Computer-assisted surgery for curettage of atypical cartilaginous tumors / chondrosarcoma grade 1 in the long bones compared to fluoroscopic guidance

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Under review
Abstract

Background and Objectives: Fluoroscopy is currently the standard imaging modality for curettage of atypical cartilaginous tumours (ACT/CS1). Computer-assisted surgery (CAS) is a possible alternative, offering higher resolution imaging and continuous three-dimensional feedback without ionizing radiation use. CAS hypothetically makes curettage more accurate, thereby improving residue or recurrence rate. This study aims to compare CAS and fluoroscopy.

Methods: Patients were selected from a prospectively kept local bone tumour database. CAS and fluoroscopy were used in parallel. Included were patients who had curettage for ACT in the long bones, with a minimum follow-up of 12 months. Tumour volume was measured on pre-operative MRI scans. Outcome comprised local recurrence and residue rates, complications like fractures and procedure time.

Results: 77 patients were included, 17 in the CAS cohort, 60 in the fluoroscopy cohort. Tumour volume was significantly larger in the CAS cohort (p = 0.04). Residual tumour (2/17 vs. 6/60), fracture rate (3/17 vs. 6/60) and surgical time (1.26h vs. 1.34h) did not differ significantly. There were no recurrences in either group.

Conclusions: CAS curettage showed good oncologic results. Outcome was comparable to fluoroscopy, while not using ionizing radiation. Residue rates can likely be decreased with specific software functions and surgical tools.
Introduction

Atypical cartilaginous tumour (ACT), previously named chondrosarcoma grade one (CS-1), is one of the most frequently treated lesions in orthopaedic oncology (1). The most commonly affected sites are the diaphysis of the proximal and distal femur, the pelvis, the proximal tibia and humerus. Incidence of chondrosarcoma as a whole was estimated in an analysis of the American Surveillance, Epidemiology and End Results (SEER) database as 1 in 200,000 per year (2). A report of the European ESMO/EUROBONET registration describes the yearly incidence of chondrosarcoma as ~0.1/100,000 (3).

Because of ACT/CS-1’s potentially malignant nature, the surgical goal is a 100% removal of the tumour to prevent local recurrences and its associated decrease in patient survival (4, 5). Up until around the 1980’s treatment of all chondrosarcoma consisted of resection with wide margin. Better clinical and pathological knowledge and improved diagnostic techniques suggested this was not necessary for the less aggressive, low grade, lesions. The current standard surgical treatment consists of intralesional curettage often supported with fluoroscopy and the use of a local adjuvant such as phenol/ethanol or liquid nitrogen (6, 7). Reconstruction is frequently done with polymethylmethacrylate (PMMA), synthetic fillers, allografts or autografts. Depending on location and tumour characteristics, like X-ray visibility, it can be difficult to perform a complete curettage. Cartilage content of the tumour does not always contain sufficient calcification to reliably depict the whole lesion on fluoroscopy. The percentage of residual tumour after curettage is possibly significant, assuming that (early) local recurrence is often in fact local residue (8). Three-dimensional intra-operative imaging based on MRI may very well be an improvement in this aspect.

Fluoroscopy, the current standard, offers two-dimensional imaging and fluoro-video using X-band radiation (9). With the advances of computer technology in the operating room, a new potential alternative has been developed. Computer-assisted surgery (CAS) is a relatively new modality, originally developed for neurosurgery in the early 1990’s. The main advantage of CAS over fluoroscopy is that it gives real-time, continuous, high resolution 3D feedback, without the use of ionizing radiation. It uses pre-operative computed tomography (CT) and/or magnetic resonance imaging (MRI) scans as visual datasets. This means the surgeon is continuously aware of the tumour location and location of the instruments, with feedback on movement in three dimensions. In theory better orientation through CAS could make the surgery less demanding and improve clinical outcome in recurrence and residue rates. Cited disadvantages for CAS use are that there is no intra-operative assessment of the actual surgical result (i.e. the system shows a virtual result) and the system takes valuable surgical time to setup and configure (10, 11). This study
aims to compare fluoroscopy and CAS in terms of safety and efficacy in treatment of ACT/CS1 in the long bones.

Patients and methods

Design
A single centre retrospective cohort study was performed using the prospectively kept local bone tumour database. All patients with the procedure code for curettages of bone tumours were analysed. In accordance to regulations of the local Medical Ethical Review Board, all patients were informed about the fact that their data could be used for scientific research. If patients had objections to the use of their data these data were not included in the study.

Patients
Inclusion criteria were: a curettage type procedure for histologically proven ACT/CS-1 in the long bones with the use of the adjuvants phenol and ethanol with a minimum follow-up of one year. Exclusion criteria were: the use of other means of treatment for the same lesion (e.g. radiofrequency ablation or cryotherapy), a non-complete follow-up and procedures that treated a recurrence. As this was a retrospective study the techniques were not actively randomised. Both techniques were used in parallel, with CAS use depending on system availability, planning and dataset quality.

Outcome measures
The primary outcome measure was potential residue or local recurrence. Potential residue was defined as a suspect lesion (i.e. showing tumour like characteristics) reported on post-operative imaging, with consensus between the radiologist and orthopaedic surgeon. When there was no consensus an independent radiologist or orthopaedic surgeon was consulted. Recurrence was defined as a positive pathological sample for ACT/CS-1 after a (radiologically) tumour-free period. Secondary outcome measures were: fractures, defined as a fracture at the surgical site regardless of adequate or inadequate trauma, other complications and intra-operative and surgical time.

Tumour volume approximation was done for each case on pre-operative MRI scans. The method used was as described by Verdegaaal et al: calculation of the volume of an imaginary cylinder ($\pi \times r_{\text{max}}^2 \times h_{\text{max}}$). For $r_{\text{max}}$ the sum of maximum measured
radii anterior-posterior and medial-lateral was divided by two to produce the maximum radius. We defined hmax as the largest measurement of proximal-distal size (8).

Technique related time requirements were compared using the surgical time and patient-in-OR time. The surgical time was defined as the hours and minutes between first incision and wound closure as registered in the operative procedures registration database. Duration of the patient-in-OR time was defined as the period between the registered times of the patient entered the operating room and patient leaving the operating room.

**Patient work-up**

Pre-operative workup included a high resolution CT scan (for the CAS navigation group), a gadolinium enhanced MRI with or without Short inversion-Time Inversion Recovery (STIR) fat suppression sequences. Core needle biopsies were performed to rule out grade 2 chondrosarcoma; they were done under CT-guidance and classified by a specialized musculoskeletal pathologist. In case of earlier biopsy and referral, the material was revised by the pathologist. Pathology classification is standardized in the Netherlands by the Dutch Bone Tumour Committee, following the WHO classifications (12). The procedures were performed by two orthopaedic surgeons, assisted over the inclusion period by multiple orthopaedic surgeons in training.

**CAS workflow**

The curettages were done without pre-operative planning. Image fusion, generally CT with MRI, was done in the operating room while the patient was being prepared for surgery. The time consumption of tracker placement and software matching was measured using a stopwatch.

After bone exposure, the procedure differentiates from a standard (fluoroscopic) procedure. During a navigated procedure a CAS patient tracker was rigidly attached to the affected bone using two 3 mm pins. The pointer tool was then used for position checking, system calibration and remote control of the software. Image-based navigation was set-up by entering reference points both in software and on the patient. The point based match was refined by surface matching where data points are entered with the pointer tool directly on the navigated bone. The system then presents an approximation of accuracy based on the difference between the entered points and the bone surface. The aim was an approximation of accuracy of lower than 1.0 mm. A Stryker Navigation System II with OrthoMap 3D software (Stryker Mahwah, NJ) was used in all cases. Surface matching on MRI is not
supported on the used system. After the setup of the CAS the place for the bone window is determined using the pointer tool and the window is made in a regular fashion. The curettage technique, from a surgical point of view, is not different from a normal procedure; curettes are used to scrape out the lesion.

The CAS system was used as a continuous-on imaging modality during the curettage process. The curette was attached to a tracker (figure 1). During the procedure the situation on screen did not update as it was still based on pre-operative imaging data (figure 2). As such there was no definitive feedback until the post-operative radiographs. A final check at the end of the procedure is performed by using the navigated curette; it should access beyond all edges of the tumour. Screenshots were taken to register the extent of the curettage, comparable to a workflow with fluoroscopy. All CAS procedures were done without intra-operative fluoroscopy control.

**Fluoroscopy workflow**

During a fluoroscopy supported curettage procedure imaging data was loaded onto digital displays in the OR for use during surgery. After dissection the lesion was localised with the fluoroscope to guide the place for the bone window. A window was made in a regular fashion in the cortex of the bone with an osteotome and hammer or electrical saw. The cavity was then curetted in a systematic way. Fluoroscopy was used for orientation during the procedure and to check if the curette reaches beyond all the visible edges of the tumour.

In both procedures the second part of the surgery is the same: when the curettage result was satisfying, the cavity was then filled with the first adjuvant: phenol. Small swabs were used to clean the edges of the cavity. The phenol was then washed out with 95% ethanol. The bone window was also cleaned using this protocol. The cavity was then filled with PMMA or allograft bone chips. When indicated preventive osteosynthesis material was applied to prevent a postoperative fracture (large window size, cortical resorption, diaphyseal localization). Plating was performed with a tibial LCP plate in diaphyseal lesions with 2 bicortical screws proximal and distal of the bone window.

**Follow-up**

After surgery, a standard X-ray was obtained as a routinely post-operative check. Three to four months later a baseline Gadolinium enhanced MRI was performed. After one year this was repeated. Further controls were done with radiographs. When a residue was suspected or if the lesion appeared active a more frequent MRI follow-up pattern was chosen. If the osteosynthesis material caused a too large
interference for radiological analysis, CT scans were used to assess follow-up.

**Statistical analyses**

Descriptive statistics were used to describe the main characteristics of the patient groups. General patient data as age and sex were compared, depending on data type, using independent sample t-tests or Pearson chi-square tests. Specific categorical or dichotomous variables, as recurrence and fracture rates, were compared with Fishers Exact test due to small sample sizes. Distribution of the different categories of reconstruction methods and the ASA classification were compared with the Freeman-Halton extension of Fisher’s exact test, using the exact method.

Numerical surgical characteristics data were tested for normality using the Shapiro-Wilk test and were tested with a Student’s t-test. Non-continuous variables were compared with a Mann–Whitney U test. To assess potential causes for fractures binary logistic regression tests were performed with the dichotomous fractures variable as a dependant and calculated lesion size variable as continuous predictor and for the fracture variable as dependant and cement use as dichotomous predictor. All tests were done two-sided when applicable. A significance level of 0.05 was chosen. Analysis of the data was performed with IBM Statistical Package for the Social Sciences (SPSS) version 22.
Results

Patient characteristics

77 patients were included who were treated between October 2006 and September 2013; 17 patients in the CAS cohort and 60 patients in the fluoroscopy cohort. Mean age at surgery was 53 years (range 24-82 years). Females were slightly more affected than males with a ratio of 1.1:1. Median follow-up was 43 months. Of the 79 patients included for analysis, 76 patients are currently alive; three patients have died of unrelated disease. Further demographic information is displayed in table 1 and figure 3.

Figure 3: General distribution of location of the ACT lesions.

Surgical characteristics

Analysis of the pre-operative data showed a significant difference between the lesion width (medial-lateral), with larger dimensions in the CAS cohort (p = 0.01). Median tumour volume was 18 cm³. Tumour volume was significantly larger (p = 0.04) in the CAS cohort; 23 cm³ (9 cm³ - 100 cm³) versus 16 cm³ (1 cm³ – 61 cm³) (see table 2).

Patient time in the operating room (patient-in-OR time) (2.15h versus 2.27h) and surgical time (1.26h versus 1.34h) was lower in the CAS cohort than in the fluoroscopy cohort, however both differences were not significant. CAS setup, measured in ten procedures, took on average 4 minutes and 25 seconds (range 2:03 min to 5:40 min).
Table 1: Demographic characteristics between the two cohorts. N is number of patients, $\bar{x}$ is cohort mean, $\tilde{x}$ is cohort median.

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>Fluoroscopy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>17</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Patient age ( $\bar{x}$ years)</td>
<td>56,1</td>
<td>53,8</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>8 (47%)</td>
<td>29 (48%)</td>
<td></td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>9 (53%)</td>
<td>31 (52%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up ( $\tilde{x}$, months)</td>
<td>41</td>
<td>45</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Table 2: Surgical characteristics between the two cohorts. $\bar{x}$ is cohort mean, $\tilde{x}$ is cohort median. Percentage displayed is percentage of cohort for that specific category. *) Tested using Freeman-Halton extension of Fisher’s exact test. **) tested using Mann–Whitney U test, uniformly for length category.

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>Fluoroscopy</th>
<th>p value</th>
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<tbody>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA I (n, %)</td>
<td>6 (35%)</td>
<td>18 (30%)</td>
<td>0.92 *</td>
</tr>
<tr>
<td>ASA II (n, %)</td>
<td>9 (53%)</td>
<td>35 (58%)</td>
<td></td>
</tr>
<tr>
<td>ASA III (n, %)</td>
<td>2 (12%)</td>
<td>7 (12%)</td>
<td></td>
</tr>
<tr>
<td>Lesion length ($\tilde{x}$ cm)</td>
<td>6.5</td>
<td>5.2</td>
<td>0.33 **)</td>
</tr>
<tr>
<td>Lesion width ($\bar{x}$ cm)</td>
<td>2.5</td>
<td>2.0</td>
<td>0.01 *</td>
</tr>
<tr>
<td>Lesion depth ($\tilde{x}$ cm)</td>
<td>2.1</td>
<td>1.9</td>
<td>0.15 *</td>
</tr>
<tr>
<td>Calculated volume ($\tilde{x}$ cm$^3$)</td>
<td>23</td>
<td>16</td>
<td>0.04 **)</td>
</tr>
<tr>
<td>Surgical time ($\bar{x}$ h:mm)</td>
<td>1:26</td>
<td>1:34</td>
<td>0.29 **)</td>
</tr>
<tr>
<td>OR time ($\tilde{x}$ h:mm)</td>
<td>2:15</td>
<td>2:27</td>
<td>0.24 **)</td>
</tr>
<tr>
<td>Reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMMA (n, %)</td>
<td>13 (76%)</td>
<td>45 (75%)</td>
<td>0.91 *</td>
</tr>
<tr>
<td>Bonegraft (n, %)</td>
<td>4 (24%)</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>Synthetic (n, %)</td>
<td>0</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>None (n, %)</td>
<td>0</td>
<td>1 (2%)</td>
<td></td>
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Clinical outcome

Eight patients, two in the CAS cohort (2/17, 12%) and six in the fluoroscopy cohort (6/60, 10%) had a potential residue (p = NS). A more frequent follow-up strategy was initiated for these cases to check the potential residue for progression. Two of the potential residues have been biopsied, both in the CAS cohort. Both biopsies showed viable ACT/CS-1 and the residues were treated using radiofrequency ablation (RFA). There were no recurrences of the treated tumours in both cohorts (see table 3).

There were nine fractures in the treated patients (9/67, 13%), all were within five months after the initial surgery and five were within one month. There were three fractures in the CAS group (3/17, 18%), all three in the diaphysis of respectively the femur (two) and humerus (one). There were six fractures in the fluoroscopy group (6/60, 10%). Five of these were in the diaphysis of the femur and one in the proximal metaphysis of the humerus. All were treated with osteosynthesis and are currently healed. The difference in fracture rate between the CAS and fluoroscopy cohort was not significant. There was no significant difference in the calculated tumour volume between the groups that had a fracture and those that did not (median of 19 cm$^3$ versus 14 cm$^3$). Prophylactic plating was done in 14 patients, although this could not prevent a fracture in two cases (12%).

There were eight fractures in the PMMA reconstruction group (8/58, 13.3%), none in the bonegraft group (0/15 patients, 0%), none in the synthetic bonegrafts group (0/3, 0%) and one in the no reconstruction group (1/1, 100%). Comparison of the tumour volume between PMMA and the non-PMMA groups showed no significant difference. The distribution of fractures over the groups was not significant (p = 0.1). In this dataset neither tumour volume, nor reconstruction method proved to be a predictive value for fractures in binary logistic regression.

No complications were associated with either imaging modality.

Table 3: Clinical outcome between the groups in events and percentage of that category. Complications were split in fractures and other complications. Other complications are split out in the text.

<table>
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<tr>
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<th>CAS</th>
<th>Fluoroscopy</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Recurrence (n, %)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Potential residue (n, %)</td>
<td>2 (12%)</td>
<td>6 (10%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Fractures (n, %)</td>
<td>3 (18%)</td>
<td>6 (10%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Other complications (n, %)</td>
<td>0</td>
<td>5</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Discussion

Computer-assisted surgery has become an accepted treatment modality for difficult tumour resections (11, 13). While it offers potentially superior imaging feedback there have been no reports on use of CAS for the curettage of bone tumours, other than a few reported cases for bone tumours located in the spine (14). The higher resolution imaging, three-dimensional feedback and no limitations in feedback time make CAS a logical and technologically superior alternative to fluoroscopy.

Clinical results of the CAS and fluoroscopy cohorts were comparable, with a significantly larger tumour volume in the CAS cohort. There were no tumour recurrences according to the definition; however eight residues were identified (12%). Although these outcome figures seem satisfying, they are difficult to compare to literature, were recurrence rates are reported between 3.5% and 13.3%, in studies with similar adjuvants (15, 16). Important is that this depends on the interval and type of follow-up imaging.

As Verdegaal et al. have demonstrated, some local recurrences might actually be residues (8). ACT/CS-1 is a low grade tumour and generally grows slowly. Thus, suspect lesions on the 3 month baseline scans should be considered tumour residue.
In fact all lesions detected within one year should probably be considered residues. Furthermore studies reporting recurrence rates using radiographs will likely miss smaller tumour residues. An example of a potentially missed residue can be seen in an image collage in figure 4. While the post-operative radiographs of the knee show no apparent tumour residue the baseline MRI shows a suspect lesion. Taking this into account, recurrence will likely be over-reported and residue under-reported in studies using radiographs during follow-up. As residue is primarily a problem of intra-operative orientation, this is something the three-dimensional and high-resolution feedback aspect of CAS can possibly improve.

Potential residues were found in two out of 17 CAS patients and in six out of 60 fluoroscopy patients. Both potential residue cases in the CAS cohorts showed tumour tissue at biopsy. Actual residue rate for the fluoroscopy cohort may be lower than six as GD-MRI has positive prediction rate of 45% for actual residue on suspect follow-up scans (8). Analysis of the CAS residue cases did not show a clear cause. Our hypothesis is that the feedback mode is currently not yet good enough for CAS to be better than fluoroscopy, especially the lack of progress tracking. It also shows that it’s not an infallible guide. While no navigational inaccuracies were experienced, regular accuracy checks, on a known landmark, are advised.

Fracture rates in this study (12%) are high compared to literature. Recent studies, with the same adjuvants, show a fracture rate ranging from 5.0 to 6.6 percent. A possible cause for this can be difference in preventive osteosynthesis strategies (7, 16-20). 58 of the 77 patients treated in this study had a reconstruction with PMMA. While it is suspected that the exothermic PMMA hardening process can have a beneficial effect as an additional adjuvant, it may have a detrimental effect on the host bone. Literature shows no significant difference in recurrence and fracture rates between using PMMA or other reconstruction methods (16, 21). As there were no recurrences, we cannot draw conclusions on PMMA and recurrence rate. Fracture rate in PMMA seems higher with 8 fractures out of 58 patient treated (14%) compared with a 6% fracture rate in the other reconstruction methods, although this did not reach significance. As the fracture rate was considered too high, a more aggressive plating strategy was adopted for procedures in the diaphysis of the femur. There was also a possible bias in fracture risk as a concurrent radiofrequency ablation (RFA) trial meant the exclusion of patients with mainly smaller ACT/CS-1 lesions in the femoral metaphysis (22).

The often cited downside of CAS use, the long set-up time, was not experienced (10). Set-up time, measured in the later cases, was on average just 4 minutes and 25 seconds. The median surgical time, even with the learning curve for CAS, was less than for fluoroscopy. While not significantly better, it shows that the set-up time is recouped during the procedure.
Use of CAS has been described by both surgeons as useful, due to the continuous three-dimensional feedback, compared with the intermittently two-dimensional feedback in fluoroscopy. Application of CAS in the humerus was considered more difficult due to issues with tracker placement in the working field. Smaller trackers could solve this issue. There were no direct complications nor any morbidity related to use of the CAS system. Possible complications as pin tract fractures or pin tract infections did not occur.

This study has some limitations. It was set-up as a retrospective cohort study, the study population was not equally divided and the techniques were not actively randomized. Both the techniques were however used in parallel, with CAS use only depending on system availability, planning and dataset quality. As far as we know, this is the first study on the usage of CAS for curettage of ACT/CS-1 in the long bones. It is encouraging that CAS as new technique achieves good results.

Some improvements to workflow and instruments will probably have a positive effect on outcome measurements. Currently it’s not possible to see the extent of already treated area. A ‘paintbrush’ mode, where the position of the tip is painted into the three-dimensional view would provide feedback on surgical progress. This together with the addition of a planning mode to the software could provide an intra-operative residue check. Furthermore it is likely that a more accurate curettage with less healthy bone removed can decrease fracture rates. Also, there should be support for non-straight tools like bended, hockey stick, shaped curettes and pointers, for easier access to tumour tissue in corners of the lesion.

Conclusions

CAS curettage with phenol/ethanol adjuvants has showed excellent oncological results, at least comparable to the fluoroscopy cohort and literature. CAS curettage is safe and effective. There were no recurrences, and no difference in the occurrence of residues between the cohorts, this despite significantly larger lesions in the CAS cohort. Fracture rates in both groups were higher than expected. In this study this was not linked to technique, PMMA use or size of the lesion. This study also supports the use of MRI follow-up for residue and recurrence detection. Studies with only radiographic follow-up likely underreport on residue- and over-report on recurrence-rate. Especially a suspected high residue rate after curettage supports the development of better intra-operative orientation. Clinical outcome of the present study supports CAS use as an alternative to fluoroscopy. With CAS no ionizing radiation was used during these surgeries and there was no increase in surgical time. Residue rates can likely be improved with specific, curettage targeted, software modules and tools.
References:


(13) Jeys L, Matharu GS, Nandra RS, Grimer RJ. Can computer navigation-assisted surgery reduce the risk of an intralesional margin and reduce the rate of


