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Density of bone metastatic lesions increases after radiotherapy in patients with breast cancer

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ABSTRACT

The aim of this study was to assess local response to radiotherapy (RT) in a quantitative manner by evaluating the bone density of metastases. Spinal and pelvic bone metastases in 44 patients with breast cancer who were treated between May 2010 and December 2016 were retrospectively assessed. Bone density values of irradiated and unirradiated bone metastases before, 1–3 months after, 4–6 months after, and 7–9 months after RT were compared. At each time point, mean bone density ± standard deviation values were measured in Hounsfield units (HU) from computed tomography (CT) scans. Student's *t*-test was used for statistical analyses of the differences in bone density and for univariate analysis of the prognostic factors for differences in bone density at various time points after RT. Mean bone densities in irradiated and unirradiated bone metastases before RT were 297.31 ± 211.93 HU and 326.29 ± 228.61 HU, respectively. At the subsequent three time points examined, the mean bone density values in the irradiated and unirradiated bone metastases were: 61.97 ± 78.58 HU ($P = 0.000$) and 36.93 ± 52.49 HU ($P = 0.001$); 149.07 ± 133.27 HU ($P = 0.000$) and 68.40 ± 101.10 HU ($P = 0.000$); and 183.94 ± 168.30 HU ($P = 0.000$) and 88.21 ± 159.49 HU ($P = 0.004$), respectively, in each case. Patients receiving bisphosphonates exhibited greater increases in bone density in their metastases 1–3 months after RT (83.04 ± 82.18 HU vs 26.86 ± 60.55 HU, respectively; $P = 0.044$), whereas chemotherapy before RT was associated with significantly lower increases in bone density at the subsequent three time points [(37.53 ± 67.66 HU vs 93.63 ± 80.36 HU, $P = 0.027$), (99.30 ± 107.92 HU vs 180.24 ± 127.85 HU, $P = 0.030$), and (126.07 ± 141.77 HU vs 236.28 ± 158.22 HU, $P = 0.024$), respectively, in each case]. Comparing bone density values determined from CT scans appears to be a practicable and reproducible method for assessing local response to RT for bone metastasis of breast cancer. Increased bone density was also observed in the irradiated bone metastases.

Keywords: breast cancer; bone metastases; bone density; radiotherapy

INTRODUCTION

Bone is the most common site of distant metastasis in breast cancer patients, and it is the site of metastasis for ~70% of patients with advanced solid cancers [1]. Unfortunately, bone metastatic disease can dramatically reduce a patient's quality of life due to pain, pathological fractures, hypercalcemia, and spinal cord compression [2, 3]. The main goals for treatment of bone metastasis are relief of symptoms and mechanical stabilization of the bone. To date, the treatments available for patients with bone metastasis include surgery, radiotherapy (RT), and combined therapy (e.g. RT in conjunction with systemic therapy). RT and systemic therapy are widely used to promote reossification of metastatic bone lesions, and this may potentially lead to increased stability of spinal bone metastases [4, 5]. Multiple randomized trials with different fractionation schedules have demonstrated that RT is an effective local treatment for patients suffering from metastatic bone pain [6–9]. Moreover, in a meta-analysis of randomized trials of palliative RT for bone metastases, up to 70% of the patients examined experienced some degree of pain relief [10].

A parameter that has commonly been used to assess response to RT is palliation of pain, although this represents a subjective parameter. Only a few studies have used bone density as a quantification marker for assessment of local response to RT [11–13]. Moreover, in all of the latter studies, bone density was observed to increase

after treatment with RT. However, most of these studies could not eliminate the impact of concurrent systemic therapy on bone density, including the potential influence of bisphosphonates, which are known to increase bone mass. Additionally, these studies did not include negative control groups (e.g. RT versus no RT). Therefore, based on these available studies, it cannot be conclusively established whether RT increases or decreases bone density. Moreover, to our knowledge, no study to date has evaluated changes in bone density in unirradiated bone metastases.

Breast cancer is prone to generating multiple metastases to bone. In these cases, there is an opportunity to compare the local response of bone metastases outside of the radiation treatment field to those within the radiation field. Therefore, the aim of this study was to evaluate the effects of RT on bone density in spinal bone metastases of breast cancer patients, and to examine changes in bone density for bone metastases outside of the irradiated region.

MATERIALS AND METHODS

Patient selection

Prior to the onset of this study, approval was obtained from the Ethics Committee of our hospital. A total of 44 patients with bone metastases from breast cancer were treated in our department between May 2010 and December 2016, and these cases were retrospectively analyzed. To be eligible for this study, the patients needed to be: female, older than 18 years, have breast cancer confirmed by histology, and have bone metastases confirmed by X-ray, computed tomography (CT), magnetic resonance imaging (MRI), or scintigraphy. The cases selected had CT scans performed prior to RT and at two or more regular follow-up appointments after RT. Patients were excluded if they had a second primary tumor or if they had previously received RT at the primary study site.

Calculation of bone density

Available images were independently reviewed by two radiologists who were blinded to the patient conditions, RT doses, and clinical outcomes. The most representative slice among the baseline images from each patient was chosen to evaluate bone densities of the metastatic bone lesions in the irradiated treatment field. Similarly, the most representative slice among the images of the unirradiated metastatic lesions of each patient was selected. Importantly, the selected unirradiated metastatic lesion was in the same anatomical region (including the spine or pelvis) as the irradiated metastatic lesion. Bone density was measured in Hounsfield units (HU) by

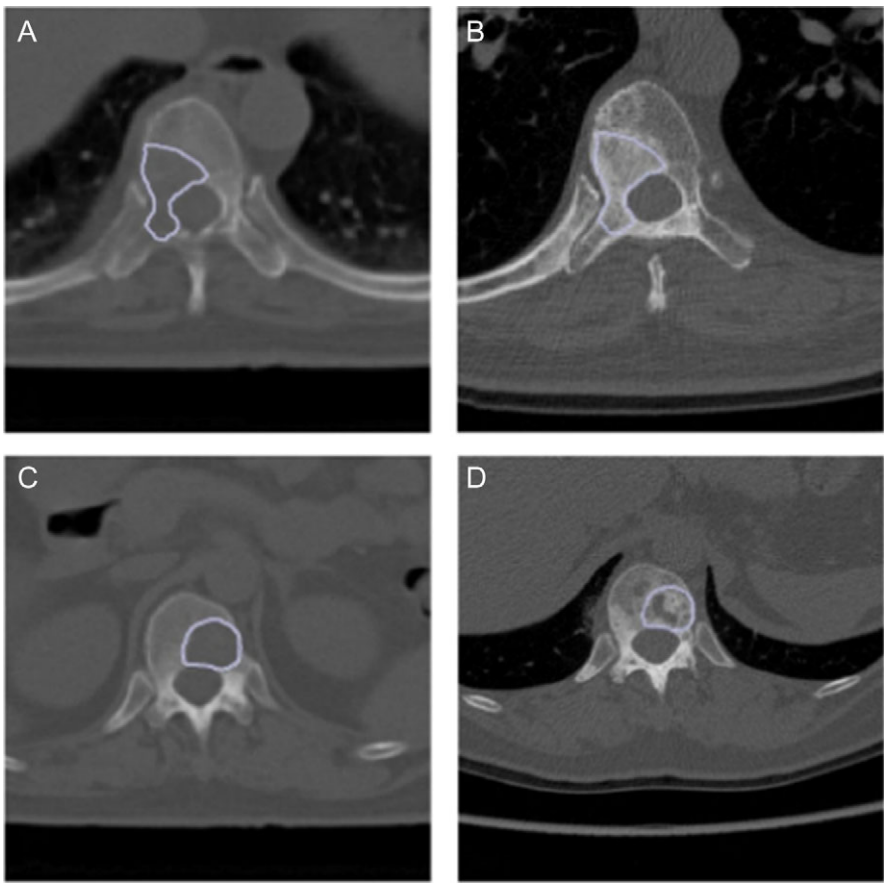

Fig. 1. Region of interest (ROI) setting in the whole irradiated and unirradiated vertebral body or pelvis before and 1–3 months after RT. (A and C) Irradiated and unirradiated osteolytic thoracic spinal metastasis before RT, respectively. (B and D) Irradiated and unirradiated osteolytic thoracic spinal metastasis 1–3 months after RT, respectively.

Table 1. Patient characteristics

Clinical characteristics	$N = 44$
Age (median, range)	44 years (23–65)
Irradiated metastatic lesions*, *n* (%)	44
Lytic	20 (46)
Mixed	20 (46)
Sclerotic	4 (8)
Unirradiated metastatic lesions, *n* (%)	34
Lytic	14 (41)
Mixed	17 (50)
Sclerotic	3 (9)
ER status, *n* (%)	
Positive	37 (84)
Negative	5 (11)
Unknown	2 (5)
PR status, *n* (%)	
Positive	34 (77)
Negative	8 (18)
Unknown	2 (5)
HER-2 status, *n* (%)	
Positive	13 (30)
Negative	23 (52)
Unknown	8 (18)
Subtypes, *n* (%)	
HR^+ (ER^+ or PR^+)	36 (81)
$HER2^+$ ($ER^-/PR^-/HER2^+$)	2 (5)
TNBC ($ER^-/PR^-/HER2^-$)	2 (5)
Unknown	4 (9)
Sites treated, *n* (%)	
Spine only	33 (75)
Pelvis only	6 (14)
Spine and pelvis	5 (11)
Dose schedule, *n* (%)	
30 Gy/10 fractions	20 (46)
36 Gy/12 fractions	20 (46)
40 Gy/20 fractions	2 (4)
45 Gy/15 fractions	2 (4)
Systemic therapy prior to RT	
Chemotherapy	23 (52)
Endocrine therapy	20 (46)
Bisphosphonates	19 (43)
No treatment	11 (25)
Systemic therapy during RT	
Chemotherapy	25 (57)
Endocrine therapy	19 (43)
Bisphosphonates	27 (61)
Pathologic fracture, *n* (%)	
Yes	29 (66)
No	15 (34)

ER = estrogen receptor, PR = progesterone receptor, HER-2 = human epidermal growth factor receptor 2, TNBC = triple-negative breast cancer, RT = radiotherapy.
*There was no significant difference regarding the type of metastatic lesions between the irradiated and unirradiated metastatic lesions($P = 0.942$).

contouring a region of interest (ROI) setting in the whole irradiated and unirradiated vertebral body or pelvis (Fig. 1). The ROI was the same for each patient's set of radiographs. Bone density measurements were performed with MATLAB software, version R2016b (China, Beijing), with bone density defined as the mass/mineral density of the bones examined. Due to differences in the follow-up intervals for each patient, bone density was calculated: 1–3 months after RT, 4–6 months after RT, and 7–9 months after RT. Mean density ± standard deviation (SD) values during these time periods were recorded.

Statistical analysis

Statistical analyses of the differences in bone density and of prognostic factors for the differences in bone density at the three time points after RT were performed with paired *t*-tests and independent *t*-tests, respectively. A *P*-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software, version 20.0.

RESULTS

Characteristics of the patients included in this study ($n = 44$) are summarized in Table 1. The median age of the cohort was 44 years

(range, 23–65). A total of 36 patients (82%) had hormone receptor–positive (HR^+) tumors. In addition, 33 patients (75%) only had spinal metastases, 6 patients (14%) only had pelvic metastases, and 5 patients (11%) had spinal and pelvic metastases. The most commonly applied dose schedules were 30 Gy × 10 fractions ($n = 20$) and 36 Gy × 12 fractions ($n = 20$). Thirty-three patients (75%) received systemic therapy prior to RT, including 23 patients (52%) who received chemotherapy and 20 patients (46%) who received endocrine therapy (ET). All of the patients received RT in conjunction with systemic therapy; and among these patients, 27 (61%) received bisphosphonates during RT.

There were 34 patients with bone metastatic lesions outside of the irradiation treatment field, and these patients served as a control group. Among the irradiated metastatic bone lesions, 20 (46%) bone metastases were defined as lytic lesions, 20 (46%) were defined as mixed lesions, and 4 (8.0%) were defined as sclerotic lesions. Among the unirradiated metastatic lesions, 14 were lytic lesions (41%), 17 were mixed lesions (50%), and 3 were sclerotic lesions (9%).

Changes in mean bone density were measured for 34 irradiated bone metastatic lesions and for their corresponding unirradiated bone metastatic lesions (Table 2). Changes in bone density were calculated based on baseline images that were collected prior to RT and from images collected at various time points during follow-up (e.g. 1–3 months after RT, 4–6 months after RT, and 7–9 months after RT). The mean bone density value for the irradiated bone metastases was 297.31 ± 211.93 HU at baseline. At the subsequent three time points after RT, the mean bone density values were 359.29 ± 207.93 HU, 450.65 ± 193.06 HU and 487.31 ± 185.94 HU, respectively. Prior to RT and at the same three time points after RT, the mean bone densities in the unirradiated bone metastases were 326.29 ± 228.61 HU, 363.22 ± 229.98 HU, 393.89 ± 219.96 HU and 418.11 ± 201.08 HU, respectively. Mean bone densities for the two sets of metastatic lesions significantly increased at the various time points after RT compared with baseline. Furthermore, the increases in bone density for the irradiated metastatic lesions were significantly higher than those for the unirradiated bone lesions.

Prognostic factors for increased bone density were also investigated for the 44 irradiated bone metastatic lesions (Table 3). Initially, changes in bone density according to bisphosphonate use was investigated. A statistically significant increase in bone density (83.04 ± 82.18 HU) was evident in the metastatic lesions of the patients who received bisphosphonates during RT, while the patients who did not receive bisphosphonates exhibited a mean increase in bone density of 26.86 ± 60.55 HU ($P = 0.044$) 1–3 months after RT. However, this significant increase was not maintained at the 4–6 months and 7–9 months time points after RT. Meanwhile, the mean bone density in the combined treatment group increased more than in the group without bisphosphonate use within 1–3 months after RT. At the same time point, the patients who did not receive chemotherapy prior to RT also showed a significantly greater increase in mean bone density at 1–3 months after RT than those who had received chemotherapy prior to RT (93.63 ± 80.36 HU vs 37.53 ± 67.66 HU, respectively; $P = 0.027$). Moreover, this difference remained significant at the 4–6 months ($P = 0.030$) and 7–9 months ($P = 0.024$) time points after RT. It was further observed that the patients who did not receive chemotherapy prior to RT more readily exhibited reossification compared with the patients who did receive chemotherapy prior to RT.

DISCUSSION

In the present study, RT was found to significantly increase bone density as measured in HUs from CT scans of irradiated bone metastases. The bone density values for metastases outside the treatment field also exhibited a significant increase as a result of systemic therapy. Previous studies have used bone density as a marker to assess local response to RT according to CT imaging [11, 14–16], although these evaluations have been limited. Furthermore, most of these available studies could not eliminate the impact of concurrent systemic therapy on bone density, because they did not include a negative

Table 2. Changes in bone density (HU) in irradiated and unirradiated bone metastases of 34 patients at various time points

	Mean	SD	Mean difference	SD	95% CI	*P*-value
Irradiated bone metastases						
Before RT	297.31	211.93				
After 1–3 months	359.29	207.93	61.97	78.58	(32.63, 91.32)	0.000
After 4–6 months	450.65	193.06	149.07	133.27	(102.57, 195.57)	0.000
After 7–9 months	487.31	185.94	183.94	168.30	(122.96, 244.32)	0.000
Unirradiated bone metastases						
Before RT	326.29	228.61				
After 1–3 months	363.22	229.98	36.93	52.49	(17.33, 56.54)	0.001
After 4–6 months	393.89	219.96	68.40	101.10	(33.13, 103.68)	0.000
After 7–9 months	418.11	201.08	88.21	159.49	(30.71, 145.72)	0.004

SD = standard deviation, CI = confidence interval, RT = radiotherapy.

Table 3. Prognostic factors for differences in bone density in the irradiated bone metastases of 44 patients

Prognostic factors	Baseline	1–3 months after RT			4–6 months after RT			7–9 months after RT		
	Mean (SD)	Mean (SD)	Mean difference (SD)	*P*-value	Mean (SD)	Mean difference (SD)	*P*-value	Mean (SD)	Mean difference (SD)	*P*-value
Bisphosphonates during RT										
Yes	300.53	382.58	83.04		457.93	154.90		481.16	172.86	
	(165.64)	(160.38)	(82.18)	0.044	(162.39)	(142.40)	0.335	(164.19)	(172.86)	0.809
No	298.14	332.92*	26.86		413.00	114.87		486.48	188.34	
	(241.13)	(248.52)	(60.55)		(220.22)	(91.75)		(209.48)	(148.93)	
Endocrine therapy during RT										
Yes	217.84	296.96	70.39		377.42	160.54		447.04	227.21	
	(121.66)	(146.13)	(83.84)	0.727	(154.83)	(134.45)	0.334	(157.79)	(159.43)	0.108
No	364.11	421.25	61.02		487.31	123.19		510.16	146.27	
	(207.79)	(202.57)	(76.24)		(185.94)	(115.47)		(186.21)	(151.82)	
Chemotherapy before RT										
Yes	362.56	406.49	37.53		467.65	99.30		494.36	126.07	
	(190.03)	(195.62)	(67.66)	0.027	(173.02)	(107.92)	0.030	(163.66)	(141.77)	0.024
No	233.47	331.35	93.63		413.71	180.24		473.09	236.28	
	(166.77)	(179.91)	(80.36)		(187.59)	(127.8)		(191.28)	(158.22)	
Endocrine therapy before RT										
Yes	333.52	388.27	55.80		461.68	128.13		500.27	157.93	
	(193.79)	(190.42)	(76.90)	0.503	(175.37)	(100.25)	0.603	(167.51)	(129.22)	0.417
No	273.78	351.50	73.37		423.59	148.13		469.93	198.74	
	(184.28)	(191.38)	(80.92)		(186.33)	(142.49)		(185.29)	(180.54)	
Bone lesions										
Lytic	178.76	249.67	87.07		353.74	177.94		404.17	239.24	
	(115.02)	(115.59)	(80.80)	0.138	(151.67)	(128.37)	0.114	(152.55)	(147.83)	0.096
Mixed	345.27	413.11	45.15		458.81	113.54		497.38	152.11	
	(99.03)	(98.90)	(76.21)		(107.54)	(119.96)		(129.01)	(160.03)	

*There was no significant difference in bone density between baseline and 1–3 months after RT in this group ($P = 0.153$), yet there was a significant difference in bone density between the baseline and the points of measurements in the remaining groups ($P < 0.05$). There was no significant difference in bone density at baseline between the patients with and without bisphosphonate use during RT ($P = 0.327$), yet there was a significant difference in bone density between the different groups at baseline in the remaining group ($P < 0.05$).

control group, and none of them examined changes in bone density in unirradiated bone metastases. In the present study, bone density in the irradiated and unirradiated bone metastases increased significantly after RT. Moreover, we found that the increase in bone density in the irradiated bone metastases was twice that in the unirradiated bone metastases. We also found that systemic therapy influenced the changes in

bone density in the irradiated bone metastatic lesions. For example, at 1–3 months after RT, a greater increase in bone density was observed in the patients who received concomitant treatment than in the patients who did not receive bisphosphonates ($P = 0.044$). In contrast, chemotherapy prior to RT had a consistently negative effect on bone density at the various time points examined following RT. The observed increase in bone density in bone metastatic lesions after RT treatment is consistent with an induction of recalcification or an increase in bone mass, and a recovery of bone structural integrity with formation of new bone[17]. It is generally accepted that newly formed bone strengthens bone that is affected by RT [18]. Taken together, these data suggest that RT can significantly promote the recalcification of bone metastasis in breast cancer patients, and systemic therapy before RT may affect the recalcification of bone metastases in an irradiated field.

The results of the present study expand on those of previous studies [11, 13, 16], which only concentrated on irradiated areas. Here, bone density values of metastases outside the irradiated areas were examined, thereby reflecting changes secondary to other systemic therapies without the effects of radiation. In a retrospective study conducted by Foster *et al.* [11], bone density was found to increase significantly in irradiated bone metastases, while neighboring vertebral bodies were unaffected following RT in the control group. However, measurements of bone density in unaffected bone do not accurately represent changes in bone density that may occur in bone metastases with systemic treatment. Therefore, the present study provides additional insight by using unirradiated bone metastases as a control in order to eliminate the effect of concurrent systemic therapy on increased bone density in irradiated bone metastases. A comparison of bone density between irradiated areas and regions outside irradiated areas has the potential to further indicate whether RT can significantly promote the recalcification of bone metastases. Thus, the data regarding bone density outside of the irradiated areas that are presented in the current study may serve as a useful reference for future studies. Moreover, consistent with previously published results [11, 12, 19, 20], our evaluation confirmed that bone density is a feasible and reliable marker for quantitatively assessing the local response of bone metastases that derive from solid tumors.

At 1–3 months after RT, a statistically significant increase in bone density was observed for bone metastases with concurrent administration of bisphosphonates and RT ($P = 0.044$). In preclinical studies, treatment with RT plus zoledronic acid has been shown to provide synergistic cytotoxic and radiosensitizing effects [21–23], as well as significant improvements in bone quality (e.g. bone density and microarchitecture) and biomechanical strength [24, 25]. The present data are consistent with those reported by Kouloulias [19] and Foerster[11], with bisphosphonates exhibiting radiosensitizing effects. Thus, patients who receive bisphosphonates during RT may exhibit a greater response to RT and undergo more rapid rebuilding of metastatic bone lesions. Denosmab is a RANKL inhibitor that is indicated for patients with bone metastases from solid tumors [26]. Denosmab has also been shown to be an effective treatment for protecting against bone loss and preventing skeletal-related events in cancer patients [27, 28]. In addition, it has been reported that denosmab increases bone mineral density as measured by dual-energy X-ray absorptiometry scans in healthy patients with osteoporosis and in cancer patients with bone loss induced by treatments [29–31]. However, to date, there are no data regarding a relationship between denosmab and the bone density of bone metastases measured in HU from CT, and none of the patients in our cohort received denosmab as a treatment.

Intriguingly, chemotherapy prior to RT consistently had a negative effect on bone density following RT in our study. Similarly, Forester *et al.* [32] reported that chemotherapy prior to RT was significantly associated with decreased stability of spinal metastases from gynecological malignancies. However, in two other retrospective studies [4, 5], RT was not associated with decreased stability of spinal metastases from breast and lung cancers. Thus, chemotherapy appears to disturb the bone remodeling process, and this may prevent recalcification of bone metastases after RT [33]. In addition, chemotherapy may cause rapid and significant long-term bone loss in the spine of breast cancer patients [34–36]. It is possible that the present results are due to the small sample size of our study. Therefore, additional studies with a larger sample number are needed to confirm the present results.

It is important to note that there were additional limitations associated with the present study in addition to the small sample size. First, due to the retrospective nature of our study, CT scans were not consistently acquired during the follow-up period after RT. Second, appendicular bone metastases could not be acquired as a second negative reference. Furthermore, an increase in bone mass does not necessarily represent a corresponding increase in bone strength. Thus, prospective studies with larger sample sizes are needed to confirm a relationship between RT and bone strength. An examination of changes in CT density measurements within an entire region of bone metastases would also be of use.

Previously, the extent of recalcification that occurred in lytic or mixed bone lesions was evaluated based on visual judgment. Also, pain management needed for osteolytic lesions has typically been used as a subjective measurement of response to therapy [7]. Here, and in previous studies, measurement of bone density has been shown to provide a quantitative and objective method for measuring treatment response to RT in metastatic bone disease. Consequently, we would advocate that future studies should focus on evaluations of bone density in clinical practice, especially in a larger cohort.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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