

Present day controversies and consensus in curettage for giant cell tumor of bone

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ABSTRACT

Background: The ideal treatment for giant cell tumor of bone (GCTB) is still controversial. The purpose of this study was to evaluate whether curettage was successful in the treatment of GCTB. Intralesional curettage with adjuvant therapies, such as high-speed burring, polymethylmethacrylate, phenol, ethanol, and liquid nitrogen, may be used to reduce the local recurrence rate. However, there is no consensus on the optimal use of curettage, along with fillers and adjuvants, to limit the recurrence rate.

Methods: We performed a systematic review of articles using the terms long bones, GCTB, and treatment. Case reports, reviews, opinion articles, or technique notes were excluded based on the abstract. Twenty-six articles included in this review were then studied to establish the index in suggesting the surgical treatment of GCTB.

Results: The patient's gender, their age, the Campanacci grade of their tumor, and the type of surgery they had were not significantly associated with the local recurrence rate. Local recurrences seemed to be associated with the site of the tumor, occurring more frequently in the proximal femur or distal radius. A pathological fracture was not a contraindication for intralesional curettage. Treatment with denosumab did not decrease the local recurrence rate in patients who had been treated with curettage.

Conclusion: The current literature seems to suggest that the ideal treatment for GCTB is to remove the tumor while preserving as much of the joint as possible. Local recurrent tumors can be treated with curettage to keep the re-recurrence rate within an acceptable limit. The choice for how to treat GCTB in the proximal femur or distal radius requires special attention.

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1. Introduction

Giant cell tumor of bone (GCTB) is a primary benign bone tumor that accounts for approximately 5% of all primary bone tumors.¹ GCTB is composed of mononucleated cells and osteoclast-like multinucleated giant cells, and presents itself as a locally aggressive lesion with unpredictable behavior.² GCTB arises in the meta-epiphyseal region of long bones, predominantly in the distal femur and proximal tibia, but they can occur in the entire skeleton.³

The best treatment for GCTB remains controversial.^{2,3} Surgical treatment options are either curettage (intralesional resection) or en bloc resection. Ideally, all patients should be treated with curettage to preserve their joint and maintain optimal function.^{4–6}

After curettage, the bone cavity is generally filled with bone allografts or polymethylmethacrylate (PMMA) to provide mechanical support and prevent collapse of articular surface.^{7,8} Some authors reported that PMMA and other local adjuvants decreased the local recurrence rate.^{3,9} However, other authors have shown that the local recurrence rates are similar with or without PMMA or other local adjuvants.¹⁰

Though several studies of GCTB have been conducted, conclusive data are minimal and a widely accepted consensus on the optimal surgical treatment and selection of adjuvants for GCTB is not available.¹¹ Therefore, we conducted a systematic review to determine the risk factors for local recurrence and the effect of adjuvants after curettage for GCTB.

2. Methods

We searched the Medline, EMBASE, and Scopus electronic databases. We searched for the terms long bones, GCTB, and

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treatment to search for studies that had evaluated curettage of GCTB in long bones. References to other literature in the selected papers were also checked to find further relevant publications. We excluded papers that were not written in English language, were published before 2000, or did not involve humans in the study. Two authors of this review (CE and ST) independently screened the titles and abstracts of the identified papers and assessed the quality of the studies. The screeners excluded articles that were not related to the purpose of this study. We also excluded case reports, reviews, opinion articles, or technique notes based on the contents of the abstract. Of the 253 relevant studies we found using the search strategy, we included 26 articles in the final review (Fig. 1). There were no disagreements between any of the authors concerning the level of evidence for any of the 26 included articles (Tables 1 and 2). The articles included in this review were then studied to evaluate the evidence available regarding the treatment of GCTB of long bones.

3. Results

The overall local recurrence rate was 0–65% (Table 1).^{1,3,6,9,10,12–32} The local recurrence rate was not significantly associated with age,^{1,9,12,14,17–19,23} gender,^{1,3,9,10,12–14,17–19,23–25} and the Campanacci grade of the tumor.^{1,9,12,14,17–19,23} (Table 2). Regarding the type of surgery, local recurrence rate following aggressive curettage using high-speed burr was lower than those following simple curettage.^{20,26} (Table 2).

Local recurrences seemed to be associated with the location of the tumor; local recurrences occurred most frequently in the proximal femur and distal radius.^{14,33} (Table 2).

Presence of a pathological fracture was not a contraindication for curettage.^{1,3,9,10,12,13,16,17,19,24,25} (Table 2). Similar local recurrence rates following curettage were found between patients with or without a pathological fracture.^{13,15–17}

Recent studies of GCTB of long bones showed that denosumab treatment did not decrease the local recurrence rate after curettage.^{18,19} Some authors recommended the use of local adjuvants after curettage to reduce the local recurrence rate,^{9,20} while other authors suggested that adjuvant therapies were unnecessary.^{10,14,17,21,33} The local recurrence rate was similar in patients treated with curettage and phenol compared to patients treated with curettage and ethanol.^{1,22,23}

Some authors reported that filling the cavity with PMMA after curettage reduced the local recurrence rate.^{3,9,14,20,24–26} In contrast, other authors reported that filling material did not significantly

affect the local recurrence rate.^{10,32}

Recent studies showed that a recurrent tumor can be treated with curettage, resulting in an acceptable re-recurrence rate.^{22,26,27,33} There is limited literature reporting on functional outcomes after treatment of GCTB.³³ Available reports show that better function and a lower local recurrence rate occur with curettage compared to joint resection; the advantage of curettage is that it preserves the joint, thus resulting in excellent functional outcomes.^{1,6,10,13–16,18,28–30,30,32,33} (Table 1). Some authors found no significant differences in functional outcomes between patients whose bone cavities were filled with PMMA compared to patients whose bone cavities were filled with other types of filler following curettage.^{10,32,33} Several studies reported no signs of degenerative arthritis after treatment of GCTB with curettage and the use of PMMA.^{14,31,34} However, other authors reported that the use of bone allografts compared to PMMA alone reduced postoperative complications without increasing the risk of a tumor recurrence.^{15,25,32} (Table 2). The use of PMMA was associated with a higher risk of the subsequent need for a joint replacement.^{25,32}

4. Discussion

Curettage is the classic treatment for GCTB.³⁵ The use of different adjuvant therapies is still controversial and there is not a clear consensus on what the most effective adjuvant treatments are.³⁶ To date there are no randomized clinical studies that prove the efficacy of any adjuvant.³⁵ Some authors reported that the use of local adjuvants following curettage reduced the local recurrence rate, while other authors reported that the local recurrence rate was not improved with adjuvant treatment.³³ Kivioja et al. reported that in the Scandinavian Sarcoma Group multicenter study, that included 294 patients with GCTB, filling the bone cavity with cement was found to reduce the local recurrence rate.⁹ On the other hand, Turcotte et al. reported that in the Canadian Sarcoma Group multicenter study, that included 186 patients with GCTB, the adjuvant method or filling material was found to be not correlated to the local recurrence rate.¹⁰ Errani et al. reported that the use of cement or adjuvants was not significantly associated with the local recurrence rate.³³ Because thorough tumor removal is of most importance to reduce the risk of local recurrence, this capacity of the thorough curettage may overshadow the effects of adjuvant therapies, as other authors have suggested.^{12,35}

The local recurrence rate was found to be highest in stage III GCTB in some studies,⁷ but the risk of recurrence was not associated with the stage of the tumor in other studies.^{26,27,33} GCTB

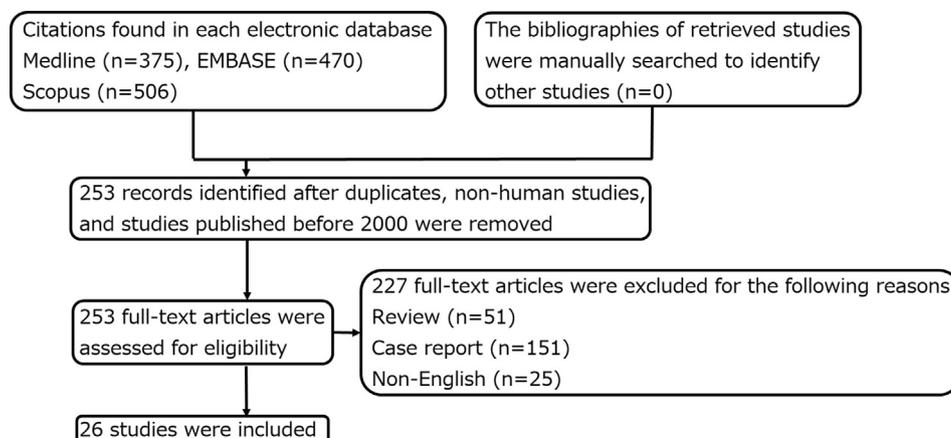


Fig. 1. This flow chart shows the search for relevant articles.

Table 1

Literature review of rate of local recurrence after curettage of GCTB; PT pathologic fracture; LR local recurrence; NR not reported; BG bone grafts; PMMA polymethylmethacrylate.

Study (year) [Reference]	Number of cases	Denosumab	Local adjuvant therapy	PMMA BG	Follow-up (months)	Recurrence	MSTS score
Trieb et al. (2001) ²¹	26	no	Phenol 12 No phenol 14	BG	121	Phenol 25% No phenol 21%	NR
Ghert et al. (2002) ¹²	51	no	Phenol 9 Electrocautery 42	PMMA	62	13%	NR
Turcotte et al. (2002) ¹⁰	148	no	Phenol 37 Liquid Nitrogen 10	PMMA 64 BG 84	60	18%	89%
Saiz et al. (2004) ⁶	40	no	Phenol	PMMA	76	12.5%	93%
Zhen et al. (2004) ³⁰	92	no	Zinc chloride	BG	132	13%	93%
Su et al. (2004) ¹³	56	no	Phenol	BG	62	18%	88%
McGough et al. (2005) ²⁷	183	no	None	PMMA BG	100	24.6%	NR
Lackman et al. (2005) ³¹	63	no	Phenol	PMMA	108	6%	93%
Jones et al. (2006) ²²	25 6 LR	no	Ethanol	none	46	20% 25%	NR
Oh et al. (2006) ²³	42	no	Alcohol	PMMA BG	48	9.5	NR
Deheshi et al. (2007) ¹⁶	128	no	none	none	80	14%	93% with PF 87% without PF
Becker et al. (2008) ²⁴	306	no	No adjuvants 103 Phenol 101	PMMA 203 No PMMA 103	64	PMMA 22% Phenol 15% PMMA and Phenol 27%	NR
Balke et al. (2008) ²⁰	188	no	No adjuvants 146 Phenol 5 Hydrogen peroxide 42	No PMMA 55 PMMA 133	60	No adjuvants 65% PMMA 29% Hydrogen peroxide 12%	NR
Kivioja et al. (2008) ⁹	194	no	NR	PMMA 147 BG 47	60	PMMA 22% BG 51%	NR
Abdelrahman et al. (2009) ²⁸	28	no	Cryotherapy	PMMA BG	34	4%	93.3%
Balke et al. (2009) ²⁶	40 with LR	no	NR	PMMA 23 No PMMA 17	77.3	PMMA 21.7% No PMMA 58.8%	NR
Muramatsu et al. (2009) ²⁹	23	no	Liquid nitrogen	PMMA	45	0%	89%
Klenke et al. (2011) ³	95	no	Phenol	PMMA 41 BG 54	108	PMMA 15% BG 32–34%	NR
Lin et al. (2011) ¹	61	no	Phenol 26 Alcohol 35	PMMA 61	58	Phenol 12% Alcohol 11%	Phenol 90% Alcohol 91%
Gaston et al. (2011) ²⁵	330	no	None	PMMA 84 No PMMA 246	76.5	PMMA 14.3% BG 29.7%	NR
Van der Heijden et al. (2012) ¹⁷	93	no	Phenol 75 No Phenol 18	PMMA 93	96	Phenol 26.6% No Phenol 27.7%	NR
Traub et al. (2016) ¹⁹	20	yes	Hydrogen peroxide	BG	30	15%	NR
Benevenia et al. (2017) ³²	43	no	Argon photo-coagulation Phenol Hydrogen peroxide	PMMA 22 BG (with or without PMMA) 21	PMMA 27 BG 44	PMMA 29% BG 32%	PMMA 93% BG 92%
Errani et al. (2017) ¹⁴	210	no	Phenol 196 No Phenol 14	PMMA 117 BG 93	89.2	PMMA 11.8% BG 21.4%	96.7%
Errani et al. (2018) ¹⁸	247	Yes (25)	Phenol 221 No Phenol 26	PMMA 187 BG 60	85.6	16% no denosumab 60% denosumab	96.7
Tsukamoto et al. (2019) ¹⁵	13 with PF	no	Phenol 13	PMMA 6 BG 7	79.5	7.6%	89%

located in the proximal femur or distal radius emerged as an unfavorable prognostic factor for local recurrence.^{14,33}

The risk of an iatrogenic fracture is high when operating for treatment of GCTB in the proximal femur or distal radius. Most authors suggest that adequate exposure of the bone cavity and high speed burring of the edge of the cavity is necessary for the treatment of GCTB, yet this can lead to an increased risk of fracture in locations where the bone is thin.³⁵ This is particularly true in the proximal femur, where the risk of fracture is very high.³⁵ The higher local recurrence rate in GCTB of the proximal femur or distal radius could have clinical implications. In fact, the difficult decision remains as to whether to minimize the risk of local recurrence with resection or to try to preserve the joint with curettage.³⁵ After resection, functional outcomes are poorer and complications occur more frequently.² We do not recommend resection instead of

curettage for GCTB of the proximal femur or distal radius. The ideal treatment is to preserve the joint despite a higher local recurrence rate, knowing that the resection of the joint is always possible if recurrence occurs.^{14,33}

We recommend curettage for GCTB when a pathological fracture is present because the local recurrence rate is similar and functional outcomes are better with curettage compared to resection.¹⁵ As mentioned above, the presence of a pathological fracture is not a contraindication for curettage.^{15,16} Deheshi et al reported that there was no association between the type of fracture and the local recurrence rate.¹⁶ Tsukamoto et al. analyzed 46 patients with GCTB and a concomitant pathologic fracture at presentation; patients were treated with surgery, having undergone either curettage (13 patients) or resection (33 patients).¹⁵ Three of the 46 patients (6.5%) experienced local recurrence at a median of 11 months after

Table 2

Literature review of association between local recurrence after curettage and each variable; LR local recurrence; NR not reported; BG bone grafts; PMMA polymethylmethacrylate.

Study (year) [Reference]	Association between age and LR	Association between gender and LR	Association between Campanacci stage and LR	Association between location and LR	Association between type of surgery and LR	Association between pathological fracture and LR	Complication (BG vs. PMMA)	Degenerative change (BG vs. PMMA)	Re-recurrence after additional curettage
Trieb et al. (2001) ²¹	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chert et al. (2002) ¹²	No	No	NR	No	NR	No	PMMA was used in 4 of the 5 fractures.	NR	NR
Turcotte et al. (2002) ¹⁰	NR	No	No	No	No	No	NR	NR	NR
Saiz et al. (2004) ⁶	NR	NR	NR	NR	All had aggressive curettage	NR	NR	NR	NR
Zhen et al. (2004) ³⁰	NR	NR	NR	NR	NR	NR	NR	NR	NR
Su et al. (2004) ¹³	NR	No	No	NR	All had aggressive curettage	No	NR	NR	NR
McGough et al. (2005) ²⁷	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lackman et al. (2005) ³¹	NR	NR	No	NR	All had aggressive curettage	NR	NR	NR	NR
Jones et al. (2006) ²²	NR	NR	No	NR	No	NR	NR	NR	NR
Oh et al. (2006) ²³	No	No	No	No	All had aggressive curettage	NR	NR	NR	NR
Deheshi et al. (2007) ¹⁶	NR	NR	NR	NR	All had aggressive curettage	No	NR	NR	NR
Becker et al. (2008) ²⁴	NR	No	No	No	NR	No	NR	NR	NR
Balke et al. (2008) ²⁰	NR	NR	No	NR	The additional use of high-speed burring reduces the likelihood of recurrence.	NR	NR	NR	NR
Kivioja et al. (2008) ⁹	No	No	NR	NR	NR	No	NR	NR	NR
Abdelrahman et al. (2009) ²⁸	NR	NR	NR	NR	All had aggressive curettage	NR	NR	NR	NR
Muramatsu et al. (2009) ²⁹	NR	NR	NR	NR	All had aggressive curettage	NR	NR	NR	NR
Balke et al. (2009) ²⁶	NR	NR	NR	NR	Re-recurrence rate without burring was 36% versus 21% with burring.	NR	NR	NR	The re-recurrence rate was 21.7% if a combination of all adjuncts (PMMA + burring) was used.
Klenke et al. (2011) ³	Patients 25 years and younger was a risk factor.	No	No	No	All had aggressive curettage	No	NR	NR	NR
Lin et al. (2011) ¹	No	No	No	No	All had aggressive curettage	No	NR	NR	NR
Gaston et al. (2011) ²⁵	NR	No	Yes	No	All had aggressive curettage	No	4 fractures in PMMA.	18.1% of those with cement needed a joint replacement, compared with 2.3% of those without cement.	NR
Van der Heijden et al. (2012) ¹⁷	No	No	NR	No	NR	No	NR	NR	NR
Traub et al. (2016) ¹⁹	No	No	No	No	All had aggressive curettage	No	NR	NR	NR

Table 2 (continued)

Study (year) [Reference]	Association between age and LR	Association between gender and LR	Association between Campanacci stage and LR	Association between location and LR	Association between type of surgery and LR	Association between pathological fracture and LR	Complication (BG vs. PMMA)	Degenerative change (BG vs. PMMA)	Re-recurrence after additional curettage
Benevenia et al. (2017) ³²	NR	NR	NR	NR	All had aggressive curettage	NR	Nononcologic complications occurred less frequently in patients treated with bone graft than those treated without.	Of 12 nononcologic complications in the group without bone graft, seven were progressions to osteoarthritis.	NR
Errani et al. (2017) ¹⁴	No	No	No	The proximal femur site was the risk factor.	All had aggressive curettage	NR	NR	NR	NR
Errani et al. (2018) ¹⁸	No	No	No	No	All had aggressive curettage	NR	NR	NR	NR
Tsukamoto et al. (2019) ¹⁵	NR	NR	NR	NR	All had aggressive curettage	NR	None in BG vs. 2 fracture and 1 cement impingement in PMMA	NR	NR

diagnosis and surgery.¹⁵ One patient had undergone curettage and the other two patients had undergone resection; the local recurrence rate was similar between the 2 surgical methods, but because of the low number of patients with local recurrence, a statistical analysis was not possible.¹⁵ Recently a meta-analysis concluded that the presence of a pathologic fracture does not significantly affect the local recurrence rate.³⁷

Clinical studies have shown that denosumab is associated with a beneficial response by the tumor, surgical downstaging, and reduced surgical morbidity in patients with GCTB.³⁸ However, these studies reported results from patients who either were still receiving denosumab treatment or had only recently stopped receiving denosumab treatment.³⁸ Errani et al. retrospectively determined the long-term recurrence-free survival of patients with GCTB who underwent curettage and received denosumab treatment. The authors found a significantly higher recurrence rate in the patients treated with both curettage and denosumab compared to curettage alone.¹⁸ Traub et al. reported the results of a prospective nonrandomized study of patients with GCTB who received neo-adjuvant denosumab treatment for 6–11 months; all patients underwent curettage.¹⁹ Three out of 18 patients (17%) experienced local recurrence.¹⁹ The median postoperative follow-up period was 30 months.¹⁹ The authors suggested that the new osseous tumor matrix and thickened cortical bone that develop with denosumab treatment raise a new surgical challenge because the surgeon cannot delineate the true extent of the tumor.¹⁹ In fact, tumor cells can hide within the thickened cortex and subchondral bone, which could increase the local recurrence rate.¹⁹

Treatment of local recurrences with curettage has been shown in recent studies to maintain the re-recurrence rate within an acceptable limit.^{26,27,33} Balke et al. showed that most patients who experienced local recurrence were successfully treated with additional curettage, with re-recurrence rate occurring at a rate of 21.7%.²⁶ In a study by McGough et al. that included 183 patients with GCTB who were treated with curettage, additional curettage was extremely effective in controlling recurrent disease.²⁷

5. Conclusions

The current literature seems to suggest that the ideal treatment for GCTB is to remove the tumor while preserving the joint as much as possible. There is no consensus on the optimal method of curettage, including the use of fillers and adjuvants, to limit the

recurrence rate. Curettage also seems to be an option for patients with GCTB and a pathologic fracture at presentation. A local recurrence can be treated with curettage and result in an acceptable re-recurrence rate. GCTB in the proximal femur and distal radius requires greater attention because of a higher local recurrence rate in these locations. Treatment with denosumab did not decrease the local recurrence rate in patients who had been treated with curettage.

Declaration of competing interest

All authors have not conflict of interest.

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