

Clinical Study

Fracture rate after conventional external beam radiation therapy to the spine in multiple myeloma patients

Jens P. te Velde, BSc^{a,b,1}, Hester Zijlstra, MD^{a,c,*}¹, Amanda Lans, MD^{a,c},
Chirayu G. Patel, MD, MPH^d, Noopur Raje, MD^e, Diyar Delawi, MD, PhD^f,
Diederik H.R. Kempen, MD, PhD^g, Jorrit-Jan Verlaan, MD, PhD^c,
Barend J. van Royen, MD, PhD^b, Joseph H. Schwab, MD, MS^a

^a Department of Orthopedic Surgery, Massachusetts General Hospital – Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA

^b Department of Orthopedic Surgery and Sports Medicine, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

^c Department of Orthopedic Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

^d Department of Radiation Oncology, Massachusetts General Hospital – Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA

^e Department of Hematology/Oncology – Center for Multiple Myeloma, Massachusetts General Hospital – Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA

^f Department of Orthopedic Surgery, St. Antonius Hospital, Soestwetering 1, 3543 AZ Utrecht, The Netherlands

^g Department of Orthopedic Surgery, OLVG Amsterdam, Oosterpark 9, 1091 AC Amsterdam, The Netherlands

Received 25 April 2023; revised 26 August 2023; accepted 16 September 2023

Abstract

BACKGROUND CONTEXT: Conventional external beam radiation therapy (cEBRT) is used in multiple myeloma (MM) to treat severe pain, spinal cord compression, and disease-related bone disease. However, radiation may be associated with an increased risk of vertebral compression fractures (VCFs), which could substantially impair survival and quality of life. Additionally, the use of the Spinal Instability Neoplastic Score (SINS) in MM is debated in MM.

PURPOSE: To determine the incidence of VCFs after cEBRT in patients with MM and to assess the applicability of the SINS score in the prediction of VCFs in MM.

STUDY DESIGN: Retrospective multicenter cohort study.

PATIENT SAMPLE: MM patients with spinal myeloma lesions who underwent cEBRT between January 2010 and December 2021.

OUTCOME MEASURES: Frequency of new or progressed VCFs and subdistribution hazard ratios for potentially associated factors.

METHODS: Patient and treatment characteristics were manually collected from the patients' electronic medical records. Computed tomography (CT) scans from before and up to 3 years after the start of radiation were used to score radiographic variables at baseline and at follow-up. Multivariable Fine and Gray competing risk analyses were performed to evaluate the diagnostic value of the SINS score to predict the postradiation VCF rate.

RESULTS: A total of 127 patients with 427 eligible radiated vertebrae were included in this study. The mean age at radiation was 64 years, and 66.1% of them were male. At the start of radiation, 57 patients (44.9%) had at least one VCF. There were 89 preexisting VCFs (18.4% of 483 vertebrae). Overall, 39 of 127 patients (30.7%) reported new fractures (number of vertebrae (n)=12) or showed progression of existing fractures (n=36). This number represented 11.2% of all radiated vertebrae.

FDA device/drug status: Not applicable.

Author disclosures: **JPV:** Nothing to disclose. **HZ:** Nothing to disclose. **AL:** Nothing to disclose. **CGP:** Nothing to disclose. **NR:** Nothing to disclose. **DD:** Nothing to disclose. **DHRK:** Nothing to disclose. **J-JV:** Nothing to disclose. **BJR:** Nothing to disclose. **JHS:** Nothing to disclose.

*Corresponding author: Department of Orthopedic Surgery/Orthopedic Oncology Service, Massachusetts General Hospital – Harvard Medical

School, 55 Fruit Street, Boston, MA 02114, USA. Tel.: (316) 1271-4123/ (185) 7302-8433.

E-mail address: hesterzijlstra@outlook.com (H. Zijlstra).

¹ These authors (JPV and HZ) contributed equally to this paper and are therefore co-first authors.

Five of the 39 (12.8%) patients with new or worsened VCFs received an unplanned secondary treatment (augmentation [n=2] or open surgery [n=3]) within 3 years. Both the total SINS score (SHR 1.77; 95% confidence interval (CI) 1.54–2.03; $p < .001$) and categorical SINS score (SHR 10.83; 95% CI 4.20–27.94; $p < .001$) showed an independent association with higher rates of new or progressed VCFs in adjusted analyses. The use of bisphosphonates was independently associated with a lower rate of new or progressed VCFs (SHR 0.47 [95% CI 0.24–0.92; $p = .027$]).

CONCLUSIONS: This study demonstrated that new or progressed VCFs occurred in 30.7% of patients within 3 years, in a total of 11.2% of vertebrae. The SINS score was found to be independently associated with the development or progression of VCFs and could thus be applied in MM for fracture prediction and possibly prevention. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords:

Multiple myeloma; Radiotherapy; Spinal instability neoplastic score; Vertebral compression fractures

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy that accounts for approximately 1% of all neoplastic diseases worldwide [1]. Distinctive for MM is infiltration and proliferation of monoclonal plasma cells in the bone marrow. This can lead to disturbances in the ratio between bone resorption and bone formation, causing osteolytic lesions and secondary osteoporosis with a reduced bone mass [2]. Osteolytic lesions are present in about 80% of newly diagnosed MM patients and negatively impact the already increased mortality and morbidity [3]. These lesions, combined with the diffuse bone loss that characterizes MM, compromise the integrity of the vertebrae, which can lead to vertebral compression fractures (VCFs) [4]. VCFs and other skeletal-related events, such as spinal cord compression, substantially impair survival and quality of life [5]. Of all new MM patients, 34% to 64% present with VCFs at the time of their diagnosis [6].

Systemic therapies, such as immunotherapy with monoclonal antibodies and bisphosphonates, play an essential role in the treatment of newly diagnosed or relapsed MM and its related bone disease [1,3]. Radiation therapy is used throughout the field of spinal oncology to treat severe pain caused by VCFs, spinal cord compression, and malignancy-related bone disease [3,7]. Radiation has been reported to be beneficial for the quality of life and functional outcomes [7]. However, radiation is thought to be associated with an increased risk of VCFs, especially after high doses [8,9]. The bone matrix within the vertebral body is thought to be further weakened by radiation-induced acute inflammatory reactions, tumor vascular mediated effects, and increased apoptotic cell-driven deaths, increasing the likelihood of VCFs [10]. The rate of VCFs after spine stereotactic body radiation therapy in spinal oncology has been well described in the literature [11–14]. Although, due to the diffuse nature of the disease in MM, conventional external beam radiation therapy (cEBRT) is the most commonly used radiation modality. However, there is limited knowledge about the occurrence of VCFs after cEBRT in patients with MM [11,12]. Therefore, the primary aim of this study

was to determine the incidence of VCFs after cEBRT in MM patients.

The Spinal Instability Neoplastic Score (SINS) is a frequently used and reliable tool in spinal oncology to determine spinal instability and guide the referral process [15,16]. However, the diffuse bone loss that characterizes MM can make it challenging to detect bone deterioration before distinct lytic lesions are visible, compared with isolated bone metastases originating from some solid tumors [17]. Furthermore, the number and severity of other or prior VCFs can aggravate sagittal imbalance and further increase the risk of new VCFs. This factor is not specified in the SINS score [18]. Since many MM patients have multiple VCFs and diffuse bone loss, the applicability of the SINS score in MM is debated. As a secondary aim of this study, the validity of the SINS score in the prediction of VCFs in patients with MM was assessed.

Methods

Study design

This retrospective study was performed using data from two tertiary academic medical centers that operate under a single umbrella institution. This study was approved by the local IRB (record number: 2018P000688), and informed consent for retrospective analysis of anonymized data was waived. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement was used to ensure adequate reporting [19].

Patient selection

We identified 569 potentially eligible patients from a tertiary inclusion center through the ICD-9 and ICD-10 codes for MM (203.0 and C90) and CPT codes for Radiation Treatment Delivery.

Inclusion criteria consisted of patients (1) diagnosed with MM, (2) receiving cEBRT treatment to the spine between January 2010 and December 2021, and (3) whom had pre-radiation computed tomography (CT) scans available and

follow-up scans between 6 weeks and 3 years after cEBRT to identify fractures or monitor fracture progression. Exclusion criteria consisted of (1) individual vertebrae with prior surgery, (2) prior radiation in the same area, (3) vertebrae not visible on follow-up scans, and (3) C1, C2, and sacral vertebrae (because of their different anatomy and fracture morphology). After manually screening the electronic medical records of potentially eligible patients, 127 patients met the in- and exclusion criteria (Appendix, Fig. A1).

Outcome measure

The primary outcome measure was the rate of new VCFs (ie, new endplate fracture or collapse deformity as compared with before radiation) or fracture progression of an existing fracture. Fractures were graded using the Genant VCF height loss assessment score, and fracture progression was defined as additional vertebral height loss of over five percent [20]. If multiple CT scans were obtained within 3 years after radiation, a maximum of three follow-up measurements were performed, evenly spaced across the duration of the follow-up. When a new fracture was detected on a follow-up CT scan, prior scans were evaluated to see when the fracture was first visible in an attempt to come as close to the fracture (progression) date as possible. Secondly, the validity of the SINS score for fracture prediction of individual vertebrae was assessed through statistical risk analyses.

Variables

Several explanatory variables were collected from the patient's electronic medical records: age at time of radiation, sex, body mass index (BMI, in kg/m²), follow-up time (until death or last follow-up), disease stage according to the international staging system (ISS) for MM [21], age-adjusted Charlson Comorbidity Index (ACCI) [22], Eastern Cooperative Oncology Group (ECOG) performance status score [23], neurological symptoms (motor, sensory or combination), back pain (numeric rating scale, NRS) [24], American Spinal Injury Association (ASIA) impairment scale [25], chemotherapy regimen, bisphosphonate use, corticosteroid use, treated region, type of radiation, and radiation dose, converted to biologically effective dose (BED) with the following equation: $BED = \text{Total dose} \times (1 + (\text{Fraction dose} / \alpha/\beta \text{ ratio}))$, assuming an α/β ratio of 10 for myeloma cells [26,27]. Radiographical variables collected for each vertebra were the total SINS score [16], Genant fracture grading [20], and bone mineral density in Hounsfield Units (HU) score. The preradiation HU score of each radiated vertebra was determined with a manually drawn circular region of interest on the mid-axial plane of CT scans [28]. An 8% conversion factor was placed on the HU score when intravenous contrast was administered, and the HU score and BED were standardized before analyses for easier interpretation of the hazard ratio [29].

SINS score

The SINS score was determined for each treated vertebra at baseline [15,16]. The individual SINS components include the location (junctional, mobile, semi-rigid, and rigid spine), type of pain (mechanical, nonmechanical, pain-free lesion), type of bone lesion (lytic, mixed, blastic), vertebral body collapse (>50% collapse, <50% collapse, no VCF/collapse but 50% of the body involved by tumor, no collapse/VCF), spinal misalignment (kyphosis/scoliosis, translation/subluxation, normal alignment), and tumor involvement of the posterolateral elements (unilateral, bilateral, none). Based on the total numeric score (0–18), the SINS categorical scoring method divides vertebrae into one of three categories: stable (0–6), potentially unstable (indeterminate) (7–12), and unstable (13–18) [15].

Statistical analysis

Descriptive statistics were applied to describe patient demographics, treatment data, related covariates, and the incidence of VCFs. Two multivariable Fine and Gray competing risk analyses were performed to evaluate the subdistribution hazard ratios (SHR) and 95% confidence intervals (CI) of both the total and categorical SINS score on the VCF rate of vertebrae, with death during follow-up as a competing risk. The variables BED, bisphosphonates use, ECOG score, HU score, and ISS were added as covariates based on their proven or assumed association with VCFs [11,14,30,31]. Patient ID was used as a cluster effect in the Fine and Gray analyses since multiple radiated vertebrae within the same patient were included, and multiple vertebrae from one patient cannot be seen as uncorrelated measurements [32]. The time to detection of a VCF was calculated in months, starting at the start of cEBRT up to the date of the first discovery of the VCF on a scan, death, or last contact. Kaplan-Meier estimates were used to assess overall cumulative survival rates. Radiographical variables were measured by a single researcher (JPV). To ensure the validity of the SINS score, a random selection of 20% of the radiographical data was remeasured by the main collecting researcher (blinded to the first measurements), and another random 20% was remeasured by an orthopedically trained resident (HZ). Intraclass correlation coefficients (ICC) for both intra- and interobserver agreement were assessed using a single-measurement, absolute agreement, two-way random effects model based on the total SINS score. The inter-observer ICC reliability was 0.85 (95% CI: 0.78–0.9), and the intra-observer ICC reliability was 0.91 (95% CI: 0.87–0.93), both considered near-perfect levels of agreement [33]. Statistical analyses were performed with Python programming language, version 3.9.7 (Python Software Foundation, <https://www.python.org/>), and R programming language, version 4.1.3 (The R Foundation, <https://www.r-project.org/>). Significance was defined as $p < .05$. All tests were two-sided.

Table 1
Baseline characteristics

	Overall (n=127)	No VCF (n=88)	VCF (n=39)	p-value
Sex (male)	84 (66.1%)	57 (64.8%)	27 (69.2%)	.775
Deceased	73 (57.5%)	51 (58%)	22 (56.4%)	1.000
Age at radiation	64 [12]	64 [12]	63 [11]	.943
BMI (kg/m ²)	27.7 [24.3–32.2]	27.6 [24.2–30.7]	28.6 [25.6–33.1]	.307
ISS disease stage	-	-	-	.439
Plasmacytoma	13 (10.2%)	9 (10.2%)	4 (10.3%)	
ISS 1	50 (39.4%)	38 (43.2%)	12 (30.8%)	
ISS 2	40 (31.5%)	24 (27.3%)	16 (41%)	
ISS 3	24 (18.9%)	17 (19.3%)	7 (17.9%)	
Back pain (NRS)	-	-	-	.745
No pain	5 (3.9%)	4 (4.5%)	1 (2.6%)	
Mild (NRS 1–3)	18 (14.2%)	14 (15.9%)	4 (10.3%)	
Moderate (NRS 4–6)	27 (21.3%)	19 (21.6%)	8 (20.5%)	
Severe (NRS 7–10)	77 (60.6%)	51 (58%)	26 (66.7%)	
Neurologic symptoms	-	-	-	.430
No neurology	78 (61.4%)	53 (60.2%)	25 (64.1%)	
Only motor	18 (14.2%)	11 (12.5%)	7 (17.9%)	
Only sensory	16 (12.6%)	11 (12.5%)	5 (12.8%)	
Combined	15 (11.8%)	13 (14.8%)	2 (5.1%)	
ECOG performance score	-	-	-	.251
0	27 (21.3%)	21 (23.9%)	6 (15.4%)	
1	58 (45.7%)	42 (47.7%)	16 (41%)	
2	26 (20.5%)	14 (15.9%)	12 (30.8%)	
3	16 (12.6%)	11 (12.5%)	5 (12.8%)	
ASIA impairment score	-	-	-	.593
E	101 (79.5%)	68 (77.3%)	33 (84.6%)	
D	20 (15.7%)	15 (17%)	5 (12.8%)	
C	6 (4.7%)	5 (5.7%)	1 (2.6%)	
ACCI	4.2 [2.7]	4.4 [3.0]	3.7 [1.9]	.151
Baseline VCFs	-	-	-	<.001*
No VCFs	70 (55.1%)	63 (71.6%)	7 (17.9%)	
One VCF	39 (30.7%)	18 (20.5%)	21 (53.8%)	
Two VCFs	12 (9.4%)	7 (8%)	5 (12.8%)	
Three VCFs	3 (2.4%)	0 (0%)	3 (7.7%)	
Four or more VCFs	3 (2.4%)	0 (0%)	3 (7.7%)	
HU score	184.2 [82.1]	194.4 [86.8]	158.6 [62.8]	.017*

ACCI, age-adjusted Charlson Comorbidity Index; ASIA, American Spinal Cord Injury Association; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HU, Hounsfield unit score (corrected for contrast); ISS, international staging system; NRS, numeric rating scale; VCF, vertebral compression fracture; HU, Hounsfield units; SINS, Spinal Instability Neoplastic Score.

Values are presented as number (%) and mean [standard deviation] for normally distributed data or median [interquartile range] for nonnormally distributed data.

* Indicates statistical significance ($p < .05$).

Results

Patient cohort

The mean age at radiation was 64 years (standard deviation [SD] 12), and the patients had an average BMI of 27.7 (interquartile range [IQR] 24.3–32.2), and 66.1% of them were male (Table 1). The 3-year fracture-free survival was 35.4%. In 39.4% of patients, ISS disease stage 1 was assigned. Back pain was reported severe (NRS 7–10) in 60.6% of patients, moderate (NRS 4–6) in 21.3%, mild (NRS 1–3) in 14.2%, and absent in 3.9% of patients. The majority of patients showed no neurological symptoms (61.4%) and were capable of self-care (ECOG scores 0–2) (87.5%). The mean ACCI was 4.2 (SD 2.7), and the mean HU score was 184.2 (SD 82.1). Chemotherapy was

administered before radiation to 73 patients (57.5%) and after radiation to 42 patients (33.1%), while 12 (9.4%) did not receive chemotherapy before or during their recorded follow-up (Table 2). Most patients (83, 65.4%) received bisphosphonates before radiation. Steroids were administered prior to radiation to 56 patients (44.1%). The most common radiation schedule was 10 fractions of 3 Gy (39.4%), and the median BED was 39 [IQR 28 – 39]. The thoracic region was the most often radiated area (47.2%). Reasons for cEBRT were pain, lytic lesions, or VCFs.

Fractures

Fifty-seven of 127 patients (44.9%) were presented with at least one preexisting VCF in the radiated zones at the start of radiation. Of the total 483 radiated vertebrae, 89

Table 2
Treatment characteristics

	Overall (n=127)	No VCF (n=88)	VCF (n=39)	p-value
Chemotherapy regimen	-	-	-	.088
RVd (lite), Rd or RV	65 (51.2%)	40 (45.5%)	25 (64.1%)	
DRd, DVd or DPd	13 (10.2%)	11 (12.5%)	2 (5.1%)	
KRd, Kd or KCd	12 (9.4%)	8 (9.1%)	4 (10.3%)	
Other regimen	25 (19.7%)	22 (25%)	3 (7.7%)	
No chemotherapy	12 (9.4%)	7 (8%)	5 (12.8%)	
Chemotherapy timing	-	-	-	.678
Before radiotherapy	73 (63.5%)	51 (63%)	22 (64.7%)	
After radiotherapy	42 (36.5%)	30 (37%)	12 (35.3%)	
Bisphosphonates	-	-	-	.515
Once	8 (7.2%)	5 (6.7%)	3 (8.3%)	
2–5 times	9 (8.1%)	6 (8%)	3 (8.3%)	
Regularly/quarterly	66 (59.5%)	48 (64%)	18 (50%)	
High-dose steroids	56 (44.1%)	36 (40.9%)	20 (51.3%)	.551
Former chronic prednisone use	13 (10.2%)	10 (11.4%)	3 (7.7%)	.753
Site treated	-	-	-	.094
Cervical	8 (6.3%)	7 (8%)	1 (2.6%)	
Cervicothoracic	7 (5.5%)	6 (6.8%)	1 (2.6%)	
Thoracic	60 (47.2%)	37 (42%)	23 (59%)	
Thoracolumbar	4 (3.1%)	1 (1.1%)	3 (7.7%)	
Lumbar	27 (21.3%)	22 (25%)	5 (12.8%)	
Lumbosacral	21 (16.5%)	15 (17%)	6 (15.4%)	
Number of levels radiated	-	-	-	.174
1–2	20 (15.7%)	13 (14.8%)	7 (17.9%)	
3–5	82 (64.6%)	58 (65.9%)	24 (61.5%)	
6–10	23 (18.1%)	16 (18.2%)	7 (17.9%)	
10+	2 (1.6%)	1 (1.1%)	1 (2.6%)	
Radiotherapy technique	-	-	-	.392
AP/PA/3D	117 (92.1%)	83 (94.3%)	34 (87.2%)	
VMAT/IMRT	7 (5.6%)	4 (4.6%)	3 (7.9%)	
SBRT	1 (0.8%)	0 (0%)	1 (2.6%)	
Dose schedule	-	-	-	.390
1 × 8 Gy	7 (5.5%)	6 (6.8%)	1 (2.6%)	
5 × 4–5 Gy	39 (30.7%)	24 (27.3%)	15 (38.5%)	
6 × 3–4 Gy	2 (1.6%)	0 (0%)	2 (5.1%)	
10 × 2.4–2.5 Gy	6 (4.7%)	4 (4.5%)	2 (5.1%)	
10 × 3 Gy	50 (39.4%)	38 (43.2%)	12 (30.8%)	
12–13 × 2–2.5 Gy	5 (3.9%)	4 (4.5%)	1 (2.6%)	
14–15 × 2–2.5 Gy	5 (3.9%)	4 (4.5%)	1 (2.6%)	
17 × 1.8 Gy	1 (0.8%)	1 (1.1%)	0 (0%)	
20 × 2 Gy	3 (2.4%)	2 (2.3%)	1 (2.6%)	
24–25 × 1.8–2 Gy	9 (7.1%)	5 (5.7%)	4 (10.3%)	
BED ^{a/β=10}	39 [28 – 39]	39 [28 – 39]	36 [28 – 39]	.584

AP, anterior posterior; BED, biologically effective dose; Gy, gray; IMRT, intensity modulated radiation therapy; PA, posterior anterior; SBRT, stereotactic body radiation therapy; VCF, vertebral compression fracture; VMAT, volumetric modulated arc therapy.

Values are presented as number (%) and mean [standard deviation] for normally distributed data or median [interquartile range] for nonnormally distributed data.

Chemotherapy regimens are combinations of cyclophosphamide (C), daratumumab (D), dexamethasone (d), carfilzomib (K), pomalidomide (P), lenalidomide/revlimid (R), bortezomib/velcade (V).

(18.4%) were fractured at baseline. Of these preexisting VCFs, 22 (24.7%) were mild according to the Genant criteria, 38 (42.7%) moderate, and 29 (32.6%) were severe. Thirty-nine of 127 patients (30.7%) suffered from new or progressed VCFs. Secondary spinal intervention after initial radiation but before the first follow-up CT scan was performed in 56 vertebrae, which were therefore excluded from further analyses. Of the 427 eligible vertebrae, 48 (11.2%) subsequently developed new or progression of

existing fractures, with the greatest rates of progression observed among potentially unstable vertebrae (n=42, 87.5%). Among these 48 fractures, 12 (25%) were new fractures, and 36 (75%) progressed were existing fractures. Thirty-nine of 127 patients (30.7%) suffered from these new or progressed VCFs. Fifty percent of the preexisting VCFs remained stable. The median time to detect a new or progressed fracture was 10 months (IQR 4–13). Five of the 39 (12.8%) patients with new or worsened VCFs received

Table 3
SINS (components) per vertebrae

	Overall (n=483)	No VCF (n=435)	VCF (n=48)	p-value
SINS total (numeric)	8 [6–9]	7 [6–9]	10 [9–11]	<.001*
SINS total (categorical)	-	-	-	<.001*
Stable	133 (28.5%)	129 (30.9%)	4 (8.3%)	
Potentially unstable	324 (69.5%)	284 (67.9%)	40 (83.3%)	
Unstable	9 (1.9%)	5 (1.2%)	4 (8.3%)	
Location	-	-	-	.295
Junctional (C7–T2, T11–L1, L5)	163 (33.7%)	144 (33.1%)	19 (39.6%)	
Mobile spine (C3–C6, L2–L4)	113 (23.4%)	105 (24.1%)	8 (16.7%)	
Semirigid (T3–T10)	190 (39.3%)	169 (38.9%)	21 (43.8%)	
Pain	-	-	-	.414
Mechanical pain	383 (79.3%)	343 (78.9%)	40 (83.3%)	
Occasional and nonmechanical	61 (12.6%)	54 (12.4%)	7 (14.6%)	
Pain-free lesion	22 (4.6%)	21 (4.8%)	1 (2.1%)	
Bone lesion type	-	-	-	.160
Lytic	469 (97.1%)	424 (97.5%)	45 (93.6%)	
Mixed	14 (2.9%)	11 (2.5%)	3 (6.4%)	
Blastic	0 (0%)	0 (0%)	0 (0%)	
Vertebral body collapse	-	-	-	<.001*
≥50%	16 (3.3%)	13 (3%)	3 (6.2%)	
<50%	68 (14.1%)	36 (8.3%)	32 (66.7%)	
No collapse with > 50% involved	31 (6.4%)	22 (5.1%)	9 (18.8%)	
None of the above	368 (76.2%)	364 (83.7%)	4 (8.3%)	
Spinal misalignment	-	-	-	.782
Normal	445 (92.1%)	401 (92.2%)	44 (91.7%)	
Subluxation/translation	0 (0%)	0 (0%)	0 (0%)	
Posterolateral involvement	-	-	-	<.001*
Bilateral	56 (11.6%)	38 (8.7%)	18 (37.5%)	
Unilateral	101 (20.9%)	88 (20.2%)	13 (27.1%)	
No involvement	326 (67.5%)	309 (71%)	17 (35.4%)	

SINS, Spinal Instability Neoplastic Score; VCF, vertebral compression fracture.

Values are presented as number (%) for normally distributed data.

* Indicates statistical significance (p<.05).

an unplanned secondary treatment, augmentation (n=2), or open surgery (n=3) within 3 years. In basic comparative analyses, no baseline differences were found between patients with new or progressed VCFs and those without.

SINS score

The median total SINS score was 8 (IQR 6–9). Table 3 shows the six individual domains and their scores. When divided into three categories, 145 vertebrae were stable (31.1%), 315 were potentially unstable (67.6%), and six were unstable (1.3%). The total SINS score at baseline was higher for individual vertebrae that fractured (new or progressed) (10, IQR 9–11) compared with vertebrae that did not fracture (7, IQR 6–9). In basic comparative analyses, vertebrae that developed a new fracture or fracture progression had mainly <50% body collapse, and more bilateral posterior involvement (all p<.001). Adjusted analyses indicated that both the total SINS score (SHR 1.77; 95% CI 1.54–2.03; p<.001) and the categorical SINS score (SHR 10.83; 95% CI 4.20–27.94; p<.001) were independently associated with future VCFs of that vertebra (Table 4). Furthermore, the use of bisphosphonates was independently associated with a lower rate of new or progressed VCFs in

Table 4
Multivariate Fine and Gray competing risk analyses with numeric and categorical SINS

	SHR	95% CI	p-value
SINS (numeric)	1.77	1.54–2.03	<.001*
BED	0.74	0.51–1.06	.100
Bisphosphonates	0.50	0.24–1.06	.070
ECOG score	1.05	0.79–1.40	.730
HU score	0.86	0.60–1.23	.410
ISS	0.96	0.66–1.38	.810
	SHR	95% CI	p-value
SINS (categorical)	10.83	4.20–27.94	<.001*
BED	0.79	0.55–1.15	.220
Bisphosphonates	0.47	0.24–0.92	.027*
ECOG score	0.97	0.71–1.33	.860
HU score	0.71	0.49–1.02	.067
ISS	0.99	0.68–1.43	.950

BED, biologically effective dose; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HU, Hounsfield units; ISS, international staging system; SHR, subdistribution hazard ratios; SINS, Spinal Instability Neoplastic Score.

* Indicates statistical significance (p<.05).

the analysis with the categorical SINS score (SHR 0.47; 95% CI 0.24–0.92; $p=.027$) (Table 4).

Discussion

In addition to systemic therapy, cEBRT is the treatment modality of choice to alleviate the severe pain caused by spinal myeloma lesions. Since MM is traditionally considered radiosensitive, cEBRT is also indicated for the treatment of impending VCFs and spinal cord compression [3,7,12]. However, it is thought that radiation increases the risk of VCFs [8,9]. The mechanism has been postulated as the induction of osteoradionecrosis, which decreases the bone quality and thereby its ability to withstand the axial load's force, hence, leading to fracture [11,34]. Our results show that 39 of 127 (30.7%) patients and 48 of the 427 (11.2%) radiated vertebrae suffered from new or progressed VCFs within 3 years. This study demonstrated that the SINS score is independently associated with the development of new or progression of preexisting VCFs, regardless of whether the total SINS score is used or the SINS categories.

So far, the role of cEBRT in developing VCFs is not clear. Studies examining patients with spinal metastases originating from solid tumors reported VCF rates ranging from 7 to 20% of vertebrae [13,35,36]. In a small study involving 12 MM patients, fractures appeared in 5% of irradiated vertebrae and 20% of nonirradiated vertebrae [37]. However, evaluation of the incidence of VCFs in a MM cohort not treated with radiotherapy demonstrated that 53% of the 143 patients suffered from new or progressed fractures at an average 25-month follow-up [30]. Despite the higher VCF rate in nonradiated patients compared with our cEBRT cohort, it should be noted that baseline measurements were done at different moments, more vertebrae per patient were included in the nonradiated cohort, and selection criteria were different. Nevertheless, the results from our study suggest that cEBRT could be supportive in preventing future vertebral collapse compared with no radiation [30,37]. Since no other recent studies have been conducted using larger MM cohorts, the generalizability of our results must be established by future research.

A consensus regarding the applicability of the SINS score in patients with MM remains to be reached [17,18]. The SINS was created to identify and discuss spinal instability for referral purposes within a patient rather than to predict fractures [10]. In spinal metastases, the SINS score (total and categorical) was also associated with new or progressed VCFs after radiation in several studies [36,38]. Our findings underline the applicability of the SINS in MM to identify individuals more likely to develop VCFs after radiation.

In addition to the SINS score, the use of bisphosphonates was associated with a lower rate of new or progressed VCFs. This is consistent with evidence of reducing VCFs in a meta-analysis with a total of 1116 patients with MM, disregarding radiation [31]. Bisphosphonates are the

cornerstone of MM-related bone disease prevention and are advised to be administered to all patients with MM [3,39]. Apart from the SINS score and bisphosphonates use, no other factors (BED, ECOG score, HU score, ISS) were found to be significant. In previous studies on spinal metastases, the dose per fraction or BED in cEBRT was associated with VCF development or progression with increased risks of VCFs for higher doses per fraction [36]. In our study, the BED was lower in the group with new or progressed VCFs compared with the group without, but this was not found to be significant. It is possible that the association with BED is not as relevant in cEBRT as in other types of radiation with higher doses (per fraction) and more precision, which has been well described [11,14]. The HU score showed no significant associations in the analyses, despite literature showing evidence of increased VCF rates with a decrease in HU score [30,40]. It is important to acknowledge that HU is more of a measurement tool for bone mineral mass and not so much for bone (micro-)architecture. ISS was found to be predictive for future VCFs in MM patients without radiation [30]. The lack of a significant association in this study may be explained by the assumption that VCFs mainly occur in the early phases of disease progression, thus making the ISS disease stage less useful for fracture prediction [3].

Limitations and recommendations

This study has several limitations. Due to the retrospective nature of the study, there was no standardized procedure for the collection of variables or follow-up imaging. Therefore, there was a reliance on the interpretation and documentation of the physician for several explanatory variables, impacting the SINS assessment. For example, no formal standardized pain assessment could be performed. When no distinction could be made between mechanical vs nonmechanical pain based on the available documentation, we scored pain scores of five and higher as mechanical and the rest as nonmechanical. This may lead to inaccurate scoring of the SINS score pain parameter. Preradiation planning CT scans were not always available, for which we used the first available diagnostic scan before RT instead. Furthermore, the exact time of development or progression of VCFs could not be determined, and the date of the scan where the fracture was first detected was used. Next, it is possible that a patient suffered from a new VCF but did not visit one of the participating hospitals for imaging and was therefore excluded from this study. This could have led to an underestimation of new fractures. Also, symptom-free VCFs may be missed because patients are less likely to visit the hospital for these fractures. However, it is questionable as to whether symptom-free fractures are as important to recognize. In line with that, we did not incorporate pain assessments at the time of new fractures. Therefore, we could not make a distinction between painful or symptom-free fractures.

Despite these limitations, we believe that our study represents one of the largest MM cohorts, adequately powered to assess fracture rate after radiation. Prospective investigations can build upon this study's findings by validating these findings in a controlled and systematic manner. The findings should be compared with a matched patient cohort who did not undergo radiotherapy to find out if there is actually a benefit from radiotherapy. Since merely developing a fracture is not the only important factor, it is valuable to include patient reported outcome measures in future research. For future research in general and application of the results in a clinical setting, it is important to realize that 31% of patients still suffered from new or progressed fractures postradiation, highlighting the need for improved strategies to prevent fractures after radiation. The study also improved our understanding of the relationship between the total SINS score and fracture rate after radiation, and we hope that our findings motivate further prospective investigations in this area, for example, to validate the applicability of the SINS score across diverse populations of MM patients (different disease stages, treatment history) to ensure generalizability of the score's predictive value.

Conclusions

This study demonstrated that new or progressed VCFs occurred in 30.7% of patients within 3 years, in a total of 11.2% of vertebrae. The SINS score was found to be independently associated with the development or progression of VCFs and thus could be applied in MM for fracture prediction and possibly prevention.

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.

Author contributions

All authors were involved in the design. JPV and HZ performed the data extraction. JPV and HZ performed the data analysis. All authors reviewed and edited the manuscript.

Approval

Investigation performed at Massachusetts General Hospital, Boston, USA. Local Institutional Review Board (IRB) approval was obtained for this study (registration number 2018P000688).

Acknowledgments

Each author certifies that they have no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.spinee.2023.09.009>.

References

- [1] Gerecke C, Fuhrmann S, Striffler S, Schmidt-Hieber M, Einsele H, Knop S. The diagnosis and treatment of multiple myeloma. *Dtsch Arztebl Int* 2016;113:470–6. <https://doi.org/10.3238/arztebl.2016.0470>.
- [2] Mirza F, Canalis E. Management of endocrine disease: secondary osteoporosis: pathophysiology and management. *Eur J Endocrinol* 2015;173:R131–51. <https://doi.org/10.1530/EJE-15-0118>.
- [3] Terpos E, Zamagni E, Lentzsch S, Drake MT, García-Sanz R, Abildgaard N, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. *Lancet Oncol* 2021;22:e119–30. [https://doi.org/10.1016/S1470-2045\(20\)30559-3](https://doi.org/10.1016/S1470-2045(20)30559-3).
- [4] Anitha D, Baum T, Kirschke JS, Subburaj K. Risk of vertebral compression fractures in multiple myeloma patients: a finite-element study. *Medicine (Baltimore)* 2017;96:e5825. <https://doi.org/10.1097/MD.0000000000005825>.
- [5] Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raju N, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol* 2013;31:2347–57. <https://doi.org/10.1200/JCO.2012.47.7901>.
- [6] Anselmetti GC, Manca A, Montemurro F, Hirsch J, Chiara G, Grignani G, et al. Percutaneous vertebroplasty in multiple myeloma: prospective long-term follow-up in 106 consecutive patients. *Cardiovasc Intervent Radiol* 2012;35:139–45. <https://doi.org/10.1007/s00270-011-0111-4>.
- [7] Tsang RW, Campbell BA, Goda JS, Kelsey CR, Kirova YM, Parikh RR, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol* 2018;101:794–808. <https://doi.org/10.1016/j.ijrobp.2018.05.009>.
- [8] Dickie CI, Parent AL, Griffin AM, Fung S, Chung PWM, Catton CN, et al. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated Bone length, volume, tumor location and dose. *Int J Radiat Oncol* 2009;75:1119–24. <https://doi.org/10.1016/j.ijrobp.2008.12.006>.
- [9] Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009;27:5075–9. <https://doi.org/10.1200/JCO.2008.19.3508>.
- [10] Faruqi S, Tseng C-L, Whyne C, Alghamdi M, Wilson J, Myrehaug S, et al. Vertebral compression fracture after spine stereotactic body radiation therapy: a review of the pathophysiology and risk factors. *Neurosurgery* 2018;83:314–22. <https://doi.org/10.1093/neuros/nyx493>.
- [11] Sahgal A, Atenafu EG, Chao S, Al-Omair A, Boehling N, Balagamwala EH, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013;31:3426–31. <https://doi.org/10.1200/JCO.2013.50.1411>.
- [12] Miller JA, Balagamwala EH, Chao ST, Emch T, Suh JH, Djemil T, et al. Spine stereotactic radiosurgery for the treatment of multiple myeloma. *J Neurosurg Spine* 2017;26:282–90. <https://doi.org/10.3171/2016.8.SPINE16412>.
- [13] Vargas E, Susko MS, Mummaneni PV, Braunstein SE, Chou D. Vertebral body fracture rates after stereotactic body radiation therapy compared with external-beam radiation therapy for metastatic spine tumors. *J Neurosurg Spine* 2020;33:870–6. <https://doi.org/10.3171/2020.5.SPINE191383>.

- [14] Cunha MVR, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol* 2012;84:e343–9. <https://doi.org/10.1016/j.ijrobp.2012.04.034>.
- [15] Fournier DR, Frangou EM, Ryken TC, DiPaola CP, Shaffrey CI, Berven SH, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol* 2011;29:3072–7. <https://doi.org/10.1200/JCO.2010.34.3897>.
- [16] Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the spine oncology study group. *Spine (Phila Pa 1976)* 2010;35:E1221–9. <https://doi.org/10.1097/BRS.0b013e3181e16ae2>.
- [17] Lee EM, Kim B. Clinical significance of trabecular bone score for prediction of pathologic fracture risk in patients with multiple myeloma. *Osteoporos Sarcopenia* 2018;4:73–6. <https://doi.org/10.1016/j.afos.2018.05.003>.
- [18] Xiao R, Miller JA, Margetis K, Lubelski D, Lieberman IH, Benzel EC, et al. Predicting the progression of vertebral fractures in patients with multiple myeloma. *Spine J* 2016;16:510–5. <https://doi.org/10.1016/j.spinee.2015.12.014>.
- [19] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9. <https://doi.org/10.1016/j.jclinepi.2007.11.008>.
- [20] Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;8:1137–48. <https://doi.org/10.1002/jbmr.5650080915>.
- [21] Greipp PR, Miguel JS, Durie BGM, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. *J Clin Oncol* 2005;23:3412–20. <https://doi.org/10.1200/JCO.2005.04.242>.
- [22] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51. [https://doi.org/10.1016/0895-4356\(94\)90129-5](https://doi.org/10.1016/0895-4356(94)90129-5).
- [23] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
- [24] Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, et al. Assessment of pain. *Br J Anaesth* 2008;101:17–24. <https://doi.org/10.1093/bja/aen103>.
- [25] Rupp R, Biering-Sørensen F, Burns SP, Graves DE, Guest J, Jones L, et al. International standards for neurological classification of spinal cord injury. *Top Spinal Cord Inj Rehabil* 2021;27:1–22. <https://doi.org/10.46292/sci2702-1>.
- [26] Fowler JF. 21 years of biologically effective dose. *Br J Radiol* 2010;83:554–68. <https://doi.org/10.1259/bjr/31372149>.
- [27] van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, et al. The alpha and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. *Radiat Oncol* 2018;13:96. <https://doi.org/10.1186/s13014-018-1040-z>.
- [28] Schreiber JJ, Anderson PA, Rosas HG, Buchholz AL, Au AG. Hounsfield Units for assessing bone mineral density and strength: a tool for osteoporosis management. *J Bone Jt Surg* 2011;93:1057–63. <https://doi.org/10.2106/JBJS.J.00160>.
- [29] Pickhardt PJ, Lauder T, Pooler BD, Muñoz del Rio A, Rosas H, Bruce RJ, et al. Effect of IV contrast on lumbar trabecular attenuation at routine abdominal CT: correlation with DXA and implications for opportunistic osteoporosis screening. *Osteoporos Int* 2016;27:147–52. <https://doi.org/10.1007/s00198-015-3224-9>.
- [30] Zijlstra H, Wolterbeek N, Drost RW, Koene HR, van der Woude HJ, Terpstra WE, et al. Identifying predictive factors for vertebral collapse fractures in multiple myeloma patients. *Spine J* 2020;20:1832–9. <https://doi.org/10.1016/j.spinee.2020.07.004>.
- [31] Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. *Cochrane Database Syst Rev* 2017;2017:CD003188. <https://doi.org/10.1002/14651858.CD003188.pub4>.
- [32] Zhou B, Fine J, Latouche A, Labopin M. Competing risks regression for clustered data. *Biostatistics* 2012;13:371–83. <https://doi.org/10.1093/biostatistics/kxr032>.
- [33] Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
- [34] Al-Omair A, Smith R, Kiehl T-R, Lao L, Yu E, Massicotte EM, et al. Radiation-induced vertebral compression fracture following spine stereotactic radiosurgery: clinicopathological correlation: report of 2 cases. *J Neurosurg Spine* 2013;18:430–5. <https://doi.org/10.3171/2013.2.SPINE12739>.
- [35] Lee J, Rhee WJ, Chang JS, Chang SK, Koom WS. Evaluation of predictive factors of vertebral compression fracture after conventional palliative radiotherapy for spinal metastasis from colorectal cancer. *J Neurosurg Spine* 2017;28:333–40. <https://doi.org/10.3171/2017.6.SPINE17282>.
- [36] Shi DD, Hertan LM, Lam TC, Skamene S, Chi JH, Groff M, et al. Assessing the utility of the spinal instability neoplastic score (SINS) to predict fracture after conventional radiation therapy (RT) for spinal metastases. *Pract Radiat Oncol* 2018;8:e285–94. <https://doi.org/10.1016/j.prro.2018.02.001>.
- [37] Lecouvet F, Richard F, Berg BV, Malghem J, Maldague B, Jamart J, et al. Long-term effects of localized spinal radiation therapy on vertebral fractures and focal lesions appearance in patients with multiple myeloma. *Br J Haematol* 1997;96:743–5. <https://doi.org/10.1046/j.1365-2141.1997.d01-2108.x>.
- [38] Kim YR, Lee C-H, Yang SH, Hyun S-J, Kim CH, Park SB, et al. Accuracy and precision of the spinal instability neoplastic score (SINS) for predicting vertebral compression fractures after radiotherapy in spinal metastases: a meta-analysis. *Sci Rep* 2021;11:5553. <https://doi.org/10.1038/s41598-021-84975-3>.
- [39] Terpos E, Roodman GD, Dimopoulos MA. Optimal use of bisphosphonates in patients with multiple myeloma. *Blood* 2013;121:3325–8. <https://doi.org/10.1182/blood-2012-10-435750>.
- [40] Borggrefe J, Giravent S, Thomsen F, Peña J, Campbell G, Wulff A, et al. Association of QCT bone mineral density and bone structure with vertebral fractures in patients with multiple myeloma. *J Bone Miner Res* 2015;30:1329–37. <https://doi.org/10.1002/jbmr.2443>.