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[Original Article]

VALIDATION OF THERAPEUTIC RESPONSE ASSESSMENT BY BONE SCINTIGRAPHY IN PATIENTS WITH BONE-ONLY METASTATIC BREAST CANCERS DURING ZOLEDRONIC ACID TREATMENT : COMPARISON WITH COMPUTED TOMOGRAPHY ASSESSMENT

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Abstract : Purpose : To validate the use of bone scintigraphy (BS) versus computed tomography (CT) for therapeutic monitoring in patients during treatment with zoledronic acid.

Materials and Methods : Eleven patients with bone-only metastatic disease and being treated with zoledronic acid were included. The effects of therapies including chemotherapy and hormone therapy were evaluated in 25 separate examinations in total as follows : complete response (CR), when no bone metastasis was visible ; partial response (PR), when a decrease in the lesion area was detected ; stable disease (SD), when no or slight change was observed ; and progressive disease (PD), when new or enlarged lesion areas were observed.

Results : The accuracies of examination by Readers 1, 2, and 3 respectively were 76%, 80% and 76% for BS, 52%, 48%, and 40% for CT, and 64%, 52% and 60% for BS and CT combined with Readers 2 and 3 observing significant differences between CT and BS results. The rates of interobserver agreement between Readers 1 and 2, between Readers 1 and 3, and between Reader 2 and 3 respectively, were 84%, 80% and 88% ($\kappa = 0.648, 0.561$ and 0.766) for BS, 52%, 56%, and 60% ($\kappa = 0.180, 0.278$ and 0.282) for CT, and 52%, 60%, and 56% ($\kappa = 0.215, 0.282$ and 0.232) for CT and BS combined.

Conclusion : BS is effective for assessing the response of bone metastasis to therapy in patients during zoledronic acid treatment.

Key words : bone scintigraphy ; computed tomography ; tumor marker ; bone metastases ; therapeutic monitoring

INTRODUCTION

Bisphosphonate (BP) drugs are a group of pyrophosphate analogues that bind to hydroxyapatite bone mineral surfaces. BPs reduce the incidence of skeletal complications in patients with bone metastases and delay the onset of skeletal-related events defined as spinal cord compression, pathological fracture, a need for external beam radiation or surgery to bone, and hypercalcemia, mainly by inhib-

iting osteoclast activity and reducing bone resorption. Consequently, BPs are increasingly being incorporated into the management of metastatic bone disease and have now become standard therapy for bone metastases¹⁻². As well as reducing skeletal-related events, BPs also directly inhibit the growth of breast cancer cells and the activity of bone-derived growth factors³⁻⁶.

Bone scintigraphy (BS) is a standard method for detecting bone metastases and assessing bone tu-

mor response^{1,7}). However several studies have found that administrating BP significantly decreased the bone uptake of BS contrast agent, Tc-99m methylene diphosphonate (MDP), through competitive binding and thus saturation of the MDP binding site⁸⁻¹⁰. This effect results in problems with interpreting BS images. In contrast, other studies found that BPs do not interfere with MDP-based imaging¹¹⁻¹³. Thus far there have been no reports of decreased bone uptake during BS in patients treated with zoledronic acid (ZA), a widely used third-generation BP². Clinically, BS is commonly performed to assess bone metastasis after ZA therapy, seemingly without problems. However, to date there has been no report of BS correctly reflecting a tumor's status during BP therapy. The present study aimed to validate the use of BS to assess the therapeutic response of bone-only metastases in breast cancer patients during treatment with ZA in comparison with serum tumor markers (TM) and computed tomography (CT).

MATERIALS AND METHODS

The Fukushima Medical University Local Research Ethics Committee approved this study, and patients were not required to provide informed consent.

Patient selection

We retrospectively investigated 5885 sequential cases who underwent BS in our institution between January 2008 and December 2011. There were 487 cases suspected of having bone metastases and of these, 11 patients were enrolled in this study. The patient population comprised 11 women affected by breast cancer, ranging for 36 to 74 years old at the time of first examination (mean age \pm SD : 60 \pm 9.9 years). The presence or absence of bone and other metastases were diagnosed by BS, CT, MRI, and other clinical data such as measurements of TMs and symptoms. Patients received 4 mg of ZA therapy intravenously every 28 days.

The first set of CT and BS images taken for each of the 11 patients was used as baseline imaging. Subsequently, 25 evaluations in total were conducted including four evaluations taken before the ZA therapy, as shown in Table 1. The number of sets of images varied among patients, and we evaluated 36 sets of CT and BS images. We enrolled patients with bone-only metastasis since anticancer effect of BP have been reported and ZA accumulates only in bone³⁻⁶. Thus any metastasis other organs could potentially increase while ZA therapy reduces the

bone lesions, meaning that levels of TM might not accurately reflect the status of bone metastasis.

The inclusion criteria for this study were as follows.

- a) The patients received ZA therapy.
- b) Resection of the primary lesion was carried out and the patients had metastases only to bone.
- c) Metastasis other than bone did not occur during the entire follow-up course and was not detected by CT or other investigations for at least 6 months after completion of the follow-up course.
- d) The patients underwent CT, BS, and TM assessment.
- e) A significant increase in the TMs, carcinoembryonic antigen (CEA) and/or carbohydrate antigen 15-3 (CA-15-3), was observed.
- f) There were bone metastases in the spine and/or ribs in the chest and abdominal region.

Besides ZA therapy, biologic therapy and chemotherapy were performed 3 times in total in 2 patients, hormone therapy and chemotherapy 6 times in total in 3 patients, and hormone therapy 16 times in total in 6 patients (Table 1).

Assessment of response by BS and CT

The evaluations of therapeutic effects using BS and CT during the course of treatment were compared with changes in TMs. The effects of therapies were classified as follows : 1) complete response (CR), when no bone metastasis was visible ; 2) partial response (PR), when a decrease in lesion number, extent or the intensity was detected ; 3) stable disease (SD), when little or no change in the number, extent, or intensity of bone metastases was observed ; 4) progressive disease (PD), when new bone lesion(s) and/or apparent enlargement of the bone metastases was visualized.

Three readers with two, six, and seven years, respectively, of experience in CT and nuclear medicine retrospectively and independently analyzed the CT and BS results. The same three readers also analyzed CT combined with BS. The three readers were aware of the presence of bone metastases and the history of ZA treatment, but were blinded to the levels of TMs, other laboratory data, clinical history, radiology reports, and other imaging data. All readers classified the bone metastases as PD, SD, PR, or CR on CT, BS, and CT combined with BS.

In addition to the response assessment, BS images were evaluated based on whether a decrease in bone uptake and a relative increase in soft tissue uptake were observed after ZA therapy. Also, CT images were evaluated by whether sclerosis of bone

Table 1. Treatment components and patient response

Examination No	Patient No	Examination interval	*Elapsed time from first ZA therapy (month)	Type of treatment	Response (% change of TM)
1	1	a	**0, 6.5	B, C	PR (CEA -60%)
2	2	a	6.5, 24.6	H, C	PD (CEA +487%, CA15-3 +182%)
3		b	24.6, 36.2	H, C	SD (CEA +13%, CA15-3 +12%)
4		c	36.2, 48.5	H, C	PR(CEA -36%, CA15-3 -25%)
5		d	48.5, 60.5	H, C	PD (CEA +104%, CA15-3 +160%)
6	3	a	11.8, 24.2	H	PD (CEA +58%)
7		b	24.2, 32.5	H	PD (CEA +50%)
8	4	a	20.7, 32.7	H	SD (CEA +11%)
9		b	32.7, 47.6	H	PD (CEA +26%)
10		c	47.6, 62.3	H	PD (CEA +71%)
11	5	a	**0, 12.1	H, C	PD (CA15-3 +141%)
12	6	a	21.3, 33.3	H	PD (CEA +136%)
13		b	33.3, 47.2	H	PD (CEA +49%)
14		c	47.2, 59.2	H	PD (CEA +28%)
15	7	a	11.0, 22.9	H	PD (CEA +211%)
16		b	22.9, 35.2	H	PR (CEA -60%)
17		c	35.2, 47.1	H	PR (CEA -25%)
18	8	a	**0, 12.0	H	PR (CEA -84%)
19		b	12.0, 26.4	H	PR (CEA -26%)
20		c	26.4, 38.4	H	PD (CEA +691%)
21	9	a	7.8, 19.6	H, C	PD (CA15-3 +463%)
22	10	a	**0, 13.3	B, C	PD (CA15-3 +40%)
23		b	13.3, 25.2	B, C	PD (CA15-3 +161%)
24	11	a	11.4, 23.3	H	SD (CA15-3 +15%)
25		b	23.3, 35.8	H	PR (CA15-3 -26%)

C, chemotherapy ; B, biologic therapy ; H, hormone therapy ; SD, stable disease ; PR, partial response ; PD, progressive disease ; ZA, zoledronic acid.

*This column shows elapsed time from first ZA therapy of baseline images and subsequent images

**Number 0 refers to numbers of images before initiating ZA therapy

metastases became stronger. The types of bone metastases in the first CT examination were classified as blastic, lytic, or mixed type in all 11 patients with agreement by three readers.

The time between the second and third CT and bone scans were considered separate treatment intervals, and the second CT and bone scans served as the baseline for comparison with the third scan.

Tumor markers

Chemiluminescent enzyme immunoassay (CLEIA) was used to measure both CEA and CA15-3 concentrations in the 11 patients. Serum CEA and CA15-3 levels of 5.0 ng/ml and 30 U/ml, respectively, were adopted as the upper normal limits, with PD was defined as >20% increase, PR as >20% decrease, SD as within a 20% change, and CR as a decrease below the upper normal limit.

CT and BS examination

Whole-skeleton BS was performed 3-4 hours after intravenous administration of 740 MBq Tc-99m hydroxymethylene diphosphonate (HMDP Nihon Mediphysics, Tokyo, Japan). Anterior and posterior views of the whole body were obtained using an e.cam instrument (Siemens Medical Systems, Chicago, IL ; USA, scan speed 15 cm/min, matrix 512 × 1,024) with dual-headed cameras equipped with a low-energy, parallel-hole collimator. A 20% window centered on the 140 keV photopeak of Tc-99m provided the energy discrimination.

Thoracic and abdominal CT was performed with 64- and 16-channel multidetector row scanners (Aquilion 64, and Aquilion 16, Toshiba Medical Systems, Tokyo, Japan), with the following scan parameters : helical scan mode, tube voltage of 135 kVp, various tube current (autoexposure), 0.5 sec/rotation, 0.5

mm collimation, pitch 21 (16-channel) or 41 (64-channel), and contiguous axial section of 7 mm thickness. A dose of 100 ml of contrast material was intravenously injected in 5 out of the 36 examinations using a power injector (Nemotokyorindo, Tokyo, Japan) at a rate of 1.2 ml/second. Contrast CT scans were performed at 120 seconds.

Statistical analysis

The accuracy of BS, CT, or BS combined with CT in evaluating the therapeutic effects on bone metastases was determined by calculating the rate of concordance with the TM changes.

Age was given as mean \pm SD. The chi-square test was used to assess differences in the accuracy of BS and CT examination. The difference was considered significant when the *p* value was less than 0.05. Statistical analysis was performed using SPSS software for Windows (17.0, SPSS, Inc).

The percentage of interobserver agreement was calculated using the kappa statistic for multiple radiologists. A kappa value of up to 0.20 represented slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81 or greater, almost perfect agreement.

RESULTS

In the first examination, blastic type bone metastases were observed in 5 patients, mixed type in 5 patients, and lytic type in 1 patient. Sclerosis of the bone metastases was judged as being increased on CT in 8, 10, and 11 examinations out of 25 examinations by Readers 1, 2, and 3, respectively.

The 11 patients were on ZA for a median of 758 days (range, 199–1896 days) with a median dose of 114 mg (range, 32–228 mg), and 36 sets of BS and CT images were taken in total; 4 sets were taken before ZA administration, 28 sets were taken immediately after ZA administration and the remaining 4 sets were taken 1, 8, 15, and 114 days after ZA administration.

None of the BS images showed decreased uptake of normal bone due to ZA administration including 28 sets of images taken on the same day as ZA administration.

Among 36 sets of CT and BS, 34 were taken on the same days as the blood sampling, and 1 set was taken 4 days before blood sampling. The remaining set and the blood sampling were taken in the order of BS, CT, and blood sampling on 3 consecutive days.

TM evaluation detected no CR, 7 PR, 3 SD, and 15 PD, with agreement in results between the two TM testing. The evaluation accuracy was 76%, 80%, and 76% for BS, 52%, 48%, and 40% for CT, and 64%, 52%, and 60% for BS combined with CT by Readers 1, 2, and 3 respectively (Table 2). The accuracy of BS and CT evaluation was significantly different ($P < 0.05$) between Readers 2 and 3.

The percentages of interobserver agreement between Readers 1 and 2, Readers 1 and 3, and Readers 2 and 3 were 84%, 80%, and 88% ($\kappa = 0.648, 0.561$ and 0.766) for BS, 52%, 56%, and 60% ($\kappa = 0.180, 0.278$ and 0.332) for CT, and 52%, 60%, and 56% ($\kappa = 0.215, 0.282$ and 0.232) for CT and BS combined, respectively (Table 3).

Fig. 1 shows the rate of concordance between TM and BS examinations performed by the 3 readers, each of whom performed 25 examina-

Table 2. Accuracy of BS, CT, and BS combined with CT among three readers

	BS	CT	BS and CT	P value for BS vs CT
Reader 1	76% (19)	52% (13)	64% (16)	0.077
Reader 2	80% (20)	48% (12)	52% (13)	0.018
Reader 3	76% (19)	40% (10)	60% (15)	0.017

N = 25

BS, bone scintigraphy; CT, computed tomography.

Table 3. Inter-agreement variability among three readers

Modality	Agreement between readers 1 and 2 (κ)	Agreement between readers 1 and 3 (κ)	Agreement between readers 2 and 3 (κ)
BS	84% (0.648)	80% (0.561)	88% (0.766)
CT	52% (0.180)	56% (0.278)	60% (0.332)
BS and CT	52% (0.215)	60% (0.282)	56% (0.232)

BS, bone scintigraphy; CT, computed tomography

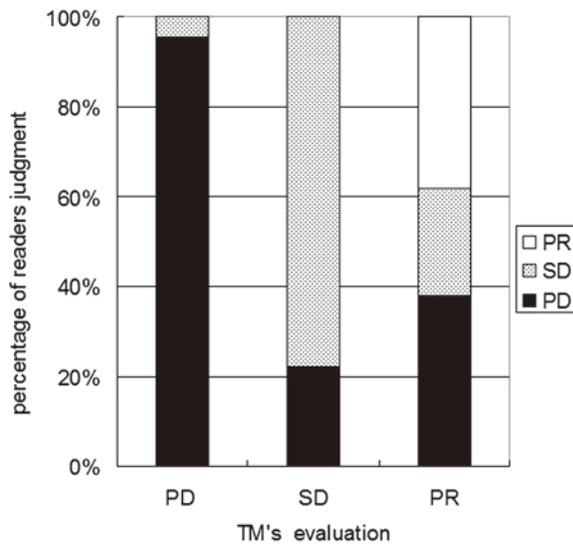


Fig. 1. Tumor marker evaluation vs. readers' bone scintigraphy evaluation

Assessments of serum tumor markers indicated 45 cases as PD while the readers judged 43 (96%) as PD and 2 as SD by bone scintigraphy. However, out of the 21 PR indicated by tumor marker levels, the readers judged 8 as either PD or SD (38%).

PD indicates progressive disease, SD stable disease, PR partial response, N number, and TM tumor markers

tions. TM indicated 45 cases as being PD while the readers judged 43 (96%) as PD and 2 as being SD by BS. However, in the case of 21 PR indicated by TM, the readers judged 8 as either PD or SD (38%). For the 15 PD, Readers 1, 2, and 3 judged consistently as 15, 14, and 14 PD, respectively, yielding respective accuracies of 100%, 93%, and 93%. However, for 7 PR, the three readers together correctly judged only 2 PR.

Although CEA decreased during the period between Figs. 2D and 2E, CT showed enlargement of sclerotic lesion to the right side of the vertebral body and arch. The readers judged this as SD or PD during the period between Figs. 2E and 2F, CT showed slight enlargement and strengthening of sclerotic change, and two of the three readers judged it as SD, however CEA was elevated (Fig. 2).

DISCUSSION

There have been several reports of the administration of BPs resulting in a significant decrease in bone uptake of Tc-99m MDP, including alendronate and etidronate taken orally or through intravenous infusion^{8-10,14,15}. In addition, Morris *et al.*¹¹ specifically examined whether BS images would change

before and after ZA treatment by evaluating 163 osseous metastases from breast cancer in 10 patients. From BS images taken 1 to 3 days before and after ZA treatment, the authors concluded that the timing of ZA did not interfere with the evaluation of bone scans. In the present study none of all 32 BS examinations performed during ZA therapy showed an apparent decrease in bone uptake. Even in the 28 BS images taken on the same days as administration of ZA, and maximum cumulative doses of 228 mg every 28 days of infusion, there was no apparent decrease in bone uptake. This result indicates that the timing and total dose of ZA did not affect BS imaging in our patients. However, our aim was to evaluate the therapeutic response during ZA administration using BS in bone-only metastatic disease because of the lack of reports on whether BS can accurately reflect therapeutic response in such patients. In a related study, Chavdarova *et al.*¹⁶ found that BS after ZA therapy was reliable for the assessment of the BP therapeutic effects; however they still only assessed imaging taken before and after BP therapy, and did not compare them to other examinations such as TM, clinical status, or other imaging studies. Therefore the value of the bone scans for truly reflecting tumor status has yet to be validated.

Our results now reveal that BS could reflect tumor burden more accurately than CT in patients with bone-only metastases of breast cancer under ZA therapy, with all readers recording a higher rate of examination accuracy with BS than with CT compared to TM data. The accuracy of BS combined with CT fell between the separate values, thus the combined assessment did not improve accuracy in comparison with BS only.

Although the readers correctly judged 96% of PD with increased levels of TM, they judged 38% of PR with decreased levels of TM as PD (Fig. 1). Thus, in cases of PR, BS could lead to a misdiagnosis of PD, and this might indicate therapeutic responses such as flare. BPs can also induce recalcification or sclerosis of osteolytic lesions^{17,18}, and thus healing might cause an increase in tracer uptake that could be mistaken for PD. However, such a flare phenomenon by BP has not yet been reported due to the difficulty in excluding the effect of other therapies¹⁹. In addition, although BS is used to support other imaging modalities for assessing tumor response in clinical practice, Hamaoka *et al.*⁷ concluded that it is not appropriate to determine the response based on changes in BS signal alone. On the other hand, a limited retrospective study of 101

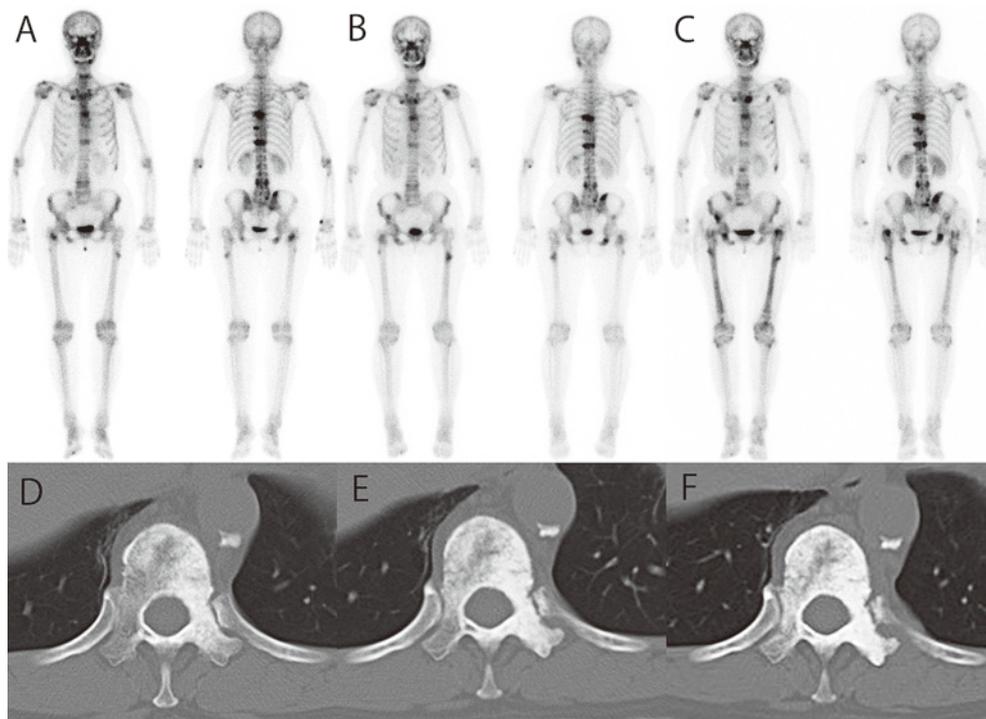


Fig. 2. A 69-year old female with breast cancer and bone metastases treated with zoledronic acid. Figs. 2A and D, B and E, C and F were taken on the same day.

A. BS shows multiple abnormal uptakes consistent with bone metastases.

B. BS obtained about 1 year after taking Fig. 2A shows new hot spots in the right humerus and more extended accumulation in the left femur, right iliac bone. Three readers judged the tumor response as PD. However the carcinoembryonic antigen level decreased from 46.5, which was measured when Fig. 2A was taken, to 29.7. Uptake of the left mandible was diagnosed as osteonecrosis.

C. BS obtained about 1 year after taking Fig. 2B shows new uptakes in the left ribs and more extended accumulation in the right humerus, left sternum head, and bilateral femur. All three readers judged the tumor response as PD. Carcinoembryonic antigen increased from 29.7, which was measured when Fig. 2B was taken, to 60.7.

D. CT of Th11 vertebra obtained on the same day that Fig. 2A was taken shows blastic bone metastases.

E. CT obtained 1 year after taking Fig. 2D (taken on the same day as Fig. 2B) shows an enlargement of sclerotic lesions to the right side of the vertebral body and arch. Although carcinoembryonic antigen decreased during the period between when Fig. 2D was taken and 2E was taken, the readers judged it as SD or PD.

F. CT obtained 1 year after taking Fig. 2E (taken on the same day as Fig. 2C) shows a slight enlargement and strengthening of sclerotic lesions. Carcinoembryonic antigen elevated during the period between when Fig. 2E was taken and 2F was taken, and the readers judged it as SD or PD.

patients with breast cancer and bone metastasis showed that scintigraphic regression of bone metastases was correlated with significant survival benefits (mean survival 5.0 ± 2.7 years) compared to stable disease (mean survival 3.7 ± 1.9 years) and progressive disease (mean survival 2.2 ± 1.3 years)²⁰.

As mentioned above, CT can reveal bone sclerosis and new sclerotic lesions could as a therapy response after BP administration^{17-19,21,22}. In the present study, sclerosis of bone metastases became stronger in 8, 10 and 11 out of 25 evaluations performed by Readers 1, 2, and 3 respectively, although the accuracy of CT examination was low for all readers, at 52, 36 and 40% by Readers 1, 2, and 3, respectively. Furthermore interobserver agreement

was lower in CT assessment with a κ index of slight or fair agreement compared with BS evaluation of moderate to substantial agreement. In addition, new sclerotic bone lesions and enlargement of sclerotic lesions could appear both as a response to therapy and due to metastatic growth, making the evaluation of therapeutic efficacy difficult²³. Moreover, the evaluation of subtle change in sclerotic bone metastases on CT is also considered difficult. Indeed there are several reported instances in present study where TMs increased, but the readers' judgments were SD, as shown in Fig. 2.

In this study, we compared TM levels as a reflection of tumor status with CT and BS imaging. Blood levels of a TM seem to correlate with tumor mass and are useful tools in both the diagnosis and

follow up of breast cancers^{24,25}). Various TMs are routinely measured by the majority of breast cancer experts in Japan^{26,27}, although according to the Response Evaluation Criteria in Solid Tumors Group, TM alone should not be used to assess treatment response if markers are initially above the upper normal limit, as they must return to the normal levels to constitute a complete response²⁸). However the guidelines of the American Society of Clinical Oncology recommends that in the absence of readily measurable disease, elevated markers of CEA and CA15-3 may be used to suggest treatment failure²⁹, and evaluating treatment response of metastatic lesions in patients with bone-only disease is inherently difficult due to the lack of measurable lesions. In addition, Kurebayashi *et al.*^{26,30} reported that CEA, CA15-3, and NCC-ST-439 levels correlated well with response to therapy in breast cancer. Their research showed that if the pretreatment serum level of these markers was over the cut-off value, changes in serum TM levels after the start of therapy correlated significantly with therapy response, and a >20% reduction in marker levels was a favorable predictive factor for time to progression during systemic treatment. Buffaz *et al.*³¹ also reported a strong correlation between CA15-3 levels and bone-scan findings, while a meta-analysis indicated that in patients with responsive disease, CA15-3 serum levels decreased in 66% of cases, of whom 73% had stable disease with no significant changes in marker concentrations, and 80% of cases with progressive disease showed increased CA15-3³²).

F-18 fluoro-deoxy-glucose positron emission tomography (FDG-PET) is a noninvasive tool used in many cancers in differentiating benign and malignant tumor, staging, and detection of recurrent tumor and therapeutic response³³). Specht *et al.*³⁴ retrospectively reviewed 28 patients who underwent FDG-PET during systemic therapy for bone-dominant metastatic breast cancer, and found that changes in serial FDG-PET images could predict the time to progression in these tumors. However, bone metastasis with clear uptake on an initial FDG was one of the inclusion criteria in their study. FDG-PET also tends to be superior to BS in the detection of osteolytic lesions, but inferior in the detection of osteoblastic lesions^{35,36}), and it has been proposed that after successful treatment, lytic metabolically active bone metastases transform into metabolically inactive blastic metastases. However, progressive blastic bone metastases with a positive bone scan, but without significant FDG avidity have been reported and attributed to hypocellularity²³). Many

bone metastases increase in density on CT and become sclerotic after BP or other therapies (e.g. hormone or biological therapy, or anti-cancer drug), thus the diagnostic accuracy of FDG-PET might become inferior to BS under ZA treatment.

In recent years, increased osteoblastic bone metastases from breast cancer, probably due to BP therapy, have been reported¹⁸). Furthermore, adjuvant therapy after surgery could be the cause of sclerotic metastases. Reported visualization rates of BS/FDG-PET for bone metastases are 100%/55.6% for blastic type, 84.2%/94.7% for mixed type, and 70%/100% for lytic type. However, although lytic-type bone metastases have a lower visualization rate on BS than FDG-PET, there was only one patient with metastases of this type among the 11 patients in our study³⁶).

In the present study, all participants were breast cancer patients. The reason is that bone-only metastases in patients with breast cancer are common and the survival rate for breast cancer is relatively high³⁷). Prostate cancer is also often involved in bone metastasis; however, as this type of cancer is common among elderly males and bone metastases are discovered during the initial phase of the disease, resection of primary tumor is not performed. Thus, there were no eligible such cases for this study. Other cancers that metastasize to bone with high frequency, such as lung cancer, have a poor prognosis providing little chance for a follow-up BS.

BS is a commonly used method in everyday practice, with a reported sensitivity of 62-100% and specificity of 78-100%^{7,11}). Although CT as well as BS could detect bone metastases, our results indicate the superiority of BS over CT in terms of monitoring response in patients under treatment with ZA³⁸). In cases of bone-only metastatic patients with normal ranges of TM, BS may therefore be the only reliable tool for monitoring responses to therapy. Another advantage of BS is the ability to assess the whole skeleton rather than the body trunk only, thus contributing to early detection of BP side effects such as osteonecrosis of the jaw or atypical diaphyseal femoral fracture^{39,40}).

LIMITATIONS

The first limitation of this study was its retrospective nature. Treatment regimens, and durations varied, and the number of patients analyzed was small. Further studies are clearly needed.

Second, in the present study we compared TM and BS; however, the level of TM was not always

parallel to the tumor amount. This could be because tumor flare associated with therapy can affect both TM and BS results, leading to evaluation of the tumor response as PD.

Third, although our study included patients without metastases other than bone, the influence of micrometastasis, which could not be detected by CT or MRI and might not have shown a parallel therapy response to the bone metastases, could also reflect the increase or decrease of TM. Also, FDG-PET was not performed thus other site of metastasis such as bone marrow and those other than chest and abdomen could potentially affect TM values.

CONCLUSION

To our knowledge, this is the first study to assess the therapeutic response in patients with bone-only metastasis during ZA treatment by BS and CT. Our findings revealed that ZA did not affect the accurate BS imaging of tumor status. Also, although BS was a more accurate modality than CT for monitoring the response of bone metastases in patients during ZA administration, the accuracy of BS was not entirely satisfactory. Additionally, the possibility of misdiagnosing tumor response as stable or progressive was indicated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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