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Giant Cell Tumor of Bone: Are We Stratifying Results Appropriately?

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Abstract

Background There is no consensus as to which surgical approach to the treatment of giant cell tumor of bone is most appropriate or which patients are at a higher risk for recurrence or metastasis.

Questions/purposes Therefore, we asked: (1) Are there subsets of patients who are associated with a more recalcitrant disease course? And (2) are surgeons appropriately stratifying patients by identifying risk factors for increased local recurrence and pulmonary metastases?

Methods We retrospectively reviewed the records of 230 patients with giant cell tumor of bone treated from 1980 to 2010, stratifying them by primary versus recurrent disease and by surgical treatment. From the records, we determined local recurrence, metastatic disease, and complications of treatment. The median follow up was 47 months (range, 0.1–312 months).

Results Overall incidence of local recurrence was 10% and pulmonary metastasis was 2%. When stratified by surgical treatment, the incidence of local recurrence among patients undergoing intralesional curettage (12%) was greater than in those undergoing resection (2%). The incidence of local recurrence among primary tumors, independent of treatment, was 9%, whereas the incidence of local recurrence after treatment of recurrent lesions was 16%. The incidence of pulmonary metastases was similar, regardless of treatment or whether primary or recurrent.

Conclusions Our observations suggest there are subsets of patients with giant cell tumor of bone who are at higher risk of recurrence and should be clinically followed more closely. This should allow surgeons to provide patients with more informed expectations.

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

Introduction

With local recurrence rates of 8% to 62% [1, 2, 4, 6, 7, 10, 12, 15, 17–19, 21, 23, 25, 27] and metastatic rates of 1.5% to 7% [3, 4, 22, 27], giant cell tumors of bone have presented a treatment challenge for almost a century. As the incidence of these tumors is relatively low and treatment is largely surgical, there are essentially no prospective randomized controlled trials to guide therapy [9, 24].

Sixty years ago, Lichtenstein [16] proposed the development of a giant cell tumor registry consisting of controlled, long-range, clinical data. Despite this recommendation, most studies continue to present series of giant cell tumor of bone that are underpowered for meaningful stratification, thereby drawing conclusions about all giant cell tumors of bone that may only be applicable to a subset. Recent literature has sparked a debate as to whether there is

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a subset of patients who are at higher risk of local recurrence or pulmonary metastasis. Several authors describe a more recalcitrant clinical course associated with recurrent giant cell tumors of bone [1, 4, 17, 25], while others refute this claim [2, 19, 20, 25]. One recent study suggests primary tumors have a lower incidence of local recurrence compared to recurrent tumors [25], while another suggests there is no difference [2]. The question of whether certain anatomic locations carry higher risk of poor outcome is also debated. For example, giant cell tumors of bone of the distal radius have been described as having a higher propensity for local recurrence, and even pulmonary metastases, when treated with curettage compared to the general population of giant cell tumors of bone [10, 11, 13, 21, 26].

We investigated the following questions: (1) Are giant cell tumors of the distal radius treated with curettage at increased risk of local or distant recurrence compared with giant cell tumors of bone elsewhere in the body treated with curettage? (2) Is there a difference in the incidence of local recurrence or pulmonary metastasis among patients treated with intralesional curettage versus resection? And (3) do patients with recurrent giant cell tumors of bone have a higher incidence of future local recurrence and pulmonary metastasis compared to patients without recurrent disease, and should physicians follow these patients more stringently?

Patients and Methods

We retrospectively reviewed all 230 patients with biopsy-proven diagnosis of giant cell tumors of bone treated between 1980 and 2010. We excluded 14 patients: two with multicentric disease, seven with confirmed malignant giant cell tumor of bone, and five treated nonoperatively. These exclusions left 216 patients (112 female, 104 male) with an average age at presentation of 36 years (range, 12–70 years). Of the 216 patients, 185 presented with primary tumors and 31 presented with biopsy-proven recurrent disease. Forty patients (19%) had a pathologic fracture of the affected extremity. We recorded the anatomic location of these lesions (Table 1). The mean followup was 69 months (range, 0.1–312 months). We graded all lesions using the radiographic method of Campanacci et al. [5], where Grade 1 lesions were well circumscribed with minimal cortical bone thinning, Grade 2 lesions were moderately expansile with moderate to severe thinning of adjacent cortical bone, and Grade 3 lesions were lesions that were no longer contained by a reactive rim of bone. We treated all 216 patients with curettage or resection. We performed curettage for all Grade 1 and 2 lesions that had no intraarticular spread on preoperative imaging and had sufficient bone stock to permit containment of polymethylmethacrylate cement (PMMA) and postoperative weightbearing. We performed resection for Grade 3 lesions with substantial soft tissue extension or in patients with insufficient bone stock to allow weightbearing or activities of daily living after intralesional excision. All patients treated with resection had margins negative for residual disease. We did not recall any patients specifically for this study and obtained all data from medical records and radiographs.

We performed all procedures according to previously described musculoskeletal tumor surgical management guidelines [8]. Intralesional curettage, performed in 165 patients, was performed with adjuvant therapies consisting of high-speed burr, pulsatile lavage, hydrogen peroxide, and phenol cautery (88% phenol solution). Reconstruction consisted of bone graft in 55 patients, PMMA in 108, and no graft support in two. Fifty-one patients underwent wide excision (resection). We performed reconstruction with an endoprosthesis in 32 patients, allograft in 5 patients, and autograft in 1 patient. We did not perform reconstruction in 13 patients either due to resection of expendable bones, such as the fibula or because amputation was performed (3 patients). Surgically treated patients received neither radiation nor chemotherapy.

We treated 23 patients with distal radius giant cell tumors with intralesional curettage and intraoperative adjuvant therapy. Mean followup for these 23 patients was 56 months (range, 0.3 to 199 months). All 23 patients received phenol adjuvant; 16 of these patients underwent reconstruction with PMMA.

We followed patients at 3-month intervals for the first 2 years, every 6 months for the third year, and then on an

Table 1. Distribution of giant cell tumor of bone locations

Location	Number of patients
Distal femur	72
Proximal tibia	48
Distal radius	25
Proximal humerus	13
Distal tibia	11
Proximal femur	10
Proximal fibula	8
Distal ulna	5
Spine	5
Pelvis	5
Distal humerus	4
Tarsal	4
Metatarsal	2
Metacarpal	2
Proximal radius	1
Patella	1

annual basis indefinitely. Initial workup included a baseline chest radiograph, chest CT scan, and plain films of the affected region. Thereafter, we obtained plain films of the affected extremity at each visit. We obtained followup chest CT scans every 6 months for the first 2 years and then a plain chest radiograph on an annual basis. If we discovered a new lesion in the lungs on plain chest radiograph during the postoperative period, we evaluated it with serial CT scans. We recorded local recurrence, pulmonary metastases, and nononcologic complications. We collected data regarding presenting age, sex, radiographic grade, presence of pathologic fracture, prior treatment, location of lesion, type of surgical treatment, recurrence, metastasis, major and minor complications, time duration to local recurrence, and date of last followup. We classified complications using a method similar to that of Malawer et al. [17], defining major complications as any postoperative complication resulting in substantial disability or required reoperation. Major complications included wound dehiscence, joint degeneration, symptomatic hardware, symptomatic graft resorption, malunion, fracture, deep infection, hardware failure, extruded intraarticular fragments, nerve injury, and aseptic loosening. Minor complications were postoperative issues that responded to nonoperative management, including asymptomatic graft resorption, nondisplaced fractures, superficial infection, asymptomatic bushing wear, and nonfatal pulmonary embolism.

We used a two-sample test of independent proportions to determine whether there was a difference in the incidence of local recurrence and pulmonary metastases between (1) patients with distal radius lesions treated with curettage and those with giant cell tumors of bone in other locations treated with curettage, (2) patients treated with curettage and those treated with resection, and (3) patients who presented with primary disease and those who presented with recurrent disease. We used a Student's t-test to compare mean duration to local recurrence among primary versus recurrent lesions, used Kaplan-Meier survival analysis to calculate estimates of median time to local recurrence, and used Cox regression analysis to compare predicted median time to local recurrence between primary and recurrent lesions. We performed statistical analysis using Stata® Version 11 (StataCorp LP, College Station, TX, USA).

Results

The overall local recurrence rate for patients in this series was 21 of 216 (10%) patients, soft tissue recurrence rate was one of 216 (0.5%) patients, and pulmonary metastasis rate was five of 216 (2%) patients. The median time to local recurrence in this series was 20 months (range, 8–277 months). Local recurrence-free survival estimates for the entire series was 86% at 122 months (CI: 79% to 91%) (Fig. 1). For primary lesions the local recurrence-free survival estimates were 90% at 122 months (CI: 83% to 94%) whereas for recurrent lesions it was 67% at 113 months (CI: 41% to 84%) (Fig 2). For lesions treated with curettage the local recurrence-free survival estimate were 84% at 122 months (CI: 75% to 89%) and for lesions treated with resection it was 96% at 127 months (CI: 77% to 100%) (Fig. 2).

There was no difference ($p = 0.58$) in the incidence of local recurrence among distal radius giant cell tumors of bone compared to giant cell tumors of bone in other regions of the body. For patients with giant cell tumors of bone in the distal radius treated with curettage, only two of 23 (9%) patients had local recurrence, and there were no pulmonary

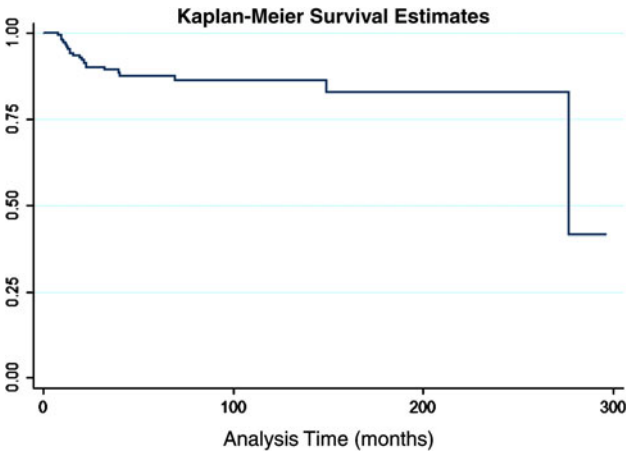

Fig. 1 A graph shows Kaplan-Meier estimates of duration to local recurrence (a surrogate for disease-free survival).

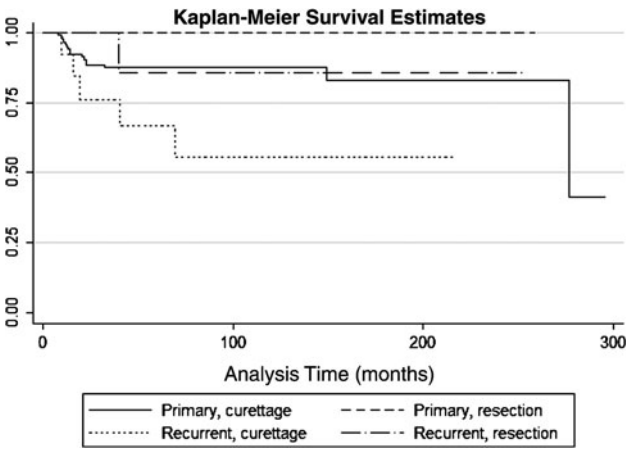

Fig. 2 A graph shows Kaplan-Meier estimates of duration to local recurrence stratified by primary versus recurrent disease and surgical treatment. The different curve morphologies are apparent and may indicate these groups of patients are best stratified regarding recurrence risk.

metastases observed. The incidence of local recurrence in nondistal radius lesions treated with curettage was 18 of 142 (13%) patients.

We found a higher incidence ($p = 0.03$) of local recurrence among patients with giant cell tumors of bone who underwent intralesional curettage, 20 of 165 (12%) patients, compared to those who underwent resection, one of 51 (2%) patients. However, there was no difference ($p = 0.38$) between the observed incidence of pulmonary metastases between these two groups (Table 2).

We were unable to demonstrate a difference in the incidence of local recurrence or pulmonary metastases between patients with primary and recurrent giant cell tumors of bone (Table 3). However, these data demonstrate a difference ($p = 0.04$) between primary and recurrent lesions for estimated median time to local recurrence (Table 3), with primary lesions having a longer estimated median time to local recurrence compared to recurrent lesions. The incidence of local recurrence in primary tumors, regardless of surgical treatment, was 16 of 185 (9%) patients, whereas the incidence of local recurrence in recurrent tumors was five of 31 (16%) patients. When we combined intrainstitutional local recurrences that had a second recurrence (three of 16 primary lesions) with extrainstitutional recurrent lesions that had local recurrence (five of 31 lesions), the local recurrence rate was eight of 47 (17%) recurrences. However, the local recurrence rate for these combined intra- and extrainstitutional recurrences also was not different ($p = 0.09$) from the local recurrence rate among the original 185 primary lesions (Table 3). Furthermore, we were unable to demonstrate a difference in the rate of pulmonary metastases between primary and recurrent lesions ($p = 0.10$). Specifically, we observed pulmonary metastases in three of 185 (2%) primary tumors, two of 31 (7%) intrainstitutional recurrent tumors, and two of 47 (4%) intra- and extrainstitutional recurrences combined (Table 3).

We observed complications in 31 of 216 (18%) patients. There were 23 major complications that occurred over a range of 0.1 to 149 months postoperatively, and there were eight minor complications that occurred over a range of 0.1 to 49 months postoperatively. Four of these major complications were due to joint degeneration, occurring at a mean time of 24 months (range, 12–53 months) after surgery. One patient had malignant degeneration at 277 months after curettage of a proximal tibia primary lesion. We recommended this patient for above-knee amputation.

Table 2. Giant cell tumor of bone lesions treated with curettage versus resection

Surgical treatment	Curettage	Resection	p value
Total patients (n = 216)	165	51	
Primary (n = 185)	147	38	
Recurrent (n = 31)	18	13	
Local recurrence rate total	12% (20/165)	2% (1/51)	0.03
Local recurrence primary lesions	11% (16/147)	0% (0/38)	0.03
Local recurrence recurrent lesions	22% (4/18)	8% (1/13)	0.27
Pulmonary metastases	2% (3/165)	4% (2/51)	0.38

Table 3. Primary versus recurrent benign giant cell tumor of bone lesions

Disease status	Primary	Recurrent	p value
Local recurrence	9% (16/185)	16% (5/31)	0.19
		17% (8/47)†	0.09
Mean duration to local recurrence (months)	41 (8–277)	25 (10–41)	0.42
	25 (8–149)*	21 (6–41)†	0.72
Kaplan-Meier estimated median time to local recurrence (months)	40	29	0.04
Pulmonary metastasis	2% (3/185)	7% (2/31)	0.10
		4% (2/47)†	0.27

* Mean value excluding malignant giant cell tumor of bone recurrence at 277 months; †intrainstitutional and extrainstitutional recurrent tumors combined.

Discussion

The metastatic potential and variable rates of local recurrence throughout the literature make the prognostication of giant cell tumor of bone challenging. Given the rarity of the diagnosis and the lack of randomized controlled trials, there are no conclusive data in the literature to guide clinicians as to how to appropriately stratify patients to determine which subset of patients may be at higher risk of local recurrence or pulmonary metastases. There is conflicting evidence in the literature regarding local recurrence and pulmonary metastasis rates among patients stratified by location (distal radius lesions), surgical treatment (curettage versus resection), or primary versus recurrent disease. Responding to these controversies, we asked: (1) Are giant cell tumors of the distal radius treated with curettage at increased risk of local or distant recurrence compared with giant cell tumors of bone elsewhere in the body treated with curettage? (2) Is there a difference in the incidence of local recurrence or pulmonary metastasis among patients treated with intralesional curettage versus resection? And (3) do patients diagnosed with recurrent giant cell tumor of bone have a higher incidence of future local recurrence and pulmonary metastasis compared to patients

without recurrent disease, and should surgeons follow these patients longer?

Our study has several limitations. First, despite being a large series of giant cell tumors of bone, the stratification into subsets rendered us somewhat underpowered to definitively determine the presence of some differences. In areas where we were underpowered, we hope future studies also present their data in a more detailed, stratified manner to empower the orthopaedic oncology community to better perform meta-analyses. Second, we did not perform subjective quality-of-life surveys that, perhaps, could more appropriately allow us to compare treatment outcomes between patients treated with curettage versus resection. While we found resection was associated with lower local recurrence rates than curettage, it was undoubtedly a more morbid surgery, and we lacked an objective and subjective measure to assess this. Third, given the use of adjuvant hydrogen peroxide and phenol, retrospective controls in the literature that do not use these adjuvants may not be fully applicable. Fourth, given this series was from a single surgeon's experience, there was potential for selection bias regarding clinical management. Our discussion attempted to clarify discrepancies among study methods found in the literature, but this nonetheless made head-to-head comparisons difficult. Despite these limitations, we can still make valuable statements about the incidence of local recurrence and pulmonary metastases in our study and, therefore, use these outcome measures to answer our study questions.

The higher rate of local recurrence among distal radius lesions treated with curettage compared to lesions in other anatomic locations is frequently described [10, 11, 21]. Our local recurrence rate in distal radius lesions treated with curettage and adjuvant phenol cautery is much lower by comparison. We believe much of this discrepancy comes from differences in the treatment modalities utilized. In the study by Harness and Mankin [11], only four of the 26 patients received adjuvant therapy. Similarly, O'Donnell et al. [21] reported they originally treated only one of the five recurrences with adjuvant phenol. In the series from Goldenberg et al. [10], they performed the surgeries before 1970, before the advent of modern adjuvant therapies. A review of the study by Vander Griend and Funderburk [26] shows only five of these patients were treated with curettage. The variability in treatment and observed results among these series causes some authors to recommend more aggressive surgical management of Grade 3 distal radius lesions with a low threshold to perform wide excision [11]. The low local recurrence rate in this series, despite 70% of the patients presenting with Grade 3 lesions, indicates distal radius giant cell tumors of bone can be successfully managed with a curettage procedure.

There is no consensus in the literature as to whether intralesional curettage portends a higher recurrence rate than wide excision [2, 5, 9, 14, 25]. Our findings of a decreased recurrence rate in patients treated with wide excision is supported by both Campanacci et al. [5] and Becker et al. [2]; however, their studies included multiple surgeons and patients from as early as 1913 and 1945, respectively, leading to the question of how applicable their results are compared to modern techniques. Turcotte et al. [25] had a contrary opinion, but their series was a compilation of several different surgeons at different institutions with potentially considerable variability in surgical techniques. Gitelis et al. [9] also reported no difference but only had 20 patients in each treatment group, and the study may have been underpowered to find a difference.

Other studies have reported increased risk of local recurrence with longer disease-free intervals among patients with recurrent giant cell tumors of bone [22, 25]. We observed local recurrence among the recurrent group of patients after a disease-free interval of as late as 41 months. Of the seven giant cell tumors of bone that had a second recurrence, four had a third recurrence after a disease-free interval as long as 127 months. We found no difference in the incidence of local recurrence or duration to local recurrence between patients with primary and those with recurrent lesions; however, we present these data in an effort to augment future meta-analyses of other giant cell tumors of bone series and believe these data reflect a clinically important trend. Interestingly, there is a trend in the estimated median time to local recurrence between primary and recurrent giant cell tumors of bone. In light of this and the potential for local recurrence at late followup, the senior author (JJE) practices close early surveillance and establishes a life-long relationship with all patients who have giant cell tumors of bone, particularly for those with documented recurrent disease.

The incidences of pulmonary metastases were similar between the various groups of patients. However, the time to pulmonary metastasis varied. One patient with recurrent disease presented with metastatic disease, while the other patients with metastatic disease demonstrated delayed presentations at periods of either 6, 8, 18 or 49 months postoperatively. Of the five patients diagnosed with pulmonary metastases, two underwent surgical excision and three were managed medically. At last followup, one of the surgically treated patients had no evidence of recurrent local or metastatic disease and the patient had spontaneous regression of the majority of his remaining pulmonary lesions after subtotal excision of several other lung lesions. All of the medically treated patients with pulmonary metastases were alive with stable pulmonary disease at last followup. Additionally, there was only one patient in the series with pulmonary metastases and local recurrence. The patient had an extrainstitutional recurrent lesion that

Table 4. Literature results stratified by surgical treatment and recurrence

Study	Total patients	Local recurrence	Primary lesions unstratified	Recurrent lesions unstratified	Primary lesions treated with curettage		Recurrent lesions treated with curettage		Primary lesions treated with resection	Recurrent lesions treated with resection
					Local recurrence	Percentage with adjuvant	Local recurrence	Percentage with adjuvant	Local recurrence	Local recurrence
Current study	216	12%	9% local recurrence	16% local recurrence	11% (16/147)	100%	22% (4/18)	100%	0 (0/38)	8% (1/13)
Turcotte et al. [25]	186	17%	12% local recurrence	35% local recurrence	12% (15/120)	95%	35% (8/23)	> 90%		
Becker et al. [2]	384	23%	23% local recurrence	22% local recurrence						
Vult von Steyern et al. [27]	137	14%			14% (19/137)	100%				
O'Donnell et al. [21]	60	25%			25% (15/60)	100%				
Prosser et al. [22]	193	19%	17% local recurrence	27% local recurrence	19% (26/137)	0%	35% (10/29)	0%	7% (1/15)	8% (1/12)
Blackley et al. [4]	59	12%			10% (5/50)	0%	22% (2/9)	0%		
Malawer et al. [17]	102	8%			2.3% (2/86)	100%	38% (6/16)	100%		
McDonald et al. [19]	85	22%	28% local recurrence	21% local recurrence	34% (29/85)	94%	45% (9/20)		7% (2/27)	8% (3/36)

presented with pulmonary metastases, was treated with curettage, and later was diagnosed with local recurrence at 10-month followup.

Our results demonstrated a consistent technique of curettage combined with adjuvant phenol therapy can result in low recurrence rates, even in the setting of Grade 3 disease. Interestingly, we observed a difference in the local recurrence rate between primary lesions treated with curettage and primary lesions treated with resection (Table 2). On further analysis of these data, we observed a general trend regarding local recurrence among our various treatment groups. Specifically, recurrent lesions treated with curettage had a higher local recurrence rate (22%) than primary lesions treated with curettage (11%). In turn, both of these groups of patients had a higher local recurrence rate than recurrent lesions treated with resection (8%). Yet, primary lesions treated with resection had the lowest overall local recurrence rate (0%). We cannot find any investigations that stratify results by both surgical treatment and recurrence. However, when we extract this information from data available in the literature and stratify these data by both of these clinical variables, we can observe a clear and consistent trend (Table 4). Giant cell lesions treated with resection are associated with lower rates of local recurrence than lesions treated with curettage. Similarly, primary lesions are associated with lower rates of local recurrence than recurrent lesions, regardless of surgical treatment. Future meta-analysis may provide information regarding different relative risks between patients stratified into one of these four categories: primary lesions treated with curettage, primary lesions treated with resection, recurrent lesions treated with curettage, or recurrent lesions treated with resection.

The varied presentation, propensity for local, distant, and late recurrence, and the multitude of potential treatments challenge orthopaedic oncologists to utilize their entire armamentarium to appropriately manage giant cell tumors of bone. Definitive recommendations for the treatment of giant cell tumor of bone remain elusive in all studies, this one included. Nonetheless, the reporting of series such as this, in an appropriately stratified manner, contributes to future meta-analyses that may ultimately provide meaningful direction in the management of giant cell tumors of bone.

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