Extended Intralesional Treatment versus Resection of Low-grade Chondrosarcomas

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Abstract The need for segmental resection versus intralesional treatment of low-grade chondrosarcomas of the appendicular skeleton remains controversial. We hypothesized extended intralesional treatment would equally control malignant disease but with improved functional outcomes and decreased postoperative complications. We retrospectively reviewed 31 patients with 32 Grade I intracompartmental chondrosarcomas of the long bones of the appendicular skeleton treated with either resection (15 lesions) or extended intralesional curetting (17) at a minimum followup of 2 years (median, 55 months; range, 24–

203 months). Lesions were larger and median followup was longer in the resection cohort. One local recurrence developed in each treatment cohort and neither transitioned to a higher grade of tumor. No patient had metastases develop or died of disease. The mean final Musculoskeletal Tumor Society functional scores were greater after extended intralesional versus resection treatment (29.5 versus 25.1). Complications were observed more frequently after resection and reconstruction (seven of 15) as compared with extended intralesional treatment (one of 17). Extended intralesional treatment of Grade I intracompartmental chondrosarcomas of the long bones of the appendicular skeleton therefore appears safe with improved functional scores and decreased complications versus segmental resection and reconstruction.

Level of Evidence: Level III, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Chondrosarcoma is the most common primary malignant bone tumor in patients older than 25 years [35]. Treatment of chondrosarcoma is predominantly surgical because adjuvant chemotherapy and radiotherapy are generally ineffective with the exception of dedifferentiated subtypes [11, 18]. Therefore, historically treatment generally has consisted of wide excision of the involved bone segment, with the goal of achieving negative margins because margin status is the most important physician-controlled factor associated with treatment [6, 33, 37, 44].

Although intermediate- and high-grade tumors have a survival rate of 40% to 60%, low-grade tumors result in long-term survival in as much as 90% of patients

[11, 13, 14, 18, 20, 37]. Based on the decreased biologic aggressiveness of low-grade cartilage neoplasms, several studies have suggested intralesional treatment may be adequate for Grade I chondrosarcomas [1, 4, 12, 19, 38]. Others have argued inadequate local treatment associated with an intralesional approach leads to higher local recurrence rates [14, 18, 36, 44] because historical local recurrence rates after intralesional treatment of chondrosarcomas have ranged from 50% to 92% [11, 33, 37].

We hypothesized extended intralesional treatment (curettage, burring, and the use of a chemical or thermal adjuvant) for intracompartmental Grade I chondrosarcomas would result in equivalent rates of local recurrence, metastasis, and patient survival as compared with patients treated with wide resection. We also supposed patients treated with intralesional procedures would experience improved function and lower rates of postoperative complications and reoperation resulting from the less invasive and morbid nature of intralesional procedures.

Materials and Methods

We retrospectively reviewed the medical records of 253 patients treated operatively for primary chondrosarcoma of bone between 1989 and 2005. We excluded patients with locally recurrent or metastatic disease at presentation; intermediate, high-grade, or dedifferentiated chondrosarcomas; patients with cartilaginous lesions of the hands, feet, spine, pelvis, or scapula; and patients diagnosed with enchondromas, active enchondromas, or so-called borderline, Grade 0 or Grade 1–2 chondrosarcomas [46]. We also excluded patients with extracompartmental (ie, extraosseous, Stage IB disease [10]) tumor extension because we believe this is an indication of increased tumor aggressiveness requiring more aggressive operative treatment. This left 31 patients with 32 intracompartmental (Stage IA [10]) Grade I chondrosarcomas of the long bones of the appendicular skeleton. Fifteen had resection and 17 had extended intralesional curettage. Power analysis revealed a sample size of 32 lesions (15 patients in the resection control group and 17 lesions/16 patients in the intralesional experimental group) would provide a 43% power to detect

a difference in survival outcomes based on the log rank test, assuming a constant hazard ratio of 2.0 during the followup and a two-sided alpha of 0.05. Although we know the actual hazard ratio is not constant (more local recurrences develop early during the postoperative course, with most occurring between postoperative years 2–5), this is a valid and common statistical assumption because we can reasonably assume the hazard ratio is approximately constant at any specific time. Thus, the study had only a 43% chance of detecting a twofold increase in the risk of local recurrence between study groups. This study had an 80% power to detect a threefold difference (hazard ratio = 3.01) in local recurrence rates between groups. Power analysis calculations were determined using the PASS 2008 software package (NCSS, Kaysville, UT). All patients were followed for a minimum of 2 years postoperatively unless death supervened. There was a mean followup of 56 months in the intralesional cohort (range, 29–130 months) and 88 months in the wide local excision cohort (range, 24–203 months); no patients were prematurely lost to followup. We had prior Institutional Review Board approval for the study.

There were 12 male and 19 female patients with a mean age at surgery of 49 years (range, 14–80 years) with no difference ($p = 0.33$) in age between treatment cohorts (Table 1). The minimum duration of followup was 24 months (median, 55 months; range, 24–203 months) and was longer ($p = 0.02$) after resection than extended intralesional treatment. This difference is the result of our more recent adaptation to extended intralesional treatment of this tumor subtype. Median lesion size was 7 cm and was larger ($p = 0.03$) in tumors treated with resection. Fifteen patients were treated with wide resections with reconstructions, including intercalary allograft (six patients), osteoarticular allograft (four), endoprostheses (three), or allograft-endoprosthesis composites (two). Seventeen Grade I chondrosarcomas were treated intralesionally in 16 patients. All patients were treated with three cycles of extended curettage [28] with a single cycle consisting of aggressive curettage, electrocauterization, high-speed burring of the cavity, and local adjuvant use (when applicable). Because of the breadth of the study period and the involvement of several musculoskeletal oncologists,

Table 1. Summary of treatment and outcome data

Operative treatment	Number of lesions	Patient age (years)	Followup (months)	Lesion size (cm)	Local recurrences	Metastasis or death	MSTS scores	Number of patients with complications
Intralesional	17	50.5	56	6	1 (6%)	0 (0%)	29.5	1 (6%)
Resection	15	46.3	88	7.5	1 (7%)	0 (0%)	25.1	7 (47%)
p Value		0.33	0.02	0.03	1	1	0.0001	0.02

MSTS = Musculoskeletal Tumor Society.

additional local adjuvant use was not standardized but included phenol (six lesions) [34, 42], liquid nitrogen (three) [5, 21–23, 26, 27, 45], polymethylmethacrylate (seven lesions, including four cases in which cement was used in conjunction with other adjuvants) [22, 23], hydrogen peroxide (one) [31], or no additional local adjuvant (four). Lesions not augmented with polymethylmethacrylate were packed with microparticulate (100–250 μm) cortical allograft powder (six lesions) or cancellous allograft chips (four). Five lesions in the intralesional cohort were treated with prophylactic internal fixation with plate and screw constructs. Postoperative rehabilitation management depended on the location and size of the lesion and the type of reconstruction, prophylactic internal fixation, and/or local adjuvant used. In general, patients treated intralesionally were limited to partial weightbearing on the involved extremity for the first 6 weeks after surgery and then were allowed to proceed to weightbearing and resistance exercises as tolerated. Radiographic surveillance for local recurrence was performed at 3 months, 6 months, 12 months, 18 months, and 24 months postoperatively with annual radiographs thereafter. Advanced imaging studies were obtained as needed to further evaluate areas of concern on radiographs.

The histopathologic and radiographic diagnosis of Grade I chondrosarcoma was made on the basis of the criteria similar to those proposed by Mirra et al. [29] and Murphey et al. [30], respectively. Specifically, moderate cellularity with bilacunar nuclei, entrapment of normal lamellar bone, rare or absent mitoses, minimal pleomorphism, absent necrosis, and scant myxoid stroma were present in all lesions on histopathologic analysis. Likewise, all tumors had radiographic evidence of Grade 2 to 3 endosteal scallops, no overt cortical breakthrough or soft tissue mass, and bone scintigraphy radiotracer uptake greater than the anterior-superior iliac spine with or without focal heterogeneity in the lesion.

Abstracted data included patient age and gender, tumor location and size (in centimeters as measured by maximal radiographic linear dimension), operative treatment including local adjuvant use and reconstructive techniques, postoperative complications and reoperations, postoperative function as assessed by Musculoskeletal Tumor Society (MSTS) scores [9], and incidence of local recurrence, metastasis, and death.

Potential differences in local recurrence rates were assessed using the Kaplan-Meier [17] method with differences in local recurrence-free survival assessed by the log rank (Mantel-Cox [25]) test. We analyzed differences in the frequency of postoperative complications with Fisher's exact test. Continuous data for patient age, duration of followup, and tumor size did not have normal distributions (Kolmogorov-Smirnov test, $p < 0.05$), and so

nonparametric analyses of potential differences were performed with Mann-Whitney U tests. The MSTS functional scores appeared to have a normal distribution (Kolmogorov-Smirnov test, $p = 0.003$) with equal variances (Levene's test, $p < 0.0001$), and the potential difference between treatment groups therefore was analyzed with Student's *t* test. All reported *p* values are two-tailed. We performed statistical analysis using SPSS® (Version 15.0; SPSS Inc, Chicago, IL).

Results

There was no difference ($p = 0.94$) in local recurrence rates between study cohorts. The Kaplan-Meier 5-year local recurrence-free survival estimate was 93.3% (95% confidence interval [CI], 66.0%–99.7%) for the resection group and 94.1% (95% CI, 69.2%–99.7%) for the extended intralesional group. One patient in the resection group had local recurrence of disease 33 months after wide resection. The patient had been treated with an intercalary allograft and had a local recurrence in bone at the proximal extent of his resection, which had a 0.5-cm margin. He subsequently underwent repeat wide resection with negative margins and total femur replacement and remains free of disease 30 months after the second procedure. One patient in the extended intralesional group had residual versus early recurrence of local disease as seen on a surveillance MRI performed 3 months postoperatively. Although possibly the result of inadequate initial treatment, this was considered a local recurrence for data analysis purposes. The patient was treated with repeat intralesional extended curetting and remains free of disease 44 months after the second procedure. The tissues analyzed from both patients with local recurrence were again interpreted as low-grade chondrosarcomas; neither lesion transitioned to an intermediate-grade, high-grade, or dedifferentiated tumor. No patient in either group had metastatic disease develop or died of their chondrosarcoma. One patient in the extended intralesional group and two patients in the resection group died of other causes during the followup period.

The mean MSTS functional score at final followup was greater ($p < 0.0001$) after intralesional treatment than after resection (mean, 29.5 versus 25.1). Excluding local recurrence of disease, postoperative complications developed more frequently ($p = 0.02$) after operative resection than after extended intralesional treatment (one of 17 versus seven of 15). Postoperative complications occurred twice in one patient in the intralesional cohort (fracture at the end of a prophylactic plate requiring revision to a longer plate and subsequent late implant removal resulting from a symptomatic plate). There were nine complications in seven patients in the resection cohort, including two

allograft fractures, one shoulder subluxation, one knee extensor mechanism failure, one patella fracture, one symptomatic locking screw requiring surgical removal, one host-graft junction nonunion, one deep infection requiring allograft removal, and one periprosthetic fracture with the latter three complications occurring sequentially in the same patient. This patient eventually underwent successful distal femoral replacement with a final MSTS functional score of 24.

Discussion

The operative management of low-grade chondrosarcomas of the appendicular skeleton is controversial. The optimal local treatment of sarcomas in general should seek to minimize the risks of local recurrence and perioperative complications while maximizing patient functional outcomes. We hypothesized extended intralesional treatment of intracompartmental, low-grade chondrosarcomas would result in equivalent rates of local recurrence of disease as compared with operative resection of similar lesions with improved functional outcomes and decreased postoperative complication rates.

Although the hypotheses appear confirmed by the data, our findings must be interpreted in light of the study limitations. Patient treatment was not randomized or standardized between or within cohorts, including local adjuvant use for extended intralesional treatment. We had relatively small numbers of patients in both treatment groups and this study was not adequately powered to detect small differences in local recurrence rates, with only a 43% power to detect a twofold increase in local recurrence rates between cohorts. Additionally, although histologic [29] and radiographic [15, 30] techniques for differentiating benign and malignant cartilaginous lesions have been well described, distinguishing between low-grade chondrosarcomas and active enchondromas is difficult for even experienced musculoskeletal radiologists and pathologists [40]. Thus, although the same musculoskeletal pathologists evaluated the histologic specimens of both treatment groups and all patients with enchondromas, active enchondromas, or Grade 1–2 chondrosarcomas were excluded, in the absence of extraosseous extension, local recurrence, or metastases, it is impossible to ascertain with certainty all tumors were truly malignant. Finally, prior studies showed the majority of local recurrences of low-grade chondrosarcomas develop within the first 2 to 5 years [6, 13]. Our followup was thus adequate for this analysis, with a mean followup of 56 months in the intralesional cohort (range, 29–130 months) and 88 months in the wide local excision cohort (range, 24–203 months). However, late local recurrences with tumor transition to a higher

grade have been reported [39], and four patients in the extended intralesional cohort and three patients in the resection cohort had followup less than the mean time to local recurrence of 35 months suggested by prior studies [4, 19, 39]. Additional studies with long-term followup after intralesional treatment are needed.

We found equivalent local recurrence rates of intracompartmental, low-grade chondrosarcomas treated with resection versus extended intralesional curetting. Historical series have reported recurrence rates of 50% to 92% [11, 33, 37] for chondrosarcomas treated intralesionally, and initial inadequate treatment has been linked to high local recurrence rates in multiple studies [6, 14, 18, 36, 37, 39, 44]. However, numerous studies have mixed low-, intermediate-, and high-grade lesions in the assessment of local recurrence and prognosis. They also have included lesions of the pelvis and axial skeleton, which have proven greater biologic aggressiveness for which intralesional treatment is generally inappropriate [8, 44, 46]. These studies also have included cases in which curetting was performed either unintentionally or owing to anatomic necessity [6, 8, 13, 18, 33, 36, 37, 44]. The biases inherent in these prior studies therefore make extrapolation of their data to the modern treatment of low-grade chondrosarcomas difficult.

Conversely, multiple prior series document low local recurrence rates using intralesional treatment of low-grade chondrosarcoma with the frequent addition of various local adjuvants [1, 4, 12, 19, 26, 38, 45, 46]. Findings in these studies [1, 4, 12, 19, 38] (Table 2), and our data, show deliberate, methodical, and extended intralesional treatment of low-grade chondrosarcomas is safe and effective. Schwab et al. [39] found better local control and overall outcomes when a patient was treated by a musculoskeletal oncologist, with a local recurrence rate of 24% in patients treated at outside institutions as compared with 5% for patients initially treated at their institution. All patients in the current series underwent primary treatment at our facility, and patients presenting with local recurrences were excluded.

Critical to the intralesional treatment of low-grade chondrosarcomas is the fact that, given appropriate operative approaches and adherence to musculoskeletal oncology principles, the opportunity for more aggressive subsequent treatment is not compromised. This is important because of the difficulties associated with the grading of chondrosarcomas by biopsy alone and concerns of higher-grade local recurrences after treatment of low-grade chondrosarcomas. Etchebehere et al. [12] reported biopsy yielded the correct diagnosis in 96% of chondrosarcoma cases, but the correct grade was identified only 46% of the time, suggesting some chondrosarcomas may be undertreated using intralesional methods based on biopsy grading. In the future, advanced immunohistochemical and

Table 2. Comparative summary data of studies

Study	Number	Stage	Mean followup (months)	Local adjuvant	Local recurrences	HG/DD transition	Metastasis or death	MSTS scores	Complications
Ahlmann et al. [1]	10	10 IA	39	10 ACS 10 PMMA	0 (0%)	0 (0%)	0 (0%)	27.0	1 (10%)
Bauer et al. [4]	23	21 IA 3 IB	78	6 PMMA 17 None	2 (9%)	0 (0%)	0 (0%)	NR	NR
Etchebehere et al. [12]	11	10 IA 1 IB	64	8 PMMA 3 None	0 (0%)	0 (0%)	0 (0%)	NR	4 (36%)
Leerapun et al. [19]	13	13 IA	102	13 Phenol 1 PMMA	1 (8%)	1 (8%)	1 (8%)	NR	NR
Schreuder et al. [38]	9	9 IA	26	9 LN	0 (0%)	0 (0%)	0 (0%)	28.8	1 (11%)
Current study	17	17 IA	43	6 Phenol 3 LN 3(7) PMMA 1 H ₂ O ₂ 4 None	1 (6%)	0 (0%)	0 (0%)	29.5	1 (6%)

HG/DD = higher grade/dedifferentiation; MSTS = Musculoskeletal Tumor Society; ACS = argon cryosurgery; PMMA = polymethylmethacrylate; LN = liquid nitrogen; NR = not reported; H₂O₂ = liquid nitrogen.

DNA analysis techniques may assist in distinguishing benign and malignant cartilaginous tumors and identifying those at greatest risk of metastases [3, 7, 16, 36, 40]. Also, local recurrence may influence survival, particularly if transition to a high-grade malignancy occurs. Schwab et al. [39] found 29% of patients with local recurrence died of disease. Their finding underscores the importance of careful evaluation of radiographic imaging studies before any major intervention. However, local recurrence may not affect survival in the absence of concomitant metastases [14], and the issue of transition to a high-grade tumor or dedifferentiation is controversial. Several studies have reported this transition [19, 32, 39], and high-grade [11, 13, 14, 18, 37] and dedifferentiated [8, 41] chondrosarcomas carry a far worse prognosis. However, others have observed no transitions and/or argued recurrence generally occurs as the same grade lesion and these reports are the result of incorrect grading or sampling error at the time of initial diagnosis [13, 36]. Neither of our two patients with local recurrence had higher-grade malignancies develop. Finally, although not an issue in our series, intralesional treatment also may eliminate the sampling error associated with biopsy of indolent cartilaginous tumors and does not preclude more aggressive subsequent treatment when necessary.

We observed improved functional outcomes after intralesional treatment as compared with resection (29.5 versus 25.1). Numerous prior studies have not examined the functional outcomes and complication rates after intralesional treatment of low-grade chondrosarcomas. Ahlmann et al. [1] and Schreuder et al. [38] reported mean

MSTS functional scores of 27.0 and 28.8 after intralesional treatment and cryosurgery in studies of 10 and nine patients, respectively. Veth et al. [45] noted good or excellent MSTS functional scores (≥ 26) in 74% of patients treated with intralesional cryosurgery for borderline or Grade I chondrosarcomas.

We also found a decreased rate of postoperative complications after intralesional treatment (one of 17) versus resection (seven of 15). Acceptable but decreased functional outcomes and relatively high complication rates after major endoprosthetic or allograft reconstructions have been reported in several large series [2, 24, 43]. Although the variety of reconstructive modalities used in our study and small patient numbers preclude comparative analysis, our data are largely consistent with data from those series. Etchebehere et al. [12] reported a slightly greater rate of complications after intralesional treatment, but three of their four intralesional complications were postoperative fractures of the distal femur. Numerous studies have reported low complication rates after intralesional treatment [1, 4, 19, 27, 38]. Therefore, our data and the literature support the hypothesis that intralesional treatment affords the potential for improved functional outcomes and decreased complications versus resection and reconstruction.

Our population included 12 male and 19 female patients. This is in contrast to the generally accepted male predilection with a reported ratio of 1.5 to 2:1 [13, 18, 36]. We cannot explain why our study group included a higher number of females as compared with males. However, we do not think this detracts from our results because, to our knowledge, no studies document any difference in

outcomes between males and females with low-grade chondrosarcomas of the appendicular skeleton.

When combined with the experience of other authors, our data suggest extended intralesional treatment with local adjuvant use is safe and effective for management of low-grade, intracompartmental chondrosarcomas of the appendicular skeleton. Intralesional treatment provides improved functional outcomes with lower complication rates as compared with more aggressive operative treatment with resection and reconstruction. Greater support for and patient enrollment in multicenter, prospective studies are needed to confirm these results and further show the effectiveness, safety, and functional outcomes of intralesional treatment for low-grade, intracompartmental chondrosarcomas of the appendicular skeleton.

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