CLINICAL ARTICLE

Recurrence of Giant Cell Tumor of the Spine after Resection: A Report of 10 Cases

Peng Lin, MD[1,2†], Nong Lin, MD[1,2†], Wangsiyuan Teng, MS[1,2], Sheng-dong Wang, MD[1,2], Wei-bo Pan, MD[1,2], Xin Huang, MD[1,2], Xiao-bo Yan, MD[1,2], Meng Liu, MD[1,2], Heng-yuan Li, MD[1,2], Bing-hao Li, PhD[1,2], Ling-ling Sun, MD[1,2], Zhan Wang, PhD[1,2], Xing-zhi Zhou, MS[1,2], Zhao-ming Ye, MD[1,2]

[1]*Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University School of Medicine and* [2]*Orthopedics Research Institute of Zhejiang University, Hangzhou, China*

Objective: To review the clinical details and further treatments for recurrent spinal giant cell tumors (SGCT), and to analyze the risk factors of recurrence and shed new light on the treatment options and prognosis of recurrent SGCT.

Methods: A retrospective analysis of recurrent SGCT between April 2003 and January 2014 was performed. A total of 10 patients comprising 3 men and 7 women with a mean age of 28.9 years (range, 21–40 years) were included in the study. All complete clinical data, radiographs, CT, MRI, scans and pathological data were reviewed. The tumor locations and the regions involved were evaluated by CT and MRI. The blood supply of the tumors was evaluated by enhanced CT and MRI. The mean follow-up was 81.3 months (range, 35.7–172.1 months).

Results: All patients had Enneking stage 3 tumors; 9 (90%) of them had different extents of spinal canal involvement in the primary time period. All patients underwent intralesional resection during their first surgery. Only 1 patient received local adjuvant treatments; no patient underwent selective arterial embolization or used denosumab at that time. Only 1 patient underwent adjuvant radiotherapy postoperatively, and another patient used bisphosphonates. After recurrence, 1 patient was cured using denosumab, and 2 patients' disease was controlled through use of other medical treatments or adjuvant treatments. There were 3 repeated recurrences and 7 repeated surgical procedures were performed in 5 patients. There were 6 intralesional excisions and 1 decompression surgery. The mean relapse-free time after the first surgery was 32.3 months (range, 10.5–62.6 months). The overall mean relapse-free time was 40.2 months (range, 10.5–157 months). No distant metastasis was found in our series. At the final follow-up, 4 patients were disease free, 3 patients' disease was under control, 2 has progressive disease aggravation, while 1 patient died as a result of progression of disease 133.9 months after first surgery.

Conclusion: Intralesional excision for recurrent spinal giant cell tumors is an effective option that may have satisfactory prognosis. However, the excision and the inactivation of the lesion should be carried out carefully and thoroughly without missing any corners. Early diagnosis of recurrence may be associated with better prognosis. Adjuvant treatments perioperatively and systemic medical treatments can decrease recurrence rates and can have therapeutic effects in the recurrent SGCT.

Key words: Giant cell tumor; Prognosis; Recurrence; Spinal giant cell tumor; Spine

Introduction

Giant cell tumor (GCT) of bone is a common benign bone tumor but has locally aggressive behavior, and it has a high rate of local recurrence[1]. It constitutes approximately 20% of all bone tumors in China[2]. GCT of the spine (SGCT) are uncommon, accounting for approximately 2%–

Address for correspondence Zhao-ming Ye, MD, Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University School of Medicine, No. 88, Jiefang Road, Hangzhou, China 310009 Tel: 0086-571-7783567; Fax: 0086-571-87783688; Email: yezhaoming@zju.edu.cn
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[†]Peng Lin and Nong Lin contributed equally to this work and are first co-authors.
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15% of all bone GCT and approximately 16.2% of all primary tumors of the spine[3–5].

The cases of SGCT reported are relatively rare, and most information comes from small case series[6–10]. Although spinal GCT have a high recurrence rate of approximately 25%–50%, surgical resection is the mainstay of management[3,11]. The management of spinal GCT is challenging, due to their adjacent critical structures, such as the spinal cord, the aorta, the vena cava, the vertebral artery, and the nerve root[12]. Radical excision of SGCT results in a lower recurrence rate and better prognosis compared with intralesional excision but is extremely difficult is and sometimes associated with considerable functional morbidity and other complications[6,12–14]. Because complete resection of these lesions remains a challenging surgical problem, many surgeons use curettage as a primary method of treatment. When treated in this way, the reported recurrence rates were extremely high[9]. Although the treatment strategy and clinical behaviors of primary SGCT have been well described in the literature, there is no unified opinion so far. Furthermore, the management of local recurrence can be more challenging, and reports on it are rare[11].

The purpose of surgery is to resect the lesions as much as possible, to relieve spinal cord compression, and to reconstruct the stability of the spine. The surgical strategy is mainly based on age, site, general condition, local stage, and possibility of the en bloc resection. The recurrent SGCT needs special attention, because it usually manifests itself as a disorder of anatomy, severe neurological deficits, and great surgical difficulties due to poor general condition. Therefore, the potential risks and benefits must be carefully evaluated during the surgical plan, and quality of life postoperatively must be carefully considered according to the patient's age and functional capacity.

Therefore, the purpose of this study was to introduce our clinical experience of treating 10 SGCT patients who had relapsed in our center, to present their clinical details and further treatments, and to gain more insight into the biology of this disease, hopefully to analyze the risk factors of recurrence and shed new light on the treatment options and prognosis for recurrent SGCT.

Materials and Methods

Patients

A retrospective analysis of recurrent GCT of the spine between April 2003 and January 2014 was performed. A total of 10 patients comprising 3 men and 7 women with a mean age of 28.9 years (range, 21–40 years) were included, with a total of 17 surgeries performed (Appendix). Mean follow-up was 81.3 months (range, 35.7–172.1 months). The study was approved by the ethics committee of the authors' institution.

Clinical Information

Diagnosis

The time to recurrence was defined as the time from the date of the last surgery till recurrence. Recurrence-free survival was defined as the time between the date of surgery and the date of recurrence. All patients who had a diagnosis of spinal GCT were confirmed by histopathological examination, and we reviewed the complete clinical data, radiographs, CT, and MRI scans. The location of the tumor in the vertebrae was assessed according to Weinstein–Boriani–Biagini classification; 7 cases were located in the anterior subarea, 2 were located in the anterior and posterior subarea, and 1 was located in the S_1–S_2 vertebral bodies[15]. The extent of invasion was evaluated by Enneking classification, which is the staging system for GCT of the extremities[16]. The neurological status was evaluated by Frankel classification preoperatively and postoperatively[17]. The recurrence of SGCT was diagnosed by clinical and radiological presentation, and part of them were further confirmed by surgery or puncture biopsy. In suspected cases where the patients did not undergo a second surgery, recurrence was diagnosed by the presence of signs indicating disease progression.

Preoperative Symptoms and Imaging Data

All patients had no obvious early symptoms at the time of tumor onset. Most of them had slight thoracolumbar pain after minor trauma or with no obvious cause, which progressively worsened. Some patients had limited thoracolumbar activity and the pain was aggravated during the activity. In 1 patient, the muscle strength of the lower extremities was grade 4 preoperatively. The remaining patients did not show lower extremity weakness, anesthesia, or leg pain. Radiological examination showed that the lesioned vertebrae had different extents of bone destruction or collapse, and 4 cases had soft tissue masses.

During the first tumor recurrence, 5 patients had no clinical symptoms, 2 patients presented with back pain, and 3 had back pain and lower extremity weakness, which were diagnosed through regular follow-up. Imaging examination showed that the residual vertebral body of the original lesion segment had different extents of bone destruction. Nine cases had soft tissue masses, one of which was large with a maximum diameter of 11 cm.

Statistical Analysis

Qualitative data were reported as percentage. Quantitative data were reported as mean and range. Kaplan–Meier survival analysis was performed to estimate the recurrence-free survival rate; the differences were compared by log-rank test. Factors with P-values <0.05 were considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Science (SPSS) software, version 22.0 (SPSS, Chicago, IL, USA).

Results

General Results

A summary of the patients is presented in the Appendix. Eight patients had one recurrence since onset, one patient had 2 episodes of recurrence, and another 1 patient had 3 episodes of recurrence. Collectively, there were 13 episodes of recurrence for the 10 patients. Two episodes of recurrence occurred within 1 year and two occurred within 2 years; the total rate of recurrence occurring within 2 years was 40%. The mean relapse-free time after the first surgery was 32.3 months (range, 10.5–62.6 months). The overall mean relapse-free time was 40.2 months (range, 10.5–-157 months). Figure 1 shows the time taken for a recurrence to develop after first surgery in 10 patients; it was expressed as a percentage of the total number of recurrences. No distant metastasis was found in our series. All patients were diagnosed with SGCT by pathological examination during the primary time period or during their recurrence; they underwent surgery or puncture biopsy, and no patient was diagnosed with aggressive or malignant SGCT (the recurrent cases without pathological examination is unknown).

Location

In the present study, 5 spinal GCT were located in the thoracic spine, 4 in the lumbar spine, and 1 in the sacrum; all tumors were Enneking stage 3. Nine (90%) of them had different extents of spinal canal involvement (see Appendix).

Soft tissue mass was found in 4 patients among the 10 during the primary time period; 1 was located in front of and lateral to the vertebral body, 1 was located lateral to the vertebral body, 1 was located in the intervertebral foramen, and 1 was located in front of the sacrum. The soft tissue mass of the sacral GCT was large, with a maximum diameter of approximately 9 cm. The remaining 3 cases had a small soft tissue mass.

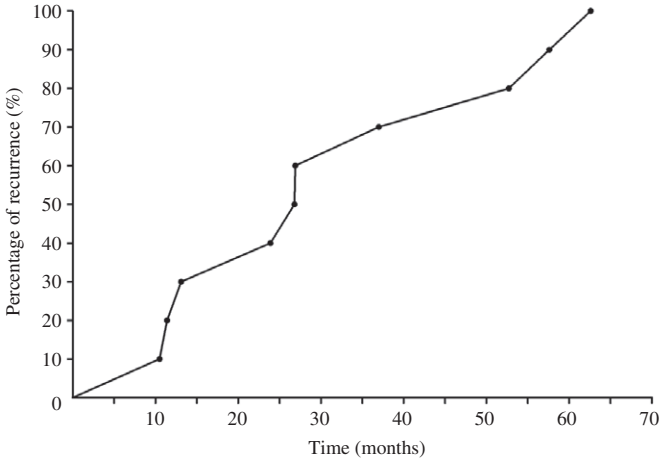

Fig. 1 This graph shows the time taken for a recurrence to develop after the first surgery in 10 patients, expressed as a percentage of the total number of recurrences.

Primary Surgery

A summary of the treatment characteristics is presented in Appendix. Four patients underwent the anterior approach during their first surgery, 5 patients underwent the posterior approach, while 1 patient underwent combined anterior/posterior approaches. All patients underwent intralesional resection during their first surgery, with all undergoing intracapsular curettage; only 1 patient underwent local electrocoagulation, and no other patient received local adjuvant treatments such as phenol, liquid nitrogen, or electrocoagulation. No patients underwent selective arterial embolization or took denosumab. Only 1 patient underwent adjuvant radiotherapy postoperatively; no other patients received adjuvant radiotherapy preoperatively or postoperatively. Only 1 patient used bisphosphonates after the first surgery. There were 2 cases (case 1, 10) reconstructed with bone cement, but only filled in the titanium cages; no other bone defects were packed with cement.

Recurrent Tumor Management

For the recurrent SGCT, 5 patients underwent 7 further surgeries (see Appendix). There was 1 anterior approach, as well as 3 posterior approaches and 3 combined approaches. The surgical strategies were 2 intralesional total spondylectomies (cases 2, 5), 4 intracapsular curettage surgeries, and 1 decompression surgery. For 1 patient (case 2), the lesion edge was inactivated with electrocoagulation, and the bone defect was packed with bone cement. The case 5 patient underwent selective arterial embolization preoperatively; the lesion edge was inactivated with electrocoagulation, and reconstructed with bone cement, which filled in the titanium cage. The other case (case 3) involved filling the bone defect with cement (Fig. 2). Three patients used bisphosphonates after the second or third surgery, while one of them also took denosumab.

In the other 5 patients without further surgeries, 1 with recurrent sacral GCT (case 9) was treated with denosumab for 1 year (14 doses). The second case (case 7) with a recurrent lumbar tumor was treated with adjuvant radiotherapy, zoledronate, and denosumab. The other 3 cases (cases 6, 8, and 10) were treated with zoledronate following the SGCT recurrence.

Follow-up and Prognosis

Among the 10 recurrent SGCT patients, 5 underwent further surgeries, 1 with a further 3 surgeries and the other 4 with 1 further surgery. A summary of the follow-up and prognosis characteristics is presented in Appendix. The first patient, with 4 surgeries (case 1), died of disease progress 133.9 months after the first surgery. The second patient (case 2) underwent intralesional total spondylectomy a second time with no recurrence of the tumor at 157 months follow-

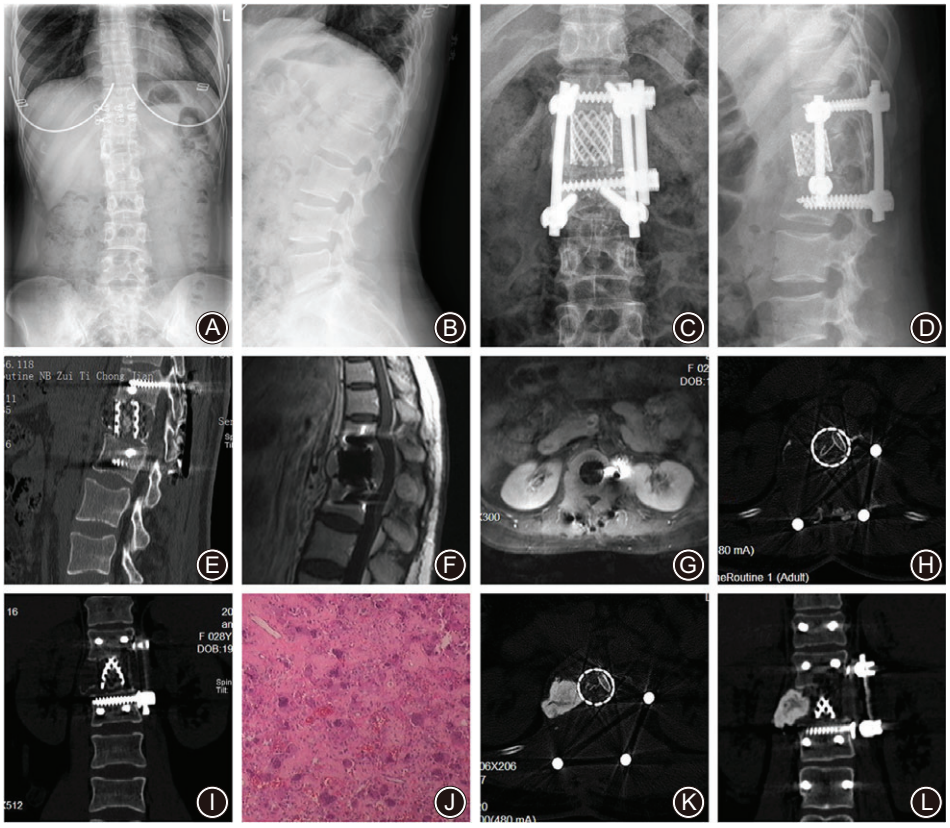

Fig. 2 Case 3, (A, B) Preoperative anteroposterior and lateral plain radiographs showing a lesion with pathological fracture at L_1. (C, D) Postoperative anteroposterior and lateral plain radiographs showing the position of the instruments. (E) Sagittal CT showing that the lesion was resected by intralesional curettage and reconstructed by titanium cage filled with bone graft. (F, G) T1-weighted sagittal and axial MR images showing a local recurrence of spinal giant cell tumors at L_1 26.8 months postoperatively. (H, I) Axial and coronal CT showing the vertebral osteolysis around titanium cage at L_1. (J) Pathological examination confirmed the recurrence of giant cell tumors. HE staining; magnification ×20. (K, L) Axial and coronal CT angiograms showing the resection of the tumo; bone cement was packed in the cavity.

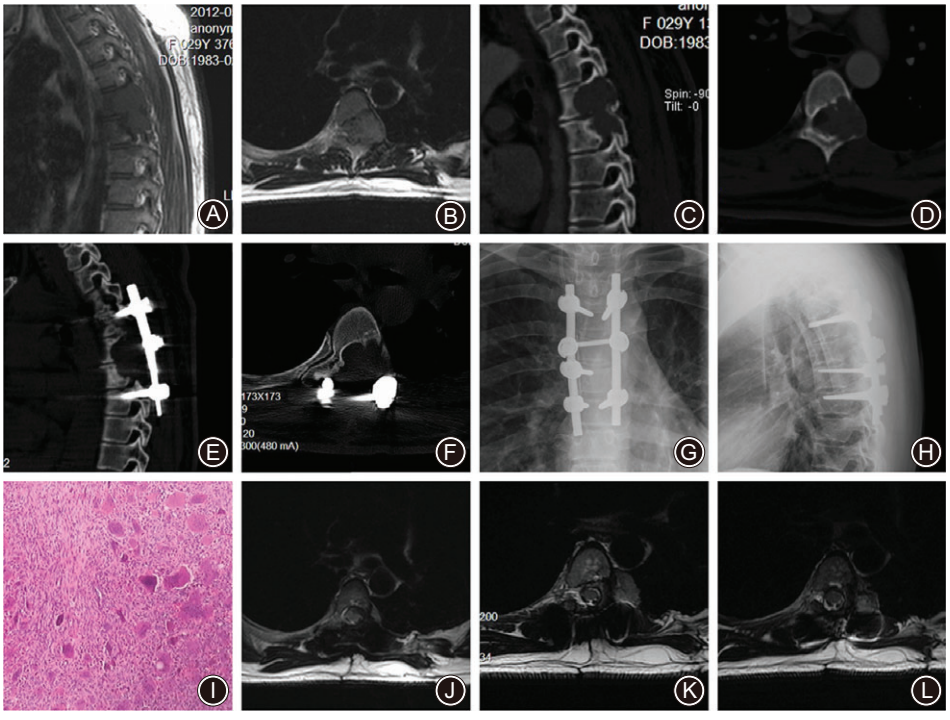

Fig. 3 Case 4, (A, B) T1-weighted sagittal and T2-weighted axial MR images showing a soft tissue mass with spinal canal involved at $T_{5–6}$ 11.4 months after the first intralesional curettage of spinal giant cell tumors. (C, D) Sagittal and axial CT showing that the left vertebral pedicles of $T_{5–6}$ were affected by the mass. (E, F) Sagittal and axial CT showing that the lesion was resected by intralesional curettage. (G, H) Postoperative anteroposterior and lateral plain radiographs showing the position of the instruments. (I) Pathological examination confirmed the recurrence of giant cell tumors. HE staining; magnification ×20. (J) T2-weighted axial MR image showing no evidence of recurrence 1 year after the repeated surgery. (K) T2-weighted axial MRI showing a moderate signal intensity of mass nearby the vertebral body of $T_{5–6}$ 38.3 months after the repeated surgery. (L) T2-weighted axial MR image showing that the mass has no further growth at 17 months follow-up.

up. The third case (case 3) underwent intracapsular curettage a second time (Fig. 2) and used bisphosphonates and denosumab postoperatively; there was no tumor recurrence at 45 months follow-up. The fourth case (case 4) had recurrent thoracic GCT for a second time 38.3 months after the second surgery (Fig. 3); he had no further disease aggravation without any treatment at 17 months follow-up. The fifth patient (case 5) underwent intralesional total spondylectomy a second time with no recurrence of the tumor at 25 months follow-up. We compared the recurrence-free survival rate among these 5 patients at first recurrence and their repeated recurrences by Kaplan–Meier analysis. No statistically significant difference was noted among them (P = 0.115, Fig. 4).

In the other 5 recurrent SGCT patients without further surgeries, 1 with recurrent sacral GCT (case 9) recovered both clinically and radiologically after treatment with denosumab for 1 year (14 doses) without reoperation at 14 months follow-up. The other recurrent lumbar tumor (case 10) was under control after treatment with zoledronate for 2 years (8 doses) following the SGCT recurrence. MRI showed that the tumor was under control and had no further growth at 30.7 months follow-up. The third case (case 7) with recurrent lumbar tumor was under control after combined treatment of adjuvant radiotherapy, zoledronate, and denosumab at 6 months follow-up. The last two cases (cases 6, 8) were alive with progressive aggravation of the diseases.

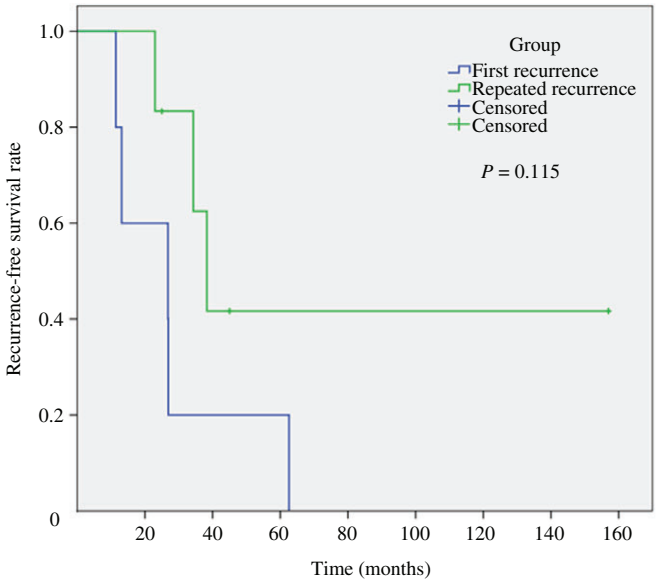

Fig. 4 Overall recurrence-free survival through Kaplan–Meier analysis for patients (case 1–5) at first recurrence and their repeated recurrences. Number of patients: 5. No statistically significant difference was noted between first and repeated recurrences (P = 0.115).

Discussion

Surgical Treatment

As demonstrated by Boriani *et al.* and Charest-Morin *et al.*, surgical margins have an important impact on local recurrence, and en bloc resection with wide/marginal margins may be associated with lower local recurrence and better prognosis[7,18]. One systematic review and meta-analysis also supported that SGCT patients treated with en bloc vertebrectomy had a lower recurrence rate[19]. Meanwhile, Boriani *et al.* point out that the choice of en bloc resection must be balanced with the inherent risks of the procedure[7].

Nevertheless, en bloc resection could not be applied in all SGCT patients. Because of the adjacent critical structures to the vertebrae, such as cervical vertebrae, or the pedicle and accessory of the vertebrae was invaded by tumor, en bloc resection could be extremely dangerous and difficult to perform in these cases. Moreover, SGCT is very soft and is easily ruptured during the operation, so it is very difficult to do en bloc resection. In our case series, 9 of 10 (90%) cases had different extents of spinal canal involvement at first, which ruled out en bloc resection. Some surgeons prefer intralesional resection, which is associated with lower functional morbidity and other complications. Xu *et al.* demonstrate that the removal of the entire osseous compartment either using en bloc or piecemeal methods is acceptable if combined with the long-term use of bisphosphonates[6]. The excision of the lesion should be done carefully and thoroughly, without missing any corners, which is the key to preventing recurrence. All patients in the present study underwent intracapsular curettage, and no patients received local adjuvant treatments; the local tumor residual may be the main cause of the recurrence. This result is similar to that reported by Charest-Morin; Patients with SGCT with intralesional resection alone are more likely to relapse[18].

Adjuvant Treatments

Because complete resection of SGCT lesions remains a challenging surgical problem, several adjuvant treatments may hold promise for decreasing the recurrence of SGCT, specifically stereotactic radiotherapy, selective arterial embolization, and inactivation of the lesion site.

Radiation Therapy

Therapeutic radiotherapy (RT) has been reported to provide a satisfactory prognosis for SGCT. RT can reduce the recurrence rate after surgery, and, furthermore, it can be used for SGCT patients not suitable for surgery[20–22]. Advances in RT technology may improve its effectiveness; however, high-level evidence for the effectiveness of these therapies is lacking, and some authors have even found that RT does not improve recurrence rates[6,23]. The risks of radiation-induced spinal cord myelitis and malignant transformation cannot be ignored[3]. Therefore, we should apply this treatment modality with caution if we have other effective approaches available. In this study, a recurrent SGCT patient who could not be

surgically treated underwent radiation therapy and took other medications; the tumor was effectively controlled.

Selective Arterial Embolization

Some published studies recommend preoperative selective arterial embolization (SAE) for SGCT; we also consider this is an effective method. Although SAE can reduce the recurrence rate of SGCT, high-level evidence for the effectiveness of this method is lacking[6,24]. Serial SAE as a stand-alone treatment for SGCT is not a highly effective approach; it is usually used in inoperable SGCT[24]. Its main role is to reduce intraoperative blood loss, especially for intralesional curettage[25]. In our practice, we performed SAE preoperatively in a recurrent SGCT of the 12th thoracic vertebral (case 5) to reduce the blood loss during the operation. This patient had no evidence of recurrence at 25 months follow-up.

Inactivation of the Lesion Site

Several local adjuvants of inactivation methods in the lesion site have been reported to decrease GCT recurrence, specifically high-speed burring, phenol, cementing, electrocoagulation, and cryotherapy[26–28].

In our clinical practice, we prefer electrocoagulation, as it is relatively simple and safe. During the procedure, we deal with the edge of the bone lesion site by applying monopolar electrocoagulation thoroughly in every corner, while using the bipolar electrocoagulation for the spinal dura mater and edge of the soft tissues. Then the surgical site was soaked with hydrogen peroxide. Meanwhile packing the bone defect with cement could also inactivate the lesion site with its thermal and toxic effect[27,28], and it is easy to find tumor recurrence on the edge. Without doubt, high-speed burring has a good effect in terms of inactivating the lesion site, which we usually use in extremities[29]. Nevertheless, it is hard to perform in spinal surgery because the surgical site is deep, and the surrounding tissues should be protected from winding. Moreover, the burring has no effect on the residual tumor in soft tissues. Special instruments are required for cryotherapy and we have no experience in applying this technique so far. The use of phenol is effective, but wound complications sometimes occurred in our early practice. It can also burn the spinal cord, so we abandoned this method.

Medical Treatment

Bisphosphonates

Bisphosphonates have bone-seeking affinity; they have been used in patients with osteoporosis, myeloma, and bone metastases to relieve pain and reduce the risk of pathologic fractures. Xu *et al.* report that bisphosphonates could significantly reduce the recurrence rate of GCT of the mobile spine[6]. Ma *et al.* demonstrate that bisphosphonate therapy could reduce the postoperative recurrence rate of the repeatedly recurrent GCT of the spine[11]. Gille *et al.* report a case of cervical GCT treated with zoledronic acid alone for 6 months (6 doses); the lesion had marked regression clinically and radiologically after 36 months follow-up[30]. We do not recommend bisphosphonates as monotherapy for primary SGCT, but this treatment can be used to reduce the recurrence rate of SGCT postoperatively and to treat recurrent SGCT that are not suitable for resection.

Denosumab

Denosumab is a human monoclonal antibody that specifically binds the receptor activator of nuclear factor kappa-B ligand (RANKL), which can inhibit osteoclast formation. It is a promising new therapy for unresectable spinal lesions[31]. Mattei *et al.* report a complete remission of GCT of the C_2 with denosumab monotherapy[32]. In our case series, a recurrent sacral GCT patient underwent denosumab treatment for 14 months; he recovered both clinically and radiologically. Doubts remain regarding its long-term effectiveness, and the potential complications. Mak *et al.* report that denosumab can eliminate the giant cells but has no effect on stromal cells, so the tumors would relapse when denosumab is stopped[33]. There is no defined endpoint reported for the use of denosumab as a stand-alone treatment in the literature.

Nevertheless, denosumab can "harden up the edges" of the SGCT, which represent the tumor calcification' it can also cause tumor shrinkage[34,35]. The calcification and shrinkage of the tumor could facilitate the subsequent surgery and reduce the surgical risk[34,36]. Thus, this could be used as a therapeutic modality for spinal GCT that cannot not be resected at initial presentation. In the present study, for the SGCT with big soft tissue mass, preoperatively 120 mg denosumab was taken subcutaneously in the 1st, 2nd and 4th week.

Recurrent Tumor Management

The treatment strategy of primary SGCT has been discussed above. En bloc resection is associated with decreased local recurrence rate and mortality[7,18,19]. The management of recurrent SGCT is relatively difficult and there is little published literature on the subject[11,37]. Management is difficult because of the scar formation and tumor range, as well as the fact that many of these patients have no opportunity to undergo total resection initially owing to the vital anatomy[3]. After all, SGCT is a benign tumor with low local invasiveness, even when recurrence occurs; we also have surgical opportunities coupled with other comprehensive therapies[3]. Patil *et al.* suggest that intralesional surgery could be a safer and more effective modality for managing recurrences of SGCT[37]. Ma *et al.* report that repeated recurrent SGCT undergoing intralesional total spondylectomy in combination with bisphosphonate therapy could achieve a good prognosis[11]. They did not stress the need to perform the en bloc resection but specify that the combined use of bisphosphonates is important.

Repeated surgical resection is still the main treatment for SGCT; early diagnosis of recurrence may be associated with better prognosis[11]. For our cases, we still choose intralesional excision for all of the recurrences. However, we were very meticulous in the removal of all parts of the tumor; the patients achieved good results and the recurrence-free

survival rate was 60%. Three patients were recurrence free and two had local recurrence after repeated resection. In one patient (case 4), who we just followed up without any treatment for 17 months, the tumor had no progress (Fig. 3). Although we considered this as a tumor recurrence through radiological examination, we have no pathology support and the presence scar tissue cannot be ruled out. The other patient (case 1) had 3 recurrences and 4 surgeries; she died due to disease progress 133.9 months after her first surgery. Boriani *et al.* report that for primary SGCT of Enneking stage 3 undergoing en bloc resection, the recurrence-free survival rate was 90%, while for tumors undergoing intralesional excision, the recurrence-free survival rate was approximately 57% [7]. Our series include recurrent SGCT; the recurrence-free survival rate was 60% after intralesional excision, which is similar to the results of Boriani *et al.* Some of the patients in our series have taken bone modifying agents, such as denosumab or bisphosphonates, which have been proven to decrease the recurrence rate of SGCT. Our recurrence-free survival rate may be overestimated for intralesional excision.

Repeated surgical resection for recurrent SGCT in the early stages is an effective option; meanwhile, adjuvant treatments and systemic medical treatment are also important. Adjuvant treatments of inactivation of the lesion edge by electrocoagulation and cementing during the procedure have been discussed above. Medical treatment with denosumab and bisphosphonates also holds promise as an adjuvant therapy or stand-alone therapy for recurrent SGCT. Some of the recurrent cases in our group received a good therapeutic effect with only medical treatments.

In general, spinal GCT should be approached as a case-by-case problem, as each case presents unique challenges. Multidisciplinary collaboration is the best practice for treating these difficult tumors[3].

Limitations

Our study has some limitations. First, the sample size of the study is small, which may decrease the power of the statistics. Second, we only retrospectively reviewed the cases of recurrence; there was no control group, which may reduce the level of evidence.

Conclusions

Intralesional excision for recurrent SGCT is an effective option which may offer a satisfactory prognosis. However, the excision and the inactivation of the lesion should be undertaken carefully and thoroughly without missing any corners. Early diagnosis of recurrence may be associated with better prognosis. Adjuvant treatments perioperatively and systemic medical treatments can decrease the recurrence rate; they also have therapeutic effects for recurrent SGCT.

Appendix

Additional appendix may be found in the online version of this article on the publisher's web-site:

Appendix Clinical data for a series of 10 SGCT cases (not including the adjuvant therapy information of RT, SAE, denosumab, and BIS usage after local recurrence.

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