Original Article

Local Recurrence After Minimally Invasive Curettage For Primary Giant Cell Tumor of Bone With Perioperative Bisphosphonate Is Comparable to Open Curettage: Retrospective Comparison With 9-Year Follow-Up

Hiu-Woo Lau, M.B.B.S. (HK), M.R.C.S.Ed.,
Kwok-Chuen Wong, M.B.Ch.B., M.D. (CUHK), H.K.C.O.S., F.H.K.A.M., F.R.C.S.Ed. (Ortho),
Wang-Kei Chiu, M.B.B.S. (HK), H.K.C.O.S., F.H.K.A.M., F.R.C.S.Ed. (Ortho), and
Shekhar-Madhukar Kumta, M.B.B.S. (Bombay), Master (Bombay), Ph.D. (CUHK), F.R.C.S. (Edin)

Purpose: To compare the long-term oncological outcome of minimally invasive curettage (MIC) with conventional open curettage (OC). **Methods:** We studied patients with primary giant cell tumor of bone (GCTB) of extremities who underwent intralesional tumor curettage and cementation and perioperative bisphosphonates from February 2003 to June 2016. All cases were histology-confirmed diagnoses of GCTB. Recurrent GCTB, malignant GCTB, cases in the axial skeleton (pelvis and spine), or cases with bone grafting of the curetted cavity were excluded. The local recurrence-free (LR-free) estimates of the OC and MIC groups were compared. The hazard ratio of a local recurrence was calculated for the various factors of the patients, disease, and treatment. **Results:** At a mean follow-up of 8.8 years, the overall LR rate was 24.2% (8 out of 33 patients). There was no statistical difference in LR in MIC and OC groups (27.8 % vs 20%; $P = .6$). The mean time to LR was 33.1 months (8 to 75). The operative time was comparable in both MIC and OC groups. None of the risk factors studied led to a significantly higher hazard of LR. **Conclusions:** At a long-term follow-up of 9 years, MIC showed similar LR-free survival to OC. Combining bisphosphonates and MIC with a less invasive approach showed reasonable LR-free survival in long-term follow-up. **Level of Evidence:** Level III, retrospective cohort study.

Introduction

Giant cell tumor of bone (GCTB) is a benign but locally aggressive primary bone neoplasm. Intralesional curettage is favored due to little disability, but with local recurrence (LR) rate varying from 25 to 65% in the literature.[1-3] The use of polymethylmethacrylate bone cement as an adjunct could reduce the LR rate.[2]

Minimally invasive surgery has the benefits of reducing the morbidity of the surgery and providing a faster functional recovery. Several case series reported the use of minimally invasive curettage (MIC) on GCTB.[4-7] The use of endoscopy and computer navigation has been reported to assist in intralesional curettage of benign bone tumors.[4] It helped assess tumor clearance with magnified endoscopic images and CT images under navigation guidance. A recent systemic review showed satisfactory oncological and functional outcomes with minimally invasive techniques.[8] However, the long-term result of arthroscopically assisted MIC on GCTB is lacking.

Bisphosphonates have been used as adjuvant treatment in GCTB. Bisphosphonates were shown to have a dose-dependent antitumor effect by inducing apoptosis in neoplastic stromal cells of GCTB in basic studies.[9,10]

Division of Musculoskeletal Oncology, Department of Orthopaedics and Traumatology, Prince of Wales Hospital, Hong Kong (H.-W.L., K.-C.W., W.-K.C.); and Professor, Division of Musculoskeletal Oncology, Department of Orthopaedics and Traumatology, the Chinese University of Hong Kong (S.-M.K.).

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Address correspondence to Hiu-Woo Lau, M.B.B.S. (HK), M.R.C.S.Ed., Department of Orthopaedics and Traumatology, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong. E-mail: lauhiuwoo@gmail.com

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Zoledronic acid is the most potent among all tested bisphosphonates.[9] In a recent meta-analysis, it has been shown that bisphosphonates could reduce LR, and bisphosphonates potentially benefit in patients undergoing intralesional curettage, but not in patients with wide resection.[11] Bisphosphonates might reduce the LR rate and be useful in controlling disease progression in short-term clinical follow-up.[12] However, the use of bisphosphonates on GCTB is controversial, as long-term results are not available. To date, there are no reports in the literature of the LR rate of patients treated with MIC and perioperative bisphosphonates.

The purpose of this study was to compare the long-term oncological outcome of endoscopy-assisted MIC with conventional open curettage (OC). We hypothesized that, for primary GCTB of the extremities with perioperative bisphosphonates, patients in MIC group and OC group had comparable local recurrence rate in long-term follow-up.

Methods

The study was performed in accordance with the ethical standards of our institution's Clinical Research Ethics Committee (reference no. 2020.480). We studied patients with GCTB of the extremities who underwent intralesional tumor curettage and cementation and perioperative bisphosphonates from February 2003 to June 2016. All cases were histology-confirmed diagnoses of GCTB. Recurrent GCTB, malignant GCTB, cases in the axial skeleton (pelvis and spine), or cases with bone grafting of the curetted cavity were excluded to minimize the heterogeneity in evaluation.

Lesions were categorized as grade 1, grade 2, and grade 3, according to the system of Campanacci.[13] Any pathological fracture was noted. The radiographs were accessed by one orthopaedic resident and one orthopaedic oncology surgeon with a good interobserver agreement. (Cohen's κ: .945, 95% CI 0.937-0.954; $P < .001$)

During the first half of the study, patients with primary GCTB over extremities underwent open curettage (OC). For the second half of the study, patients received minimally invasive curettage (MIC) surgery, except for three patients with pathological fractures. Open curettage and internal fixation were performed on cases of pathological fracture. Conventional open curettage (OC) was performed in 15 patients, while MIC was performed in 18 patients.

In the OC group, a cortical window was made so that the peripheral extent of the tumor could be fully visualized and reached by curetted instruments. The main tumor bulk was first removed with angled curettes and suction, and the tumor cavity was further cleared with a high-speed bone burr (Fig 1).

In the MIC group, the technique of navigation and endoscopy-assisted tumor (NEAT) surgery has been used at our institution since 2008, as described in a 2010 article.[4] Preoperative CT images of the affected areas were acquired at the same setting when the patient underwent a CT image-guided tissue biopsy. Slices with .625-mm thickness were obtained using a soft tissue algorithm. The axial CT images in the format of DICOM were used for three-dimensional (3D) surgical planning. They were imported into either the CT-based navigation system when intraoperative navigation guidance was performed or the biomedical engineering software (Mimics 15.0; Materialise, Leuven, Belgium) when navigation assistance was not required. The 3D bone-tumor models were generated to decide the optimal skin incision and cortical bone window. Between 2008 and 2010, the CT navigation system (Spine, version 2.0.1, VectorVision, BrainLAB, Feldkirchen, Germany) was used, in which an image-to-patient registration was achieved by using a CT-fluoro matching technique. The preoperative CT images of the affected bone were matched to intraoperatively acquired (AP and lateral) fluoroscopic images. The CT navigation system used in the later part of the study (OrthoMap 3D module, version 2.0, Stryker, Mahwah, NJ) had been used since 2011. It allowed easier image manipulation in 3D surgical planning and more accurate image-to-patient registration with intraoperative 3D imaging. After performing the first three cases in the MIC group, we adopted the intraoperative navigation guidance only in cases with internal bone septae, where there were anticipated difficulties in intralesional curettage. Endoscopic technique without navigation was used in uncomplicated cases to reduce the operative time spent on the navigation setup.

The skin incisions and the planned cortical bone windows were marked. A pneumatic tourniquet was then inflated, and the skin was incised precisely over the planned portal sites. We changed to one portal technique with one cortical window in 2009 instead of a two-portal technique, with two cortical windows that were initially used in the authors' institution in 2008.[4] The one portal technique was more flexible in manipulating both arthroscope and curetted instruments via one larger cortical window. The central part of the tumor was removed with curettes, the same as in the OC group. A dry 4-mm 30° arthroscope was then introduced into the cortical window. Under the direct magnified endoscopic visualization, the tumor was further removed from the intraosseous surface of the tumor cavity by angled curettes and high-speed bone burr (Video 1). The additional real-time feedback from navigation CT imaging facilitated the removal of bone septae, and the curettage reached the peripheral edge of the tumor cavity. This ensured the adequacy of intralesional tumor clearance (Fig 2). The curetted tumor cavity of all of the patients with intralesional curettage was filled up with bone cement

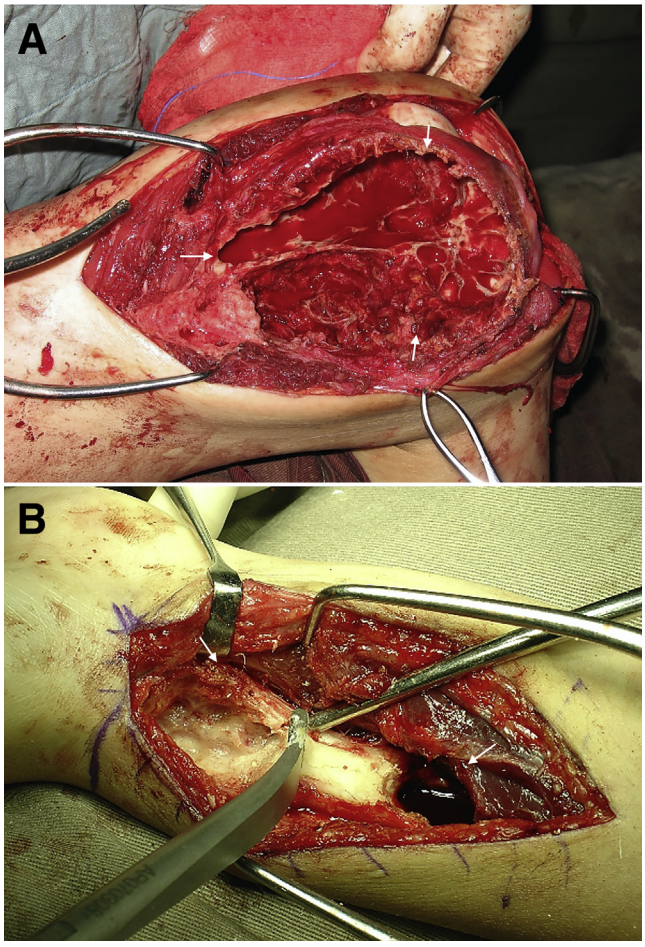

Fig 1. Photographs demonstrating the conventional open curettage in patients with the distal femur giant cell tumor of bone (GCTB) (A) and recurrent distal radius GCTB (B). Large surgical incision and cortical window (white arrows) over the tumor were performed in order to access the peripheral edge of the tumor.

in both OC and MIC groups. The bone cement was mixed uniformly by vacuum system and then injected into the cavity with cement gun and pressurization. Finger pressurization via the bone window was also added as necessary, so to ensure the cement filling up the whole bone defect. In our experience, no imaging was needed during and after cementation in the operation.

Thirty (out of 33) patients were given perioperative intravenous zoledronic acid (4 mg in 100 mL normal saline over 15 minutes) once per month for five doses since year 2005. Two doses were given before the operation, and three doses were given after operation. Clodronate, pamidronate, and ibandronate were also given in three patients in the OC group when zoledronate acid was not readily available in the early part of the study. One patient received oral clodronate (520 mg) twice daily for 6 months after operation. One patient was given oral ibandronate (150 mg) once per month for 2 months after the operation. One patient underwent CT-guided local pamidronate (60 mg) injection monthly for 6 doses before operation. All patients were also given calcium supplements during the bisphosphonates treatment. No severe adverse side effects of the drugs were noted.

All patients were allowed to resume immediate joint movement and full weight-bearing walking after the drains were removed 1 or 2 days after the surgery. Patients were followed at the time of bisphosphonate infusion or 1 month, 2 months, every 3 months for 2 years, every 6 months until 5 years, and then annually. At each visit, we checked the patients for local recurrence by clinical examination and plain radiographs of the operated sites (Fig 3). We also recorded other parameters, including the operative time, complications (wound infection or subsequent joint degeneration), and adverse side effects of the bisphosphonates.

Statistical analysis was performed using SPSS version 24. The results of the OC and MIC groups were compared by Pearson's χ^2 test, Fisher's exact test, and the t test. Kaplan-Meier event-free estimates were calculated for the LR-free estimates in the two groups. The hazard ratio of a local recurrence was calculated with the use of univariate Cox regression, for the various factors of the patients, disease, and treatment. $P < 0.05$ was considered statistically significant.

Results

General Data

Thirty-three patients of GCTB in the extremities underwent intralesional tumor curettage during the study period (Table 1). At a mean follow-up of 8.8 years (3 to 17), the overall LR rate was 24.2% (8 out of 33 patients). The mean time to LR was 33.1 months (8 to 75). Two patients with LR underwent wide resection, and the bone defect was reconstructed with arthroplasty and vascularized bone graft, respectively. The rest of the patients with LR (six patients) had second intralesional curettage. Two out of the six patients developed the second LR requiring the third intralesional curettage. No further LR was noted in the relapsed patients during the subsequent follow-up assessment.

MIC versus OC

Further data, according to whether the surgical procedure was OC or MIC, are compared in Table 2. The demographic data of the MIC and OC groups were comparable in terms of age, gender, tumor location and pathological fracture. Open curettages were more commonly performed in patients with higher Campanacci grade ($P = .003$). The follow-up time of convention open curettage group was longer ($P = .031$).

The OC group had a mean follow-up of 10.0 years (5-17) that was significantly longer than that in the MIC

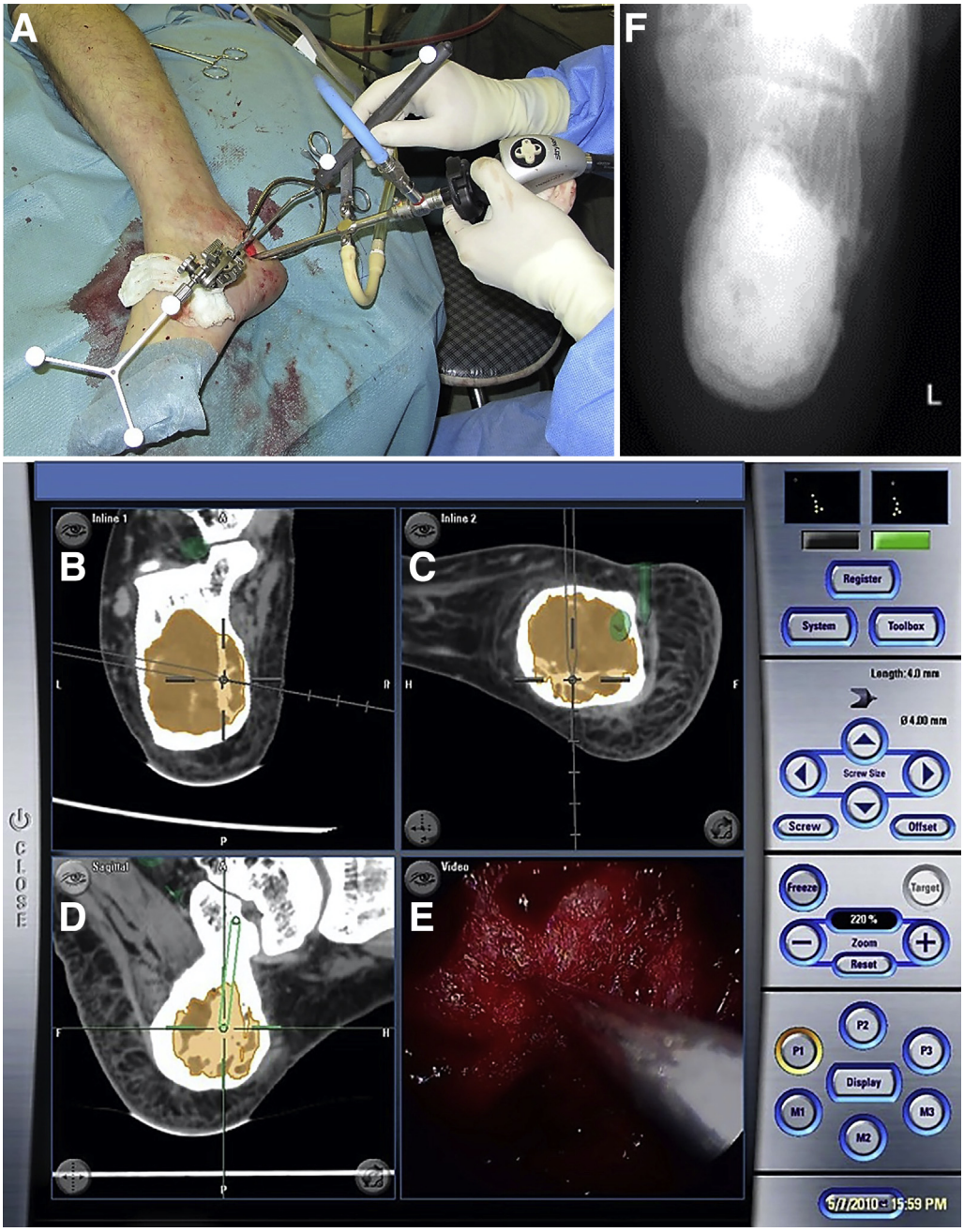

Fig 2. (A) Setup of the navigational and endoscopy-assisted curettage in a patient with calcaneal giant cell tumor of bone (GCTB). The tip of the navigation pointer (gray cross) is touching the internal calcified septae of the tumor (orange), as it could be visualized on the computed tomography axial view (B), reformatted coronal view (C) and sagittal view (D) and also endoscopic view (E). The real-time navigation feedback helped removing the septae to ensure the edge of tumor cavity to be adequately cleared. (F) The postoperative plain radiograph confirmed that the cement filled up the entire tumor cavity of the calcaneus.

group (7.8 years, 3-11). However, there was no statistical difference in LR in both groups (27.8 % vs 20%, $P = .6$). At 10 years, the overall LR-free outcome was 76%. The MIC group achieved a 72% LR-free outcome, while the OC group achieved 80% (Fig 4). The difference was not statistically significant ($P = .6$).

The operative time was comparable in both MIC and OC groups (Table 2). In the MIC group, eight patients used the assistance of both CT navigation and endoscope (NEAT), while 10 patients used only endoscopic assistance (EAT). The operative time spent on NEAT (152 ± 30 minutes) was longer than that of EAT (99 ± 23 minutes). The difference in operative time was statistically significant ($P = .001$).

Hazard Ratio (HR) of Various Patient, Disease, and Treatment Factors

None of the risk factors studied led to a significantly higher hazard of LR (Table 3). HR of the lesion at the distal radius was greater than lesions at other locations, but the result was not significant ($P = .137$).

No wound complications or infection was noted. There were no bisphosphonate-related complications, such as osteonecrosis of the jaw or atypical femur

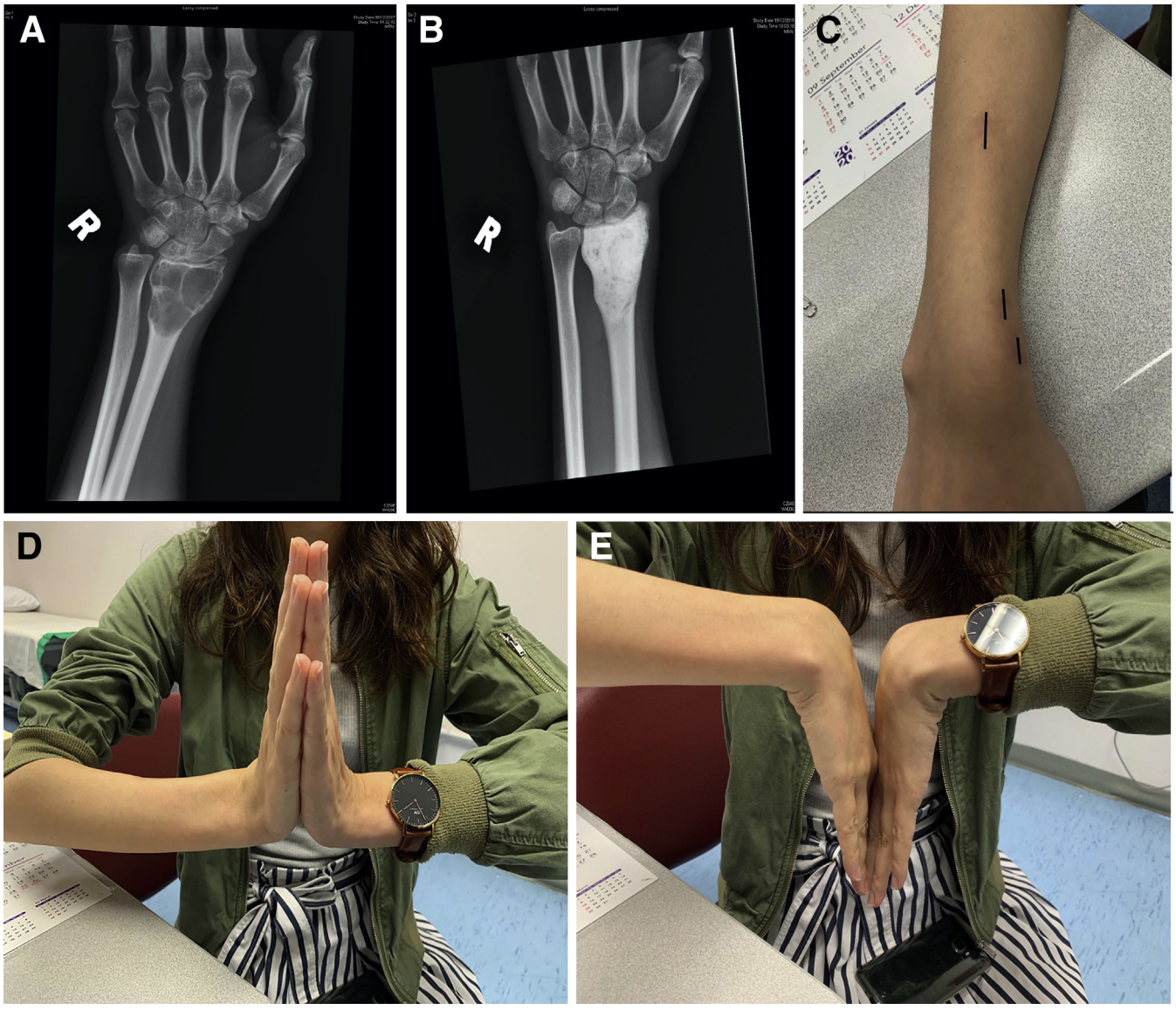

Fig 3. 29-year-old woman with Campanacci grade 2 right distal radius giant cell tumor of bone underwent minimally invasive curettage. (A) Navigation and endoscopy-assisted curettage was performed because of the presence of septa inside the lesion. (B) Radiograph 4 years after minimally invasive curettage showed no local recurrence. (C) Three small skin incisions healed well. She had excellent range of wrist extension (D) and flexion (E).

fracture. No patients suffered from joint degeneration that needed joint replacement.

Discussion

The LR-free survival proportion in the MIC group was comparable to that of the conventional OC in the study ($P = .604$). However, MIC is believed to have superior limb function when compared with OC. Cortical windows were made just large enough to allow tumor curettage with endoscopic or navigated assistance in MIC. Our results have shown a smaller cortical window for curettage appears not to compromise LR-free survival. Also, small cortical windows preserve more native bone and, thus, mechanical stability, so that patients were allowed to resume full weight-bearing walking and full joint mobilization immediately after surgery. Further studies are necessary to investigate the possible superior limb function in the bone-preserving technique of MIC in GCTB of the extremities.

The treatment of GCTB should ensure local control and maintain function. Intralesional curettage has been established as the preferred treatment method for GCTB.[14] MIC in GCTB of the extremities is a new technique and had been only rarely reported in several case series in the literature.[4,7] Little is known regarding the comparison of MIC versus the conventional OC. On the other hand, bisphosphonate was found to have potential antitumor effects by inducing dose-dependent

Table 1. Summary of the Age and Gender of Patients, Types of Surgical Procedures, Bisphosphonate Uses, the Follow-Up Period, Local Recurrence Rate, and the Time to Local Recurrence

Parameter	Value
Age	33.8 ± 13.8 (13-69)
Gender	Male 16 (48.5%)
	Female 17 (51.5%)
Surgery	MIC 18 (54.5%)
	OC 15 (45.5%)
Bisphosphonate	Clodronate 1 (3%)
	Ibradronate 1 (3%)
	Pamidronate 1 (3%)
	Zoledronate 30 (90.9%)
FU period in years	8.81 ± 3.00 (3-17)
Local recurrence rate	24.2% (8/33)
Time to recurrence ($n = 8$)	33.1 ± 24.1 (8-75)

apoptosis on neoplastic stromal cells of GCTB in basic studies.[10] Short-term clinical results suggested that it might lower the LR rate after intralesional tumor curettage. However, the long-term oncological result is unknown. Data are lacking on the subgroup of patients with MIC and adjuvant bisphosphonate in GCTB. In this study, with an average follow-up of 9 years, we analyzed the LR-free survival in primary GCTB undergoing either MIC or OC with adjuvant bisphosphonates.

All patients were treated with intralesional curettage, bone cement filling, and adjuvant bisphosphonate in this 9-year follow-up study. The overall LR rate was 24.2%. It was similar to that of other studies,[1-3,15] with intralesional curettage and bone cement but without adjuvant bisphosphonates, in which LR rate ranged from 12.5 to 23.3%. The mean time to recurrence in the study was 2 years and 9 months. This concurred with the reported finding that most instances of recurrence occur in the first 2-3 years after surgery.[16] The LR rate in MIC group was 27.8%. Combining bisphosphonates and MIC with endoscopy could work equally without compromising the local control. We believe that the endoscopic assistance and selected cases with navigation guidance may facilitate the intralesional tumor curettage, while preserving more native juxta-articular bone for better limb function.

Intraoperative navigation guidance was used only in cases with internal bone septae where there were anticipated difficulties in intralesional curettage. The operative time of MIC with navigational and endoscopic assistance (NEAT) is longer than that of MIC with endoscopy alone (EAT) ($P = .001$). The intraoperative setup of computer navigation and the initial learning curve of the technique could account for the longer operative time in the MIC group with NEAT. The technique and its indication of using computer navigation have been refined initially during the study period. We believe the final simplified workflow of the technique is less technically demanding. The operative time would be reduced with more surgical experience as computer navigation has been gaining popularity in orthopaedic oncology during the last decade.

Table 2. Comparison of Data of Minimal Invasive Curettage and Open Curettage Group

	MIC ($n = 18$)	OC ($n = 15$)	P Value
Age	33.22 ± 10.37	34.47 ± 17.44	$P = .629$
Gender	Male 8	Male 8	$P = .611$
	Female 10	Female 7	
Campanacci grade [13]	grade 1:3	Grade 1: 1	**P = .003**
	Grade 2: 14	Grade 2: 5	
	Grade 3: 1	Grade 3: 9	
Tumor location	Distal femur: 3	Distal femur: 5	$P = .578$
	Proximal tibia: 6	Proximal tibia: 4	
	Distal radius: 4	Distal radius:2	
	Proximal femur: 1	Proximal femur: 2	
	Distal tibia: 1	Distal tibia: 1	
	Distal humerus: 1	Distal humerus: 1	
	Calcaneum: 2	Calcaneum: 0	
	Talus: 1	Talus: 0	
Pathological fracture	Yes 0	Yes 3	$P = .083$
	No 18	No 12	
OT time	122.78 ± 37.43	110.33 ± 39.46	$P = .919$
	NEAT: 152 ± 30 minutes		
	EAT: 99 ± 23 minutes		
Local recurrence rate	27.8% (5/18)	20% (3/15)	$P = .604$
Follow-up period (years)	7.84 ± 2.07 (3-11)	9.97 ± 3.56 (5-17)	***P = .031***
LR-free estimates	.72 (.50-.93)	0.80 (.60-1.00)	$P = .604$
Overall .76 (.61-.90)			

Among the MIC group, 8 patients underwent navigation and endoscopy-assisted tumor (NEAT) surgery, and 10 patients received endoscopy-assisted tumor (EAT) surgery. MIC, minimal invasive curettage; OC, open curettage.

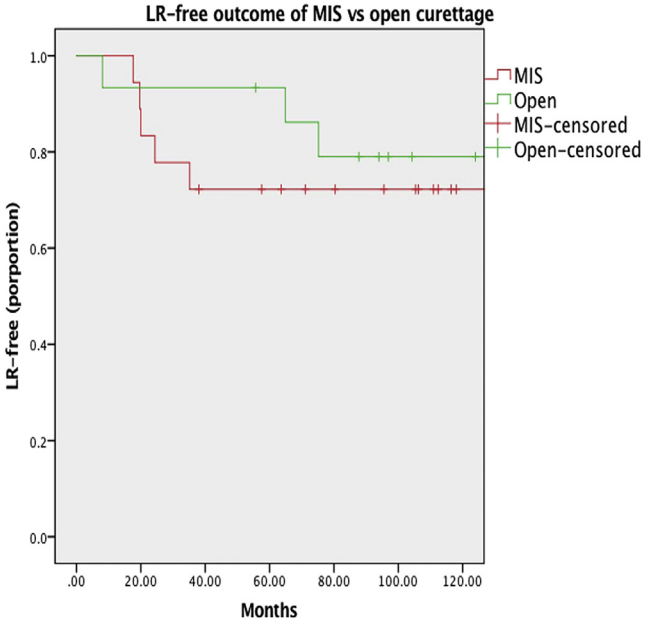

Fig 4. Diagram showing the local recurrence-free (LR-free) outcome of the two curettage approaches.

Table 3. Results of the Cox Regression Analysis

	Hazard Ratio	95% CI	*P* Value	Standard Error
Gender		.404-7.084	.688	.731
Male	1			
Female	1.692			
Age		.244-4.269	1.000	.730
Less than 30	1			
30 or above	1.020			
Location		.859-15.339	.137	.735
others	1			
Distal radius	3.63			
Campanacci		.346-6.084	.673	.731
Grade 1 and 2	1			
Grade 3	1.452			
Pathological fracture		.254-16.991	1.000	1.072
No	1			
Yes	2.078			
Surgical approach		.3843-6.807	.699	.734
Open	1			
MIC	1.616			

The effect of bisphosphonate on lowering the LR of GCTB is still controversial. A recent meta-analysis showed bisphosphonate had beneficial effect on patients who underwent intralesional curettage.[11] However, Lipplaa et al. reported adjuvant treatment with zoledronic acid did not decrease the recurrence rate of GCTB in the recent randomized control trial with 14 patients.[19] In our opinion, with the present evidence from the literature, an adequate intralesional tumor curettage is still the key in local tumor control and reducing LR in GCTB of extremities.

In all patients with Grade 3 GCTB, the extraosseous tumor components were resected while the intraosseous components were removed by curettage. In this study, the group with open curettage had a higher Campanacci grade than the group of patients that had minimal invasive curettage ($P = .003$). However, the prognostic significance of the radiological system of GCTB remains questionable. Multiple authors, including Campanacci et al., found no correlation between radiographic grading of tumor and risk of LR.[3,13,17] In a recent review article, the authors considered the radiological system of GCTB used by Campanacci et al. as not providing reliable prognostic significance in terms of the recurrence rate or functional results.[18] Therefore, the radiological grading of GCTB may not reflect its tumor aggressiveness. The LR may be more related to the adequacy of tumor removal that surgeons can control.

Limitations

First, this was a retrospective study with data obtained from hospital clinical files and electronic medical records. Second, the study population was relatively small, with only 33 patients in the study. The inclusion criteria were strict. Only patients with primary GCTB treated with intralesional curettage, bone cement, and perioperative bisphosphonate were included. This minimized the number of confounders in the groups and made comparisons easier and more meaningful. Third, the follow-up period in the OC group was longer than in the MIC group (10.0 vs 7.8 years, $P = .031$). Given that most of the LR occurs at 2 to 3 years after surgery (mean time to LR: 2 years, 9 months), the comparison of the LR in the two groups may not be affected at long-term follow-up. Fourth, the MIC technique is a relatively new technique that requires operative experience and facilities with computer navigation and endoscopy capability. The results may not be readily reproducible in other institutions. Finally, the treatment strategy of GCTB has evolved in our institution. Bisphosphonates had been given to all of our patients as adjuvant systemic treatment after intralesional curettage in the study period. Direct comparison between bisphosphonates and bisphosphonate-free group was not possible and was beyond the scope of the study.

Conclusion

At a long-term follow-up of 9 years, MIC showed similar LR-free survival compared with OC. Combining bisphosphonates and MIC with a less invasive approach showed reasonable LR-free survival in long-term follow-up.

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