Journal of Bone Oncology 15 (2019) 100218

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Local control and vertebral compression fractures following stereotactic body radiotherapy for spine metastases

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ARTICLE INFO

Keywords:
SBRT
Spine metastases
Vertebral compression fracture
Bisphosphonate
PET/CT

ABSTRACT

Purpose: We aimed to retrospectively assess the incidence of vertebral compression fractures (VCF), examine clinicopathologic factors potentially associated with VCF, and evaluate treatment response in patients who received stereotactic body radiotherapy (SBRT) for spine metastases (spMets).

Methods and Materials: We identified 78 patients with 125 spMets at baseline and subsequent assessments. Patients received SBRT doses of 16 or 18 Gy. Patients with pre-existing VCF and co-existing local progression were excluded. Spine instability neoplastic score (SINS) was used for spMets categorization. Response to SBRT and VCF were assessed according to the Positron Emission tomography Response Criteria In Solid Tumors (PERCIST) and Genant scores, respectively. Kaplan–Meier analyses were used to assess local control of disease and vertebral compression fracture-free survival (FFS).

Results: We treated 103 cases with single spMets and 11 cases involving double spMets with SBRT. Progressive disease was reported in 3.2% and 8.2% of the cases in the first and last PET/CT reports, respectively. The distribution of treatment response in the remaining patients was: complete response in 30.6% of patients, partial response in 47.1% of patients, and stable disease in 22.3% of patients in the first PET/CT; complete response in 62.3% of patients, partial response in 16.7% of patients, and stable disease in 21% of patients at the last monitoring. Local failures were observed in 15 (12%) of cases. Median SINS was 5 (range: 1 − 13); majority of patients in our cohort (70.4%) were categorized as stable according to SINS, five (4%) patients had Grade 3 VCF at a median time of 16 months after SBRT (range: 2 − 22 months), and 60% of VCF occurred after an interval of at least 12 months after SBRT. No bisphosphonate usage was significantly associated with VCF ($r = -0.204$; $p = 0.022$). Median FFS was 21 months. Univariate analyses indicated that female gender ($p < 0.001$), bisphosphonate use ($p = 0.005$), >6 months of bisphosphonates use ($p = 0.002$), and the lowest vertebral body collapse score ($p = 0.023$) were associated with higher FFS. Female gender ($p = 0.007$), >6 months of bisphosphonates usage ($p = 0.018$), and the lowest vertebral body collapse score ($p = 0.044$) retained independent significance.

Conclusions: This study demonstrated that spine SBRT with doses of 16–18 Gy promises good local control of disease with acceptable VCF rates. Lowest vertebral body collapse score, female gender, and >6 months of bisphosphonate use were significantly associated with longer FFS.

1. Introduction

Spinal metastasis (spMets) may develop in up to 60–70% of all cancer patients either at presentation or as a component of progressive disease during the course of disease [1]. Prolongation of survival in metastatic patients as a result of modern systemic therapies, not only

Abbreviations: FFS, vertebral compression fracture-free survival; PERCIST, Positron Emission tomography Response Criteria in Solid Tumors; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiotherapy; SINS, spine instability neoplastic score; spMets, spine metastases; SUL, lean body mass SUV; SUV, standardized uptake values; VCF, vertebral compression fractures

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https://doi.org/10.1016/j.jbo.2019.100218
Received 6 November 2018; Received in revised form 16 January 2019; Accepted 16 January 2019
Available online 24 January 2019

increases rates of spMets, but may also necessitate re-treatment of the previously irradiated metastatic spine if recurrence develops [2]. Nevertheless, the limited radiation tolerance of the spinal cord may render re-irradiation of spinal relapses quite difficult, especially when technically inferior and old-fashioned radiotherapy modalities are employed [3]. This therapeutic challenge encouraged clinicians to reserve conventional treatment techniques for palliative purposes, and instead, to adopt stereotactic body radiotherapy (SBRT) for ablative purposes; SBRT allows delivery of higher biologically equivalent doses, while providing more effective protection of the spinal cord and other critical organs. In addition, the enhanced multi-dimensional accuracy afforded by SBRT permits more effective protection of bone marrow in the contiguous spine so that systemic treatments can continue uninterrupted and in parallel with SBRT [3–6].

In spite of its aforementioned advantages, implementation of high-dose radiation to the spine may induce vertebral compression fractures (VCF), which are reported to develop more commonly (3–39%) than the most serious complication of radiotherapy, namely, myelopathy (1–5%) [7–12]. Given the negative impact of VCF on patients' quality of life even in the absence of progressive disease, the prevention and/or timely diagnosis and treatment of VCF are of paramount importance in patients undergoing SBRT for spMets [13,14].

Therefore, this study primarily aims to evaluate the incidence of de novo VCF and examine associations between clinicopathologic factors and VCF among patients who underwent SBRT for spMets. Secondly, the radiotherapy response rates of spMets after SBRT were evaluated using ^{18}F-FDG PET-CT and Ga^{68}-prostate-specific membrane antigen (PSMA) PET-CT, as indicated.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board. We retrospectively reviewed 180 vertebral segments in 120 metastatic patients treated with SBRT between January 2013 and September 2017 in our center. The inclusion criteria for this study were: age $\geq$18 years, Eastern Cooperative Oncology Group Performance Status of 0 − 2, pathological proof of primary tumors excluding radiosensitive small-cell lung carcinoma or hematological malignancies before SBRT, no previous radiotherapy to treated segment, availability of pre- and post-SBRT PET scans, and availability of detailed information about the SBRT and bisphosphonate usage. In our department, patients with $>$grade 1 VCF were not included in the analysis because of the preference for conformal radiotherapy instead of SBRT in patients with grades 2 and 3 VCF. Patients who experienced both VCF and progressive disease in the irradiated segment were excluded to avoid confounding effects of progressive disease on VCF. The final study cohort included 78 patients and 125 vertebral segments (Fig. 1).

Each spMet lesion was scored according to the spinal instability neoplastic score (SINS) [15] to predict the probability of instability

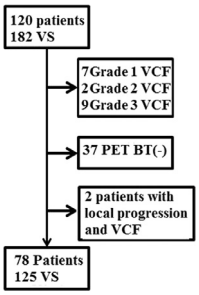

Fig. 1. Flowchart for inclusion criteria.
Abbreviations: VS, vertebral segment; VCF; vertebral compression fracture; PET-BT, positron emission computerized tomography.

[16], which categorizes patients into stable (SINS 0–6), potentially unstable (SINS 7–12), and unstable (SINS 13–18) groups (Table 2).

2.2. Stereotactic body radiotherapy procedure

Volumetric modulated arc technique was performed using 6 MV energy linear accelerators with a 4-mm multi-leaf collimator and kilovoltage cone beam CT image guidance. Each patient was immobilized in the Elekta Bodyfix stereotactic body frame with the whole-body vacuum cushion. A 1.25 mm thick planning CT scan was performed. Axial T1 volumetric MRI or ^{18}F-FDG PET-CT was performed if planning CT was not sufficient to delineate spMets with paraspinal component. Clinical target volume was defined according to International Spine Radiosurgery Consortium Guidelines published in 2012 [17], with no further expansion for the planning target volume.

We used one of two treatment approaches for spinal SBRT: the target volume received 16 Gy or 18 Gy with the optimized isodose lines of 80% and 100%, respectively. In each approach, the planned target volume received 95% of the prescribed dose (Fig. 3). A maximum of two contiguous vertebral segments were permitted to be treated in a single SBRT session. The dose to 0.035 cm^3 of the spinal cord, and a maximum dose point, were mandated to be $<$10 Gy and 14 Gy, respectively.

2.3. Baseline and follow-up vertebral heights and VCF evaluations

Vertebral heights were assessed using either the sagittal sections of the PET/CT and baseline planning CT, or MRI. Fractures were graded in a blinded manner by an experienced radiologist (A.G.). The VCF degree was scored according to the method of Genant and co-workers [18]: Grade 0, no fracture; Grades 1, 2, and 3 represent 0–25%, 26–40% and $>$40% height reductions, respectively.

2.4. Monitoring tumor response

Patients were asked to follow up every 3 months for the first 2 years, every 6 months for years 3–5, and then yearly thereafter. All patients continued the required systemic therapies after SBRT. In our center, PET/CT is utilized frequently by both radiation and medical oncologists to monitor disease status. MRI was also performed for refractory pain and neurological symptoms to exclude VCF or if the baseline tool before SBRT was MRI.

The maximum standardized uptake values (SUV_{max}) were measured by an experienced nuclear medicine specialist (N.T.), and response was scored according to Positron Emission tomography Response Criteria in Solid Tumors (PERCIST), which uses peak lean body mass SUV (SULpeak). Briefly, complete response (CR) was defined as complete resolution of FDG uptake within the target lesion, with FDG uptake lower than the mean lean body mass SUV (SUL) of the liver, and indistinguishable from surrounding background. Partial response (PR) was defined as $a \geq$ 30% decrease in SUL. Progressive disease (PD) was defined as $a >$ 30% increase in SUL, and stable disease [19] was any metastasis not fitting these criteria (Fig. 2). The response of each spinal metastatic lesion was assessed independently for SBRT of two contiguous segments.

2.5. Statistical analysis

Categorical variables were described as frequency distributions. Quantitative variables were described as median and ranges. All time intervals were calculated from the SBRT date to the event date or date of last follow-up imaging. Vertebral compression fracture-free survival (FFS) estimates were calculated using Kaplan–Meier analyses. Log-rank test was utilized to identify factors significantly associated with FFS, and multivariate Cox regression analyses were performed for significant variables. A p-value $\leq$0.05 was considered as statistically significant.

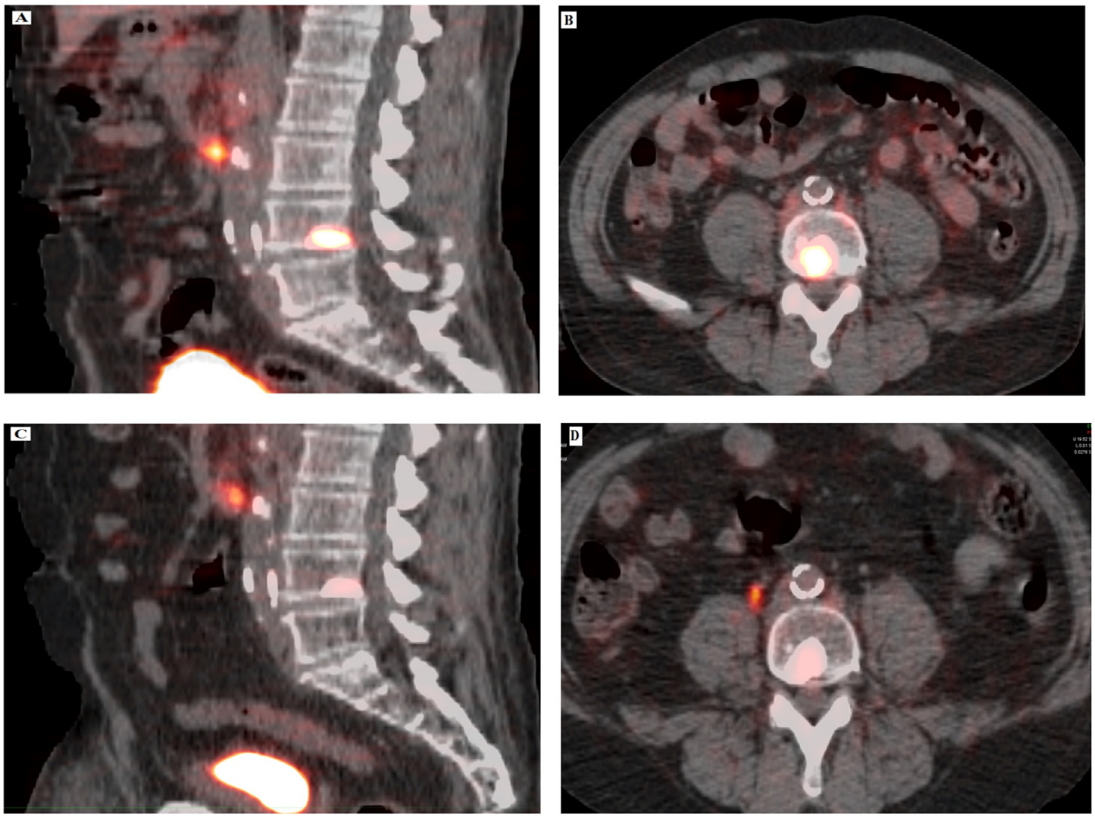

Fig. 2. PSMA-PET/CT scans of a patient with prostate cancer. (A) Pre-SBRT sagittal section, (B) pre-SBRT axial section, (C) post-SBRT (3 months after SBRT) axial section with partial response, (D) post-SBRT sagittal section.

3. Results

A total of 78 patients with 125 vertebral segments (103 single, 11 double) were included in the analyses. Patients' demographics are presented in Table 1. The study cohort included patients with the following types of primary tumors: 66.4% with breast tumors, 16.8% with non-small cell lung cancer, 13.6% with prostate cancer, and 3.2% with other tumor types. There were no significant proportional differences between patient groups, except that female patients had a significantly higher frequency of bisphosphonate use ($p < 0.001$).

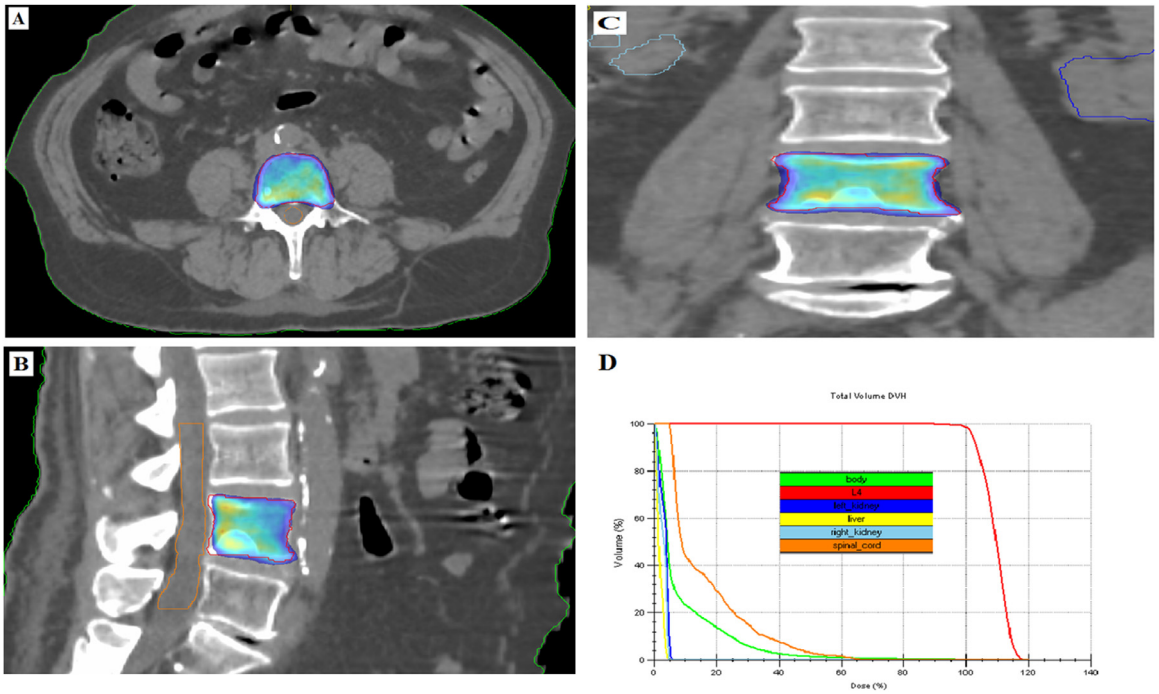

Fig. 3. A prostate cancer patient who was treated with a SBRT dose of 18 Gy with the optimized isodose line 80% and dose volume histogram.

Table 1
Patient demographics according to VCF status in 125 vertebral segments in 78 patients.

Variables	All patients (n = 78, VS = 125)	VCF (−) (n = 120 VS) (%)	VCF (+) (n = 5 VS) (%)	p-value
Age category (%)				0.58
Median (range)	51(28–79)			
≤55	42 (53.8)	36 (46.1)	3 (3.8)	
>55	36 (45.2)	37 (47.4)	2 (2.7)	
Gender (%)				0.25
Female	50 (64.1)	48 (61.5)	2 (2.7)	
Male	28 (35.9)	25 (32.0)	3 (3.8)	
Histology (%)				0.60
Breast	52 (66.6)	80 (64)	3 (2.4)	
Prostate	12 (15.4)	15 (12)	2 (1.6)	
NSCLC	12 (15.4)	21 (16.8)	0	
Others	2 (2.6)	4 (3.2)	0	
Bone lesion (%)				0.90
Lytic	83 (66.4)	80 (64)	3 (2.4)	
Blastic	40 (32.0)	38 (34.4)	2 (1.6)	
Mixed	2 (1.6)	2 (1.6)	0	
Local relapse (%)				0.399
Present	15 (4)	15 (16)	0	
Absent	120 (96)	105 (84)	5(4.0)	
First PET response (%)				0.42
CR	37 (29.6)	36 (28.8)	1 (0.8)	
PR	57 (45.6)	53 (42.4)	4 (3.2)	
SD	27 (21.6)	27 (21.6)	0	
PD	4 (3.2)	4 (3.2)	0	
Bisphosphonates use (%)				
Presence	100 (80)			<0.001
M	26 (20.8)	25 (20)	1 (0.8)	
F	74 (59.2)	73 (58.4)	1 (0.8)	
Absence	25 (20)			
M	19 (15.2)	17 (13.6)	2 (1.6)	
F	6 (4.8)	5 (4)	1(0.8)	
Duration of bisphosphonates (%)				0.29
≥6 months	77 (61.6)	75 (60)	2 (1.6)	
<6 months	48 (38.4)	45 (36)	3 (2.4)	
SBRT dose (%)				0.47
16 Gy	41 (32.8)	40 (32)	1 (0.8)	
18 Gy	84 (67.2)	80 (64)	4 (3.2)	
Assessment tool (%)				0.07
PET-CT	78 (62.4)	77 (61.6)	1 (0.8)	
MRI and PET-CT	47 (37.6)	43 (34.4)	4 (3.2)	

VCF = vertebral compression fracture; NSCLC = non-small cell lung carcinoma; CR = complete response; PR = partial response; SD = stabile disease; PD = progressive disease; SBRT = stereotactic body radiotherapy; Gy = gray; PET-CT = positron emission computerized tomography; MRI = magnetic resonance imaging.

The median follow-up time was 13 months. A median of 3 serial PET/CT scans (range: 1–5) per spinal metastatic lesion were performed, with 22.4% of spMets being assessed with only one PET/CT scan. No MRI was available for 54.4% of the patients in the cohort, while the median number of MRI scans available for the remaining 45.6% of patients was 1 (range: 1–3). PD was observed in 3.2% and 8.2% of the 125 spMets in the first and last PET/CT, respectively. Among the remaining spMets, the distribution of treatment responses was as follows: CR in 30.6%, PR in 47.1%, and stable disease in 22.3% in the first PET/CT; CR in 62.3%, PR in 16.7%, and stable disease in 21% in the last monitoring. The median period between the first and last PET/CT was 6 months (range: 0–49 months). All spMets with CR in the first PET/CT maintained their status at the final PET/CT as well. The presence of CR in the first PET/CT was negatively correlated with local failure rates in a significant manner (r = 0.48; p < 0.001). A total of 15 (12%) local failures were diagnosed during the follow-up period. Among the 15 patients with local failures, 11 (73.2%) had PD at the last monitoring, 2 (13.4%) showed a CR, 1 (6.7%) exhibited a PR, and 1 (6.7%) patient had stable disease (Fig. 2).

At baseline evaluation the median SINS score for the entire cohort was 5 (range: 1–13), and the majority (70.4%) of cases were categorized as stable according to SINS. No grade 1 or 2 VCF were reported. Out of the total of 125 spMets, 5 (4%) patients experienced grade 3 VCF at 2, 4, 16, 20 and 22 months post-SBRT (median: 16 months) (Fig. 4). Spearman's correlation analyses indicated that lack of bisphosphonate usage was the sole factor significantly correlated with post-SBRT grade 3 VCF incidence (r = −0.204; p = 0.022).

Median FFS was 21 months (range: 16.4 − 25.6 months), with FFS rates of 87.8, 67.2, 40.9, and 23.5% at 6, 12, 24, and 48 months, respectively. Univariate analyses indicated that female gender (p < 0.001), bisphosphonate use (p = 0.005), >6 months of bisphosphonate use (p = 0.002), and the lowest vertebral body collapse score (p = 0.023), which is a component of SINS, were associated with higher FFS rates. Multivariate analyses restricted to these variables identified female gender (p = 0.007), >6 months of bisphosphonates use (p = 0.018), and the lowest vertebral body collapse score (p = 0.044) as the factors that were independently and significantly associated with favorable FFS (Table 2 and Fig. 5).

4. Discussion

Our retrospective analyses of 78 patients with 125 spMets who had undergone SBRT revealed a local control rate of 88% and a VCF rate of 4%; these results are comparable to previous reports of outcomes and complications following SBRT. The present study also revealed that the female gender, >6 months of bisphosphonate use, and the lowest vertebral body collapse score were significantly associated with longer FFS (Table 3).

SBRT may stimulate different radiobiological pathways such as tumor antigen-specific immune responses, endothelial injuries distinct from apoptosis, and mitotic catastrophe, all of which are well-recognized mechanisms underlying conventional radiotherapy-induced cell death [20–22]. In the absence of a consensus regarding dose for a single-fraction spinal SBRT, dose schedules of 16 − 24 Gy are commonly used in radiotherapy protocols [23–28]. Gerszten et al. [29] reported a 21-month local control rate of 90% upon administration of 12–25 Gy (median: 20 Gy) in a patient cohort with different primary tumors. Yamada et al. [23] analyzed 93 patients treated with SBRT doses of 18 − 24 Gy and observed that doses >23 Gy were associated with improved local control rates. However, the reported superior outcomes with higher doses should be interpreted with caution because of the predominance of radioresistant histologies in these studies, namely sarcoma, melanoma, and renal cell carcinoma. Despite our relatively lower SBRT doses, an 88% local control rate is consistent with previous reports of >84% local radiographic control rates [27,29]. The SBRT schedules of 10–16 Gy/fraction are reported to be questionable for optimal disease control [30] and the 16–18 Gy/fraction utilized herein appear to be superiorly efficacious for local control of disease. Importantly, a satisfactory objective response rate of 88% and limited grade 3 VCF of 4% offer an acceptable therapeutic index. However, we cannot exclude the possibility that the additive effect of systemic therapies after SBRT, the absence of radioresistant histologies, and spMets with soft tissue extensions may have contributed to these results.

Commonly occurring as an acute or sub-acute event, VCF is a frequent complication of spinal SBRT that has been reported in 3–39% of patients [7–10,31–35]. Cunha et al. [9] analyzed 167 spMets in 90 patients who received single-fraction 20 − 24 Gy SBRT, or 18 − 35 Gy in 2 − 5 fractions of SBRT, and observed 12 (63%) and 7 (37%) cases of de novo and progressed VCF, respectively, with a median time to SBRT-induced VCF of 3.3 months. The present relatively lower 4% VCF rate at a median time to SBRT-induced VCF of 16 months (range: 2 − 22 months) concords well with the lower VCF range reported previously [32,36], which might be related to our relatively lower SBRT doses and strict exclusion of patients with pre-existing VCF [8,9]. Adding support

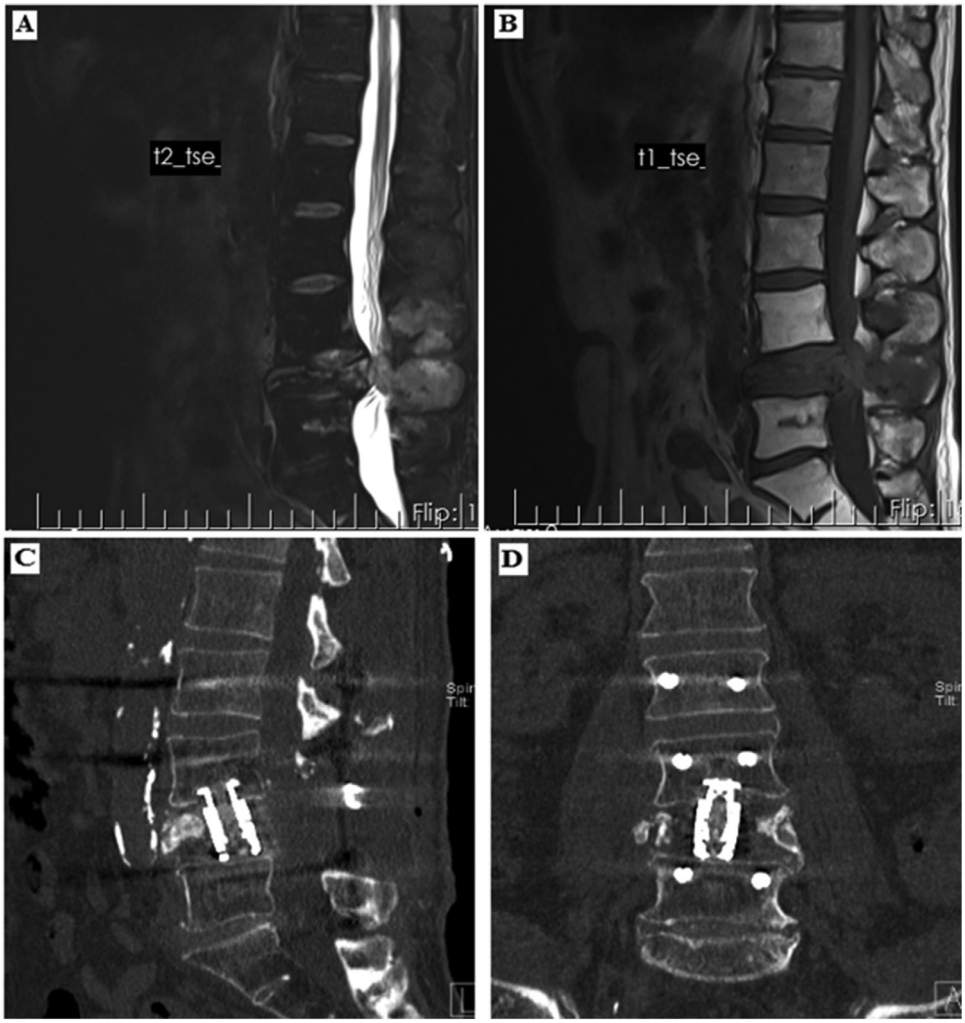

Fig. 4. Prostate cancer patient presenting with grade 3 L3 vertebral compression fracture 16 months after SBRT: (A) T2-weighted sagittal section, (B) T1-weighted sagittal section, (C) post-operative sagittal CT section following L3 decompression and instrumentation, (D) post-operative coronal CT section following L3 decompression and instrumentation.

to our observation of relatively low VCF rates with 16–18 Gy, a multi-institutional analysis of 410 spMets (including spMets with pre-existing VCF) found that dose schedules of $\geq$24 Gy and 20–23 Gy were associated with significantly higher VCF rates compared to the doses of $\leq$19 Gy, and the median time to VCF was 2.46 months [10]. We also excluded hematological malignancies like multiple myeloma, which have an intrinsically higher tendency to exhibit VCF (11–24%) after any radiotherapy protocol [37]. All these factors may have resulted in the lower VCF rates and the longer time to VCF occurrence observed in our study. The study of Rose et al. [31] reported a median time to SBRT-induced VCF of 25 months and a significantly prolonged time to SBRT-induced VCF for blastic and mixed spMets despite the higher VCF rate of 39% in their patients who received an SBRT dose of 16 − 24 Gy; these results appear to be comparable to the median time to VCF of 16 months observed in our present study.

Bisphosphonates function as protective agents against VCF and new bone metastases in patients with spMets [38]. To the best of our knowledge, only Pichon et al. [39] has previously reported reduced VCF rates in patients treated with fractionated SBRT and concomitant bisphosphonate previously. Here, we found that bisphosphonate use longer >6 months was associated with higher FFS ($p = 0.016$) in multivariate analyses, suggesting that longer duration of bisphosphonate use has a significant protective effect against VCF development. Our results are also consistent with studies demonstrating a reduction in VCF risk within 6 months of anti-resorptive therapies [40,41]. Our finding that female gender is associated with higher FFS may be counter-intuitive in light of the well-known effects of aging-related osteoporosis and estrogen deficiency, which may accelerate bone turnover and increase VCF risk [42]. However, bisphosphonate use has been reported to be associated with a 3 − 4% improvement in lumbar spine body mass density and reduced VCF risk [43,44]. Moreover, bisphosphonate use seems to reduce the inherent osteoporotic compression risk in females. Therefore, the fact that all females in our study were breast cancer patients with a 92.5% rate of bisphosphonate use may explain the association we observe between the female gender and prolonged FFS.

The relatively lower rate of VCF in our study should be considered in the context of the median SINS score of 5, which classifies patients as stable in terms of vertebral integrity. However, we found that only one out of the six SINS criteria, namely the vertebral body collapse score, was significantly associated with FFS. Since pre-existing VCF was an exclusion criterion in our study, all analyses were performed according to the following patient classifications: either the presence of >50% vertebral body involvement by disease without any VCF, or solitary disease with an initial SINS component that predicted poor FFS ($p = 0.044$). Due to the higher VCF risk of single-fraction SBRT, some modifications, such as SBRT with a fractionated schedule, may improve VCF rates in patients with higher tumor bulk without compromising

Table 2
Patient distribution according to SINS criterion.

Parameters	SINS (0–6)	SINS (7–12)	SINS (13–18)	*p*
Location				**>0.05**
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	35	15	1	
Mobile spine (C3–C6, L2–4)	17	12	0	
Semirigid (T3–T10)	36	9	0	
Rigid (S2–S5)	0	0	0	
Pain				**<0.001**
Mechanical	16	28	1	
Occasional and non-mechanical	26	5	0	
Pain-free	46	3	0	
Bone lesion				**<0.05**
Lytic	51	31	1	
Mixed	2	0	0	
Blastic	35	5	0	
Radiographic spinal alignment				**<0.001**
Subluxation or translation	0	1	0	
Kyphosis or scoliosis	0	5	1	
Normal	88	30	0	
Vertebral body collapse				**<0.001**
≥50%	0	0	0	
<50%	0	0	0	
No collapse but >50% body involvement by tumor	5	14	1	
None of the above	83	22	0	
Posterior element, facet involvement				**<0.001**
Bilateral	0	5	1	
Unilateral	11	7	0	
Not involved	77	24	0	

SINS= spinal instability neoplastic scoring system.

Table 3
Results of univariate and multivariate analyses in terms of VCF-FS.

Variable	VCF-FS, mo (95% CI)	Univariate *p*-value	Multivariate *p*-value
Age (years)			
≤55	21 (15–27)	0.67	–
>55	19 (10.7–27.3)		
Gender			
Male	14 (8.5–19.4)	<0.001	0.007
Female	28 (4.2–51.7)		
Bisphosphonates use			
Present	22 (16.8–22.1)	0.005	–
Absent	16 (8.6–23.3)		
Bisphosphonates Duration			
≥6 months	25 (18.8–31.1)	0.002	0.018
<6 months	14 (6.1–21.9)		
Vertebral tumor involvement			
≥50%	10 (3.9–16.1)	0.022	0.044
<50%	22 (18.8–25.2)		
Bone lesion type			
Lytic	Not reached	0.82	–
Mixed			
Blastic	Not reached		

VCF-FS= vertebral compression fracture free survival.

local control rates (in the patient subgroup with >50% vertebral body involvement by disease).

Due to the high-dose radiation delivered by SBRT, monitoring the response and possible complications of the treatment are also crucial issues, particularly in those patients for whom prolonged survival times are anticipated. Bone scintigraphy, MRI, and CT have been the most common assessment tools for tumor response, although there is currently no standardized recommendation. MRI and CT depend on morphological changes in the treated lesion, which may be practical for spMets with gross mass [45]. However, these methods may prove insufficient for spMets lacking soft tissue involvement. Furthermore, MRI and CT utilize the principle of change in tumor size for monitoring tumor shrinkage; thus, these methods may not be suitable for disease that cannot be easily measured with calipers or a ruler [46]. The inability of these modalities to distinguish whether the VCF was SBRT-induced, or induced by factors stemming from local relapse, is an additional limitation worthy of note [47,48]. Although bone scintigraphy is a sensitive modality for evaluation of osteoblastic spMets [49], the increased bone turnover in VCF may lead to high false positivity rates and decrease the reliability of this methodology. In this regard, PET [2] provides more reliable information on tumor metabolic changes and enables clinicians to better discriminate between the osteoblastic nature of spMets and the inherently enhanced bone turnover in VCF [49]. The sagittal CT sections of PET may provide a clinically facile tool to monitor changes in vertebral body heights after SBRT.

The choice of PET/CT for monitoring the SBRT response in the current study may be reasonable considering the superiority of PET/CT over conventional imaging modalities in detecting recurrences and metastasis; however, we acknowledge the caveat that PET/CT may be inadequate for osteoblastic spMets with lower affinity for FDG [50,51]. Additionally, assessment of metabolic responses on PET/CT rather than monitoring anatomic tumor shrinkage on conventional MRI and CT, which takes months after SBRT, may enable earlier commencement of salvage alternative therapies in patients with unsatisfactory objective responses [52]. However, the inability of PET/CT to accurately distinguish viable tumors from inflammatory processes is a major limitation of PET/CT particularly in the 6-month period right after SBRT [53]. Diffusion-weighted MRI is another functional imaging tool that has been reported to predict treatment responses in some cancers. The changes in signal intensity of T1-weighted non-contrast-enhanced MRI sequences may indicate progression or regression; however,

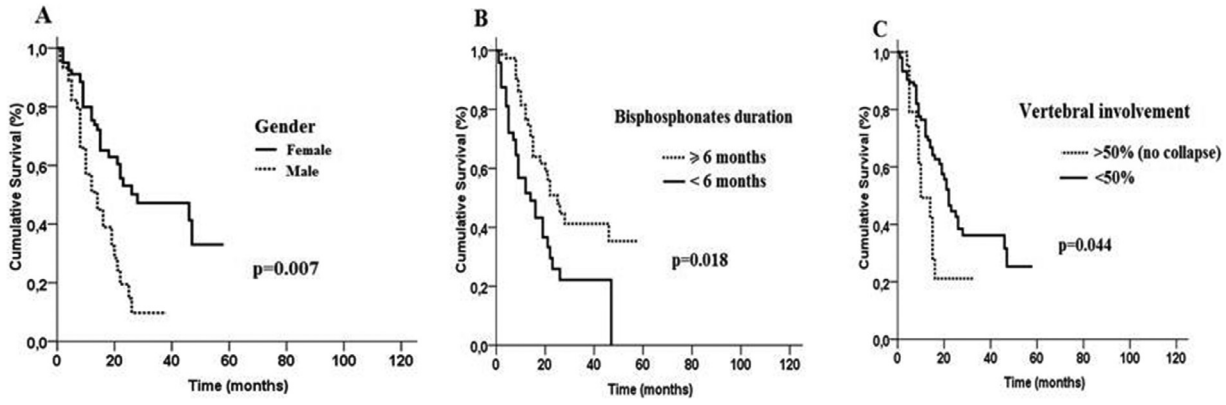

Fig. 5. Comparison of FFS rates according to (A) gender, (B) duration of bisphosphonates use, (C) vertebral tumor involvement.

uncertainties such as the type of signal changes indicating response or relapse, and emergent T1 and T2 signal changes in patients experiencing non-tumor-related VCF, remain problematic [33]. The long processing time and claustrophobia experienced by many patients may be other disadvantages of MRI. Future studies will demonstrate the most efficient imaging tool for response assessments after SBRT.

The current study has several strengths. First, exclusion of patients with pre-existing VCF may produce more reliable results in terms of evaluating the precise impact of SBRT on VCF development. Second, exclusion of patients who experienced both VCF and local disease progression might diminish confounding effects of disease progression on VCF. Third, the use of PET/CT for spine SBRT response evaluation along with the use of PERCIST response criteria ensures more robust and reliable response assessments.

This study has several limitations. First, it is a retrospective single-institutional study with limited cohort size, which may lead to inherent biases such as a lack of standardization of imaging modality and follow-up intervals for response and VCF assessments. Second, absence of objective pain assessment data limits our ability to assess patients' clinical response to spinal SBRT beyond that permitted by imaging tools. Third, the impact of chemotherapy, targeted therapies, and hormonal treatments on FFS and local control of disease was not analyzed, which might cause some confounding effects. Fourth, exclusion of the vertebral segments with pre-existing VCF from the analysis might have artificially improved our local control outcomes; however, we believe our approach allows thorough assessment of the true influence of SBRT on VCF development. Fifth, although the association between bisphosphonates use and favorable FFS may indicate the importance of bisphosphonates use for decreasing VCF, bisphosphonate use might be also a biasing factor.

5. Conclusions

This study demonstrated that a single 16–18 Gy dose of spine SBRT is associated with favorable local control rates and acceptable grade 3 VCF rates. PET/CT serves as a feasible imaging modality of choice for SBRT as it allows ready evaluation of both the response spectrum as well as the status of vertebral integrity. However, more studies are warranted to confirm these results in patient cohorts with more homogeneous characteristics related to tumor histology, systemic therapy and use of bisphosphonates.

Author contributions

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Declarations of interest

None.

Acknowledgments

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100218.

References

[1] L.M. Shah, K.L. Salzman, Imaging of spinal metastatic disease, Int. J. Surg. Oncol. 2011 (2011) 769753.

[2] W.F. Hartsell, C.B. Scott, D.W. Bruner, C.W. Scarantino, R.A. Ivker, M. Roach 3rd, J.H. Suh, W.F. Demas, B. Movsas, I.A. Petersen, et al., Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases, J. Natl. Cancer Inst. 97 (11) (2005) 798–804.

[3] E. Massicotte, M. Foote, R. Reddy, A. Sahgal, Minimal access spine surgery (MASS) for decompression and stabilization performed as an out-patient procedure for metastatic spinal tumours followed by spine stereotactic body radiotherapy (SBRT): first report of technique and preliminary outcomes, Technol. Cancer Res. Treat. 11 (1) (2012) 15–25.

[4] A.K. Anand, G. Venkadamanickam, A.U. Punnakal, B.S. Walia, A. Kumar, A.K. Bansal, H.M. Singh, Hypofractionated stereotactic body radiotherapy in spinal metastasis – with or without epidural extension, Clin. Oncol. (R. Coll. Radiol.) 27 (6) (2015) 345–352.

[5] I. Laufer, D.G. Rubin, E. Lis, B.W. Cox, M.D. Stubblefield, Y. Yamada, M.H. Bilsky, The NOMS framework: approach to the treatment of spinal metastatic tumors, Oncologist 18 (6) (2013) 744–751.

[6] M. Foote, D. Letourneau, D. Hyde, E. Massicotte, R. Rampersaud, M. Fehlings, C. Fisher, S. Lewis, N.L. Macchia, E. Yu, et al., Technique for stereotactic body radiotherapy for spinal metastases, J. Clin. Neurosci. 18 (2) (2011) 276–279.

[7] M. Sharma, E.E. Bennett, G. Rahmathulla, S.T. Chao, H.K. Koech, S.N. Gregory, T. Emch, A. Magnelli, A. Meola, J.H. Suh, et al., Impact of cervicothoracic region stereotactic spine radiosurgery on adjacent organs at risk, Neurosurg. Focus 42 (1) (2017) E14.

[8] N.S. Boehling, D.R. Grosshans, P.K. Allen, M.F. McAleer, A.W. Burton, S. Azeem, L.D. Rhines, E.L. Chang, Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases, J. Neurosurg. Spine 16 (4) (2012) 379–386.

[9] M.V. Cunha, A. Al-Omair, E.G. Atenafu, G.L. Masucci, D. Letourneau, R. Korol, E. Yu, P. Howard, F. Lochray, L.B. da Costa, et al., Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors, Int. J. Radiat. Oncol. Biol. Phys. 84 (3) (2012) e343–e349.

[10] A. Sahgal, E.G. Atenafu, S. Chao, A. Al-Omair, N. Boehling, E.H. Balagamwala, M. Cunha, I. Thibault, L. Angelov, P. Brown, 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. 31 (27) (2013) 3426–3431.

[11] A. Sahgal, L. Ma, J. Fowler, V. Weinberg, I. Gibbs, P.C. Gerszten, S. Ryu, S. Soltys, E. Chang, C.S. Wong, et al., Impact of dose hot spots on spinal cord tolerance following stereotactic body radiotherapy: a generalized biological effective dose analysis, Technol. Cancer Res. Treat. 11 (1) (2012) 35–40.

[12] J. Grimm, A. Sahgal, S.G. Soltys, G. Luxton, A. Patel, S. Herbert, J. Xue, L. Ma, E. Yorke, J.R. Adler, et al., Estimated risk level of unified stereotactic body radiation therapy dose tolerance limits for spinal cord, Semin. Radiat. Oncol. 26 (2) (2016) 165–171.

[13] B. Ettinger, D.M. Black, M.C. Nevitt, A.C. Rundle, J.A. Cauley, S.R. Cummings, H.K. Genant, Contribution of vertebral deformities to chronic back pain and disability. The study of osteoporotic fractures research group, J. Bone Miner. Res. 7 (4) (1992) 449–456.

[14] M.H. Bilsky, E. Lis, J. Raizer, H. Lee, P. Boland, The diagnosis and treatment of metastatic spinal tumor, Oncologist 4 (6) (1999) 459–469.

[15] A. Elson, J. Bovi, K. Kaur, D. Maas, G. Sinson, C. Schultz, Effect of treatment modality on the hypothalamic-pituitary function of patients treated with radiation therapy for pituitary adenomas: hypothalamic dose and endocrine outcomes, Front. Oncol. 4 (2014) 73.

[16] C.G. Fisher, C.P. DiPaola, T.C. Ryken, M.H. Bilsky, C.I. Shaffrey, S.H. Berven, J.S. Harrop, M.G. Fehlings, S. Boriani, D. Chou, 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) 35 (22) (2010) E1221–E1229.

[17] B.W. Cox, D.E. Spratt, M. Lovelock, M.H. Bilsky, E. Lis, S. Ryu, J. Sheehan, P.C. Gerszten, E. Chang, I. Gibbs, et al., International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery, Int. J. Radiat. Oncol. Biol. Phys. 83 (5) (2012) e597–e605.

[18] M. Grigoryan, A. Guermazi, F.W. Roemer, P.D. Delmas, H.K. Genant, Recognizing and reporting osteoporotic vertebral fractures, Eur. Spine J. 12 (Suppl 2) (2003) S104–S112.

[19] K.J. Redmond, R.K. Hales, H. Anderson-Keightly, X.C. Zhou, M. Kummerlowe, H.I. Sair, M. Duhon, L. Kleinberg, G.L. Rosner, T. Vannorsdall, Prospective study of hippocampal-sparing prophylactic cranial irradiation in limited-stage small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 98 (3) (2017) 603–611.

[20] J.M. Brown, D.J. Carlson, D.J. Brenner, The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int. J. Radiat. Oncol. Biol. Phys. 88 (2) (2014) 254–262.

[21] M.Z. Dewan, A.E. Galloway, N. Kawashima, J.K. Dewyngaert, J.S. Babb, S.C. Formenti, S. Demaria, Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody, Clin.

Cancer Res. 15 (17) (2009) 5379–5388.
[22] C.L. Tseng, W. Eppinga, R. Charest-Morin, H. Soliman, S. Myrehaug, P.J. Maralani, M. Campbell, Y.K. Lee, C. Fisher, M.G. Fehlings, et al., Spine stereotactic body radiotherapy: indications, outcomes, and points of caution, Global Spine J. 7 (2) (2017) 179–197.
[23] Y. Yamada, M.H. Bilsky, D.M. Lovelock, E.S. Venkatraman, S. Toner, J. Johnson, J. Zatcky, M.J. Zelefsky, Z. Fuks, High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions, Int. J. Radiat. Oncol. Biol. Phys. 71 (2) (2008) 484–490.
[24] A. Sahgal, C. Ames, D. Chou, L. Ma, K. Huang, W. Xu, C. Chin, V. Weinberg, C. Chuang, P. Weinstein, et al., Stereotactic body radiotherapy is effective salvage therapy for patients with prior radiation of spinal metastases, Int. J. Radiat. Oncol. Biol. Phys. 74 (3) (2009) 723–731.
[25] M. Guckenberger, F. Mantel, P.C. Gerszten, J.C. Flickinger, A. Sahgal, D. Letourneau, I.S. Grills, M. Jawad, D.K. Fahim, J.H. Shin, et al., Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis, Radiat. Oncol. 9 (2014) 226.
[26] I. Thibault, A. Al-Omair, G.L. Masucci, L. Masson-Cote, F. Lochray, R. Korol, L. Cheng, W. Xu, A. Yee, M.G. Fehlings, et al., Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: analysis of outcomes and risk of vertebral compression fracture, J. Neurosurg. Spine 21 (5) (2014) 711–718.
[27] E.L. Chang, A.S. Shiu, E. Mendel, L.A. Mathews, A. Mahajan, P.K. Allen, J.S. Weinberg, B.W. Brown, X.S. Wang, S.Y. Woo, et al., Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure, J. Neurosurg. Spine 7 (2) (2007) 151–160.
[28] A.K. Garg, A.S. Shiu, J. Yang, X.S. Wang, P. Allen, B.W. Brown, P. Grossman, E.K. Frija, M.F. McAleer, S. Azeem, et al., Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases, Cancer 118 (20) (2012) 5069–5077.
[29] P.C. Gerszten, S.A. Burton, C. Ozhasoglu, W.C. Welch, Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution, Spine (Phila Pa 1976) 32 (2) (2007) 193–199.
[30] M.M. Gestaut, N. Thawani, S. Kim, V.R. Gutti, S. Jhavar, N. Deb, A. Morrow, R.A. Ward, J.H. Huang, M. Patel, Single fraction spine stereotactic ablative body radiotherapy with volumetric modulated arc therapy, J. Neurooncol. 133 (1) (2017) 165–172.
[31] P.S. Rose, I. Laufer, P.J. Boland, A. Hanover, M.H. Bilsky, J. Yamada, E. Lis, Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases, J. Clin. Oncol. 27 (30) (2009) 5075–5079.
[32] D. Boyce-Fappiano, E. Elibe, L. Schultz, S. Ryu, M.S. Siddiqui, I. Chetty, I. Lee, J. Rock, B. Movsas, F. Siddiqui, Analysis of the factors contributing to vertebral compression fractures after spine stereotactic radiosurgery, Int. J. Radiat. Oncol. Biol. Phys. 97 (2) (2017) 236–245.
[33] A. Sahgal, V. Weinberg, L. Ma, E. Chang, S. Chao, A. Muacevic, A. Gorgulho, S. Soltys, P.C. Gerszten, S. Ryu, et al., Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice, Int. J. Radiat. Oncol. Biol. Phys. 85 (2) (2013) 341–347.
[34] J.H. Chang, J.H. Shin, Y.J. Yamada, A. Mesfin, M.G. Fehlings, L.D. Rhines, A. Sahgal, Stereotactic body radiotherapy for spinal metastases: what are the risks and how do we minimize them, Spine (Phila Pa 1976) 41 (Suppl 20) (2016) S238–S245.
[35] M.S. Virk, J.E. Han, A.S. Reiner, L.A. McLaughlin, D.M. Sciubba, E. Lis, Y. Yamada, M. Bilsky, I. Laufer, Frequency of symptomatic vertebral body compression fractures requiring intervention following single-fraction stereotactic radiosurgery for spinal metastases, Neurosurg. Focus 42 (1) (2017) E8.
[36] M.S. Jawad, D.K. Fahim, P.C. Gerszten, J.C. Flickinger, A. Sahgal, I.S. Grills, J. Sheehan, R. Kersh, J. Shin, K. Oh, et al., Vertebral compression fractures after stereotactic body radiation therapy: a large, multi-institutional, multinational evaluation, J. Neurosurg. Spine 24 (6) (2016) 928–936.
[37] M.H. Bilsky, S. Azeem, Multiple myeloma: primary bone tumor with systemic manifestations, Neurosurg. Clin. N. Am. 19 (1) (2008) 31–40.
[38] T. Yoneda, A. Sasaki, C. Dunstan, P.J. Williams, F. Bauss, Y.A. De Clerck, G.R. Mundy, Inhibition of osteolytic bone metastasis of breast cancer by combined treatment with the bisphosphonate ibandronate and tissue inhibitor of the matrix metalloproteinase-2, J. Clin. Invest 99 (10) (1997) 2509–2517.
[39] B. Pichon, L. Campion, G. Delpon, F. Thillays, C. Carrie, P. Cellier, P. Pommier, C. Laude, A. Mervoyer, H. Hamidou, et al., High-dose hypofractionated radiation therapy for noncompressive vertebral metastases in combination with zoledronate: a phase 1 study, Int. J. Radiat. Oncol. Biol. Phys. 96 (4) (2016) 840–847.
[40] R.G. Russell, M.J. Rogers, Bisphosphonates: from the laboratory to the clinic and back again, Bone 25 (1) (1999) 97–106.
[41] J.T. Harrington, L.G. Ste-Marie, M.L. Brandi, R. Civitelli, P. Fardellone, A. Grauer, I. Barton, S. Boonen, Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis, Calcif. Tissue Int. 74 (2) (2004) 129–135.
[42] Z. Cheng, W. Yao, E.A. Zimmermann, C. Busse, R.O. Ritchie, N.E. Lane, Prolonged treatments with antiresorptive agents and PTH have different effects on bone strength and the degree of mineralization in old estrogen-deficient osteoporotic rats, J. Bone Miner. Res. 24 (2) (2009) 209–220.
[43] U.A. Liberman, S.R. Weiss, J. Broll, H.W. Minne, H. Quan, N.H. Bell, J. Rodriguez-Portales, R.W. Downs Jr., J. Dequeker, M. Favus, Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The alendronate phase III osteoporosis treatment study group, N. Engl. J. Med. 333 (22) (1995) 1437–1443.
[44] S.T. Harris, N.B. Watts, H.K. Genant, C.D. McKeever, T. Hangartner, M. Keller, C.H. Chesnut 3rd, J. Brown, E.F. Eriksen, M.S. Hoseyni, et al., Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral efficacy with risedronate therapy (VERT) study group, JAMA 282 (14) (1999) 1344–1352.
[45] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2) (2009) 228–247.
[46] C.M. Costelloe, H.H. Chuang, J.E. Madewell, N.T. Ueno, Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST, J. Cancer 1 (2010) 80–92.
[47] R.L. Wahl, H. Jacene, Y. Kasamon, M.A. Lodge, From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors, J. Nucl. Med. 50 (Suppl 1) (2009) 122S–150S.
[48] A.J. de Langen, V. van den Boogaart, M. Lubberink, W.H. Backes, J.T. Marcus, H. van Tinteren, J. Pruim, B. Brans, P. Leffers, A.M. Dingemans, et al., Monitoring response to antiangiogenic therapy in non-small cell lung cancer using imaging markers derived from PET and dynamic contrast-enhanced MRI, J. Nucl. Med. 52 (1) (2011) 48–55.
[49] T. Liu, S. Wang, H. Liu, B. Meng, F. Zhou, F. He, X. Shi, H. Yang, Detection of vertebral metastases: a meta-analysis comparing MRI, CT, PET, BS and BS with SPECT, J. Cancer Res. Clin. Oncol. 143 (3) (2017) 457–465.
[50] I. Thibault, E.L. Chang, J. Sheehan, M.S. Ahluwalia, M. Guckenberger, M.J. Sohn, S. Ryu, M. Foote, S.S. Lo, A. Muacevic, et al., Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group, Lancet Oncol. 16 (16) (2015) e595–e603.
[51] S. Sheikhbahaei, E. Mena, C. Marcus, R. Wray, M. Taghipour, R.M. Subramaniam, 18F-FDG PET/CT: therapy response assessment interpretation (Hopkins criteria) and survival outcomes in lung cancer patients, J. Nucl. Med. 57 (6) (2016) 855–860.
[52] T. Okuma, T. Matsuoka, A. Yamamoto, S. Hamamoto, K. Nakamura, Y. Inoue, Assessment of early treatment response after CT-guided radiofrequency ablation of unresectable lung tumours by diffusion-weighted MRI: a pilot study, Br. J. Radiol. 82 (984) (2009) 989–994.
[53] Y. Matsuo, Y. Nakamoto, Y. Nagata, K. Shibuya, K. Takayama, Y. Norihisa, M. Narabayashi, T. Mizowaki, T. Saga, T. Higashi, et al., Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer, Radiother. Oncol. 97 (2) (2010) 200–204.