Recurrence Factors in Giant Cell Tumors of the Spine

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Abstract

Background: Giant cell tumors (GCTs) are benign, locally aggressive tumors. We examined the rate of local recurrence of spinal GCTs and sought to identify recurrence factors in patients who underwent surgery.

Methods: Between 1995 and 2014, 94 mobile spine GCT patients were treated at our hospital, comprising 43 male and 51 female patients with an average age of 33.4 years. Piecemeal intralesional spondylectomy and total *en bloc* spondylectomy (TES) were performed. Radiotherapy was suggested for recurrent or residual GCT cases. Since denosumab was not available before 2014 in our country, only interferon and/or zoledronic acid was suggested.

Results: Of the 94 patients, four underwent conservative treatment and 90 underwent operations. Seventy-five patients (79.8%) were followed up for a minimum of 24 months or until death. The median follow-up duration was 75.3 months. The overall recurrence rate was 37.3%. Ten patients (13.3%) died before the last follow-up (median: 18.5 months). Two patients (2.6%) developed osteogenic sarcoma. The local recurrence rate was 80.0% (24/30) in patients who underwent intralesional curettage, 8.8% (3/34) in patients who underwent extracapsular piecemeal spondylectomy, and 0 (0/9) in patients who underwent TES. The risk factors for local recurrence were lesions located in the cervical spine ($P = 0.049$), intralesional curettage ($P < 0.001$), repeated surgeries ($P = 0.014$), and malignancy ($P < 0.001$). Malignant transformation was a significant risk factor for death ($P < 0.001$).

Conclusions: Cervical spinal tumors, curettage, and nonintact tumors were risk factors for local recurrence. Intralesional curettage and malignancy were the most important significant factors for local recurrence and death, respectively.

Key words: Extracapsular Spondylectomy; Giant Cell Tumors; Intralesional Curettage Spine; Recurrence; Total *En bloc* Spondylectomy

INTRODUCTION

Giant cell tumors (GCTs) account for 4–8% of all primary bone tumors. They are most commonly found in the juxta-articular metaphysis of long bones.[1] The incidence of spinal involvement above the sacrum ranges from 1.4% to 9.4%.[2-4] Although GCTs are benign, they can be locally aggressive. Spinal GCTs have a considerably poorer prognosis than those in the extremities, with recurrence rates of up to 70%.[5] GCTs are known to metastasize or undergo malignant transformation with an incidence of 2–3%.[6,7]

The National Comprehensive Cancer Network recommendation is surgery for resectable GCTs and serial arterial embolization with denosumab, interferon, and/or radiation therapy for unresectable GCTs.[8,9] For GCTs in the extremities, the surgical choice includes excision and intralesional curettage, while *en bloc* spondylectomy is the first choice for spinal GCTs before the application of denosumab. Fidler reported nine cases of GCTs successfully treated with *en bloc* resection.[10] Boriani *et al*. reported a retrospective

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review of 49 GCT cases of the mobile spine treated surgically, 11 (22%) of which involved local recurrences. They concluded that *en bloc* resection should be considered for Enneking stage 3 GCTs of the mobile spine.[11] The treatment principle has been revised with the advance of denosumab, which was not available in our country before 2014.

We were specifically interested in identifying the rate of local recurrence and elucidating factors associated with local recurrence in patients who underwent surgery for GCTs of the mobile spine between 1995 and 2014. This retrospective study was approved by the ethics committee of our university hospital. For this type of study, formal consent was not required.

METHODS

Ethical approval

The requirement for written informed consent of the patients was waived by the Ethics Committee because of the retrospective nature of the study.

Patients

Between 1995 and 2014, 94 consecutive mobile spine GCT cases were treated at our hospital (43 male and 51 female patients). The average age at diagnosis was 33.4 years (range: 11–69 years). All medical charts were reviewed, including the hospital charts, surgical reports, office charts, radiology reports, and pathology reports. We focused on factors that might be associated with local tumor recurrence, including patient age, sex, tumor boundary, Enneking stage, and treatment (surgery, radiotherapy, and/or chemotherapy). Radiographs, computed tomography (CT) scans, and magnetic resonance images of the spinal lesions were available for all cases. The cases were reviewed using the staging systems described by Enneking[12] and Weinstein-Boriani-Biagini (WBB).[13] The visual analog scale/score (VAS), Karnofsky scores, Frankel scale rating, and Eastern Cooperative Oncology Group (ECOG) score were documented to assess the quality of life.

Surgery

The surgical strategy was based on the WBB and Enneking classifications, the lesion's location, and the patient's condition, as well as the preference of the patient and his/her family after thorough consultation with the surgeons [Figure 1]. Single (anterior or posterior), combined, or staged approaches were selected for each patient.[14-16] We performed piecemeal intralesional spondylectomy with a combined anterior and posterior approach prior to 2008. Since 2008, we have performed total *en bloc* spondylectomy (TES) according to Tomita's technique.[17,18] With a better understanding of the principles of oncologic management, a new treatment algorithm for GCTs has been developed and applied in our practice [Figure 1]. Usually, tumors located in the thoracolumbar spine (T2 to L3) with little paravertebral mass can be removed through a solely posterior approach. In cases with a large paravertebral mass, an anterior or lateral approach should be performed first to free the lesion from the surrounding structures. A combined posterior and anterior approach is indicated for the cervical and cervicothoracic spine (C2 to T2), and a combined posterior and anterior/lateral approach is indicated for the lower lumbar spine (L4 to L5).

In the cervical spine, we tried to preserve the vertebral artery (VA) where possible. After exposure of the cervical facet and transverse process through the surrounding muscle, the posterior bony structures (especially the posterior transverse processes and pedicles) were removed by a piecemeal technique to free the VA and nerve root. In the subsequent anterior approach, the vertebral body was removed *en bloc*. If contamination was suspected, postoperative radiosurgery was indicated.[19]

Radiation therapy

Radiotherapy was suggested for recurrent or residual GCTs [Figure 2]. After CT simulation, CT images were fused with magnetic resonance imaging (MRI) or positron emission tomography-CT images to contour the gross tumor volume and the organs.[20,21] Prior to 2012, we administered conventional radiotherapy (CRT) at doses ranging from 40 to 50 Gy across 20 to 25 fractions. Since 2012, we have employed intensity-modulated radiation therapy (IMRT) or intensity-modulated arc therapy (IMAT), with doses to the tumor ranging from 60 to 65 Gy across 22–25 fractions, and doses to the normal surrounding tissue with the clinical target volume, ranging from 40 to 50 Gy across 22–25 fractions.[22] Since denosumab was not available before 2014 in our country, only interferon and/or zoledronic acid was suggested or recurrent or residual GCTs.

Follow-up

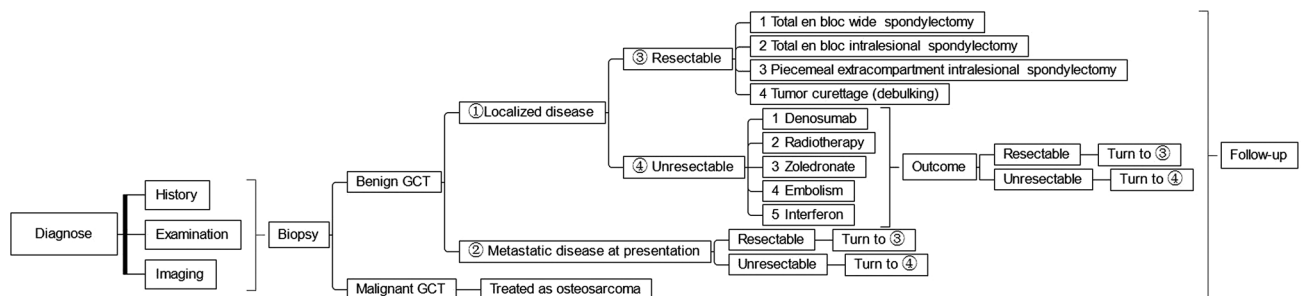We obtained radiographs and CT and MRI scans every

Figure 1: Flow chart for the diagnosis and treatment of giant cell tumor in the mobile spine. 1 = maximum priority, 5 = minimum priority. GCT: Giant cell tumor.

3 months in the first 2 years postoperatively, every 6 months for the following 3 years, and annually thereafter [Figure 3]. If the patient displayed symptoms indicative of tumor recurrence, immediate CT and MRI scans were requested. If recurrence could be neither confirmed nor rejected, biopsy under CT guidance was suggested.

Statistical analysis

We used SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) for statistical analyses. Local relapse-free survival was calculated using Kaplan-Meier method and Cox regression analysis.[23] Both univariate and multivariate analyses were performed to identify factors influencing recurrence and death. The log-rank test was used for comparison. If all cases were censored, we utilized Fisher's exact test to identify an association. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 94 patients, four received conservative treatment (radiotherapy or medicine alone) and 90 underwent a total of 129 operations, including 77 intralesional curettages and 52 extracapsular spondylectomies. Of the 52 spondylectomies, 39 were intralesional extracapsular excisions and 13 were *en bloc* excisions. There were 38 perioperative complications, including neurological function deterioration, 16 (all patients

recovered with conservative treatment); superficial infection, seven (treated by conservative treatment); pleural effusion, five; dural tear, five; deep venous thrombosis, three; pulmonary embolism, one; and pneumonia, one.

Seventy-five patients (79.8%; 36 males, 39 females) were followed up for a minimum of 24 months or until death. Median follow-up was 75.3 months (range: 1–188 months). All 75 patients had Enneking stage 3 (S3) tumors; 32 tumors were located in the cervical spine, 28 in the thoracic spine, and 15 in the lumbar spine [Figure 4]. Sixty-four tumors were intact and 11 were nonintact (these patients were initially treated elsewhere and referred to our department after recurrence).

The overall recurrence rate was 37.3% (28/75). Before the last follow-up, ten patients (13.3%) had died, with a median survival of 18.5 months (range: 1–101 months). Twenty patients (26.7%) were alive with a tumor at a median follow-up of 78.5 months (range: 25–181 months). Forty-five patients (60.0%) were disease free at a median follow-up of 86.5 months (range: 24–188 months). The longest time to recurrence was 188 months after surgery. Six patients (8.0%) developed distant metastases or multiple tumors. Two patients (2.6%) developed osteogenic sarcoma (Enneking stage IB) after repeated surgeries. Sixteen patients had instrument failure (rod breakage and/or screw loosening).

Surgery

Of the 75 patients in follow-up, 73 underwent surgeries. Intralesional curettage was performed in 30 patients. Forty-three patients underwent spondylectomy, including 34 extracapsular intralesional piecemeal excisions and nine total *en bloc* spondylectomies (five intralesional and four nonintralesional excisions) [Figure 5].

Radiation therapy

Of 75 patients, 37 received radiotherapy with surgery [Figure 6]. Thirty patients received CRT before 2012. After 2012, seven patients received IMRT/IMAT. Fifteen patients developed local recurrences with a median disease-free survival of 93.5 months (range: 3–214 months), including 12 receiving CRT and three receiving IMRT/IMAT. The local control rates of CRT and IMRT/IMAT were 60% and 58%, respectively.
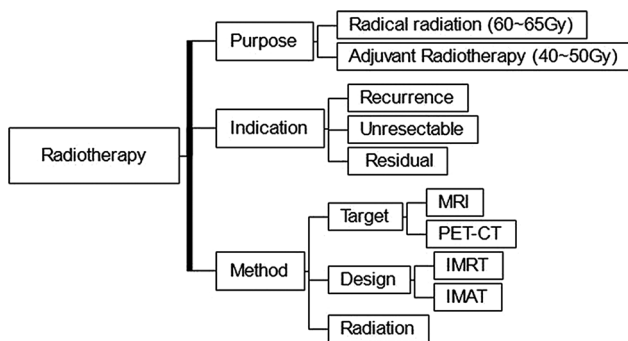
Figure 2: Flow chart for radiotherapy of giant cell tumors in the mobile spine. MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computed tomography; IMRT: Intensity-modulated radiation therapy; IMAT: Intensity-modulated arc therapy.
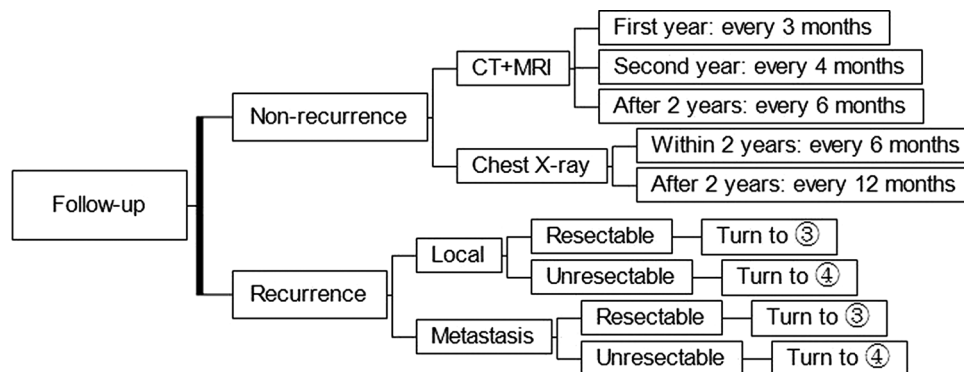
Figure 3: Flow chart for the follow-up protocol for giant cell tumors in the mobile spine (③ and ④ refer to Figure 1). CT: Computed tomography; MRI: Magnetic resonance imaging.

Quality of life

The preoperative average VAS and ECOG scores were 5.8 and 1.8, respectively, and they decreased to 2.1 and 0.9, respectively, at the 3-month follow-up ($P < 0.01$). Similarly, the 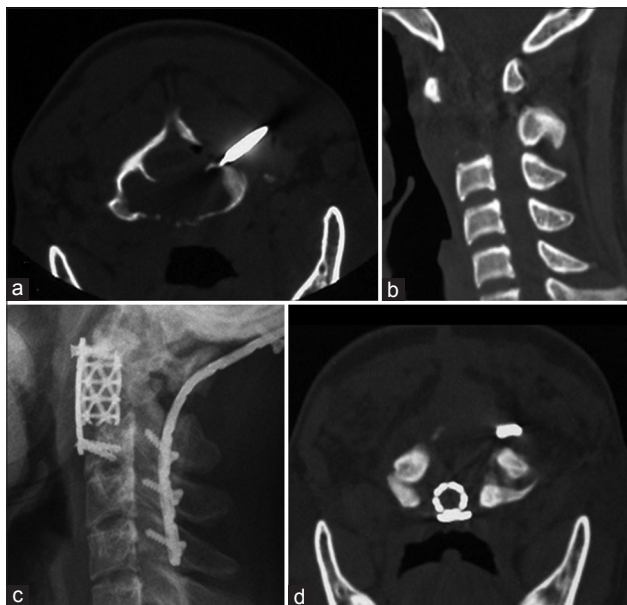preoperative average Karnofsky score was 65.4, which increased to 84.2 at the 3-month follow-up ($P < 0.01$). The average Frankel scale rating also improved postoperatively ($P < 0.01$).

Risk factors for recurrence and death

Age and sex

The average patient age was 32.9 years (range: 11–69 years). Thirty-six patients were male and 39 were female. After the univariate analysis, age and sex were not significant risk factors for recurrence or death ($P = 0.075$ and 0.713, respectively).

Tumor distribution in the spine

The local recurrence rates for tumors in the cervical, thoracic, and lumbar spine were 50% (16/32), 32.1% (9/28), and 20.0% (3/15), respectively. Fifty-three patients had GCT lesions in one vertebra, 12 in two adjacent vertebrae, and ten had involvement in three or more adjacent vertebrae. Sixty patients had lesions in the vertebral body and 15 had lesions in the vertebral appendices ($P = 0.144$). Lesions located in the cervical spine were a risk factor for local recurrence ($P = 0.049$).

Surgical treatment

Of the 73 patients who underwent surgery, 27 (37.0%) had local recurrence with a median 76.4-month follow-up period (range: 24–181 months). The median interval of relapse was 35.6 months (range: 3–175 months). The local recurrence rate was 80.0% (24/30) in patients who underwent intralesional curettage, with a median follow-up period of 79.2 months (range: 3–181 months). The local recurrence rate was 8.8% (3/34) in patients who underwent extracapsular
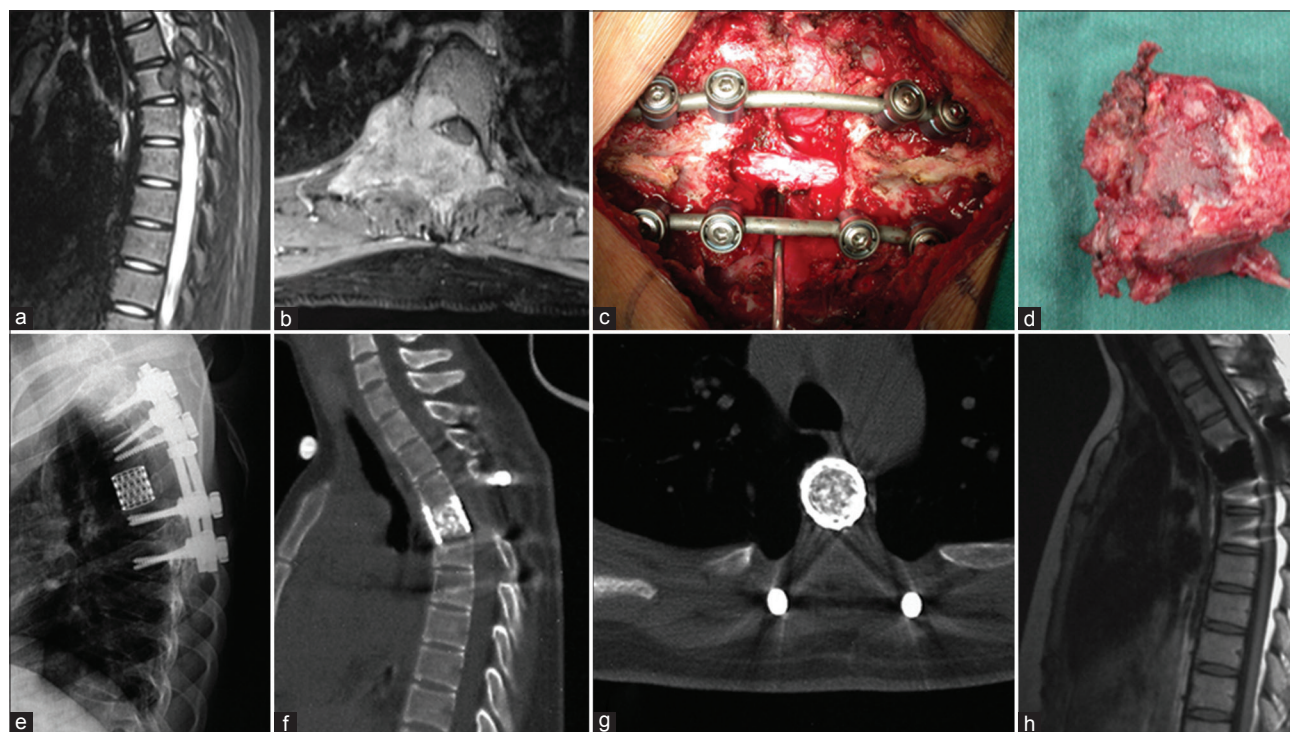

Figure 4: A 20-year-old male presented with a C2 giant cell tumor, treated through intralesional curettage in 2008. (a) CT-guided percutaneous biopsy. (b) Preoperative CT scan. (c and d) Lateral radiograph and axial CT image showing local recurrence at the 3-year follow-up, respectively. CT: Computed tomography.

Figure 5: A 17-year-old female presented with a T4 giant cell tumor, which was removed through intralesional total *en bloc* spondylectomy using Tomita technique. (a and b) Preoperative sagittal and axial magnetic resonance images, respectively. (c and d) Intraoperative photographs of the surgical field and specimen, respectively. (e-h) Lateral radiograph, sagittal/axial computer tomography scan, and sagittal magnetic resonance image, respectively, at the 7-year follow-up, showing no local recurrence.
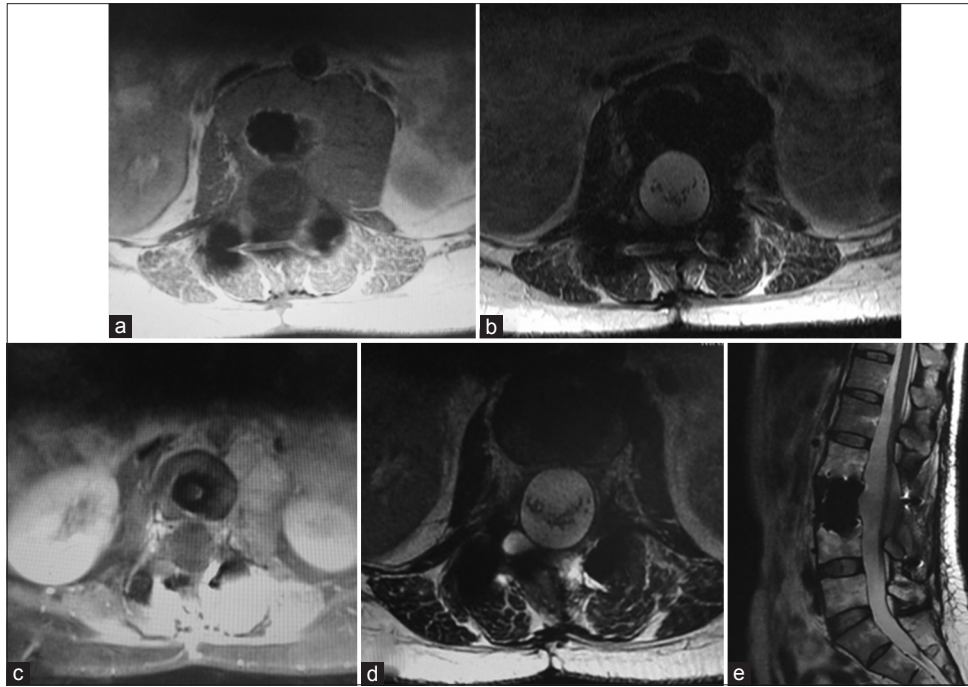
Figure 6: A 35-year-old female underwent intensity-modulated arc therapy (60 Gy/2.7 Gy/22 fractions) for an L3 giant cell tumor after recurrence. She underwent intralesional curettage with local recurrence. (a-c) Axial magnetic resonance image (T1, T2, and T2 with contrast, respectively) after local recurrence showing bilateral paravertebral masses. (d and e) Axial and sagittal magnetic resonance image at the 36-month follow-up, respectively.

piecemeal spondylectomy, with a median follow-up of 83.5 months (range: 1–169 months). No local recurrence was observed in nine patients who underwent TES, with a median follow-up of 44.9 months (range: 24–85 months). Forty-three patients had a survival time longer than 5 years, of whom 24 had a relapse-free survival. The cumulative relapse-free survival rate at 5 years was 66.3%. Curettage was a risk factor for both local recurrence and death ($P < 0.001$ and $P = 0.015$, respectively).

Primary treatment

Eleven patients underwent operations at other hospitals before presenting at our hospital with nonintact tumors that we diagnosed as recurrent GCTs; eight (72.7%) had further recurrences. Of 64 patients who presented at our hospital with intact GCTs, 20 (31.3%) had local recurrences. According to the univariate analysis, nonintact tumors were a significant risk factor for death ($P = 0.014$).

Metastasis and malignancy

Six of the 75 patients (8%) developed distant or multiple metastases and one died. The average survival time for patients with a metastatic tumor was 80.7 months. Metastasis was not a significant risk factor for death ($P = 0.146$). Lesions from two patients underwent malignant transformation (from Enneking S3 to IB), and the intervals between malignancy and patient death were 2 and 5 months. According to the univariate analysis, malignant transformation was a significant risk factor for death ($P < 0.001$).

Multivariate analyses

On univariate analysis, we found that cervical spinal tumors, curettage, and nonintact tumors were risk factors for local recurrence. Similarly, curettage, nonintact tumors, and malignancy were risk factors for death. After multivariate and Cox regression analyses, we found that curettage and malignancy were the most important significant factors for local recurrence and death, respectively ($P < 0.001$).

DISCUSSION

The incidence of GCTs is reportedly higher in East Asia (China and Japan) than in Europe and America.[24] Boriani *et al*.[11] reported that the overall recurrence rate for GCTs was 22% (11/49), and most of these cases were thoracolumbar spine GCTs. Yin *et al*.[25] reported on 71 GCTs of the spine and sacrum, with a recurrence rate of 33.8%. In our single-center, retrospective study of spinal GCTs over 21 years, the recurrence, metastasis, malignancy, and mortality rates were 36.2%, 10.0%, 2.5%, and 15.0%, respectively, with a median follow-up of 72.1 months (range: 1–188 months).

Surgery

En bloc spondylectomy reduced local recurrence in Enneking S3 GCTs. In the study, the local recurrence rates for patients who underwent intralesional curettage, extracapsular piecemeal spondylectomy, and TES were 81.3% (26/32), 8.6% (3/35), and 0% (0/9), respectively. In Boriani *et al*.'s[11] study, the recurrence rates for *en bloc* and intralesional resection were 7.7% (1/13) and 47% (8/17), respectively. Yin *et al*. reported similar results [Table 1].[25]

GCTs in the extremities have been successfully treated through extensive intralesional curettage with a high-speed burr and additional adjuvants to preserve the joint adjacent to

Table 1: Giant cell tumor recurrence rate across different studies

Study	Tumor location	Number of patients	Median follow-up (months)	Overall recurrence rate, % (*n/N*)	Surgery, % (*n/N*)			Radiation, % (*n/N*)	Systemic treatment, % (*n/N*)
					En bloc	Extracapsular piecemeal spondylectomy	Curettage		
Martin and McCarthy 2010[5]	Spine	23	42.5	26.1 (6/23)	15.4 (2/13)	NA	50 (4/8)	NA	NA
Boriani *et al.* 2012[11]	Mobile spine	49	145	22.4 (11/49)	7.7 (1/13)	NA	47 (8/17)	35 (6/17)	NA
Yin 2015[25]	Spine and sacrum	71	73.9	33.8 (24/71)	7.7 (1/13)	14.8 (4/27)	61.3 (19/31)	30.0 (12/40)	13.3 (4/30)
Current study	Mobile spine	75	75.3	37.3 (28/75)	0 (0/9)	8.8 (3/34)	80.0 (24/30)	40.5 (15/37)	NA

NA: Not applicable.

the tumor.[8,26,27] Local recurrence of GCTs in the extremities might be treated successfully with extensive curettage. Intact or recurrent tumors with extensive bone destruction, large soft tissue mass, or without the possibility to save the adjacent joint are treated preferentially with a wide resection. However, the removal of local spinal recurrences with wide margins might lead to catastrophic complications such as massive bleeding and neurological deficits. Therefore, *en bloc* spondylectomy is recommended for intact S3 GCTs.

Radiation therapy

Radiation therapy has been used alone or as adjuvant therapy for GCTs. Local control rates with radiation have been reported to be as high as 77%.[28] In the study, the local control rates for CRT and IMRT/IMAT were 61% and 67%, respectively. Bhatia *et al.* reported on 58 patients from nine participating North American and European institutions who received radiotherapy for marginally resected, unresectable, and recurrent GCTs.[22] The median radiation dose was 50 Gy in a median of 25 fractions. The 5-year local control and overall survival rates were 85% and 94%, respectively, and none of the patients experienced grade 3 or higher acute toxicity. Radiotherapy was correlated with a higher disease-free survival rate, distant metastasis-free survival rate, and local control rate at 5 years.[29] The risk of postirradiation sarcoma is a particular concern in patients with GCTs. The median latency period is 10 years or more, which means that the follow-up period after radiation must be sufficiently long.[30]

Study limitations

One of the main limitations of this retrospective study was the relatively low methodological quality. It was susceptible to selection bias, which would reduce its validity and cogency.[31] Another limitation was a lack of homogeneity in the assessment of outcome evaluation; the time span from 1995 to 2014 is very long, the treatments were not uniform, and the interference factors were complex. Moreover, the application of denosumab in GCT has fundamentally changed its treatment protocol. Therefore, high-quality, randomized controlled trials with more comprehensive therapeutic strategies are required to further resolve these issues and establish long-term outcomes.

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