



Total spondylectomy for Enneking stage III giant cell tumor of the mobile spine

Noriaki Yokogawa¹ · Hideki Murakami¹ · Satoru Demura¹ · Satoshi Kato¹ · Katsuhito Yoshioka¹ · Takaki Shimizu¹ · Norihiro Oku¹ · Ryo Kitagawa¹ · Hiroyuki Tsuchiya¹

Received: 8 February 2018 / Accepted: 5 September 2018 / Published online: 12 September 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

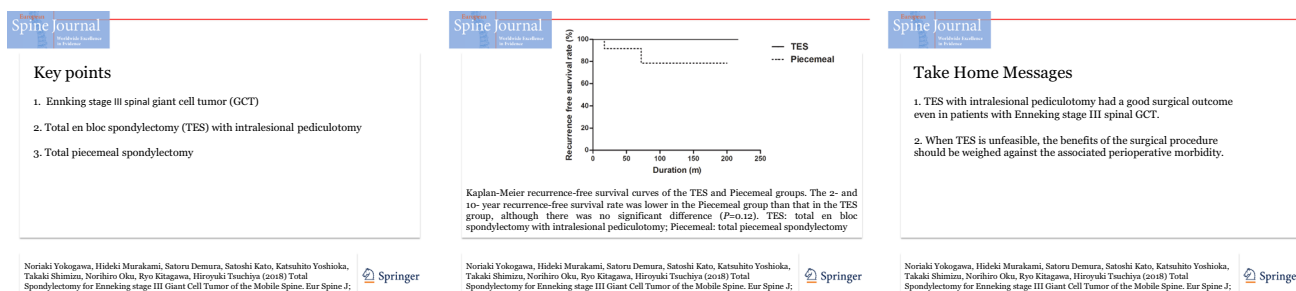
Purpose We reported the surgical outcomes of total en bloc spondylectomy (TES) with intralesional T-saw transpedicular osteotomy in patients with Enneking stage III spinal giant cell tumors (GCTs).

Methods The medical records and imaging and pathological studies of 25 consecutive patients with Enneking stage III spinal GCTs undergoing surgery at our institution who were followed for at least 2 years were retrospectively reviewed.

Results Eight men and 17 women (mean age: 34.2 years, range 16–51 years, at the time of surgery) were included. Six patients underwent previous tumor excision at another hospital, and one patient had a history of denosumab treatment. The GCTs were at the cervical, thoracic, and lumbar levels in three, nine, and 13 patients, respectively. TES was performed in 13 patients; 12 required intralesional pediculotomy. The remaining patients underwent total piecemeal spondylectomy with further intralesional tumor resection. During a mean follow-up of 99.2 months (range 24–216), two patients who underwent total piecemeal spondylectomy had local tumor recurrence, but no patients who underwent TES with intralesional pediculotomy had recurrence. The 2- and 10-year recurrence-free survival rates of patients treated with total piecemeal spondylectomy were 91.7% and 78.6%, respectively, while those of patients treated with TES were both 100%.

Conclusions TES with intralesional pediculotomy had a good surgical outcome even in patients with Enneking stage III spinal GCT, suggesting that minimal intralesional procedures could radically cure spinal GCTs.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.



Keywords Giant cell tumor · Mobile spine · Total en bloc spondylectomy · Total piecemeal spondylectomy · Tumor resection

Introduction

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00586-018-5761-3>) contains supplementary material, which is available to authorized users.

A giant cell tumor (GCT) is a benign primary bone tumor that occurs in the mobile spine in only 1.9–9.4% of patients [1]. Because GCTs may be locally aggressive,

Extended author information available on the last page of the article

curettage-based surgery can lead to a high rate of local recurrence [2]. Combined adjuvant therapy (e.g., phenol, cryotherapy, and burr drilling) has been reported to reduce the rate of local recurrence in the extremities [3]. However, in the spine, these adjuvant therapies increase the risk of perioperative morbidity because of the major blood vessels and spinal cord. Therefore, complete en bloc excision of spinal GCTs is generally agreed to be the gold standard treatment, particularly for better local control of Enneking stage III tumors [1, 4]. However, complete en bloc resection for Enneking stage III tumors is often challenging [5]. In our institution, we typically perform total en bloc spondylectomy (TES) with T-saw pediculotomy according to the protocol of Tomita et al. [6], which allows the posterior elements of the spine to be removed en bloc and facilitates dissection of the spinal cord and nerve roots (Fig. 1). Although T-saw pediculotomy often involves an intralesional procedure, we believe that TES that includes the margin of the tumor would achieve curative resection of Enneking stage III tumors.

The risk of local recurrence after intralesional tumor excision for Enneking stage III spinal GCT is considered to be very high; however, the intralesional procedure level associated with recurrence is still unclear. The purpose of this study was to evaluate the surgical outcomes of TES with intralesional pediculotomy in patients with Enneking stage III GCT and to compare the outcomes with those in patients who underwent total piecemeal spondylectomy.

Materials and methods

This study was approved by the ethics committee of our institution. Written informed consent to undergo surgery and be included in the study was obtained from all patients. In the case of a minor, the informed consent process invariably involved the minor's parent.

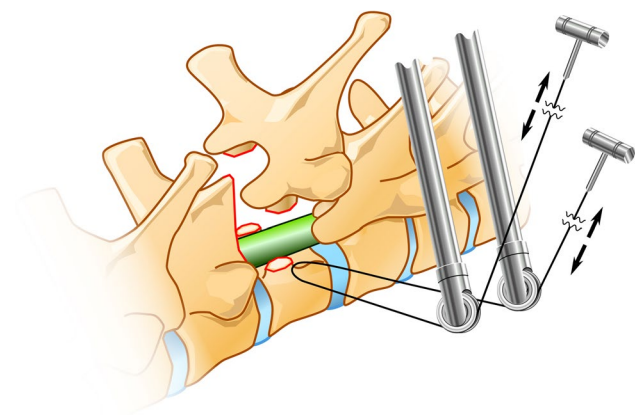


Fig. 1 Operative schema for pediculotomy using a T-saw during total spondylectomy

We examined the data of 25 consecutive patients with Enneking stage III spinal GCTs who were treated surgically at our institution between May 1994 and April 2015. Surgical decision making was based on the patients' overall medical and neurological conditions, with the aim of removing GCTs of the spine as completely as possible. Although TES was considered the first-line therapy, total piecemeal spondylectomy was performed if TES was not anatomically feasible (e.g., in patients with cervical spine tumors) and/or if the patient had undergone prior surgery. Data from physical examinations, imaging studies, medical records, and pathological studies were reviewed retrospectively. To detect local tumor recurrence, we examined all patients using computed tomography every 6 months for the first 24 months after surgery and then annually for life. Then, contrast-enhanced magnetic resonance imaging was performed when local recurrence was suspected.

A univariate analysis was performed using Mann–Whitney's *U* tests for continuous variables and Pearson's Chi-square or Fisher's exact tests for categorical variables. Survival curves were estimated using the Kaplan–Meier technique with respective 95% confidence intervals, and they were compared using the log-rank test. Statistical significance was set at a *P* value < 0.05. SPSS statistical software version 19 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses.

Results

Table 1 shows the clinical results of all of the patients in this study. The study population included eight men and 17 women with spinal GCTs who underwent surgical resection at our institution. The patients' mean age at the time of surgery was 34 years (range 16–51 years). Six of the 25 patients had initially undergone tumor excision surgery at another hospital. Among them, two patients were treated with adjuvant bisphosphonate, one patient had a history of adjuvant denosumab treatment, and one patient had a history of adjuvant radiotherapy. All patients had a histological diagnosis of GCT. The GCTs were located at the cervical level in three patients, at the thoracic level in nine, and at the lumbar level in 13. All patients had Enneking stage III (aggressive) tumors with soft tissue masses and indistinct borders [7, 8], and the surgical classification of spinal tumors (SCST) according to the system of Tomita et al. [9] was type 4 (spinal canal extension) in four patients, type 5 (paravertebral extension) in nine, and type 6 (adjacent vertebral extension) in 12. TES was performed in 13 patients; 12 of them required intralesional pediculotomy. The other 12 patients underwent total piecemeal spondylectomy (Fig. 2). The diagnosis of GCT was confirmed via a pathological examination in all cases, and

Table 1 Clinical data of a series of 25 cases

No.	Age (y)	Sex	Tumor location	SCST	Prior treatment	Initial FS	Surgical procedure	Complications	F/U (mo)	Final	Local recurrence	Mets	Final status
1	36	M	L2	5	None	E	TES with IL pediculotomy	None	216	E	No	No	NED
2	42	F	T11	5	P. decompression & instrumentation	E	Total piecemeal spondylectomy	None	200	E	No	No	NED
3	40	M	L5	4	None	D	TES with IL pediculotomy	Surgical site infection, rod breakage	154	D	No	No	NED
4	38	F	L3	4	None	E	TES with IL pediculotomy	None	215	E	No	No	NED
5	36	M	T12	6	None	E	Total piecemeal spondylectomy	Pseudoarthrosis	161	E	Yes, 12 months after last surgery	No	NED
6	24	F	L4	5	None	E	TES with IL pediculotomy	Lower-extremity muscle weakness	141	E	No	No	NED
7	33	F	T2	6	A. curettage & bone graft, Radiotherapy	D	Total piecemeal spondylectomy	Pleural effusion, CSF leakage	65	D	No	No	NED
8	16	F	C3-5	6	A/P curettage & instrumentation, bisphosphonate	D	Total piecemeal spondylectomy	Upper-extremity muscle weakness, esophageal fistula	100	E	No	No	NED
9	42	M	T1,2,3	6	None	C	Total piecemeal spondylectomy	Upper-extremity motor dysfunction	109	E	No	No	NED
10	33	F	C7-T2	6	Total spondylectomy, bisphosphonate	E	Total piecemeal spondylectomy	Upper-extremity motor dysfunction, intracranial hypotension syndrome	96	D	No	No	NED
11	37	F	L3-5	6	None	E	Marginal TES	Lower-extremity muscle weakness, rod breakage	38	D	No	No	NED
12	32	F	L3-5	6	None	D	TES with IL pediculotomy	Lower-extremity muscle weakness, rod fracture	102	E	No	No	NED
13	32	F	L1	5	None	E	TES with IL pediculotomy	None	91	E	No	No	NED
14	39	M	L4	5	None	B	Emergent p. decompression/total piecemeal spondylectomy	Deep venous embolism, surgical site infection	82	D	No	No	NED
15	38	F	L2	5	None	E	TES with IL pediculotomy	None	77	E	No	No	NED
16	36	F	L3-5	6	A/P curettage & instrumentation	E	Total piecemeal spondylectomy	Lower-extremity muscle weakness, surgical site infection, rod breakage	79	D	Yes, 72 months after last surgery	No	AWD
17	20	F	C5-7	6	Transarterial embolism	D	Total piecemeal spondylectomy	Upper-extremity muscle weakness	25	D	No	No	NED
18	49	F	L4-5	6	Three-time curettage & P. instrumentation	D	Total piecemeal spondylectomy	Surgical site infection, CSF leakage, rod breakage, lower-extremity muscle weakness,	66	D	No	No	NED

Table 1 (continued)

No.	Age (y)	Sex	Tumor location	SCST	Prior treatment	Initial FS	Surgical procedure	Complications	F/U (mo)	Final Local recurrence	Mets	Final status
19	25	F	L4	6	None	E	TES with IL pediculotomy	Lower-extremity muscle weakness, rod breakage	68	E	No	NED
20	44	M	T11	5	None	E	TES with IL pediculotomy	None	64	E	No	NED
21	21	F	T11	5	None	E	TES with IL pediculotomy	None	36	E	No	NED
22	36	F	C4	5	None	E	Total piecemeal spondylectomy	Upper-extremity muscle weakness	24	E	No	NED
23	34	F	T11	4	None	E	TES with IL pediculotomy	None	24	E	No	NED
24	51	M	T12	6	Denosumab	E	Total piecemeal spondylectomy	None	24	E	No	NED
25	20	M	L2	4	None	E	TES with IL pediculotomy	None	29	E	No	NED

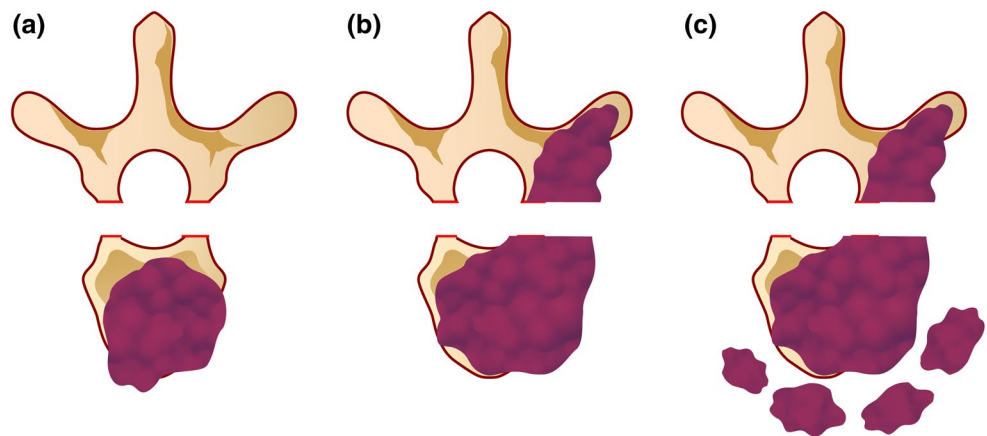
SCST surgical classification of spinal tumor; FS Frankel score; F/U follow-up; Mets Metastasis; P posterior; A anterior; A/P combined anterior and posterior; TES total en bloc spondylectomy; IL intralesional; CSF cerebrospinal fluid; NED no evidence of disease; AWD alive with disease

no malignancy was found. Postoperative adjuvant therapy with short-term bisphosphonate was administered to three patients to avoid local recurrence in the future. Postoperative complications occurred in 15 patients (60%). Among them, six (24%) required reoperation (one for surgical site infection, one for a delayed esophageal fistula, three for instrumentation failure, and one for both surgical site infection and instrumentation failure). Although upper or lower motor function was deteriorated in 11 patients (44%) after surgery because of extensive nerve root dissection, most deterioration was transient, and none of the patients had any difficulty performing activities of daily living at the latest follow-up examination.

During a mean follow-up period of 99 months (range 24–216 months), local tumors recurred in two patients (recurrence rate: 9%). One patient who primarily had a large extravertebral lesion that was greater than 20 cm in the thoracic cavity had tumor recurrence at the subcutaneous level at 12 months postoperatively, likely due to seeding of the site during the primary surgery. The recurrent tumor was successfully excised, and imaging studies that were performed 13 years postoperatively revealed that there was no evidence of tumor recurrence. In another patient who had curettage-based surgery at another hospital, recurrence was observed around the dura mater at 72 months postoperatively. Since curative resection was not feasible, we decided to begin adjuvant treatment with denosumab while investigating the possible need for curative surgery in the future. None of the patients had lung metastases or sarcoma transformation during the follow-up period.

The clinical outcomes of the 12 patients who underwent TES with intralesional pediculotomy (TES group) and those of the 12 patients who underwent total piecemeal spondylectomy (Piecemeal group) are shown in Table 2. There were significant differences between these two groups in the following characteristics: prior tumor excision surgery, tumor location, SCST, and the number of staged surgeries. The mean total operative duration was significantly longer in the Piecemeal group than that in the TES group ($P=0.03$), and the postoperative complication rate was also significantly higher in the Piecemeal group than that in the TES group ($P=0.01$). Although no significant differences were found, there was a trend toward increased intraoperative bleeding in patients in the Piecemeal group ($P=0.18$), and there was a trend toward a lower local recurrence rate in patients in the TES group (0%) than in those in the Piecemeal group (18%). The 2- and 10-year recurrence-free survival rates for patients who were treated with total piecemeal spondylectomy were 91.7% and 78.6%, respectively, while those for patients who were treated with TES were both 100% (Fig. 3).

Fig. 2 Schema of each surgical procedure. **a** Total en bloc spondylectomy without intralesional pediculotomy, **b** total en bloc spondylectomy with intralesional pediculotomy, and **c** total piecemeal spondylectomy



Discussion

The clinical outcomes of the 25 patients who underwent total spondylectomy for Enneking stage III GCTs in the mobile spine at our institution were retrospectively reviewed in the current study. During a median follow-up period of 99 months, spinal GCTs were well managed with total spondylectomy, even though most surgeries involved intralesional procedures. Local tumor recurrence was not detected in patients who underwent TES with intralesional pediculotomy.

Owing to the locally aggressive characteristics of GCTs, insufficient excision may result in a high rate of local recurrence. En bloc resection was recommended by the Spine Oncology Study Group in 2009 [10], and it is particularly required for patients with aggressive Enneking stage III GCTs of the spine to achieve curative resection because the local recurrence rate after intralesional tumor excision was reported to be very high (62%) [1]. However, Xu et al. [11] suggested that total spondylectomy with either en bloc resection or piecemeal resection was associated with a lower risk of local tumor recurrence. Additionally, in patients with cervical GCTs, for whom en bloc resection is not always feasible, total spondylectomy was reported to be associated with a low recurrence rate [12]. Similarly, in our current case series, although most total spondylectomy procedures involved intralesional procedures, the recurrence rate was much smaller than that in previous reports. Particularly, patients who underwent TES with intralesional pediculotomy did not have local recurrence, suggesting that intralesional pediculotomy may be an acceptable procedure for curative tumor resection, even in patients with Enneking stage III GCTs of the spine. Thus, excisional surgery should be considered a first-line therapy when the tumor is likely to be resectable with TES, with or without intralesional pediculotomy.

In contrast, total piecemeal spondylectomy was associated with a higher recurrence rate and a significantly higher

surgical morbidity rate than with TES in this study. These results are consistent with the findings of a recent systematic review [13]. In the current study, the significant differences in patient demographics between the TES and Piecemeal groups (all patients with recurrence and those with cervical spinal tumors were included in the Piecemeal group, and most SCST type 6, i.e., adjacent vertebral extension, tumors required total piecemeal spondylectomy) affected the surgical morbidity rate and significantly limited the comparison study. However, these significant characteristics of patients in the Piecemeal group would be useful for anticipating that TES is unfeasible and that the clinical outcomes would be relatively poor. They may determine the fate of patients with GCTs regarding whether they can be cured with an excisional surgery. Furthermore, another important consideration for spinal GCT treatment is that the benefits of the surgical procedure must be weighed against the associated perioperative morbidity [10]. The predicted surgical morbidity must be evaluated carefully during surgical planning, especially in patients with the above-described characteristics. When necessary, adjuvant therapy should be considered to reduce surgical invasiveness and morbidity.

Recently, denosumab, a monoclonal antibody against the receptor activator of nuclear factor κ - β ligand, has been approved by the US Food and Drug Administration to treat adults and skeletally mature adolescents with unresectable GCTs of the bone or when severe surgical morbidity is predicted [14]. Thomas et al. [15] treated 37 unresectable GCTs with denosumab in a phase II trial, and a favorable effect was seen in 86% of the patients within 6 months of treatment. In a subsequent phase II trial, Chawla et al. [16] demonstrated that in 163 of 169 patients (96%), including 63 patients with spinal GCTs, the disease did not progress after a median follow-up period of 13 months. In another phase II trial, Rutkowski et al. [17] found that 106 of 222 patients (48%), including 21 patients with spinal GCTs, did not undergo surgery, and 84 patients (38%) had a less morbid procedure than that originally planned.

Table 2 Comparison of clinical outcomes between total en bloc spondylectomy with intralesional pediculotomy and total piecemeal spondylectomy

	TES with IL pediculotomy <i>n</i> = 12	Total piecemeal spondylectomy <i>n</i> = 12	<i>P</i> value
Patient characteristics			
Age, <i>y</i> (SEM)	33 (2)	36 (3)	0.27
Sex, female, <i>n</i> (%)	8 (67)	8 (67)	1.00
Prior tumor excision surgery, <i>n</i> (%)	0 (0)	6 (50)	<0.01
History of bisphosphonate therapy, <i>n</i> (%)	0 (0)	2 (17)	0.14
History of denosumab therapy, <i>n</i> (%)	0 (0)	1 (8)	0.31
Preoperative Frankel score, <i>n</i> (%)			0.08
≤ D	2 (17)	6 (50)	
E	10 (83)	6 (50)	
Tumor characteristics			
Tumor location, <i>n</i> (%)			0.03
Cervical	0 (0)	3 (25)	
Thoracic	3 (25)	6 (50)	
Lumbar	9 (75)	3 (25)	
Enneking classification, <i>n</i> (%)			
III	12 (100)	12 (100)	–
SCST, <i>n</i> (%)			<0.01
4	4 (33)	0 (0)	
5	6 (50)	3 (25)	
6	2 (17)	9 (75)	
Surgical characteristics			
Approach, <i>n</i> (%)			0.10
Posterior only	7 (58)	3 (25)	
Combined anterior and posterior	5 (42)	9 (75)	
Staged surgery, <i>n</i> (%)	2 (17)	7 (58)	0.04
Operative duration, min (SEM)	696 (96)	1099 (146)	0.02
Intraoperative bleeding, ml (SEM)	2280 (1013)	3261 (820)	0.09
Postoperative adjuvant therapy			
Bisphosphonate	1 (8)	2 (17)	0.54
Surgical outcomes			
Duration of follow-up, mo (SEM)	101 (19)	86 (16)	0.62
Complications, <i>n</i> (%)	4 (33)	10 (83)	0.01
Reoperation due to complications, <i>n</i> (%)	1 (8)	4 (33)	0.13
Final Frankel score, <i>n</i> (%)			0.02
≤ D	1 (8)	6 (50)	
E	11 (92)	6 (50)	
Local recurrence, <i>n</i> (%)	0 (0)	2 (17)	0.14
Residual tumor at latest follow-up, <i>n</i> (%)	0 (0)	1 (8)	0.31

TES total en bloc spondylectomy; IL intralesional; SEM standard error of the mean; SCST surgical classification of spinal tumor

Furthermore, the therapeutic effects of denosumab were recently reported, even in cases of cervical and recurrent spinal GCT [18, 19]. Thus, denosumab is potentially effective as a neoadjuvant therapy to treat GCTs and can downstage the surgical procedure. However, there is still a shortage of high-quality evidence, especially regarding the long-term effects and optimal treatment duration [20]. Recently, some case reports raised concerns that GCTs might become malignant while patients receive denosumab

treatment [21, 22]. Even in the previously mentioned phase II trial, two of the four patients who discontinued the denosumab regimen did so because of progression of a malignant GCT of the bone [15]. In addition, an in vitro study revealed that neoplastic stromal cells remain proliferative upon denosumab exposure [23], while Yonezawa et al. [24] showed that neoplastic stromal cells survived around the newly formed woven bone despite long-term denosumab treatment for spinal GCT. Further, rapid recurrence after

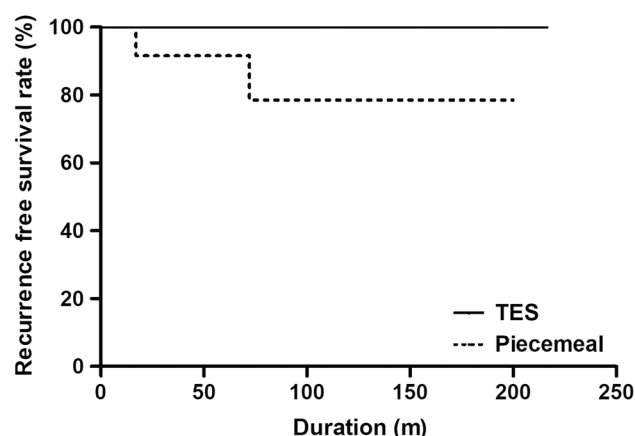


Fig. 3 Kaplan–Meier recurrence-free survival curves of the TES and Piecemeal groups. The 2- and 10- year recurrence-free survival rate was lower in the Piecemeal group than that in the TES group, although there was no significant difference ($P=0.12$). *TES* total en bloc spondylectomy with intralesional pediculotomy; *Piecemeal* total piecemeal spondylectomy

long-term denosumab therapy is ceased was reported in a case study [25]. Therefore, although denosumab would be a useful option when surgery is likely to result in severe morbidity, similar to the patients in our piecemeal group, patients who are administered denosumab should undergo careful follow-up imaging examinations, considering that only surgical resection can radically cure GCTs.

There are limitations to the current study, including its retrospective design and small sample size, in addition to the significant differences in patient demographics between the groups. Moreover, the follow-up duration was insufficient to assess the recurrence rate, since late local relapse could occur [1, 26].

However, to the best of our knowledge, this is the first study to focus on the intralesional procedure level likely to be associated with local recurrence and surgical morbidity in patients undergoing total spondylectomy for aggressive Enneking stage III spinal GCTs. The findings of the current study could aid in surgical decision making and counseling of patients about the benefits and risks of surgery.

Compliance with ethical standards

Conflicts of interest Noriaki Yokogawa, Hideki Murakami, Satoru Demura, Satoshi Kato, Katsuhito Yoshioka, and Hiroyuki Tsuchiya declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Informed consent Informed consent was obtained from all individual participants included in the study.


IRB approval This study was approved by the ethics committee of Kanazawa University (Japan).

References

- Boriani S, Bandiera S, Casadei R, Boriani L, Donthineni R, Gasbarrini A, Pignotti E, Biagini R, Schwab JH (2012) Giant cell tumor of the mobile spine: a review of 49 cases. *Spine (Phila Pa 1976)* 371:E37–E45
- Campanacci M, Baldini N, Boriani S, Sudanese A (1987) Giant-cell tumor of bone. *J Bone Joint Surg Am* 69:106–114
- Balke M, Schremper L, Gebert C, Ahrens H, Streitbuerger A, Koehler G, Harges J, Gosheger G (2008) Giant cell tumor of bone: treatment and outcome of 214 cases. *J Cancer Res Clin Oncol* 134:969–978
- Luksanapraksa P, Buchowski JM, Singhatanadgige W, Rose PC, Bumpass DB (2016) Management of spinal giant cell tumors. *Spine J* 16:259–269
- Elder BD, Sankey EW, Goodwin CR, Kosztowski TA, Lo SF, Bydon A, Wolinsky JP, Gokaslan ZL, Witham TF, Sciubba DM (2016) Surgical outcomes in patients with high spinal instability neoplasm score secondary to spinal giant cell tumors. *Glob Spine J* 6:21–28
- Tomita K, Kawahara N, Baba H, Tsuchiya H, Fujita T, Toribatake Y (1997) Total en bloc spondylectomy: a new surgical technique for primary malignant vertebral tumors. *Spine (Phila Pa 1976)* 22:324–333
- Enneking WF (1986) A system of staging musculoskeletal neoplasms. *Clin Orthop Relat Res* 204:9–24
- Hart RA, Boriani S, Biagini R, Currier B, Weinstein JN (1997) A system for surgical staging and management of spine tumors. A clinical outcome study of giant cell tumors of the spine. *Spine (Phila Pa 1976)* 22:1773–1782
- Tomita K, Kawahara N, Baba H, Tsuchiya H, Nagata S, Toribatake Y (1994) Total en bloc spondylectomy for solitary spinal metastases. *Int Orthop* 18:291–298
- Harrop JS (2009) Aggressive “benign” primary spine neoplasms. *Spine (Phila Pa 1976)* 34:S39–S47
- Xu W, Li X, Huang W, Wang Y, Han S, Chen S, Xu L, Yang X, Liu T, Xiao J (2013) Factors affecting prognosis of patients with giant cell tumors of the mobile spine: retrospective analysis of 102 patients in a single center. *Ann Surg Oncol* 20:804–810
- Junming M, Cheng Y, Dong C, Jianru X, Xinghai Y, Quan H, Wei Z, Mesong Y, Dapeng F, Wen Y, Bin N, Lianshun J, Huimin L (2008) Giant cell tumor of the cervical spine: a series of 22 cases and outcomes. *Spine (Phila Pa 1976)* 33:280–288
- Luksanapraksa P, Buchowski JM, Singhatanadgige W, Bumpass DB (2016) Systematic review and meta-analysis of en bloc vertebrectomy compared with intralesional resection for giant cell tumors of the mobile spine. *Glob Spine J* 6:798–803
- Lewin J, Thomas D (2013) Denosumab: a new treatment option for giant cell tumor of bone. *Drugs Today (Barc)* 49:693–700
- Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, Dansey R, Jun S (2010) Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 11:275–280
- Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, Kroep J, Grimer R, Reichardt P, Rutkowski P, Schuetz S, Skubitz K, Staddon A, Thomas D, Qian Y, Jacobs I (2013) Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol* 14:901–908

17. Rutkowski P, Ferrari S, Grimer RJ, Stalley PD, Dijkstra SP, Pienkowski A, Vaz G, Wunder JS, Seeger LL, Feng A, Roberts ZJ, Bach BA (2015) Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. *Ann Surg Oncol* 22:2860–2868
18. Lin P, Lin N, Teng W, Wang SD, Pan WB, Huang X, Yan XB, Liu M, Li HY, Li BH, Sun LL, Wang Z, Zhou XZ, Ye ZM (2018) Recurrence of giant cell tumor of the spine after resection: a report of 10 cases. *Orthop Surg* 10:107–114
19. Kumar R, Meis JM, Amini B, McEnery KW, Madewell JE, Rhines LD, Benjamin RS (2017) Giant cell tumor of cervical spine presenting as acute asphyxia: successful surgical resection after down-staging with denosumab. *Spine (Phila Pa 1976)* 42:e629–632
20. Gaston CL, Grimer RJ, Parry M, Stacchiotti S, Dei Tos AP, Gelderblom H, Ferrari S, Baldi GG, Jones RL, Chawla S, Casali P, LeCesne A, Blay JY, Dijkstra SP, Thomas DM, Rutkowski P (2016) Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. *Clin Sarcoma Res* 6:15
21. Broehm CJ, Garbrecht EL, Wood J, Bocklage T (2015) Two cases of sarcoma arising in giant cell tumor of bone treated with denosumab. *Case Rep Med* 2015:767198
22. Aponte-Tinao LA, Piuze NS, Roitman P, Farfalli GL (2015) A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with denosumab. *Clin Orthop Relat Res* 473:3050–3055
23. Mak IW, Evaniew N, Popovic S, Tozer R, Ghert M (2014) A translational study of the neoplastic cells of giant cell tumor of bone following neoadjuvant denosumab. *J Bone Joint Surg Am* 96:e127
24. Yonezawa N, Murakami H, Kato S, Takeuchi A, Tsuchiya H (2017) Giant cell tumor of the thoracic spine completely removed by total spondylectomy after neoadjuvant denosumab therapy. *Eur Spine J* 26:236–242
25. Matcuk GR, Patel DB, Schein AJ, White EA, Menendez LR (2015) Giant cell tumor: rapid recurrence after cessation of long-term denosumab therapy. *Skelet Radiol* 44:1027–1031
26. Patil S, Shah KC, Bhojraj SY, Nene AM (2016) Recurrent spinal giant cell tumors: a study of risk factors and recurrence patterns. *Asian Spine J* 10:129–135

Affiliations

Noriaki Yokogawa¹ · Hideki Murakami¹  · Satoru Demura¹ · Satoshi Kato¹ · Katsuhito Yoshioka¹ · Takaki Shimizu¹ · Norihiro Oku¹ · Ryo Kitagawa¹ · Hiroyuki Tsuchiya¹

✉ Hideki Murakami
hmuraka@med.kanazawa-u.ac.jp

Noriaki Yokogawa
chakkun1981chakkun@yahoo.co.jp

Satoru Demura
demudon@med.kanazawa-u.ac.jp

Satoshi Kato
skato323@gmail.com

Katsuhito Yoshioka
ortho0825yoshy@yahoo.co.jp

Takaki Shimizu
takaki.shimizu0928@gmail.com

Norihiro Oku
norihiron09_0820@yahoo.co.jp

Ryo Kitagawa
ryo415k@gmail.com

Hiroyuki Tsuchiya
tsuchi@med.kanazawa-u.ac.jp

¹ Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan