Conservative surgery in the treatment of giant cell tumor of the sacrum: 35 years' experience

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OBJECTIVE There is no consensus regarding the appropriate treatment of sacral giant cell tumor (GCT). There are 3 main management problems: tumor control, neurological loss, and pelvic instability. The objective of this study was to examine oncological, neurological, and structural outcomes of sacral GCT after intralesional excision and local intraoperative adjunctive treatment.

METHODS The authors retrospectively reviewed the records of 24 patients with sacral GCT who underwent conservative surgery (intralesional resection/curettage) at Memorial Sloan Kettering Cancer Center from 1973 through 2012. They analyzed patient demographic data, tumor characteristics, and operative techniques, and examined possible correlations with postoperative functional outcomes, complications, recurrence, and mortality.

RESULTS There were 7 local recurrences (30%) and 3 distant recurrences (13%). Three of 24 patients (12.5%) had significant neurological loss after treatment—specifically, severe bowel and/or bladder dysfunction, but all regained function within 1–4 years. Larger tumor size ($> 320 \text{ cm}^3$) was associated with greater postoperative neurological loss. Radiation therapy and preoperative embolization were associated with prolonged disease-free survival. There were no local recurrences among the 11 patients who were treated with both modalities. Based on radiographic and clinical assessment, spinopelvic stability was present in 23 of 24 patients at final follow-up.

CONCLUSIONS High local and distant recurrence rates associated with sacral GCT suggest the need for careful local and systemic follow-up in managing these patients. Intraoperative preservation of sacral roots was associated with better pain relief, improvement in ambulatory function, and retention of bowel/bladder function in most patients. Fusion and instrumentation of the sacroiliac joint successfully achieved spinopelvic stability in cases deemed clinically unstable. Despite improvement in the management of sacral GCT over 35 years, a need for novel therapies remains. The strategy of combining radiotherapy and embolization merits further study.

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KEY WORDS giant cell tumor; sacrum; cryosurgery; embolization; therapeutic; radiotherapy; spinal fusion; sacroiliac joint; oncology

GIANT cell tumor (GCT) of the sacrum presents management problems of a rare tumor in a rare location, with little published information to help guide treatment. Given its rarity, prospective therapeutic trials have not been performed, relegating investigators to analyzing descriptive case series and extrapolating treatment strategies from reports of GCT in other locations.^{24,25}

To improve management of sacral GCT, investigators must address critical issues regarding tumor recurrence, neurological loss, and pelvic instability. Issues related to tumor recurrence include determining the true incidence of local recurrence and of distant metastasis and understand-

ing how well local treatment options improve these rates. Questions about neurological preservation pivot around the extent of nerve sacrifice needed for disease control, the functional significance of the resultant neurological deficit, and whether preoperative neural status influences outcome. The important spinopelvic stability issues include identifying the indications for stabilization and characterizing the degree of success achieved. These questions are interrelated and would ideally be examined using multivariate analysis, which a small series does not permit.

In this retrospective study, we describe our single-institution experience with sacral GCT management and

ABBREVIATION GCT = giant cell tumor; MSKCC = Memorial Sloan Kettering Cancer Center.

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characterize the neurological and structural outcomes associated with conservative surgery in combination with adjunctive treatments, addressing each of the aforementioned management issues in a dedicated fashion.

Methods

With institutional review board approval, we searched the tumor registry and operative logs of the Orthopaedic Surgical Service at Memorial Sloan Kettering Cancer Center (MSKCC) for the period 1973–2012, and identified 254 patients treated for histologically confirmed GCT of bone. We selected for analysis cases involving patients with sacral tumors who underwent intralesional surgery with curative intent and reviewed chart data for demographic characteristics, tumor characteristics, pathological and radiographic aspects, preoperative and postoperative neurological function, surgical approach, neoadjuvant and adjuvant treatments, surgical interventions, peri- and/or postoperative complications and mortality, as well as oncological and functional outcomes. Our study analyzed a final cohort of 24 patients and included further follow-up on 7 patients previously reported on by our group.²⁵

We graded tumor histology according to the Huvos classification¹⁷ and retrospectively calculated tumor volume (assuming an ellipsoid volume)¹⁸ using radiographic and pathological data as well as any original imaging studies available for patients treated in the last 24 years.

Depending on tumor size and surgeon preference, patients underwent either intralesional excision with a posterior approach alone or a combination of posterior and anterior excisions.⁹ Spinopelvic biomechanical stability, which had been defined as “the ability of the pelvis to withstand normal physiologic loads without displacing,”¹⁹ was determined by the attending surgeons based on preoperative clinical and radiographic evaluation and intraoperative manual assessment. Vertical and rotational instability caused by total or near-total destruction of the sacroiliac joint was an absolute indication for sacroiliac instrumentation and fusion. Cephalad extension of tumor into the lumbar spine required lumbopelvic spine fusion after tumor excision.¹⁶ Spinopelvic stability was considered intact if we preserved bilaterally at least the cephalad 50% of the S-1 vertebra and sacroiliac joints (Fig. 1).^{11,12}

Attending surgeons addressed functional issues, spinopelvic stability, local recurrence, and metastasis individually during regularly scheduled follow-up visits. Appointments included physical examination and radiography of the sacrum and chest; regular use of CT began in 1991. MRI was also performed to detect local recurrence.

Using SPSS version 22.0.0 (IBM Corp.), we performed univariate analyses to correlate tumor characteristics and treatment modalities with neurological complications and mortality. Categorical and parametric variables were analyzed by means of descriptive statistics, the chi-square test or Fisher exact test, and the Student t-test. Nonparametric data were analyzed by means of the Mann-Whitney and Kruskal-Wallis tests. We used the Kaplan-Meier method to estimate the disease-free survival and illustrate the effect of individual factors. The log-rank test was used to evaluate differences between survival curves.

FIG. 1. Schematic illustration demonstrating GCT of the sacrum. Midline tumor from S-3 and below (middle) (A), midline tumor from S-2 and below (high) (B), midline tumor with S-1 and lumbosacral involvement (whole sacrum) (C), or eccentric tumor with S1 and sacroiliac involvement (SI) (D). Midline tumors with less than 50% S1 involvement and tumors located bilaterally with pelvic continuity are considered stable, while tumors with pelvic discontinuity are associated with instability. Figure is available in color online only.

Results

Of 254 patients with GCT of bone, 24 patients underwent surgery for sacral GCT (Tables 1 and 2). Their mean age was 31.8 years (range 11–56 years), and 11 patients (46%) were female. Five patients (21%) had previous surgery elsewhere and were admitted to MSKCC with recurrence.

Twenty-two (92%) of 24 patients presented with low-back, buttock, or tailbone pain. One of the 2 patients who did not experience pain presented with progressive loss of bowel and bladder function, and in the other patient, sacral GCT was found incidentally after a gunshot wound to his thigh. Retrospectively, he revealed a history of prolonged constipation, and he was found to have an abdominal mass on the physical examination. In addition to pain, 11 patients (46%) had sciatica, 6 (25%) had muscle weakness that resulted in walking difficulty, 4 (16%) had complete bowel and bladder incontinence, 2 (8%) had diminished bladder function, and 1 patient had leg edema. MRI was the preferred method of preoperative workup and tumor size reckoning.¹⁸ Tumors were located eccentrically in 10 patients (42%) and centrally in 14 patients (58%) (Fig. 1).

Tumors were typically located more proximally, with S-1 segment involvement in 62.5% of cases (Tables 1 and 2). Lesion volume varied widely (range 40–1418 cm³, mean 445 cm³), and most (20 [83%]) had soft-tissue extension. One patient (Case 21), who initially presented with Grade 1 GCT, did not receive radiotherapy, developed a malignant recurrence 6 months after surgery and ultimately died of disease. All others had conventional Grade 1 (14, [59%]) or Grade 2 (9 [37%]) GCT. An aneurysmal

TABLE 1. Demographic and clinical characteristics of 24 patients

Variable	Value*
Mean age in yrs (range)	31.8 (11–56)
Male	36.3 (11–56)
Female	26.5 (16–39)
Sex	
Male	13
Female	11
Tumor vol in cm ³	
<320	15
≥320	9
Histological grading (Huvos)	
1	14
2	9
3	1†
Campanacci grading	
1	2
2	5
3	17
No. of recurrence cases at presentation	5
Highest level of tumor involvement‡	
Total (bilat S-1 & below, bilat/unilat L-5)	16
High (bilat S-2 & below, unilat S-1+S-2 & below)	6
Middle (bilat S-3 & below)	2
Low (bilat S-4 & below)	0
Distal (S-4 & above preserved)	0
Preop treatment	
Radiation	13
Embolization	16
Approach	
Posterior	18
Anterior-posterior	6
Surgery	
Spinopelvic fusion	8
Spinal instrumentation	5
Adjuvant therapy	
Cryosurgery	19

* Values represent numbers of patients unless otherwise indicated.

† Malignant transformation.

‡ Based on Biagini et al.³ and Fourny et al.⁸

bone cyst component was described in 9 cases (37%). There were no secondary, radiation-associated sarcomas.

Thirteen (54%) of 24 patients had preoperative radiotherapy (median dose 50 Gy, range 40–66 Gy), and 1 patient (4%) had radiotherapy (30 Gy) postoperatively. Sixteen (67%) of 24 patients underwent embolization 1 day before surgery, including 3 who had multiple embolizations in unsuccessful attempts at cure. This included 11 patients who had both radiotherapy and embolization, which constituted primary treatment for 8 patients and secondary treatment for recurrent disease in 3 patients.

Eighteen patients (75%) underwent intralesional resection via a posterior approach alone, and 6 (25%) underwent a combination of posterior and anterior approaches. All procedures were classified as intralesional, with preservation of at least the S-1, S-2, and S-3 nerve roots. Most

operative records described a combination of translesional or subtotal en bloc excision of tumor followed by careful dissection of tumor from the nerve roots and tumor edges.²⁴ Gross-total removal of the tumor was achieved in all cases. There were no classical wide resections. In many cases, a cavitational ultrasonic surgical aspirator was also used. Adjuvant cryosurgery was used in 19 (79%) of 24 cases, employing either a direct pour technique or, in less surgically accessible, non-gravity-dependent areas, a spray method (Cry-Ac, Brymill).

Assessment of spinopelvic stability was based on the presenting pattern of the sacral lesion and the type of surgical treatment required (Fig. 1). Patients with midline tumors located at the second sacral segment and below (Fig. 2), as well as those who had tumors involving less than 50% of the S-1 vertebra in the presence of pelvic continuity (Figs. 3A–C), were considered to have spinopelvic stability. Eccentric or midline tumors that involve more than 50% of the S-1 segment with pelvic discontinuity are associated with instability (Figs. 3D–F). Preoperative or intraoperative assessment revealed sacroiliac instability in 8 patients (33%). Spinopelvic fusion was performed using structural allograft without metal fixation in 3 patients (Fig. 3) and instrumentation and bone grafting in 5 patients. Two of the instrumentation constructs (40%, Cases 3 and 6) required subsequent revision surgery (Fig. 4). We analyzed oncological outcomes in 24 patients followed for at least 2 years or until death (mean 87 months, range 2–288 months) (Tables 1 and 2). There were no perioperative deaths.

One patient (Case 21) who was initially treated for benign GCT developed a recurrence that showed transformation into malignant fibrous histiocytoma; this patient died 15 months after the initial surgery and was excluded from our analysis of recurrence. Of the remaining 23 patients, 7 (30%) developed local recurrence (Fig. 5). The time to recurrence was less than 2 years in 2 patients (28%), 2–5 years in 4 patients (57%), and 7 years in 1 patient (17%). We evaluated the relationship between preoperative treatment and local recurrence using the Kaplan-Meier method with log-rank test, which demonstrated a significant reduction in local recurrence among patients who underwent embolization ($n = 16$, $p = 0.0007$, HR 0.10 [95% CI 0.02–0.53]) and among those who received neoadjuvant radiation therapy ($n = 13$, $p = 0.01$, HR 0.11 [95% CI 0.03–0.43]). There was no statistical correlation between local recurrence and perioperative cryotherapy. All 7 patients with local recurrence underwent additional surgery, with adjuvant cryosurgery in 6 cases and radiotherapy in 5. Six of 7 patients were disease free during follow-up, which ranged from 4.5 to 16 years after the second surgery. One patient developed a second local recurrence that was treated with wide resection and mesh graft for reconstruction of a resected quadratus lumborum muscle (Case 24). This patient remained disease free for 12 years. The local recurrence rates among patients who had a posterior approach (6 of 18; 33%) and among those who underwent combined anterior and posterior approaches (2 of 6; 33%) were not significantly different ($p = 0.95$). Two (8%) of 23 patients developed lung metastases and underwent thoracotomy and metastasectomy, which resulted in disease-free survival of

TABLE 2. Demographic and clinical characteristics, treatment modalities, and outcomes in 24 cases of sacral GCT

Case No.	Pt Age (yrs), Sex	RT				Surg Approach	Adjuvant Tx	Spinopelvic Fusion			Neuro Status			Local Recurrence	Pulm Mets/Tx	Follow-Up
		Embolization	Preop	Postop	Reconstruction			Status/Tx	Complications	Preop	Postop					
1*	20, M	S2-3	—	—	A/P	Cryo	—	—	—	Infection, skin necrosis requiring wound revision	Pain, sciatica, motor deficit, neurogenic bowel & bladder	Neurogenic bowels & bladder	10 mos: curette, cryo, RT 40 Gy	12 mos: wedge	NED (14 yrs)	
2*	50, M	S1-3	—	—	P	Cryo	—	—	—	Skin necrosis requiring wound revision	Pain, swelling	Intact	30 mos: curette, cryo	No	NED (14 yrs)	
3*	34, F	S1-3	Yes	44 Gy	A/P	Cryo	SI fusion, autograft, internal fixation	Nonunion, revision at 23 yrs	None	Pain	Intact	No	No	No	NED (24 yrs)	
4†	20, F	S1-5	—	—	P	Cryo	—	—	None	Pain, swelling, neurogenic bladder	Neurogenic bladder	2.5 yrs: curette, cryo, RT 31 Gy	No	NED (16 yrs)		
5*	26, F	S1-3	—	—	30 Gy	P	—	—	Infection resolved w/ antibiotics	Pain	Intact	No	No	NED (7.8 yrs)		
6†	25, F	S3-5	—	50.4 Gy	A/P	Cryo	SI, SS, & LS fusion, allograft, internal fixation	Revision of IF	AVN, skin necrosis, rectal fistula, flap closure, colostomy	Pain, pressure Sx	Intact	2 mos: curette, cryo	7 mos: wedge	NED (6.3 yrs)		
7*	31, M	S1-5	—	50.4 Gy	P	Cryo	—	—	None	Pain, sciatica	Intact	No	No	NED (25 mos)		
8	25, F	S1-2	Yes (×4)	50 Gy	P	Cryo	SI fusion, autograft, internal fixation	Union, broken rod, but stable	None	Pain, sciatica, problem in bladder emptying	Normal bladder, painful sciatica after RT	No	No	NED (7 yrs)		
(continued)																

(continued)

TABLE 2. Demographic and clinical characteristics, treatment modalities, and outcomes in 24 cases of sacral GCT (continued)

Case No.	Pt Age (yrs), Sex	RT				Surg Approach	Adjuvant Tx	Spinopelvic			Neuro Status				Pulm Mets/Tx	Follow-Up
		Embolization	Preop	Postop	RT			Reconstruction	Status/Tx	Fusion	Complications	Preop	Postop	Local Recurrence		
9	35, M	S1–3 Yes (x3)	40 Gy	—	P	Cryo	—	—	—	—	none	Incidental finding	Colostomy (diverted w/ full function), urinary cath (2 yrs) → void (Credé maneuver), able to retain erection, but no ejaculation	No	No	NED (2.9 yrs)
10	56, M	S1–3 Yes	45 Gy	—	P	Cryo	—	—	—	—	7 mo: stress Fx sacrum	Pain	Intact	No	No	NED (6 yrs)
11†	40, M	S1–2 Yes (x3)	50 Gy	—	P	Cryo	—	—	—	—	None	Acute loss of bowel & bladder fn (cauda equina)	Neurogenic bladder (urinary cath)	No	No	NED (4.7 yrs)
12†	17, M	S1–3 Yes	50 Gy	—	A/P	Cryo	—	—	—	—	AVN right hip (from prolonged steroid use), core decompression	Pain, sciatica, difficulty walking (bilat 2/5 ankle dorsiflexion),	Normal gait, ankle dorsiflexion 4/5	No	No	NED (10.8 yrs)
13†	39, F	S1–2 Yes	45 Gy	—	P	Cryo, argon beam	—	—	—	—	None	Sciatica, neurogenic bowel, bladder from 1st Sx elsewhere	Neurogenic bowel & bladder	No	No	NED (10 mos)
14	16, F	S3–5 Yes	—	—	P	—	—	—	—	—	None	Pain, constipation, neurogenic bladder (sitting in hot tub to urinate)	Intact, fully re-turned bowel & bladder fn	4 yrs: RT 36 Gy,	No	NED (6 yrs)

(continued)

TABLE 2. Demographic and clinical characteristics, treatment modalities, and outcomes in 24 cases of sacral GCT (continued)

Case No.	Pt Age (yrs), Sex	RT				Surg			Adjuvant Tx	Spinopelvic Fusion			Neuro Status				Pulm Mets/Tx	Follow-Up
		Level	Embolization	Preop	Postop	Approach	Reconstruction	Status/Tx		Complications	Preop	Postop	Local Recurrence					
15	34, M	S2-3	Yes	—	—	P	—	—	Cryo	—	—	None	Pain	Intact	No	No	NED (4.6 yrs)	
16	20, F	S-1	Yes	—	—	P	—	—	—	—	—	None	Intact	Loss of sensation in right leg	3 yrs: RT 63 Gy	No	NED (4.5 yrs)	
17	30, F	S2-4	Yes	66 Gy	—	P	SI, SS, & LS fusions, internal fixation	N/A	Cryo	Subclinical PE, IVC filter before surgery, infected wound, debridement, hardware removal, gluteus max flap, sepsis, (<i>E coli</i> , <i>E cloacae</i> , Strep coag neg)	LBP on narcotics, sciatica, weakness in push-off, shuffling gait, numbness	Walking w/o assistance, force voiding, decreased narcotic use	No	No	No	DOC (2 mos)†		
18	25, F	S-1	Yes	—	—	P	SI fusion, autograft, repair abdom hernia with mesh	Union	Cryo	Wound dehiscence (neg culture), debridement, 1° closure	Sciatica	Intact	No	No	No	NED (9 yrs)		
19	52, M	S2-5	Yes	RT	—	A/P	—	—	—	Wound dehiscence (enterococci), debridement, 2° healing	Pressure Sx	Intensive pain	No	No	No	NED (2.7 yrs)		
20	11, M	S2-4	Yes	RT	—	P	—	—	—	None	Pain, difficult to walk	Improved gait	No	No	No	NED (8 yrs)		
21	39, M	S-2	—	—	—	P	SI fusion, allograft, internal fixation	N/A	Cryo	4 mos: malignant transformation	Pain, erectile dysfunction	Regained normal sexual fn, urinary urgency	6 mos: curette, cryo, RT	7 mos: wedge	DOD (15 mos)			

(continued)

TABLE 2. Demographic and clinical characteristics, treatment modalities, and outcomes in 24 cases of sacral GCT (continued)

Case No.	Pt Age (yrs), Sex	RT				Embolization	Surg		Adjuvant Tx	Spinopelvic Fusion			Neurol Status				Local Recurrence	Pulm Mets/Tx	Follow-Up
		Level	S2–5	Yes	63 Gy		Preop	Postop		Approach	Status/Tx	Reconstruction	Complications	Preop	Postop				
22	31, F	S2–5	Yes		63 Gy	—	P	—	—	—	13 mos: stress Fx sacrum, healed	Pain, sciatica, difficulty walking, constipation	Normal ambulation, urinary cath (1 yr) → self-void by Credé maneuver	No	No	NED (3 yrs)			
23	32, M	S1–4	Yes		—	—	A/P	Cryo	SI fusion, fibular autograft, allograft	Union → stress Fx, nonunion	15 mos: fibular autograft Fx, hypertrophic nonunion, Rx pain med, walking aid	Pain, sciatica, weak left hip flexor (used crutches), numbness	Walking w/o crutches after Sx, but using crutches again w/ Fx nonunion, normal sexual fn, urinary cath (4 yrs) → self-void, incr freq, no Credé maneuver	No	No	NED (6 yrs)			
24	55, M	S1–2	—		—	—	P	Cryo	SI fusion, autograft	Union	None	Pain, sciatica	Intact	7 yrs: curette, cryo, cement, screws; 8 yrs: wide resection, mesh graft	No	NED (12 yrs)			

Abdom = abdominal; A/P = combined anterior and posterior surgical approaches; AVN = avascular necrosis; cath = catheter; cryo = cryosurgery; DOC = died of complications; DOD = died of disease; fn = function; Fx = fracture; gluteus max = gluteus maximus; IF = internal fixation; incr freq = increased frequency; IVC = inferior vena cava; LBP = low-back pain; LS = lumbosacral; N/A = not applicable; NED = no evidence of disease; neg = negative; neurol = neurological; P = posterior surgical approach; PE = pulmonary embolism; pt = patient; pulm mets = pulmonary metastasis; RT = radiotherapy; Rx = prescription; SI = sacroiliac; SS = sacrospinal; Strep coag = Streptococcus coagulase; surg = surgical; Sx = symptom(s); Tx = treatment; 1° = primary; 2° = secondary.

*These 7 patients were included in a previous report by Marcove et al.²⁴

† Indicates recurrent cases.

‡ Septicemia.

FIG. 2. Midline GCT from S-2 and below. **A–C:** Case 5. Preoperative CT 3D reconstruction, anteroposterior (AP) view of the pelvis (A) showed GCT located at S-2 with the remaining bone. The patient underwent preoperative RT and then intralesional curettage with cryosurgery. Postoperative AP pelvic radiographs obtained 1 month (B) and 7 years (C) after surgery showed reossification and sclerosis. **D–F:** Case 22. The preoperative AP pelvic radiograph (D) revealed that the tumor extended from S-2 to the entire lower sacrum. Preoperative radiotherapy and intralesional curettage were performed. The postoperative radiograph obtained 1 month after surgery (E) showed a stable pelvic ring. At 3 years, the patient presented with a stress fracture of the S-1 body (F, arrow).

7 years in 1 patient and 14 years in the other. None of the 11 patients who had both radiotherapy and embolization suffered recurrence, although 2 had sacral fractures and 2 had wound infections.

Preoperative, postoperative, and overall neurological outcomes, which were assessed according to a modification of the scoring system described by Fourney et al.⁸ and Biagini et al.,³ are outlined in Tables 2 and 3. Ambulatory function was preserved in all patients who had normal function preoperatively, and ambulatory function was improved in 2 of 3 patients who required assistive devices preoperatively. With respect to bowel and bladder function, the degree of preoperative impairment was correlated with the location of tumor involvement within the sacrum. Four patients who presented with complete loss of bowel and bladder function did not regain function postoperatively. Three (12.5%) of 24 patients completely lost bladder and/or bowel function as a result of surgery, with all requiring urinary catheterization and 2 requiring colostomy. However, all 3 of these patients regained urinary control (in 1, 2, and 4 years postoperatively) using the Credé maneuver. One patient who had a diverting colostomy regained full bowel function 1 year after a subsequent reanastomosis. Two other patients reported diminished bladder function postoperatively but considered their disability mild and acceptable. On the other hand, 2 other patients who reported impaired bowel/bladder function preoperatively regained full function within the

months following surgery. Twenty-two patients presented with pain, 11 of whom had sciatica. Postoperatively, sciatica was relieved in 9 of 11 patients, including one who lost sensation in the distribution of the sciatic nerve. One patient experienced increased pain after surgery. In most patients with preoperative pain, the level of required analgesia (dosage and/or type of pain medication) was reduced. Overall neurological function was classified as normal in 11 patients during follow-up.

For most patients with postoperative neurological deficits, operative reports described dense adherence of tumor to the roots, requiring sharp perineural dissection or nerve root sacrifice. The 13 patients without neurological impairment had significantly lower mean tumor volume (322 cm³) than the 11 patients with impaired neurological status (799 cm³; $p < 0.015$, Mann-Whitney test).

Spinopelvic stability was present in 23 of 24 patients at the time of final follow-up. Two patients who required stabilization with fusion (Cases 3 and 6) had nonunion and underwent revision surgery. In Case 3 (Fig. 4), radiographic evidence of nonunion was noted early in the postoperative period and continued for 23 years, during which time the patient was able to walk without assistance. She then began to experience increasing mechanical back pain and underwent successful revision. The patient in Case 6 had multiple surgeries, including flap coverage and colostomy for severe myonecrosis and enterocutaneous fistula. She developed local recurrent GCT and pulmonary metastases

FIG. 3. Eccentric GCT at S-1 with sacroiliac (SI) involvement (stable type, with pelvic continuity; unstable type, with pelvic discontinuity). **A–C:** Case 18. The preoperative AP pelvic radiograph (A) shows GCT of the left SI joint without disruption of the pelvic ring. The patient underwent curettage and bone grafting. Radiographs obtained at the 1 year (B) and 9 years (C) postoperatively, showed union and a stable pelvis. **D–F:** Case 23. The preoperative AP pelvic radiograph (D) showed a tumor at the left SI joint with destruction through the sciatic notch resulting in pelvic discontinuity. The patient underwent intralesional curettage with cryosurgery and reconstruction with a free fibular autograft and cancellous allograft. Two years later, the patient had a fracture and nonunion of the fibular graft (E). Nonunion persisted with bone resorption at 6 years (F, arrow). The patient walks well with a cane.

that were treated surgically. Fusion for nonunion was performed 2 years after the infection had subsided. This patient made a successful recovery and was pain and disease free at 7-year follow-up.

Other complications included wound infections and stress fractures of the sacrum. Seven patients (29%) developed infections (Table 4); 1 patient (Case 5) had a superficial infection that was treated with antibiotics. Six patients with deep infections required multiple debridements and antibiotics. Wound closures required local gluteus maximus flaps in 2 cases. One patient (Case 17) had an infected

sacral wound and septicemia. She died 2 months after the infection was identified. Stress fracture of the sacrum occurred in 2 patients (Fig. 2F), both of whom were successfully managed conservatively.

Discussion

This study evaluated oncological, neurological, and structural outcomes of multimodal treatment of sacral GCT. A retrospective design was necessary to accrue the largest single-institution case series. Our cohort of 24 pa-

FIG. 4. Midline GCT at S-1 with lumbosacral involvement. Case 3. In this patient, GCT destroyed the SI joint, S-1, the S-1 lateral process, and parts of the body of L-5. She was treated with radiation therapy, intralesional curettage with cryotherapy, and reconstruction with a plate and bone graft 24 years ago. Nonunion (arrows) and a broken plate were evidenced by plain radiograph (A) and coronal CT (B) since the first postoperative year. Revision surgery was performed, with placement of additional instrumentation (C), 23 years after the original operation. As of this writing, at 1 year after that procedure, the patient is recovering without mechanical pain or neurological deficit.

FIG. 5. Kaplan-Meier survival curve showing time to recurrence in patients who underwent intralesional curettage of GCT of the sacrum.

tients, treated during 35 years at our tertiary care cancer center, highlights the rarity of sacral GCT, and offered an opportunity to examine the pertinent questions about the surgical management of sacral GCT.

Despite aggressive multimodality therapy, we achieved only fair oncological control of this disease. Intralesional surgery locally controls sacral GCT in most cases when used in combination with embolization, radiotherapy, and/or local adjuvants such as cryosurgery. The high local and systemic relapse rates highlight the tumor's aggressive nature and the need for better therapies. Our recurrence rate (30%) is similar to that reported in other studies that included patients treated with wide resection (20.3%–38.9%).^{13,20,21,26,35} The absence of local recurrence in patients who received both radiotherapy and embolization is noteworthy.

Predictably, neurological loss was frequent, but it was of variable severity and was somewhat dependent on preoperative neurological status. Remarkably, ambulatory function was reportedly normal in these patients, which reflected preservation of S-1 function. Three patients who lost bladder function as a result of surgery recovered within 1–4 years without further need for urinary catheterization. The variety of therapeutic combinations used precludes drawing any inferences about the relative risks or merits of one approach over another. However, we can conclude that larger tumor size (> 320 cm³) increases the likelihood of neurological loss after sacral GCT treatment. This information greatly facilitates preoperative patient counseling. Complete resolution of sciatica in 9 of 11 patients and restoration of bowel and bladder function in some cases strongly support our intralesional approach with nerve preservation. Wide resection inevitably results in permanent neurological impairment, may not reduce the recurrence rate, and results in significant morbidity

TABLE 3. Preoperative and postoperative neurological functional status in 24 cases*

Variable & Score	Preop	Postop
Ambulation		
0 (normal/mild deficit)	21	23
1 (need device)	3	1
2 (no ambulation)		
Bladder function		
0 (normal)	18	15
1 (mild–moderate)	2	2
2 (incontinent)	4	7
Bowel function		
0 (normal)	21	21
1 (mild–moderate)	2	1
2 (incontinent)	1	2
Pain		
0 (none, mild)	13	21
1 (requires NSAIDs)	8	2
2 (requires narcotics)	3	1

NSAIDs = nonsteroidal antiinflammatory drugs.

* Classification of sacral tumor resection based on Biagini et al.³ and Fournier et al.⁸ The postoperative neurological status in this series reflected the conservative surgery that preserved all of the sacral nerve roots. It was not based on the "low," "middle," "high," or "total" level of the sacrectomy as described in the articles cited above.

and mortality in many of these large, vascular, and proximally situated tumors.

Structurally, sufficient sacrum was preserved in most patients (71%). Our approach of preoperative and intraoperative assessments identified all cases of instability and allowed successful fusion and internal fixation. The majority of patients presented with tumors involving the first sacral segment and had sacroiliac stability radiographically or on clinical examination. Therefore, not all patients with S-1 disease require fusion; those with preservation of the upper half of S-1 and the adjacent sacroiliac joint (with pelvic continuity) certainly do not.² Furthermore, intralesional excision with preservation of bone and iliolumbar and sacroiliac ligaments avoids the universal instability and the necessity of fixation/fusion that result from wide excision. In 5 patients with spinopelvic instability and pelvic discontinuity, fusion procedures with instrumentation were necessary, with nonunion and subsequent revision in 2 of those patients (Fig. 4).

There are several significant limitations to this study. The small cohort, long study period, and evolution of imaging, radiotherapy, and surgical techniques all may have influenced the results. Furthermore, the small case number precluded multivariate analysis of the merits or deficiencies of different treatments. Despite these issues, the retrospective observational study design enabled us to assemble the largest cohort reported to date to shed light on appropriate sacral GCT treatment strategies. However, our cohort may not be representative of GCT in the general population. Although the 8% prevalence of sacral tumors among all GCTs treated at our center is comparable to that

TABLE 4. Complications

Complication	No. of Pts	Treatment
Acute		
Wound infection	7	
Superficial	1	IV ABx
Deep	6	Debridement in all 6 cases, hardware removal in 2, gluteus max flap in 2
Enterocutaneous fistula	1	Colostomy
Subclinical pulmonary embolism	1	IVC filter, anticoagulant Tx
Late		
Stress Fx of the sacrum	2	Conservative Tx
Fusion nonunion	3	Conservative Tx in 1 case, revision surgery in 2 cases
Intermittent dysuria & UTI	1	Medication & rehabilitation

ABx = antibiotic therapy; IV = intravenous; max = maximus; UTI = urinary tract infection.

found in other analyses, we noted a prevalence of men in our cohort, which differs from the more commonly reported female prevalence ratio of 2 to 1.^{29,31,33} This may have been a chance phenomenon. Additionally, compared with patients in other series, our patients had significantly larger tumors, which made resection more difficult and correlated strongly to poor oncological and neurological results.

Comparison of our oncological results with those of other centers is also hampered by the diversity of surgical and adjuvant therapies used.^{26,31,33,36,37} We consider intralesional excision of as much tumor as possible, followed by curettage, preferable to standard curettage alone, which contaminates more local tissue, requires greater tumor manipulation, and may consequently contribute to local and systemic tumor spread.²⁴ Our study did not prove this, however. Some advocate wide excision for sacral GCT, but have not reported significantly better oncological results. With our approach, the local recurrence rate was 30%, which was comparable to that reported in previous studies of sacral GCT that was managed with multiple treatments, including wide resection. Our use of the physical adjuvant therapy (cryosurgery) may have contributed to the better local control achieved. Nevertheless, there were insufficient cases for statistical comparison of individual methods.

Recent reports have suggested that embolization alone may be an effective treatment for sacral GCT.^{14,22,27} This was not our experience; in fact, 4 patients referred to us had experienced tumor growth after undergoing that treatment modality. Embolization treatment alone confers potentially serious risks of diagnostic error, since only a needle biopsy determines diagnosis, whereas our trans- and intralesional approach allows diagnosis from immediate frozen

section and subsequent full examination of the resected tumor. Furthermore, embolization leaves bulk tumor behind, increasing recurrence risk, and the outcomes reported to date are based on limited follow-up. Thus, we advocate a more substantive biopsy, with embolization used only as preoperative treatment to reduce intraoperative bleeding. Preoperative embolization may account for the lower rate of blood loss in our cohort (average 2 L) compared with other series.^{22,26,33} Patients who underwent embolization did have a lower recurrence rate ($p = 0.0007$).

Given the high incidence of recurrence in sacral GCT, and based on reported radiotherapy use,^{7,10,20} we employed this adjuvant modality preoperatively in 13 cases and postoperatively in 1 case. The median dose was 50 Gy (range 30–66 Gy). Indications for radiotherapy included 1) cases in which negative surgical margins would be difficult to achieve with acceptable morbidity, 2) tumors greater than 8.5 cm in the longest dimension, and 3) in cases of local recurrence. In female patients of childbearing age, ovary relocation may be undertaken prior to RT, as was performed in one of our patients. To date, none of the tumors treated with radiotherapy have transformed to malignant GCT. However, 1 patient experienced spontaneous malignant transformation. Among 13 patients who received radiotherapy, infection developed in 3 (superficial in 1 case and deep in 2 cases), sacral stress fractures occurred in 2, and there was nonunion of spinal fusion in 1 patient. Local recurrence was observed in only 1 patient treated with radiotherapy. Our analysis demonstrated that radiation therapy was significantly associated with prolonged disease-free survival ($p = 0.01$). The combination of radiotherapy and embolization was efficacious. This strategy should be investigated through further study.

In our view, radiotherapy using modern techniques remains a reasonable approach for patients with sacral GCT, a condition in which negative surgical margins can only be achieved with unacceptable morbidity. When considering use of this adjunctive treatment, an individual assessment of potential risks, such as malignant transformation, infertility, or postoperative wound complications, must be carefully weighed against potential benefits, such as minimizing operative blood loss or reducing the risk of recurrence. Again, we could not demonstrate statistically significant superiority over surgery alone. However, based on our clinical observations, we believe its preoperative use facilitates tumor excision and reduces the potential risk of radiation-induced sarcoma.

It is unclear whether adjuvant therapies such as phenol, hydrogen peroxide, or cauterization contribute to reductions in recurrence rates in skeletal GCTs, as similar local recurrence rates have been observed in patients treated with and without these adjuvants.^{23,28,36} It is more likely that the adequacy of the tumor removal rather than the use of adjuvant modalities is what determines the risk of recurrence.^{4,34} Based on our institutional experience with the use of cryosurgery for GCT in the appendicular skeleton,²⁵ we believe it is useful to achieve local control of the disease in the sacrum, especially for patients in whom wide resection margins cannot be achieved. Complications of cryosurgery, such as tissue necrosis, temporary or permanent nerve damage, and infection, can be minimized by us-

ing meticulous soft-tissue protection, a quality-controlled cryospray and cryoprobe, and well-vascularized soft-tissue coverage of the incisions. However, in this series, we found no association between the use of cryosurgery and wound complications and infection.

Six patients developed deep infections. They were successfully managed with debridement and primary or secondary healing in 4 cases and hardware removal with gluteus maximus myocutaneous flap in 2. Our series included 1 death in the patient who had an infected sacral wound. The most common pathogens were gastrointestinal bacteria—e.g., *Escherichia coli*, *Streptococcus agalactiae* (Group B *Streptococcus*), and *Enterococcus faecalis*, presumably due to bacterial translocation from the adjacent colon. Adequate bowel preparation and the addition of antibiotic prophylaxis against gut flora (ampicillin or vancomycin) to the routine antibiotic treatment administered for orthopedic procedures (cefazolin+gentamicin) resulted in significant reduction of the infection rate during the later years of our study period. Skin and soft-tissue necrosis from cryosurgery can be minimized by using adequate exposure, soft-tissue protection, and multilayer closure. The use of local myocutaneous flap closure can be especially helpful in preventing wound breakdown and infection.

The high rate of complications may be attributable to larger tumor sizes and the magnitude of surgery in our cohort. Regardless of the cause, sacral GCT remains a morbid condition with significant mortality risk. Our multimodality approach serves as a baseline comparison for studies of targeted anti-giant cell therapies.

RANKL (receptor activator of nuclear factor κ -B ligand) has been implicated in GCT.^{15,30} The human monoclonal antibody denosumab binds to RANKL to prevent RANK activation, thereby limiting the destructive properties of GCT and reducing the giant cell population.^{1,5} Denosumab has been approved by the FDA to treat unresectable GCT of bone in adults or adolescents who are skeletally mature (FDA Press Announcement, June 13, 2013; <http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm356667.htm>). Denosumab's approval was based on the durable objective responses achieved in 2 multicenter open-label trials.^{6,33} One of these was a multicenter Phase II trial involving 37 patients with unresectable or recurrent GCT who were treated monthly with subcutaneous denosumab. Of 35 assessable patients, 30 (84%) reported improved functional status or decreased pain.³² In the second trial, a multinational Phase II study of denosumab in 282 GCT patients, the drug was well tolerated and was associated with inhibition of disease progression (99%) and a reduced requirement for surgery.⁶ These positive results may herald the introduction of a preoperative regimen of denosumab for patients with sacral GCT to help diminish the high morbidity associated with sacral tumor resection.

Conclusions

Based on our analysis of 24 cases involving patients with sacral GCT who underwent multimodality treatment at our institution, management of GCT of the sacrum remains challenging. Despite achieving local tumor control, preserving spinopelvic stability, and minimizing neuro-

logical complications with our intralesional approach, the recurrence and mortality rates remain high, necessitating careful follow-up and highlighting the urgent need for new therapies.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Boland, Domovítov, Healey. Acquisition of data: Boland, Domovítov, Chandhanayingyong, Healey. Analysis and interpretation of data: all authors. Drafting the article: Domovítov, McKeown. Critically revising the article: Boland, Chandhanayingyong, McKeown, Healey. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Boland. Statistical analysis: Domovítov, Chandhanayingyong, McKeown. Study supervision: Boland, Healey.

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