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Chapter 5

Low-grade chondrosarcoma of long bones treated with intralesional curettage followed by application of phenol, ethanol and bone-grafting


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Background
A common treatment of low-grade cartilaginous lesions of bone is intralesional curettage with local adjuvant therapy. Because of the wide variety of different diagnoses and treatments, there is still a lack of knowledge about the effectiveness of the use of phenol as local adjuvant therapy in patients with grade I central chondrosarcoma of a long bone.

Methods
A retrospective study was done to assess the clinical and oncological outcomes after intralesional curettage, application of phenol and ethanol, and bone-grafting in 85 patients treated between 1994 and 2005. Inclusion criteria were histologically proven grade I central chondrosarcoma and location of the lesion in a long bone. The average age at surgery was 47.5 years (range, 15.6 to 72.3 years). The average duration of follow-up was 6.8 years (range, 0.2 to 14.1 years). Patients were evaluated periodically with conventional radiographs and Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) scans. When a lesion was suspected on the basis of the MRI, the patient underwent repeat intervention. Depending on the size of the recurrent lesion, biopsy followed by radiofrequency ablation (lesions <10 mm) or curettage (lesions ≥10 mm) was performed.

Results
Of the 85 patients, eleven underwent repeat surgery because a lesion was suspected on the basis of the Gd-MRI studies during follow-up. Of these eleven, five had a histologically proven local recurrence (a recurrence rate of 5.9% [95% confidence interval, 0.9% to 10.9%]), and all were grade I chondrosarcomas. General complications consisted of one superficial infection, and two femoral fractures within six weeks after surgery.

Conclusions
This retrospective case series without controls has limitations, but the use of phenol as an adjuvant after intralesional curettage of low-grade chondrosarcoma of a long bone was safe and effective, with a recurrence rate of <6% at a mean of 6.8 years after treatment.

Level of Evidence
Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.
Malignant cartilaginous tumours are the second largest group of primary bone tumours.\textsuperscript{1-4} Most arise \textit{de novo}, although a small subset appears to be secondary to a pre-existing enchondroma.\textsuperscript{2,3} Approximately 90% of chondrosarcomas are of the conventional type. These are subdivided into peripheral and central subtypes on the basis of their distinct oncogenic pathway.\textsuperscript{3} Central chondrosarcomas constitute about 75% of all chondrosarcomas; the majority are low-grade.

The most important predictors of poor survival of patients with chondrosarcoma are a high histological grade and a patient age of more than fifty years.\textsuperscript{5} Surgery is the primary treatment of cartilage tumours, with the extent of the resectional margins depending on the tumour grade and location.\textsuperscript{6,7} Radiation therapy and chemotherapy have no substantial role in the treatment of chondrosarcomas.\textsuperscript{4,8-12}

Grade I tumours are characterized by a local destructive growth pattern and a tendency for local recurrence after surgery without adequate margins.\textsuperscript{13} The clinical course cannot always be predicted on the basis of the histological grade alone.\textsuperscript{1,13} Distant metastasis of low-grade chondrosarcoma is very rare (2% to 5%).\textsuperscript{10,13-15} Five-year patient-survival rates of 85% to 90% have been described for grade I chondrosarcoma.\textsuperscript{13-15}

The outcome of treatment of low-grade chondrosarcoma of long bones is good, but obtaining wide margins of resection can be associated with complications and morbidity. As a result, intralesional treatment has been used for low-grade chondrosarcoma. Different forms of adjuvant therapy to reduce the local recurrence rates have been reported.\textsuperscript{16-19}

The use of polymethylmethacrylate (PMMA)\textsuperscript{20} is based on the hypothesis that it kills the residual tumour cells by thermal heating of the bone cavity following curettage. The maximum peripheral extent of a thermal lesion induced by polymethylmethacrylate ranges from 2 to 5 mm in cancellous bone.\textsuperscript{20,21} An advantage of using polymethylmethacrylate is the possibility of early weight-bearing.\textsuperscript{21} Cryosurgery is performed with cycles of low temperature to induce tissue necrosis with the intent of ablation by freezing, holding of freeze, thawing, and repetition of this cycle.\textsuperscript{17} The local extent of treatment with cryosurgery is at least 7 to 12 mm beyond the surgical margin.\textsuperscript{22} The side effects of cryosurgery are nerve damage (temporarily), fractures, and infections.\textsuperscript{18,23}

Application of 85% phenol as adjuvant therapy followed by washing of the cavity with 96% ethanol has been found to be effective treatment of chondrosarcoma-derived cell lines \textit{in vitro}.\textsuperscript{24} It is difficult to measure the depth of necrosis after application of phenol because phenol causes cell-wall disruption precipitation and coagulation necrosis. We are not aware of any clinical studies of the \textit{in vivo} effect of
phenol as an adjuvant to curettage in the treatment of low-grade chondrosarcoma. The reported results of treatment of patients with chondrosarcoma are difficult to interpret because of differences in grading criteria, combining of axial and appendicular tumours, and mixing of treatments.\textsuperscript{8,10,14,15,25} The goal of this study was to determine the clinical outcomes of patients with grade I chondrosarcomas of appendicular long bones, all of whom were treated, during one procedure, with intralesional curettage, followed by adjuvant therapy consisting of 85\% phenol and 96\% ethanol, followed by bone-grafting.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{skeleton.png}
\caption{Distribution of the eighty-five chondrosarcomas in the appendicular long bones. The proximal part of the humerus and the distal part of the femur were most frequently affected.}
\end{figure}
Materials and methods

We performed a retrospective study of 85 patients in whom a grade I central chondrosarcoma of a long bone had been treated in our hospital between 1994 and 2005. Patients from hospitals in the surrounding areas who were suspected of having chondrosarcoma were referred to our musculoskeletal oncology department. All patients underwent a preoperative gadolinium enhanced magnetic resonance imaging (Gd-MRI) scan prior to surgery.

The indication for surgery was the likely presence of low-grade chondrosarcoma located in one of the long bones on the Gd-MRI scan. The average age at surgery was 47.5 years (range, 15.6 to 72.3 years). Surgery consisted of an oncologically safe biopsy, followed by intralesional curettage immediately or two weeks later.

There were 85 patients in this series. Frozen-section biopsy followed by curettage was performed during the same operation in 25 cases, whereas sixty patients had a two-stage procedure. In 13 of these 60 patients, the biopsy had already been done by the referring physician. All biopsy results were reviewed again by an experienced pathologist at our hospital (P.C.W.H.) who specializes in the pathology of bone and soft tissue tumours. The lesions were histologically classified according to the recently published consensus criteria and graded according to the system described by Evans et al. Patients were included in this study on the basis of a histological diagnosis of grade-I central chondrosarcoma located in a long bone (Figure 1).

The initial volume of the tumour was measured preoperatively with use of dynamic Gd-MRI scans. Due to the difficulty in measuring a three-dimensional structure on two-dimensional MRIs, all lesions were measured by projecting an imaginary cylinder. The average maximal radius \( r \) (anterior-posterior and medial-lateral) and maximal height of the tumour \( h \) (craniocaudal) were used as parameters to calculate the volume of a cylinder \( V = \pi r^2 h \). Depending on the largest diameters, different sequences of the MRIs were used.

Depending on the site of the tumour, patients received general or regional anaesthesia for definitive treatment. Following preoperative identification of the precise location of the bone window on MRI, a small incision was made without the use of any Hohmann retractors to avoid possible tumour spill to other anatomical compartments. A window was thus created in the middle of the length of the tumour. The chondrosarcoma was removed macroscopically with use of small curets. No high-speed burr was used. The mechanical extension of the margin was determined by both the cortical border and the intramedullary canal. If there was doubt about whether all of the cartilage had been removed, fluoroscopy was used to detect any...
calcified cartilage. A solution of 85% phenol (Liquid Phenol, Ph Ned Ed VI quality; BUFA bv, Pharmaceutical Products, Uitgeest, The Netherlands) was applied for a period of five minutes to the interior of the remaining bone cavity with a surgical swab. The phenol was subsequently rinsed with a 96% ethanol solution. Finally, the bone cavity was filled with deep-frozen, non irradiated allograft bone chips derived from donor femoral heads (Bio Implant Services, Leiden, The Netherlands). During surgery, the bone window was submerged in a phenol solution and then rinsed with ethanol. Following placement of the bone graft, the bone window was replaced.

Prior to discharge, a postoperative radiograph was made for all patients to ensure that there were no postoperative complications. Additional radiographs were obtained six and twelve weeks after the procedure to establish the extent to which the patient could safely resume normal activities.

Patients were also scheduled for a dynamic Gd-MRI scan six months after the procedure. The first scan was used as a baseline so that, with the following scans, a distinction could be made between the postoperative effects and the possible recurrence of chondrosarcoma. Dynamic Gd-MRI scans, in addition to radiographs, repeated six months later and then periodically (Figure 2). Patients were evaluated clinically on an annual basis. The average duration of follow-up was 6.8 years (range, 0.2 to 14.1 years).

In case a recurrence of the cartilaginous tumour was suspected on evaluation of the Gd-MRI scan, and the recurrent lesion was ≥10 mm, curettage, phenol application, and bone-grafting, as described for the index procedure, was repeated and the curedt tissue was evaluated histologically. With small lesions (<10 mm), a computed tomography-guided biopsy was performed and the specimens were evaluated histologically. In the same procedure, radiofrequency ablation was performed, with acceptance of overtreatment in the cases in which no recurrence of tumour would be diagnosed. Following these procedures, patients with recurrent chondrosarcomas were treated according to the postoperative protocols described above, including follow-up Gd-MRI scans.

Data analysis was performed with Excel (Microsoft, Redmond, Washington), SPSS (version 17.0 for Windows; SPSS, Chicago, Illinois), and R (version 2.10.0; R Foundation for Statistical Computing, Vienna, Austria).

We used the Kaplan-Meier product-limit estimator to analyze the survival rate, with recurrence as the end point. We treated patients who were lost to follow-up as censored at their last recorded visit. One patient died of an unrelated cause during the follow-up period, and we treated this death as a competing risk.
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Figure 2. A series of T2-weighted Gd-MRI scans of a 62-year-old female patient with a grade I chondrosarcoma.

A Preoperatively, the typical ring-and-arc structure of a cartilage tumour is seen in the proximal part of the humerus.
B On the first postoperative MRI, acquired eight months postoperatively, postoperative edema persists.
C After seven years, the bone graft is incorporated, and no signs of tumour recurrence are seen.

Results

General

The average duration of follow-up for the patients was 6.8 years (range, 0.2 to 14.1 years), with five patients being followed for less than two years. One patient, followed for two months, came from abroad to have surgery in our clinic and returned to his home country after surgery. One female patient, 72 years of age at the time of surgery, lived at a substantial distance from the hospital; given her age, she was referred to a hospital near her home for follow-up. Three other patients were lost to follow-up. With use of the Kaplan-Meier estimator, the patients who were followed for a limited duration were censored at their last recorded visit.

Patients were admitted to the hospital for one to three days, depending on the site of the chondrosarcoma. Postoperative management depended on the tumour site and the size of the bone window. Patients with a chondrosarcoma in the upper extremity were managed with a sling for two to six weeks postoperatively. Following curettage in the lower extremities, patients were either non-weightbearing or partially weight-bearing for six weeks and used crutches once they were mobile. None of the patients were treated with internal fixation, and casts were not necessary because of the less
invasive and limited nature of our surgical procedure compared with wide resection and reconstruction of the long bone.\textsuperscript{29}

**Tumour volume**

The preoperative mean volume of the lesions, measured on MRI scans, was 23.7 cm\(^3\) (range, 1 to 104 cm\(^3\)). The median volume was 18.8 cm\(^3\) (Figure 3).

![Figure 3. Box plot for preoperative tumour volume, showing a median volume of 18.8 cm\(^3\) (range, 1 to 104 cm\(^3\)) and a large spread of volumes for the larger tumours above the median.](image)

**Histological findings**

All patients were diagnosed with a grade I central chondrosarcoma, according to the recently published consensus criteria\textsuperscript{28} and the system described by Evans et al.\textsuperscript{13} (Figure 4).
Comorbidity

Four (7%) of the 55 women had a history of breast cancer or developed this tumour during the period of follow-up of the cartilage tumour.

Complications

One patient developed a superficial wound infection postoperatively, which resolved with antibiotics. Two (5%) of the 39 patients treated for a tumour in the femur experienced a femoral fracture, which was likely due to the bone window, within six weeks after surgery. One of these patients was treated with open reduction and internal plate fixation, and the other was treated with an intramedullary nail. Gd-MRI performed five years after removal of the nail did not show any sign of tumour recurrence. Patients with chondrosarcoma of the femur appear to have a higher fracture risk, which can be addressed with a hip spica cast and non-weightbearing with two crutches. The prophylactic use of internal fixation should be avoided, to allow follow-up MRI and to avoid a second surgical procedure for removal of the metallic implants.
Repeat interventions

Remaining tumour was suspected in eleven patients on the basis of postoperative Gd-MRI scans. All of these patients underwent repeat procedures. Depending on the size of the lesion, biopsy followed by radiofrequency ablation (for tumours of <10 mm) or repeat curettage (for those of ≥10 mm) was performed. All tissue obtained with biopsy prior to radiofrequency ablation or with curettage was sent for histological analysis. These analyses showed recurrence of the grade-I chondrosar-

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CHS I = grade I chondrosarcoma
CPEB = curettage, 85% phenol, 96% ethanol, and bone-grafting
RFA = radiofrequency ablation

Eleven patients with a suspected lesion on Gd-MRI had repeat intervention. Five patients had a histologically proven recurrence of a grade I chondrosarcoma. No tumour progression was seen.
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coma in three of the six patients who underwent radiofrequency ablation and no signs of recurrence in the other three. Of the five patients who underwent repeat curettage, two were found to have recurrence of the grade-I chondrosarcoma and three had no signs of recurrence (Table 1). The recurrence rate in this series was 5.9% (95% confidence interval [CI], 0.9% to 10.9%).

The serial Gd-MRI scans did not show any signs of tumour recurrence in the remaining 74 patients. With regard to the ability of the Gd-MRI to predict recurrence of chondrosarcoma in this series, the positive predictive value was 45% and the negative predictive value was 100% (Table 2).

<table>
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*Eleven of the eighty-five patients had, on the postoperative Gd-MRI scans, a suspected lesion and underwent a second surgical procedure. Of these eleven patients, five had a recurrence proven by histological examination.
Positive predictive value = 45%, negative predictive value = 100%, sensitivity = 100%, and specificity = 93%.

Survival

The survival rate, with histologically proven recurrence of grade-I chondrosarcoma as the end point, was 91.3% (95% CI, 84% to 99.4%) at a mean of 6.8 years after the first surgery (Figure 5).

Mortality

One patient died, due to an adenocarcinoma of the pancreas, during the follow-up period.
from histologically proven recurrence of grade I chondrosarcoma as the end point, was 91.3% (95% CI, 84.4% to 99.4%) at a mean of 6.8 years after the first surgery.

Figure 5.
Survival curve, showing five patients with a postoperative recurrence of a grade I chondrosarcoma as the event. The survival rate, with histologically proven recurrence of grade I chondrosarcoma as the end point, was 91.3% (95% CI, 84.4% to 99.4%) at a mean of 6.8 years after the first surgery.

Discussion

We describe a large group of patients with grade I central chondrosarcomas of the long bones who were treated with intralesional curettage followed by application of phenol and ethanol as adjuvant therapy and then by bone-grafting. The use of phenol as an adjuvant in the treatment of bone tumours has been described only in small patient series that have included a variety of tumours, both benign and malignant. Although efficacy of this treatment has been proven *in vitro*, it has been difficult to convincingly demonstrate the efficacy of phenol as an adjuvant in humans.

This study is limited by its observational and retrospective design. We did not use a control group to compare the results. The ideal situation would be to perform a prospective, multicenter, randomized trial comparing phenol with cryotherapy or polymethylmethacrylate adjuvant treatment.

Four (7%) of the 55 women in our series had also been diagnosed with breast cancer in the past or during the follow-up period. Odink et al. described an odds ratio of 7.62 to be diagnosed with both breast cancer and a cartilaginous tumour. Therefore,
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Performing follow-up only with radiographs to detect local recurrence overestimates the disease-free survival. We therefore use Gd-MRI to follow our patients. On the first postoperative scan, it is sometimes difficult to distinguish between the normal postoperative appearance as a consequence of the use of bone grafts from femoral heads and the presence of postoperative edema at the surgical site. A second scan is therefore often decisive because the postoperative changes are lessened and the lesion suspected of containing residue is still clearly enhanced within ten seconds on the dynamic series of the Gd-MRI scan. In retrospect, the cause of the residual tumour in the two recurrent femoral cases in our series was surgical in nature. The residual tumour remained as a result of incomplete curettage, primarily as a consequence of a bone window that was too small or had been placed in a suboptimal location; this is particularly a risk for femoral diaphyseal lesions. No significant correlation was seen between preoperative tumour size and recurrence rates (Table I).

The distinction between benign and malignant cartilaginous tumours is often subject to discussion. To improve the reliability of the diagnosis of these lesions, Eefting et al. performed a study on interobserver variability. With use of the recently proposed consensus criteria, 94.7% of their cases were diagnosed correctly (sensitivity, 95%; specificity, 95%). Eighteen pathologists from Europe and the United States participated in that study. In our study, all specimens were reviewed again by an experienced pathologist who is familiar with the above criteria. In our series, recurrence was identified in five patients (5.9% [95% CI, 0.9% to 10.9%]). None of the recurrent tumours had a higher histological grade than the original tumour. However, eleven patients underwent repeat surgery because residual lesion was suspected. Regarding the use of Gd-MRI to predict recurrence of tumour, the positive predictive value was 45% and the negative predictive value was 100%. In this series, postoperative Gd-MRI overestimated the number of recurrent lesions. We started using this new method of treating low-grade central chondrosarcoma in 1994, at which time the technique was deemed controversial in Europe because of concerns about its oncological safety. In light of this, the threshold for surgery in the event of a suspected lesion on postoperative Gd-MRI was low. Throughout the past fifteen years, we have gained greater insight into the benign nature of these residuals or recurrent lesions and we now take a more conservative approach toward repeat surgery for small suspected lesions. Despite the large number of false-positive results in the past, Gd-MRI remains the most sensitive tool for
detection of small residual or recurrent lesions. The use of phenol as an adjuvant as described in this study has potential advantages for the patients. In contrast to cryosurgery, where up to 14% of patients sustain a postoperative fracture, there was no need for prophylactic implant placement to prevent fractures. Moreover, joints adjacent to the surgical site are not impaired by this procedure.
Source of funding

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References