European Spine Journal (2023) 32:254–260
https://doi.org/10.1007/s00586-022-07455-w

ORIGINAL ARTICLE

Comparison of the prognostic factors of total en bloc spondylectomy and total piecemeal spondylectomy in patients with Enneking stage III giant cell tumor in the thoracic and lumbar spine

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Received: 27 May 2022 / Revised: 13 September 2022 / Accepted: 5 November 2022 / Published online: 16 November 2022
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Abstract

Purpose To compare total en bloc spondylectomy with marginal margins against piecemeal spondylectomy with intralesional margins in the surgical treatment of Enneking stage III spinal giant cell tumor (GCT) in terms of local recurrence.

Methods A retrospective survival analysis of patients with Enneking stage III GCT who underwent TES with marginal margins or total piecemeal spondylectomy with intralesional margins was performed between January 2006 and April 2020. Local recurrence-free survival (LRFS) was the time between the date of surgery and recurrence. Factors with p-values < 0.05 in the univariate analysis were included in the multivariate analysis using proportional hazard analysis.

Results Sixty patients (25 men and 35 women) with a mean age of 35.6 (range 11–71) years were included. The mean follow-up duration was 93 (range 24–198) months. Two patients were lost to follow-up 6 and 14 years after the procedure. Over a 10-year period, the recurrence rate was 13.3%. The 2-, 5-, and 10-year LRFS rates were 95%, 88%, and 78%, respectively. Univariate analysis identified total piecemeal spondylectomy and no adjuvant radiotherapy as prognostic factors for LRFS. Multivariate Cox-regression models showed a significant association between local recurrence and total piecemeal spondylectomy and no adjuvant radiotherapy.

Conclusion TES with marginal margins is better than total piecemeal spondylectomy with intralesional margins owing to its lower postoperative recurrence rate. Adjuvant radiotherapy should be administered to reduce postoperative recurrence rates.

Keywords Giant cell tumor · Spinal tumor · Local recurrence · Total en bloc spondylectomy · Surgical margins

Introduction

Giant cell tumors (GCT) of the spine may be aggressive, and intralesional curettage can lead to a high rate of local recurrence [1]. Enneking stage III GCT is defined as symptomatic and extra-compartmental. Surgery remains the mainstay of treatment for spinal GCT, even in light of recent treatments such as denosumab [2]. The local recurrence rate of Enneking stage III spinal GCT after intralesional excision is very high (62%) [3]. Radical excision of GCT is extremely difficult and associated with considerable functional morbidity and other complications [4]. Total en bloc spondylectomy (TES) is recommended by the Spine Oncology Study Group (2009) for better local control of Enneking stage III GCT. Current literature shows that the recurrence rate of TES is lower than that of curettage [3, 5]. 90% of patients with spinal GCT have a disease-free interval of at least five years if en bloc resection can be performed in patients with Enneking stage III [3]. Yin et al. [6] reported that en bloc surgery had a lower local recurrence rate (7.7%) compared to subtotal resection (61.3%) and total piecemeal spondylectomy (14.8%). However, resection margins were not described in their study. Charest-Morin et al. [7] compared favorable resection margins. Only 4% of patients who achieved wide/marginal margins had local recurrences compared to 28% in the intralesional margins group. A study of 12 patients with Enneking stage III mobile spine GCTs found that TES (even intralesional pediculectomy) provided effective local disease

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control with no local recurrence based on a median follow-up time of 101 months [8]. Because the numbers of cases were too small, the prognoses of the two resection methods were not compared. Three patients with Enneking stage III spinal GCT underwent intralesional pediculectomy TES, and none had local recurrence at 13–25 months of follow-up [9]; however, an extended follow-up period is required to accurately evaluate local recurrence.

There are few prognostic studies on Enneking stage III spinal GCTs due to a lack of cases and long-term follow-up data. Therefore, there is a need to define the surgical margins for TES and total piecemeal spondylectomy and then compare their recurrence rates in Enneking stage III spinal GCT. This study aimed to compare TES with marginal margins against piecemeal spondylectomy with intralesional margins in the surgical treatment of Enneking stage III spinal GCT in terms of local recurrence.

Materials and methods

A retrospective review was performed to identify all GCT cases treated at our institution from January 2006 to April 2020. Inclusion criteria were as follows: Enneking stage III GCT; GCT primary site is in the thoracic and/or lumbar spine; initial surgery was TES or total piecemeal spondylectomy at our center; and with a minimum follow-up period of 24 months. The exclusion criteria were total spondylectomy for a primary tumor at another institution, involvement of the cervical spine or sacrum, or inability to undergo surgery. Ethical permission was granted by the relevant ethics committee, and written informed consent was obtained from all patients.

Overall, 60 consecutive patients were enrolled in the study. Clinicopathologic characteristics, including patient age, sex, neurological symptoms, tumor location, number of segments affected, type of surgical margins of the primary surgery, adjuvant radiotherapy, denosumab administration, and further follow-up information, such as local relapse, distant metastases, and survival, were evaluated (Table 1). The surgical approach for each patient was decided based on radiological information from the GCT lesions. Histopathology of the postoperative specimen verified the diagnosis. The GCTs removed using TES in our center had marginal margins (Figs.1 and 2). The GCTs removed by total piecemeal spondylectomy had intralesional surgical margins. All patients were treated according to the follow-up protocol. Clinical follow-up was conducted at 3, 6, 12, 18, and 24 months and annually thereafter, with the time of surgery used as the starting date.

The clinicopathologic characteristics were evaluated for their potential prognostic value for local relapse-free survival (LRFS). LRFS was defined as the time interval between total spondylectomy and the first local relapse. In case of loss to follow-up, the date of the last available follow-up was used for census. Kaplan–Meier survival analyses were performed to evaluate LRFS. Univariate analysis was conducted using the log-rank test to identify prognostic variables, with a significance level of $p \leq 0.05$. Subsequently, to develop a multivariate Cox proportional hazard model, clinically relevant variables with p-values ≤ 0.2 in the univariate analysis were included to investigate their predictive value for LRFS. Statistical analyses were performed using STATA (version 14.0, College Station, TX, USA).

Table 1 Patient characteristics and univariate analysis of the prognostic factors for local recurrence-free survival

Factor	No.	Rate of recurrence	†Kaplan–Meier of LRFS	
			Chi-square	*P*
Age group I, < 25/ ≥ 25	10/50	10%/14%	0.29	0.59
Age group II, < 40/ ≥ 40	42/18	11.9%/16.7%	0.85	0.36
Gender, male/female	25/35	12%/14.3%	0.10	0.75
Back pain VAS > 6/ ≤ 6	17/43	23.5%/9.3%	0.89	0.34
Location, L4-L5/above L4	15/45	20%/11.1%	0.54	0.46
Segments involved, single/contiguous	49/11	9.1%/24.3%	0.40	0.53
Pathological fracture, < 50%/ ≥ 50%	27/33	12.8% / 14.1%	0.18	0.67
Total spondylectomy, intralesional / marginal	26/34	26.9%/2.9%	5.37	0.02*
WBB sectors 3 and 9 involved, yes/no	36/24	16.7%/8.3%	0.78	0.38
Soft tissue invasion, < 5 cm/ ≥ 5 cm	32/28	10.7%/15.6%	0.27	0.60
Denosumab administration, yes/no	31/29	6.5%/20.7%	0.44	0.51
Radiotherapy, no/yes	42/18	30%/5%	8.36	0.007*

**P*-value less than 0.05 for the univariate analysis, †Local recurrence rates have been estimated according to the Kaplan–Meier method

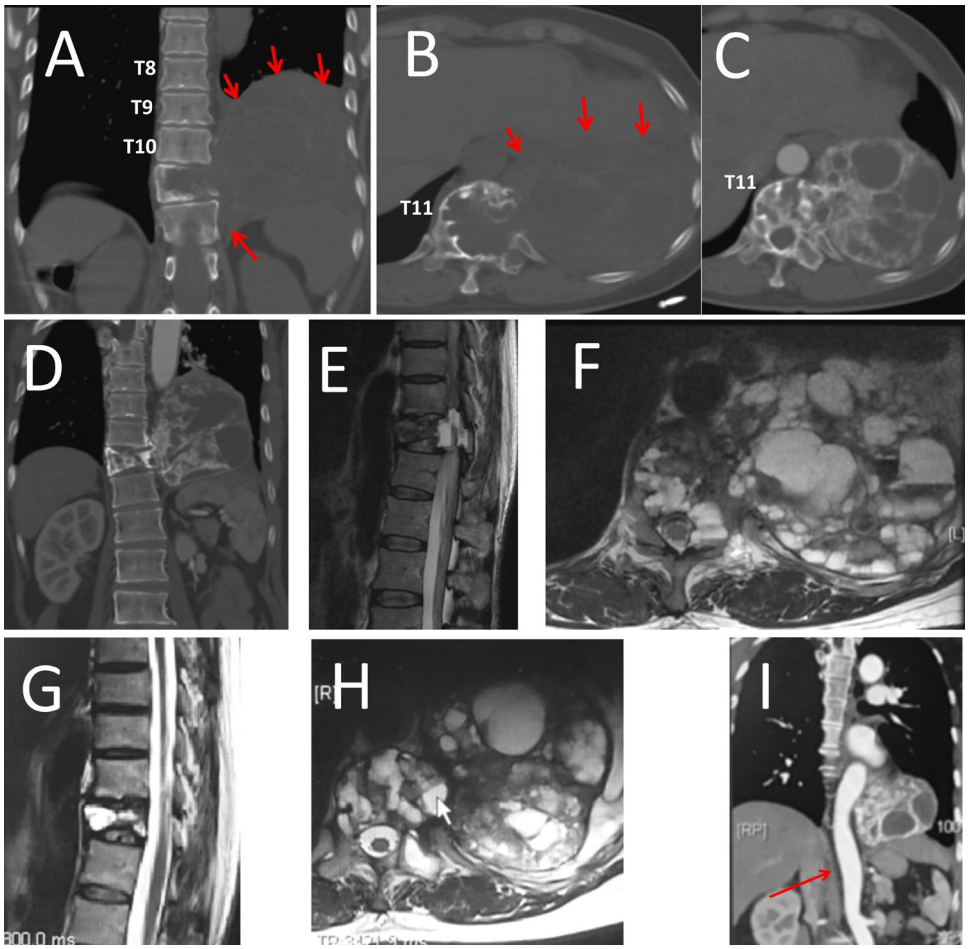

Fig. 1 Preoperative coronal (**A**) and cross-sectional (**B**) computed tomography (CT) shows the relationship between the tumor and T8-T11. Preoperative cross-sectional (**C**) and coronal (**D**) CT show the changes in the tumor after denosumab treatment. Preoperative sagittal (**E**) and cross-sectional (**F**) MRI showed the relationship between the tumor and T11. Preoperative sagittal (**G**) and cross-sectional (**H**) MRI showed the changes in the tumor after denosumab treatment. CT angiography reveals the slight compression of the abdominal aorta by the tumor (**I**)

Results

The mean follow-up duration was 93 (range 24–198) months. The study group comprised 25 men and 35 women, with a mean age of 35.6 (range 11–71) years. The site of origin was at the level of L4-L5 in 15 patients (40%) and above L4 in 45 (60%). The primary procedure performed was TES (marginal margins) in 34 patients (55%) and/or total piecemeal spondylectomy (intralesional margins) in 26 (45%). Two or more contiguous levels were involved in 11 patients (18.3%). A specific en bloc resection was developed according to the Weinstein-Boriani-Biagini (WBB) staging system, which describes eight types of en bloc resections related to the spine. A type 2B resection was performed in 21 patients by a single posterior approach. A type 3B resection was performed in four patients by an anterior-posterior approach. A type 5 resection was performed in two patients by a posterior-anterior-posterior approach. A type 6 resection was performed in three patients by an anterior-posterior to anterior approach, and a type 7 resection was performed in four patients by a posterior-anterior approach. Titanium mesh prostheses were used in 17 patients, and three-dimensional-printing prostheses (from 2016) were used in 17 patients for anterior spinal reconstruction. The prostheses were implanted anteriorly in eight patients and posteriorly in 26.

Eighteen patients (30%) received adjuvant radiation therapy. Eleven patients with total piecemeal gross excision and seven with En bloc resection had received postoperative radiotherapy. A multidisciplinary team discussed all the patients after the operation and decided whether or not to give postoperative radiotherapy. Thirty-one patients received denosumab before surgery. None of the patients received chemotherapy.

Two patients were lost to follow-up 6 and 14 years after the procedure. Over a 10-year period, the recurrence rate was 13.3% (8/60). The cumulative 2-, 5-, and 10-year LRFS rates were 95%, 88%, and 78%, respectively (Fig. 3). None of the patients had lung metastases during the follow-up period.

Univariate analysis (Table 1) identified total piecemeal spondylectomy ($p = 0.02$) and no adjuvant radiotherapy ($p < 0.007$) as prognostic factors for LRFS in Enneking Stage III GCTs. The other known risk factors for local recurrence showed no statistically significant differences between the intralesional and marginal groups (Supplement Table).

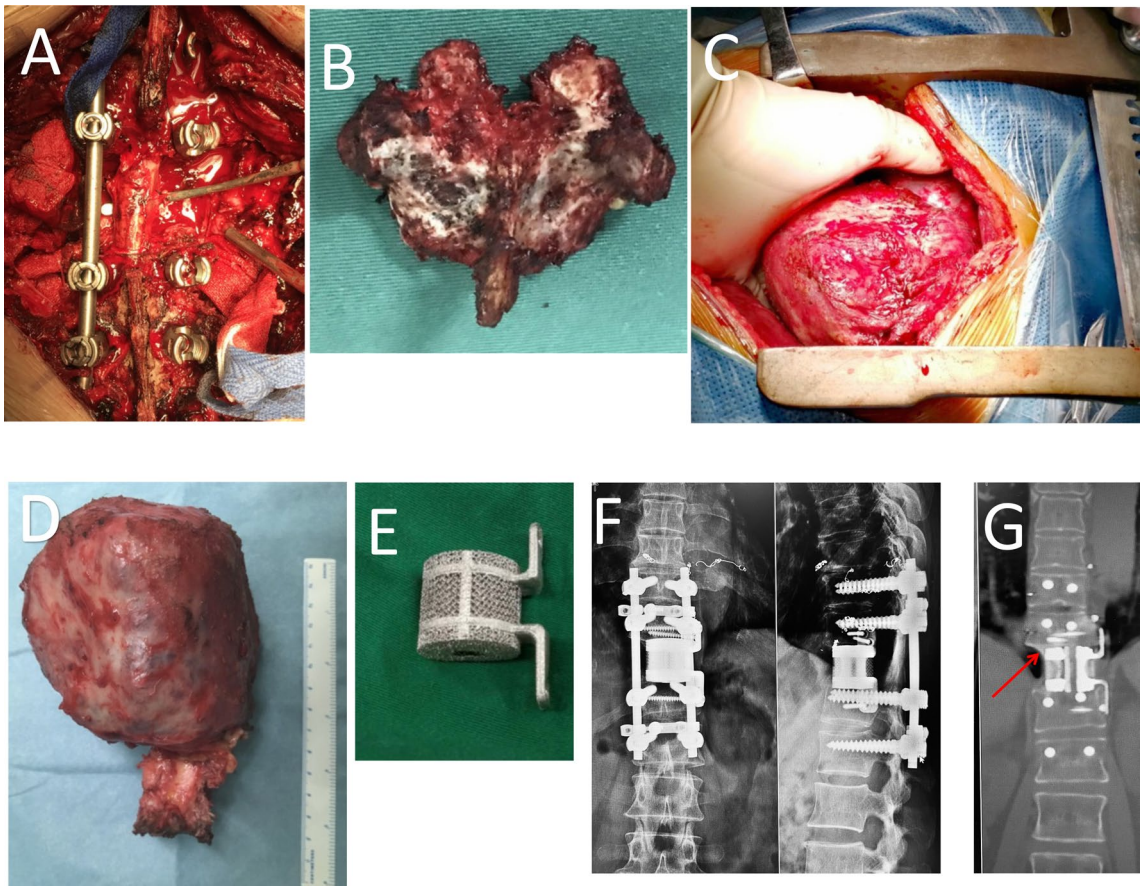

Fig. 2 **A** and **B** show en bloc resection of the posterior structures of T11 through the posterior approach. **C** shows the complete removal of the tumor through the lateral approach. Tumor gross specimen is shown in (**D**). **E** shows the actual 3D customized prostheses. The anteroposterior and lateral radiograph of the thoracic spine (**F**), obtained 5 years after the operation, shows no instrumentation failing. CT obtained 5 years after the operation shows new bone growing around the 3D prosthesis (**G**)

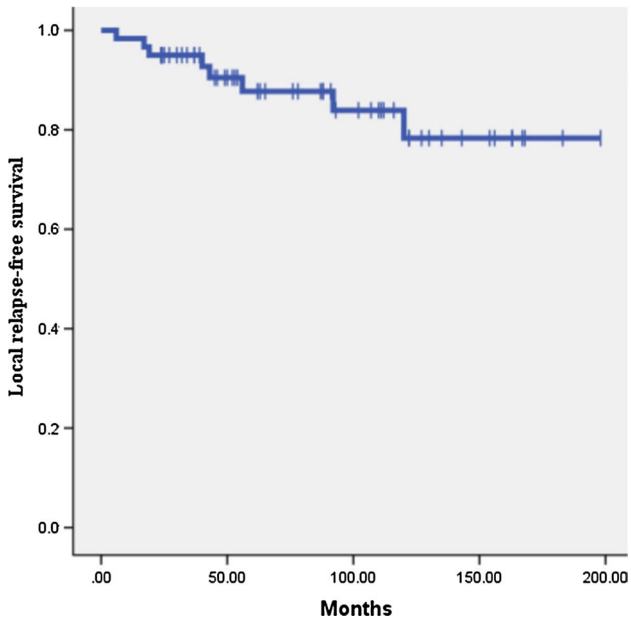

Fig. 3 The local disease-free survival for all surgical patients

Table 2 Multivariate results derived from Cox-regression analysis evaluating variables possibly associated with local recurrence over a 10-year period following surgery

Variables	Exp(B)	(95% CI)	*P*-value
Adjuvant radiotherapy (no vs. yes)	5.64	1.13–28.26	0.02
Surgical margin (intralesional vs. marginal)	6.62	0.81–54.24	0.03

Age, sex, soft tissue invasion > 5 cm, contiguous segments involved, lower lumbar spine involvement, presence of pathological fracture, back pain, and denosumab administration had no prognostic value for LRFS.

Multivariate Cox-regression models were built to investigate the prognostic factors for local recurrence (Table 2). With total piecemeal spondylectomy and no adjuvant radiotherapy as independent variables, a significant association between local recurrences and total piecemeal

spondylectomy ($p = 0.03$) was found. However, there was none for no adjuvant radiotherapy ($p = 0.02$).

Discussion

This study of 60 surgical cases identified total piecemeal spondylectomy with intralesional margins and no adjuvant radiotherapy negative prognostic factors for LRFS.

In our study, gender is not a prognostic factor for LRFS, similar to the findings of previous reports [3, 6, 10]. GCT usually occurs in people aged 20–40 years, with peak prevalence in the third decade of life [11]. Boriani et al. [3] previously reported that age < 25 years is a risk factor for local recurrence. Xu et al. [12] found that patients aged > 40 years had a significantly higher recurrence rate than those aged < 40 years. However, in patients aged < 25 years or >40 years, age evaluation was not a prognostic factor in this study. The average age of the patients < 25 years was younger than that of those aged > 40, and the aggressive behavior of prepubertal participants may be related to hormone secretion. Another difference between the two study patients was ethnicity.

The incidence of pathological fractures was the highest for GCTs than for other tumors of the spine [13], which might cause spinal cord compression and neurologic symptoms [14]. GCT of the upper and lower extremities, pathological fracture was a significant risk factor for recurrence [15]. However, a recent meta-analysis suggested that fractures do not increase the risk of local recurrence [16]. In our study, pathological fracture and back pain were not prognostic factors for LRFS in Enneking stage III spinal GCT. The effects of pathological fractures need to be studied further.

Lin et al. [5] found that patients with soft tissue invasion and tumors > 5 cm were more likely to relapse. In our study, soft tissue invasion > 5 cm and contiguous segments involved were not prognostic factors for LRFS in Enneking stage III spinal GCTs. Concomitantly, lower lumbar spine and WBB sectors 3 and 9 were not statistically negative prognostic factors. The WBB staging system can be useful in the surgical planning of en bloc resection [4]. When nerve roots cannot be sacrificed, complete en bloc resection of WBB sectors 3 and 9 involving tumors is often challenging [17]. Some important anatomical structures often preclude TES for lesions of the lower lumbar spine [18]. The surgical approaches for total spondylectomy of L4-5 GCT differ from those at other mobile spine levels [19]. These factors were not statistically significant, which may be related to the insufficient sample size in this study.

TES is associated with an excellent prognosis. Xu et al. [12] suggest that total spondylectomy, using either en bloc or piecemeal methods, could significantly reduce the recurrence rate of spinal GCT. Jia et al. performed total piecemeal spondylectomy in 14 patients, and only three developed local recurrence; however, log-rank analysis of LRFS indicated no difference between TES and total piecemeal spondylectomy [10]. Yokogawa et al. [8] reported 25 consecutive patients with Enneking stage III spinal GCT. Their results showed no significant difference in local recurrence rate in patients in the TES group (0%) than in those in the piecemeal group (18%). Most of the aforementioned studies compared TES with intralesional curettage or TES combined with total piecemeal spondylectomy and intralesional curettage. In our study, TES surgical margins were marginal, while surgical margins by total piecemeal spondylectomy were intralesional. Our results show that total piecemeal spondylectomy with intralesional margins is a negative prognostic factor for LRFS in Enneking stage III GCT. The recurrence rate in patients who underwent total piecemeal spondylectomy with intralesional margins was 6.62 times higher than that in patients who underwent TES with marginal margins. Our results suggest that en bloc resection with wide/marginal margins should be performed when technically feasible because of its significantly lower recurrence rates.

Denosumab is a potentially effective treatment for patients with spinal GCT and is increasingly used in the treatment of spinal GCT, either as an adjuvant or as a standalone treatment [20]. Denosumab can harden the edges of the GCT [21], facilitating tumor calcification [22]. The calcification and shrinkage of the tumor can enable subsequent surgery and reduce surgical risk [2]. Since 2014, denosumab has been used as a preoperative treatment at our center for patients with GCT to reduce tumor size. In our study, preoperative denosumab treatment was not a positive prognostic factor for LRFS in Enneking stage III spinal GCTs. The use of denosumab to prevent local recurrence of primary GCT has not been fully assessed, and further studies are required.

GCTs of the bone are highly radiosensitive; therefore, radiotherapy should be performed for GCT of the spine [23]. Xu et al. [12] reported that LRFS was much higher in patients who received radiotherapy than in those who did not. Radiotherapy has been reported to provide a satisfactory prognosis for GCT and can reduce the recurrence rate after surgery [24]. Radiation is recommended for those with total piecemeal gross excision with intralesional margins if the surgical margins are contaminated due to significant tumor extension into the pedicles, strong dural attachment, and/or extensive invasion of the paraspinal soft tissue [17]. In our study, seven patients with En bloc resection underwent postoperative radiotherapy. In four cases, the tumors invaded the spinal canal or thoracic cavity with dural or pleural tear during tumor resection; in three cases, tumors extensively invaded the paraspinal soft tissue, and the surgeon was worried about tumor cell contamination or tumor satellite focus after tumor removal. The results showed that the absence of adjuvant radiotherapy was a negative prognostic factor

for LRFS in patients with Enneking stage III spinal GCT. The recurrence rate in patients who did not receive adjuvant radiotherapy was 5.64 times higher than that in patients who received adjuvant radiotherapy. Radiation techniques should be evaluated for spinal GCT to deliver targeted doses with lower complication risks [25].

Our study had several limitations. First, the study group was small, which resulted in limited options for statistical analysis. Second, this was a retrospective study, which may have reduced the level of evidence. Third, the median follow-up of 93 months is still relatively short for this disease since recurrences can occur after 10 years.

Conclusion

TES with marginal margins is better than total piecemeal spondylectomy with intralesional margins owing to its lower postoperative recurrence rate in patients with Enneking stage III spinal GCT, and adjuvant radiotherapy should be administered to reduce postoperative recurrence rates.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00586-022-07455-w.

Acknowledgments We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by H. Z., F. W and F. W. The first draft of the manuscript was written by H. Z., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by grants from Key Clinical Projects of Peking University Third Hospital (BYSY2017001).

Declarations

Conflicts of interest No potential conflicts of interest were disclosed.

Ethics approval and informed consent Ethical permission was granted by the Ethics Committee of Peking University of Health Science Center (No. IRB00001052-08044), and written informed consent was obtained from all patients.

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