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Research Paper

Clinical and dosimetric risk factors for vertebral compression fracture after single-fraction stereotactic body radiation therapy for spine metastases

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ABSTRACT

Objectives: This analysis was performed to evaluate the incidence of vertebral compression fracture (VCF) and determine the contributing factors for VCF in patients undergoing single-fraction stereotactic body radiotherapy (SBRT) for spinal bone metastases (SBM).
Methods: A retrospective review of medical records was conducted for patients undergoing SBRT for SBM at our institution between January 2010 and December 2018. Patients who had undergone neither pre-SBRT surgical excision nor post-SBRT prophylactic fixation were included. The effects of clinical and dosimetric parameters were analyzed with respect to VCF risk. The following dosimietric parameters of the planning target volume (PTV) were calculated: mean/minimum/maximum dose, radiation dose to 10–90% volume, and irradiated volume receiving more than 10–25 Gy ($PTV\_V_{10-25\ Gy}$).
Results: Among 163 patients (179 vertebrae), 21 (12.8%) experienced VCF. The 1-year and 2-year VCF rates were 12.1% and 13.2%, respectively. Among dosimetric parameters, PTV_V15 Gy was the most significant for VCF prediction. In a univariate analysis, breast or prostate primary, no vertebral body collapse, and $PTV\_V_{15\ Gy} \leq 42\ cm^3$ were significantly associated with a lower incidence rate of VCF. In a multivariate analysis, $PTV\_V_{15\ Gy}$ was the only significant factor for VCF risk. The 1-year VCF rate was 3.8% in patients with $PTV\_V_{15\ Gy} \leq 42\ cm^3$, while it was 22.1% in those with $PTV\_V_{15\ Gy} > 42\ cm^3$ ($p < 0.01$).
Conclusions: SBRT-related VCF was found in 12% of patients in our institution. The $PTV\_V_{15\ Gy}$ is a significant factor for VCF prediction.

1. Introduction

Bones are one of the most common sites for metastases either at primary cancer diagnosis or at the time of cancer progression [1]. Approximately 88% of prostate cancers, 53% of breast cancers, and 36% of lung cancers spreads to bones in stages of metastasis [2]. Bone metastasis may cause pain, fractures, and neurologic complications [1]. In cases with spinal bone metastases (SBM), metastatic bone lesions can result in spinal instability or cord compression, which may deteriorate the patient's quality of life [3]. Since the spine protects the spinal cord and allows carrying loads [4], it is important to preserve spinal stability while treating SBM.

Radiotherapy is an effective modality for relieving pain and stabilizing the spine in patients with SBM [5,6]. Conventional radiotherapy that delivers 0.8–4 Gy per daily fractions over 1–2 weeks has been proven to be effective for the palliation of painful bone metastasis [5]. However, conventional radiotherapy has a limitation in delivering a high radiation dose to the spine due to the tolerance of the spinal cord or cauda equina. Stereotactic body radiation therapy (SBRT) has been increasingly used to administer a potentially ablative radiation dose to the tumor while sparing other organs at risk [7]. Given the dosimetric merit, SBRT has emerged as an effective modality for treating SBM [8]. Several studies have shown local tumor control rates of>80% after SBRT for SBM [9]. However, 4%-39% of patients develop vertebral

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compression fracture (VCF) after SBRT [10–12]. Since VCF itself may result in spinal instability and neurologic compromise, it is necessary to minimize the risk of VCF in patients receiving SBRT for SBM [13]. Risk factors for VCF development have not been well recognized so far, which makes it difficult for physicians to select suitable patients for SBRT in the treatment of SBM. This analysis was performed to evaluate the incidence of VCF at our institution and determine the contributing factors for VCF in patients undergoing SBRT for SBM.

2. Materials and Methods

2.1. Patients and radiotherapy

Between January 2010 and December 2018, 323 patients received SBRT for SBM at our hospital. Of the 323 patients, patients who met the following criteria were included in this study: (1) minimum follow-up duration of 6 months after SBRT, (2) no prophylactic fixation after SBRT, and (3) no surgical excision of the spinal tumor prior to SBRT. Patients were excluded from the study if they (1) underwent multiple fractionated SBRT (n = 9), (2) had died within 6 months after SBRT (n = 107), (3) were lost to follow-up (n = 35), (4) had spinal tumor resection prior to SBRT (n = 5), or (5) underwent prophylactic fixation (n = 4). Accordingly, a total of 163 patients (179 vertebrae) were analyzed in this study with the approval of our institutional review board (SMC 2020–04-044–001).

The median age of the patients was 58 years (range, 34–86 years). Thirty-three (20.2%) patients had solitary SBM without the involvement of another organ. The histologic type of primary cancer was adenocarcinoma in 50 (30.7%), hepatocellular carcinoma in 45 (27.6%), ductal carcinoma in 23 (14.1%), renal cell carcinoma in 21 (12.9%), squamous cell carcinoma in 5 (3.1%), sarcoma in 4 (2.5%), and others in 15 (9.2%) patients. As per our institutional protocol, all patients were evaluated using spine magnetic resonance imaging (MRI) before SBRT. Based on the MRI, the Spinal Instability Neoplastic Sore (SINS) [14] was assessed. After SBRT for SBM, 26 (15.9%) patients received bone-modifying agents (BMA); 5 (3.1%) patients had less than 2 months of BMA while 21 (12.9%) patients were treated with BMA for more than 1 year. Details of patient characteristics are presented in Table 1.

Radiotherapy simulation and planning were conducted following our institutional SBRT protocol as previously reported [15]. Briefly, all patients underwent simulation with dedicated computed tomography (CT) and MRI with an immobilization device. Organs at risk and target volumes, including gross tumor volume and clinical target volume (CTV), were delineated on CT and MRI according to the Radiation Therapy Oncology Group 0631 protocol [16] or the International Spine Radiosurgery Consortium guideline [17]. Involved vertebral body (VB), pedicles, and/or gross paraspinal lesions were included in the CTV. The planning target volume (PTV) was equally treated as CTV, with no CTV expansion. The treatment plan was optimized to cover ≥90% of the PTV by the prescription dose. Volumetric modulated arc radiotherapy using a 6MV linear accelerator was conducted in all patients. The median radiation dose was 20 Gy (range, 10–24 Gy).

2.2. Evaluation of VCF and local control

After SBRT, patients underwent clinical and imaging follow-ups with spinal MRI or CT every 1–3 months for the first 2 years, and every 6 months for the years 3–5, and then yearly thereafter. Post-SBRT VCF was defined as either a new development of VCF or the progression of an existing fracture at the treated vertebra. New end-plate fracture or any loss of VB height, which was identified by comparisons of pre- and post-SBRT spinal images, was classified as VCF. Concomitant VCF development and tumor progression were not considered as VCF events to distinguish SBRT-related VCF from tumor-related VCF. This VCF definition is consistent with that of prior studies [11,12,18,19]. Local control was defined as the absence of radiographic tumor progression within the SBRT field. An increase in tumor size or osteolytic lesion within the SBRT field was defined as local progression. Diagnoses of VCF or local progression were made after discussions with neuroradiologists, neurosurgeons, and radiation oncologists.

To evaluate the effects of dosimetric parameters on VCF risk, the dose-volume histogram (DVH) of the PTV was analyzed. The following parameters of PTV were obtained from the DVH: mean dose (PTV_D_{mean}), maximum dose (PTV_D_{max}), minimum dose (PTV_D_{min}), radiation dose to 10%, 50%, 60%, 70%, 80%, and 90%

Table 1
Patient characteristics.

Characteristics		Number of patients (%)
Age	≤58	84 (51.5)
	>58	79 (48.5)
Sex	Male	101 (62.0)
	Female	62 (38.0)
Previous history of RT at involved vertebra	No	153 (93.9)
	Yes	10 (6.1)
Type of primary cancer	Breast	23 (14.1)
	Prostate	12 (7.4)
	Urogenital	21 (12.9)
	Colorectal	12 (7.4)
	Lung & thorax	16 (9.8)
	Hepatobiliary	57 (35.0)
	Others	22 (13.5)
Site of bone metastasis	Body and/or pedicle	143 (87.8)
	Spinous or transverse process	20 (12.2)
Number of vertebrae receiving RT	1	150 (92.0)
	2	10 (6.2)
	3	3 (1.8)
Region of involved spine	Cervical spine	17 (10.4)
	Thoracic spine	77 (47.2)
	Lumbar spine	67 (41.1)
	Sacral spine	2 (1.3)
Pre-RT fracture	Absent	136 (83.4)
	Present	27 (16.6)
SINS location score	1	39 (23.9)
	2	47 (28.8)
	3	77 (47.2)
SINS pain score	0	56 (34.4)
	1	74 (45.4)
	3	33 (20.2)
SINS bone lesion score	0	27 (16.6)
	1	58 (35.6)
	2	78 (47.9)
SINS alignment score	0	161 (98.8)
	2	2 (1.2)
SINS VB collapse score	0	107 (65.6)
	1	32 (19.6)
	2	21 (12.9)
	3	3 (1.8)
SINS posterolateral involvement score	0	107 (65.6)
	1	55 (33.7)
	3	1 (0.6)
SINS total score	≤ 6	92 (56.4)
	> 6	71 (43.6)
Use of bone-modifying agents	Never	137 (84.0)
	Intermittently	5 (3.1)
	Continuously	21 (12.9)
Dose fractionation schedule	10–16 Gy/1 fx	8 (4.9)
	18–24 Gy/1 fx	155 (95.1)

Abbreviations: VB, vertebral body; RT, radiotherapy; SINS, Spinal Instability Neoplastic Score; Gy, gray; fx, fractionation.

volume of the PTV (PTV_$D_{10-90\%}$), and an irradiated volume receiving more than 10, 15, 20, and 25 Gy (PTV_$V_{10-25\ Gy}$).

2.3. Statistical analysis

A comparison of variables between patients with and without VCF was performed using the Fisher's exact test or the Student's *t*-test. Logistic regression analysis and stepwise selection were used to evaluate the relationship between dosimetric parameters and VCF. The area under the curve (AUC) in the receiver operating characteristics (ROC) analysis was calculated for each dosimetric parameter. The AUC values of the dosimetric parameters were compared to assess the most predictive dosimetric factor for VCF. Some continuous variables were dichotomized using a cut-off point indicated by the ROC analysis. The Probit regression analysis was use to analyze the dose–response relationship between dosimetric parameters and the probability of VCF. Survival duration was assessed using the Kaplan–Meier method and comparisons of survivals between groups were conducted using the log-rank test. The VCF incidence rate, local progression-free survival (LPFS), and overall survival (OS) were defined as the interval from the date of SBRT to the date of VCF, local progression, and death, respectively. The Cox proportional-hazards regression analysis was used to analyze the effect of variables on the VCF incidence rate. Variables with a significance at $p < 0.05$ on univariate analysis were retained in the multivariable analysis. *P*-values < 0.05 were considered significant. All statistical analyses were performed using the MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

3. Results

A total of 21 (12.8%) patients (21 vertebrae) experienced VCF with a median follow-up of 16 months (range, 6–90 months). Of the patients with VCF, 16 (9.8%) had a de novo fracture and 5 (3.0%) showed the progression of a prior fracture. The median time to VCF occurrence was 6 months (range, 1–45 months), and 60% of VCF developed within 8 months after SBRT. The 1-year and 2-year VCF rates were 12.1% and 13.2%, respectively (Supplementary Fig. 1). The region of the spine involved in VCF was the thoracic spine in 10 patients and lumbar spine in 11 patients. All VCF lesions were found within the radiotherapy field. Patients with VCF were managed as follows: observation, 4 (19.1%); analgesics, 9 (42.9%); vertebroplasty, 6 (28.5%); and spinal surgery using screw fixation, 2 (9.5%). There were 41 patients with local progression after SBRT. The 2-year LPFS and OS rates were 71.1% and 65.2%, respectively.

In a comparison of dosimetric parameters between patients with - and without VCF, the mean values of PTV_D_{max}, PTV_D_{mean}, PTV _$D_{10-95\%}$, and PTV_$V_{10-25\ Gy}$ were significantly higher in patients with VCF than in those without VCF (Table 2). Among dosimetric parameters, PTV_$V_{15\ Gy}$ was the most significant parameter for predicting VCF risk (AUC = 0.710, 95% confidence interval 0.636 – 0.776). In a univariate analysis, breast or prostate primary, no VB collapse before SBRT, and PTV_$V_{15\ Gy} \leq 42\ cm^3$ were significantly associated with a lower incidence rate of VCF. In a multivariate analysis, PTV_$V_{15\ Gy}$ was the only significant factor related to the VCF rate (Table 3). The 1-year VCF rate was 3.8% in patients with PTV_$V_{15\ Gy} \leq 42\ cm^3$, while it was 22.1% in those with PTV_$V_{15\ Gy} > 42\ cm^3$ ($p < 0.01$) (Fig. 1). The probability of VCF increases as the value of PTV_$V_{15\ Gy}$ increases, with a statistical significance ($p < 0.01$). The estimated probability of VCF according to PTV_$V_{15\ Gy}$ is depicted in Fig. 2.

4. Discussion

In this retrospective single-center analysis, we found that 12% of our patients experienced VCF, and approximately 60% of the VCF occurred within 8 months after single-fraction SBRT for SBM. Even in patients presenting with VCF, >60% of cases were manageable with conservative treatment. Clinical parameters, including primary cancer type and VB collapse before SBRT, were significantly associated with the VCF risk. Besides, there was also a significant relationship between VCF and dosimetric parameters, including PTV_$V_{10-25\ Gy}$, PTV _$D_{10-90\%}$, and PTV_D_{max}. Among dosimetric parameters, PTV_$V_{15\ Gy}$ was found to be most closely associated with VCF development. In an analysis incorporating PTV_$V_{15\ Gy}$ and clinical parameters, VCF incidence was significantly different depending on the values of PTV_$V_{15\ Gy}$. Furthermore, the probability of VCF occurrence is estimated to increase as the value of PTV_$V_{15\ Gy}$ increases. PTV_$V_{15\ Gy} \leq 42\ cm^3$ was a statistically significant factor for predicting low VCF incidence. Therefore, PTV_$V_{15\ Gy} \leq 42\ cm^3$ is expected to be used as a dosimetric guidance to minimize VCF incidence in patients receiving SBRT for SBM.

SBM itself increases fracture risk by altering bone turnover and decreasing bone quality [20]. In addition to the effect of metastatic tumors, radiation may induce VCF by damaging the collagen molecular structure with breaking the peptide bond [21] in patients undergoing radiotherapy for SBM. Moreover, bone strength and fracture resistance progressively decrease with increasing radiation dose to the bone [21,22]. Therefore, patients undergoing high-dose radiotherapy using SBRT are at high risk for VCF development. According to prior literature, radiation dose levels are closely related to the degree of degradation in bone strength and bone remodeling cells [23]. Furthermore, radiation-induced bone losses are also resulted from vascular destruction [24] and bone microenvironmental changes [23]. Therefore, fracture risk is likely to be affected by the extent of irradiated volume as well as by the level of radiotherapy dose. These findings suggest that dosimetric parameters have a significant influence on VCF risk in patients receiving SBRT for SBM. However, there have been few data showing the relevance of dosimetric parameters to VCF risk.

Previous studies showed that the rate of VCF was significantly dependent on the radiation dose level in patients undergoing SBRT for SBM [20,25,26]. In studies by Cunha et al. [25] and Sahgal et al. [20], doses per fraction of 20 Gy or greater was a significant predictor of VCF after SBRT. In their studies, various fractionation schedules of 8–26 Gy /1 fraction, 18–26 Gy/2 fractions, 18–35 Gy/3 fractions, 25–35 Gy/4 fractions, and 25–35 Gy/5 fractions were used. In addition to the fractional dose, a total prescription dose of 38.4 Gy or more was associated with an increased risk of VCF after 1–5 fractionated SBRT in a multi-center study by Jawad et al. [26]. The studies by Cunha et al. and Sahgal et al. did not incorporate an irradiated target volume into their evaluation; only the radiation dose was taken as a dosimetric factor to be analyzed. In a study by Jawad et al., a prescription dose to a high-dose target volume was not associated with increased VCF risk. Therefore, there have been limitations in understanding the effects of an irradiated volume on VCF risk. More recent studies have reported that the radiation dose administered to a certain percentage of PTV was a significant predictor for VCF development [27,28]. Tseng et al. showed that higher PTV_$D_{90\%}$ was significantly associated with increased VCF risk in patients receiving 24 Gy in 2 fractionations SBRT [27]. Similarly, Chen et al. reported in a single institutional study that PTV_$D_{80\%}$ was a significant dosimetric parameter for VCF prediction in patients treated with 15–30 Gy/1–5 fractions SBRT [28]. Likewise, we also found that there was a significant association between VCF and values of PTV_$D_{80\%}$ and PTV_$D_{90\%}$ in our study. However, when several dosimetric parameters were

Table 2
Comparison of dosimetric parameters according to vertebral compression fracture.

Parameters	Mean value*		Comparison of mean value	AUC†	Logistic regression		
	VCF+ (95% CI)	VCF− (95% CI)	*p*-value*		*p*-value‡	OR	95% CI
PTV_D_{min} (cGy)	1159 (985, 1333)	1049 (1006, 1093)	0.44	0.574	–	–	–
PTV_D_{mean} (cGy)	1896 (1617, 2174)	1771 (1722, 1820)	< 0.01	0.587	–	–	–
PTV_D_{max} (cGy)	2264 (1854, 2674)	2085 (2033, 2137)	0.02	0.641	–	–	–
PTV_$D_{10\%}$ (cGy)	2247 (1926, 2569)	2002 (1960, 2044)	< 0.01	0.620	–	–	–
PTV_$D_{50\%}$ (cGy)	1974 (1791, 2158)	1803 (1755, 1851)	0.01	0.595	–	–	–
PTV_$D_{60\%}$ (cGy)	1915 (1746, 2084)	1746 (1696, 1796)	0.02	0.593	–	–	–
PTV_$D_{70\%}$ (cGy)	1859 (1692, 2026)	1684 (1632, 1737)	0.02	0.596	–	–	–
PTV_$D_{80\%}$ (cGy)	1793 (1622, 1964)	1617 (1563, 1671)	0.02	0.600	–	–	–
PTV_$D_{90\%}$ (cGy)	1706 (1527, 1884)	1526 (1472, 1581)	0.02	0.609	–	–	–
PTV_$D_{95\%}$ (cGy)	1663 (1455, 1816)	1443 (1389, 1496)	0.01	0.633	–	–	–
PTV_$V_{10\ Gy}$ (cm^3)	83 (59, 107)	56 (48, 63)	< 0.01	0.677	–	–	–
PTV_$V_{15\ Gy}$ (cm^3)	78 (54, 103)	46 (39, 53)	< 0.01	0.710	< 0.01	1.11	1.05–1.13
PTV_$V_{20\ Gy}$ (cm^3)	31 (8, 53)	14 (11, 18)	0.01	0.623	–	–	–
PTV_$V_{25\ Gy}$ (cm^3)	11 (0, 33)	1 (0, 2)	< 0.01	0.554	–	–	–
PTV volume (cm^3)	83 (59, 107)	57 (49, 64)	< 0.01	0.668	–	–	–

Abbreviations: VCF, vertebral compression fracture; VCF+, patients with VCF; VCF-, patients without VCF; CI, confidence interval; AUC, area under the curve; OR, odds ratio; PTV, planning target volume; D_{min}, minimal radiation dose to PTV; D_{mean}, mean radiation dose to PTV; D_{max}, maximal radiation dose to PTV; $D_{x\%}$, radiation dose receiving × % volume of PTV; $V_{x\ Gy}$, PTV volume receiving more than × cGy.
*Analyzed by the Student's *t*-test.
†Area under the receiver operating characteristics curve.
‡Analyzed by a multiple logistic regression analysis and stepwise selection.

Table 3
Analyses for risk factors for vertebral compression fracture.

Characteristics		1-year VCF (%)	2-year VCF (%)	Univariate *p*-value	Multivariate *p*-value	HR (95% CI)
Age	≤ 55	10.3	10.3	0.20	–	
	> 55	13.7	15.9			
Sex	Male	9.5	11.5	0.51	–	
	Female	16.0	16.0			
Previous history of RT at involved vertebra	No	11.5	12.7	0.39	–	
	Yes	20.0	20.0			
Primary cancer	Breast or prostate	0.0	0.0	0.01	0.06	6.63 (0.86–50.95)
	Others	15.8	17.5			
Site of bone metastasis	Body or pedicle	13.7	15.0	0.07	–	
	Spinous or transverse	0.0	0.0			
Number of vertebrae receiving RT	Single	12.8	14.1	0.37	–	
	Multiple	8.2	8.2			
Pre-RT fracture	Absent	10.8	12.1	0.23	–	
	Present	18.5	18.5			
SINS_VB collapse score	≤0	7.3	8.9	0.01	0.12	2.02 (0.83–4.94)
	>0	21.7	21.7			
SINS total score	≤6	8.2	10.0	0.11	–	
	>6	15.4	15.4			
Use of bone-modifying agents	Never/intermittently	14.0	14.0	0.16	–	
	Continuously	0.0	5.9			
Dose per fraction	≤21 Gy	12.1	12.1	0.49	–	
	>21 Gy	11.9	20.7			
PTV_V15 Gy	≤42 cm^3	3.8	5.6	< 0.01	< 0.01	3.6 (1.43–9.09)
	>42 cm^3	22.1	22.1			

Abbreviations: VCF, vertebral compression fracture; CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SINS, Spinal Instability Neoplasm Score; VB, vertebral body; Gy, gray; PTV, planning target volume; $V_{15\ G}$, volume receiving ≥15 Gy.

compared using the AUC of ROC, PTV_$V_{15\ Gy}$ showed better performance than any other dosimetric parameters for distinguishing between positive and negative VCF. Based on this analysis, we can postulate that PTV volume receiving a certain radiation dose has a significant impact on VCF development in patients with SBRT. Therefore, it is necessary to consider the irradiated PTV volume, as well as the radiotherapy dose level, in the prediction of each patient's VCF risk.

Even if PTV_$V_{15\ Gy}$ was analyzed as the best dosimetric classifier in identifying a group of patients with VCF risk, the AUC value (0.710) was not outstandingly high in our study. More than 95% of our patients underwent single-fraction SBRT using a narrow range of radiotherapy doses at 18–24 Gy. Additionally, the proportion of VCF events was relatively small at 12%. These findings may have contributed to the modest AUC value of PTV_$V_{15\ Gy}$ in our study. Further studies with a larger number of patients are necessary to identify more optimal parameters for VCF prediction. Although PTV_$V_{15\ Gy}$ showed a modest AUC in VCF discrimination, VCF incidence rates were significantly different by PTV_$V_{15\ Gy}$ values. Patients with PTV_$V_{15\ Gy}$ > 42 cm^3 had a VCF risk of 22.1%, while those with PTV_$V_{15\ Gy}$ ≤42 cm^3 had a VCF risk of 3.8% at 1-year after SBRT. Given these results, close follow-up care and prophylactic vertebroplasty should be considered for patients who are deemed to receive ≥15 Gy to more than 42 cm^3 of their PTV. Considering that the involved VB was entirely delineated as PTV and more than 87% of our

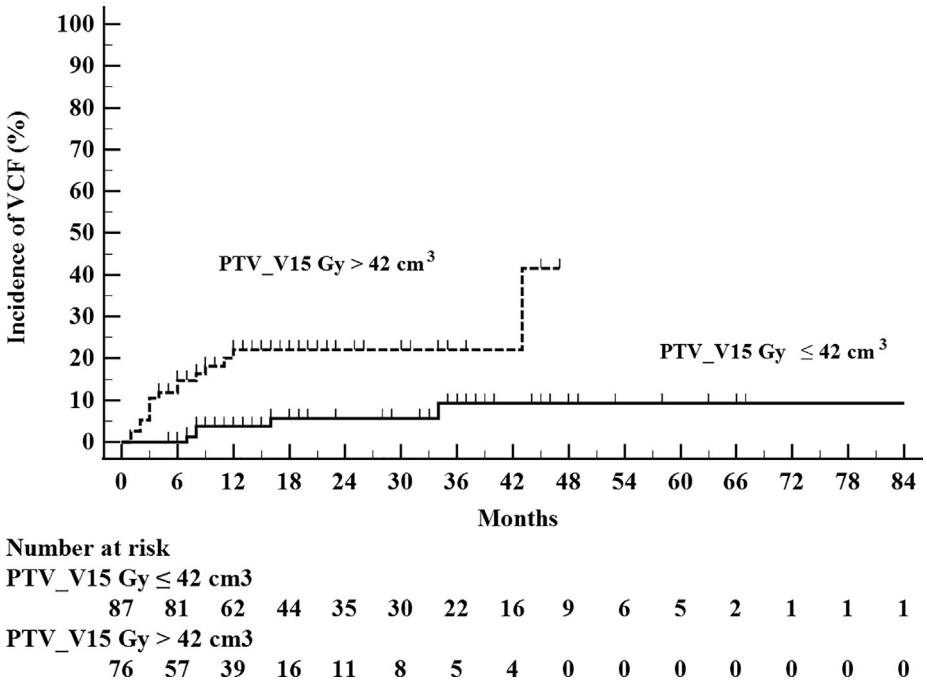

Fig. 1. Incidence of VCF in patients with PTV_V_{15} ≤42 cm^3 and those with PTV_V_{15} > 42 cm^3. Abbreviations: VCF, vertebral compression fracture; PTV, planning target volume; $V_{15\ G}$, volume receiving ≥15 Gy.

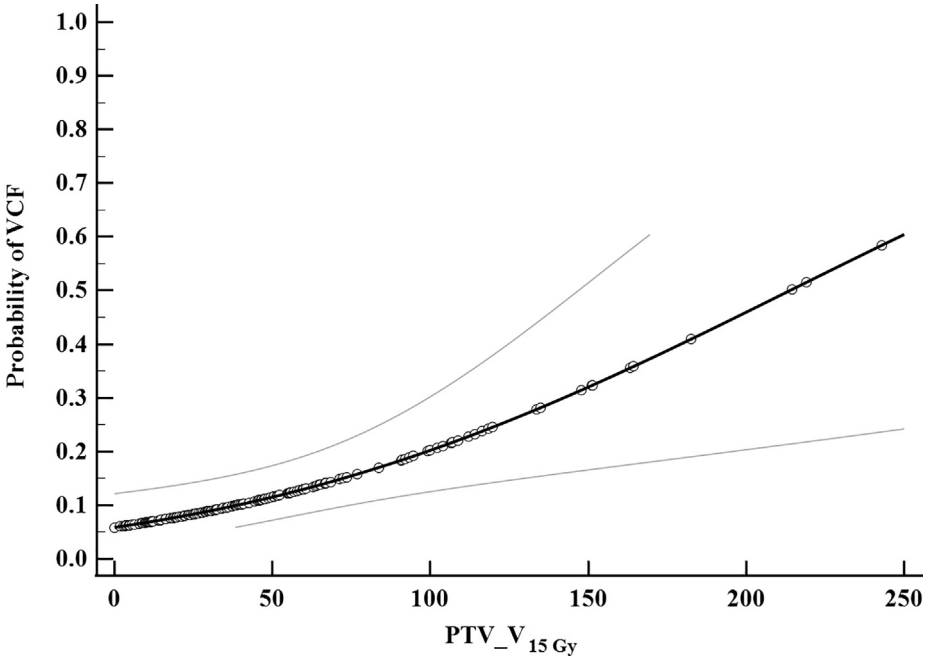

Fig. 2. Estimated probability of VCF according to PTV_V_{15}. Abbreviations: VCF, vertebral compression fracture; PTV, planning target volume; $V_{15\ G}$, volume receiving ≥15 Gy.

patients had VB involving lesions, our PTV volume almost represents the VB volume within the SBRT field. Therefore, our finding that a specific PTV volume receiving a certain radiation dose was associated with VCF risk suggests that irradiated VB volume is likely to have a significant impact on VCF development. Further studies are needed to clarify the relationship between irradiated VB volume and VCF risk.

In addition to dosimetric parameters, the primary cancer type was also a significant determinant of VCF in our analysis. Approximately 21% of our patients had primary tumor in the breast or prostate. Among them, no patient developed VCF after SBRT. When variables were compared between patients with breast or prostate primary and those with other cancers, the distribution of sex, SINS score, and BMA usage was significantly different between the two groups (Table 4**).** Patients with breast or prostate primary tend to have lower scores in SINS pain and bone lesion components. That is, more patients with breast or prostate primary had non-lytic bone lesions and pain-free SBM than those with other cancers. Additionally, 48% of patients with breast or prostate primary were treated with BMA for more than 1 year after SBRT, while only 3% of

Table 4
Patient characteristics according to primary cancer type.

Characteristics		Breast or prostate primary N = 35	Others N = 128	*p*-value*
Age	≤55	20	64	0.45
	>55	15	64	
Sex	Male	12	89	< 0.01
	Female	23	39	
Previous history of RT at involved vertebra	No	32	121	0.49
	Yes	3	7	
Site of bone metastasis	Body or pedicle	31	112	0.86
	Spinous or transverse	4	16	
Number of vertebrae receiving RT	Single	32	103	0.12
	Multiple	3	25	
Pre-radiotherapy fracture	Absent	33	103	0.05
	Present	2	25	
SINS_ location score	1	8	31	0.84
	2	9	38	
	3	18	59	
SINS pain score	0	21	35	< 0.01
	1	9	65	
	3	5	28	
SINS bone lesion score	0	12	15	< 0.01
	1	13	45	
	2	10	68	
SINS alignment score	0	35	126	0.45
	2	0	2	
SINS VB collapse score	0	28	79	0.11
	1	6	26	
	2	1	20	
	3	0	3	
SINS posterolateral involvement score	0	25	82	0.09
	1	9	46	
	3	1	0	
SINS total score	≤ 6	27	65	<0.01
	> 6	8	63	
Use of bone-modifying agents	Never/intermittently	18	124	<0.01
	Continuously	17	4	
Dose per fraction	≤21 Gy	34	111	0.08
	>21 Gy	1	17	
PTV_$V_{15\ Gy}$	≤42 cm^3	23	64	0.09
	>42 cm^3	12	64	

Abbreviations: VCF, vertebral body compression fracture; RT, radiotherapy; SINS, Spinal Instability Neoplastic Score; VB, vertebral body; Gy, gray; PTV, planning target volume; $V_{15\ G}$, volume receiving ≥15 Gy.
* Analyzed by the Fisher's exact test.

patients with other cancers received BMA. The significant imbalance in the proportion of BMA usage between patients with breast or prostate cancer and those with other cancers is likely caused by the reimbursement policy under the Korean health insurance system [29]. In the Republic of Korea, the national health insurance covers the costs of BMA for bone metastasis; however, the coverage is limited to cases with osteolytic metastasis from breast or prostate primary cancer. Patients with bone metastasis with sites of origin other than the breast or prostate should pay for BMA with their own out-of-pocket money. BMA, including bisphosphonate and denosumab, increases bone mineral density and significantly decreases skeletal-related events from bone metastasis [30]. In patients undergoing radiotherapy for bone metastasis, the irradiated bone exhibits increased density, which lasts for several months following conventionally fractionated radiotherapy [6]. Moreover, in cases with osteolytic metastasis, concurrent administration of BMA and radiotherapy results in a higher response rate and bone density improvement compared with BMA alone [6,31]. Such synergistic effect of BMA and radiotherapy on bone quality was also observed in our study. In the current analysis, PTV_$V_{15\ Gy}$ was not significantly different between patients with breast or prostate primary cancer and those with other cancers. Even with similar dosimetric characteristics between the groups, the risk of VCF was significantly lower in patients with breast or prostate primary tumors than in those with non-breast or prostate primary tumors. The protective effect of breast or prostate primary against VCF is likely to result from the characteristics of metastatic lesions and BMA usage. Considering the probable protective effect of BMA on VCF, the BMA prescription needs to be considered in patients at high risk for SBRT-related VCF. Specifically, in patients whose SBRT plan shows PTV_$V_{15\ Gy}$ > 42 cm^3, BMA may be useful to mitigate VCF risk. In the current analysis, the radiation dose did not differ according to the receipt of BMA (Table 5), because the total SBRT dose was determined by the physician's preference regardless of BMA administration. If the effect of BMA in reducing the risk of VCF is more clearly identified in the future, the SBRT dose is expected to be safely escalated when BMA is concurrently administered in patients with SBM. However, currently, there is insufficient evidence regarding the effects of BMA in preventing SBRT-related VCF. Further studies are necessary to determine the optimal approach for VCF prevention in patients undergoing SBRT for SBM.

This study has a limitation. The prescribed radiation dose was not converted to the biologically equivalent dose in our analysis. This was because the biologically effective dose model in high-dose per fraction treatments has been questioned [32,33]. Thus, there may be limitations in the universal applications of our dosimetric results to other SBRT studies where different fractionational schedules are used. However, given that all our patients underwent single-fraction SBRT, the dosimetric constraint suggested by our analysis can be useful for patients undergoing single-fraction SBRT for SBM.

Table 5
Patient characteristics according to bone-modifying agent usage.

Characteristics		BMA (+) N = 26	BMA (−) N = 137	*p*-value*
Age	≤55	16	49	0.01
	>55	10	88	
Sex	Male	6	95	<0.01
	Female	20	42	
Previous history of RT at involved vertebra	No	24	129	0.72
	Yes	2	8	
Primary cancer	Breast or prostate	21	14	<0.01
	Others	5	123	
Site of bone metastasis	Body or pedicle	21	122	0.23
	Spinous or transverse	5	21	
Number of vertebrae receiving RT	Single	24	111	0.16
	Multiple	2	26	
Pre-radiotherapy fracture	Absent	25	111	0.06
	Present	1	26	
SINS_ location score	1	9	30	0.29
	2	5	42	
	3	12	65	
SINS pain score	0	14	42	0.07
	1	8	66	
	3	4	29	
SINS bone lesion score	0	10	17	<0.01
	1	8	50	
	2	8	70	
SINS alignment score	0	26	135	0.53
	2	0	2	
SINS VB collapse score	0	23	84	0.04
	1	3	29	
	2	0	21	
	3	0	3	
SINS posterolateral involvement score	0	21	86	0.20
	1	5	50	
	3	0	1	
SINS total score	≤ 6	21	71	<0.01
	> 6	5	66	
Dose per fraction	≤ 21 Gy	25	120	0.20
	> 21 Gy	1	17	
PTV_$V_{15\ Gy}$	≤ 42 cm^3	19	68	0.02
	> 42 cm^3	7	69	
Vertebral compression fracture	None	25	117	0.13
	Yes	1	20	

Abbreviations: BMA, bone-modifying agent; RT, radiotherapy; SINS, Spinal Instability Neoplastic Score; VB, vertebral body; Gy, gray; PTV, planning target volume; $V_{15\ G}$, volume receiving ≥15 Gy.
* Analyzed by the Fisher's exact test.

5. Conclusions

In conclusion, SBRT-related VCF was found in 12% of patients with SBM in our institution. PTV_$V_{15\ Gy}$ was a significant factor for VCF prediction. Considering that patients with PTV_$V_{15\ Gy}$ > 42-cm_3 had a 1-year VCF risk of 22.1%, specific preventive approaches against VCF are needed for these patient groups.

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CRediT authorship contribution statement

Haeyoung Kim: Conceptualization, Data curation, Writing - original draft. **Hongryull Pyo:** Writing - review & editing. **Hee Chul Park:** Writing - review & editing. **Do Hoon Lim:** Writing - review & editing. **Jeong Il Yu:** Writing - review & editing. **Won Park:** Writing - review & editing. **Yong Chan Ahn:** Writing - review & editing. **Doo Ho Choi:** Writing - review & editing. **Dongryul Oh:** Writing - review & editing. **Jae Myoung Noh:** Writing - review & editing. **Won kyung Cho:** Writing - review & editing. **Gyu Sang Yoo:** Writing - review & editing. **Sang Hoon Jung:** Data curation, Software, Validation. **Eun-Sang Kim:** Writing - review & editing. **Sun-Ho Lee:** Writing - review & editing. **Se-Jun Park:** Writing - review & editing. **Chong-Suh Lee:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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