SHORT COMMUNICATION

Giant Cell Tumor of the Sacrum: Series of 19 Patients and Review of the Literature

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Abstract

There are still some debates regarding the best treatment of Giant Cell Tumor (GCT) of the sacrum. Since GCT of this location is rare, therapeutic strategies are mainly based on the treatment of GCT in other anatomic locations. The objective of this study was to evaluate the oncologic and clinical results of surgical management of sacral GCT with and without local adjuvant therapy.

Medical records of 19 patients diagnosed with GCT of the sacrum, were retrospectively reviewed. Sixteen patients were treated by intralesional curettage and three patients with marginal resection. Musculoskeletal tumor society (MSTS) score was used for the evaluation of functional outcome.

Prolonged pain was the most common complication after treatment. Mean Pre and post-operative pain based on visual analogue scale (VAS) was 6.1 ± 1.99 and 3.05 ± 1.64, respectively. Postoperative neurologic deficit appeared in six patients. In addition, infection occurred in five patients. One case of spinopelvic instability was also observed after surgery. At average follow up of 158.5 ± 95.9 months (25 to 316 months), recurrence was seen in eight (42.7%) out of seventeen patients treated by intralesional curettage. The size of the tumor significantly correlated with the tumor recurrence (r=0.654, *P=0.001*). Mean MSTS score was 74.7 ± 16.78. Those patients, in whom sacral nerve roots remained intact before and after surgery, had better functional outcome.

Preservation of sacral nerve roots is associated with better functional outcome and less pain. Although an acceptable surgical outcome was observed in our cohort, the problem of local recurrence still warrants further investigations for better local control of the tumor.

Keywords: Intralesional curettage, Giant cell tumor, Sacrum, Recurrence

Introduction

In the axial skeleton, sacrum is the most common place of involvement by where Giant cell tumors (GCT) form. The incidence of GCT in the sacrum is between 6.7% to 9.4% in different series (1, 2). Currently, there is no agreement regarding the treatment of GCTs of rare localizations, including small bones, pelvis, spine, or sacrum (1, 3, 4). Treatment of GCTs of axial skeleton even is more complicated (1). This is most likely due to its rarity, and also owing to the limited surgical accessibility and proximity of the tumor to the nerve roots (1). The literature provides only small case series of GCT of the spine or sacrum with mostly short-term follow-ups (5). In this review, we explain the results of the treatment of 19 cases of sacral GCT, with respect to the current literature.

Materials and Methods

During 1990 to 2014, 286 patients with confirmed GCT were surgically treated in Shafa OrthopedicHospital, from which, sacral GCT were identified in 26 patients. Seven patients were absent during follow-up, but the remaining 19 patients were assessed in the final evaluation.Patient's medical and surgical records were reviewed and required necessary documents, including pathological and radiological assessments, were obtained from their medical files. Tumor size was retrospectively assessed using imaging or pathological data, available for patients treated in the last 24 years. The latest follow-up

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was performed by personal contact in the ambulatory clinic.

Treatment decisions were made by a multidisciplinary team, including orthopedic oncologist, radiologist, pathologist, and clinical oncologist. Depending on the extent and level of the tumor, patients underwent intralesional curettage or marginal excision with a posterior approach alone or a combination of posterior and anterior approaches. In this regard, in those tumors, which had a large anterior soft tissue component, an anterior approach was performed in order to release anterior organs from the tumor before the posterior approach, at the same operating session. Accordingly, three patients of our series were treated by combined anteroposterior approach, while in the case of the remaining 16 patients, posterior approach was used.

All of the marginal excisions were performed on tumors that were distally located (S3-S4) in sacrum and had small sizes (4 cm in largest diameter). There was no attempt for reconstruction of these defects, because the tumors were not in the weight-bearing area of the skeleton.

In those patients with posterior-only approach, a posterior midline incision was used to approach the sacrum. Intra-operative radiographies were used to confirm the sacral level when necessary. After removal of the lamina of the corresponding sacral segments by using a high-speed burr, thecal sac was reached, and was dissected free from the tumor mass. By using rubber bands, sacral nerve roots were protected, and were kept away from the tumor. From this point on, dissection was different in those who had an excision and those who had curettage. In the patients with excision, ventral organs were dissected away from the tumor mass. By making an interrupted cut in the sacrum and connecting them together. Subsequently, osteotomy of the sacrum was completed and the tumor was dissected away from the remaining sacrum. In those patients with curettage, complete intralesional curettage was performed, using currets and high- speed burs.

Preoperative radiographs were used for the evaluation of spinopelvic stability. Spinopelvic stability was considered intact if we could bilaterally preserve at least the cephalad, 50% of the S-1 vertebra and sacroiliac joints (6). Spinopelvic biomechanical stability, which had been previously defined as “the ability of the pelvis to withstand normal physiologic loads without displacing”, was assessed by the attending surgeons based on preoperative and intraoperative manual assessment (7). Spinopelvic fixation was performedin cases with spinopelvic instability.

In order to manually assess sacroiliac stability, vertical and rotational forces were applied to the pelvis at the end of each surgery by the attending surgeon. If there was any vertical or rotational instability caused by destruction of the sacroiliac joint, sacroiliac instrumentation or structural allograft were implemented [Figure1] (2).

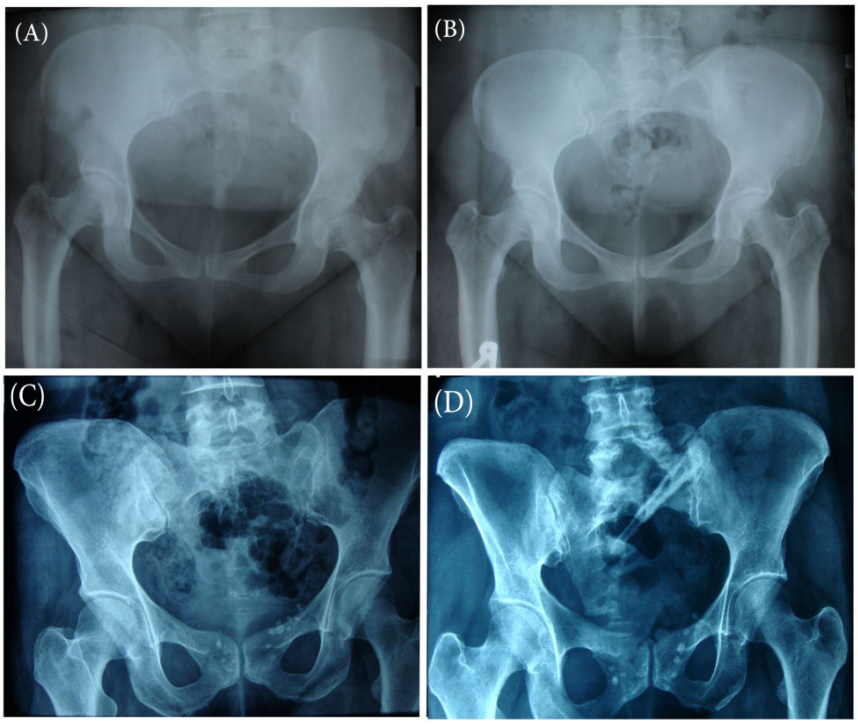

Figure 1. (A&B) X-ray before and after curettage and cortico cancellous bone graft of a sacral giant cell tumor (case 1); (C&D) X-ray before and after curettage and structural bone graft of a sacral giant cell tumor (case 3).

After curettage, either bone grafting, or bone cement packing was used for reconstruction of the defect. The choice between bone graft and bone cement was made considering the following facts: in cases where the void was contained, corticocancellous bone grafting was used [Figure 1]. In those patients with a non-contained defect after curettage, bone cement packing was used. In the cementing group of patients, gel foam and saline irrigation were used to protect sacral nerve root against the heat of the cementing process.

None of our patients received radiotherapy as the sole treatment modality, or as the adjuvant therapy for the primary operation. External beam irradiation was performed in two patients, both as postoperative adjuvant therapy, in the treatment of tumor recurrence.

All patients were followed up every three months for the first two years, every six months for the third year, and yearly thereafter. In each follow-up visit, plain radiography of the pelvis and chest had been taken. In case of finding any abnormality in plain radiographs, computed tomography of the area was requested and further imaging evaluations were performed. Patients with recurrence were followed similar to primary patients with serial clinical examination and radiographs.

For the functional outcome, musculoskeletal tumor society score, MSTS, was used. According to the this scoring system, numerical values (0 to 5) are given to each of the six categories of pain, function, emotional acceptance, supports, walking and gait. The total score for the system between 0 and 30 is given to each patient with 0 indicating poor and 30 indicating excellent functional result (8). Pain was assessed based on visual analogue scale (VAS) (9).

Results

The average follow-up time was 158 months, ranging from 25 to 316 months. The mean age of the patients was 29.47± 8.14 years, ranging from 18 to 46 years. Six patients were male, and 13 were female. The mean size of the tumors was 6.26 ± 3.12 cm, ranging from 2 to 15 cm.

Table 1. The Location of GCT of sacrum in our series

location	Side		
	Right	Left	Middle
S2 or above	7	9	0
S3 or below	0	0	3

Eighteen tumors were located in the sacrum and one was in the sacrum extending to Ilium. Location of the tumors is seen in Table 1. Chief complaint of the patients was pain. Pain was present in all but one patient who was referred to us for evaluation of an incidental finding in the pelvic radiograph. Four patients had paresthesia of the lower limb or buttock, and one patient presented with had cauda equina syndrome. Clinical and demographic characteristics of the patients have been demonstrated in Table 2.

After primary surgery, eight out of 19 patients had local recurrence (42.1%), which in one case coincided with pulmonary metastasis. All recurrences were observed in patients who had undergone intralesional curettage, while no recurrence was observed in the excision group (three patients). The mean time to first recurrence was 11.87 months ranging from 4 to 26 months. Mean recurrence- free survival of patients was 186.5 ± 34.8 months (95% CI, from 118.3 to 254.7) [Figure 2].

All of recurrent tumors underwent re-operation. In all of the second surgeries, methyl methacrylate was used for the purpose of the reconstruction of the defect and as an adjuvant therapy. We had two repeat recurrences (Cases 5 and 15). Two patients of the recurrent tumor group received external beam irradiation

Table 2. Demographic and clinical characteristics of the patients

Variable	Case																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Gender	F	F	F	M	F	F	M	F	F	M	F	F	M	M	F	F	F	F	M
Age (years)	32	35	40	19	25	24	29	18	26	28	42	27	31	46	32	33	19	18	36
Preop (VAS)	7	5	5	6	9	8	8	0	5	6	5	7	7	6	9	6	5	5	7
Pre-op neurology	I	I	I	I	P	I	P	I	I	P	I	I	I	P	C	I	I	I	I
Level & side of sacral involvement	S13, L	S1-2 L	S1-3 L	S3-4 mid	S1-4&I L	S1-2 L	S1-4 R	S1 R	S1-2 R	S1-3 R	S1-2 L	S1-4 R	S1-2 L	S3-4 mid	S1-3 L	S1-3 L	S3-4 mid	S2-4 R	S2-5 R
Tumor size (cm)	5	5	7	4	15	8	12	2	8	8	5	9	7	4	5	7	4	7	6
Approach	P	P	P	P	A/P	P	A/P	P	P	P	P	A/P	P	P	P	P	P	P	P
Follow up time (months)	63	197	46	187	298	246	237	293	316	84	145	83	224	25	63	67	80	240	118
Campanacci Grade	2	3	3	2	3	3	3	1	3	3	3	3	3	2	3	3	3	2	2

F: Female, M: Male, I: Intact, P: Paresthesia, C: Cauda equine; R: right; L: left; Mid: Middle, A: anterior, P: posterior

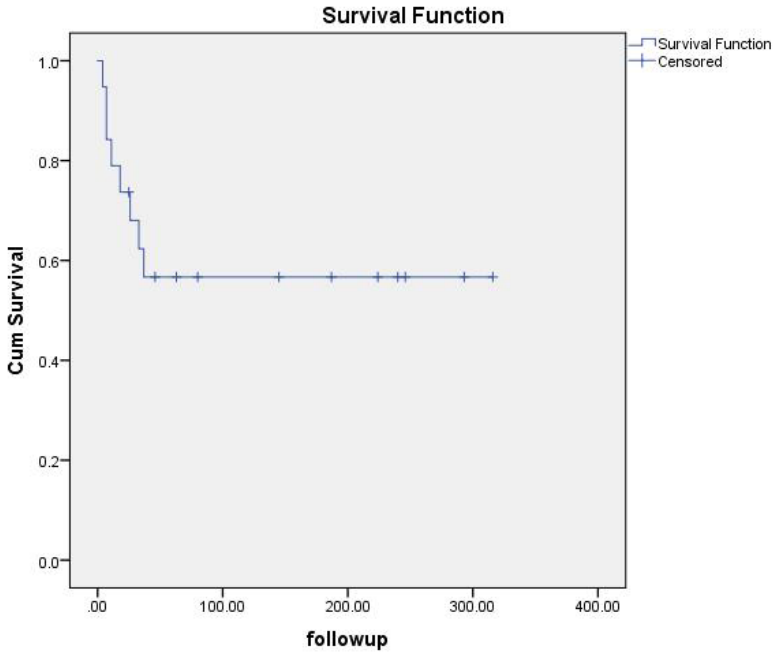

Figure 2. Kaplan-Meier curve of recurrence free survival of patients with sacrum GCT.

(EBI) as an adjuvant therapy for local control of their recurrent tumors. No further recurrence was observed afterwards.

At the last follow-up visit, none of the patients had any sign of tumor recurrence. Infection was seen in five patients after surgery, which was superficial in two cases, and deep in three. All patients were managed by debridement, and use of intravenous antibiotics based on the culture results. Primary or secondary wound closure was finally done in all patients. After irrigation and debridement, infection was resolved in all except one patient (Case 15). She was reluctant to have another surgery and we decided to control the infection by antibiotics. This patient is still under oral antibiotic therapy for infection control whenever there is sign of infection. Neurologic status of the patients at the time of presentation is demonstrated in table 2. We did not encounter any weakness in preoperative period in our patients. It is possible to have paresthesia without weakness when there are sacral injuries such as fractures (10). Neurologic complication after surgery occurred in 6 out of 19 patients, and these ranged from numbness to bladder or bowel dysfunctions. The patient with cauda equina syndrome showed incomplete recovery after surgery, and claw toes and neurogenic bladder were present. Patients with injury to sacral nerve roots manifested by sensory, motor disturbance, or incontinence (all cases except number 1, 2, 4, 6, 8, 11, 17, and 19), had more pain based on VAS, and lower functional outcome, according to MSTS score. The average preoperative VAS was 6, which was reduced to 2 postoperatively [Table 3]. One patient developed pulmonary metastasis;this was resolved by thoracotomy and metastasectomy leading to disease-free survival. In the last follow-up, all patients were alive. Six out of the 19 patients were free of pain. From 16 patients, who were treated by curettage, cement packing and bone grafting was used in four and twelve patients respectively. The average size of the tumors was 6.73 ± 3.01cm, ranging from 2 to 15 cm. We had only one recurrence in the group with cement packing (25% recurrence), and seven recurrences in the group with bone grafting (53.8%). A significant positive correlation was observed between local recurrence and the size of the tumors (r=0.443, *P=0.029*).

Discussion

Giant Cell Tumor (GCT) is slightly more common in female than in male, with a ratio of 1.2 to 1. In sacral GCT this gender difference is more pronounced, so that in one study 69.2% of sacral GCT patients were female (1). In our patients, 13 out of the 19 (68.4%) patients were female, but due to small numbers of patients in this study, these ratios may be incidental.

Recommendations for treatment of GCT in extremities are based on the retrospective series of patients and not on randomized trials. On this basis, most authors consider intralesional excision as the treatment of choice (11). Some authors advocate the use of adjutants like phenol, alcohol, hydrogen peroxide, liquid nitrogen, or methyl methacrylate to decrease the rate of local recurrence, while others find this unnecessary (11, 12). After a tumor was is curetted, the cavity can be left unfilled or filled with bone graft or cement (11). Based

Table 3. Patients' treatment, complication and outcome

Case	Surgical Treatment	Recurrence	Treatment rec.	Complications, post-op neurol. status	Post-op pain(VAS)	Post-op MSTS%
1	C&BG	-		2cm LLD& Normal neurology	3	80
2	C&BG	4M	C&CE	Normal neurology	2	86.6
3	C&BG	-		Paresthesia	4	80
4	R	-		Normal neurology	2	93.3
5	C&BG	9M/37M	C&CE&EBI	Neurogenic bladder & Paresthesia	5	50
6	C&BG	-		Normal neurology	4	86.6
7	C&BG&LP	11M	C&CE&EBI	Paresthesia& Weakness	4	53.3
8	C&BG	-		Normal neurology	2	93.3
9	C&CE	-		Superficial Infection (Oral antibiotics).& Paresthesia	1	80
10	C&BG	26M	C&CE	Neurogenic bladder	6	50
11	C&BG	-		Infection(I&D).& normal neurology	2	83.3
12	C&BG	7M	C&CE	Foot drop	4	70
13	C&CE	-		Superficial Infection (oral antibiotics).& Foot drop	2	66.6
14	R	-		Paresthesia	2	83.3
15	C&BG&LP	13M/33M	C&CE	Infection. (I&D)&Neurogenic bladder (Urinary Cath.), Claw toes, paresthesia,	6	33.3
16	C&BG	18M	C&CE&LP	Paresthesia	5	73.3
17	R	-		Normal neurology	1	90
18	C&CE	-		Paresthesia	1	83.3
19	C&CE	7M	C&CE	Infection(I&D), Normal neurology	2	83.3

C: Curettage; R: Resection; BG: Bone graft; CE: Cement; LP: Lumbopelvic fixation; EBI: External beam irradiation
N: normal;P: paresthesia; W: Weakness; Claw: claw toes; LLD: Leg length discrepancy; I&D: Irrigation and debridement.

on some reports, the nature of the filling material or the type of adjuvant method or any combination of both did not have any significant effect on the recurrence rate after surgery, while other reports are in favor of using high-speed burr of the margins after curettage, and bone cement packing for achieving the lowest recurrence rate (11, 13).

In GCT of sacrum or pelvis, the treatment goal of GCT of long bones cannot be fullyachieved. Tumors in these areas, especially in the sacrum, often compress the spinal nerve roots; therefore, complete curettage is hardly possible. In addition, local adjutants such as bone cement, phenol, or cryotherapy have limited use close to nerve roots, due to their toxic effects on nervous tissue (12). Treatment modalities of GCT of the sacrum include either surgical or nonsurgical. Possible surgical treatment options include intralesional curettage, and partial sacrectomy combined with either irradiation or arterial embolization (5, 14, 15). Wide or marginal excision of the tumoror en bloc resections may result in a lower recurrence rate but often cause unacceptable neurological damage (14). Nonsurgical treatments include a variety of modalities including external beam irradiation (EBI), selective arterial embolization (SAE), bisphosphonates and Demosumab. Nowadays, many authors would prefer to perform SAE instead of primary irradiation whenever surgery is not reasonable (1). Surgical treatments can be combined with nonsurgical methods in an attempt to decrease the rate of local recurrence.

En bloc excision of the GCT of the sacrum is the best method of obtaining local control, and whenever is practically possible, it is the treatment of choice. This is mostly applicable to giant cell tumors below the S3 level (5). In Leggon's series, surgical excision with wide margins had the best results in terms of local control, with 0% of local recurrence, but at the expense of iatrogenic nerve injury. This complication will be greater if the higher levels are involved (3). In 16 out of 19 patients of our series, the location and extent of the tumor would have impeded achieving wide margins without damaging multiple nerve roots leading to almost certain incontinence and impotence as well as lower limb weakness and complete lumbopelvic disassociation in the majority of the cases. Due to high morbidity and complications, resection of GCT of sacrum with wide surgical margins, is only justified when the tumor is

distal enough to minimize the risk of iatrogenic nerve damage (5). This treatment modality was performed in just three tumors among our patients. After resection, no attempt was performed made to reconstruct the missing part, mainly due to the small size, and distal position of the defect within the sacrum. There was no recurrence in these patients. The lack of recurrence in these patients was in concordance with the literature that shows that with en bloc excision of the GCT of sacrum, tumor recurrence is the lowest among other methods of surgery (3, 5).

Intralesional curettage as the method of treatment of the GCT of sacrum, either alone or in combination with adjuvant has had results that is lower than either en bloc resection or SAE. Leggon et al. found a 48% risk of local recurrence in patients treated with curettage alone and a 47% risk of local recurrence with curettage combined with radiotherapy (3). Based on some reports, intralesional curettage in most parts of the tumor as possible may have less recurrence and distant metastasis compared with the standard curettage (2, 16).

Local recurrence was observed in eight cases patients (47%) who had intralesional curettage, and in no patient who was managed by excision. We had a 25% recurrence rate in the group of patients with bone cement packing and 53.8% in those with bone grafting, which was in accordance with the previous reports favoring bone cement as a method of adjuvant and reconstruction of the tumor after surgery (12, 17). We decided to manage the local recurrences by repeat curettage and cementing, which is a well-known method of treatment in the recurrence of GCT in long bones (18). The recurrence is always more difficult to treat than the primary tumor, thus, every attempt should be made to avoid its occurrence as much as possible.

Serial Arterial Embolization (SAE) offers the best results published so far in managing giant cell tumor of the sacrum (19-21). In the patient series published by Hosalkar et al., this treatment option was successful in seven out of nine cases (19). In this method, repeated embolization was stressed by Hosalkar to ensure that all the major blood vessels feeding the tumor have been controlled. Due to its high success and low morbidity, SAE is suggested as the primary treatment option for any patient with giant cell tumor of the sacrum. If the patient develops local progression or recurrence, then an alternative treatment is needed. SAE, as the sole treatment modality, may have a risk of diagnostic error, because only needle biopsy is used in this method (19). Since required equipment was not available at our center, we did not use SAE as the sole therapy, or pre-operative treatment modality in our patients.

Radiotherapy has been used to treat sacral giant cell tumors, but recurrence rates as high as 49% have been reported, and other complications, such as post-radiation fibrosis and radiation-induced malignancy, also may arise (3). The risk of radiation-induced sarcomas, was between 3% to 11% in the series reported by different authors (3, 22). Chakravarti reported five cases of sacral giant cell tumor treated with radiotherapy with doses between 40 and 70 Gy. Two of the patients did not respond and developed progression at 5 and 8 months, respectively and both required surgery, while the other three patients remained disease free at follow-up between 3 and 10 years. Based on this data, they recommended a dose of 50 Gy to maximize local control (22). We only used radiotherapy in two patients after repeat surgery following local recurrence. In our two cases, a dose of 50 Gy in 25 fractions was used. We did not use radiotherapy after 2004 for in any patient mainly due to the results of the series published by Leggon, which showed that the outcome of intralesional curettage with or without radiotherapy is similar (3). In addition, due to conflicting results of radiotherapy in GCT of sacrum, and the risk of malignant transformation in those receiving EBI, we were hesitant to use radiotherapy in primary surgeries, and only used this modality as an adjuvant for tumor recurrence. Improvements in radiotherapy targeting, notably the use of intensity-modulated radiotherapy, may increase efficacy and decrease the side effects in the future for these tumors.

Cryotherapy is other non-surgical therapeutic modality, and different results have been reported for it. Although favorable results are reported by Marcove et al., the outcomes published by Leggon et al., who reported a 62% rate of local recurrence in eight patients treated with curettage and cryosurgery, is not fascinating (3, 16). In addition, the potential complications such as permanent nerve damage make this treatment available at a few centers in the world only that have the expertise. Although there have been promising reports of biphosphonates and Denosumab in the management of giant cell tumor at the present time, these remain unproven in any clinical trial, and they might offer alternative treatment options in the future (23). We did not use any of these medications in the treatment of our patients.

Pulmonary metastases have been described for GCT of long bones and axial skeleton (4, 12, 14, 24). The rate of pulmonary metastasis in GCT of the axial skeleton in different series is variable. While in some series its occurrence is higher than its rate in GCT of the appendicular skeleton, in other series there was not any case reported (14, 24). Young age during diagnosis, axial location of the primary GCT, Enneking's stage-3 disease, and local recurrence are found as risk factors for pulmonary metastasis, according to a recent report (24). Our patient series included just one pulmonary metastasis. The person was a patient with tumor recurrence and diagnosed with aneurismal bone cyst, ABC, superimposed on GCT.

Receptor activator of nuclear factor κ-B ligand (RANKL) has been implicated in pathophysiology of GCT (25). Denosumab, a human monoclonal antibody, binds to RANKL and prevents its activation, thereby restraining both the destructive properties and the population of giant cells (26). It has been shown that subcutaneous injection of the Denosumab can decrease pain and increase functional levels of patients withunresectable or recurrent GCT (27). In another study, it is demonstrated that Denosumab can inhibit progression of GCT, leading to decreased need for surgery (28). Unresectable

pulmonary metastases have also been changed to resectable metastases by using Denosumab (29). Still, another report demonstrated that neoadjuvant therapy with Denosumab can make osteoclast-type giant cells disappear, both in the original tumor location, and in its pulmonary metastasis (30). All these encouraging results may introduce Denosumab as a new preoperative adjuvant therapy for patients with GCT of the sacrum as a modality to decrease the high morbidity associated with the surgery of this tumor.

The small number of patients is one of limitations of this study, which makes statistical comparisons less valuable. SAE was not available in our patients, and this was another limitation of this study.

We observed that preservation of sacral nerve roots was associated with better functional outcome and less pain in our patients. Although an acceptable surgical outcome was observed in our cohort, the problem of local recurrence still warrants further therapeutic modalities for better local control of the tumor.

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