

EUROSPINE 2018

19-21 September, Barcelona, Spain

Morphologic changes in the thoracolumbar giant cell tumor after denosumab therapy

Noritaka Yonezawa, Hideki Murakami, Satoru Demura, Satoshi Kato,
Katsuhito Yoshioka, Kazuya Shinmura, Noriaki Yokogawa,
Takaki Shimizu, Norihiro Oku, Ryo Kitagawa, Hiroyuki Tsuchiya

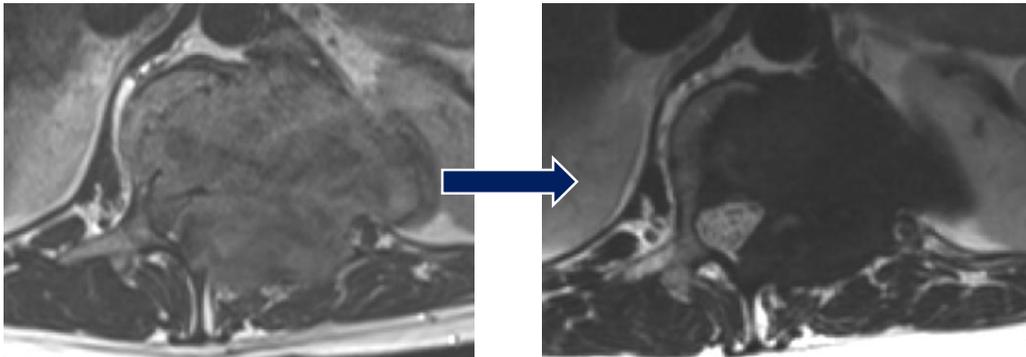


Department of Orthopedic Surgery, Kanazawa University, Kanazawa, Japan



Background

- ✓ Denosumab has been used successfully as a neoadjuvant therapy prior to total spondylectomy (TS) for giant cell tumors (GCTs) of the spine.
de Carvalho Cavalcante RA, et al. Spine (Phila Pa 1976) 41:E178-E182, 2016
- ✓ Denosumab induces shrinkage of an extraosseous tumor, thereby facilitating complete en bloc tumor resection and reducing the risk of perioperative complications.
Goldschlager T, et al. J Neurosurg Spine 22:526-533, 2015
- ✓ However, the optimal dose of neoadjuvant denosumab therapy (DT) and adverse effect of neoadjuvant DT for GCTs of spine are still well unknown.



Kumar R, et al. Spine (Phila Pa 1976) 42:E629-E632, 2017

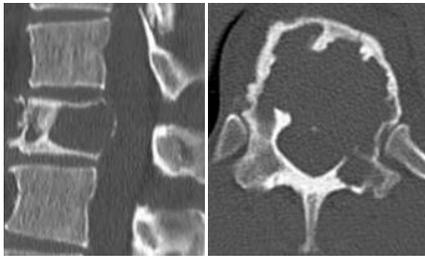


Purpose

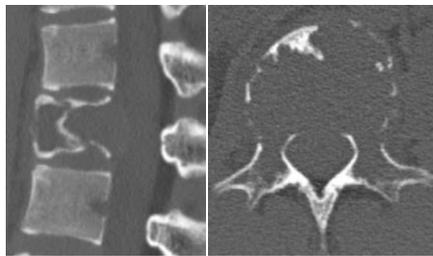
- ✓ This study aimed to evaluate the morphologic and histological effects of neoadjuvant DT on spinal GCTs and consider an optimum dose for neoadjuvant DT prior to TS.

Methods

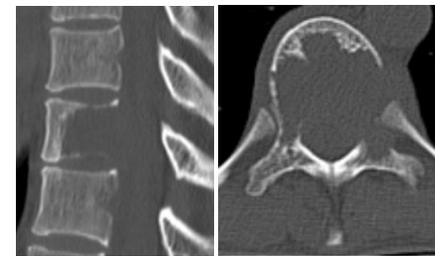
- ✓ We collected data from 3 consecutive patients with spinal GCTs who underwent TS after neoadjuvant DT at our institution between 2015 and 2017.



Case 1: 51 y.o. M. T12



Case 2: 16 y.o. F. L1



Case 3: 42 y.o. F. T10

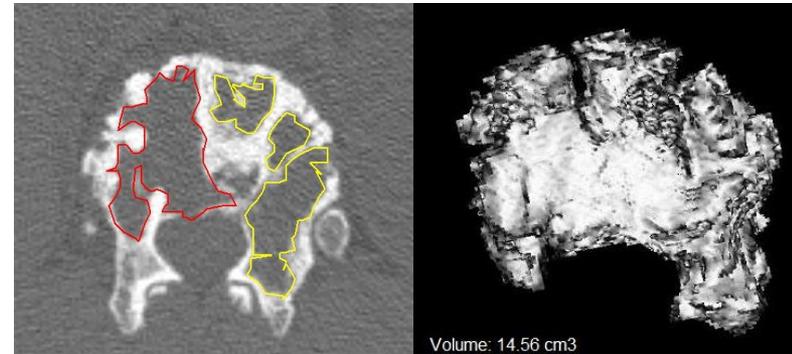
- ✓ Changes in tumor volume, vertebral body height, maximum transverse diameter, anteroposterior diameter, and spinal canal area occupied by the tumor following DT were analyzed.
- ✓ Histological analysis of the resected vertebral body sections was performed.

Methods

1. Tumor volume

We evaluated tumor volume using a three-dimensional workstation (Aquarius Net Station®, TeraRecon, San Mateo, CA, USA).

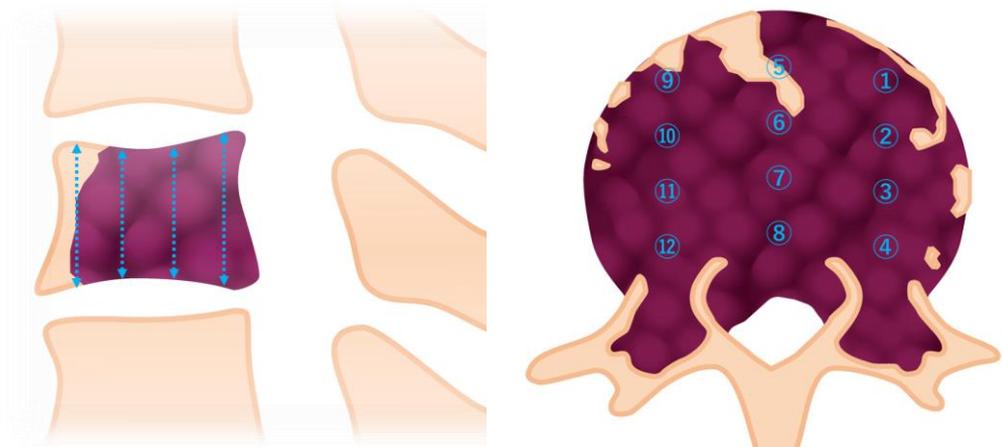
The tumor volume was calculated by using the manual contour-tracing method. Tumor volume was measured using a region of interest (ROI) from each CT slice on the workstation.



2. Vertebral body height

We evaluated the vertebral body height at 12 points.

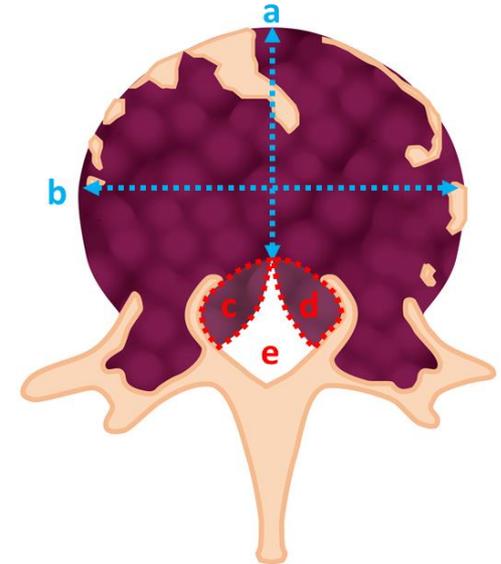
A, anterior (1, 5, 9)
AM, anteromedial (2, 6, 10)
PM, posteromedial (3, 7, 11)
P, posterior. (4, 8, 12)



Methods

3. Maximum transverse diameter, anteroposterior diameter,
4. Spinal canal area occupied by the tumor

We evaluated the anteroposterior diameter (a) and maximum transverse diameter (b) of the vertebral body, and the area of the spinal canal occupied by the tumor (c+d)/(c+d+e).



5. Histological and pathological analyses

Histological analysis of the resected vertebral body sections was performed to determine the presence of multinucleated giant cells and RANKL-positive stromal cells. RANKL expression was evaluated using a rabbit anti-RANKL polyclonal antibody (1:500; ab9957, Abcam, Cambridge, UK) and a peroxidase-labeled secondary antibody (EnVision, Dako, Carpinteria, CA, USA).

Demographic data for 3 patients with spinal GCTs

Factor	Case 1	Case 2	Case 3
Demographic			
Sex	M	F	F
Age (years at surgery)	51	15	42
Clinical symptom at diagnosis			
Initial presentation	pain	pain	Pain
Duration of symptom (mos)	8	5	3
Frankel classification	E	E	E
Neurological deficits	None	None	None
Tumor at diagnosis			
Location	T12	L1	T10
Pathological fracture	No	Yes	No
WBB sector	3—9	3—10	3—10
Enneking class	Stage III	Stage III	Stage III
SINS score	11	16	8
Neoadjuvant denosumab treatment			
Dose of denosumab	10	1	2
Drug-related adverse events	None	Hypocalcemia, Tetany	None
Surgery			
Perioperative embolization	multiple	multiple	multiple
Planned surgery	TES	TES	TES
Performed surgery	TS	TS	TES
Follow-up time after surgery (mos)	24	12	6
SINS: score the spinal instability neoplastic scale score TES: total en bloc spondylectomy, TS: total spondylectomy			

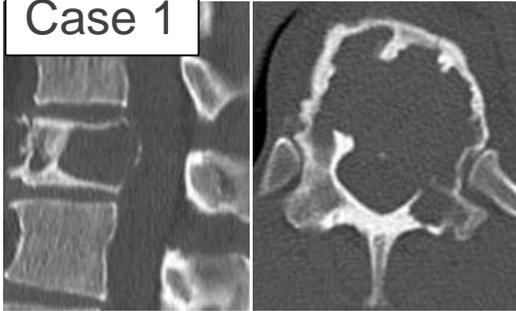
Characteristics of morphologic radiological change and histological findings in 3 patients

Factor	Case 1	Case 2	Case 3
Duration between pre NDT-CT evaluation and NDT start (days)	15	30	33
Duration between NDT start and preoperative CT evaluation (days)	273	8	40
Duration between NDT start and surgery (days)	277	9	46
Morphologic change			
Tumor volume before NDT (initial CT) (cm ³)	18.7	28.1	18.0
Tumor volume after NDT* (cm ³)	14.6	21.8	14.6
Reduction rate of the tumor volume (%)	21.9	22.4	18.9
Mean loss of vertebral body height at 12 points (%)	17.3	9.0	8.0
The main site of the collapse (loss of vertebral body height (%))	2, 3 (43.1, 50)	10, 11 (12.9, 13.8)	7, 8 (14.4, 14.6)
Histological findings			
Multinucleated giant cells	None	detected	None
RANKL-positive stromal cells	detected	detected	detected
Woven bone	+++	+	+
Sclerotic rim formation	++	+	+
NDT: neoadjuvant denosumab therapy			

Results

1. Tumor volume

Case 1



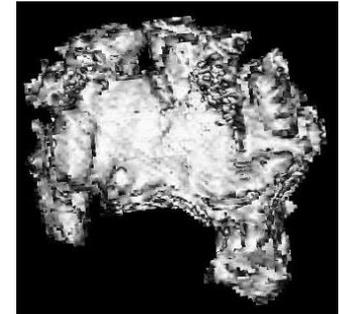
Before DT

After DT

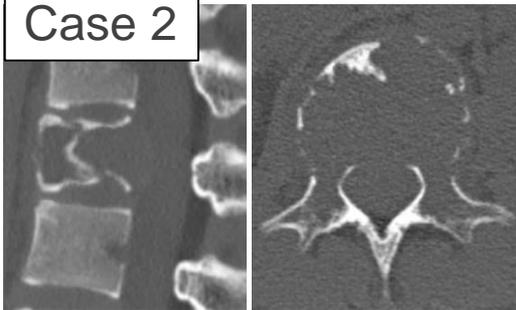
18.7 cm³ → 14.6 cm³

10 courses of DT

22 % reduction



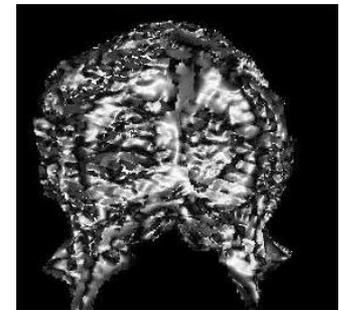
Case 2



28.1 cm³ → 21.8 cm³

1 course of DT

22 % reduction



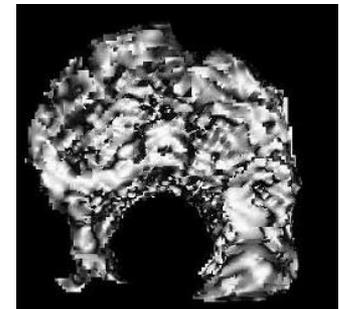
Case 3



18.0 cm³ → 14.6 cm³

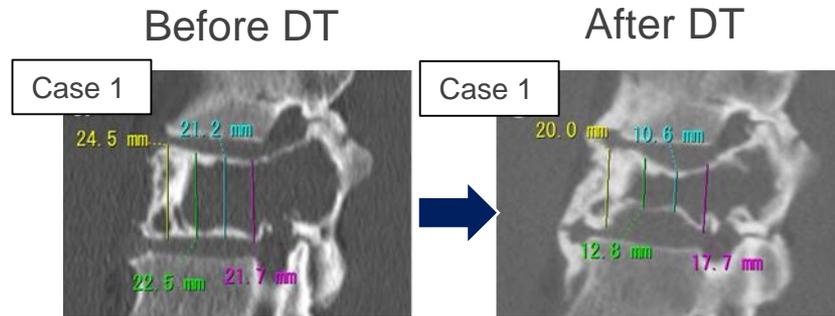
2 courses of DT

19 % reduction

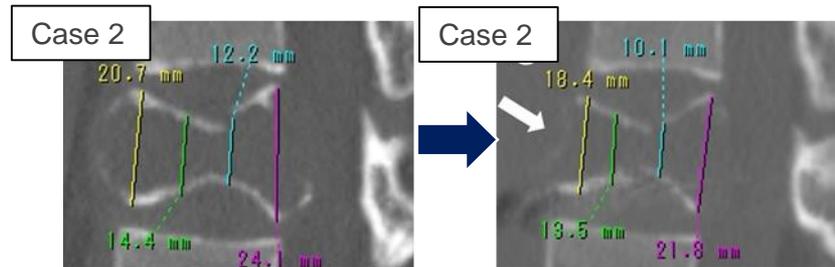


Results

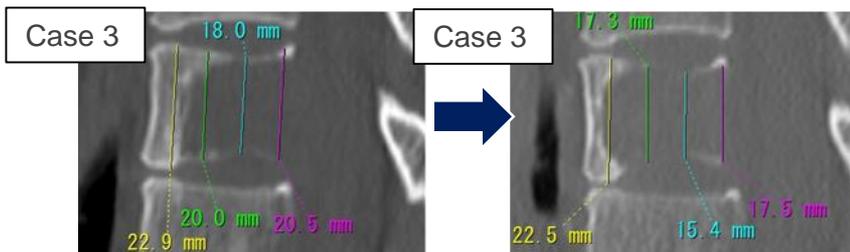
2. Vertebral body height



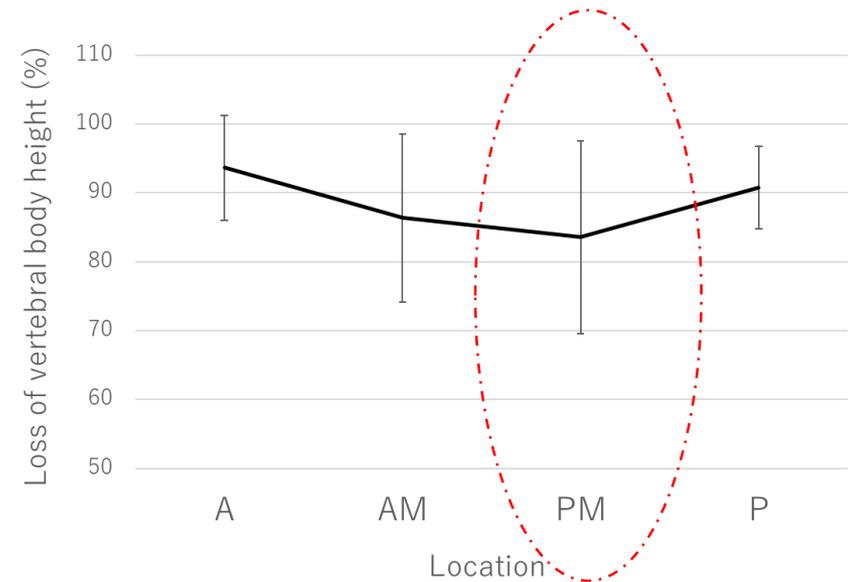
10 courses of DT



1 course of DT



2 courses of DT



Loss of vertebral body height was observed in all cases, with a mean loss of 11.4%. In all cases, the main site of collapse in the vertebral body was the posteromedial part of the vertebral body (16.5% loss of vertebral body height), which consisted of mainly the tumor and little cortical bone. The white arrow indicates an anterior protruded tumor reduction.

A, anterior; AM, anteromedial; PM, posteromedial; P, posterior.

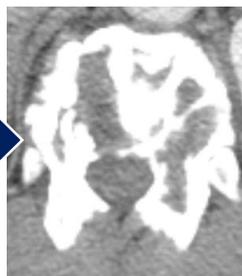
Results

3. Maximum transverse diameter, anteroposterior diameter,

4. Spinal canal area occupied by the tumor

Before DT

After DT



Case 1

Transvers diameter

50mm



55mm



Anteroposterior diameter

37mm



36mm

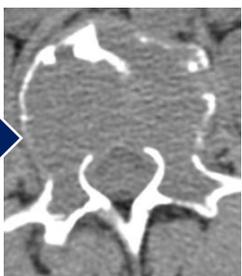


Spinal canal area
Occupied tumor

37%



0%



Case 2

Transvers diameter

50mm



49mm



Anteroposterior diameter

36mm



33mm



Spinal canal area
Occupied tumor

57%



10%



Case 3

Transvers diameter

40mm



38mm



Anteroposterior diameter

30mm



26mm



Spinal canal area
Occupied tumor

45%

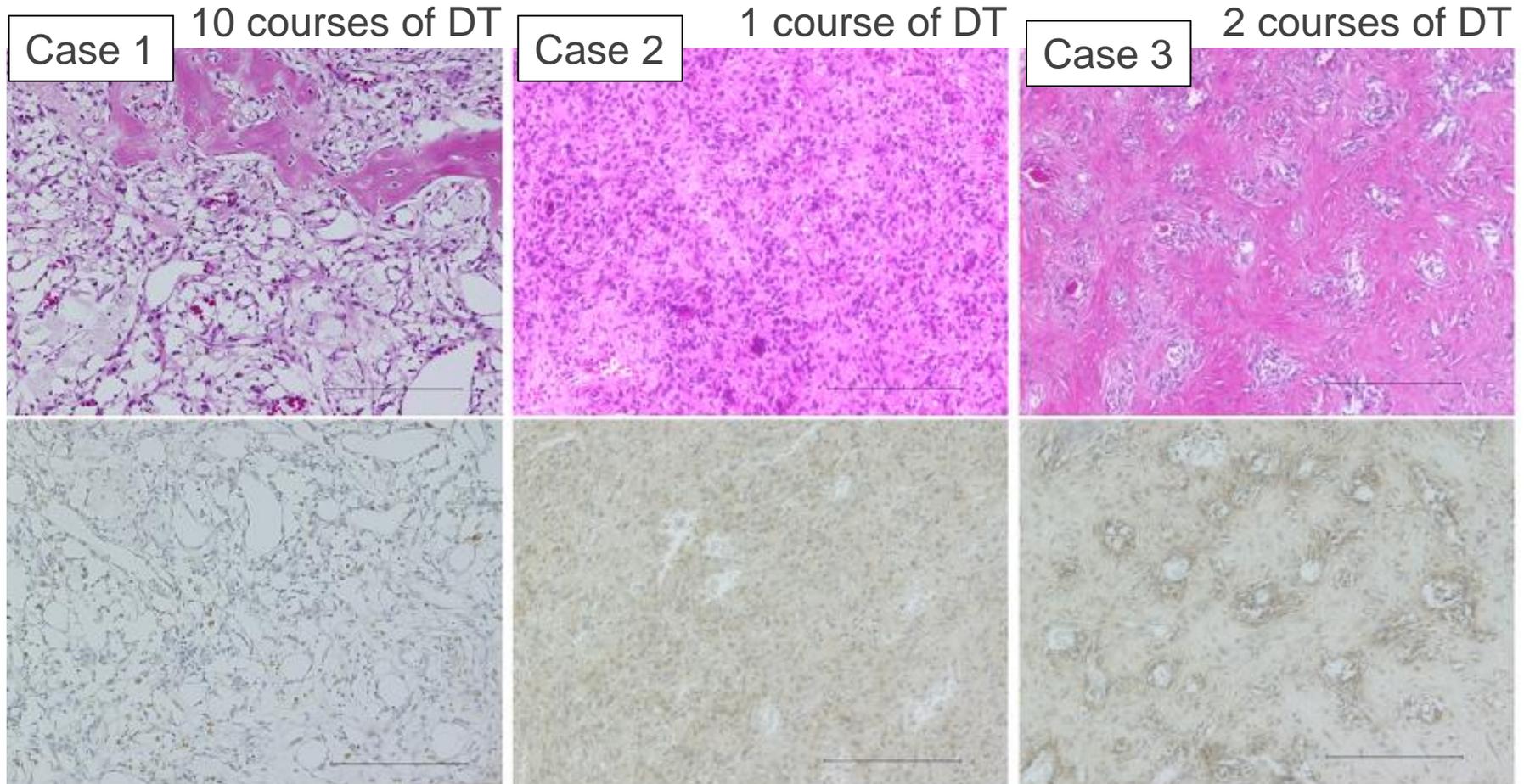


0%



Results

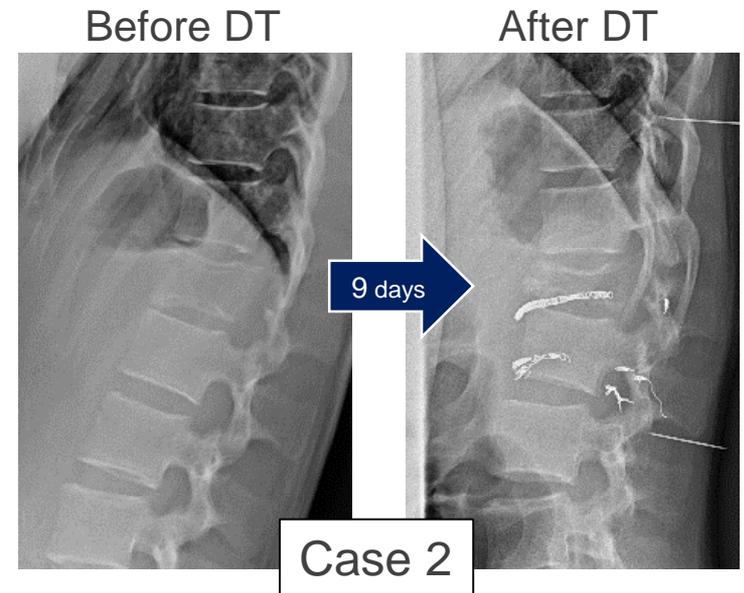
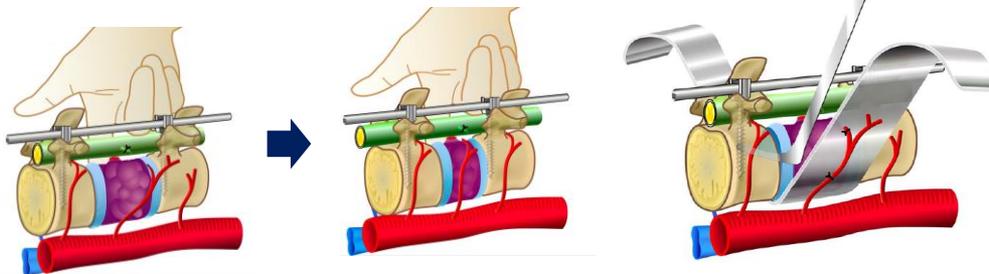
5. Histological and pathological analyses (Hematoxylin and eosin staining and RANKL staining)



In case 2, a few multinucleated giant cells were detected, whereas none were detected in cases 1 and 3. Although cases 2 and 3 showed a highly cellular tumor with focal bone formation in the background of a highly cellular stroma, the tumor in case 1 was less cellular with increased woven bone. RANKL-positive stromal cells were detected in all cases. Scale bar corresponds to 200 μm .

Discussion

- Case 3 showed vertical tumor shrinkage and a decrease in vertebral height in the part of tumor. However, vertebral collapse was not observed. This finding suggests that the presence of adequate anterior cortical bone could prevent vertebral collapse.
- Denosumab caused horizontal shrinkage of both the epidural tumor and the anterior protruded tumor, and also caused shrinkage in vertical direction. This vertical tumor shrinkage induced by denosumab may increase the mechanical stress on the thin cortical rim, leading to collapse of the affected vertebral body, which may account for the pathological fractures seen in case 1 and 2 (which consisted of mainly osteolytic lesions and a thin anterior cortical rim).
- Posterior total en bloc spondylectomy requires digital dissection of segmental arteries from the vertebral body. After that, the surgeon's fingertips meet each other at the anterior end of the vertebra from both sides, allowing the insertion of a vertebral spatula to protect the large vessels and other organs. However, a collapsed vertebra makes it difficult to perform this procedure due to decreased working space, as in case 1 and 2.



- If the affected vertebrae consist of mainly osteolytic lesions, strict bed rest may be recommended during neoadjuvant DT to prevent the progression of such drug-induced pathological fractures and early surgical intervention of posterior en total spondylectomy after neoadjuvant DT may be desirable.

Conclusions

- Although the limitations of our study include short-term outcomes, small sample size, unequal timing of image assessment, and lack of control group, we consider short-term neoadjuvant DT induces adequate epidural and extraosseous tumor shrinkage to facilitate complete en bloc tumor resection.
- However, if affected vertebrae consist mostly of osteolytic lesions, vertical tumor shrinkage can increase the mechanical stress on the thin cortical rim, leading to the collapse of the affected vertebral body and making it difficult to perform posterior total en bloc spondylectomy.

Disclosure

I have nothing to disclose.

