Vertebral body collapse after radiotherapy for spinal metastases

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Abstract. Spinal metastases are common in patients with advanced stages of cancer and frequently cause vertebral body collapse (VBC). Although conventional radiotherapy (RT) is used for spinal metastases, the rates of occurrence of new VBC and progression of VBC at RT initiation have not been fully investigated. The present retrospective study assessed VBC and its associated risk factors after RT over time and evaluated new VBC and progression of VBC in patients who presented with VBC at RT initiation. The study evaluated 177 patients who received RT for vertebral metastases without paralysis between July 2012 and November 2016. Radiological responses of the irradiated vertebrae were assessed using computed tomography. Follow-up assessments were performed at RT initiation and 1, 2, 3, 4 and 6 months after RT. New VBC occurred in 12% of patients with no prior VBC within 1 month of RT. Multivariate analysis revealed that numeric rating scale (NRS) score (≥4) [relative risk (RR), 27.1; 95% confidence interval (CI), 1.86 to 394.9; P=0.016] was associated with the occurrence of new VBC at the 1 month follow-up time point. VBC progression occurred in 51% of the patients with collapse at RT initiation. Multivariate analysis revealed that bone quality (lytic metastases) (RR, 3.1; 95% CI, 1.28 to 7.70; P=0.013), NRS score (≥4) (RR, 3.0; 95% CI, 1.18 to 7.45; P=0.021) and tumor involvement of posterolateral elements of the spine (RR, 2.7; 95% CI, 1.03 to 7.29; P=0.04) were associated with the progression of VBC at the 1 month follow-up time point. The current study findings suggested that clinicians should pay attention to the factors that predict the occurrence of new VBC and VBC progression to ensure proper evaluation of conservative treatment effectiveness and facilitate the determination of patients who need close monitoring.

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Introduction

Spinal metastases are most common in patients with advanced disease among all cancer types (1-5). They frequently cause vertebral body collapse (VBC) and malignant spinal cord compression (MSCC), resulting in pain and paralysis. VBC is caused by the destruction of the vertebral body. It often accompanies pain and sometimes has paralysis when spinal cord is compressed by collapsed vertebral body (1,2). MSCC is usually caused by the compression of spinal cord by metastatic tumor which extends into the vertebral column. Its common symptoms are radicular pain, motor weakness, sensory complaints and bladder dysfunction (3). These spinal skeletal-related events (SREs) drastically reduce patients' activities of daily living (ADL) and quality of life (QOL) (1-3). If the patient has symptoms of VBC and/or SREs, radiotherapy (RT) and surgery would be preferred to chemotherapy because of their direct local effect such as shrinkage of the tumor, decompression with the removal of lamina or pedicle, and removal of the compressing tumor (4-6). In patients with paralysis, decompression and fixation are the first treatment choices (6-9). However, conservative treatment using orthoses is often preferred in patients without paralysis (10). In addition, VBC can progress even after RT (10,11). Although conventional RT is most commonly used for spinal SREs, the rate of occurrence of new VBC and its progression at RT initiation has not been fully investigated (10,11).

Rief *et al* reported the occurrence of new VBC following RT in 2% of patients diagnosed with various cancer types (10). Among colorectal cancer patients, new VBC occurred in 9% of patients after RT completion (11). However, in these studies, the time points chosen to examine potential VBC manifestations were inconsistent in terms of interval frequencies and lengths, making an accurate and comparative evaluation of VBC development over time extremely difficult. Moreover, investigation of VBC occurrence in these studies is limited due to a lack of information on the degree of VBC prior to RT.

To the best of our knowledge, no study has focused on the evaluation of VBC occurrences and progression in patients with vertebral bone metastases without paralysis by MSCC. Therefore, development of an approach that allows for a more detailed evaluation of VBC development were performed. In this regard, the patients were divided based on their degree of VBC at RT initiation and investigated for changes in VBC for up to 6 months after RT. In addition, potential risk factors

for VBC in patients with painful spinal metastases without paralysis were also examined. The study specifically focused to answer the following two questions with respect to the new VBC cases: (1) What are the incidence rates, timing, and degree of new VBC cases, and when does it cease? (2) What are the potential risk factors for the occurrence of new VBC? In addition, the study also attempted to answer the following questions with regard to VBC before RT: (3) What are the incidence rates and degree of VBC progression, and when does it occur and cease to occur? (4) What are the risk factors for the progression of VBC?.

Patients and methods

Study population. The records of patients who received RT for palliation of painful vertebral bone metastases at our institution between July 2012 and November 2016 were retrospectively investigated. The last follow-up time point for the evaluation of patients involved in this study was January 2017. The patients who underwent treatment for metastatic lesion at the same irradiated vertebrae, including surgery, RT or other local interventional therapies were excluded. The patients with clinical MSCC, sacral lesions, and those who were followed up for less than one month were also excluded. In the same period of this study, there were two patient who developed paralysis for MSCC during the follow-up period. These cases were resistant to RT and their pain got worse again. Then, they were excluded in our study.

This retrospective chart review study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the Shikoku Cancer Ethics Committee approved this study (Approval No. 2017-26). All the participants provided written informed consent for this study.

Assessment of pain at metastatic vertebrae. A numeric rating scale (NRS) was used to evaluate the degree of pain at the metastatic vertebrae at the time of movement (mechanical pain). NRS is a patient-based assessment tool that evaluates pain intensity on a scale of 0 (no pain) to 10 (worst pain) (12). Based on the National Comprehensive Cancer Network guidelines, the level of pain was determined as none (0), mild (1-3), moderate (4-6), or severe (7-10) (13).

Radiological assessment. The status of the vertebral bone was evaluated using CT (Aquilion, Canon) at 120 kV and a slice thickness of 5 mm. All images were viewed with routine bone window settings (window level 200 HU, window width 2000 HU) with axial, coronal, and sagittal planes. Bone quality was classified as lytic, mixed, or blastic at RT initiation. There was no patients with intra-trabeculae metastases.

VBC was defined as a reduction in vertebral body height compared to the height of the upper and lower vertebral bodies. The degree of VBC was determined as severe (≥50% collapse) or mild (>0 and <50% collapse) based on the approach of a previous report assessing VBC development (14). The progression of VBC was defined as the advancement of the collapse of the vertebral body in the irradiated vertebral bone with

collapse at RT initiation. Progression of VBC in patients who presented with VBC at RT initiation were evaluated at RT initiation and 1, 2, 3, 4, and 6 months after RT.

The patients without VBC were also divided as follows: no collapse with ≥50% body involvement of the tumor and no collapse with <50% body involvement of the tumor, based on the approach of a previous report assessing VBC development (14). The 'body involvement' was defined as the occupation of the tumors in the vertebral body. The rate of the occupation of the tumors in the vertebral body was evaluated in the axial view of CT. For them, radiological evaluations were performed at RT initiation and 1, 2, 3, 4, and 6 months after RT. The new VBC was defined as a reduction in vertebral body height compared to the height of the upper and lower vertebral bodies in the irradiated vertebral bone.

Statistical analyses. The potential risk factors in patients with new VBC, in patients without VBC, and progression of VBC at RT initiation and one month after RT were assessed. The clinical data of the patients included information on age, sex, primary cancer site, radiation site, chemotherapy before RT, chemotherapy after RT, the overall dose of RT, degree of pain as measured by NRS, bone quality, lung metastases, vertebral body collapse, and tumor involvement of posterolateral elements of the spine. The progression of vertebral body collapse was estimated by CT at 1, 2, 3, 4, and 6 months after RT. The rates of cease of the progression of the collapse at each time point were estimated by the Kaplan-Meier method. The endpoint was the time to the stop of the progression of vertebral body collapse. Those who had dead was ceased.

Univariate analysis was performed using the chi-square test, and multivariate analysis was performed using logistic regression. For all analyses, associations were considered significant if the P-value was <0.05. The COX hazard model analysis was thought to be inappropriate due to the low power of detection because the time units are months instead of days. All statistical analyses were performed using the statistical computing software R (R version 3.5.0, R Core Team, Vienna, Austria).

Results

Patients' characteristics. A total of 177 patients were included in this study, of whom 95 were males and 82 were females, with a median age of 67 years (range, 30-91) (Table I). The primary tumor sites in the participants were the lung (n=58), breast (n=39), prostate (n=22), colorectum (n=17), stomach (n=10), liver (n=9), pancreas (n=4), and others (n=18). The spine locations were the cervical (n=14), thoracic (n=91), and lumbar (n=72) regions. They were divided into the junctional level (C1, C2, C7 to T2, T11 to L1, and L5) (n=57), mobile segments (C3 to C6 and L2 to L4) (n=58), and rigid segments (T3 to T10) (n=62). The types of metastases were lytic (n=64), mixed (n=74), and blastic (n=39). All patients underwent RT. Chemotherapy was administered to 88 patients (50%) before RT. All patients were treated conservatively. The decompression and spine stabilization was performed for patients with paralysis by metastatic spinal cord compression. There was one patient who had paralysis during the study period. The patient also had severe pain who cannot get out of bed

Table I. Patient characteristics.

Characteristic	Value
Sex	
Male	95
Female	82
Median age (range)	67 (30-91)
Primary tumor sites	
Lung	58
Breast	39
Prostate	22
Colorectum	17
Stomach	10
Liver	9
Pancreas	4
Others	18
Spine locations	
Cervical	14
Thoracic	91
Lumbar	72
Spine locations (based on segments)	
Junctional level (C1, C2, C7 to T2, T11 to L1 and L5	57
Mobile segments (C3 to C6 and L2 to L4)	58
Rigid segments (T3 to T10)	62
Types of metastases	
Lytic	64
Mixed	74
Blastic	39
Chemotherapy before RT	
Yes	88
No	89
Chemotherapy after RT	
Yes	111
No	66
Lung metastases	
Yes	79
No	98

with instability of the spine as measured by spine instability neoplastic score (6). The surgery was performed (laminecomy and spine stabilization) for the patient.

Assessment of pain at metastatic vertebrae. All patients experienced reduced pain during the follow-up period. None of them required surgery to alleviate the pain. The level of pain at RT initiation was none in 72, mild in 46, moderate in 29, and severe in 30 patients.

Patients with or without VBC at RT initiation. The number of patients that presented without and with VBC at RT initiation was 68 (38%) and 109 (62%), respectively (Table II). Of 68 patients without VBC, 19 presented with ≤50% body

involvement of the tumor and 49 with >50% body involvement of the tumor. Of 109 patients with VBC at RT initiation, 8 presented with ≥50% collapse, and 101 presented with >0 and <50% collapse. The number of patients with or without VBC decreased during the follow-up period due to death from the disease (Table II).

Analysis of patients without collapse before RT initiation. New VBC occurred in 8 patients (12%) without collapse at RT initiation. New VBC did not occur in any patient without collapse and ≤50% body involvement of the tumor. New VBC occurred in 8 of 49 patients (16%) without collapse and >50% body involvement of the tumor. All new VBC advanced to <50% collapse, occurred briefly after the initiation of RT until a median of one month [1st month (5 patients) and 2nd month (2 patients)]. Among them, there were 2 patients in whom VBC occurred in asymptomatic patients after RT. Univariate analysis revealed that primary cancer site (lungs), bone quality (lytic metastases), NRS score (≥4), and tumor involvement of posterolateral elements of the spine were risk factors for new VBC (Table III). Multivariate analysis revealed that NRS score (≥4) [Relative risk (RR), 27.100; 95% confidence interval (CI), 1.859 to 394.884; P=0.016] was associated with the occurrence of new VBC at the one-month follow-up time point.

Analysis of patients with collapse before RT initiation. VBC progression occurred in 56 patients (51%) with collapse and 50 out of 101 patients (50%) who presented with mild collapse at RT initiation. VBC occurred briefly after the initiation of RT until a median of one month [1st month (38 patients), 2nd month (10 patients), 3rd month (2 patients), and no patient in 4th and 6th month]. Among these patients, VBC progressed to ≥50% collapse in 11 patients (12%) at a median of one month [1st month (8 patients), 2nd month (2 patients), 3rd month (1 patient), and no patient in 4th and 6th month]. VBC progression occurred in 6 out of 8 patients (75%) who presented with severe collapse at RT initiation and briefly after the initiation of RT until a median of one month [1st month (3 patients), 2nd month (3 patients), and no patient in 3rd, 4th and 6th month].

Univariate analysis revealed that bone quality (lytic metastases), NRS score (≥4), and tumor involvement of posterolateral elements of the spine were risk factors for the progression of VBC at the one-month follow-up time point (Table IV). Multivariate analysis revealed that bone quality (lytic metastases) (RR, 3.138; 95% CI, 1.280 to 7.698; P=0.013), NRS score (≥4) (RR, 2.963; 95% CI, 1.179 to 7.446; P=0.021), and tumor involvement of posterolateral elements of the spine (RR, 2.735; 95% CI, 1.026 to 7.294; P=0.044) were associated with the progression of VBC at the one-month follow-up time point.

The collapse progression-free rates estimated by the Kaplan-Meier method were 62, 47, 44, 44, and 44% at the 1-, 2-, 3-, 4-, and 6-month time points, respectively (Fig. 1).

Discussion

Although conventional RT is most commonly utilized for spinal SREs, the occurrence of new VBC during RT has not been fully investigated previously (10,11,15-23). Shi *et al* reported that a total of 51 out of 250 (20.4%) lesions subsequently

Table II. Vertebral body collapse at the beginning of RT and at 1, 2, 3, 4 and 6 months after RT.

| Before RT	RT	1 month	2 months	3 months	4 months	6 months
≥50% collapse (n=8)	≥50% collapse	8	7 (88%)	5 (63%)	5 (63%)	3 (37%)
	Dead	0	1	3	3	5
>0<50% collapse (n=101)	>0<50% collapse	93	66 (65%)	54 (53%)	43 (43%)	33 (33%)
	≥50% collapse	8	6 (6%)	5 (5%)	5 (5%)	4 (4%)
	Dead	0	29	42	53	64
No collapse with >50% body involved of the tumor (n=49)	No collapse with >50% body involved of the tumor	42	36	28	25	22
	>0<50% collapse	7	6	5	3	2
	≥50% collapse	0	0	0	0	0
	Dead	0	7	16	21	25
No collapse with ≤50% body involved of the tumor (n=19)	No collapse with ≤50% body involved of the tumor	19	13 (68%)	8 (42%)	7 (37%)	6 (32%)
	>0<50% collapse	0	0	0	0	0
	≥50% collapse	0	0	0	0	0
	Dead	0	6	11	12	13
Total number of the patients		177	134	105	88	70
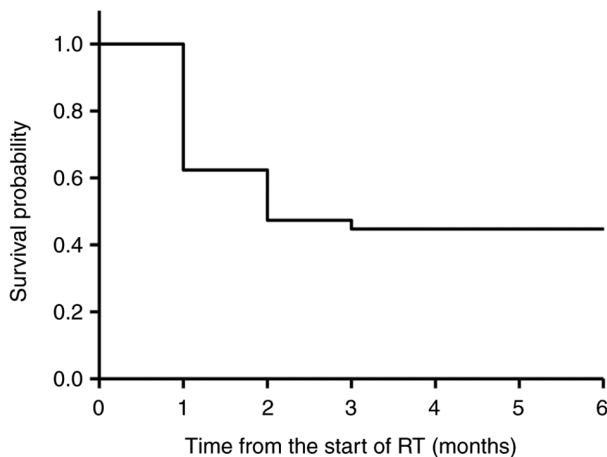
Figure 1. Collapse progression-free rates estimated by the Kaplan-Meier method. The collapse progression-free survival rates were 62, 47, 44, 44 and 44% at the 1-, 2-, 3-, 4- and 6-month time points, respectively.

developed new fracture or progression of existing fracture after RT for spinal metastasis (23). Of these new or worsened fractures, 30 (58.8%) were asymptomatic, and 21 (41.2%) were painful fractures. Rief *et al* reported the occurrence of a new VBC in 2% of patients at the 6-month timepoint after conventional RT in various cancer types (10). In addition, they reported that the thoracic spine showed significantly more fractures than the other vertebrae. However, they did not perform a radiological evaluation to investigate the degree and timing of VBC, especially in the acute period of 1-3 months after RT initiation during which the patients need the most intense clinical care for pain and VBC. Lee *et al* investigated VBC every 2-4 months and reported the occurrence of new VBC in 18% of patients with colorectal cancer who received conventional RT (11). In addition, they also reported that

previously performed irradiation and pre-existing compression fracture were independent risk factors for VBC using the multivariate analysis. However, the application of inconsistent examination time points has led to difficulties in interpreting their outcomes. In this study, the new VBC occurred in 12% of patients that presented without collapse at RT initiation. The study by Lee *et al* did not find pain as the risk factor for VBC in patients with colorectal cancer who received conventional RT (11). However, the present study reports that the degree of pain was a predictor of VBC, as found that moderate or severe pain (NRS (≥4)) was associated with the risk of the occurrence of new VBC. Thus, clinicians should pay attention to moderate or severe pain (NRS (≥4)) to predict the occurrence of new VBC in patients without VBC at RT initiation. Furthermore, it was found that its degree was mild (<50% collapse), occurred within one month after RT initiation and did not progress any further after two months.

In patients presenting with VBC at RT initiation, VBC progressed in 51% of them upon RT treatment. The VBC occurred one month after RT and ceased within two months in most patients with collapse progression-free rates of 62, 47, 44, 44, and 44% at the 1-, 2-, 3-, 4-, and 6-month(s) time points, respectively. In patients with mild collapse at RT initiation, VBC progression occurred in 50%. The collapse occurred briefly after the start of RT until a median of one month. Among them, the VBC progressed to become severe (≥50% collapse) in 12% of patients until a median of one month. However, in patients with severe collapse at RT initiation, VBC progressed within a median of one month in 75% of patients.

Precise assessment of risk factors for the potential progression of VBC is critical during RT initiation to determine patients who require close observation. Multivariate analysis revealed that bone quality (lytic metastases), NRS score (≥4), and tumor involvement of posterolateral elements of the spine were associated with the progression of VBC at the one-month

Table III. Risk factors for new vertebral body collapse at 1 month after RT.

Covariates	Patients without new collapse	Patients with new collapse	Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value
Age, years						
<65	25	3				
≥65	35	5	1.19 (0.260-5.446)	>0.999		
Sex						
Male	36	7				
Female	24	1	0.214 (0.025-1.854)	0.242		
Primary cancer site						
Lung	15	6				
Others	45	2	0.111 (0.020-0.610)	0.009[a]	6.947 (0.889-54.312)	0.065
Radiation site						
Junctional level	17	4				
Mobile segments/ rigid segments	43	4	0.395 (0.089-1.764)	0.240		
Chemotherapy before RT						
Yes	39	2				
No	21	6	5.571 (1.032-30.072)	0.051		
Chemotherapy after RT						
Yes	44	4				
No	16	4	2.750 (0.614-12.317)	0.221		
Overall dose (RT)						
≤35	10	1				
>35	50	7	1.400 (0.155-12.667)	>0.999		
NRS score						
<4	49	3				
≥4	11	5	0.135 (0.028-0.650)	0.015[a]	27.100 (1.859-394.884)	0.0158[a]
Bone Quality						
Lytic	16	6				
Mixed or blastic	44	2	0.121 (0.022-0.663)	0.024[a]	9.305 (0.935-92.564)	0.057
Lung metastases						
Yes	25	4				
No	35	4	0.714 (0.163-3.131)	0.714		
Vertebral body collapse						
No collapse with <50% body involved of the tumor	19	0				
No collapse with >50% body involved of the tumor	41	8	-	0.094		
Posterolateral involvement of spinal elements						
Bilateral /unilateral	5	3				
No involvement	55	5	0.152 (0.028-0.829)	0.046[a]	10.990 (0.687-175.753)	0.090

[a]P<0.05.

follow-up time point. In the vertebral bones, posterolateral elements of the spine (facet, pedicle, or costovertebral joint) play an essential role in spinal stability (24,25) which was previously reported by Taneichi *et al* in patients with lytic vertebral metastases (26). They reported that the risk factors for vertebral body fractures were costovertebral joint destruction in the thoracic region (T1-T10) and pedicle destruction in the thoracolumbar and lumbar region (T10-L5). Therefore,

Table IV. Risk factors for progression of VBC at 1 month after RT.

Covariates	Patients without progression of VBC	Patients with progression of VBC	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years						
<65	20	26				
≥65	33	30	1.430 (0.666-3.071)	0.439		
Sex						
Male	20	26				
Female	33	30	1.401 (0.659-2.980)	0.445		
Primary cancer site						
Lung	16	21				
Others	37	35	1.388 (0.625-3.081)	0.544		
Radiation site						
Junctional level	16	20				
Mobile segments/rigid segments	37	36	1.285 (0.576-2.864)	0.550		
Chemotherapy before RT						
Yes	27	20				
No	26	36	0.535 (0.248-1.152)	0.125		
Chemotherapy after RT						
Yes	32	31				
No	21	25	0.814 (0.380-1.743)	0.699		
Overall dose (RT)						
≤35	44	53				
>35	9	3	0.277 (0.071-1.085)	0.069		
NRS score						
<4	41	25				
≥4	12	31	4.237 (1.845-9.731)	<0.001[a]	2.963 (1.179-7.446)	0.021[a]
Bone Quality						
Lytic	12	30				
Mixed or blastic	41	26	3.942 (1.718-9.045)	0.002[a]	3.138 (1.280-7.698)	0.013[a]
Lung metastases						
Yes	26	24				
No	27	32	0.779 (0.366-1.657)	0.567		
VBC						
<50% collapse	2	6				
≥50% collapse	51	50	3.060 (0.589-15.888)	0.272		
Posterolateral involvement of spinal elements						
Bilateral/Unilateral	9	25				
No involvement	44	31	3.943 (1.619-9.599)	0.002[a]	2.735 (1.026-7.294)	0.044[a]

[a]P<0.05. Vertebral body collapse, VBC.

clinicians should pay close attention to the destruction of the posterolateral elements of the spine for the assessment and prediction of potential VBC progression. In previous studies, lytic metastases were reported to be associated with spinal instability (14,27). The present study also found an association between bone lesions (lytic metastases) and the progression of VBC. Lytic metastases without bone formation can be at a higher risk for compression since they cannot withstand axial load.

This study demonstrated that moderate or severe pain (NRS (≥4)) was associated with the risk of both new VBC occurrence and progression of VBC. Pain can be easily measured at the bedside and is often used in the treatment of bone metastasis. Therefore, the study findings suggest that NRS is a useful index for predicting the occurrence and progression of VBC.

The present study had a few limitations. First, not all the patients were followed up for 6 months. However, this

is a common limitation of studies involving patients with bone metastases, given their relatively shorter survival time. Second, the inherent bias in the choice of fractionation used, where radiotherapy with fewer dose fractions was given for patients with greater metastatic burden or for the histologies known to be predictive of shorter survival.

In conclusion, new VBC with a mild degree (<50% collapse) occurred in 12% of patients without collapse within a month. Moderate or severe pain (NRS (≥4)) was the predictor of the occurrence of new VBC. However, progression of VBC after RT occurred in 51% of patients with collapse at RT initiation. Bone quality (lytic metastases), NRS score (≥4), and tumor involvement of posterolateral elements of the spine were associated with the progression of VBC at the one-month follow-up time point. This ensures proper evaluation of the effectiveness of conservative treatment and facilitates the determination of patients who require close monitoring.

Acknowledgements

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

EN, SS, and TO designed the study. EN and SS collected and analyzed data. EN and RN confirm the authenticity of the raw data. RN, HK and TI analyzed the data. EN and SS treated the patients presented in this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective chart review study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the Shikoku Cancer Ethics Committee approved this study (approval No. 2017-26). Written informed consent was obtained from every participant included in this study.

Patient consent for publication

All the participants provided written informed consent for this study.

Competing interests

The authors declare that they have no competing interests.

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