Evaluation of the Therapeutic Results of Giant Cell Bone Tumor

Abstract

**Background:** Giant cell tumor (GCT) is a benign bone tumor that may present with invasion and even metastasis in some cases. Despite several techniques for surgical excision of the tumor, its post-operative recurrence is still a critical challenge for orthopaedic surgeons. Therefore, this study aimed to evaluate the result of the surgical treatment of GCT by curettage, burring, alcohol and cementation to reduce the risk of recurrence.

**Methods:** This cross-sectional study was conducted on participants referring to two university hospitals with the diagnosis of GCT in a 12 years period. The subjects underwent surgery using curettage, burring, alcohol irrigation, and cementation. Regular follow-ups were carried out every three months in the first year, and then every six months in the second year and annually from then on. The recurrence-free survival rate was analyzed by the Kaplan-Meier method.

**Results:** Surgery was performed on 28 patients. The most common tumor site was distal femur, and the most pre-operative and post-operative complaints were pain and limitation of motion, respectively. At the end of the study, local recurrence was observed in only four cases, and lung metastasis was found in one case. The results showed that recurrence-free survival was 91.7% in 21 and 76% in 108 months according to Kaplan-Meier analysis.

**Conclusion:** Although using the above-mentioned protocol seems to reduce the risk of local recurrence in patients with GCTs, complete excision of the tumor is also a crucial factor influencing the rate of local recurrence.

**Keywords:** Curettage; Giant Cell Tumor; Bone Cement; Alcohol

*Received: 6 months before printing; Accepted: 1.5 Month before printing*

**Introduction**

Giant cell tumors (GCT) is an uncommon benign bone tumor, forming five percent of all bone neoplasms. While they may have an invasive behavior, compared to other benign tumors, CGTs are generally classified as benign (1). The formation of this type of tumor in soft tissues has been reported even though the emergence of such tumors is initiated in bone tissues (2). In five percent of cases, the tumor may be a malignant giant cell. The malignant type of GCT is divided into primary and secondary types: the primary type is sarcomas developed inside a benign GCT, whereas the secondary type is observed following the treatment and control of GCTs by radiation therapy (1, 3).

GCTs can occur in various bone locations; however, approximately 50% of GCTs are located around the knee, especially the distal femur. Other common sites of the tumor include the distal radius and humerus. However, the tumor will have a more invasive when it involves radius in case of involving the distal radius (4). While GCTs are usually solitary, multiple tumors might occur in one or two percent of cases. Although GCTs are benign tumors, metastasis may occur in up to three percent of people. While metastasis may be unclear or asymptomatic for many years in most people, it may progress in some and even lead to patient mortality (5).
On radiography, GCTs are found close to the joint, typically engaging the epiphysis in an eccentric form. Cortical erosion and soft tissue involvement are also not uncommon \(^6\). In MRI, the lesions are dark in T1 and light in T2 images. It also shows the liquid-liquid level that indicates ABC in 20% of patients. Microscopically, GCTs are originated from a large number of multinucleated giant cells (40-60 nuclei in a cell), dispersed among mononuclear stromal cells. The nucleus of mononuclear cells is equal to the nucleus of the giant cells, which distinguishes this tumor from other tumors that have giant cells \(^7\). The tumor mostly occurs in the youth aged 20-40 years \(^8\), and its common symptoms include pain and inflammation \(^9\).

In the past, this condition was treated with curettage or curettage and bone grafting. However, due to high local recurrence in treated patients, different methods were evaluated to reduce the recurrence rate in later studies. In addition, recent studies on how to treat a GCT reported that single curettage and bone grafting do not meet the standards of treatment for these patients and are not sufficient treatments in this regard \(^10\).

Therefore, some researchers have tested other methods, such as adding phenol to the tumor walls, adding methyl methacrylate (cement) to the cavity formed after curettage, resection followed by distraction osteogenesis and then adding hydroxyapatite, resection and allograft reconstruction, or prosthetic replacement \(^11\). While effective, extensive resection can be associated with high morbidity \(^12\). It is recommended that curettage along with one of the adjuvant treatments (e.g., phenol or liquid nitrogen) be applied to eliminate all cells and fill the remaining cavity by bone grafting or cement (methyl methacrylate) \(^13\). Based on the results of previous reports and given the few number of studies on the use of alcohol along with other common surgical techniques, the present study aimed to evaluate the level of recurrence and surgical treatment results of GCTs using a curettage, burring, alcohol and cementation.

**Method**

This cross-sectional research was conducted on patients with GCTs referred to two hospitals during 2001-2013 (code of ethics: IR.SUMS.REC.1391.3977). After taking the medical history of patients with suspected GCTs, conducting clinical examinations and evaluating the level of pain by visual analogue scale (VAS), all patients underwent paraclinical tests, such as calcium (Ca), phosphor (P), alkaline phosphatase, complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and C-reactive protein (CRP) for more precise evaluation and final diagnosis. Moreover, radiography, bone scan (to evaluate multicenterness), lung image (to evaluate metastasis) and MRI were carried out on patients. The cases were included only if definite pathologic diagnosis of GCT was available on the basis of biopsy, and if the patients agreed to participate. Prior to the research, the research objectives, surgery method, and the follow-up technique were explained to the participants and a written informed consent was obtained before the tumor extraction surgery.

**Technique**

The GCTs were removed using curettage, burring, alcohol irrigation and filling of the cavity with PMMA cement. Initially, the bone window was opened at least the size of the tumor, and all tumor tissues were removed by the Curette. Extensive curettage of all tumor walls (with the exception of areas with a very thin articular surface) was carried out via burring. After washing the cavity with normal saline, it was washed with 96% alcohol twice, keeping the alcohol inside the cavity for one-two minutes each time, and then rinsed with normal saline. In the next stage, the cavity was filled with bone cement. In cases where the tumor distance to the articular surface was
very thin and the articular surface was visible, a bone graft was placed below the articular surface from the ilium and then filled with bone cement. Finally, the samples were sent to the pathology laboratory in order to obtain the final results.

A standard GCT follow-up was carried out for patients, which included taking radiographs from all patients after the surgery and maintaining them to be compared with the following radiographs. In the case of observing lucency around the cement in the post-surgical radiography, its amount was recorded in order not to be mistaken with a recurrence. Then, clinical and radiographic examinations of the site of surgery and chest were performed for recurrence or complications every three months in the first year and every six months in the two years, and annually afterwards. If lucency around the cement reached more than two mm during the next referrals, a CT scan would be taken to evaluate the presence or absence of recurrence.

### Results

In this research, a total of 45 patients were evaluated, 17 of whom were excluded from the research due to the lack of a definitive diagnosis or patient's unwillingness to participate in the research. Therefore, 28 patients underwent surgery, including 19 women (67.9%) and nine men (32.1%). The mean age of the participants was 28.3 years, and the minimum and maximum ages were 14 and 48 years, respectively (Diagram 1).

![Diagram 1. Age groups of participants](image)

Pain, reduced mobility, fever and chills, palpable mass, and fracture were among the reasons for referrals. The most common presurgical complaint was pain at the lesion's site (57.14%), followed by a palpable tumor (35.7%). The most common tumor sites were distal femur (12 patients), tibia (nine patients), head of the femur (three patients), the end of each tibia (one patient), end of ulna (one patient), the beginning of the humerus (one patient), and the end of the humerus (one patient). In addition, the most common postoperative complaint of patients was limited mobility (12 patients), four of whom reported improvement after the surgery. Moreover, six patients had less than 20 degrees of motion restriction and two patients had mild movement restriction (less than five degrees). In the common location for remission of remission, the primary tumor was found around the knee. In addition, four patients had severely limited knee range of motion due to other non-surgical reasons. The first patient was a 60-year-old woman with severe knee pain, who underwent surgery for a tibia bone tumor about 12 years ago. She had severely restricted flexion mobility of both knees, and erosion of bone was observed in the radiographs. Another patient was a 40-year-old man with primary pathologic fractures of the distal femur, who underwent surgery about nine years ago. There was a 30% decrease in the mobility of his knee joint, compared to the opposite side. The third patient was a 50-year-old woman with a tumor in her distal femur, who underwent surgery about nine years ago. Despite the severe decrease in the joint mobility, there was only a 10% difference with the opposite side. Symptoms of severe joint erosion were observed in both knees, and the main cause of decreased mobility was the age-dependent degeneration of joints. The fourth patient was a 41-year-old woman with intra-articular pathologic fracture of the tibia, who underwent surgery about 11 years ago. While
she had a severely limited range of motion in one knee, no specific problem was observed in the opposite knee. After the surgery, 11 patients complained about pain at the surgical site, which showed a 60% decrease compared to before the surgery (P-value: 0.12). Of these patients, about five individuals felt pain only at night and had no considerable pain during daily activities. However, six people had pain during daily activities, for which they had consumed non-steroidal analgesics. Only two of these patients had severe pain that would interrupt their daily activities. It should be noted that these patients were among those who referred with a pathological fracture at the diagnosis stage. Postoperative complications included both cases of superficial infection at the surgical site (1.7%), where complete recovery was achieved with drug treatment.

In addition, four out of 28 cases (14.28%) had a recurrence, including a 32-year-old man who underwent surgery with curettage and cementation after the diagnosis of GCTs at the distal femur and referred with recurrence symptoms after three years. Biopsy results were indicative of a malignant GCT. In addition, metastasis to two lungs was detected, and the patient underwent a below-the-knee amputation. Another case was a 25-year-old woman who referred with a tumor at distal ulna about three years. After observing the recurrence complete resection of the ulna was performed. The third case was a 32-year-old woman who referred with the diagnosis of GCT at distal femur along with a pathological fracture and received normal treatment in 2004. After one year, she was re-treated with fixation after the diagnosis of recurrence. The last case was a 29-year-old woman who underwent surgery with proximal tibial tumor and referred with recurrence symptoms after two years, undergoing a re-surgery after the diagnosis. The chance of tumor recurrence was estimated at 91.7% for 21 months and 76% for 108 months using the Kaplan-Meier estimate.

**Discussion**

Treatment of GCTs with curettage and cementation was introduced by Vidal in 1969 (14). However, many questions remain such as the rate of recurrence after this technique, the toxic effect of cement on cartilage, and the rate of systemic osteosynthesis (15). The high rate of recurrence after curettage and cementation, without the use of adjuvants, is widely accepted in many studies (16). A retrospective study in the US assessed the records of 475 patients with GCTs, reporting a 54% rate of recurrence in patients. In addition, 13 patients (seven women and six men) were diagnosed with pulmonary metastasis (3% prevalence). Nonetheless, the prevalence of metastasis was higher in the age group of 25-30 years, and the distal radius was the most common site for GCTs (38%). Pulmonary metastasis occurred in 54% of patients within three years after initial tumor diagnosis and in 92% within 7.5 years (17). In another research in Canada on 59 patients with GCTs (1999), treatment was carried out by curettage, burring, and bone grafting. The mean follow-up period for patients was 18 months (28-132 months), and local recurrence was observed in seven patients (12%). In one of the patients who experienced pulmonary metastasis, the researchers in this study found no significant difference in the treatment results between the use of the mentioned study and the cementation method (11). In a study by Durr et al. in Germany during 1981-1997, 26 patients (13 men and 13 women) with a mean age of 33.5 years and a mean follow-up of 61 months were evaluated using curettage with burring, and applying phenol and bone grafting. Similar to most studies, this study showed that most tumors were observed in the third decade of life. In total, 14 patients had knee tumors, and four pulmonary metastasis cases were observed, three of whom had a local recurrence as well. In total, five out of 26 patients had a local recurrence (19.23%), observed in three patients two years
Evaluation of the therapeutic results of Giant cell bone tumor after the surgery and in two patients four years after the surgery\(^{[18]}\).

Researchers from Hungary conducted a study on a group of patients with GCTs (N=69) during 1975-1989, comparing the two methods of curettage and bone grafting and curettage, phenol and cementation. These scholars reported a significant decrease in the disease recurrence when a combination of curettage, phenol and cementation was used as treatment. In the end, tangible results were obtained regarding the decrease of recurrence and complications in the group treated with curettage, phenol and bone grafting\(^{[19]}\). In a research by Mortazavi et al. (2000-2004) in Imam Khomeini Hospital in Tehran, Iran, 20 patients with GCTs underwent curettage with high-speed burring and cryosurgery (using liquid nitrogen). In the mentioned research, the mean age of the patients was 29.2 years and most of them were in the age range of 20-40 years. In terms of the location of involvement, the most common site was the tibia (seven cases), followed by the distal femur (six cases). Moreover, the mean follow-up was 34 months.

In one case, there was a five-percent recurrence after treatment of tumors at the tibia bone within 10.5 months after treatment. Other complications after treatment include decreased joint movements and nerve damage in five percent of patients. Of the 20 patients with GCTs examined, there was only one patient with secondary ABC\(^{[13]}\). In a research by Steyern et al., the level of topical recurrence was evaluated in 137 patients with GCTs after treatment by curettage and cementation. The mean follow-up of the participants was 60 months (3-166 months), and the results were indicative of 19 cases of recurrence (14%). In addition, the mean duration to relapse was 17 months (3-29 months). Of these patients, 13 were re-treated with curettage and cementation, and no recurrence was detected during the follow-up period\(^{[20]}\). In a retrospective study by Malek et al. at the University of Tehran, the reseachers assessed the effect of treatment with curettage, burring and bone grafting without the use of an adjuvant during 1997-2002. In total, 47 patients were included, seven of whom were removed from the study due to a lack of regular referral. Moreover, the mean follow-up period was 48 months (18-78 months). In total, 21 patients were female and 19 were male with a mean age of 43.5 years (12-75 years). According to the results, the most common tumor site was the distal femur (13 cases), followed by the tibia. Furthermore, 13 patients experienced local recurrence (32.5%). Moreover, seven other patients had post-operative complications such as lack of union (two cases), decreased joint movements (three cases), and infection (two cases). The mean duration from surgery to recurrence in patients was 28 months (9-60 months), and the 30-month survival rate of patients was 78% based on the Kaplan–Meier estimator\(^{[21]}\).

In a research by Jamshidi et al. on 168 patients with GCTs in Iran University of Medical Sciences, the female to male ratio was 1.4:1, and the participants had a mean age of 34 years. The minimum duration of follow-up of patients was 24 months and their mean was 75 months. Moreover, 135 patients had tumors around the knee (80.4%), and the participants were treated with two methods of burring and cementation and/or bone grafting. Furthermore, the recurrence rate was reported at 18.2%. According to the results of the mentioned study, the use of burring and the surgeon’s expertise to completely extract the tumor would determine the treatment results in more than the effect of the treatment method and the use of adjuvant therapy\(^{[22]}\). In another study conducted by Fraquet et al. during 1992-2005 in France, 30 patients with GCTs were treated by curettage using burring and cementation. In total, 26 patients had tumors around the knee, and the mean follow-up of the participants was 76 months. About 30% of recurrence was observed over two years of follow-up, which was much higher than similar studies in Iran.
and other countries. Furthermore, patients undergoing surgery had complications such as infection (one case) and hematoma (one case)\(^{(15)}\).

In addition, the use of liquid nitrogen in the surgical treatment of patients reduced the chance of recurrence by two-eight percent. Nonetheless, this is a difficult technique associated with a high level of complications\(^{(19)}\). The thermal effect of cement decreases the chance of recurrence by 17-25\% via eliminating the tumor cells\(^{(23)}\). Therefore, all remainings of tumors were evacuated as much as possible to reduce the possibility of recurrence. In addition, alcohol was applied as adjuvant while cement was exploited to fill the cavity. Using the mentioned technique, the recurrence rate was reported at 14.28\% in the present study. Compared to the results obtained by Mortazavi et al.\(^{(13)}\), there was a higher rate of recurrence in the current research. However, almost similar results were obtained by Steyern et al.\(^{(20)}\). On the other hand, a lower recurrence rate was reported in the present research, compared to the studies by Fraquet et al.\(^{(15)}\), Jamshidi et al.\(^{(22)}\), Malek et al.\(^{(21)}\), and Durr et al. Most of the aforementioned studied included treatment with curettage and cementation without the use of adjuvants, and a higher rate of recurrence was observed in previous studies, compared to other surgical methods\(^{(24)}\).

In the present research, the chance of a lack of recurrence of tumors performed by Kaplan-Meier estimator was 91.7\% for 21 months and 76\% for 108 months. Compared to the study by Malek et al., where the 30-month survival of patients was estimated at 78\%, the method applied in the present study increased the chance of lack of tumor recurrence\(^{(22)}\). There was a considerable improvement in the extent of post-operative joint function in the current research (46.6\% without a functional problem), and the remaining impairment in the joint function of other patients might be due to the use of cement. Toxic effects of cement on articular cartilage can lead to decreased joint function due to damage to the articular surface. In terms of the prevalence based on age and gender, most participants were female in the age range of 20-30 years, similar to other studies\(^{(13, 21, 22)}\). In the present study, pulmonary metastasis was observed in just one case, who was a 32-year-old man (3.6\%). This amount was a little higher, compared to a retrospective research in the United States, where 13 out of 475 patients with GCTs had pulmonary metastasis (3\% prevalence)\(^{(17)}\). With regard to the nature of the tumor and since five percent of cases may be a malignant GCT\(^{(3)}\), pulmonary metastasis is expected in a percentage of patients. Therefore, regular and periodic examinations and tests are necessary to prevent, diagnose and treat these tumors in a timely manner.

In the current research, post-operative complications (i.e., infection at the surgical site) were observed in two patients (7.1\%), treated with pharmaceutical treatments. In the study by Malek et al., there were two cases of infection at the surgical site (5\%)\(^{(21)}\). Infection at the surgical site can be due to the contamination of the surgical instruments or surgical environment,

**Conclusion**

According to the results of the study, a combination of curettage, burring, alcohol and cementation can be a suitable technique with a low recurrence rate. However, different levels of recurrence were observed in studies that applied surgical methods, and this lack of consistency might be due to different complete evacuation of tumoral tissue from the involved area.

**Acknowledgments**

This article was funded by the vice-chancellor for research of Shiraz University of Medical Sciences with the code of 3977 and was
carried out with the cooperation of bone and joint disease research center of Shiraz University of Medical Sciences.

Figure 1. Giant Cell tumor of the proximal Tibia in a 32 years old woman

Figure 2. Same patient in figure-1, 5 years after surgery without any local recurrence

References