Vertebral Compression Fracture After Spine Stereotactic Body Radiotherapy: The Role of Vertebral Endplate Disruption

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BACKGROUND AND OBJECTIVES: Vertebral compression fracture (VCF) is a common, but serious toxicity of spinal stereotactic body radiotherapy (SBRT). Several variables that place patients at high risk of VCF have previously been identified, including advanced Spinal Instability Neoplastic Score (SINS), a widely adopted clinical decision criterion to assess spinal instability. We examine the role of tumoral endplate (EP) disruption in the risk of VCF and attempt to incorporate it into a simple risk stratification system.

METHODS: This study was a retrospective cohort study from a single institution. Demographic and treatment information was collected for patients who received spinal SBRT between 2013 and 2019. EP disruption was noted on pre-SBRT computed tomography scan. The primary end point of 1-year cumulative incidence of VCF was assessed on follow-up MRI and computed tomography scans at 3-month intervals after treatment.

RESULTS: A total of 111 patients were included. The median follow-up was 18 months. Approximately 48 patients (43%) had at least one EP disruption. Twenty patients (18%) experienced a VCF at a median of 5.2 months from SBRT. Patients with at least one EP disruption were more likely to experience VCF than those with no EP disruption (29% vs 6%, $P < .001$). A nomogram was created using the variables of EP disruption, a SINS of ≥7, and adverse histology. Patients were stratified into groups at low and high risk of VCF, which were associated with 2% and 38% risk of VCF ($P < .001$).

CONCLUSION: EP disruption is a novel risk factor for VCF in patients who will undergo spinal SBRT. A simple nomogram incorporating EP disruption, adverse histology, and SINS score is effective for quickly assessing risk of VCF. These data require validation in prospective studies and could be helpful in counseling patients regarding VCF risk and referring for prophylactic interventions in high-risk populations.

KEY WORDS: Endplate, Radiosurgery, Metastasis

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ABBREVIATIONS: BED10, biologically effective dose alpha/beta 10; **CRC,** colorectal cancer; **ECM,** extracellular matrix; **EP,** endplate; **HR,** hazard ratio; **NSCLC,** non–small-cell lung cancer; **PTV,** planning target volume; **SBRT,** stereotactic body radiotherapy; **SINS,** spine instability neoplastic score; **VCF,** vertebral compression fracture.

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An increasing global incidence of cancer coupled with improving life expectancy has naturally resulted in more patients living longer with spine metastases.[1] Optimizing treatment for spinal metastases and understanding the risks/benefits of these procedures are essential. Spinal stereotactic body radiotherapy (SBRT) is a specialized radiation therapy

technique that delivers high doses of radiation to a very conformal target. This technique provides excellent tumor and pain control compared with conventionally fractionated radiotherapy.[2-5] Despite these benefits, vertebral compression fracture (VCF) is a serious potential side effect. Sahgal et al estimated the risk of VCF after SBRT to be 11%–39%, compared with 5% with conventional fractionation.[6]

Various factors have been associated with an increased incidence of VCF, including a gross tumor volume of >10 cc, lumbar location, epidural extension, and a Spinal Instability Neoplastic Score (SINS) of greater than 6.[7] Five of the six SINS components have been independently associated with an increased risk of VCF.[7] Specific dosimetric thresholds have also been shown to increase VCF risk, including D80% above 25 Gy, D50% above 30 Gy, prescription isodose line below 70%, and dose per fraction of more than 12 Gy.[8]

An understanding of the physiology of the spine can help explain why VCFs occur. The functional spinal unit consists of two adjacent vertebrae, the intervertebral disk with endplates (EP), spinal ligament, and facet joints.[9] Vertebral EPs play an important role in maintaining the mechanical environment and the proper nutrition of avascular disks. Maintaining hydrostatic pressure between vertebral bodies is essential to decrease the chance of VCF.[10] To our knowledge, tumoral disruption of the vertebral EPs has not yet been shown to increase the risk of VCF after spine SBRT. If demonstrated, this association could be important to properly counsel patients regarding the risk of VCF, recommend prophylactic interventions, and select the frequency of follow-up imaging. The purpose of this study was to investigate the correlation of VCF with tumor-related EP disruption.

METHOD

Study Design

In this Institutional Review Board–approved retrospective study, analysis was conducted for patients with spine metastases treated with SBRT between 2013 and 2019 at a single, high-volume institution. Patient consent was not sought nor required by our Institutional Review Board for this retrospective chart review study. Guidelines from the Strengthening the Reporting of Observational studies in Epidemiology statement were followed. Patients with previous surgical intervention to any spine site or previous radiation to the site of stereotactic radiotherapy were excluded. Demographic and treatment information was collected, including age, sex, performance status, body mass index (BMI), osteoporosis which was defined based on dual energy X-ray absorptiometry scan, use of steroids for more than 1 month, different systemic therapies received ±4 weeks from SBRT, and bone antiresorptive medication use within 4 weeks from radiation (eg, bisphosphonate, denosumab). In addition, radiotherapy information including dose, fractionation, planning target volume (PTV) coverage, and conformity index was collected. Finally, we also collected disease characteristics including histopathology, SINS criteria, bone lesion quality (osteoblastic, osteolytic, and mixed), Bilsky grade, and EP disruption. EP disruption was defined as cortical disruption of the superior and/or inferior EP by tumor (Figure 1). The presence of EP disruption was evaluated on pre-SBRT computed tomography scan by two independent neuroradiologists. Using relevant significant variables, we developed a nomogram that can help predicting the risk of VCF.

Spine SBRT volumes based on the extent of the disease and bone anatomy followed the established contouring guidelines. No additional margin from clinical target volume to PTV was added.[11] All patients underwent either image-guided stereotactic radiosurgery or fractionated stereotactic radiosurgery. Immobilization was achieved using an Aquaplast frameless mask for cervical spine and a stereotactic body frame with a Vac-Lok bag for thoracic, lumbar, and sacral spine. Radiation dose aimed for 95% of PTV to receive at least 95% of the prescription dose, considering spinal cord tolerance based on the treatment schedule and AAMP TG 101 recommendations.[12]

Study End Points

The primary study end point was the 1-year cumulative incidence of VCF, assessed by two independent neuroradiologists on follow-up MRI and computed tomography scan at 3, 6, 9, and 12 months after SBRT. VCF was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events CTCAE v5.0. Secondary end points included local control, overall survival, and other acute/chronic toxicities.

Statistical Analysis

The R statistical programming language (R Core Team, 2023) using the rms package (Harrell Jr, 2023) was used to prepare the data and generate the nomograms. Continuous patient demographics were described using medians and ranges. Frequency counts and proportions were used to describe discrete variables. Inverse Kaplan–Meier curves were used to assess the primary end point of 1-year cumulative incidence of VCF. The VCF-free

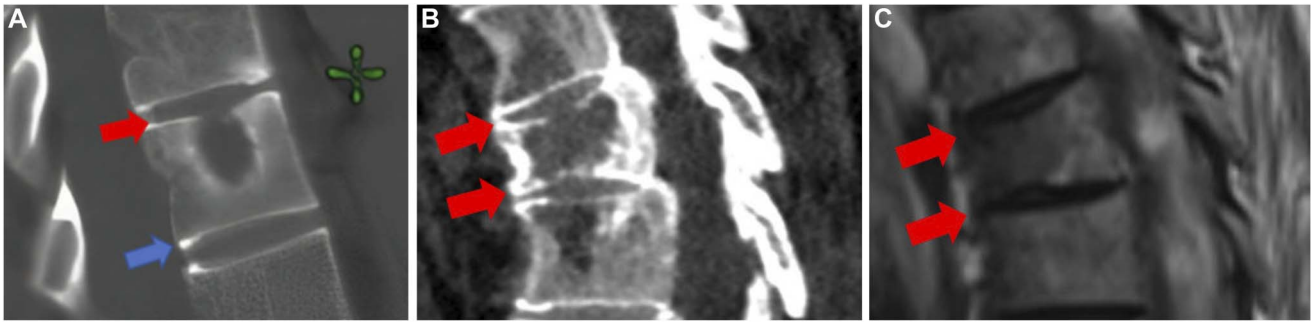

FIGURE 1. **A**, *An example of T11 superior EP disruption from the tumor (red arrow) and intact inferior EP (blue arrow). T5 superior and inferior EP disruption from the tumor (red arrows),* **B**, *computed tomography scan and* **C**, *MRI. All previous radiation. EP, endplate.*

TABLE 1. Demographic Data of 111 Patients With Metastatic Spinal Disease Treated by SBRT, Included in This Study

Variable	Number
No. of patients	111
Median follow-up (mo) (range)	18 (1.2-107)
Median age (y) (range)	60 (24-87)
Sex	
Male	59 (53%)
Female	52 (47%)
Karnofsky performance status	
≥70%	96 (86%)
<70%	15 (14%)
Median BMI	27 (16-47)
Osteoporosis	
Yes	9 (8%)
No	102 (92%)
Steroid use ≥4 weeks	
Yes	12 (11%)
No	99 (89%)
Bisphosphonate use	
Yes	20 (18%)
No	91 (82%)
Denosumab use	
Yes	8 (7%)
No	103 (93%)
Concurrent systemic therapy	
None	58 (52%)
Chemotherapy	19 (17%)
Immunotherapy	15 (14%)
Targeted therapy	19 (17%)
Median prescription dose (Gy) (range)	27 (10-35)
Median prescribed BED10 (Gy) (range)	51.3 (20-60)
Median D80% (Gy)	27 (10.2-36)
Median D50% (Gy)	28 (10.3-38)
Isodose line	
≥95%	74 (67%)
<95%	37 (33%)

TABLE 1. Continued.

Variable	Number
Median PTV (cc) (range)	50 (8-465)
Median conformity index (range)	1.05 (0.42-1.4)
PTV coverage	
Partial vertebra	83 (75%)
Circumferential	28 (25%)
Fractionation	
Single fraction	22 (20%)
Multifraction	89 (80%)
No. of treated spinal levels	
1 level	64 (58%)
2 levels	32 (29%)
3–7 levels	15 (13%)
Histopathology	
Renal cell carcinoma	28 (25%)
Sarcoma	11 (10%)
Non–small-cell lung cancer	14 (13%)
Breast	12 (11%)
Thyroid	9 (8%)
Prostate	5 (4%)
Colorectal	6 (5.5%)
Melanoma	5 (4.5%)
Head and neck	5 (4.5%)
Neuroendocrine tumor	4 (3%)
Metastatic pituitary	1 (1%)
Metastatic paraganglioma	2 (2%)
Anal squamous cell carcinoma	5 (4.5%)
Hepatobiliary	2 (2%)
Adenoid cystic carcinoma	1 (1%)
Hemangioma	1 (1%)
Spinal instability neoplastic score criteria	
<7	73 (66%)
7	13 (11%)
>7	25 (23%)
Bone lesion quality	
Blastic	38 (34%)

TABLE 1. Continued.

Variable	Number
Mixed	24 (22%)
Lytic	49 (44%)
Bilsky grade	
0	88 (79%)
1a	7 (6%)
1b	13 (12%)
1c	3 (3%)
VCF	
Yes	20 (18%)
No	91 (82%)
Median time to VCF (mo) (range)	5.2 (1.1-57.4)
One EP-disrupted	
Yes	48 (43%)
No	63 (57%)
Median time to VCF	5.7 (1.1-53)
Two EP-disrupted	
Yes	20 (18%)
No	91 (82%)
Median time to VCF	2.4 (1.1-9)

BMI, body mass index; BED10, biologically effective dose alpha/beta 10; EP, endplate; PTV, planning target volume; VCF, vertebral compression fracture.

survival was calculated based on the event of fracture or death of the patient. Univariate analysis was performed using a proportional hazards model to assess the correlation between clinically relevant variables and an increased likelihood of VCF. These variables included age, sex, pathology, BMI, steroid use, bone remodeling medical therapy, fractionation, radiotherapy dose, SINS score (location, pain characteristic, bone lesion type, spinal alignment, vertebral body collapse, and posterior spinal element involvement), bone lesion quality, and EP disruption. A *P*-value of <.05 was considered statistically significant. Continuous variables were dichotomized by the median. Cox proportional hazards multivariate analyses were performed to assess the effect of relevant variables on VCF. Statistically significant univariate variables were included in the multivariate analysis. Finally, these variables were used to formulate a nomogram for risk stratification of likelihood of the VCF event.

RESULTS

Patient Characteristics

One hundred and eleven patients were found to meet our eligibility criteria, which had a median age of 60 years. The median and mean follow-ups for the cohort were 18 months (1.2-107 months) and 30.3 months, respectively. There was a slight male predominance (53%). Most of the patients (86%) had a Karnofsky performance score of ≥70%. Primary tumor pathology varied significantly, but the most common histologies were renal cell carcinoma (25%), sarcoma (10%), non–small-cell lung cancer (13%), and breast cancer (11%). A majority of patients (66%) had a SINS of <7 with most tumors (79%) rated as Bilsky grade 0. Almost half of patients (52%) did not receive systemic therapy during a 4-week range from radiation. About 43% of patients had at least one EP disruption (43%), whereas 18% of patients had disruption of two EPs (Table 1).

Vertebral Compression Fracture

Twenty patients (18%) experienced a VCF at a median of 5.2 months from SBRT (0.2-57.4 months). Patients with two EP disruptions had a shorter median time to VCF than those with only one EP (2.4 vs 5.2 months, $P = .02$).

Among 20 patients with VCF, five experienced grade 3 fractures and underwent surgical intervention with either vertebroplasty (two patients) or laminectomy with fixation (three patients). The remaining 15 patients who experienced grade 1 fractures were treated conservatively.

The number of VCF events was higher in patients who had non–small-cell lung cancer (NSCLC), breast invasive ductal carcinoma, and anal squamous cell carcinoma/colorectal adenocarcinoma, which was 43%, 33%, and 30%, respectively (**Supplemental Digital Content 1, Table 1**, http://links.lww.com/NEU/D994). In addition, our analysis of bone lesion quality indicated that 34% (n = 38) were blastic, 22% (n = 24) were mixed, and 44% (n = 49) were lytic. We found that none of the patients with blastic lesions developed VCF with a median follow-up of 18 months. For mixed lesions, we found that three of 24 patients experienced a VCF event; these were lung, breast, and colorectal histologies. Among the 49 lytic lesions, 17 patients developed VCF, where 10 of the 17 patients had lung, breast, and anal squamous cell carcinoma. Among mixed bone lesions, the 1-year cumulative incidence of VCF in relation to adverse histologies was 43% vs 0%, $P < .001$ and it was 48% vs 22% $P < .001$ among the lytic bone lesions (**Supplemental Digital Content 2, Figure 1**, http://links.lww.com/NEU/D995). Therefore, we assumed that these patients have adverse pathology.

On univariate analysis, we found that adverse histology (NSCLC, breast adenocarcinoma, ano-colorectal cancer), a SINS score of ≥7, and EP disruption were associated with a statistically significant increased rate of VCF (Table 2). No other variables were statistically significant. On multivariate analysis, these variables were found to be statistically significant. Adverse histology (hazard ratio [HR] 4.37, 95% CI 1.71-11.2), a SINS score of ≥7 (HR 7.2, 95% CI 2.3-22.56), and EP disruption (HR 3.34, 95% CI 1.1-10.52) were all found to significantly increase the risk of VCF (Table 3). Other factors such as sex, various systemic therapies, and bone remodeling medicine were excluded as confounding factors with adverse histologies based on multivariate analysis (the HR for adverse histology is 4.4, 95% CI 1.76-11.13,

TABLE 2. Univariate Analysis Examining the Variables Associated With the Increased Likelihood of VCF

Variable	Number	One-year cumulative incidence of VCF	*P* value
Age, years			
≥60	49	18%	
<60	62	14%	.843
Sex			
Male	59	11%	
Female	52	21%	.064
Primary cancer			
NSCLC/breast/ano-colorectal	36	30%	
Others	75	10%	<.001
BMI			
<25	38	10%	
25–29.9	36	15%	
≥30	37	22%	.102
Steroid use			
Yes	12	20%	
No	99	14%	.103
Antiresorptive medicine			
Yes	26	16%	
No	85	17%	.447
Osteoporosis			
Yes	9	0%	
No	102	16%	.893
Fractionation			
Single	22	20%	
Multiple	89	15%	.924
Radiotherapy dose			
BED10 <51.3 Gy	47	18%	
BED10 ≥51.3 Gy	64	13%	.944
D80% <27 Gy	48	14%	
D80 ≥27 Gy	63	16%	.506
D50% <28 Gy	60	12%	
D50% ≥28 Gy	51	18%	.256
SINS score			
≥7	38	42%	
<7	73	4%	<.001
EP disruption			
Yes	48	29%	
No	63	6%	<.001

BMI body mass index; BED10, biologically effective dose alpha/beta 10; EP, endplate; NSCLC, non–small-cell lung cancer; SINS spinal instability neoplastic score; VCF, vertebral compression fracture.

P = .002) (**Supplemental Digital Content 3, Table 2**, http://links.lww.com/NEU/D996).

In this cohort, we found that three of six SINS components were associated with high likelihood of VCF (**Supplemental Digital Content 4, Table 3**, http://links.lww.com/NEU/D997). The 1-year cumulative incidence of VCF was higher in lytic bone quality metastatic disease (32%). Mechanical pain of metastatic spine disease and worse vertebral collapse were associated with higher risk of VCF.

Vertebral Compression Fracture Nomogram

A nomogram was created to predict the risk of VCF. Variables included adverse histology, SINS score, and EP disruption. Using the lookup table for predicted probability of VCF, we divided our cohort into eight groups (Table 4). A significant jump in the VCF probability was observed if there was EP disruption along with adverse histology and higher SINS. The scoring method is demonstrated in **Supplementary Table 4** (**Supplemental Digital Content 5**, http://links.lww.com/NEU/D998). The number of VCF events was higher among patients with 2–3 points. We classified patients into two groups based on their cumulative nomogram score: low (0-1) or high risk (2-3) for VCF. The 1-year cumulative incidence of VCF for low vs high risk was 2% vs 38%, respectively, *P* < .001 (Figure 2). The 1-year VCF-free survival is 62% vs 42%, with a *P* value of .023 (**Supplemental Digital Content 6, Figure 2**, http://links.lww.com/NEU/D999).

Local Control, Overall Survival, and Other Toxicities

The 1-year local control in this cohort was 92%. The overall survival at 1 year was 68%. Grade I–II fatigue was the most experienced acute toxicity, occurring in around 22 patients. Other adverse events included grade I dysphagia in patients with T-spine radiotherapy, grade I skin reaction, and mild pain flare secondary to radiation treated with dexamethasone, each occurring in one patient.

TABLE 3. Multivariate Analysis Examining the Variables Associated With the Increased Likelihood of VCF

Variable	HR	95% CI	*P* value
Adverse histology	4.37	1.71-11.2	.002
SINS score	7.2	2.3-22.56	<.001
EP disruption	3.34	1.1-10.52	.04

EP, endplate; HR, hazard ratio; SINS, spinal instability neoplastic score; VCF, vertebral compression fracture.

DISCUSSION

This study demonstrates that disruption of EP is associated with a significantly higher risk of VCF after spinal SBRT. To the best of our knowledge, this has not previously been investigated in the literature. A recent article identified several risk factors for VCF after spine SBRT.[7] These factors included many of the same variables used in our study, including Bilsky and SINS scores. This previous study found that an increased number of risk factors correspond to an increased risk of VCF. Our data support many of these findings.

EP is a bilayer of cartilage and bone that separates the intervertebral disks from the adjacent vertebrae. It is critical for maintaining disk and vertebral health because it has an extensive network of blood vessels that provide nutrients and oxygen to the bone.[13-16] However, by being rich in blood supply and having a unique microenvironment, the EP can be transformed into a "homing" niche for cancer cells that reach the spine through bloodstream or lymphatics, facilitating their growth and survival.

Both, the EP cartilage and the bony component of EP, are different from the articular cartilage and vertebral cortex, respectively.[13-16] Specifically, the EP cartilage consists of chondrocytes interspersed throughout an extracellular matrix (ECM) of proteoglycans and collagen types I and II that show different fiber organization from articular cartilage, whereas the bony part of the EP presents as a porous layer of fused trabecular bone with osteocytes entombed within saucer-shaped lamellar packets.

Further research is needed to understand why breast, NSCLC, and colorectal cancer pathologies are more likely to develop fracture risks with lytic lesions. All three types of cancers are of epithelial origin that have acquired a migratory, invasive mesenchymal cell phenotype to reach EP. Epithelial to mesenchymal transition of cancer cells also involves the production of ECM-degrading enzymes that enable them to degrade the basement membrane in their tissue of origin.[17] It is thus likely that the same ECM-degrading enzymes are involved in EP lytic and EP degradation by the cancer cells. The involvement of cancer cell–specific factors in EP homing and lysis could also explain why in our cohort, the consumption of antiresorptives did not protect against VCF. Identifying the ECM-degrading enzymes used by cancer cells would be of interest in the future because corresponding enzyme inhibitors could potentially impair EP lysis and reduce VCF.

From a clinical standpoint, we have introduced a new variable—EP disruption—which appears to be predictive of VCF. In our cohort of patients, breast, lung, and ano-colorectal primaries had higher VCF events, even with osteolytic bone lesions (1-year cumulative incidence of VCF 48% vs 22%, $P < .001$). None of these patients received concurrent antiangiogenic therapy. We created a simple nomogram to stratify patients into groups that would estimate 1-year VCF risk. Patients in the high-risk group (two of the three following features, SINS >7, EP disruption, and adverse histology) were more likely than others to develop VCF. One may envision clinical scenarios where we see two of the three adverse factors, and we can consider prophylactic kyphoplasty or vertebroplasty to help with the increased fracture risk.[18,19] Specifically, patients with one or two EP disruption(s) may benefit from prophylactic interventions because of their high probability of experiencing VCF.

In dosimetry, a biologically effective dose (a/b ratio of 10) above 60 has previously been shown to be associated with higher risks of VCF.[7,20] Our cohort median prescribed biologically effective dose

TABLE 4. Lookup Table for Predicted Probability for VCF and the Nomogram

SINS total	Endplate disruption	Adverse histology	Probability (95% CI)	Nomogram
<7	No	Other	0.008 (0.001, 0.054)	0
<7	Yes	Other	0.042 (0.010, 0.162)	1
<7	No	Breast/lung/anal/CRC	0.068 (0.018, 0.226)	0
≥7	No	Other	0.088 (0.021, 0.306)	1
<7	Yes	Breast/lung/anal/CRC	0.278 (0.096, 0.584)	2
≥7	Yes	Other	0.337 (0.176, 0.547)	2
≥7	No	Breast/lung/anal/CRC	0.458 (0.171, 0.776)	2
≥7	Yes	Breast/lung/anal/CRC	0.817 (0.551, 0.942)	3

CRC, colorectal cancer; SINS, spinal instability neoplastic score; VCF, vertebral compression fracture.

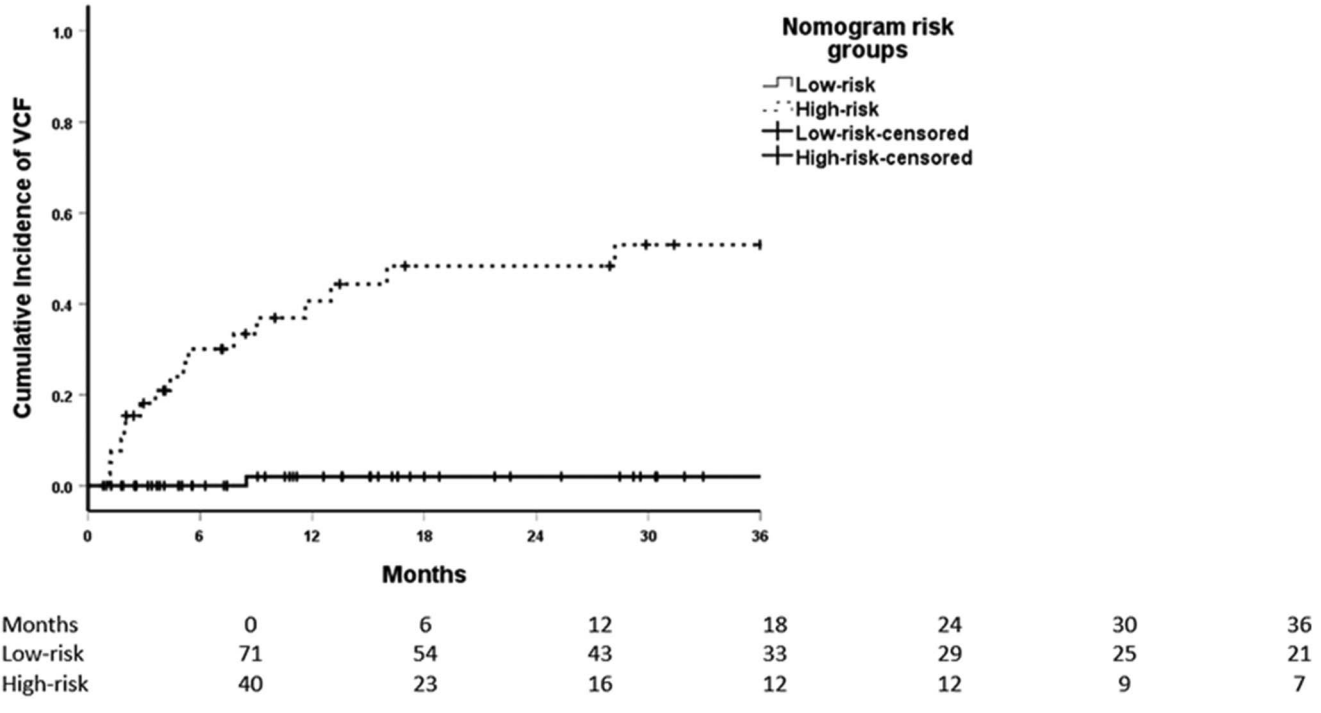

FIGURE 2. *The 1-year cumulative incidence of VCF for low- vs high-risk groups (the 1-year cumulative incidence of VCF for low vs high risk was 2% vs 38%, respectively, P < .001). VCF, vertebral compression fracture.*

was 51.3 Gy (20-60). Other factors, such as D80% above 25 Gy and D50% above 30 Gy of the PTV, have been correlated with an increased risk of VCF. In our cohort, the median D80% and D50% of the PTV were 27.5 Gy and 28 Gy, respectively.[8] There was no correlation between the D80% and D50% of the PTV and the incidence of VCF within our cohort.

Antiresorptive agents are commonly used in the treatment of osteoporosis to re-establish the balance between bone resorption and formation. A recent study showed that initiation of these agents before the spine SBRT may reduce the risk of VCF.[21] In our cohort, the consumption of antiresorptives did not protect against VCF although only 7% of patients received denosumab and 18% received bisphosphonates.

CONCLUSION

Our study showed that EP disruption is correlated with a higher incidence of VCF, and a simple nomogram was created to help stratify the risk categories for VCF. Patients who exhibit EP disruption had higher likelihood of developing VCF compared with those without EP disruption (29% vs 6%, $P < .001$). Patients were stratified into groups at low and high risk of VCF according to the EP status, histology, and SINS, which were associated with 2% and 38% risk of VCF ($P < .001$). This VCF nomogram can be used to improve patient selection for surgical intervention before or after spine SBRT.

Limitations

While the results are very promising, there are limitations and further prospective clinical trials are warranted to validate these findings. We examined a retrospective data set, which limits the generalizability of our findings. A larger sample size, longer follow-up duration, and more VCF cases are needed to further elicit the effect of various subgroups in our data set.

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Supplemental Digital Content 1. Table 1. Number of VCF events in different primaries.

Supplemental Digital Content 2. Figure 1. The cumulative incidence of VCF among mixed bone lesions in correlation with histology (A), The cumulative incidence of VCF among lytic bone lesions in correlation with histology (B).

Supplemental Digital Content 3. Table 2. Multivariate analysis examining variables associated with the increased likelihood of VCF in correlation with adverse histology.

Supplemental Digital Content 4. Table 3. Univariate analysis examining SINS components' association with the likelihood of VCF.

Supplemental Digital Content 5. Table 4. Rates of VCF among risk groups.

Supplemental Digital Content 6. Figure 2. VCF-free survival curve. The one-year VCF-free survival is 62% vs 42%, with a *P* value of .023.