1. Introduction

The skeleton is the most frequently involved organ of distant metastasis in advanced breast cancer, and bone metastasis develops in over 70% of metastatic breast cancer patients. Despite skeletal metastasis-related morbidities, including pain, fractures, hypercalcemia, and spinal cord compression, the survival of patients with bone metastases alone is relatively longer than that of patients with visceral disease. Therefore, appropriate response monitoring of bone metastasis during therapy is vital in terms of cumulative morbidity and healthcare costs.

In nuclear medicine, whole-body bone scintigraphy (BS) and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) are widely used to evaluate bone metastasis in breast cancer patients. However, the uptake mechanisms in metastatic bone lesions of each imaging modality are very different, in that BS reflects osteoblastic responses in metastatic bones, and FDG PET/CT reveals high-level glucose metabolism bone sites. Despite the superiority of FDG PET/CT in terms of evaluating osteolytic bone metastasis compared with BS, BS remains a valuable diagnostic method detecting osteo-sclerotic responses in metastatic bone lesions, and FDG PET/CT reveals high-level glucose metabolism bone sites.

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to BS in evaluating bone metastases regardless of whether the lesions were osteolytic or sclerotic.\textsuperscript{[13,15,16]} Up to now, the evidence of efficacy and consensus regarding effective monitoring of a treatment response in imaging are lacking.\textsuperscript{[16,17]} After treatment, it is not uncommon for the follow-up findings of metastatic breast cancer bone lesions to differ between BS and FDG PET/CT. Such differences in findings between imaging methods confuse the interpretation of patient status for clinicians in daily oncological practice.

We thus hypothesized that the prognostic values of BS and FDG PET/CT during follow-up are different, and we sought to establish which method is more valuable for predicting patient survival.

2. Materials and methods

2.1. Patients

In all, 100 female patients (mean age ± standard deviation [SD] 48.1 ± 9.8 years; range 48–75 years) diagnosed with invasive ductal breast cancer with bone-only metastasis from March 2004 to March 2012 at a single institution (Ajou University Hospital, Suwon, Korea) were included in this study. All patients underwent both BS and FDG PET/CT at baseline (initial diagnosis of bone metastasis) and at follow-up 1 year after treatment. The patients’ clinical characteristics, including age, histology, and treatment modalities, were obtained by chart review blinded to the BS and FDG PET/CT results. Clinical follow-up was performed at least every 6 months, and the mean follow-up duration was 45.0 ± 23.7 months (range 15–131 months). Patient characteristics are summarized in Table 1.

The clinical design of this retrospective study was approved by the institutional review board of Ajou University (AJIRB-MED-MDB-17-162). The need for informed consent was waived.

| Table 1 |
| **Patient characteristics.** |
| Characteristics | Number |
| --- | --- |
| Age, y | 48.1 (48–75) |
| Histopathology | 100 |
| Invasive ductal carcinoma | 94 |
| Treatment modalities | 64 |
| Chemotherapy: yes/no | 94/6 |
| Radiotherapy: yes/no | 88/12 |
| Hormone therapy: yes/no | 78/22 |
| Bisphosphonate therapy: yes/no | 64/36 |
| Nuclear grade | 47 |
| Grade 1/2/3 | 44/9 |
| Histological grade | 12 |
| Grade 1/2/3 | 40 |
| Tumor subtype | 25 |
| HER2-positive | 25 |
| ER and/or PR-positive, HER2-negative | 65 |
| Triple negative | 10 |
| Morphologic characteristics of bone lesions at baseline | 78 |
| Predominantly osteolytic | 12 |
| Predominantly osteosclerotic | 12 |
| Mixed osteolytic/sclerotic | 10 |

ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

2.2. Bone scintigraphy protocol

Whole-body bone scintigraphy was performed 4 hours after the injection 740 MBq of Tc-99m methylene diphosphonate. Anterior and posterior views were acquired using a dual-headed gamma camera equipped with low-energy, high-resolution collimator (Varicam, GE Healthcare, Milwaukee, WI).

2.3. FDG PET/CT protocol

After fasting for at least 6 hours, patients were administered 5 MBq/kg FDG intravenously. The blood glucose level at the time of FDG injection was <150 mg/dL in all patients. Patients were instructed to rest comfortably for 60 minutes and to urinate before scanning. Whole-body PET/CT images were obtained using the Discovery ST scanner (GE Healthcare, Milwaukee, WI). Seven or 8 frames (3 min/frame) of emission PET data were acquired in 3-dimensional mode after noncontrast CT scanning from the base of the skull to the upper thigh (120 kV, 30–100 mA in the Auto mA mode, 3.75 mm section width). Emission PET images were reconstructed using an iterative method (ordered subset expectation maximization with 2 iterations and 20 subsets, 600 mm field of view, 3.27 mm slice thickness) and attenuation-corrected by noncontrast CT.

2.4. Image analysis

Images were assessed visually by consensus between 2 experienced nuclear medicine physicians (SP with 6 years of experience and YSA with 12 years of experience) who were blinded to all other clinical information. The morphologic characteristic of metastatic bone lesions (predominantly osteolytic, osteosclerotic, or mixed osteolytic/sclerotic) was determined on bone window setting CT images from baseline FDG PET/CT on an AW workstation (version 4.4). Baseline and follow-up images were compared for response evaluation. A patient was confirmed as a responder if disappearance of all lesions or a reduction in uptake activity in bone lesions was documented on follow-up scans. Follow-up images without significant interval changes or increased uptake activity of bone lesions compared with baseline with or without new lesions were indicative of nonresponders. The responders and nonresponders were evaluated using each imaging modality (BS and FDG PET/CT).

2.5. Histopathological evaluation

Surgical specimens from macroscopic tumors were sliced serially at 5-mm intervals, prepared as paraffin wax-embedded sections, and stained with hematoxylin and eosin. The specimens were evaluated according to the following histopathological features: histological type of carcinoma, black nuclear grade (nuclear grade 1, poorly differentiated; grade 2, moderately differentiated; and grade 3, well-differentiated), and modified Bloom–Richardson histological grade (histological grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated). Expression levels of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were evaluated in surgically removed specimens using standard avidin–biotin complex immunohistochemical staining methods. All primary antibodies used were monoclonal, as follows: ER (1:50; Dako Corp., Carpinteria, CA), PR (1:50; Dako Corp.), and c-erbB2 (1:200; Novocastra Laboratories Ltd., Newcastle-Upon-Tyne, UK). ER or PR positivity was defined as the presence of at least 1% positively stained cells.
stained nuclei at ×10 magnification. The intensity of c-erbB-2 staining was scored as 0, 1+, 2+, or 3+. Tumors with a 3+ score for c-erbB-2 staining were classified as HER2-positive, and tumors with a 0 or 1+ score were classified as HER2-negative; in tumors with a 2+ score, gene amplification using fluorescence in situ hybridization was used to determine the HER2 status. All specimens were reviewed by a pathologist with 18 years of experience.

2.6. Statistical analysis
A sample size calculation was performed using MedCalc (ver. 14.8.1; MedCalc Software bvba, Ostend, Belgium). A significance (α) level of 5% and a statistical power (1-β) level of 80% were used and considered acceptable for the purpose of the study. A sample size of 95 was required to attain an appropriate confidence range; thus, the sample size of our study (n = 100) was sufficient to perform the statistical analysis.

The Kappa test was used to assess whether parameter distributions differed significantly from a normal distribution. All data were normally distributed; thus, parametric analyses were used, and all data are presented as means with SDs.

Level of agreement between BS and PET results was quantified using the kappa statistics. The kappa value was interpreted according to the criteria presented by Altman (with 0.81–1 being very good agreement; 0.61–0.80 being good agreement; 0.41–0.60 being moderate agreement; 0.21–0.40 being fair agreement; <0.20 being poor agreement).[18] Overall survival (OS) was measured to assess the prognosis of patients and was defined as the interval from the initial diagnosis of bone metastasis to death from any cause. To assess the prognostic significance of clinico-pathological and imaging parameters, univariate and multivariate analyses using a Cox proportional hazards regression model were performed. Covariates that achieved a significance level of <0.2 in the univariate model were included in the multivariate model. Survival functions of parameters were estimated using the Kaplan–Meier method and compared using the log-rank test. The MedCalc software package was used for all statistical analyses. P values <0.05 were considered to indicate statistical significance.

3. Results
3.1. Assessment of the agreement between BS and PET findings
According to BS images, 27% (27/100) of patients were classified as responders and 73% (73/100) as nonresponders. On the contrary, based on FDG PET/CT, 48% (48/100) of patients were identified as responders and 52% (52/100) as nonresponders. The kappa value showed a poor agreement between BS and PET findings (kappa 0.20, 95% confidence interval [CI] 0.03–0.38).

3.2. Assessment of prognostic parameters for OS
In all, 36 patients (36%) were alive during the follow-up period (45.0 ± 23.7 months). The mean OS after the diagnosis of bone-only metastasis was 57.6 (95% CI 49.7–65.5) months.

The OS rate at 5 years was 49%, and the remaining 51% of patients died within 5 years of initial diagnosis of bone-only metastasis. On univariate analysis, the response statuses based on PET imaging were identified as significant prognostic factors for 5-year OS (P < 0.001 and P = 0.016, respectively). Other factors including age, histologic grade, tumor subtype, treatment modalities, morphologic characteristics of bone lesions, and response status based on BS imaging did not show statistical significance as prognostic factors (all P > 0.05; Table 2). Multivariate analyses showed that only response status based on PET imaging was independently prognostic of OS (P = 0.001; Table 2).

The Kaplan–Meier survival estimates at 5 years based on response status as revealed by BS and FDG PET/CT imaging are shown in Fig. 1. The OS rate at 5 years according to BS imaging was higher for responders than nonresponders (66.7% vs 42.5%), but statistical significance was not attained (P = 0.090, Fig. 1A). The OS rate based on PET imaging was significantly poorer for nonresponders than responders (32.7% vs 66.4%; P < 0.001; Fig. 1B).

4. Discussion
Bone scintigraphy and FDG PET/CT are convenient whole-body imaging tools used by physicians to evaluate bone metastasis in
breast cancer patients. However, previous prognostic surveillance studies using BS and FDG PET to evaluate bone metastasis in breast cancer patients are very few in number. Cook et al. reported that FDG PET is superior to BS for the initial detection of osteolytic breast cancer metastasis, which is associated with a shorter OS than is osteosclerotic metastasis. To our knowledge, comparison of the prognostic utilities of BS and FDG PET in terms of response assessment in bone-only metastatic breast cancer patients has not been attempted.

We found that only the responses based on FDG PET imaging reliably predicted survival of breast cancer patients with bone-only metastases. Response assessment using BS was not of assistance. These results might be originated from that FDG PET acted as a tumor-specific tracer and reflected the glucose usage by tumor cells in viable metastatic lesions regardless of the characteristic of bone lesions (osteolytic, osteosclerotic or mixed osteolytic/sclerotic). On the contrary, BS mainly reflects the altered bone microenvironment in metastatic bone lesions; persistent high uptake evident on BS imaging may be observed in osteosclerotic lesions that are already reduced in viability because of their response to treatment. In fact, in our present study, the responder group according to PET imaging findings was larger than that based on BS imaging findings (48 vs 27 patients), and a discrepancy between the PET and BS findings was evident (kappa 0.20).

The nuclear grade was a significant prognostic factor only on univariate analysis, but not on multivariate analysis, consistent with the finding of a previous study by Lee et al. who showed poorer distant relapse-free survival of patients with an aggressive nuclear grade compared with breast cancer patients with bone-only metastasis. Furthermore, the nuclear grade was not significantly prognostic on multivariate analysis in the cited study. More studies may be required to validate the prognostic utility of the nuclear grade for bone-only metastatic disease.

Better survival of bone metastatic breast cancer patients without visceral disease was reported in previous studies. In our study, the mean OS of patients with bone-only metastasis was 57.6 months, and 49% of these patients were alive 5 years from the time of the initial diagnosis of bone metastasis; the survival was quite different from the median survival of 40 to 55 months reported in previous studies. The relatively long survival in these patients means that prediction of survival and proper management of bone metastatic disease are important to keep patients alive with a tolerable quality of life for as long as possible. In this context, our study provides useful information for clinicians in predicting the prognosis of their patients. Moreover, we enrolled a homogeneous group with only the invasive ductal type of breast cancer. In addition, the tumor subtype did not affect the response evident on PET imaging, being generally prognostic in our study. We thus expect that our results could be applied in clinical practice.

It is known that most breast cancer metastasis to bone results in osteolytic lesions. In our study, 78% of the patients showed predominantly osteolytic features, which is consistent with previous known value (~80%). Although osteolytic metastases tend to be aggressive than sclerotic metastases, the morphologic characteristics of bone at baseline did not appear to be a significant predictor of OS in our study. There are few previous studies that reported the relationship between morphologic characteristics of metastatic bone lesions and the survival, so it was hard to explain the reason for this result. One possible explanation is that the survival of patients might not be affected by morphologic characteristics of bone at initial diagnosis, if the patients were treated properly. Further studies will be necessary to clarify this issue.

In our study, to avoid the flare phenomenon, images obtained 1 year after treatment were selected as follow-up images. The flare phenomenon is well-known in BS, and it renders the differentiation between progression and a temporary healing osteoblastic response to successful therapy difficult. Also, the flare phenomenon on FDG PET, known as metabolic flare, has been described after treatment of breast cancer. To avoid the flare phenomenon on both BS and PET images, we assumed that the proper time lag for predicting prognosis via imaging response assessments in routine clinical practice is 1 year after therapy.

A previous study by Ahn et al. reported that biphosphonate treatment was a significant prognostic factor for predicting patient’s survival. However, in our study, the response status based on PET image was only significant independent prognostic factor for OS, irrespective of treatment modality. To date, the optimal treatment for bone-only metastatic patients remains unclear; more studies are needed.

There are several limitations to our study. First, we did not include standardized uptake values (SUVs) obtained from FDG PET in our imaging analysis. Most of our patients (97/100) had multiple metastatic bone lesions, and it was difficult to compare SUVs lesion by lesion on before and after-treatment images. Moreover, SUVs are useful when evaluating PET images of soft-tissue metastases only; bone lesions remain “nonmeasurable.” Thus, we did not use SUV data in our study.
Second, we did not include data on the morphological changes of bone lesions as evident on CT images. A previous study by Tateishi et al.\(^\text{29}\) showed that only PET changes predicted progression of bone metastasis, CT changes did not. We thus focused on metabolic changes on PET images. Third, the guideline for treatment of bone metastases was changed within the study period,\(^\text{30}\) so the enrolled patients were not treated with the same guideline. Given that this type of study is retrospective, we could not control for this factor that may influence outcome. The final limitation of our study was that, although solitary bone metastases are significant prognostic factors in patients with skeletal metastasis,\(^\text{20,31}\) we could not explore this topic in our study, because only 3 patients had single bone metastases. Further studies including more patients with solitary bone metastases may be needed.

5. Conclusion

In conclusion, the response evident on FDG PET images after treatment predicts OS in breast cancer patients with bone-only metastases.

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