Local Treatment with Adjuvant Therapy for Central Atypical Cartilaginous Tumors in the Long Bones
Analysis of Outcome and Complications in One Hundred and Eight Patients with a Minimum Follow-up of Two Years

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In this study, we present the outcome for a large cohort of patients with ACT/CS1 in the long bones who were treated with curettage and adjuvant phenolization and followed for a minimum of two years according to national guidelines.

**Background:** A central atypical cartilaginous tumor (ACT)—formerly known as chondrosarcoma grade 1 (CS1)—is a tumor of intermediate-type malignancy, often treated with surgery. The extent of surgery remains controversial, as some advocate resection and others favor local treatment by curettage. Because of the low prevalence of ACT/CS1, the available data are limited and generally not uniform. The purpose of this study was to present the outcome for a large cohort of patients with ACT/CS1 in the long bones who were treated with curettage and adjuvant phenolization and followed for a minimum of two years according to national guidelines.

**Methods:** A retrospective study was designed to analyze data from 108 patients treated for central ACT/CS1 in the long bones between 2006 and 2012. All patients were treated with curettage and adjuvant phenolization, and defects were filled with polymethylmethacrylate, bone graft, or bone substitutes. The primary end point was local recurrence or residual tumor. Secondary end points included the type and rate of complications and reoperations.

**Results:** All patients were free from local recurrence at a mean follow-up of 48.7 months (range, 24.3 to 97.5 months). Residual tumor was suspected in five patients, leading to a 95.4% disease-free survival rate. A fracture occurred in eleven patients (10.2%). Other complications were osseous penetration during the surgery (two patients), wound infection (one patient), arthrofibrosis (one patient), and skin necrosis (one patient). Tumor volume was related neither to the risk of fracture nor to the occurrence of residual tumor.

**Conclusions:** In our experience, curettage of ACT/CS1 in the long bones with adjuvant phenolization is safe, even with large tumors of up to 100 cm³. Most worrisome is the risk of fracture, which occurred in 10.2% of our patients. Considering the relatively mild behavior of ACT/CS1, less aggressive treatment, by observation or by minimally invasive surgery, could be the next step that should be evaluated prospectively.

**Level of Evidence:** Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.
dedifferentiated chondrosarcoma. Grade-1 tumors were recently renamed atypical cartilaginous tumors (ACTs) by the World Health Organization (WHO). ACTs of the long bones are cartilaginous tumors with very limited metastatic potential but unpredictable local aggressive growth. They are frequently incidental findings, and are being found more often as a result of an increasing use of computed tomography (CT) and magnetic resonance imaging (MRI) for common shoulder and knee symptoms. This presents a growing challenge for the oncological orthopaedist, since only a few of these patients will ever develop a chondrosarcoma. Historically, a diagnosis that is based on imaging has been deemed unreliable. To prevent a tumor upgrading after recurrence or a misdiagnosis of a grade-2 for an ACT/CS1 tumor, the latter was also treated by en bloc resection or amputation. In general, if treatment is necessary, surgery is the mainstay of treatment for cartilaginous malignancies, since they are relatively insensitive to systemic therapy and irradiation. Higher-grade tumors show detrimental survival curves and need more aggressive surgery, and ACT/CS1 localized in the axial skeleton may require such an approach. More recent data have shown that central ACT/CS1 tumors involving the long bones seem to do well with local therapy. Several case series have demonstrated that the outcomes from curettage with adjuvant phenol and ethanol irrigation or cryosurgery are not inferior to the outcomes from wide resection in terms of survival. Obviously, functional outcome improves dramatically when limbs and joints are saved. Outcome data for this approach are scarce. Additional data on these patients are therefore valuable, particularly if tumor volume is taken into account together with mid-term to long-term follow-up. Therefore, the purpose of the present study was to analyze the oncological outcome for all consecutive patients in our hospital with ACT/CS1 in the long bones treated with intralesional curettage with local adjuvant therapy.

Materials and Methods
A retrospective analysis was done from a prospectively gathered database. All patients with a final diagnosis of ACT/CS1 in the long bones who were treated with curettage, application of phenol and ethanol as adjuvant therapy, and additional bone-grafting were included (Fig. 1). Patients were surgically treated between October 2006 and November 2012 at our hospital and had a minimum follow-up of two years. Patients who had been previously treated with radiofrequency ablation were included as well (Figs. 2-A and 2-B). Exclusion was based on previous treatment for the same lesion elsewhere. All patients were informed that clinical and radiographic data could be used for scientific purposes. This is in accordance with the regulations of the medical ethical review board of our hospital, which approved our study. If patients had objections to the use of their data, these data were not included in the study.

Treatment Protocol
If a patient was suspected of having an ACT/CS1 tumor on the basis of the history, physical examination, and imaging, agreement about diagnosis and treatment type was achieved during the weekly multidisciplinary meeting with an orthopaedic oncologist, musculoskeletal pathologist, musculoskeletal radiologist, and general oncologist. On the basis of gadolinium-enhanced MRI, lobular intramedullary lesions were diagnosed as ACT/CS1 in the presence of intermediate T1-weighted signal intensity, increased T2-weighted STIR (short tau inversion recovery) signal intensity, and mild endosteal scalloping. Peritumoral edema, cortical expansion, periostitis, cortical destruction, or soft-tissue extension had to be absent, since they are suggestive of a higher-grade malignancy.

After informed consent was obtained from the patients, a specialty-trained oncological surgeon performed the operations. In this procedure, the tumor was reached through a cortical window under the guidance of fluoroscopy or computer-assisted surgery and subsequently was removed using a curet. Technical details concerning the computer-assisted surgery have been described previously. After phenolization (85% concentration) lasting at least two minutes, ethanol irrigation (96% concentration), and saline solution rinsing, polymethylmethacrylate (PMMA) cement (Palacos; Heraeus Medical) or other fillings were used to fill the cavity (Figs. 3-A through 3-D). If needed, a prophylactic surgical stabilization was performed. Tissue retrieved during surgery was sent for histological evaluation by a senior musculoskeletal pathologist. After surgery, patients were admitted to the hospital and then were discharged if the pain level and wound drainage were acceptable. During admission, a conventional radiograph was made to check for osseous complications and to serve as a baseline image for follow-up. Patients were instructed regarding mobility and weight-bearing, which was supervised by physiotherapists. Further follow-up was done according to protocol.

End Points and Statistical Analysis
The primary end point was local recurrence or evidence of residual tumor after surgery. Secondary end points were death from disease, metastasis, tumor upgrading or dedifferentiation, and type and rate of complications. Outcome data were obtained from clinical charts and our hospital database.

Fig. 1
T1-weighted MRI scan of a typical image of an ACT in the proximal part of the humerus, showing a large lesion, wall-to-wall filling, but no signs of higher-grade aggressiveness.
Complications were defined as an unintended adverse event leading to reintervention, increased duration of admission, or readmission within three months of the primary operation. The mean and range of values were noted for all variables. Measurements of tumor size were based on MRI scans with a 4-mm slice thickness and CT scans with 1.5-mm slice thickness. Tumor volume was estimated as \( \pi \times \text{radius}_{\text{max}}^2 \times \text{height} \), where \( \text{radius}_{\text{max}} \) is the mean of the maximum anterior-posterior and mediolateral radii. Analysis of the data was performed with IBM SPSS Statistics for Windows (version 22; IBM). If applicable, differences in means were tested with the Student t test, and a p value of <0.05 was considered significant.

Source of Funding
No external funding was received for this study.

Results

Demographics (Table I)

A total of 112 patients were included. The mean age was 53.6 years (range, 25.7 to 82.1 years), with a male-to-female ratio of 1:1.8. The most commonly affected bone was the femur (sixty-three patients), followed by the humerus (thirty-three patients). The mean tumor volume was calculated as 17.5 cm³ (range, 1 to 100 cm³), with the craniocaudal length of the tumor ranging from 10 to 165 mm. Neoadjuvant radiofrequency ablation was performed in forty patients, followed by conventional curettage after three to four months. In thirty patients, curettage was done by conventional means, but with image guidance using computer assistance instead of fluoroscopy. Filling of the cavity was done with PMMA cement (Palacos; Heraeus Medical) in ninety-two patients (82.1%), with (autologous) bone chips in seventeen, and with synthetic bone (Vitoss [Stryker] or PRO-DENSE [Wright Medical]) in three. Prophylactic surgical stabilization with a plate was used in fifteen patients (13.4%) who had a lesion in the femur.

Outcome (Table II)

Four patients were lost to follow-up, leaving 108 patients (96.4%) for analysis. Of the four patients, three wanted routine

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**Fig. 2-A**

**Figs. 2-A and 2-B** T2-weighted MRI scans of a patient with an ACT in the femur that had been previously treated with radiofrequency ablation. **Fig. 2-A** The tumor is surrounded by a dense ring—a so-called halo—suggesting that the tumor is completely within the ablation zone.
checkup at their nearest hospital and one patient had rectal carcinoma, which required palliative treatment.

All patients were free from local recurrence at a mean follow-up of 48.7 months (range, 24.3 to 97.5 months). Residual tumor was suspected in five patients, leading to a 95.4% disease-free survival rate at a minimum follow-up of two years. Four of these five patients had a tumor in the humerus, which was significantly more frequent than in the disease-free population (p = 0.014) (Table III). An observation strategy was agreed on for four patients in whom residual tumor was suspected. None of these patients showed growth of the tumor over time. The fifth patient needed a total knee replacement because of concomitant osteoarthritis and was treated for the residual tumor in the same session (Figs. 4-A, 4-B, and 4-C). Neither metastatic disease nor upgrading of the tumor was seen in any of the patients; no patient died of the disease.

Regarding complications, a fracture occurred in eleven patients (10.2%) after a mean of five weeks (range, one to 13.3 weeks) (Fig. 3-B). Fractures were seen in the diaphysis of the femur (nine patients) and the humerus (two patients). All patients were treated with open reduction and internal fixation; four patients needed multiple surgeries for nonunion or hardware removal (Fig. 3-C). Other complications were local crack creation during the surgery as a result of the bone window (two patients who both had a crack in the femoral diaphysis), wound infection (one patient), arthrofibrosis (one patient who needed manipulation), and skin necrosis of a pretibial wound (one patient). Tumor volume was related neither to the risk of fracture nor to the occurrence of residual tumor.

Discussion

Over the last two decades, treatment of low-grade cartilaginous lesions has increasingly become a topic of debate. The need for awareness of potential misdiagnosis of the entity is stressed, to prevent possible overtreatment or undertreatment. A negative impact on survival as a result of local recurrences has been seen in previous studies. A decade ago, local treatment of a recurrence was regarded...
Figs. 3-A through 3-D Radiographs of a patient with a tumor in the distal end of the femur. **Fig. 3-A** Postoperative image of the distal end of the femur after curettage and filling of the defect with PMMA. **Fig. 3-B** After a low-energy trauma led to a fracture in the cement zone, open reduction and internal fixation was performed. **Figs. 3-C and 3-D** An atrophic nonunion developed (**Fig. 3-C**) for which a repair was needed, eventually leading to a satisfying result twenty-eight months after the initial trauma (**Fig. 3-D**).
as undesirable from an oncological perspective, since a less harmful lesion can turn into a more aggressive tumor, thus increasing morbidity and even mortality. As a result, some authors have questioned whether local treatment of low-grade cartilaginous tumors such as ACT would be sufficient. Currently, local recurrence is often said to be a sign of higher-grade tumors. With overall improvement of the diagnostic imaging tools available and increased experience in treating these low-grade cartilaginous tumors, a trend toward less extensive local surgery can be observed in the literature. One must be aware that objective histological criteria for intramedullary cartilaginous tumors of the long bones have not been defined. As a consequence, even pathologists with a special interest and expertise in bone tumors cannot accurately discriminate between enchondroma and ACT. Histologically, host bone entrapment is currently the best criterion of aggressive invasive growth, by which the tumor may be diagnosed as an ACT. However, this feature is seldom evident in the initial diagnostic needle biopsy or in tumor tissue obtained by curettage. As a consequence of this diagnostic dilemma and because of our lack of understanding of the natural behavior and progression of these tumors, the term atypical cartilaginous tumor was created in the 2013 WHO classification of bone tumors. In addition, the age of the patient, size of the lesion, and erosion of cortical bone cortex can only be considered surrogate markers of potential aggressive growth.

Our current knowledge of the genetic and epigenetic events occurring in cartilaginous tumors of the long bones and their relation to tumor progression is still limited. Isocitrate dehydrogenase 1 (IDH1) and IDH2 mutations, which are considered to be an early event in the genesis of central cartilaginous tumors in the long bones, are found in at least half of the lesions diagnosed as enchondromas, in addition to their presence in most chondrosarcomas. Both enchondromas and ACT/CS1 are diploid or nearly diploid tumors, whereas only chondrosarcomas of higher grades (grades 2 and 3) show polyploidization and aneuploidy. Thus, to date, it is impossible to reliably predict the future local aggressive behavior of a cartilaginous tumor of the long bones by routine histological or genetic analysis.

With this in mind, we demonstrated that a minority (4.6%) of our patients had a tumor mass remaining after surgery if it had been treated with curettage and adjuvant phenolization. This finding had no impact on patient survival. Moreover, neither actual local recurrence nor upgrading in the local residue occurred. If residual tumor was evident, it was found significantly more often in the humerus than in other bones, which might be because it is more

<table>
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<tr>
<th>TABLE I Demographics of All Patients Included</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Mean age at time of treatment (range) (yr)</td>
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<tr>
<td>Location of tumor</td>
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<tr>
<td>Femur</td>
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<td>Humerus</td>
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<td>Tibia</td>
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<td>Fibula</td>
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<td>Ulna</td>
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<td>Mean calculated tumor volume (range) (cm³)</td>
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<tr>
<td>Surgery type</td>
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<tr>
<td>Curettage and phenolization</td>
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<tr>
<td>Neoadjuvant radiofrequency ablation*</td>
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<tr>
<td>Computer-assisted surgery*</td>
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<tr>
<td>Bone-grafting</td>
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<td>Bone chips</td>
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<td>Synthetic bone</td>
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*Regardless of other surgical interventions (radiofrequency ablation, computer-assisted surgery, or prophylactic hardware).
challenging to have adequate fluoroscopy in the humerus. Moreover, lesions within the humeral head often display tentacle-like features.

To our knowledge, the present study is the largest case series to date (Table IV), with a very satisfying 96.4% of patients who had complete follow-up of over two years. Follow-up was done according to a consensus-based, nationwide follow-up protocol\(^9\). We know of no evidence in the literature with regard to the frequency and content of follow-up evaluations. In our opinion, peer-based national (and preferably international) agreement on treatment and follow-up for rare tumors such as these is very useful and should possibly even be mandatory to improve overall outcome.

Limitations of the present study include its retrospective nature and the lack of control subjects. One may argue that selection biases our findings, yet large lesions were also treated by curettage. Only one previously published series, to our knowledge, has assessed tumor volume, although minimum follow-up was relatively short (0.2 year)\(^16\). In our series with a minimum follow-up of two years, we demonstrated that it is safe to treat ACT/CS1 lesions of up to 100 cm\(^3\) in the long bones, with no association seen between tumor volume and occurrence of

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex, Age (yr)</th>
<th>Location</th>
<th>Tumor Volume (cm(^3))</th>
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<tr>
<td>1</td>
<td>F, 40</td>
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<td>2</td>
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<td>26</td>
<td>PMMA</td>
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<tr>
<td>3</td>
<td>M, 44</td>
<td>Diaphysis of humerus</td>
<td>26</td>
<td>PMMA</td>
</tr>
<tr>
<td>4</td>
<td>F, 50</td>
<td>Distal metaphysis of femur</td>
<td>13</td>
<td>Bone chips</td>
</tr>
<tr>
<td>5</td>
<td>F, 52</td>
<td>Proximal metaphysis of humerus</td>
<td>9</td>
<td>PMMA</td>
</tr>
</tbody>
</table>
A patient who had a residual tumor. Figs. 4-A and 4-B Gadolinium-enhanced T2-weighted MRI scan (Fig. 4-A) and conventional radiograph (Fig. 4-B), made thirty-five months after curettage, showing the residual tumor. Fig. 4-C Because of osteoarthritis, total knee replacement was performed, curetting the lesion in the same session.
residual tumor, local recurrence, or risk of fracture. None of the patients who had local treatment had higher-grade tumors. This finding is in line with a recent study by Brown et al., who stated that it is safe to treat ACT/CS1 tumors without biopsy if imaging seems conclusive.

The exact role of phenol and ethanol as adjuvants is unknown, although Verdegaal et al. demonstrated in a previous in vitro study that they both had cytotoxic effects on chondrosarcoma tumor cells [27]. Since no adverse events due to phenolization have been reported in larger case series, its use can be deemed safe and, given the earlier studies, it is expected to enhance local tumor control.

We did not include functional results according to the Musculoskeletal Tumor Society (MSTS) scores, as this was not adequately done on a prospective basis. However, from published reports, we know that after curettage, MSTS scores are consistently good to excellent, with mean scores of 88% to 98% [9,10,12-15]. Considering the nature of the surgical procedure, we expected our patients to perform equally well. As can be seen in Table IV, patients treated with resection had lower mean MSTS scores, ranging from 73% to 84%.

Our main concern was the occurrence of a fracture in up to 10.2% of patients, which is relatively high compared with that in previous studies. Because of this observation, we agreed on using prophylactic plate fixation with a low threshold, on the basis of the surgeons’ judgment, which is reflected in our data from this cohort. Most fractures occurred in the first weeks after surgery in lesions treated in the midpart of the femur. In general, such fractures lead to a reoperation for open reduction and internal fixation, which is often followed by removal of the hardware months to years later and prolonged rehabilitation periods. This treatment carries an increased risk of perioperative complications, so the cure might be worse than the disease.

Ongoing debate remains with regard to whether small lesions should be treated surgically at all. There is some agreement among experts that it seems safe to monitor these tumors. In line with this opinion, we tend to follow the more indolent tumors closely, instead of immediately treating them surgically (Fig. 5). However, there is a lack of literature that supports this strategy, and we therefore favor the performance of a (multinational) prospective cohort study that could address this matter. In the absence of definitive answers, we believe that a physician should discuss the pros and cons of each strategy with his or her patient.

In conclusion, not a single patient who had an ACT in the long bones and was treated with curettage and adjuvant phenolization had local recurrence, metastatic disease, or upgrading of the tumor. The present study adds valuable data to the limited existing evidence that it is oncologically safe to surgically treat these tumors intrasesionally. Although residual tumor was seen in 4.6% of the patients, this finding did not influence patient survival, and intralesional treatment can be considered noninferior in oncological outcome compared with wide resection. On the basis of the literature, curettage is superior in terms of functional results; however, despite preventive measures, fracture rates were relatively high after curettage in our patients. Future research needs to focus on improving diagnostic accuracy and on less invasive or even conservative strategies to spare patients from...
unnecessary surgical interventions, without compromising oncological results.

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References


Fig. 5
T1-weighted MRI scan of a patient with an CS1/ACT in the femur who was managed with four years of conservative treatment. The tumor showed no signs of aggressiveness over time.