Intralesional nerve-sparing surgery versus non-surgical treatment for giant cell tumor of the sacrum

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Abstract

Background: There is no standard treatment for giant cell tumors of the sacrum. We compared the outcomes and complications in patients with sacral giant cell tumors who underwent intralesional nerve-sparing surgery with or without (neo-) adjuvant therapies versus those who underwent non-surgical treatment (denosumab therapy and/or embolization).

Methods: We retrospectively investigated 15 cases of sacral giant cell tumors treated at two institutions between 2005 and 2020. Nine patients underwent intralesional nerve-sparing surgery with or without (neo-) adjuvant therapies, and six patients received non-surgical treatment. The mean follow-up period was 85 months for the surgical group (range, 25–154 months) and 59 months (range, 17–94 months) for the non-surgical group.

Results: The local recurrence rate was 44% in the surgical group, and the tumor progression rate was 0% in the non-surgical group. There were two surgery-related complications (infection and bladder laceration) and three denosumab-related complications (apical granuloma of the tooth, stress fracture of the sacroiliac joint, and osteonecrosis of the jaw). In the surgical group, the mean modified Biagini score (bowel, bladder, and motor function) was 0.9; in the non-surgical group, it was 0.5. None of the 11 female patients became pregnant or delivered a baby after developing a sacral giant cell tumor.

Conclusions: The cure rate of intralesional nerve-sparing surgery is over 50%. Non-surgical treatment has a similar risk of complications to intralesional nerve-sparing surgery and has better functional outcomes than intralesional nerve-sparing surgery, but patients must remain on therapy over time. Based on our results, the decision on the choice of treatment for sacral giant cell tumors could be discussed between the surgeon and the patient based on the tumor size and location.

Keywords: Giant cell tumor of bone, Sacrum, Denosumab, Embolization, Surgery, Intralesional nerve sparing surgery, Curettage

Background

Giant bone tumor of bone (GCTB) is a locally aggressive, benign bone tumor with a high risk of local recurrence [1]. GCTB of the sacrum is very uncommon [2] and accounts for approximately 2% of all cases of GCTB [2]. Sacral GCTBs are often asymptomatic and cause symptoms only when they are considerably enlarged [3].
Sacral GCTBs usually occur in eccentric positions but can extend to both sides of the median line and anterior sacral space [4, 5]. It is close to important organs such as the large blood vessels, spinal cord, colon, and ureter; thus, surgery is difficult due to the complicated anatomy, and there is a high risk of massive bleeding during surgery. Most sacral GCTBs occur at the S1–2 levels [6], and wide resection, including the nerve roots of S1-S3, can reduce the local recurrence rate. However, it can cause severe functional losses, such as motor deficits and bowel, bladder, or sexual dysfunction, as well as lumbopelvic discontinuity [7]. Therefore, wide resection is usually unacceptable for the treatment of benign bone tumors [7]. Nerve-sparing surgery (also called intralesional curettage or piecemeal resection) can preserve the S1–3 nerve roots and maintain the stability of the pelvic ring, avoiding neurological deficits and lumbopelvic instability [8–10]. Although the recurrence rate is high, intralesional nerve-sparing surgery is recommended as a general surgical procedure for GCTBs [8–10]. Apart of local recurrence, intralesional nerve-sparing surgery could be associated with complications such as postoperative infection and massive bleeding during surgery [8–10].

The use of denosumab for GCTB was approved by the US Food and Drug Administration in 2013, and denosumab is indicated for GCTB that is inoperable or might cause severe dysfunction after surgery. It has been reported that the rate of disease control with denosumab therapy for inoperable GCTB is up to 96% [11]. However, complications such as osteonecrosis of the jaw, peripheral neuropathy, skin rash, hypophosphatemia, and atypical femoral fracture associated with long-term administration of denosumab have been reported [12]. Preoperative administration of denosumab makes curettage difficult and increases the risk of local recurrence [13]. Embolization has been performed for a long time for sacral GCTB, and a systematic review reported that the disease control rate is up to 75% [14]. Recently, Puri et al. reported that non-surgical treatment, which is a combination of denosumab therapy and embolization, was able to control disease progression in 11 of 12 patients (92%) with sacral GCTB during an average follow-up period of 31 months [15], and it has been proposed as a new treatment option for these tumors [15]. However, no study has compared the oncological and functional outcomes and complications between intralesional nerve-sparing surgery and non-surgical treatment (denosumab therapy and embolization) for sacral GCTB. We conducted this retrospective, comparative study in patients with GCTB of the sacrum to compare the oncological and functional outcomes and complications following intralesional nerve-sparing surgery and non-surgical treatment.

Methods
We retrospectively investigated 16 cases of sacral GCTB treated at two institutions (IRCCS Istituto Ortopedico Rizzoli and Nara Medical University) between January 2005 and April 2020. One patient was excluded due to missing data, and the data of the remaining 15 patients were analyzed. Nine patients underwent intralesional nerve-sparing surgery with or without (neo-)adjuvant therapies (zoledronic acid, denosumab, or embolization), and six patients underwent non-surgical treatment (three patients received denosumab and embolization, and three patients received denosumab alone). We retrieved the following data from the patients’ medical records: age; sex; tumor size measured by computed tomography (CT) or magnetic resonance imaging (MRI); anatomical level of the tumor; Campanacci stage [2]; tumor involvement of the sacroiliac joint; involvement of the vascular or other organ systems; location; spinal instability (spino-pelvic stability was considered intact if at least the cephalad 50% of the S-1 vertebra and sacroiliac joints were preserved bilaterally [16]); surgical approach; reconstruction; local recurrence or tumor progression; treatment for local recurrence; neurological status and pain before and after treatment; lung metastasis; oncological outcome; complications related to surgery, denosumab, zoledronic acid, or embolization; Karnofsky performance status; and evaluation of bowel, bladder, and motor function using modified Biagini score (Table 1) [17]. For female patients, we also collected data on whether they were pregnant or delivered a baby after developing sacral GCTB and their follow-up period. The follow-up period (mean, 59 months; range, 17–94 months) of the non-surgical treatment group was shorter than that of the intralesional nerve-sparing surgery group (mean, 85 months; range, 25–154 months) (Table 2). There was no difference between the two groups in terms of clinical symptoms and staging at presentation: all 15 patients had pain and Campanacci stage III tumor at presentation. In the intralesional nerve-sparing surgery group, the mean tumor volume was 111 cm³ (range 14–235), the tumor level was above S3 in 33% of the patients, at or below S3 in 11% of the patients, and involved the whole sacrum in 56% of the patients. Tumor involvement of the sacroiliac joint was observed in 56% of patients, tumor involvement of the vascular or other organ systems was observed in 56% of patients, and the tumor was located centrally in 22% of patients (Table 2). In the non-surgical treatment group, the mean tumor volume was 272 cm³ (range 99–678), the tumor level was above S3 in 17% of patients, and it involved the whole sacrum in 83% of patients. Tumor involvement of the sacroiliac joint was not observed,
tumor involvement of the vascular or other organ systems was observed in 17% of patients, and the tumor was located centrally in 83% of patients (Table 2).

Intralesional nerve-sparing surgery was indicated in patients who had tumors located eccentrically. In the intralesional nerve-sparing surgery group, preoperative denosumab therapy (weekly for the first month, then once a month for a total of 10 cycles) was administered in 3 cases, preoperative zoledronic acid (once a month for a total of 2–6 cycles) and embolization was performed in 3 cases, and the remaining 2 patients did not receive any preoperative adjuvant treatment (Table 3). Surgery after the end of administration of denosumab and zoledronic acid was scheduled before the start of drug administration. Preoperative embolization was performed within 48 h prior to surgery. Seven cases were operated using the posterior approach, and two cases were operated using the anterior/posterior approach (Table 3). The indications for an anterior approach were large tumors with anterior extraosseous lesions. Through the anterior approach, we ligated the hypogastric, internal iliac, and tumor vessels and separated the tumor from the rectum. Through the posterior approach, we performed a wide laminectomy and complete curettage with a curette and high-speed burr. Sacral nerve roots were identified and preserved. The bilateral nerve roots of S1–3 were preserved using curettage. Phenol was used as a local adjuvant therapy in six patients but not in areas close to the sacral nerve roots (Table 3) [6].

Non-surgical treatment (denosumab therapy or embolization) was indicated for patients in whom large tumors were centrally located. Denosumab 120 mg was administered subcutaneously to all six patients once a month for 1–5 years (weekly for the first month) and then every 2–3 months (Table 3). The patients also received daily calcium (2500 mg) and vitamin D (≥ 400 IU). Surgery was not scheduled before the start of denosumab administration. Embolization was performed in 3 of the 6 patients. It was performed once a month for a total of three times in one of the three patients (case 10) and, in the remaining two cases, every three months for a total of two and three times (Cases 14 and 15, respectively) (Table 3). Embolization was discontinued when the hypervascular tumor disappeared, no tumor growth was observed on imaging, and the clinical symptoms improved. Intra-arterial embolization was performed using femoral access to selectively embolize the main arteries feeding the tumor. Angiography was performed at the beginning of each treatment session to identify arteries of adequate caliber to facilitate embolization. The arteries were embolized based on the arterial supply to the sacrum, resulting in occlusion of the internal iliac, lateral sacral, and median sacral arteries. Selective delivery of substances, including embosphere microspheres or gelatin sponges, was used to achieve central occlusion of the vessels. Postprocedural angiography showed complete interruption of the tumor blood supply and more than 80% devascularization of the tumor in all cases (Fig. 1).

Routine follow-up evaluation was performed every 3 months for the first 3 years, every 6 months for the next 2 years, and then annually. Each follow-up evaluation included assessment of sexual dysfunction, clinical examination of motor, sensory, bladder, and bowel deficits, and imaging evaluation, including CT or MRI of the pelvis. Chest CT was performed annually [6]. Postoperative local recurrence was defined as bone resorption, expansile osseous destruction, or local soft tissue mass formation on CT and MRI. Tumor progression during non-surgical treatment was defined as a new area of osteolysis or new cortical destruction on CT and MRI [18].

The independent ethics committee of each institution approved the study. Informed consent was obtained from all individual participants in IRCCS Istituto Ortopedico Rizzoli, and the requirement for written consent from

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**Table 1** Modified Biagini score (classification of neurologic function after resection of the sacrum) [17]

| Function | Score | Description |
|----------|-------|-------------|
| Bladder  | 0     | Normal      |
|          | 1     | Feels stimulus to micturate and has limited continence at varying times and quantities of urine and/or has increasing postmicturition vesical residual and/or urinary loss in conditions of stress |
|          | 2     | Does not feel stimulus to micturate and/or is completely incontinent |
| Bowel    | 0     | Normal      |
|          | 1     | Feels stimulus to defecate and is incontinent when feces are soft or under stress |
|          | 2     | Does not feel stimulus to defecate and/or is completely incontinent |
| Motor    | 0     | Normal or mild deficit not requiring the help of external support for motion and common activities |
|          | 1     | Deficits requiring the help of external support for walking and common activities |
|          | 2     | Deficits that make walking impossible |
participants in Nara Medical University was waived, because an “opt-out” process was used and the study had the retrospective nature.

Results
The local recurrence rate was 44% (4 of 9 patients) in the intralesional nerve-sparing surgery group, whereas the tumor progression rate was 0% (none of 6 patients) in the non-surgical treatment group. The lung metastasis rate was 11% (1 of 9 patients) in the intralesional nerve-sparing surgery group and 0% (none of 6 patients) in the non-surgical treatment group. The patient with lung metastasis received neo- and adjuvant denosumab therapy. Six of nine patients (67%) in the intralesional nerve-sparing surgery group achieved a disease-free status. In the intralesional nerve-sparing surgery group,
Table 3  Details of the 15 patients with sacral giant cell tumors

| Case | Age (years) | Sex | Tumor volume (cm³) | Tumor level | Involvement of the sacro-iliac joint | Involvement of the vascular or other organ system | Location | Preoperative treatment | Surgical approach | Local adjuvant therapy | Local recurrence or tumor progression | Treatment for local recurrence |
|------|-------------|-----|--------------------|-------------|-------------------------------------|-------------------------------------------------|----------|-----------------------|-------------------|------------------------|---------------------------------|--------------------------|
|      |             |     |                    |             |                                     |                                                 |          |                       |                   |                        |                                 |                          |
| Nerve-sparing surgery group | | | | | | | | | | | | |
| 1    | 35          | F   | 91                 | S2-S4       | Yes                                 | None                                            | Eccentric| Denosumab (pre-op: 10 cycles and post-op: every 3 months) | Posterior | None                  | Yes (3 years after surgery) | Embolization and curettage |
| 2    | 36          | F   | 14                 | S2-S3       | No                                  | None                                            | Eccentric| None                  | Posterior | Phenol                | Yes (52 months after surgery) | Denosumab (monthly for 10 months) |
| 3    | 48          | F   | 75                 | S1-S2       | Yes                                 | None                                            | Eccentric| Embolization and zoledronate (2 cycles) | Posterior | Phenol                | Yes (53 months after surgery) | Denosumab (monthly for a year) and curettage |
| 4    | 16          | F   | 14                 | S1-S3       | Yes                                 | Involvement of sacral plexus                    | Eccentric| Embolization          | Posterior | Phenol                | No                | NA                       |
| 5    | 30          | F   | 80                 | S1-S2       | No                                  | None                                            | Eccentric| Denosumab (10 cycles) | Posterior | Phenol                | No                | NA                       |
| 6    | 43          | M   | 295                | S3-S5       | No                                  | Rectum compression                              | Central  | None                  | Posterior | None                  | No                | NA                       |
| 7    | 15          | M   | 62                 | S1-S2       | Yes                                 | None                                            | Eccentric| Embolization (three times) and zoledronate (one cycle) | Posterior | Phenol                | No                | NA                       |
| 8    | 15          | F   | 132                | S1-S4       | No                                  | Rectum and uterus compression                   | Central  | Denosumab (pre-op: 10 cycles and post-op: 6 cycles) | Anterior/ posterior | None                  | Yes (1 4 months after surgery) | Denosumab (every 6 months for 5 years and 10 months) |
| 9    | 19          | F   | 235                | S1-S3       | Yes                                 | Rectum compression                              | Eccentric| Embolization and zoledronate (pre-op: 6 cycles and post-op: 6 cycles) | Anterior/ posterior | Phenol                | No                | NA                       |
|      |             |     |                    |             |                                     |                                                 |          |                       |                   |                        |                                 |                          |
|      |             |     |                    |             |                                     |                                                 |          |                       |                   |                        |                                 |                          |
| Non-surgical treatment group | | | | | | | | | | | | |
| 10   | 14          | F   | 99                 | S1-S3       | No                                  | Uterus compression                              | Central  | NA                    | NA                 | NA                    | No                | Monthly for 5 years and bimonthly for 2 years |
| Case | Age (years) | Sex | Tumor volume (cm³) | Tumor level | Involvement of the sacro-iliac joint | Involvement of the vascular or other organ system | Location | Preoperative treatment | Surgical approach | Local adjuvant therapy | Local recurrence or tumor progression | Treatment for local recurrence |
|------|-------------|-----|--------------------|-------------|-------------------------------------|-----------------------------------------------|----------|-----------------------|-------------------|---------------------|-------------------------------|-----------------------------|
| 11   | 32          | M   | 230                | S2-S5       | No                                 | None                                         | Central  | NA                    | NA                | NA                  | NA                           | Monthly for 3 years and every 3 months for 4 months |
| 12   | 66          | F   | 678                | S1-S4       | No                                 | None                                         | Central  | NA                    | NA                | NA                  | NA                           | Monthly for 3 years and every 3 months for 4 years |
| 13   | 65          | F   | 146                | S1-S4       | No                                 | None                                         | Central  | NA                    | NA                | NA                  | NA                           | Monthly for 3 years and every 3 months for 4 years |
| 14   | 31          | M   | 252                | S1-S2       | No                                 | None                                         | Central  | NA                    | NA                | NA                  | NA                           | Monthly for a year and then bimonthly for 4 months |
| 15   | 29          | F   | 226                | S1-S4       | No                                 | None                                         | Eccentric | NA                    | NA                | NA                  | NA                           | Monthly for a year |

NA, not applicable; M, male; F, female
complications occurred in 44% of the patients (4 of 9 patients): 1 case each of postoperative infection, intraoperative bladder laceration, stress fracture of the sacroiliac joint, and denosumab-related apical granuloma of the tooth, whereas denosumab-related osteonecrosis of the jaw occurred in 1 patient (17%) (1 of 6 patients) in the non-surgical treatment group. There were no complications related to zoledronic acid or embolization. In the intralesional nerve-sparing surgery group, the Karnofsky performance status was 87 (range, 65–95), whereas in the non-surgical treatment group, it was 88 (range, 75–100). In the intralesional nerve-sparing surgery group, the mean modified Biagini score was 0.9 (range, 0–4), whereas in the non-surgical treatment group, it was 0.5 (range, 0–2) (Table 2).

None of the 15 patients had spinal instability or required reconstruction. None of the patients underwent radiotherapy or malignant transformation. Of the four patients who experienced local recurrence following intralesional nerve-sparing surgery, one underwent embolization and re-curettage, one underwent denosumab therapy and re-curettage, and the remaining two received denosumab therapy with which the disease remained stable (Table 3). In the intralesional nerve-sparing surgery group, two of the three patients (67%) who received preoperative or pre- and postoperative denosumab therapy experienced local recurrence, whereas two of six patients (33%) who did not receive preoperative denosumab therapy experienced local recurrence (Table 3). The details of the 15 cases are presented in Tables 3 and 4. None of the 11 female patients became pregnant or delivered a baby after the development of sacral GCTB.

Discussion

The recurrence rate in the intralesional nerve-sparing surgery group was higher than that in the non-surgical treatment group; however, 67% of the patients (6 of 9 patients) in the intralesional nerve-sparing surgery group achieved disease-free status. According to the literature, the local recurrence rate of intralesional nerve-sparing surgery was 0–100% [6–10, 16, 19–31], and the local recurrence rate of intralesional nerve-sparing surgery combined with preoperative denosumab therapy was 11–67% [9, 10, 22, 29, 30, 32] (Table 5). The combination of denosumab therapy and embolization led to
Table 4 Details of the 15 patients with sacral giant cell tumors

| Case | Neurological status before treatment | Neurological status after treatment | Lung metastasis | Oncological outcome | Complications | Karnofsky performance status | Modified Biagini score | Follow-up (months) |
|------|-------------------------------------|-----------------------------------|----------------|--------------------|---------------|------------------------------|------------------------|------------------|
|      |                                     |                                   |                |                    |               |                              |                        |                  |
|      | Nerve-sparing surgery group          |                                   |                |                    |               |                              |                        |                  |
| 1    | Hypotonia of the lower limb, urinary and fecal incontinence, and local pain | Paralysis in the S1-S3 regions, urinary retention, and severe local pain | Yes             | AWD                | Infection. Treatment: Debridement three times and antibiotic agents | 65             | Bi-2, Bo-1, Mo-1 | 96               |
| 2    | Left-sided sciatica                 | Paresthesia in the right S2 region | No             | AWD                | None          | 90             | Bi-0, Bo-0, Mo-0 | 63               |
| 3    | Constipation and local pain         | Perianal hypoesthesia, residual voiding, constipation, and slight local pain (improved over time) | No             | NED                | Apical granuloma of the tooth occurred 14 months after discontinuing denosumab. | 90             | Bi-1, Bo-0, Mo-0 | 154              |
| 4    | Sciatica and local pain             | Slight pain                       | No             | CDF                | None          | 95             | Bi-0, Bo-0, Mo-0 | 63               |
| 5    | Right-sided sciatica and local pain | Local pain                        | No             | CDF                | None          | 90             | Bi-0, Bo-0, Mo-0 | 25               |
| 6    | Local pain                          | Dysuria                           | No             | CDF                | None          | 95             | Bi-0, Bo-0, Mo-0 | 84               |
| 7    | Left-sided sciatica                 | Slight pain                       | No             | CDF                | None          | 95             | Bi-0, Bo-0, Mo-0 | 46               |
| 8    | Local pain and urinary retention    | Occasional urinary incontinence   | No             | AWD                | Stress fracture of the sacro-iliac joint. Treatment: Oral painkillers | 80             | Bi-1, Bo-0, Mo-0 | 100              |
| 9    | Local pain and urinary incontinence | Anal sphincter deficiency (manual evacuation), weakness of the right triceps surae muscle | No             | CDF                | Bladder laceration. Treatment: Immediately repaired | 80             | Bi-0, Bo-2, Mo-0 | 132              |
|      | Non-surgical treatment group         |                                   |                |                    |               |                              |                        |                  |
| 10   | Bilateral sciatica and urinary incontinence | Mild pain in the S1 region | No             | AWD                | None          | 75             | Bi-1, Bo-1, Mo-0 | 89               |
| 11   | Paresthesia in the S1-S2 region, dysuria and dyschezia | Symptoms are relieved | No             | AWD                | None          | 100            | Bi-0, Bo-0, Mo-0 | 54               |
| 12   | Local pain                          | No pain                           | No             | AWD                 | Osteonecrosis of the jaw occurred 6 years after starting denosumab. | 80             | Bi-1, Bo-0, Mo-0 | 94               |
| 13   | Local pain                          | Slight pain                       | No             | AWD                | None          | 90             | Bi-0, Bo-0, Mo-0 | 77               |
| 14   | Local pain, left-sided sciatica, and loss of dorsiflexion of the right toe | Slight pain | No             | AWD                | None          | 90             | Bi-0, Bo-0, Mo-0 | 22               |
| 15   | Local pain, right-sided sciatica, urinary retention, and muscle weakness of the lower limbs | No pain, no sphincter disorders, and no muscle weakness | No             | AWD                | None          | 90             | Bi-0, Bo-0, Mo-0 | 17               |

CDF, continuous disease free; NED, no evidence of disease; AWD, alive with disease; Bl, bladder; Bo, bowel; Mo, motor

a Now the disease remains stable without denosumab therapy. b Denosumab was discontinued, jaw surgery was performed, and denosumab was resumed two months later.
Table 5 Overview of studies reporting the result of nerve sparing surgery in sacral giant cell tumor

| First author, year of publication | Tumor level | Campanacci stage | Local adjuvant therapy | Interval between the first surgery and local recurrence (months) | Number of patients | Local recurrence | Follow-up (months) | Functional outcome | Complications |
|-----------------------------------|-------------|------------------|------------------------|---------------------------------------------------------------|-------------------|----------------|-----------------|-------------------|---------------|
| Balke, 2012 [20]                  | NR          | NR               | Post-op RT: 30%        | Mean 12                                                       | 10                | 2 (20%)        | Mean 52         | NR                | Infection: 10% |
| Chen, 2015 [21]                   | Above S3: 25%; at or below S3: 25%; in both parts: 50% | NR               | Zoledronic acid-loaded cement: 100% | NA | 4 | 0 | Mean 28 | Improved: 100% | None |
| Chen, 2018 [22]                   | NR          | NR               | Pre-op RT: 54%; post-op RT: 4%; liquid nitrogen: 79% | NR | 10 | 3 (30%) | NR | NR | Improved: 79%; stable: 13%; worsen: 8% |
| Domovitov, 2016 [16]              | Above S3: 9%; at or below S3: 8%; in both parts: 92% | Stage 1: 8%; stage 2: 21%; stage 3: 71% | NA | Mean 24 | 7 (30%) | Mean 86 | NR | Infection: 21%; Skin necrosis: 13%; Rectal fistula: 4%; Avascular necrosis: 8%; Stress fracture due to RT: 8%; Malignant transformation: 4% |
| Guo, 2009 [8]                     | Above S3: 4; at or below S3: 2; in both parts: 18 | Stage 2: 79%; stage 3: 21% | Post-op RT: 8% | Mean 13 | 24 | 7 (29%) | Mean 58 | All the patients were able to walk without an assistive device. Seventeen (70.8%) patients retained normal urinary function and 16 (66.7%) patients preserved normal bowel function. |
| Kollender, 2003 [23]              | NR          | NR               | Cryosurgery: 100%      | NA | 3 | 0 | Mean 61 | NR | Infection: 33% |
| Li, 2012 [24]                     | Above S3: 38%; at or below S3: 6%; in both parts: 56% | NR               | Post-op RT: 25%        | NR | 32 | 12 (38%) | Median 42 | Five patients (15.6%) developed urinary bladder dysfunction and two patients (6.3%) developed bowel dysfunction requiring medication. Four patients with marginal resections had lower limb dysfunction (12.5%). | Malignant transformation: 6%, Infection: 34% |
| Study            | S1 involvement | Stage | NR | NR | 36 | 12 (33%) | NR | Mean MUD score increased from 23.9 preoperatively to 25.4 postoperatively | NR |
|------------------|----------------|-------|----|----|----|----------|----|--------------------------------------------------------------------------------|----|
| Lim, 2020 [9]    | S1 involvement: 78% | Stage: 3: 100% | NR | NR | 36 | 12 (33%) | NR |                                                                                |    |
| Martin, 2010 [25] | Above S3: 50%; at or below S3: 0%; in both parts: 50% | NR | Post-op RT: 50% | Mean 7 | 6 | 2 (33%) | Mean 34 | Normal: 80%, pain and fecal incontinence: 20% | NR |
| Ruggieri, 2010 [6] | Above S3: 32%; at or below S3: 6%; in both parts: 61% | Stage 2: 3%, stage 3: 97% | Pre-op RT: 3%; post-op RT: 65%; phenol: 45%; liquid nitrogen: 3% | Within 34 | 31 | 3 (10%) | Median 108 | The incidence of L5-S2 neurologic deficits decreased from 23% preoperatively to 13% postoperatively. The incidence of S3-S4 neurologic deficits increased from 16% preoperatively to 33% postoperatively. |    |
| Sung, 1982 [31]  | S1–3: 100% | NR | NR | 8 | 2 | 1 (50%) | 84 |                                                                 |    |
| Turcotte, 1993 [19] | Above S3: most frequent | NR | RT: 81% | NR | 17 | 17 (100%) | Mean 94 | Improved: 53%; stable: 35%; worsened: 12% |    |
| Thangaraj, 2010 [7] | Above S3: 13%; at or below S3: 13%; in both parts: 75% | NR | NR | Mean 16 | 8 | 3 (38%) | Mean 152 | Improved: 25%; stable: 38%; worsen: 38% |    |
| van der Heijden, 2014 [26] | Above S3: 58%; at or below S3: 4%; in both parts: 38% | RT: 19%; phenol: 15%; liquid nitrogen: 35%; argon beam coagulation: 12% | Median 13 | 26 | 14 (54%) | Median 98 | Median MSTS 24 | Massive bleeding: 15%; Infection: 13%; RT-induced menopause: 13% |    |
| Wang, 2020 [27]  | Above S3: 27%; at or below S3: 9%; in both parts: 64% | Stage 2: 18%; stage 3: 82% | NR | NR | 11 | 5 (45%) | Mean 60 | Normal: 64%, urinary and fecal incontinence: 27%, bowel obstruction: 9% |    |
| Xu, 2017 [28]    | Above S3: 19%; at or below S3: 0%; in both parts: 81% | Stage 2: 13%; stage 3: 88% | RT: 38% | Mean 15 | 16 | 7 (44%) | Mean 92 | Normal: 56% |    |
| Yang, 2018 [29]  | Above S3: 100% | Stage 3: 100% | NR | NA | 10 | 0 | Mean 35 | Mean MSTS: 73% |    |
**Table 5** (continued)

| First author, year of publication | Level | Campanacci stage | Number of patients | Local recurrence | Preoperative denosumab | Postoperative denosumab | Follow-up (months) | Functional outcome | Complications |
|-----------------------------------|-------|------------------|--------------------|------------------|------------------------|------------------------|-------------------|-------------------|---------------|
| Chen, 2018 [22]                  | NR    | NR               | 10                 | 2 (20%)          | 1–11 doses             | 4–24 doses (9 patients) | NR                | NR                |               |
| Lim, 2020 [9]                    | S1 involvement: 94% | Stage 3: 100% | 17                 | 3 (18%)          | 1–4 doses              | Mean 148 doses (16 patients) | NR                | Mean UMD score increased from 23.9 preoperatively to 25.4 postoperatively. | Osteonecrosis of the jaw: 0%; Malignant transformation: 10% |
| Niu, 2019 [32]                   | NR    | Stage 3: 100%    | 6                  | 3 (50%)          | 3–12 months           | None                   | Mean 19           | NR                |               |
| Yang, 2018 [20]                  | Above S3: 100% | Stage 3: 100% | 6                  | 4 (67%)          | Mean 5.2 months       | None                   | Mean 12           | Mean MSTS 87%     | NR             |
| Zhang, 2019 [30]                | S1: 3.67%; S2: 4.33% | Stage 3: 100% | 3                  | 2 (67%)          | 6 doses                | None                   | Mean 38           | NR                | NR             |
| Zhao, 2020 [10]                 | Above S3: 24% at or below S3: 6% | Stage 2: 18%; stage 3: 82% | 19                | 6 (32%)          | 1–4 doses              | 2–30 doses (18 patients) | Median 58         | NR                | NR             |

NR, not reported; NA, not applicable; MUD, Motor function and sensation of lower limb (M) Urination and uresiethesia (U) Defecation and rectal sensation (D); RT, radiotherapy; MSTS, musculoskeletal tumor society
stable disease in 42–100% of patients [3, 15]. Embolization alone showed a response in 67–82% of the patients and led to stable disease in 5% of patients [33–37]. Bisphosphonate alone showed a response in 11% of the patients, leading to stable disease in 67% of the patients and disease progression in 22% of the patients [38] (Table 6). Our results confirm the previous data in the literature that the local recurrence rate after intralesional nerve-sparing surgery appears to be higher than the disease progression rate after non-surgical treatment.

The effects of embolization include pain relief, reduced vascularity, and peripheral ossification on radiographs [7, 39]. Typical embolization intervals have been reported to be 4–6 weeks [39, 40]. Lin et al. reported that the local recurrence rate following embolization for sacral GCTB was 31% at 10 years and 43% at 20 years [36]. Lackman et al. reported 5 cases of sacral GCTB treated with embolization alone; the tumor size remained stable in four patients (80%) after an average of 6.7 years of follow-up [35]. According to a systematic review by He et al. [14], during a mean follow-up period of 86 months, the frequency of embolization ranged from 1 to 10 times (mean, 4.1 times). All 44 patients were responsive to embolization, and the objective radiographic response rate was 82% (36/44) [14]. The local recurrence rate following embolization for sacral GCTB was 31% at 10 years and 43% at 20 years [36]. Lackman et al. reported 5 cases of sacral GCTB treated with embolization alone; the tumor size remained stable in four patients (80%) after an average of 6.7 years of follow-up [35]. According to a systematic review by He et al. [14], during a mean follow-up period of 86 months, the frequency of embolization ranged from 1 to 10 times (mean, 4.1 times). All 44 patients were responsive to embolization, and the objective radiographic response rate was 82% (36/44) [14]. The local recurrence rate following embolization for sacral GCTB was 31% at 10 years and 43% at 20 years [36]. Lackman et al. reported 5 cases of sacral GCTB treated with embolization alone; the tumor size remained stable in four patients (80%) after an average of 6.7 years of follow-up [35].

According to the results of a phase 2 study of denosumab by Tsukamoto et al. [41], the incidence of neurological complications following embolization was 14% (6/44). None of the patients experienced bowel, bladder, or sexual dysfunction due to embolization [14]. No complications were associated with bisphosphonate use alone [38] (Table 6). Contrary to our results, the literature showed that the frequency of complications associated with intralesional nerve-sparing surgery appears to be higher than that with non-surgical treatment.

Tang et al. reported that sacral tumors located in S1–2 or those larger than 200 cm³ in volume had a higher risk of massive bleeding during surgery [41]. Lim et al. reported that preoperative denosumab administration could reduce surgical time by reducing bleeding [9]. According to the results of a phase 2 study of denosumab for GCTB, during the treatment phase, the most common grade 3 or higher adverse events were hypophosphatemia (24% [5%] of 526 patients), osteonecrosis of the jaw (17% [3%], pain in extremities [12% [2%]), and anemia (11% [2%]) [42]. Four (1%) patients had atypical femur fractures, and four (1%) had hypercalcemia occurring 30 days after denosumab discontinuation [42]. There were 4 cases (1%) of malignant transformation, consistent with historical data [42].

In our study, although non-surgical treatment was more frequently performed for larger GCTBs that were centrally located in the sacrum, the Karnofsky performance status was similar in both groups (mean 87 vs. 88 in the intralesional nerve-sparing surgery and non-surgical treatment groups, respectively), and the total modified Biagini score was better in the non-surgical treatment group (mean 0.5) than in the intralesional nerve-sparing surgery group (mean 0.9). According to the literature, intralesional nerve-sparing surgery showed improvement of symptoms in 25–100%, maintenance in 13–38%, and deterioration in 8–38% of the patients [7, 16, 19, 21]. The proportion of patients who were asymptomatic at the final follow-up was 56–80% [25, 27, 28] (Table 5). In patients treated with intralesional nerve-sparing surgery following preoperative denosumab therapy, the proportion of patients who were asymptomatic at the final follow-up was 75–89% [27, 28] (Table 5). In
### Table 6  Studies reporting the result of non-surgical treatments excluding radiotherapy in sacral giant cell tumor

| First author, year of publication | Tumor level | Campanacci stage | Number of patients | Response | Follow-up (months) | Functional outcome | Complications |
|-----------------------------------|-------------|-------------------|--------------------|----------|-------------------|--------------------|---------------|
| Denosumab combined with embolization | S1–4        | Stage 3: 100%     | 1                  | Stable: 100% | 31                | Asymptomatic: 100% | None          |
|                                    | S1: 77%; S2: 15%; S3: 8% | Stage 3: 100%     | 12                 | Stable: 42%; Progression: 58% | Mean 49            | 10 patients (83%) were asymptomatic. The patient with loss of bladder control at presentation recovered. |
| Puri, 2020 [15]                   |             |                   |                    |          |                   |                    |               |
| Chuang, 1981 [33]                 | NR          | NR                | 3                  | Response: 67% | Mean 34           | 2 patients (67%) recovered from pain. Foot drop: 33%. Foot numbness: 33% | NR |
| Hosalkar, 2007 [34]               | Above S3: 0%; at or below S3: 0%; in both parts: 100% | Stage 2: 67%; stage 3: 33% | 9                  | Partial response: 78%; progression: 22% | Mean 108        | Mean MSTS 29 |
| Lackman, 2002 [35]                | NR          | NR                | 4                  | Stable: 50%; progression: 50% | Mean 80          | All the patients (100%) recovered from pain. | NR |
| Lin, 2002 [36]                    | Above S3: 50%; at or below S3: 33%; in both parts: 17% | NR                | 17                 | Partial response: 82%; progression: 18% | Median 105 | 14 patients (73%) recovered from pain and neurologic symptoms. Foot drop: 12%. Foot numbness: 6%. Malignant transformation due to RT: 12% | Foot drop: 25% |
| Nakanishi, 2013 [37]              | NR          | NR                | 4                  | Partial response: 75%; progression: 25% | Mean 78          | Mean MSTS increased from 28% preoperatively to 90% postoperatively. |               |
| Bisphosphonate                     | NR          | NR                | 9 (3 patients underwent surgery; 1 received interferon therapy, 2 received RT, 7 underwent embolization) | Partial response: 11%; stable: 67%; progression: 22% | Mean 24          | NR          | None |

NR, not reported; RT, radiotherapy; MSTS, musculoskeletal tumor society
the patients treated with the combination of denosumab therapy and embolization, the proportion of patients who were asymptomatic at the final follow-up was 83–100% [3, 15] (Table 6). In patients treated with embolization alone, the proportion of patients who were asymptomatic at the final follow-up was 67–100% [33, 35, 36] (Table 6). Thus, patients undergoing non-surgical treatment appear to have a better functional outcome than those who underwent intralesional nerve-sparing surgery, and our results confirm the data in the literature.

In this study, of the 11 women with sacral GCTB, 8 (73%) were under the age of 40 years, which is the child-bearing age. There were no patients in either the intralesional nerve-sparing surgery and non-surgical treatment groups who were pregnant or delivered a baby. Because denosumab is teratogenic, female patients need to be contraceptive during denosumab administration (non-surgical treatment) [43, 44]. It is necessary to develop a drug that has fewer side effects than denosumab, can be used in pregnant women, and has the same effect as denosumab.

Our study has several limitations. First, this was a retrospective study with indication bias. Non-surgical treatment was performed more frequently in patients with large, centrally located tumors. Second, this study has the relatively short length of follow-up, especially for the non-surgical treatment group. Third, statistical analysis was not possible because of the small sample size. A well-designed randomized controlled trial with long-term follow-up is required to determine the optimal treatment for sacral GCTB. However, randomized controlled trials on sacral GCTB are quite difficult to conduct because sacral GCTB is very uncommon. To our knowledge, this is the first comparative study of patients with sacral GCTB who underwent intralesional nerve-sparing surgery or non-surgical treatment.

Conclusions
The local recurrence rate was 44% in the intralesional nerve-sparing surgery group, and tumor control was achieved in all patients in the non-surgical treatment group. Non-surgical treatment has a similar risk of complications to intralesional nerve-sparing surgery and has better functional outcomes than intralesional nerve-sparing surgery. However, intralesional nerve-sparing surgery is the only option for achieving a disease-free condition for sacral GCTB. Non-surgical treatment seems to be a possible treatment option for GCTB of the sacrum. Based on our results, the decision on the choice of treatment for sacral GCTB could be discussed between the surgeon and patient based on the tumor size and location, considering that surgery can cure in over 50% of the patients, compared to the possibility of a non-surgical treatment that cannot achieve a disease-free status over time. In the future, it will be necessary to conduct a randomized clinical trial using a multicenter prospective collaborative study.

Abbreviations
CT: computed tomography; GCTB: giant bone tumor of the bone; MRI: magnetic resonance imaging.

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Authors’ contributions
ST designed the study, analyzed the data, and wrote the manuscript. NA designed the study and gathered the data. AFM integrated the study and revised the manuscript. KH, YT, DMD, and PS were involved in the care of the patients included in this study and integrated the study. CE was involved in the care of the patients included in this study, designed the study, gathered the data, and revised the manuscript. All authors have read and approved the final manuscript.

Availability of data and materials
The datasets generated, analyzed, or both during the present study are not publicly available because of privacy problems, but are available from the corresponding author upon reasonable request.

Declarations
Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the institutional review board of each institution.

Consent for publication
Informed consent was obtained from all individual participants in IRCCS Istituto Ortopedico Rizzoli, and the requirement for written consent from participants in Nara Medical University was waived, because an “opt-out” process was used and the study has the retrospective nature.

Competing interests
The authors declare that they have no competing interests.

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