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Original Research Article

A STUDY ON ROLE OF VARIOUS TREATMENT MODALITY IN GIANT CELL TUMOR TREATMENT

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Abstract

Introduction: Giant cell tumors in bone make up 5% of all primary bone tumors. Their location, progression and osteolytic nature quickly lead to a disabling functional impact, especially since younger patients are typically affected.

Materials and Methods: Data was collected from, Department of Orthopaedics, Shri Atal Bihari Vajpayee Medical College and Research institute, Bengaluru patients with giant cells tumors of the appendicular skeletal who were treated by intralesional curettage. The hazard ratio for tumor recurrence was calculated for the different variables collected and a multifactorial analysis carried out.

Results: One hundred and ninety-three surgical procedures were included from nine centers. One hundred and seventy-one (89%) were primary tumors and 22 had been referred after one or more recurrences. The distal femur andproximal tibia were the most common locations: 42.5 and 34.2% of cases, respectively. Thebone defect after curettage was filled in 176 cases (91.2%) and left empty in 16 cases.

Conclusion: They confirms that an elevated risk of local recurrence exists after curettage of a giant cell tumor in the appendicular skeleton. No tumor-specific factor was found to influence the risk of local recurrence, which would have driven the need to resect the tumor.

Keywords: Giant cell tumor, Treatment ,Pathology.

INTRODUCTION

Giant cell tumors in bone make up 5% of all primary bone tumors. Their location, progression and osteolytic nature quickly lead to a disabling functional impact, especially since younger patients are typically affected. Intralesional curettage is the preferred treatment to maintain function [1], but it has a high risk of local recur- rence (12.5 to 45%) [2—6]. For this reason, many local adjuvant treatments have been used, including phenol[2,4,6—8], alcohol [4,9] and cryotherapy [6,10—12]; how- ever, their effectiveness is debatable. Similarly, filling of the curettage defect with polymethylmetacrylate cement isfavored by many surgeons as a way to limit local recurrence, but this stated benefit is also debated [13]. More recently,results of treatment with systemic anti-osteoclastic agentshave been published [14] or are being evaluated [15—

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17]. Because of the wide range of practices, a study was initi-ated with the GSF-GETO (French Sarcoma Group and FrenchBone Tumor Study Group). The goal of this study was to eval- uate various tumor-specific and surgery-specific factors andidentify which ones have an effect on local recurrence aftertreatment by curettage of giant cell tumors of the appen- dicular skeleton.

Materials and Methods

This study done at Department of Orthopaedics, Shri Atal Bihari Vajpayee Medical College and Research institute, Bengaluru. Cases were included if surgical treatment by curettage had been performed on a giant cell tumor of bone confirmed histologically, either as a primary treatment or upon recurrence when the patient had been referred after a single or multiple local procedures. This analysis only comprised the first procedure performed by the team; if a recurrence was treated by the same team, only the first procedure was taken into consideration. Resections were excluded.Tumors located in the axial skeleton (spine, sacrum, pelvis) were excluded. The primary outcome was the occur-rence of a recurrence confirmed by histology. The follow-upwas calculated relative to the surgical procedure at inclu- sion on the primary tumor or on the recurrence if the patient had been referred.The patient's epidemiological data, primary or recurrent nature of the tumor and location on the appendicular skele-ton were recorded. Tumor locations with less than 10 caseswere grouped together for the statistical analysis. The sizeof the tumor was recorded relative to the width of the boneon an A/P X-ray view (0.5 bone width at the level of the largest diameter). The participating center where the patient had been treated and the surgeon's experience (Junior, Senior) were noted. All patients were treated by curettage (inclusion crite- rion). The use of a local chemical adjuvant treatment was determined based on the surgery report. If the defect left by curettage was subsequently filled, the type of mate-rial was recorded: polymethylmetacrylate (PMMA) cement,autograft, allograft (chips or structural) or bone substi- tute. In some cases, multiple materials were used to fill the defect, but an insufficient number of cases existed to perform a statistical analysis for each grouping. As a con- sequence, if cement was used, the case was considered a PMMA treatment; if an autograft or an allograft bone sub- stitute was used, the case was considered an allograft chip treatment. And finally, some patients were treated with a systemic adjuvant.

Statistical analysis

Categorical and ordinal data were described by the frequency of observations. The mean and standard deviation were calculated for the age and follow-up data. Student's *t*- test was used to compare quantitative variables and the Chi^2 test used with qualitative variables. If a variable revealed asignificant risk ($P < 0.1$), a stepwise multivariate regression analysis was performed. A 0.05 threshold was used for significant findings and the odds ratio was calculated. All of the statistical tests were performed on IBM SPSS Statistics 19 software.

Results

One hundred ninety-three GCT cases were included from the nine surgical centers; two centers contributed more than 20GCT cases. Of these, 171 (87%) were performed for a pri- mary tumor and 22 for a recurrence **(Table 1).** Eight tumors(0.4%) had resulted in a fracture at the time of diagnosis. Two patients (1%) presented with a pulmonary metastasis at the time of their recurrence, which was treated surgically.They were still alive and in full remission at the time of thereview. No patient died because of their GCT; six patients died of intercurrent causes. A local chemical treatment was used in 39 proce- dures (20.2%): phenol 17 times, phenol-alcohol combination 13 times and alcohol seven times. Twenty-four patients received a systemic treatment. Zoledronic acid (ZOL), 4 mg every 3 weeks for 3 months was given to 13 patients (6.7%)

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after the surgical procedure. Calcitonin (CALC) was given to 11 patients. There were 71 recurrences (36%) that occurred at 760 days 773 on average. The recurrence occurred at 761(755) days for primary tumors and at 756 (993) days forrecurrent tumors ($P = 0.987$). The majority of recurrences(59 patients, 83%) occurred within 3 years .The average follow-up after the surgical procedure was2,161 days (1452). The recurrence rate was not sig-nificantly greater in patients with more than 3 years of follow-up: 56 recurrences out of 143 with more than 3 years follow-up versus 15 recurrences out of 50 with less than3 years ($P = 0.248$). The tumor location, bone extension and treatment in theprimary or recurrent stage did not affect the recurrence risk.There was also no effect of surgeon experience and using alocal treatment (no matter the type) on the recurrence risk.The factors that increased the risks of local recurrence are given in (**Table 2)**. Treatment provided before 2005(42% before 2005 and 16% after 2005), not using a bonedefect filler, using an autograft to fill the defect, calcitonintreatment and no bisphosphonate treatment were factors significantly related to a risk of local recurrence in theunivariate analysis ($P < 0.1$). In the multivariate analysis,treatment before 2005 and filling the defect with an autograft were identified as risk factors for local recurrence.

Table 1: Main descriptive data and information on local tumor progression.

	Overall series No. (%)	Progression without local recurrence (%)	Progression with local recurrence (%)
Number of patients	193	122 (63.2)	71 (36.8)
Age	34.2 (± 12)	31.9 (± 13)	35.4 (± 11)
Gender F/M	119/74 (61.3/38.7)	76/46	43/28
Location			
Distal femur	82 (42.5)	53 (64.6)	29 (35.4)
Proximal tibia	66 (34.2)	41 (62.1)	25 (37.9)
Distal tibia	10 (5.2)	5 (50)	5 (50)
Proximal fibula	3 (1.5)		
Distal fibula	2 (1)		
Proximal humerus	9 (4.7)		
Distal radius	15 (87.8)	7 (46.7)	8 (53.3)
Distal ulna	2 (1)		
Other	4 (2)		
1st surgery/recurrence	171/22 (88.6/11.4)	107/15 (87.7/12.3)	64/7 (90.1/9.9)
Tumor extension			
> ½ bone width	127 (67.8)	81 (68.6)	46 (51.7)
Junior surgeon	26 (13.5)	17 (65.3)	9 (34.6)
Surgery before 2005	151 (78.2)	87 (57.6)	64 (42.4)
Void filler			
None	16 (8.8)	6 (41.2)	10 (58.8)
Cement	94	63 (73.2)	23 (26.8)
Autograft	17	6 (35.3)	11 (64.7)
Allograft (bone chips/structural)	62	42 (64.6)	23 (35.4)
Biomaterials	4	3 (75)	1 (25)
Local adjuvant treatment	39 (20.2)	27 (69.2)	12 (30.8)
Systemic bisphosphonate treatment	13 (6.7)	11	2

Systemic calcitonin treatment	11 (5.7)	3	8

No.: number of patients; data in (): percentage; F: female; M: male.

Table 2: Factors significantly related to risk of local recurrence based on univariate ($P < 0.1$) and multivariate ($P < 0.05$) analysis.

Number of patients		Progression without recurrence	Local recurrence	Univariate analysis (*P*)	Multivariate analysis
Treatment before 2005	151	87	64	0.002	OR = 3.6 *P* = 0.017 (1.2; 7.9)
Void filling material					
None	16	6	10	0.026	n/s
Autograft	17	6	11	0.012	OR = 3.9 *P* = 0.013 (1.3; 11.6)
Calcitonin treatment	11	3	8	0.011	n/s
Bisphosphonate treatment	13	11	2	0.098	n/s

OR: odds ratio for local recurrence (confidence interval); n/s: not significant.

Discussion

The results of this study showed that no tumor-related factors increased the risk of local recurrence after curettage of appendicular skeleton giant cell tumors. The only factor significantly associated with reduced risk of local recurrence was more recent (2005 and later) treatment of the tumor. Moreover, using an autograft to fill the defect was an independent risk factor for local recurrence (odds ratio3.9). These overall results are consistent with the results of various curettage-only series (with or without defect filling) published before 2005 that reported a local recurrence rateof 30 to 55% [18-21]. It has been reported that tumors in the distal radius andproximal femur have greater risk of local recurrence [22]. Although the same trend was found in our series for the dis-tal radius, it was not statistically related to an increased risk of recurrence, likely because of the small number of cases ($n = 15$). There were an insufficient number of GCT casesin the proximal femur to analyze this trend. Extension to soft tissues [23] and aggressive appearance on X-rays [24] have also been reported to be prognostic factors. But theseparameters could not be evaluated in our study because some patient records had incomplete imaging of soft tissuesand our patients could not be classified because we lacked a centralized facility to evaluate the X-ray images. Also, a few recent studies have found no correlation between radiological classification and the risk of recurrence. We were onlyable to use the relative width of the lesion on X-ray imagesas a parameter, but this was not related to the recurrencerisk. Moreover, we found no differences in terms of recurrence risk as a function of the management of a primary tumor ora recurrent one. As reported by Becker et al. [25] in a serieswith 384 patients, we also did not find a greater recurrencerisk in patients with a primary or recurrent tumor.The role of local adjuvant treatment on recurrence isa long-standing controversy. Many have reported a notice- able benefit of local adjuvant treatment: the recurrence risk of 45—65% without adjuvants was reduced to 12—18% with adjuvants [25-27]. However, this result was taken from a comparison of historical data over a long period of time, without any controlled studies. Cryotherapy has beenreported to be effective [28-30] but local complications have occurred in up to 30% of cases. Since it was used onlyonce in our series, no conclusions can be drawn here. Chemical adjuvants were used 34 times (phenol,

alcohol, phenol-alcohol combination). No matter what type of chemical adjuvant was used or if a chemical adjuvant was used at all, the risk of local recurrence was unchanged in our study. But these products have been shown effective in some *in vitro* studies [31,32] .In addition, recurrence rates below 15% have been reported by surgical teams usingethanol-based or absolute alcohol-based solutions.However, these typically are studies with a small number ofpatients and no control group. Finally, our series was consistent with the conclusion of a recent meta-analysis that found no benefit to local adjuvant treatment when a meticulous, motorized curettage is performed . Although most surgical teams filled the defect left by curettage of giant cell tumors, believe that defect filling is useless; this conclusion was based ona series of 197 cases where neither adjuvant nor defect filling was performed and the recurrence rate was only 19%. Inthe current study, not filling the defect was associated with a significantly increased risk of recurrence that could not be confirmed in the multivariate analysis. However, in mostof the cases where the defect was not filled, the patients had been treated either locally or systemically with calcitonin. Disappointing results with this treatment strategy have been recently reported [33-35].

Conclusion

Our series confirms that an elevated risk of local recurrenceexists after curettage of a giant cell tumor in the appendicular skeleton. No tumor-specific factor was found to influence the risk of local recurrence, which would have driven the need to resect the tumor. Local adjuvant treatment does not seem to prevent recurrences. Good curettage using modernmotorized burrs is the key to the success of this conservative treatment modality. This study also suggests that filling thedefect with an autograft must be avoided, but this finding must be confirmed in other studies.

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