

# Packing with alpha-tricalcium phosphate followed by curettage and phenol-ethanol ablation for appendicular giant cell tumor of bone

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## Abstract

Giant cell tumor of bone (GCTB) is an intermediate and locally aggressive bone tumor. Alpha-tricalcium phosphate (alpha-TCP) is an adjustable bone substitute used to fill various sizes of bone cavities after curettage for GCTB. This study aimed to evaluate the surgical outcome of packing with alpha-TCP followed by curettage and phenol-ethanol ablation. We retrospectively reviewed data of 16 patients with GCTB who underwent primary surgery in our institute between January 2009 and April 2021. Data of Campanacci grading system; number of local recurrences and distant metastases; local recurrence-free survival rate using the Kaplan-Meier method; oncological outcomes; and complications after surgery (secondary osteoarthritis and postoperative fracture) were evaluated in this study. Regarding the Campanacci grading system, 2 patients were classified as grade I, 14 as grade II, and none as grade III. The 5-year local recurrence-free survival rate was 77.8% in all cases. Lung metastasis was not detected in this study. Oncological outcomes were: continuous disease free, 13 patients; alive with disease, 3 patients; and no evidence of disease or death of disease, none of the patients. Secondary osteoarthritis after surgery was not detected in the present study. Packing with alpha-TCP followed by curettage and phenol-ethanol ablation for appendicular GCTB may be safe and effective in suppressing the risk of secondary osteoarthritis.

**Abbreviations:** CPC = calcium phosphate cement, GCTB = giant cell tumor of bone, K-L = Kellgren-Lawrence, LRFS = local recurrence-free survival, MPa = megapascal, PMMA = poly methyl methacrylate, TCP = tricalcium phosphate.

**Keywords:** alpha-tricalcium phosphate, giant cell tumor of bone, local recurrence, metastasis, phenol-ethanol ablation, secondary osteoarthritis

## 1. Introduction

Giant cell tumor of bone (GCTB) is an intermediate and locally aggressive bone tumor, which accounts for 5% of all bone tumors and usually arises between 20 and 40 years of age. The frequent site of tumor is the metaphyseal region of long bones (distal femur and proximal tibia). The osteolytic lesion can be observed on plain radiographs.<sup>[1,2]</sup> GCTB sometimes occurs with high local recurrence rate after surgical resection and has potential for distant metastasis. Lung metastasis is the most commonly occurring distant spread, approximately detected in 2% to 5% of cases, and is associated with poor outcomes and even mortality due to disease.<sup>[3,4]</sup>

Surgical resection is the first-line therapy for GCTB. Curettage using high-speed burr with phenol ablation has been frequently performed to reduce GCTB recurrence.<sup>[5,6]</sup> Secondary osteoarthritis is 1 of the main postoperative complications after resection of GCTB. Polymethyl methacrylate (PMMA) or bone grafts were used for filling bone cavities after curettage for GCTB. However, secondary osteoarthritis is often observed after curettage and using these materials.<sup>[6–8]</sup>

Alpha-tricalcium phosphate (Alpha-TCP) is calcium phosphate cement (CPC). Alpha-TCP is an adjustable and injectable bone substitute used to fill various sizes of bone cavities during orthopedic surgeries.<sup>[9–11]</sup> In a previous study, CPC demonstrated a low incidence of secondary osteoarthritis in the long

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Written informed consent was obtained from all patients prior to surgery and in the form of opt-out on the poster at our institution (those who rejected were excluded).

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study was approved by the Institutional Review Board of our institution (IRB No. 1794). The study was conducted in accordance with the Declaration of Helsinki.

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follow-up period.<sup>[12]</sup> Therefore, alpha-TCP can potentially prevent secondary osteoarthritis after curettage for GCTB around joint spaces.

This study aimed to evaluate how secondary osteoarthritis could be prevented by packing alpha-TCP after curettage for appendicular GCTB.

## 2. Materials and Methods

### 2.1. Patient selection

The current study was a retrospective observational study at a single institution. We retrospectively reviewed data of patients with GCTB who underwent primary surgery in our institute between January 2009 and April 2021. The study included patients with more than 12 months of follow-up duration. All patients were pathologically diagnosed with GCTB.

The patients were regularly followed up with radiographs of lesion sites and chest every 3 to 4 months until 2 years after surgery to detect metastasis or recurrence. Afterward, the patients were followed up with radiographs every 6 months or 1 year until 5 years.

Evaluation parameters in the current study were: Campanacci grading system<sup>[11]</sup>; number of local recurrences and distant metastases; local recurrence-free survival (LRFS) rate using Kaplan-Meier method; oncological outcomes; and complications after surgery (secondary osteoarthritis and postoperative fracture). Secondary osteoarthritis was evaluated at the latest follow-up on radiographs using the Kellgren-Lawrence (K-L) classification.<sup>[13]</sup> We defined secondary osteoarthritis as K-L grade 2 to 4 at the latest follow-up using radiography.<sup>[13]</sup>

This study was approved by the Institutional Review Board at the University of the Ryukyus. Written informed consent was obtained from all patients prior to surgery and in the form of opt-out on the poster at our institution (those who rejected providing consent were excluded).

### 2.2. Surgical procedure

Surgical treatments used in the current study were curettage using high-speed burr, phenol and ethanol ablation, and packing with alpha-TCP. The surgical procedure was as follows: the cortical bone window was opened to access bone tumor. Bone tumor was resected using a curette, and the septum in the bone cavity was shaved with high-speed burr. A gauze ball with phenol was put on the bone cavity, and a gauze ball with

95% ethanol was put on the bone cavity to neutralize phenol. Distilled water was used to irrigate the bone cavity. These procedures were repeated 3 times. Phenol-ethanol ablation for opened cortical bone was processed using the same procedures. After phenol-ethanol ablation, alpha-TCP, Biopex (HOYA Technosurgical Co., Tokyo, Japan), was filled in bone cavity. This material's strength could reach 65 megapascals (MPa) within 3 days.<sup>[14]</sup> Finally, the opened cortical bone was returned to cover with a cortical window.

### 2.3. Statistical analyses

The Kaplan-Meier method was used for the analysis of LRFS. LRFS was defined from the date of surgery to the date of local recurrence or the last follow-up for survivors. Data are reported as survival curves and 2-sided 95% confidence intervals. Statistical analysis was performed with JMP version 13 (SAS Institute Inc., Cary, NC).

## 3. Results

### 3.1. Patient characteristics

The study included 16 patients (9 men and 7 women). No patients were excluded from this study due to follow-up duration < 12 months or incomplete data. The median follow-up period was 38.0 months (range, 12.0–122.0 months). The median age of the patients who underwent 1<sup>st</sup>-time surgery was 28.0 years old (range, 9–58 years old). Tumor locations were the distal femur in 5 patients; proximal humerus and proximal tibia in 3 patients each; distal radius in 2 patients; and other locations in 3 patients. The patient characteristics are shown in Table 1.

According to the Campanacci grading system,<sup>[11]</sup> 2 patients were classified as grade I, 14 patients as grade II, and none of the patients as grade III.

### 3.2. Oncological outcomes

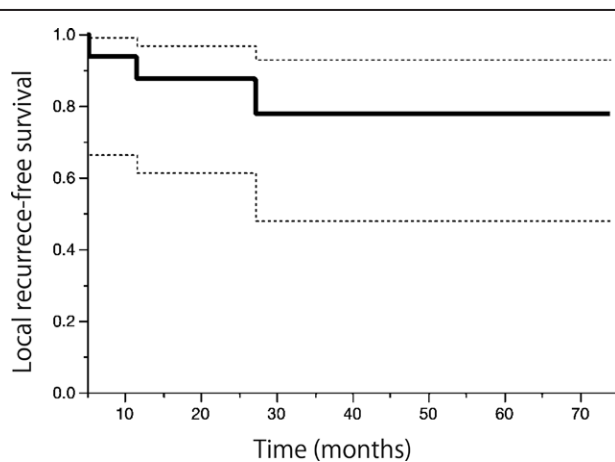
In the study, local recurrence after surgery occurred in 3 patients (18.8%), all of whom were classified as grade II according to the Campanacci grading system. Three patients with recurrence in the study after 2013 were treated with denosumab, which was approved for GCTB by the Food and Drug Administration in 2013.<sup>[15]</sup>

Kaplan-Meier curve for LRFS is shown in Fig. 1. The 5-year LRFS rate was 77.8% in all cases. Lung metastasis was not detected in this study.

**Table 1**  
Patient characteristics.

No.	Sex	Age	F-U (mos)	Location	Campanacci grade	Outcome	L/R	D/M	K-L grade on latest F-U	Complications	Additional therapy
1	F	42	38	Dist femur	II	CDF	No	No	1	–	
2	M	27	44	Prox humerus	II	CDF	No	No	0	–	
3	F	20	122	Dist femur	II	AWD	Yes	No	0	–	Denosumab
4	M	15	74	Prox humerus	II	CDF	No	No	0	–	
5	M	25	30	Patella	I	CDF	No	No	0	–	
6	F	14	70	Prox humerus	I	CDF	No	No	0	–	
7	F	19	67	Dist femur	II	CDF	No	No	0	–	
8	M	22	85	Prox tibia	II	AWD	Yes	No	0	–	Denosumab
9	M	29	38	Prox fibula	II	CDF	No	No	1	–	
10	F	42	48	Prox tibia	II	CDF	No	No	1	–	
11	M	47	24	Dist radius	II	CDF	No	No	0	–	
12	M	58	12	Dist femur	II	CDF	No	No	1	–	
13	F	56	23	Dist radius	II	CDF	No	No	1	–	
14	M	32	20	Dist femur	II	CDF	No	No	1	–	
15	M	9	12	Prox tibia	II	CDF	No	No	0	–	
16	F	46	15	Dist tibia	II	AWD	Yes	No	1	–	Re-curettage, denosumab

AWD = alive with disease, CDF = continuous disease free, D/M = distant metastasis, Dist = distal, F = female, F-U = follow-up, K-L = Kellgren-Lawrence classification, L/R = local recurrence, M = male, mos = months, no = number, prox = proximal, Surg = surgery.



**Figure 1.** Kaplan-Meier curve of local recurrence-free survival. The 5-year local recurrence-free survival rate is 77.8%.

Oncological outcomes were: continuous disease free, 13 patients; alive with disease, 3 patients; no evidence of disease or death of disease, none of the patients. In this study, 3 patients with alive with disease were administered denosumab for recurrence of GCTB. Patient No. 3 who experienced recurrence 27 months after the 1<sup>st</sup> surgery received denosumab treatment for 1 year. Patient No. 8 who had recurrence 11 months after the first surgery received denosumab treatment for 6 years. Patient No. 16 who was affected by recurrence 5 months after the 1<sup>st</sup> surgery received re-curettage. However, re-recurrence occurred 6 months after re-curettage, and administration of denosumab has been performed for 3 months. The recurrent tumors in all patients did not progress.

### 3.3. Radiographic outcomes

Secondary osteoarthritis after surgery was not detected in the present study. K-L grade on the last follow-up was: grade 0, 9 patients; grade 1, 7 patients; grade 2, 3, and 4, no patients.

### 3.4. Case presentation

**3.4.1. Case 10.** A 42-year-old woman was referred to our institution with a 2-month history of pain in the left knee. Magnetic resonance imaging revealed a tumor located in the left proximal tibia (Fig. 2A). Open biopsy resulted in a diagnosis of GCTB. The patient underwent curettage and phenol-ethanol ablation. Afterward, packing with alpha-TCP was performed for bone cavity, followed by curettage and phenol-ethanol ablation (Fig. 2B and C). No recurrence or progression of osteoarthritic change were found 4 years postoperatively on radiography (Fig. 2D).

## 4. Discussion

The present study demonstrated that the local recurrence rate was 18.8% (3 out of 16 patients) in packing with alpha-TCP, followed by curettage and phenol-ethanol ablation. Moreover, secondary osteoarthritis after surgery was not observed in this study. According to K-L classification on the last follow-up radiographs, grade 0 was detected in 9 patients, grade 1 was in 7, and grade 2 to 4 was in none.

After curettage for GCTB, management of large bone cavities is important to reduce complications, such as local recurrence, postoperative fracture, and secondary osteoarthritis.<sup>[5,6]</sup> Secondary osteoarthritis occurs when degenerative change in the cartilage results from another disease or medical condition, such as infection, trauma, gout, rheumatoid arthritis, or surgery.<sup>[6,16-18]</sup>

Secondary osteoarthritis is a serious problem that leads to pain, limping gait, and additional surgery, which comprises total arthroplasty and osteotomy.<sup>[16,19]</sup> Additionally, secondary osteoarthritis has several complications after total arthroplasty compared with primary osteoarthritis.<sup>[16,20]</sup> Therefore, prevention of secondary osteoarthritis is needed to improve patient's quality of life.

PMMA, bone graft, and CPC were used for filling bone cavity after curettage for GCTB in previous studies.<sup>[7,8,14,21]</sup> In these previous studies, the rate of secondary osteoarthritis after curettage with filling PMMA was 7% to 31% with 55 to 100 months follow-up period.<sup>[6-8]</sup> In addition, regarding filling bone graft and CPC with alpha-TCP, this rate was 33% with 92 months follow-up period<sup>[8]</sup> and 16% with 131 months follow-up period, respectively.<sup>[12]</sup> In this study, no secondary osteoarthritis was detected. However, the follow-up period was short compared with previous studies. Further follow-up will be needed to observe secondary osteoarthritis after curettage for GCTB.

PMMA has been revealed to achieve immediate bone mechanical strength and full weight-bearing after surgery, showing good conformability and killing residual tumor cells with the heat of polymerization.<sup>[22-24]</sup> However, it is considered that the risk of secondary osteoarthritis after curettage for periarticular GCTB increases due to the hyperthermal reaction of PMMA.<sup>[25,26]</sup> Bone graft was used for filling the cavity after curettage for GCTB. Bone graft showed a better bone healing effect by filling bone cavity after curettage.<sup>[27]</sup> However, it was indicated that bone grafting could not achieve mechanical strength in the early postoperative period.<sup>[28]</sup> Therefore, bone graft was not used individually and adopted with other materials to support bone healing.<sup>[6]</sup>

Alpha-TCP is 1 of the materials of CPC. CPC has several advantages: accuracy, adaptability, relatively high bone strength, and easy manipulation.<sup>[29]</sup> In this study, alpha-TCP was used for filling bone cavity after curettage for GCTB, and the strength of alpha-TCP reached 65 MPa within 3 days after mixing and over 70 MPa in 1 week.<sup>[14,30]</sup> The CPC is not hard compared with PMMA. However, it is sufficient to prevent postoperative fracture.<sup>[31,32]</sup> In addition, alpha-TCP has a relatively low thermal reaction compared with PMMA, which might affect suppression of degenerative change in joint cartilage.<sup>[33]</sup>

Our study has several limitations. First, the number of this series was small, and the follow-up period in a single institute was relatively short. The number of patients with secondary osteoarthritis and local recurrence might increase in a long follow-up period. Therefore, future studies on long-term follow-up evaluation are needed to evaluate complications after surgery. Second, the evaluation of osteoarthritis was performed only with plain radiographs. Magnetic resonance imaging or arthroscopy may be effective in providing more accurate observation of joint cartilage. However, evaluation with radiographs is convenient in outpatient clinics. Therefore, secondary osteoarthritis could be detected with radiographs. Third, the current study could not compare control, such as only curettage or filling PMMA, because this study was a single institute study with small samples. However, packing alpha-TCP did not induce secondary osteoarthritis after the curettage for GCTB in the present study. The results indicated that packing bone cavity with alpha-TCP might reduce secondary osteoarthritis after surgery for periarticular GCTB.

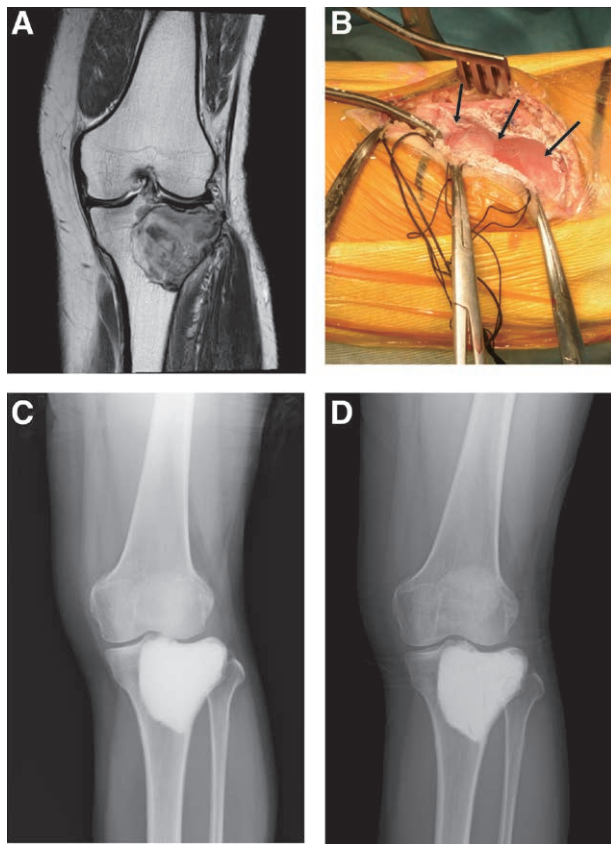
## 5. Conclusions

Packing with alpha-TCP followed by curettage and phenol-ethanol ablation for appendicular GCTB may be safe and effective in suppressing the risk of secondary osteoarthritis.

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**Figure 2.** A 42-year-old woman with giant cell tumor of bone in left proximal tibia (A) Preoperative magnetic resonance imaging. A tumor located in the proximal tibia. (B) Intraoperative findings. Alpha-tricalcium phosphate (arrows) is packed in the bone cavity, followed by curettage and phenol-ethanol ablation. (C) Postoperative radiograph. (D) Final follow-up radiograph. No recurrence and progression of osteoarthritic change with radiograph are found.

### Author contributions

All authors have read and agreed to the published version of the manuscript.

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