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Giant cell tumor of the bone: an evaluation of prognostic factors associated with local recurrence and a comparison with the current literature

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ABSTRACT

Aim: Results of the surgical and medical treatments of giant cell tumor of the bone (GCT) in terms of local recurrence and prognostic factors associated with local recurrence are evaluated in this study.

Material and Method: Patients treated with either surgical or medical methods for GCT between 2011 and 2021 were retrospectively evaluated. Gender and age of the patients, localization of tumors, the existence of pathological fractures, grade of the tumor, soft tissue expansion, and resection types were evaluated. Postoperative local recurrence and metastasis were analyzed, and the risk factors associated with local recurrence were determined.

Results: The mean age of the 117 patients (51 female and 66 male) was 36.1±9.3 years. The mean follow-up was 71.2±48.3 months. Forty patients were Grade I, 56 were Grade II, and 21 were Grade 3, according to the Campanacci Grading System. Soft tissue expansion was present in 21 (17.9%) patients. 59.8% of the patients were undergone intralesional curettage, 32.4% of the patients were treated with marginal or wide local excision combined with adjuvant therapy with liquid nitrogen and poly-methyl methacrylate (PMMA) application, and 5.9% of the patients have treated with en bloc wide resection and reconstruction or arthrodesis. Two patients suffering from sacral involvement were treated with radiotherapy. There was local recurrence after surgery in 19 (16.2%) of the patients.

Conclusion: Local recurrence is an important cause of morbidity in the treatment of GCT, which is a benign but aggressive tumor of the bone. In this study, in which we investigated the causes of local recurrence, Campanacci Grade and soft tissue expansion were found to be associated with the development of local recurrence.

Keywords: Giant cell tumor, osteoclastoma, neoplasm, prognosis, recurrence

INTRODUCTION

Giant cell tumor of the bone (GCT) is a local aggressive primary bone tumor and accounts for 6% of the primary bone tumors (1). GCT is characterized by mononuclear stromal cells, primarily macrophages, and osteoclast-like giant cells in the histopathological examination. GCT is commonly seen in the 4th and 5th decades, and the most common symptom is pain (2). GCT is typically a solitary bone tumor, and 85% of them are seen in the metaphysio-epiphyseal regions of long bones (3). 10% of them are seen in the axial skeleton, and rarely (5%) of the GCTs are seen in the short bones of the hand and the foot (3).

GCTs are typically benign but rarely malignant de novo or due to the malignant transformation of the primary tumor. The main diagnostic challenge is that osteoclast-like giant cells may be seen in several pathological situations of the bone, such as aneurismal bone cysts, non-ossifying fibroma, chondroblastoma, and histiocytic fibroma. Henceforth, a thorough histopathological evaluation is crucial for the differential diagnosis of GCT.

There is no consensus on the treatment of the GCT, and several surgical and adjuvant techniques were defined in the literature. The main treatment modality for the primary local disease is surgery. Common

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adjuvant treatment options are liquid nitrogen, phenol, argon, and monoclonal antibodies. Generally applied treatment protocol for the treatment of GCT is adjuvant application after intralesional curettage and replacement of the defect with bone cement. On the other hand, reconstruction with endoprostheses or arthrodesis is another option for patients with broad soft tissue involvement or pathological fractures. The decision for the surgical treatment option generally depends on the feasibility of the curettage and local adjuvants against resection and partially the possibility of the local recurrence. Protection of the functionality of the limb while diminishing the risk for recurrence is aimed with local adjuvant treatments (4).

The main problem after the treatment of GCT is the local recurrence after surgery. Local recurrence is reported in 10% to 65% of the patients (5-8). Treatment options adjuvant to the surgery are reported as the main factor for the control of local recurrence (5-8). On the other hand, localization of the tumor, size of the tumor, grade, and several other factors may affect the local recurrence. This study aims to determine the recurrence rate after resection of GCTs and the factors associated with recurrence.

MATERIAL AND METHOD

After obtaining approval from Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 2022/151), medical records of 117 patients operated on between 2011 and 2021 in a single center with the diagnosis of primary GCT were evaluated retrospectively. All the study procedures complied with the principles of the Declaration of Helsinki.

Gender, age, tumor localization, the existence of pathological fractures, Campanacci Grading System, Enneking Classification, soft tissue expansion, and the chosen therapeutical modality, i.e., intralesional curettage, curettage combined with resection, or en bloc resection were evaluated. Exclusion criteria were unconfirmed diagnosis of GCT despite the preoperative suspicion, admission with local recurrence and primary treatment made in an-other institution, missing medical records, unable to follow-up, and local recurrence of GCT treated with nonsurgical methods. All patients were discussed at the institutional musculoskeletal tumor council, and all these patients underwent surgery after biopsy.

The surgical technique of intralesional resection was performed from a cortical window, and curettage was done with a high-speed burr until no macroscopic tumor tissue was seen. After that, cryoablation was done with liquified nitrogen, and the bony defect was filled with polymethyl methacrylate (PMMA). Marginal or wide resection was performed on the patients if the tumor was big enough to lead to a pathological fracture or a pathological fracture existed, a broad soft tissue component existed, the joint was involved, or the defect was too wide for reconstruction. Two patients with iliac bone involvement were treated with segmental resection only. A patient with metatarsal involvement was treated with total excision of the metatarsal bone and reconstruction with an autologous nonvascularized fibular graft. Other patients were treated with endoprosthetic reconstruction or arthrodesis. Two patients with sacral involvement were treated with radiotherapy since their tumors were unsuitable for surgical resection.

All the patients were called for a follow-up examination in the 1st, 3rd, and 6th months after surgery. Local recurrence was screened with physical examination, radiograms, and CT scans. A yearly chest X-ray scan was performed for screening a possible pulmonary metastasis. A restaging was done for the treatment of local recurrences.

The data were analyzed with SPSS 22 statistical software (Chicago, IL, ABD). Univariate survival analysis was done with Kaplan-Meier survival estimation, and multivariate analysis of significant risk factors for local recurrence was done with the Cox regression analysis model.

RESULTS

The mean age of 117 patients (51 female, 66 male) was 36.1±9.3 years. The mean follow-up was 71.2±48.3 months. Ten patients (8.5%) had pathological fractures on admission. Forty-seven (40.2%) had tumors in the distal femur (**Figure 1** and **2**), 40 (34.2%) in the tibia, 12 (10.2%) in the distal radius, 6 (5.1%) in the proximal fibula, 5 (4.3%) in the pelvis (two in the sacrum, one in the acetabulum, two in the ilium), 5 (4.3%) in metatarsals, and 2 (1.7%) in phalanges of the hand. Forty (34.2%) of them were Campanacci Grade I, 56 (47.9%) were Grade II, and 21 (17.9%) were Grade III. Twenty-one (17.9%) patients had soft tissue expansion.

59.8% of the patients were treated with intralesional curettage (**Figure 1**) and 32.4% with marginal or wide resection. 5.9% of the patients were treated with en bloc wide resection, and two (1.7%) patients, who had sacral involvement, were treated with radiotherapy. Local recurrence after surgery was found in 19 (16.2%) of the patients, and six patients (5.1%) had pulmonary metastases.

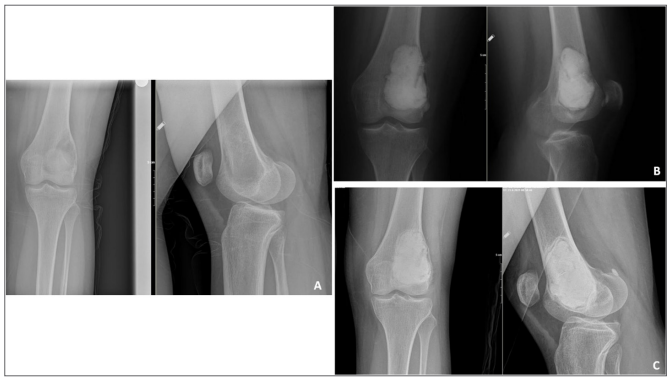

Figure 1. A) Conventional radiography of the left knee AP/Lateral projection, showing lytic lesion, septal, soap bubble appearance, narrow transition region, geographic destruction, cortical thinning, medullary, eccentrically located, hypodense lesion, no matrix calcification, no periosteal reaction, no soft tissue involvement. B) Postop radiography; intralesional curettage and augmentation with PMMA. C) Postop 3rd year radiography.

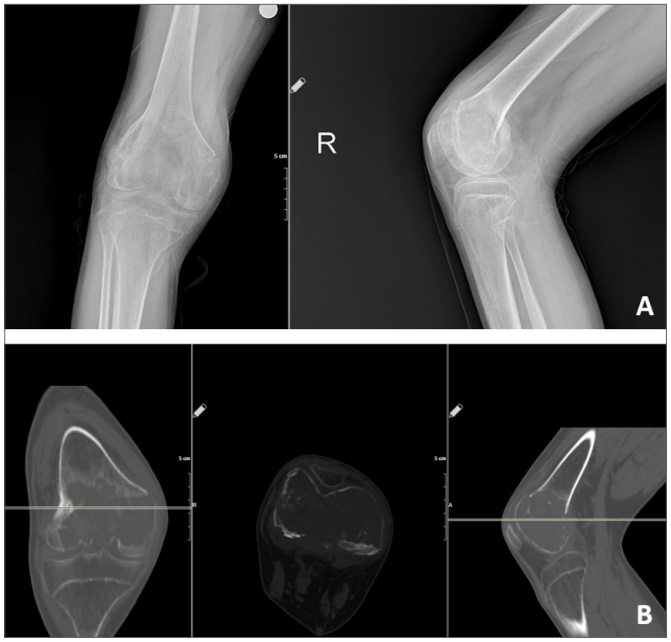

Figure 2. A) Conventional radiography of the right knee AP/Lateral projection, showing lytic lesion, septal, soap bubble appearance, narrow transition region, cortical destruction, medullary located, hypodense lesion, with pathological fracture. B) Coronal, axial and sagittal computed tomography images.

Three patients with femoral involvement were treated with endoprosthetic reconstruction after en bloc resection, and the local recurrence rate was 33.3%. Forty-four other patients were treated with curettage or marginal/wide resection, and only five had a recurrence. Two patients with proximal tibial involvement were treated with en bloc resection, and one of them had a recurrence. In contrast, only four patients treated with intralesional curettage had a recurrence. Two patients with iliac involvement were treated with segmental resection without reconstruction. Two patients with sacral involvement were treated with radiotherapy and one had recurrence. One patient with acetabular involvement was treated with intralesional curettage, and no recurrence was seen. Patients with distal radial involvement were treated with curettage or marginal/wide resection, and four of the 12 patients had a recurrence. All the recurrence patients were Campanacci Grade II. Five patients with fibular involvement were treated with intralesional curettage, and two of them had a recurrence, while one patient treated with wide resection had a local recurrence. One patient with metatarsal involvement was treated with total metatarsal excision and reconstruction with fibular autograft, while the other five were treated with curettage and reconstruction with PMMA. One of the patients with phalangeal involvement was treated with intralesional curettage, and the other was treated with wide resection and arthrodesis. None of these patients had a recurrence.

Demographic characteristics of cases and the specificities of tumors were summarized in **Table 1**. The median time for the first recurrence was 18.4 (6-38) months. Survival rates of the patients in the 1st, 2nd, and 5th years were 95.7%, 98.6%, and 84.3%, respectively. In the 1st, 2nd, and 5th years, survival rates without recurrence were 95.7%, 87.9%, and 84.4%, respectively. Potential risk factors for local recurrence are summarized in **Table 2**.

Table 1. Demographic characteristics of cases and the specificities of tumors

Parameters	Subgroups	N	%
Age			
	< 40		60.4
	≥40		39.6
Gender			
	Male	66	56.5
	Female	51	43.5
Localization			
	Distal Femur	47	40.2
	Proximal Tibia	40	34.2
	Distal Radius	12	10.3
	Proximal Fibula	6	5.1
	Pelvis	5	4.3
	Metatarsals	5	4.3
	Phalanges	2	1.7
Pathological fractures			
	Existent	10	8.5
	Absent	107	91.4
Soft tissue expansion			
	T1	96	80.1
	T2	21	17.9
Campanacci Grade			
	Grade I	40	34.2
	Grade II	56	47.9
	Grade III	21	17.9
Type of Resection			
	Intralesional Curettage	67	57.3
	Marginal /Wide local resection	41	35
	En bloc resection	7	6
	No resection	2	1.7
Local recurrence			
	Existent	19	16.2
	Absent	98	83.8

Table 2. Potential risk factors for local recurrence

Parameters	Subgroup	2-year Recurrence-Free Survival	5-year Recurrence-Free Survival	p
Age				0.235
	< 40	94.5	56.3	
	≥40	96.2	59.2	
Gender				0.309
	Male	86.8	75.3	
	Female	94.6	86.2	
Localization				0.142
	Distal femur	89.4	87.2	
	Proximal tibia	92.3	89.3	
	Distal radius	83.3	60.9	
	Proximal fibula	83.3	66.7	
	Pelvis	80.0	50.0	
	Metatarsals	100	100	
	Phalanges	100	100	
Pathological fractures				0.534
	Existent	90.0	80.0	
	Absent	91.7	82.8	
Soft tissue expansion				0.028
	T1	91.6	86.6	
	T2	71.4	65.9	
Campanacci grade				0.047
	Grade I	97.5	87.8	
	Grade II	92.6	84.8	
	Grade III	69.6	64.6	
Type of resection				0.169
	Intralesional curettage	93.7	87.3	
	Marginal /wide local resection	82.7	76.8	
	En bloc resection	71.4	71.4	
	No resection	50.0	50.0	

Gender and age were irrelevant to recurrence-free survival (p>0.05). Campanacci grade of the patients was related to five-year recurrence-free survival (p=0.047), and the rates for Campanacci grades I, II, and III were 87.8%,84.8%, and 64.6%, respectively. The 1st- and 5th-year recurrence-free survival rates were 90.0% and 80.0% in the patients with pathological fractures, while 97.2% and 82.8% in other patients, respectively. The existence of pathological fracture was not associated with recurrence-free survival (p=0.534). 60% of the pathological fractures were around the knee joint, and these patients were treated with marginal resection combined with augmentation with PMMA or en bloc resection combined with endoprosthetic reconstruction. The least recurrence-free survival rates according to the localization of the tumor were the distal radius and fibula, with 66.7% 5-year recurrence-free survival rates. Localization of the tumor was not associated with local recurrence (p=0.181). The 2- and 5-year recurrence-free survival rates in the T1 soft tissue expansion were 91.6% and 86.6%, respectively, while 71.4% and 65.9% were in the T2 group. The grade of soft tissue expansion was associated with local recurrence (p=0.028).

One- and 5-year recurrence-free survival rates were 97% and 87.9% in the intralesional curettage group, 92.7% and 76.8% in the marginal/wide resection group, and 85.7% and 71.4% in the en bloc resection group, respectively. The type of resection was not associated with local recurrence (p>0.05).

Nineteen patients with local recurrence were treated with a second intralesional curettage or wide resection, and none of them had re-recurrence. Six patients had pulmonary metastases. One of them had a pathological fracture after the treatment. Four of them had unifocal metastases and took denosumab adjuvant to the surgery. Two patients with multifocal metastases were treated with re-curettage only. None of the metastatic patients had secondary metastases or local recurrence.

Campanacci Grade of the tumor and soft tissue expansion were found to be risk factors for local recurrence. Age, gender, localization of the tumor, pathological fractures, and type of resection were not associated with local recurrence.

DISCUSSION

The pathogenesis of GCT is controversial and reported local recurrence rates were between 12% and 49% (2,8). Age, distal radius localization, proximal femur localization, intralesional curettage, soft tissue expansion, proximal fibula localization, pathological fractures, grade, marginal resection are previously reported risk factors for local recurrence (4,5,7-14). While age and gender were not found to be associated with local recurrence in this study, some studies claim that younger age is a risk factor for local recurrence (5,11). This may result from more conservative surgical choices for younger patients since broader resection decreases local recurrence in exchange for more morbidity, and surgeons may prefer intralesional curettage instead of wide resection for younger patients.

Some authors reported that localization of the tumor is associated with local recurrence (4,7,15). We found that the highest prevalence of local recurrence was seen in distal radial, with an odds ratio of 1.1 and a 66% 5-year recurrence-free survival rate, and proximal fibular involvement, but this difference was not statistically significant. Errani et al. (4) also reported that distal radial and proximal femoral involvement is associated with the risk of local recurrence. Other studies reported local recurrence rates between 20% and 88.9% for

tumors in the distal radius (4,9,15). The highest reported recurrence rate in the literature was 88.9% (7), and in this study, Balke et al. (7) reported that most of those patients had soft tissue expansion. Also, they did not use PMMA for bony defects. This may increase the local recurrence rate. We performed intralesional curettage for local lesions (Campanacci Grade I and II) and marginal or wide resection for Grade III lesions. We combined cryotherapy with surgery and applied PMMA to the defect. We found similar local recurrence rates after both treatment modalities. Three patients with GCT in the proximal fibula were treated with intralesional curettage, cryotherapy and PMMA; one had local recurrence; the other two had peroneal nerve damage. Local recurrence was treated with segmental resection. The proximity of neurovascular structures to the distal radius and the proximal fibula may challenge local control. Contrary to this, some reports claim that localization does not affect local recurrence (10,13).

Surgical treatment of GCT aims to ensure local control with minimum surgical morbidity and protect the limb's function. Intralesional curettage is associated with higher local recurrence rates but lesser morbidity than en bloc resection (6,7,16). Because of this, intralesional curettage is the main pillar of surgical treatment for most patients with Campanacci Grade I or II tumors, while the choice of wide resection is spared for more aggressive tumors with extraosseous invasion and unresectable tumors. On the other hand, curettage alone has the worst recurrence rate (21%-65%), and because of that usually combined with local adjuvants (5,7,11,17). Local adjuvant applications like phenol, hydrogen peroxide, cryotherapy with liquified nitrogen, augmentation with PMMA, and combinations of these decrease local recurrence rates (7,13,18-20).

We found lowest but insignificant ($p>0.05$) recurrence rate, 10.4%, after intralesional curettage. Recurrence rates after marginal/wide local resection and en bloc resection were 21.9% and 28.5%, respectively. The recurrence rate after intralesional curettage is reported between 12% and 65%, and approximately 20% after en bloc resection (7,11,17,21-23). Kivioja et al. (11) reported the lowest recurrence rate after wide resection as 12%, compared to intralesional curettage as 27%. Klenke et al. (5) reported that the type of surgical resection is not associated with recurrence-free survival.

Contrary to the current literature, we reported higher local recurrence rates after wide or en bloc resection than intralesional curettage. Two reasons may explain this. First, patients treated with wide or en bloc resection had soft tissue expansion or higher grades. We preferred marginal resection to wide resection to avoid higher complication rates and worse functional outcomes.

We applied cryoablation and PMMA augmentation to all patients after curettage or marginal/wide resection. After the combination of curettage and cryoablation, local recurrence rates were between 8% and 42%, while the combination of cryoablation and PMMA yielded better local recurrence rates (0%-20%) (4, 6, 24). Our previous report of 40 patients treated with curettage, cryotherapy, and PMMA found a recurrence rate of 7.5% (14). In this study, we reported a 14.4% recurrence rate, which is in accordance with previous reports. While we did not have another method for comparison in this study, it is evident that the combination of cryotherapy and PMMA is an effective adjuvant method.

On the other hand, usage of local adjuvants has reported complication rates between 12% and 50%(25, 26). Indeed, we observed temporary nerve paralysis in two patients with proximal fibular involvement and iatrogenic fractures in four patients with tumors around the knee. While nerve palsy of two patients recovered with observation, removing the cement, repeat augmentation with PMMA, and osteosynthesis with plates and screws were needed to treat the iatrogenic fractures. So, adjacent neurovascular structures and soft tissue should be well-preserved.

The effect of Campanacci grade on local recurrence is also controversial (6,9,12,15,27). We report that in Grade III patients, the risk of recurrence increased one-fold to the Grade I and two-fold to the Grade II ($p<0.05$). Parallel to our results, some authors reported that Grade III disease is associated with a higher risk of local recurrence(6,9,27). Still, Campanacci et al. (15) reported that the grade of the lesion is not associated with the risk of recurrence. Some studies performed in Eastern Asian countries reported lower recurrence rates in Grade III patient (8,12). This may be a result of the change in the type of surgical resection. Niu et al. (12) reported that they performed resection on 67.8% of Grade III tumors, and Pan Hu et al. (8) reported a resection rate of 47.5%. We performed wide local or en bloc resection on 76.1% of Grade III tumors, which is obviously more common than the aforementioned reports (8,12). We report a higher recurrence rate than these studies, despite the choice of a more aggressive surgical technique. This raises concerns about some other parameters affecting the local recurrence risk other than the grade and the type of resection.

There are conflicting reports about the association between the existence of a pathological fracture and the risk of local recurrence (9,12,28). O'Donnell et al. (9) reported that the existence of a pathological fracture is associated with a higher risk of local recurrence, but Niu et al. (12) reported that there is no relationship between pathological fractures and local recurrence risk. We performed intralesional curettage on the patients with pathological fractures and marginal or wide resection to others and found that

pathological fractures are not associated with recurrence rates (p>0.05). Among the patients with pathological fractures, we observed one local recurrence in a patient treated with intralesional curettage and one treated with marginal resection. We did not observe any recurrence in the patients treated with en bloc resection. Heijden et al. (3) reported a higher recurrence rate for curettage than resection. Our findings support that report. On the other hand, since we observed soft tissue expansion in the patients with pathological fractures, and the number of patients with pathological fractures is relatively low, our findings are inconclusive.

Soft tissue expansion is associated with a higher risk of recurrence (7,10,13). Becker et al. (10) reported 2.7 folds more, Balke et al. (7) reported 4 folds more, and Heijden et al. (13) reported 5 folds more risk of local recurrence with soft tissue expansion. We report 1.6 folds more risk of local recurrence in patients with soft tissue expansion (p<0.05). We performed intralesional curettage on 64.5% of T1 patients, and 23.8% of T2 patients. Technical difficulties for total excision of the tumor during curettage, possible incompetence of local adjuvants, and the need for better surgical margin for the patients with pathological fractures are reasons for the choice of resection as the treatment modality. The choice of surgical modality may lead to a bias.

Neoadjuvant denosumab is highly effective for advanced GCT, and a short-course is advised to facilitate surgery, whereas increased recurrence rates remain of concern. Randomized controlled trials are conducted on bisphosphonate-loaded bone cement and on optimal dose and duration of neoadjuvant denosumab (29). There are studies that say that denosumab and zoledronic acid have similar tumor responses and clinical benefits. Denosumab is a safe but costly alternative to zoledronic acid for treatment of surgically unsalvageable GCT (30). These treatments are used in cases of GCT. We used denosumab as adjuvant therapy in our four cases.

This study has several limitations. First, there may be some bias because of the retrospective nature of the study. Our relatively low sample size hardens our capacity to make a statistically significant conclusion for every parameter analyzed and every treatment group. Lastly, since we used same adjuvant modalities for every patient, we could not compare different options.

CONCLUSION

We observed that Campanacci grade and soft tissue expansion are associated with local recurrence after the treatment of GCT. We also observed a higher, but statistically insignificant risk of recurrence in the patients with distal radial or proximal fibular involvement. Because of this and the higher rate of surgical morbidity observed after curettage in the proximal fibular region, segmental resection is a preferable surgical. Soft tissue expansion in the scenario of a pathological fracture can increase the risk of recurrence.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 2022/151).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. López-Pousa A, Martín Broto J, Garrido T, Vázquez J. Giant cell tumour of bone: new treatments in development. Clin Transl Oncol 2015; 17: 419-30.
2. Liede A, Bach BA, Stryker S, et al. Regional variation and challenges in estimating the incidence of giant cell tumor of bone. J Bone Joint Surg Am 2014; 96: 1999-2007.
3. van der Heijden L, Dijkstra PD, van de Sande MA, et al. The clinical approach toward giant cell tumor of bone. Oncologist 2014; 19: 550-61.
4. Errani C, Ruggieri P, Asenzio MA, et al. Giant cell tumor of the extremity: A review of 349 cases from a single institution. Cancer Treat Rev 2010; 36: 1-7.
5. Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant cell tumor of bone: risk factors for recurrence. Clin Orthop Relat Res 2011; 469: 591-9.
6. Turcotte RE. Giant cell tumor of bone. Orthop Clin North Am 2006; 37: 35-51.
7. Balke M, Schremper L, Gebert C, et al. Giant cell tumor of bone: treatment and outcome of 214 cases. J Cancer Res Clin Oncol 2008; 134: 969-78.
8. Hu P, Zhao L, Zhang H, et al. Recurrence rates and risk factors for primary giant cell tumors around the knee: a multicentre retrospective study in China. Sci Rep 2016; 6: 36332.
9. O'Donnell RJ, Springfield DS, Motwani HK, Ready JE, Gebhardt MC, Mankin HJ. Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. J Bone Joint Surg Am. 1994; 76: 1827-33.
10. Becker WT, Dohle J, Bernd L, et al. Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. J Bone Joint Surg Am 2008; 90: 1060-7.
11. Kivioja AH, Blomqvist C, Hietaniemi K, et al. Cement is recommended in intralesional surgery of giant cell tumors: a Scandinavian Sarcoma Group study of 294 patients followed for a median time of 5 years. Acta Orthop 2008; 79: 86-93.

12. Niu X, Zhang Q, Hao L, et al. Giant cell tumor of the extremity: retrospective analysis of 621 Chinese patients from one institution. J Bone Joint Surg Am 2012; 94: 461-7.
13. van der Heijden L, van de Sande MA, Dijkstra PD. Soft tissue extension increases the risk of local recurrence after curettage with adjuvants for giant-cell tumor of the long bones. Acta Orthop 2012; 83: 401-5.
14. Dabak N, Göçer H, Çıraklı A. Advantages of pressurized-spray cryosurgery in giant cell tumors of the bone. Balkan Med J 2016; 33: 496-503.
15. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. J Bone Joint Surg Am. 1987; 69: 106-14.
16. Kafchitsas K, Habermann B, Proschek D, Kurth A, Eberhardt C. Functional results after giant cell tumor operation near knee joint and the cement radiolucent zone as indicator of recurrence. Anticancer Res 2010; 30: 3795-9.
17. Gaston CL, Bhumbra R, Watanuki M, et al. Does the addition of cement improve the rate of local recurrence after curettage of giant cell tumours in bone? J Bone Joint Surg Br 2011; 93: 1665-9.
18. Balke M, Ahrens H, Streitbuerger A, et al. Treatment options for recurrent giant cell tumors of bone. J Cancer Res Clin Oncol 2009; 135: 149-58.
19. Benevenia J, Patterson FR, Beebe KS, Abdelshahed MM, Uglialoro AD. Comparison of phenol and argon beam coagulation as adjuvant therapies in the treatment of stage 2 and 3 benign-aggressive bone tumors. Orthopedics 2012; 35: e371-8.
20. Moon MS, Kim SS, Moon JL, Kim SS, Moon H. Treating giant cell tumours with curettage, electrocautery, burring, phenol irrigation, and cementation. J Orthop Surg (Hong Kong) 2013; 21: 209-12.
21. Trieb K, Bitzan P, Lang S, Dominkus M, Kotz R. Recurrence of curetted and bone-grafted giant-cell tumours with and without adjuvant phenol therapy. Eur J Surg Oncol 2001; 27: 200-2.
22. Dürr HR, Maier M, Jansson V, Baur A, Refior HJ. Phenol as an adjuvant for local control in the treatment of giant cell tumour of the bone. Eur J Surg Oncol. 1999; 25: 610-8.
23. Capanna R, Fabbri N, Bettelli G. Curettage of giant cell tumor of bone. The effect of surgical technique and adjuvants on local recurrence rate. Chir Organi Mov. 1990; 75: 206.
24. Boons HW, Keijser LC, Schreuder HW, Pruszczynski M, Lemmens JA, Veth RP. Oncologic and functional results after treatment of giant cell tumors of bone. Arch Orthop Trauma Surg 2002; 122: 17-23.
25. Veth R, Schreuder B, van Beem H, Pruszczynski M, de Rooy J. Cryosurgery in aggressive, benign, and low-grade malignant bone tumours. Lancet Oncol 2005; 6: 25-34.
26. Malawer MM, Bickels J, Meller I, Buch RG, Henshaw RM, Kollender Y. Cryosurgery in the treatment of giant cell tumor. A long-term followup study. Clin Orthop Relat Res 1999: 176-88.
27. Prosser GH, Baloch KG, Tillman RM, Carter SR, Grimer RJ. Does curettage without adjuvant therapy provide low recurrence rates in giant-cell tumors of bone? Clin Orthop Relat Res 2005: 211-8.
28. van der Heijden L, Dijkstra PD, Campanacci DA, Gibbons CL, van de Sande MA. Giant cell tumor with pathologic fracture: should we curette or resect? Clin Orthop Relat Res 2013; 471: 820-9.
29. van der Heijden L, Lipplaa A, van Langevelde K, Bovée J, van de Sande MAJ, Gelderblom H. Updated concepts in treatment of giant cell tumor of bone. Curr Opin Oncol 2022; 34: 371-8.
30. Yue J, Sun W, Li S. Denosumab versus zoledronic acid in cases of surgically unsalvageable giant cell tumor of bone: A randomized clinical trial. J Bone Oncol 2022; 35: 100441.