
</tbody>
</table>

<sup>1</sup>ACT = Atypical cartilaginous tumour. <sup>2</sup>Necrotic response based on curetted material three months after radiofrequency ablation (RFA). R0 = complete necrosis; R1 = 95-99% necrosis, R2 = <95% necrosis.
PATIENTS AND METHODS

A prospective, proof-of-principle study was designed to evaluate the amount of tumour necrosis after RFA for ACT. Patients were included if there was clinical suspicion of ACT, which did not exceed 35 mm in its largest diameter on diagnostic MRI, in a long bone. Patients had to be aged 18 years or older and able to give informed consent after being told about the purpose of the study. Patients were excluded if the tumour was in the hand, foot, pelvis or axial skeleton. Other exclusion criteria were the presence of cognitive impairment; clear breakthrough of the cortex and infiltration of the surrounding soft-tissue by the tumour; previous treatment of the same lesion and a histological diagnosis of enchondroma. Between 2009 and 2011, we identified 20 patients, (two male, 18 female) in whom ACT was suspected for inclusion in the study. The mean age of the patients was 56 years (36 to 72) at the time of RFA. Their demographic details are presented in Table I. The study was approved by our institutional medical ethics committee (18th September 2009 – M09.07334).

Patients first underwent CT-guided needle biopsy. After obtaining representative material, RFA under CT guidance was performed in the same session, using a Soloist Single Needle Electrode (Boston Scientific, Natick, Massachusetts). The ablation session was performed or supervised by a musculoskeletal interventional radiologist (PJME). The RFA needle was inserted through the access hole of the biopsy needle and ablation was performed starting with 2 watts, and increasing by 1 watt per minute until automatic switch-off. Patients were discharged the same day and instructed about weight-bearing, which depended on the size and localisation of the tumour, and post-operative pain management. After 14 days, the patients visited the outpatient department to have the wound checked and for their histological results. The bone biopsy was examined by a senior histopathologist with experience in bone and soft-tissue tumour pathology (AJHS) to confirm the diagnosis. Three months after thermal ablation, each patient underwent G-MRI to check for residual tumour and to assess the effect of ablation. Within four weeks of the MRI, patients underwent curettage at the site of the previously identified lesion with adjuvant phenol and ethanol, thereby receiving the conventional treatment for the condition. The tumour was approached through a cortical window under radiological guidance and removed with a curette. After phenolisation of at least
two minutes, ethanol washout and saline rinsing, polymethylmethacrylate (PMMA) was used to fill the cavity. The material retrieved during surgery was sent for histological evaluation. Each specimen was checked by the same pathologist to confirm the diagnosis of ACT and to assess the extent of any necrosis. In this way, patients served as their own control for the RFA procedure. All operations were carried out by the orthopaedic oncologist in our hospital (PCJ). Three months after curettage, G-MRI was undertaken as a baseline study for follow-up.

The primary endpoint was the proportional necrosis of the material retrieved during curettage. This was classified as complete necrosis (R0); focal viable tissue (R1) with 95% to 99% necrosis; and substantial viable tissue (R2), with >5% viable tumour tissue. Histological analysis was performed according to World Health Organization standards.3 Secondary endpoints were signs of residual tumour on post-RFA G-MRI; correlation of G-MRI with histological findings; local recurrence after curettage; complications; functional outcome and duration of admission.

Radiological results based on MRI were also divided into R0 (no sign of residual tumour or contrast enhancement and the tumour clearly within the ablation halo), R1 (little or doubtful gadolinium uptake and the tumour on the border of the halo with no clear tumour outside the halo) and R2 (clear residual tumour with contrast enhancement and localisation outside the halo) (Figure 1).

Complications were defined as an unintended adverse event leading to re-intervention, increased duration of admission or re-admission within three months of primary operation. Judgement of local recurrence was based on follow-up with G-MRI according to our national protocol14. Functional outcome was assessed using the Musculoskeletal Tumour Society (MSTS) scores with a maximum score of 30/30 points15. These scores were documented by the treating physician (PCJ) after RFA and after curettage. Functional scores were measured six and 12 weeks after both types of treatment (T1 = six weeks after RFA, T2 = 12 weeks after RFA, T3 = six weeks after curettage, T4 = 12 weeks after curettage). We assessed the MSTS scores in ten random patients after one year (T5). Weight-bearing regimes were also noted. Duration of admission was calculated from the clinical charts.
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FIGURE 1. Images corresponding with radiological grading of tumour response after radiofrequency ablation (RFA). A) no sign of residual tumour (R0) in the right distal femur (arrowed); B) little or doubtful uptake of gadolinium (R1) in the right proximal humerus (arrowed); C) obvious residual tumour lying outside the zone of ablation (R2) in the left distal femur (arrowed).
STATISTICAL ANALYSIS

For all variables, the mean and range of values were noted. Measurements of tumour size were based on 4 mm slice MR images and 1.5 mm slice CTs. SPSS version 22.0 software (IBM-SPSS, Armonk, New York) was used for all statistical testing. A univariate analysis was undertaken, while a p-value < 0.05 was considered to be statistically significant.

RESULTS

ACT was confirmed histologically in all 20 patients. None were diagnosed by CT-guided biopsy as an enchondroma or tumour higher than grade 1. Tumours were located in the femur, humerus (4) or tibia (3). There were 14 tumours in the metaphysis and six in the diaphysis. The mean tumour size was 29.7 mm (15 to 37) in its largest diameter. RFA was performed using 1 to 3 cycles of 1 to 14 minutes in duration. Typically, two or three procedures were performed within one session, with a mean cumulative roll-off time of 16 minutes (11 to 27).

Complete necrosis (R0) was found histologically in nine patients, focal areas of viable ACT (R1) in five, and more than focal areas of viable ACT (R2) in six patients (Figure 2). Complete necrosis was present in five of the six tumours located in the diaphysis and four of the 14 tumours in the metaphysis (p = 0.02). There was no sign of enchondroma or a higher-grade tumour in any of the viable tissue.

All patients with a tumour in the lower extremity (n = 16) were kept half-weight-bearing for the first six weeks after curettage: this was increased to full weight-bearing after three months.

The mean MSTS score six weeks after RFA (T1) was 27.1 (23 to 30) compared with a mean score of 18.1 (12 to 25) six weeks after curettage (T3) (p < 0.001). The mean MSTS score 12 weeks after RFA (T2) was 27.2 (23 to 30) compared with a mean score of 22.9 (15 to 30) 12 weeks after curettage (T4) (p < 0.001). One year after curettage (T5) the mean MSTS score, measured in ten patients, was 27.4 (24 to 30) (Figure 3).
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FIGURE 2. Histology showing an example of the focal area (R1) of viable atypical cartilaginous tumour after radiofrequency ablation treatment (Haematoxylin and Eosin 400x).

FIGURE 3. Functional outcome reflected by Musculoskeletal Tumor Society (MSTS) scores. MSTS scores are a doctor-dependent score with a maximum of 30 points. Scores six and 12 weeks after radiofrequency ablation (RFA) were significantly higher than scores after curettage (*p < 0.001 compared with MSTS 6 weeks after RFA, §p< 0.001 compared with MSTS 12 weeks after RFA).
After a mean follow-up of 35.8 months (18 to 50) from curettage there were no signs of residual tumour or local recurrence. No adverse events were seen after RFA. A pathological fracture occurred in two patients after curettage, which required open reduction and internal fixation. All patients were discharged from the hospital the same day after the RFA procedure. Patients remained in hospital for three to five days after curettage.

As shown in Table II, ten patients with positive histology (focal or more than focal remnants of viable ACT) after curettage also had positive MRI results. One positive case was missed on MRI. Six of nine patients were truly negative, leaving three false-positive cases. A calculation based on these outcomes shows that G-MRI has a 91% sensitivity for detecting residual tumour after curettage, and a specificity of 67%. The positive predictive value (PPV) is 77% and negative predictive value (NPV) 86%. The one case missed on MRI showed a R1 tumour response histologically. The three false-positive cases on MRI were all considered R1 (little or doubtful gadolinium uptake). Finally, one R2 case histologically was adjudged to be R1 on MRI.

**TABLE 2.** Results and correspondence between histological response and G-MRI findings.

<table>
<thead>
<tr>
<th>Histological response</th>
<th>MRI&lt;sup&gt;1&lt;/sup&gt;</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R0</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>R1</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>R2</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>1</sup>Tumours fully surrounded by a halo and no Gadolinium uptake were R0, tumours within the halo but with some Gadolinium uptake were R1, and tumours that lied partially or totally outside the ablation zone and had substantial uptake were R2.
DISCUSSION

Surgery is the mainstay of treatment for chondroid tumours as they are mostly unresponsive to radiotherapy or adjuvant chemotherapy. Currently, most patients with a central ACT are treated by local curettage. This does not in itself reduce overall survival, but does improve functional outcome\(^1\). However, surgery has some disadvantages such as prolonged hospital admission, risk of complications and restricted weight-bearing afterwards. Moreover, recurrence occurs in up to 7.7% of patients requiring further intervention, with the risk of additional complications\(^6\).

We hypothesised that minimally-invasive treatment using RFA can eradicate the chondroid tumour cells thereby lowering the rate of complications and improving functional outcome.

This pilot study shows that only nine of 20 tumours were completely necrosed by RFA. Although this confirms that RFA has the capacity to eradicate ACT, the remaining patients were undertreated. Consequently, on the one hand its effectiveness has to be improved, and on the other, follow-up must be sensitive to the detection of residual tumour. These conditions have to be met before one could safely state that RFA is a reliable alternative to curettage with adjuvant phenolisation.

To increase the precision of the RFA procedure, the factors that determine the efficiency of ablation need to be considered. First, the proportional necrosis is directly related to the volume of the tumour, as the area heated is limited. Our primary inclusion criteria stated that the diameter of the tumour should not exceed 35 mm. However, in three patients the actual diameter was a little over 35 mm on CT with a maximum of 37 mm. These cases were included on the basis of the baseline MRI studies, but appeared larger on CT during RFA. Since this study is about initial experiences, we decided that these cases should also be included. Of all tumours > 30 mm ablated, only five of 11 were R0 or R1, compared with nine out of nine in tumours < 30 mm (\(p = 0.006\)). There were no significant differences between localisation and total ablation time in these two groups but the groups are small. RFA might cover a diameter > 30 mm, but asymmetrical placement of the needle carries a greater risk of insufficient heating at the borders of the tumour. If larger tumours are to be ablated, we would recommend using more needle positions.
Second, the number and duration of the sessions varied substantially. A session automatically ended when there was an increase in tissue impedance due to necrotic tissue, the so-called ‘roll-off’. Although we could not find any significant difference, we feel that at least three ablation cycles are needed to provide a more constant result and to improve reliability of the procedure.

Third, the tissue response may not only be dependent on tumour size and exposure to heat: the surrounding tissue may also have an influence. Adjacent blood vessels may extract heat from the zone of ablation by their blood flow – the so-called heat sink effect – a phenomenon that occurs when a vessel > 3 mm lies within the ablation zone. In order to study the capability of G-MRI to detect residual tumour after ablation, we undertook this three months after the RFA session, just prior to curettage. By comparing the results of G-MRI and histopathology it was possible to determine sensitivity and specificity of G-MRI for showing signs of residual tumour three months after RFA.

Of all the tumours that were not completely destroyed (R1 and R2), ten of 11 were also identified on MRI. Hence G-MRI is 91% sensitive to detecting residual tumour. As six of nine patients with an R0 histological response were correctly predicted on MRI, specificity is 67%. All false-negative and false-positive cases were R1, so neither R2 tumours were missed nor were R0 pathological responses presumed to be R2 on MRI. Given these facts, we feel that G-MRI is sufficiently accurate to detect residual tumour and therefore to safely monitor and guide further treatment.

On this basis, we propose that patients with R0 radiological results be monitored in the same way as patients after curettage in current clinical practice, since there is an 86% NPV of MRI. Patients who show clear signs of residual malignancy on MRI (R2) should undergo a second session of RFA or curettage. We think that patients for whom the radiologist describes the MR image as R1 should be followed more closely than R0 patients. In such cases there is an 87.5% chance of there being no residual tumour, or only a little tumour tissue left. The latter might be hazardous, since it can lead to local recurrence, upgrading or dedifferentiation.

The expected benefits of using RFA have all been confirmed by the current study. All patients were treated on an outpatient basis, unlike when treated by curettage, those of whom needed three to five days in hospital.

After RFA, patients were allowed to bear full weight and rapidly returned to normal daily activities (Figure 3). In the ten patients reviewed one year after curettage, levels of
function and comfort were equal to those achieved by ablation. In two cases, fracture occurred after curettage and internal fixation was needed. No adverse events were seen after RFA.

One could argue that ACT could be mistaken for an enchondroma or even a higher grade of tumour, since it is known that this diagnosis has high inter-observer variability\textsuperscript{17}. We are aware that biopsy alone is not a reliable method of differentiating ACT from a grade II chondrosarcoma. However, in our experience, G-MRI is a reliable method of detecting signs of higher grade tumour\textsuperscript{18}. Moreover, in this study the final histology always included all material harvested during curettage, and grade II chondrosarcoma was found in none of the viable tissue, nor did extensive follow-up with G-MRI, ranging from 18 to 50 months, show signs of recurrent tumour. We therefore think that the advantages of minimally-invasive therapy outweigh the disadvantages given the relatively benign nature of ACT. Nevertheless, we underscore the fact that if there is any doubt about the original diagnosis, curettage is still the safer option.

The purpose of this study was to demonstrate the ablative effect of RFA on cartilage cells. The histological differences between enchondroma and ACT are subtle and it seems reasonable that this small difference does not influence the efficiency of RFA. While our investigation was intended to study lesions measuring < 35 mm in diameter on MRI, future developments might include monitoring lesions of this size and only treating them if they enlarge or show other aggressive features. Larger tumours (> 50 mm), on which we would currently operate, might be treatable with RFA using multiple tip positions.

In conclusion, in this proof-of-principle study we have shown that RFA has the potential to eradicate cartilaginous tumour cells. If residual tumour after ablation is present, G-MRI has a 91% sensitivity for detecting residual tumour. RFA can safely be performed on an outpatient basis, with a rapid return to normal daily activities. We believe that the concept of minimally-invasive therapy using RFA is an attractive alternative to surgery, although its effectiveness in achieving local control has to improve. Currently, the size and location of the tumour in the bone are the main predictors of success. More consistency is needed and further research is being conducted to improve the accuracy of the ablation procedure.
REFERENCES


