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Clinical Investigation

Analysis of the Factors Contributing to Vertebral Compression Fractures After Spine Stereotactic Radiosurgery

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Summary

Retrospective analysis revealed a vertebral compression fracture (VCF) rate of 11.9% (8.4% with exclusion of patients undergoing surgical fixation) from a total of 1070 vertebral bodies (448 patients) who received spine stereotactic radiosurgery (SRS) at our institution. Patients with a previous VCF, primary hematologic malignancies, tumors located in thoracic spine, and lytic lesions had increased rates of developing a VCF. Single-fraction SRS doses of 16 to 18 Gy to the

Purpose: To determine our institutional vertebral compression fracture (VCF) rate after spine stereotactic radiosurgery (SRS) and determine contributory factors.

Methods and Materials: Retrospective analysis from 2001 to 2013 at a single institution was performed. With institutional review board approval, electronic medical records of 1905 vertebral bodies from 791 patients who were treated with SRS for the management of primary or metastatic spinal lesions were reviewed. A total of 448 patients (1070 vertebral bodies) with adequate follow-up imaging studies available were analyzed. Doses ranging from 10 Gy in 1 fraction to 60 Gy in 5 fractions were delivered. Computed tomography and magnetic resonance imaging were used to evaluate the primary endpoints of this study: development of a new VCF, progression of an existing VCF, and requirement of stabilization surgery after SRS.

Results: A total of 127 VCFs (11.9%; 95% confidence interval [CI] 9.5%-14.2%) in 97 patients were potentially SRS induced: 46 (36%) were de novo, 44 (35%) VCFs progressed, and 37 (29%) required stabilization surgery after SRS. Our rate for radiologic VCF development/progression (excluding patients who underwent surgery) was 8.4%. Upon further exclusion of patients with hematologic malignancies the VCF rate was 7.6%. In the univariate analyses, females (hazard ratio [HR] 1.54, 95% CI 1.01-2.33, $P=.04$), prior VCF (HR 1.99, 95% CI 1.30-3.06, $P=.001$), primary hematologic malignancies (HR 2.68, 95% CI 1.68-4.28, $P<.001$), thoracic spine lesions (HR 1.46, 95% CI 1.02-2.10, $P=.02$), and lytic lesions had a significantly increased risk

Note—An online CME test for this article can be taken at http://astro.org/MOC.

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spine seem to be associated with a low rate of VCFs.

for VCF after SRS. On multivariate analyses, prior VCF and lesion type remained contributory.

Conclusions: Single-fraction SRS doses of 16 to 18 Gy to the spine seem to be associated with a low rate of VCFs. To the best of our knowledge, this is the largest reported experience analyzing SRS-induced VCFs, with one of the lowest event rates reported.

Introduction

Metastatic involvement of the vertebral bodies is often seen in patients with advanced-stage cancers. A majority of these patients present with pain and occasionally neurologic compromise. Standard external beam radiation therapy has been used extensively in this situation, with good symptom control with minimal toxicity. However, because of the nonconformal nature of these treatment plans, surrounding normal tissues receive a significant amount of dose. With the development of better immobilization, treatment planning techniques, and image verification, the use of stereotactic radiosurgery (SRS) in cases of vertebral body metastases has increased. This allows for the delivery of highly conformal radiation to lesions of the spine while minimizing the amount that reaches surrounding healthy tissue (1-5). With worldwide cancer rates increasing, and more than 30% of all cancer patients developing spinal metastasis (6, 7), the role of SRS will likely increase (8-10).

Two major potential complications are of concern with this technique of delivering high dose per fraction radiation. One initial concern was the likely neurologic complication of spinal cord myelopathy. However, multiple studies have shown that spine SRS is a safe technique, with low risk of myelopathy as long as recommended dose constraints are met (4). The second complication, vertebral compression fractures (VCFs), has also been described in the literature as an SRS-related complication (1, 11-16). Vertebral compression fractures can significantly impact the quality and duration of patients' lives by causing severe pain and neurologic deficits (17, 18).

The factors contributing to the development of VCF are still not completely understood, and thus clinicians are presented with a challenge when selecting suitable candidates for spine SRS. Our retrospective analysis was performed to determine the rate of VCFs in our institution and to elucidate some of the factors that might increase the risk.

Methods and Materials

Patient selection and endpoints

Seven hundred ninety-one patients (1905 vertebral bodies) were treated with SRS for the management of their primary or metastatic spinal lesions at our institution between June 2001 and December 2013. All patients were presented and discussed in a multidisciplinary spine tumor board attended by radiation oncologists, neurosurgeons, neuroradiologists, and medical oncologists. All treatment decisions and recommendations, including whether a patient was a suitable candidate for spine SRS, were made according to consensus opinions. Patients had vertebral body metastases from C1 to the sacrum. Patients who had up to 3 separate areas of involvement and a maximum of 3 contiguous vertebral bodies were treated using SRS. In cases in which the metastatic involvement of the vertebral bodies exceeded these limits, standard fractionated external beam radiation therapy was delivered. Because there is no well-accepted universal definition of VCFs after spine SRS, we relied on the neuroradiologists' report and multidisciplinary spine tumor board discussion to assess for the presence of new fractures or progression of existing fractures. All patient images were reviewed by neuroradiologists at our institution, vertebral body heights were measured in every spine image series, and a VCF was classified as any measurable height loss noted on a vertebral body compared with prior imaging. The patient images were then subsequently reviewed at a multidisciplinary tumor board to determine fracture progression and treatment indications.

We analyzed data from 448 patients (1070 vertebral bodies) who had follow-up imaging studies available at our institution for review. One hundred ninety-seven patients were lost to follow-up, 117 died within 3 months of receiving SRS, and 29 were patients referred from outside facilities for SRS (Fig. E1, CONSORT diagram; available online at www.redjournal.org). Electronic medical records of these patients were retrospectively reviewed in this institutional review board–approved study. Computed tomography and magnetic resonance imaging were used to evaluate the primary endpoint. Consistent with prior reports, our events were the development of a new VCF and the progression of an existing VCF (11-15). Additionally, we included pre-existing VCFs that required stabilization surgery beyond 1 week after SRS as an event. To be classified as an event, the VCF development/progression or stabilization surgery must have occurred within vertebral bodies treated with SRS. To distinguish between VCFs caused by tumor progression as opposed to SRS, VCFs that developed or progressed concurrently with tumor progression were not included as events. Vertebral bodies that underwent stabilization surgery before SRS were excluded from the analysis.

Potential contributing factors

Factors considered included the spinal instability neoplastic score (SINS) criteria (19) previously found to correlate with VCF risk: lesion type (12-15), spinal alignment (12, 14),

Table 1 Fracture rates for demographic, tumor, and dosimetric factors

Variable	No. (%) of patients	No. of fractures (n=127)	Total no. of vertebral levels (n=1070)	% With fractures
Age category (y)				
<40	17 (4)	1	45	2
40-49	44 (10)	14	113	12
50-59	117 (26)	42	268	16
60-69	138 (31)	35	350	10
70-79	97 (22)	28	218	13
80+	35 (8)	7	76	9
Sex				
Female	202 (45)	68	462	15
Male	246 (55)	59	608	10
Ethnicity*				
Caucasian	250 (57)	73	596	12
African American	163 (37)	45	395	11
Other	22 (5)	7	51	14
Primary tumor location				
Breast	79 (18)	26	212	12
Hematologic	55 (12)	29	115	25
Lower gastrointestinal	26 (6)	6	51	12
Lung	96 (21)	26	190	14
Prostate	62 (14)	7	174	4
Other†	103 (23)	28	248	11
Unknown	27 (6)	5	80	6
Previous VCF				
Yes		73	446	16
No		54	624	9
No. of levels				
1		74	488	15
2		47	379	12
3+		6	203	3
Prior RT				
Yes		10	116	9
No		117	954	12
Lesion type				
Blastic		16	231	7
Lytic		57	294	19
Mixed		31	220	14
Unknown		23	325	7
Dose per fraction				
≤15		10	139	7
16		42	314	13
18		73	577	13
>18		1	31	3
Tumor volume (cm^3) (missing information for n=191 vertebral levels)				
<30		23	239	10
30-<50		28	226	12
50-<80		32	195	16
80+		24	219	11

Abbreviations: RT = radiation therapy; VCF = vertebral compression fracture.

* Thirteen missing ethnicity information.

† Includes bladder (n=5), bone (n=8), gynecologic (n=9), head and neck (n=7), kidney (n=19), liver (n=10), muscle (n=1), nervous system (n=16), pancreas (n=3), skin (n=4), thymus (n=1), thyroid (n=10), and upper gastrointestinal (n=10).

and presence of a pre-existing VCF (11, 12, 14). The SINS classification for spine type (junctional, mobile, semi-rigid, rigid) was also considered (19). Consistent with prior reports (11-15), bisphosphonate use, histology, dose/fraction, number of vertebral levels in treatment target, additional radiation to spine, spine tissue involvement (eg, paraspinal, epidural, intradural), spine level (cervical, thoracic, lumbar, sacral), sex, and age were considered. Additionally, the use

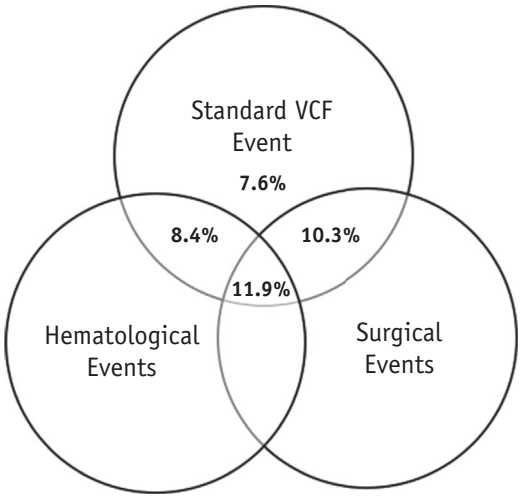

Fig. 1. Crude rates of vertebral compression fracture (VCF).

of antiangiogenic therapy, tumor volume, bone disease (eg, osteoporosis, spondylosis), and ethnicity were looked at as potential contributing factors.

Procedure

The Novalis system (Brainlab, Munich, Germany) was used for spine SRS. Patient immobilization was achieved with the aid of vacuum bags. A contrast-enhanced simulation computed tomography scan with a slice thickness of 3 mm was performed with infrared fiducial markers (ExacTrac, Brainlab). These images were fused with diagnostic T1- and T2-weighted magnetic resonance images in the treatment planning system to define the target volume, consisting of the gross tumor and the involved vertebral body. No expansion margin was added to the gross tumor, and thus the gross tumor volume (GTV) was equal to the planning target volume. T2-weighted magnetic resonance images were used to delineate the spinal cord 6 mm above and 6 mm below the defined GTV. A spinal cord planning organ at risk volume was not constructed. Multiple coplanar intensity modulated radiation beams were used to optimize the radiation dose to the target volume and minimize the dose to surrounding tissue. All doses were prescribed to the 90% isodose line. The primary dose constraint for plan selection was to achieve the objective of 10 Gy to 10% of the partial volume of the spinal cord and a

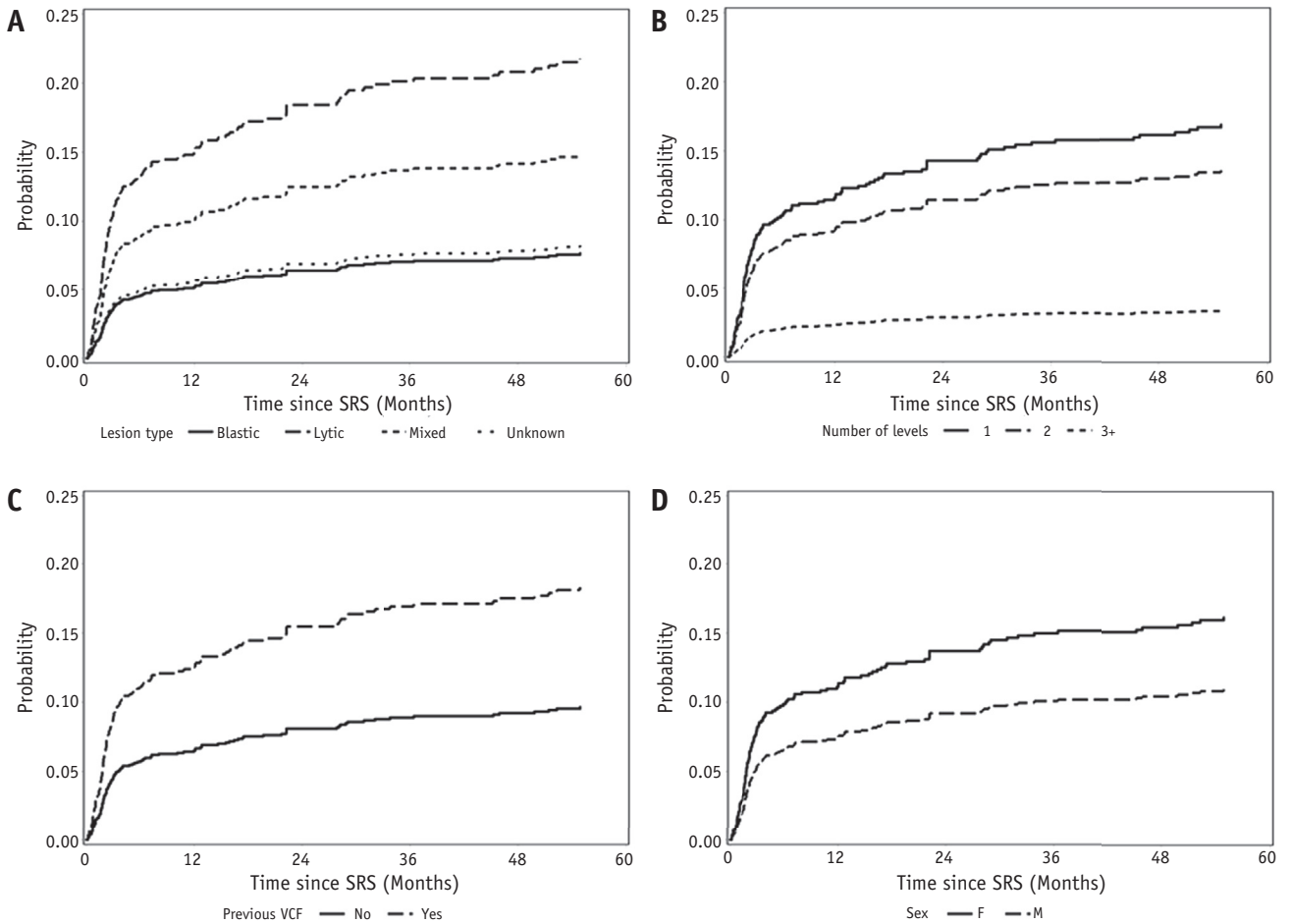

Fig. 2. Competing risk cumulative incidence functions for vertebral compression fracture (VCFs) based on (A) lesion type, (B) number of vertebral levels treated, (C) prior VCF, and (D) gender. *Abbreviation:* SRS = stereotactic radiosurgery.

Table 2 Hazard ratios and confidence intervals from the Fine-Gray model using competing risk methods for significant factors in the univariate and multivariate analyses

	Univariate		Multivariate	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Prior VCF	1.99 (1.30-3.06)	.001	1.69 (1.11-2.59)	.01
Sacrum spine	0.22 (0.07-0.71)	.01	0.30 (0.10-0.91)	.03
Cervical spine	0.42 (0.19-0.95)	.03	0.41 (0.18-0.94)	.03
Lesion type				
Lytic vs blastic	3.07 (1.52-6.21)	.001	3.04 (1.49-6.18)	.002
Mixed vs blastic	2.01 (0.93-4.32)	.07	1.95 (0.89-4.28)	.09
Unknown vs blastic	1.08 (0.50-2.33)	.85	1.22 (0.54-2.74)	.63
Lytic vs mixed	1.53 (0.89-2.63)	.12	1.56 (0.92-2.63)	.09
Unknown vs mixed	0.54 (0.29-1.01)	.05	0.63 (0.33-1.18)	.14
Lytic vs unknown	2.85 (1.63-4.97)	<.001	2.49 (1.43-4.34)	.001
No. of vertebral levels				
3+ vs 1	0.19 (0.08-0.43)	<.001	0.23 (0.10-0.53)	<.001
3+ vs 2	0.24 (0.10-0.56)	.001	0.25 (0.11-0.61)	.002
2 vs 1	0.79 (0.53-1.18)	.25	0.90 (0.60-1.35)	.61
Female	1.54 (1.01-2.33)	.04		
Thoracic spine	1.54 (1.07-2.21)	.02		
Rigid spine type	0.11 (0.02-0.77)	.02		
Primary tumor origin*				
Breast	1.02 (0.59-1.75)	.94		
Hematologic	2.68 (1.68-4.28)	<.001		
Lower gastrointestinal	1.08 (0.40-2.94)	.88		
Lung	1.22 (0.73-2.08)	.43		
Prostate	0.28 (0.11-0.72)	.008		
Other	0.93 (0.58-1.50)	.75		
Unknown	0.49 (0.19-1.27)	.14		

Abbreviations: CI = confidence interval; HR = hazard ratio. Other abbreviation as in Table 1.

* Hazard ratio for specific locations compared with all other tumor locations.

maximum point dose of 14 Gy. In cases in which this constraint was not achievable, under-dosage to the GTV was accepted to meet the above dosimetric objective. Prescribed dose did not vary on the basis of the presumed radio-resistance of the histopathology. This procedure has been detailed in previous reports (2, 20, 21).

Statistics

Descriptive statistics were used to describe the demographic and histologic factors. Death before a fracture was considered a competing risk to fracture. Competing risk analyses using the Fine and Gray method were done to assess the univariate and multivariate relationship between the demographic, tumor, and dosimetric factors and time to VCF. In addition, the robust sandwich covariance matrix for computing the standard errors was used to take into account the possibility of multiple levels and treatments within a patient. The factors considered in the multivariate analyses were those that were significant in the univariate analyses. Cumulative incidence functions (CIFs) for VCF were computed using the competing risk models. For survival analyses, the time variable was computed as the difference between the date of first SRS and date of death or last contact. Patients still alive at last contact were censored. Kaplan-Meier estimates were used to compute the cumulative incidence rates for survival. All testing was 2-sided, and α was set at 0.05. SAS version 9.4 (SAS Institute, Cary, NC) was used for the analyses.

Results

Of the 448 patients included in this analysis, 246 (55%) were males, 250 (57%) were Caucasian, and the mean age at first SRS was 62.5 years (range, 17-92 years). Twenty-one percent of the patients had lung cancer as their primary tumor location, 18% had breast, 14% had prostate, and 12% had hematologic primaries (Table 1).

Three hundred ten patients (69%) died during follow-up. The 1- and 2-year survival rates were 60.5% (95% CI 55.6%-65.4%) and 40.4% (95% CI 35.7%-45.9%), respectively. Median survival time was 17.7 months (95% CI 14-20.1 months). Follow-up imaging in this group of patients ranged from 1 follow-up magnetic resonance image done approximately 6 weeks after SRS to 25 images done up to 7 years after SRS, with a median of 11 follow-up images up to 22 months.

On the basis of our expanded definition of events (new VCFs, progressing VCFs, and surgical events), we noted

127 (11.9%, 95% CI 9.5%-14.2% [crude rate]; 13.2%, 95% CI 11.3%-15.5% [CIF]) VCFs during follow-up. Of these, 46 (36%) were de novo, 44 (35%) were VCFs that progressed, and 37 (29%) vertebral bodies required stabilization surgery beyond 1 week after SRS. Of these 37, 11 vertebral bodies underwent vertebroplasty, 10 had ballon kyphoplasty, and the remaining had other surgical instrumentation/fixation procedures. Vertebral compression fracture due to tumor progression was noted in 62 bodies out of the 1070 vertebral bodies treated.

When calculating the rate of VCFs excluding patients classified as surgical events (not described in other published reports), our VCF rate was as follows: 8.4% (95% CI 6.4-10.4) (crude rate), 9.6%, (95% CI 7.8%-11.7%) (CIF) (11, 12, 14-16, 22, 23). Upon further exclusion of patients with hematologic malignancies, the VCF rate was as follows: 7.6% (95% CI 5.6%-9.7%) (crude rate), 8.7% (95% CI 7.1%-10.6%) (CIF) (Fig. 1). Among the vertebral bodies with a VCF, the median time to VCF was 2.7 months, with a range from 5 days to 54.9 months. Sixty-six percent occurred within the first 6 months. The 1- and 2-year cumulative incidence rates of VCF using the competing risk estimates were 9% (95% CI 7.3%-11.1%) and 11.2% (95% CI 9.4%-13.3%), respectively. Excluding only the hematologic malignancy group, there were 98 VCFs with a corresponding event rate of 10.3% (95% CI 7.9%-12.6%) (crude rate) and 11.4% (95% CI 9.6%-13.5%) (CIF) (standard inclusion criteria plus surgical fixation patients).

The VCF rates for the demographic, tumor, and dosimetric factors can be found in Table 1. In the univariate analyses, females, prior VCF, primary hematologic malignancies, and thoracic spine and lytic lesion types had a significantly increased risk for VCF after SRS (Fig. 2 and Table 2). Prostate tumors, sacrum and cervical spine, three or more treated levels, and rigid spine type were associated with a decreased risk of VCF (Table 2). The associations of VCF after SRS with age, ethnicity, prior radiation therapy, epidural tissue involvement, paraspinal tissue involvement, use of bisphosphonates and anti-angiogenesis medications, other bone disease, dose per fraction, and tumor volume were not significant ($P>.10$ for all). On multivariate analyses, prior VCF, sacrum and cervical spine, number of treated levels, and lesion type (Table 2) remained significant.

One patient experienced symptoms of radiation myelopathy that was confirmed on magnetic resonance imaging. This patient had a diagnosis of breast cancer and was treated to the cervical spine with a dose of 30 Gy in 10 fractions at an outside institution, followed by 16 Gy reirradiation to the C1 vertebral body owing to tumor progression with epidural extension. The patient underwent surgical fixation 1 month after SRS because of instability. She developed quadriplegia approximately 7 months after the SRS treatment and died after a further 10 months with progressive metastatic disease.

Discussion

We analyzed our patient cohort to determine the incidence and risk factors for SRS-induced VCFs. To the best of our knowledge this is the largest reported experience, with one of the lowest rates of VCF. Our overall incidence with our expanded inclusion criteria (inclusion of surgical events) was 11.9% and 10.3% with the exclusion of patients with hematologic malignancies. Upon exclusion of patients undergoing stabilization surgery, these rates were 8.4% and 7.6%, respectively, with the inclusion and exclusion of patients with hematologic malignancies. The surgical event was initially included in our analysis to err on the side of caution and overestimate our fracture rate. A majority of these patients were symptomatic after SRS but did not have definitive imaging to confirm a new or existing fracture. In reality not all of these patients would have in fact had a true VCF according to imaging studies; therefore we have provided a rate with exclusion of these events to be more indicative of our true institutional VCF rate. With our data being a single institutional experience, all clinical practices were consistent during the 13-year period. Factors contributing to VCFs on multivariate analysis were previous VCF and lytic lesions.

The median time to VCF was 2.7 months, with a majority (66%) occurring within the first 6 months. With the exception of Memorial Sloan-Kettering Cancer Center (median 25 mo) (13), this is consistent with other reports indicating that VCFs caused by SRS are more often acute or subacute complications (Table 3) (12, 13, 21).

Of the 3 SINS criteria previously found to correlate with SRS-induced VCFs, our results supported having a prior VCF and a lytic lesion type. We did not find spinal alignment to be related to SRS-induced VCFs; however, SINS may still have some clinical value in identifying patients who may be at a higher risk of incurring a VCF.

A majority of the hematologic malignancies in this study were multiple myeloma. We have previously reported on our institutional experience with treating multiple myeloma involving the vertebral bodies with SRS (24). The natural course of multiple myeloma typically yields numerous VCFs throughout the patient's spine at both treated and untreated levels, thus making it difficult to distinguish between pathologic and SRS-induced fractures (25, 26).

A majority of our VCFs occurred in the thoracic spine owing to the high incidence (70%) of metastases in this location (27). Female patients were found to be at an increased fracture risk. Although previous reports have not supported this finding, the result seems plausible because females at baseline have approximately twice the risk of developing a VCF compared with males. Furthermore, 25% of postmenopausal women develop VCFs, and with a majority of our patients being at postmenopausal ages, their lower bone density would likely increase their susceptibility to radiation-induced bone damage (28).

Table 3 Table summarizing large radiation therapy and stereotactic radiosurgery spinal series reporting vertebral compression fracture rates

Study	Total patients (evaluable)	Total vertebral bodies (evaluable)	Follow-up (mo), median (range)	Overall survival (mo)
Radiation therapy				
Marzano et al, 1995, University School of Medicine, Perugia, Italy	275 (209 evaluable)	NR	49 (13-88)	6
Chow et al, 2007, University of Toronto	3508 (1776 for single-fx RT)	NR	NR	NR
Stereotactic radiosurgery				
Rose et al, 2009, MSKCC	62	71	13	NR
Boehling et al, 2012, MDACC	93	123	14.9 (1-71)	NR
Sahgal et al, 2013, MDACC, Cleveland Clinic, University of Toronto	252	410	11.5 m	16
Cunha et al, 2013, University of Toronto	90	167	7.4	NR
Sung et al, 2014, KCCH	72	NA	11 (mean)	NA
Thibault, 2014, Sunnybrook Odette Cancer Centre	37	71	12.3 (1.2-55.4)	18
Guckenburger, 2014, University of Würzburg	301	387	11.8	19.5
Germano et al, 2015, Mount Sinai	79	143	16	NR
Jawad et al, 2016, Oakland University William Beaumont School of Medicine	541	594	8.8 (0-57)	NR
Present study	791 (448)	1905 (1070)	17.7	10.2

Abbreviations: fx = fraction(s); EQD2 = equivalent dose in 2 Gy fractions; KCCH = Korea Cancer Center Hospital; MDACC = MD Anderson Cancer Center; MSKCC = Memorial Sloan-Kettering Cancer Center; M/V = multivariable analysis; NA = not applicable; NR = not reported; RT = radiation therapy; SBRT = stereotactic body radiation therapy; U/V = univariate analysis; VCF = vertebral compression fracture.

Table 3 Table summarizing large radiation therapy and stereotactic radiosurgery spinal series reporting vertebral compression fracture rates *(continued)*

Dose (Gy) per fraction (fx)	Fracture no. (%)	Significant U/V factors	Significant M/V factors
3-30 Gy in 10 fx; 30 Gy/8 fx (15 Gy/3 fx, 15 Gy/5 fx) 16 Gy/2 fx NR	65 (31)	NR	NR
	<5%	NR	NR
24 Gy/1 fx	27 (39)	NR	• CT appearance • Lesion location • Percent vertebral body involvement
Median doses of: 18 Gy/1 fx 27 Gy/3 fx 30 Gy/5 fx	25 (20)	• Age >55 y • Pre-existing fracture • Baseline pain • Narcotic use before and after SBRT	• Age >55 y • Preexisting fracture • Baseline pain
24 Gy/1 fx	57 (14)	• Dose per fraction • Pre-existing VCF • Lesion type (lytic) • Spinal deformity/misalignment • Paraspinal/epidural extension	• Dose per fraction • Pre-existing VCF • Lesion type (lytic) • Spinal deformity/ misalignment • Paraspinal/epidural extension
24 Gy/2 fx	19 (11)	• Spinal misalignment • Lesion type (lytic) • Degree of pre-existing VCF	• Spinal misalignment, • Lesion type (lytic) • Dose per fraction ≥20 Gy • Lung primary • Hepatocellular primary
18-45 Gy/1-5 fx	26 (36)	• Spinal defomity • Whole vertebral body involvement • Vertebral body osteolysis rate	• Vertebral body osteolysis rate
24 Gy/2 fx	10 (16)	NR	• Single-fraction SBRT • Pre-existing VCF
24 Gy/3 fx Range, 8-60 Gy/1-20 fx	30 (7.8)	NR	• NR
18 Gy/1 fx Range, 10-18 Gy/1 fx	30 (21)	• Colorectal primary • Pre-existing VCF • Severe pain	• NR
Median, 20 Gy/1 fx Range, 8-40 Gy/1-5 fx	5.7%	• SBRT <36.8 days after diagnosis • No additional bone metastases • No prior chemotherapy • Pre-existing VCF • Tumor volume ≥37.3 cm^3 • EQD_2 tumor ≥41.8 Gy • EQD_2 spinal cord Dmax ≥46.1 Gy	• Pre-existing VCF • No additional bone metastases • ≥38.4 Gy prescribed to the target volume
18 Gy/1 fx	1279 (11.9) Adjustment for hematologic malignancies, 97 (9.9)	• Pre-existing VCF • Hematologic primary • Thoracic spine tumors • Lytic lesion • Female patients	• Pre-existing VCF • Lytic lesions

Patients with prostate cancer were at a significantly lower risk of developing a VCF. Although the spine is a common site of metastasis for prostate cancer (29, 30), its typical slow and less aggressive nature, coupled with the tendency to form blastic lesions may explain the lower fracture rate (31). Another variable correlating with decreased risk of VCF was receiving SRS to 3 or more vertebral levels. The irradiation of multiple levels in the spine could potentially result in a balancing of the mechanical load on the spine if multiple levels are treated at once (32). Both the cervical spine and sacrum were found to be associated with a decreased fracture risk. This was expected in the sacrum owing to its fused and rigid nature, and was likely found in the cervical spine owing to the significantly lower loads of weight placed on the cervical vertebrae. Similar to prior reports (11-14), bisphosphonates were not shown to be protective against SRS-induced VCFs. Although we postulated that antiangiogenic therapy may potentiate damage to bone marrow within the spine, no correlation was shown between use and VCF risk (33).

With regard to the association of dose per fraction and risk of subsequent VCF, others reported that the risk increases significantly upon dose escalation above 19 Gy (Table 3) (12, 14). Our results do not directly address this issue due to the fact that 97% of our patients were treated with 18 Gy or less. However, this may be one of the main reasons our fracture rate is one of the lowest reported; doses over 18 Gy were seldom used. Using doses over 18 Gy to the spine has been shown to carry an increased risk for adverse events (12, 14, 34, 35). Table 3 summarizes a number of large radiation therapy/SRS spinal series reporting on VCF rates. The Memorial Sloan-Kettering Cancer Center was the first institution to report on the rate of SRS-induced VCF finding that 27 (39%) of 71 treated spinal levels developed a VCF (13). Reports by the MD Anderson Cancer Center (11), the University of Toronto (12), and the Korea Cancer Center Hospital (15) found the rate to be 11%, 20%, and 36%, respectively. One of the largest reports pooled data from the MD Anderson Cancer Center, Cleveland Clinic, and University of Toronto for a total of 252 patients with 410 treated vertebral bodies, and found the rate to be 14% (14). A study by Mount Sinai evaluated single-fraction SRS constrained to 18 Gy or less, but surprisingly had a fracture rate of 21% (22). A recent study by Jawed et al (23) was a multi-institutional study that included a total of 594 vertebral bodies and displayed a fracture rate of 5.7%. The previous major studies reported rates of the development or progression of a VCF. Our rate for radiologic VCF development/progression (excluding patients who underwent surgery) was 8.4%. Instead of solely calculating VCF development/progression, our study calculated an event rate and has accounted for all potential SRS-induced spinal instability by also including in our rate the need of stabilization surgery after SRS likely due to an impending fracture. Other reports did not consider this finding. In reality not all cases of stabilization surgery would be a result of an SRS complication, thus by including these as events we are potentially over-estimating our event rate.

This study is limited in that it is a retrospective analysis. Because of the subjective nature of obtaining Karnofsky performance status scores and pain scores from a retrospective chart analysis, we did not evaluate these variables. However, previous reports have not suggested that any relationship exists between either of these variables. As shown in Figure E1 (available online at www.redjournal.org), not all treated patients were evaluable for the purposes of this study. Finally, our study did not evaluate radiation myelopathy, another significant complication of spine SRS, owing to its rarity, with rates being reported at <5% (22). A currently ongoing prospective Radiation Therapy Oncology Group study (protocol 0631) may address some of these limitations of a retrospective analysis.

Despite the limitations of this study, strengths such as the diverse ethnicities and histologies in our patient population add to the clinical utility of our findings. We had 38% African Americans, 5% other ethnicities, and varied histologies, including multiple myeloma, making ours one of the few institutions that has reported its findings on spine SRS for this histology. Another strength of this study is that all patients were treated using standardized institutional protocols for treatment planning, immobilization, dose fractionation, and follow-up. Having a homogenous treatment population allows our results to eliminate these variables from consideration and focus on other potential contributing factors.

Conclusion

Our study demonstrates that the use of SRS for spinal tumors results in a low VCF rate when using single-fraction doses of 16 to 18 Gy. With continued research and improved SRS protocols, toxicity rates can further decline, and the role of spine SRS can become more prominent.

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