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Clinical Study

Remineralization of lytic spinal metastases after radiotherapy

Bart J. Pielkenrood, MD PhD[a,*], Thomas F. Visser, MD[a], Floris R. van Tol, MD[b], Wouter Foppen, MD, PhD[c], Wietse S.C. Eppinga, MD[a], Joost J.C. Verhoeff, MD, PhD[a], Gijs H. Bol, PhD[a], Joanne M. Van der Velden, MD, PhD[a], Jorrit-Jan Verlaan, Md, PhD[b]

[a] *Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*

[b] *Department of Orthopedic Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*

[c] *Department of Radiology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*

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Abstract

BACKGROUND CONTEXT: Palliative radiotherapy (RT) can lead to remineralization of osteolytic lesions thereby potentially restoring some of the weight-bearing capacity and preventing vertebral collapse. It is not clear, however, under which circumstances remineralization of osteolytic lesions occurs.

PURPOSE: The aim of this study was to investigate the change in bone mineral density in spinal metastases after RT compared to a reference region, and find associated factors.

STUDY DESIGN: Retrospective analysis within prospective observational cohort

OUTCOME MEASURES: change in bone mineral density measured in Hounsfield Units (HU).

PATIENT SAMPLE: patients treated with RT for (painful) bone metastases.

METHODS: Patients with spinal metastases were included if computed tomography scans both pre- and post-RT were available. Bone density was measured in HU. A region of interest (ROI) was drawn manually in the metastatic lesion. As a reference, a measurement of bone density in adjacent, unaffected, and non-irradiated vertebrae was used. Factors tested for association were origin of the primary tumor, RT dose and fractionation scheme, and concomitant use of bisphosphonates.

RESULTS: A total of 31 patients with 49 spinal metastases, originating from various primary tumors, were included. The median age on baseline was 58 years (IQR: 53−63) and median time between baseline and follow-up scan was 8.2 months (IQR: 3.0−18.4). Difference in HU in the lesion before and after treatment was 146.9 HU (95% CI 68.4−225.4; p<.01). Difference in HU in the reference vertebra between baseline and first follow-up was 19.1 HU (95% CI -47.9 to 86.0; p=.58). Difference between reference vertebrae and metastatic lesions on baseline was -194.1 HU (95% CI -276.2 to -112.0; p<.01). After RT, this difference was reduced to -50.3 HU (95% CI -199.6 to 99.0; p=.52). Patients using bisphosphonates showed a greater increase in HU, 194.1 HU versus 60.6 HU, p=.01.

CONCLUSIONS: Palliative radiation of osteolytic lytic spinal metastases is positively associated with an increased bone mineral density at follow-up. The use of bisphosphonates was linked to an increased bone mineral density when used during or after RT.

Keywords: Bone metastases; Orthopedic surgery; Radiotherapy; Spinal metastases; Remineralization; Vertebral Fractures; Hounsfield Units; Bone Density

FDA device/drug status: Not applicable.

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*Corresponding author. Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.

E-mail address: b.j.pielkenrood@umcutrecht.nl (B.J. Pielkenrood).

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Introduction

The spine is the most commonly affected site in patients with metastatic bone disease [1]. Locally secreted tumor cell factors increase osteoclast activity, thereby adversely affecting the bony architecture of the vertebrae, which leads to a decrease in bone mineral density (BMD). Continued weakening of the osseous structures can lead to instability due to increased stress and subsequent failure of the vertebra [2,3]. Pathologic fractures often cause severe pain and may lead to neurological impairment.

Treatment of (spinal) bone metastases aims at improving the patient's quality of life by reducing pain and preserving or improving the patient's neurological function [4,5]. Unstable spinal metastases often need surgical stabilization [6–8]. Although effective spinal surgery is subject to risks of serious complications and adverse events [6,9]. Nevertheless, surgery usually resolves spinal instability. If there is no gross mechanical instability and/or neurological impairment, surgical stabilization is not essential and treatment of symptomatic spinal metastases can be performed using radiotherapy (RT) to achieve local tumor control and reduce pain [6,8,10,11].

When local tumor control is achieved after RT, the balance between osteoblast and osteoclast activity may be restored since these cells, responsible for bone turnover, no longer respond to the negative influences of tumor cytokines [12]. Osteoclast activity is triggered after RT and therefore the osteoclast inhibiting property of bisphosphonates (if administered) is considered to attribute to an additional remineralization effect following RT [13,14]. The restored balance between osteoblast and osteoclast activity, together with improved patient mobility and subsequent increase in axial loading, may promote bone growth and partially restore bone architecture [3,15]. The improved bone architecture and new bone depositions are associated with elevated BMD, measurable on imaging. The improved bone architecture and higher BMD are also associated with an increased weight-bearing capacity of vertebrae [12,16–18]. However, little is known about how treatment and disease-related factors influence the extent of restoration of bone strength that may be achieved with RT. Understanding and quantifying the remineralization process after RT can help to tailor the radio therapeutic dose and scheme. It can further help to retain ideal patient circumstances for remineralization and improving mechanical stability. This could potentially reduce the need for surgical stabilization [2,18]. BMD could be measured using Hounsfield Units (HU), a standardized linear coefficient representing the X-ray attenuation. HU values for bone range from -300 to 2000 and air has an HU of -1,000. Higher HU reflect an increased BMD [19]. The study by Patel et al. showed mean HU for vertebrae of 195.7 (95% CI 171.4–220.0) in non-osteoporotic bone [20].

The primary aim of this retrospective analysis was to quantitatively evaluate the phenomenon of remineralization of osteolytic spinal metastases following RT, and compare the change in BMD in the lytic lesion to a reference vertebra outside of the irradiation field. The secondary aim was to determine a possible association between disease and treatment-related factors and the remineralization effect.

Methods

Patient selection and data collection

For this retrospective study, patients were collected from the observational PRospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort [21]. All patients treated with radiotherapy for bone metastases were systematically invited to participate in the PRESENT cohort. Patients were asked for informed consent to prospectively collect baseline demographics, treatment characteristics, and clinical follow-up data. For the current analysis, data of patients included in the period of June 2013 until January 2018 were used.

Inclusion criteria were palliative RT for at least one osteolytic spinal lesion. The classification of a lesion being osteolytic was based on the description of the lesion in the patient records and was re-assessed on CT data before inclusion. Metastases were considered osteolytic when an evident region of bony destruction/disappearance, and therefore a visible decrease in HU, was observed within a vertebra on CT imaging. For a reliable measurement, the lesion had to be larger than the predefined region of interest (ROI [5mm]). Furthermore, patients could only be included if they had at least one follow-up CT scan available between treatment and the end-of-study period. Patients were excluded when they had surgical implants or collapsed vertebrae at the level of the ROI, as these could influence the measurement. In a collapsed vertebra, the density might be increased due to the collapse, and not necessarily due to the RT, so the measurement of BMD could be influenced false-positively. Patients' medical records were used to collect patient baseline and treatment characteristics. These data included primary tumor, location of metastases, radiotherapy fractionation scheme, and the use of bisphosphonates.

Measurements

BMD was measured using a circular ROI in the axial plane of the CT images with an approximate diameter of 5 mm, dependent on CT voxel size. The center point of the ROI was set manually on the estimated 3D-centroid of the osteolytic lesion (Fig. 1). The ROI, as established in the first examination, was also used for the follow-up examination. Thus, the placement of the ROI on follow-up was identical

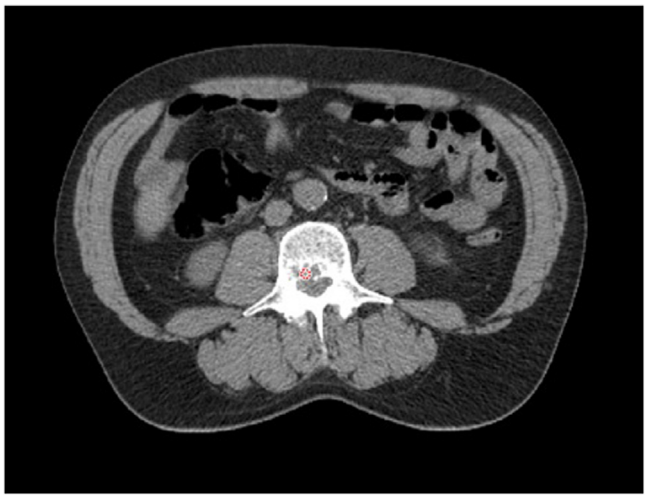

Fig. 1. Example of placement of the region of interest (ROI) to measure bone mineral density

to the location of the ROI on baseline. Due to the expected change in size and border of the metastasis, a single ROI was considered more reliable than the delineation of the whole metastasis. Independent of tumor size and vertebral characteristics, one ROI was set per vertebra. If a patient had multiple affected vertebra treated with RT, a ROI was set for each vertebra. These measurements were executed the same way for all patients, assuring paired measurements of the metastatic lesions.

A reference measurement was performed in each patient if present on the CT images. For this measurement, a vertebra without any metastases two levels cranial to the lesion, and outside the irradiated area, was chosen. The placement of the ROI for the reference measurement was placed on an anatomically similar location in the vertebra as the ROI in the metastasis. In the case of a fracture, the presence of osteosynthesis material, or other anomalies, the adjacent cranial vertebra was selected. The reference measurement was used to estimate the effect of for example, (disuse) osteoporosis, use of bisphosphonates, or effects of any systemic therapy on BMD.

All measurements were performed by the same observer (TV) who was not blinded for patient characteristics and outcome during assessment of scans. A random sample of ROI placement in 15 patients was assessed again by four observers to check for accuracy of the observer's measurements: an orthopedic surgeon (JJV), a radiation oncologist (WSCE), a PhD-candidate of the department of radiation oncology (BJP) and a radiologist in training (WF).

Outcome

The primary outcome of this study was the change in mean HU in the ROI, compared between baseline scan before RT and the follow-up scan(s) in the 3 months following radiotherapy, and compared with the reference ROI. Secondary outcome was the change in HU in the ROI at any point in time during follow-up. In addition, clinical factors such as primary tumor and the use of bisphosphonates associated with change in HU, were evaluated.

Statistical analysis

The difference in mean HU between two separate points in time was analyzed with a paired T-test. The difference in mean HU between metastatic lesions and reference vertebrae was analyzed with a Welch T-test. A *t* test was performed to analyze the association between the use of bisphosphonates and receiving five fractions and less, or more than five fractions. In addition, a Kruskall-Wallis test was performed to analyze the change in BMD and the differences between primary tumor histology. Data were analyzed using SPSS, IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp [22].

Results

Demographic data

Out of the 1,025 patients available in the PRESENT database, 215 patients (21%) had spinal metastases and the baseline and follow-up CT scans available within our institution. Of these patients, 195 (91%) received RT, and 119 (55%) had at least one osteolytic spinal lesion. Of these 119 patients, 70 patients were excluded because of unsuitable baseline or follow-up scans in which the ROI was not completely visible, 12 because of osteosynthesis material at the ROI, and 4 because of a pathological fracture at the ROI. Two patients with multiple myeloma were excluded due to the date of first follow-up being more than 36 months after RT. There were no patients who had undergone reirradiation. This resulted in a study group of 31 patients, with 49 osteolytic metastases eligible for analysis (Table 1).

Remineralization

Mean density of all osteolytic lesions at baseline was 71.4 HU (95% CI 61.1–81.7). A total of 13 patients (42%) had a follow-up CT scan within 3 months after RT, in 8 patients a reference vertebra was available for measurements. The median interval between pre-RT and follow-up CT scans within this group was 1.9 months (interquartile range (IQR) = 1.5–2.7) In affected vertebrae, the bone density increased with 64.2 HU (95% CI 9.3–73.6; p=.04; Table 2) compared with a non-significant decrease in the reference vertebrae of -3.2 HU (95% CI -33.9 to 27.4; p=.84; Table 2). The difference at baseline between metastatic lesions and reference vertebrae was -165.8 HU (95% CI -348 to 16.5; p=.07; Table 2), and -92 HU after RT (95% CI -192.7–8.5; p=.07; Table 2) Figure 2.

Of all available scans and patients up to 2 years after radiotherapy, the median time between RT and follow-up

Table 1
Baseline characteristics

Age at baseline, median (IQR*)	58 (53–63)
Sex, n (%)	
Male	17 (55)
Number of bone metastases, n (%)	
1	12 (39)
2	13 (42)
3	4 (13)
4	1 (3)
5	1 (3)
Primary tumor, n (%)	
Breast	8 (26)
Kidney	5 (16)
Lung	4 (13)
Prostate	4 (13)
Esophagus	3 (10)
Other	7 (23)
Location of metastases in the spine†	
Cervical	3 (16)
Thoracic	26 (53)
Lumbar	16 (33)
Sacrum	4 (8)
Radiotherapy scheme‡, n (%)	
1×8Gy	24 (47)
10×3Gy	13 (27)
1×18Gy	3 (6)
5×4Gy	6 (12)
Other	3 (6)
Bisphosphonates during RT*, n (%)	13 (42)
Chemotherapy during RT*, n (%)	13 (42)
Corticosteroids during RT*, n (%)	24 (77)

percentages may not add up to 100% due to rounding
* IQR, Inter quartile Range, RT, radiotherapy
† Some patients had metastases on multiple sites
† Some patients received multiple RT schemes

imaging was 7 months (IQR 3–17) for metastatic lesions and 7 months (IQR = 3–18) for reference vertebrae as the reference vertebra was not available for ROI placement on all follow-up scans. The difference between baseline and follow-up BMD for metastatic lesions was 146.9 HU (95% CI 68.4–225.4; p<.01; Table 3) and 19.1 HU for the reference vertebrae (95% CI -47.9 to 86.0; p=.58; Table 3). At baseline, the difference between reference vertebrae and metastatic lesions was -194.1 HU (95% CI -276.2 to -112.0; p<.01; Table 3) and after RT the difference was -50.3 HU (95% CI -119.6 to 990; p=.52; Table 3). During the quality check by four raters of the random sample of measurements in 15 patients, there was complete agreement on the placement of the ROIs.

Factors associated with remineralization

In the T-test analysis, lesions in patients using bisphosphonates showed a mean 133.5 HU larger increase in bone density compared with lesions in patients who did not (194.1 HU vs 60.6 HU; p< .01; Table 4). The proportion of patients using bisphosphonates did not differ between primary tumor types (Supplementary Table 1). Lesions in patients treated with more than five fractions showed a greater, but non-significant, change in HU compared to lesions treated with less than five fractions (145.8 vs 100.5; p=.12; Table 4). Metastases from primary tumors located in the breast, lung and kidney showed the largest increase of BMD (p=.05).

Discussion

In the present study, we found that bone mineral density (BMD) increased significantly in osteolytic lesions after radiotherapy, while this did not occur in the unaffected, non-irradiated adjacent reference sites. The use of bisphosphonates was associated with a further increase in remineralization. In addition, the primary tumor was of influence on the degree of remineralization. Remineralization did not differ among patients receiving five or more fractions compared with treatment with less than five fractions.

This is one of the first studies comparing changes in BMD between irradiated vertebrae and reference vertebrae outside the radiation field.

Our finding of the positive effect of RT on BMD is in line with previous studies. In a recent study, Jensen *et al.* analyzed the change of BMD, based on a change in HU, in patients with spinal metastases. In their study, 117 vertebrae were analyzed, including a control vertebra that was outside the 50% isodose, to adjust the BMD measurement of the lesion [23]. In the study by Jensen *et al.* the (lack of) change in BMD in the reference vertebra was used for the adjusted density change, but was not reported separately. Metastases

Table 2
Change in BMD 3 months after radiotherapy. p-value is based on a Welch *t* test

	N	Mean difference in HU (95% CI)	Change (in %)	p-value
Change in BMD* after RT* in:				
Metastatic lesions	13	64.2 (9.3–73.6)	203	.04
Reference vertebrae	8	-3.2 (-33.9 to 27.4)	99	.84
Difference between reference vertebrae and metastatic lesions:				
Before RT*		-165.8 (-348.0 to 16.5)		.07
After RT*		-92.0 (-192.7 to 8.5)		.07

A p-value <.05 was considered statistically significant.
* BMD: Bone Mineral Density, RT: Radiotherapy, HU: Hounsfield Units.

Table 3
Change in mean BMD in all available follow-up scans. p-value is based on a Welch t-test. A p-value <0.05 was considered statistically significant

	N	Mean difference in HU (95% CI)	Change (in %)	p-value
Change in BMD* after RT* in:				
Metastatic lesions	49	146.9 (68.4–225.4)	306	<.01
Reference vertebrae	31	19.1 (-47.9–86.0)	107	.58
Difference between reference vertebrae and metastatic lesions:				
Before RT*		-194.1 (-276.2– -112.0)		<.01
After RT*		-50.3 (-199.6–99.0)		.52

* BMD, Bone Mineral Density; RT, Radiotherapy; HU, Hounsfield Units.

came from various primary tumors, and received various dose and fractionation schedules. Jensen and coauthors found a density change of 104% (p<.0001) in the unadjusted and 102% in the measurement adjusted for the control measurement within a median follow-up of 14 months. In contrast to our study, Jensen et al. only included patients with a follow-up of >9 months. In addition, our study also shows an early effect on BMD as we saw remineralization within 3 months. Foerster et al. assessed the change in BMD after RT in 135 spinal metastases in 115 patients with breast cancer. Patients received 30 Gy in 10 fractions, 35 Gy in 14 fractions or 20 Gy in 2 fractions. Mean BMD was 194.8 HU (SD 123.0) at baseline. Mean BMD increased by 146 HU after 3 months (p.0001) and 250 HU after 6 months (p<.0001). They also confirmed that BMD did not change significantly in a neighboring unaffected vertebra receiving radiotherapy [24]. Wachenfeld et al. examined remineralization on CT in 14 patients with vertebral metastases from breast cancer, treated with a total dose of 30 Gy to 36 Gy in 2 fractions. In the published abstract, Wachenfeld and coauthors found a significant increase in BMD in lytic lesions 6 weeks after RT, increasing further to 150% at 3 months [25]. McDonald et al. analyzed the effect of stereotactic body radiation therapy (SBRT) on lytic non-spine bone metastases [12]. The BMD was assessed in 22 cases, with a median follow-up of 7 months after RT. The change relative to baseline in median BMD for all lytic lesions was 104%, 139%, 188% and 186% after respectively 3, 6 and 9 and 12 months. At 1 year after RT, there was a decrease in BMD in only 3 of 22 lesions. Sprave et al. performed a secondary analysis on the data from their trial, comparing pain response after conventional RT vs SBRT for painful bone metastases. In this secondary analysis, 46 patients were available for evaluation at 3 months, and 39 at 6 months [26]. They found a significant increase after 3 and 6 months, an increase of 33.8 HU and 72.1 HU respectively in the conventional RT arm and an increase of 64.0 HU and 97.5 HU respectively in the SBRT arm (p=.01 for all within group changes). Moreover, no between-group difference was observed at 3 or 6 months, p=.63 and p=.33 respectively). Furthermore, they found a higher number of vertebral fractures 6 months after SBRT compared to conventional RT, 28%(n=5) versus 5% (n=1) respectively, p=.054 [27]. While the between group differences in remineralization and vertebral fractures between cRT and SBRT are non-significant, the results are still remarkable. In prior studies on SBRT, vertebral fractures were seen more often after SBRT, possible due to SBRT-induced necrosis [28].

Table 4
Factors associated with change in BMD after radiotherapy. p-value based on a univariable t-test for the change of BMD after use of the bisphosphonate during RT or in the reference group,

			Change in mean BMD*	
		N		p-value
	Bisphosphonates use			
Metastatic lesion	Yes	26	194.1	
	No	23	60.6	.01*
Reference vertebra	Yes	23	34.7	
	No	12	7.2	.15
			lesion	
Number of fractions	1–5	35	100.5	
	More than 5	14	145.8	.12
Primary tumor	Breast	13	181.4	.05*
	Kidney	9	132.2	
	Prostate	6	26.9	
	Lung	4	148.1	
	Other	17	23.5	

number of fractions, and on a Kruskal-Walis test for the primary tumor comparison
* A p-value <.05 was considered statistically significant.

However, due to the limited number of patients with a fracture, no definitive conclusions can be drawn from this data. Our study confirmed the occurrence of remineralization after RT, relative to a non-irradiated reference. The latter is important to correct for the major effect that systemic therapies and/or increased physical activity following effective palliation can have on the BMD of (non-)irradiated vertebrae during follow-up. As the BMD in unaffected, non-irradiated adjacent reference sites did not significantly increase while the BMD did increase in irradiated affected lesions, this effect is suggested to be attributable to radiotherapy.

Remarkably, despite previous studies finding an increase in BMD after radiotherapy for lytic spinal metastases, the baseline mean HU for the lesion was different in all these studies. In this study, we found a mean BMD of 71.4 HU (95% CI 61.1−81.7). In the study by Sprave et al. this was 178.5 (SD 74.4) and in the study by Mcdonald *et al.* the baseline mean HU was 92.5 (95% CI: 54.7−130). While data are limited, it may be concluded that remineralization occurs even with higher baseline BMDs [12,26]. The difference in baseline mean HU could be due to the difference of ROI placement. In the study by Sprave et al. a ROI was placed in the tumor while in the study by Mcdonald et al. the whole lesion was contoured.

Results of studies on the effects of RT on bone formation by osteoblasts and bone resorption by osteoclasts are conflicting, and the cellular mechanism of remineralization is not well known [15]. Studies found the osteoblast activity to deteriorate after RT, while others found osteoblasts to be resistant to RT, with low dose RT even promoting proliferation of osteoblasts. In addition, the effects of RT on osteoclasts are ambiguous too. While RT could decrease osteoclasts activity, and therefore decrease bone resorption, RT could also increase osteoclast activity [15]. In the healthy physiological state, the interaction between osteoblasts and osteoclasts is finely balanced and increased osteoclast activity induces increased osteoblast activity [29]. It could therefore be hypothesized that after RT-induced destruction of tumor cells, the disturbed bone turnover − under the influence of tumor secreted cytokines in the micro-environment − may return to normal, with osteoclasts actively resorbing damaged bone and osteoblasts responding accordingly with increased activity to form bone locally [30]. In the systematic review by Groenen et al. it was shown that there was an increase in BMD and trabecular bone in animal studies [31].

In agreement with the current study, Foerster et al. reported an increased remineralization after RT in patients using bisphosphonates [24]. At 3 months after RT an improvement of 157.5 HU was observed in the bisphosphonate group, versus an increase of 52.2 HU in the non-bisphosphonate group (p=.01). In an animal model with osteolytic metastases, Krempien et al. observed an increase in BMD at 42 days after RT (p=.001), but only in the animals receiving bisphosphonates [3]. Krempien et al. showed a significantly better-preserved bone microstructure in the pre-RT bisphosphonate group compared with the other two groups (p<.001). They hypothesized that an increased or preserved bone microstructure leads to an increased weight bearing capacity. A loss of the microstructure leads to increased formation of fibrous scar tissue [3]. The use of bisphosphonates can preserve the structural integrity by the inhibition of bone resorption, and accordingly improve the ability of osteolytic lesions to remineralize after RT. Our study found a strong positive association between the use of bisphosphonates and remineralization. After RT, the lesions in patients receiving bisphosphonates showed a greater increase in BMD compared with the patients not receiving bisphosphonates. For the reference vertebrae, this effect of bisphosphonates was not observed. This supports the hypothesis that bisphosphonates contribute to remineralization of lytic bone metastases especially when combined with RT [3]. Due to the limited number of patients included in this study, the independent effect of RT and use of bisphosphonates could not be assessed in multivariate analysis, and remains to be evaluated in future research.

We found a non-significant higher degree of remineralization in patients who underwent a radiation schedule with more than five fractions. The total RT dose in RT schedules below five fractions was under 20 Gy, compared with over 20 Gy in RT schedules with five fractions or more. Generally, patients with a higher life expectancy receive an hyperfractionated dose. It is hypothesized that by delivering a hyperfractionated dose, tumor cells are being killed while osteoclasts and osteoblast survive. All while the palliative effect is comparable. A prospective study by Koswig et al. compared patients with fractionated (10×3Gy) and single dose (1×8Gy) [32]. After 6 months, a significant difference in BMD was observed between patients in the fractionated group of 173% compared with a BMD increase of 120% in the single dose group. Nonetheless, this increase was only observed in patients with breast cancer [19,32]. In a multivariable analysis, Stölting et al. found a trend towards increased remineralization for RT administered five times a week compared with one to four times a week (OR 8.4; p=.054), a total RT dose was not specified in this analysis [16]. In addition, in the same analysis they found a total dose of 50 Gy or more, compared with 30 Gy or less, to be associated with increased remineralization [17[. In the same way, Sprave et al. found a significant difference between short course (≤10 fractions) and long course (>10 fractions) in the proportion of patients who went from an unstable vertebra at baseline to a stable vertebra 3 months after RT. Six months after RT, however, this difference was not found [33].

Due to these diverse findings, it is therefore not clear whether the increased remineralization can be contributed to a more fractionated scheme or a higher total dose.

The primary tumor origins may have substantial influence on the potential for remineralization after RT. Koswig et al. assessed the association between primary tumor and the magnitude of remineralization. In a patient group receiving a fractionated scheme of 10×3Gy for (spinal)

bone metastases originating from various primary tumors, lesions showed increases in BMD of 184% for breast cancer, 174% for prostate cancer, 147% for kidney cancer and 138% for lung cancer respectively, although these differences were not statistically significant. Only when multiple primary tumors were put together, a significant difference was found for the combined groups breast/prostate, and lung/kidney (p=.02). This could be due to a lack of power with their number of patients [21]. Another study by Macdonald et al. distinguished between renal cell carcinoma (RCC) and 'other' primary tumors. Lesions from RCC showed an ongoing decrease in BMD during initial follow-up and this decrease stopped at approximately 12 months after RT [18]. In contrast to the study by Macdonald et al. in the present study metastases originating from the kidney also showed remineralization after RT.

The main limitation of this study is the limited sample size, with 31 patients with 49 lytic spinal metastases and follow-up scans available. By measuring the remineralization of multiple lesions within the same patient, the impact of the treatment, such as the radiotherapy scheme, could be overestimated. Furthermore, the retrospective design of this study hindered follow-up as we were dependent on follow-up scans obtained during daily clinical practice. To obtain more robust data, follow-up CT scans at predetermined time intervals would be highly useful. Furthermore, it is still unknown whether remineralization of bone actually improves bone strength and, ultimately, spinal stability, and could become a viable alternative to surgery in a selected group of patients with potential instability (SINS score 7–12) [10]. Subsequently, excluding patients with a vertebral fracture limits the generalizability of this study to patients with a potential unstable vertebra. Furthermore, while radiotherapy might induce remineralization, there is no evidence yet it stabilizes fractured vertebra. Therefore, surgery remains necessary in fractured vertebrae or evidently unstable lesions.

In this study, the use of clinical factors is limited to the primary tumor, number of fractions and the use of bisphosphonates. Due to the limited number of patients included in the study, adding additional factors in the analysis could result in false positives as a consequence of multiple comparison. For example, the rate of remineralization could be influenced by the radiotherapy scheme and primary tumor. In addition, the location of the metastases could influence the rate of remineralization as a higher rate could be expected in more load-bearing vertebra, for example the lumbar and sacral spine, compared to the cervical or thoracic spine. However, as the lumbar vertebrae have a larger load-bearing surface, the load per squared cm could be comparable. This is outside of the scope of current study however.

Future research should be focused on the restoration of mechanical integrity after radiotherapy and should include a larger number of patients to analyze predictive or contributing factors for remineralization.

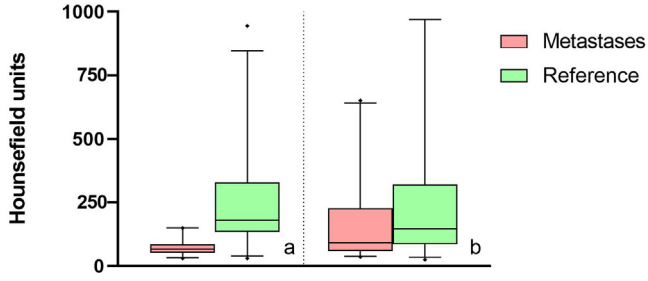

Fig. 2. Comparison of mean HU between the metastases and reference vertebra before RT (Left) and after RT (Right).

Conclusion

Radiotherapy of lytic spinal metastases is positively associated with increased bone mineral density at a median follow-up of 7 months. Bisphosphonates and a fractionated radiotherapeutic schedule are associated with increased remineralization in lytic spinal metastases after RT. Improvements in mechanical integrity and a possible reduction in surgical interventions for metastatic spinal disease may be achieved after remineralization and are the topic of further study.

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.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2022.12.018.

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