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# Diagnostic accuracy of bone metastases detection in cancer patients: Comparison between bone scintigraphy and whole-body FDG-PET

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$^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become widely available and an important oncological technique. To evaluate the influence of PET on detection of bone metastasis, we compared the diagnostic accuracy of PET and conventional bone scintigraphy (BS) in a variety of cancer patients. ***Methods:*** Consecutive ninety-five patients with various cancers, who received both PET and BS within one month, were retrospectively analyzed. A whole-body PET (from face to upper thigh) and a standard whole body BS were performed and these images were interpreted by two experienced nuclear medicine physicians with and without patient information using monitor diagnosis. Each image interpretation was performed according to 8 separate areas (skull, vertebra, upper limbs, sternum and clavicles, scapula, ribs, pelvis, and lower limbs) using a 5-point-scale (0: definitely negative, 1: probably negative, 2: equivocal, 3: probably positive, 4: definitely positive for bone metastasis). ***Results:*** Twenty-one of 95 patients (22.1%) with 43 of 760 areas (5.7%) of bone metastases were finally confirmed. In untreated patients, 12 of 14 bone metastasis positive patients were detected by PET, while 9 of 14 were detected by BS. Three cases showed true positive in PET and false negative in BS due to osteolytic type bone metastases. In untreated cases, PET with and without clinical information showed better sensitivity than BS in patient-based diagnosis. For the purpose of treatment effect evaluation, PET showed better results because of its ability in the evaluation of rapid response of tumor cells to chemotherapy. Out of 10 cases of multiple-area metastases, 9 cases included vertebrae. There was only one solitary lesion located outside of FOV of PET scan in the femur, but with clinical information that was no problem for PET diagnosis. ***Conclusion:*** Diagnostic accuracy of bone metastasis was comparable in PET and BS in the present study. In a usual clinical condition, limited FOV (from face to upper thigh) of PET scan may not be a major drawback in the detection of bone metastases because of the relatively low risk of solitary bone metastasis in skull bone and lower limbs.

**Key words:** FDG-PET, bone scintigraphy, bone metastasis

## INTRODUCTION

THE SKELETON is one of the most common sites of distant metastasis in many cancers. Bone scan or scintigraphy (BS) using $^{99m}$Tc-methylenediphosphonate (MDP) or hydroxymethylene diphosphonate (HMDP) is considered the most sensitive method of detecting skeletal metastases, and has been used routinely in higher-risk cancer patients, especially in breast, prostate, and lung cancers, which are known for their high incidence rate of bone metastasis.[1–3] However, a move of minimalism policy in terms of prognostic values and economic restrictions has had a great influence on the use of BS.[4] BS is now used less often and is not considered routine in all cases of breast or prostate cancer, where the use of BS is now restricted to higher-risk groups, such as breast cancer in clinical stage 3 or 4 or cases with high prostate-specific antigen (PSA).[5]

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The clinical role of BS in the diagnosis of bone metastases has to be re-evaluated.

$^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an important non-invasive technique in a variety of cancers for differentiation of benign tumor from malignancy, cancer staging, detection of recurrent neoplasm, and evaluation of therapeutic effect.[1,6–9] The rationale for the use of FDG is based on the increased glucose metabolism of malignant cells, in which FDG, an analogue of glucose, is absorbed, phosphorylated, and trapped in the cytosol of the cells.[10–13] Therefore, in the detection of bone metastatic lesion, FDG-PET detects the presence of malignant cells in bone and bone marrow, not the osteoblastic response against metastastic lesions, which is the target of conventional BS. Because of the different mechanism in the detection of bone metastasis, diagnostic results of bone metastasis are supposed to be somewhat different between PET and BS imagings. A considerable number of papers comparing PET to BS in the detection of bone metastases have been published, but it is still controversial which is better.[14–19] If PET has a comparable diagnostic accuracy to that of BS, it would be better to skip BS and to perform PET only, because PET can detect not only bone metastasis but also other organ lesions. Therefore, a direct comparison of diagnostic abilities in the detection of bone metastasis of FDG-PET and BS needs to be made.

In the present study, in order to evaluate the role of FDG-PET in usual clinical conditions as a possible substitute for conventional BS in the detection of bone metastasis, we examined the diagnostic accuracy of PET and conventional BS in a variety of cancer patients and also compared the results of both modalities with and without clinical data.

## MATERIAL AND METHODS

*Subjects of study*

In this retrospective study, ninty-five patients (68 men, 27 women; age range, 2 to 84 y.o.; mean age, 63.7 ± 15.7 y.o.) with 32 hepatocellular carcinomas, 23 lung cancers, 11 biliary cancers (intra and extrahepatic cholangiocellular carcinomas, gall bladder cancers), 9 gastrointestinal cancers (esophageal, gastric and colonic cancers), 5 bone and soft tissue tumors, 4 urinal tract tumors, 4 head and neck tumors, 3 breast cancers, and 4 other tumors, who were suspected of having bone metastases, were enrolled in this study. All patients consulted or were admitted to Kyoto University Hospital from Jan. 2004 to Jun. 2004 and had undergone both whole-body FDG-PET (PET) and conventional bone scintigraphy (BS) within one month. Sixty-five patients (68%) were examined before treatment for a newly-diagnosed disease. Twenty-one cases (22%) were examined for pretreatment evaluation in post-operative follow-up or post-operative state with suspected recurrent lesion(s). Of the other 9 cases (9%), 7 were examined for post-chemotherapeutic evaluation of known bone metastases, while 2 were under chemotherapy for recurrence in non-bony lesion(s). Final diagnoses of bone metastasis were confirmed histopathologically, or by further evaluation using other imaging modalities including magnetic resonance imaging (MRI) and CT and/or by clinical follow-up. Absence of bone metastasis was also confirmed by several imaging modalities and clinical follow-up for more than one year. Patients with diabetes mellitus (treated with insulin injection or oral hypoglycemic agents) and patients whose serum glucose level just before FDG injection was more than 140 mg/d*l* were excluded from the present study. Before being enrolled in this study, each patient gave written informed consent, as required by the Kyoto University Human Study Committee.

*PET study*

$^{18}$F was produced by a 20Ne (d, alpha) $^{18}$F nuclear reaction, and $^{18}$F-FDG was synthesized by the nucleophilic substitution method using an $^{18}$F-FDG-synthesizing instrument F-100 (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan) and a cyclotron, CYPRIS-325R (Sumitomo Heavy Industries, Co. Ltd.).[20,21] All patients were examined with a high-resolution, whole-body PET scanner with an 18-ring detector arrangement (Advance, General Electric Medical Systems, Milwaukee, WI). The patients fasted for more than 4 hours before the injection of FDG. All subjects received an intravenous injection of FDG (296 ± 74 MBq), and the acquisition of whole body PET images started 50 minutes later. The patients lay supine on the PET table with the arms positioned beside their bodies. The patient was then fixed in place by wrapping a holding belt around the abdomen. Data acquisition (emission and transmission scan) was performed in two-dimensional imaging mode with septae in place. Emission images were acquired for 3 minutes per bed position and each post-emission transmission scan was obtained for 1 min per position. A whole body scan (from face to upper thigh) was performed in each patient using 5 or 6 bed positions according to the height of each patient. The data were reconstructed using the ordered subsets expectation maximization method (OSEM) using 16 subsets, 3 iterations, and 128 × 128 array size.

*Bone Scintigraphy (BS) study*

$^{99m}$Tc-hydroxymethylene diphosphonate (HMDP) was commercially available and provided by Nihon-Medi-Physics Co., Ltd. (Hyogo, Japan). A standard whole body BS (from toes to top of the head) was performed using whole-body moving camera technique (anterior and posterior) three to four hours after IV injection of 550 MBq of $^{99m}$Tc-HMDP for 15–20 min. Dual-head gamma-cameras used for BS were either HITACHI RC-2500IV (Hitachi Medical Co., Tokyo, Japan) or SIEMENS BODYSCAN (Siemens Medical Systems, Issaquah, WA). The scan speed was 15 cm/min for the former and 10 cm/

**Table 1** Patient-based diagnosis of confirmed metastatic bone lesions

| Purpose of studies | age | gender | primary tumor | past treatment for primary lesion | present treatment | confirmation of metastases by | location | PET | | BC | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | clinical information | | clinical information | |
| | | | | | | | | without | with | without | with |
| Untreated cases: 14 cases | | | | | | | | | | | |
| #1 | 50 | M | lung cancer | not treated | none | pathology | solitary | FN | FN | TP | TP |
| #2 | 80 | M | lung cancer | not treated | none | pathology | solitary | TP | TP | FN | TP |
| #3 | 48 | M | lung cancer | not treated | none | MRI | solitary | TP | TP | TP | TP |
| #4 | 74 | F | lung cancer | not treated | none | MRI | solitary | FN | FN | FN | FN |
| #5 | 65 | M | esophageal cancer | not treated | none | MRI | solitary | TP | TP | TP | TP |
| #6 | 62 | M | hypopharyngeal cancer | not treated | none | MRI | solitary | TP | TP | FN | FN |
| #7 | 73 | M | gall bladder cancer | not treated | none | clinical course | multiple | TP | TP | TP | FN |
| #8 | 2 | M | neuroblastoma | not treated | none | MRI | multiple | TP | TP | TP | TP |
| #9 | 63 | F | lung cancer | operated | none | MRI | solitary | TP | TP | TP | TP |
| #10 | 64 | F | lung cancer | operated | none | MRI | multiple | TP | TP | TP | TP |
| #11 | 56 | F | breast cancer | operated | none | CT | solitary | TP | TP | TP | TP |
| #12 | 42 | F | breast cancer | operated | none | MRI | solitary | TP | TP | TP | FN |
| #13 | 61 | F | esophageal cancer | operated | none | MRI | solitary | TP | TP | FN | TP |
| #14 | 56 | F | renal cell carcinoma | operated | none | pathology | multiple | TP | TP | FN | FN |
| | | | | | | | | 12/14 | 12/14 | 9/14 | 9/14 |
| Evaluation of treatment effect (during treatment): 7 cases | | | | | | | | | | | |
| #15 | 68 | M | lung cancer | not operated | chemotherapy | clinical course | multiple | TP | TP | TP | TP |
| #16 | 71 | F | lung cancer | not operated | chemotherapy | clinical course | multiple | N | TP | TP | TP |
| #17 | 50 | F | breast cancer | operated | chemotherapy | MRI | multiple | N | N | TP | N |
| #18 | 70 | M | prostate cancer | operated | chemotherapy | MRI | multiple | N | N | TP | TP |
| #19 | 17 | F | Ewing sarcoma | not operated | chemotherapy | MRI | multiple | N | TP | TP | TP |
| #20 | 20 | M | Ewing sarcoma | not operated | chemotherapy | MRI | solitary | TP | TP | N | TP |
| #21 | 59 | M | rectal cancer | operated | radiation | CT | multiple | TP | TP | TP | TP |

TP: true positive, FN: false negative, N: negative (probably therapeutic effect)

min for the latter, and the Matrix size was 256 × 1024 pixels for both. BS images were printed out in planar view with a pair of appropriate window levels (dark and bright). When a positive finding was suspected, oblique view or SPECT images (axial and coronal) were obtained additionally using HITACHI RC-2500IV, and then printed out in films.

*Image Analysis*

PET images were interpreted first by two independent experienced nuclear medicine physicians without any available clinical information, previous PET scan imaging or any correlative conventional imaging as an anatomic guidance. Whole-body was separated into eight areas (skull, vertebra, upper limbs, sternum and clavicles, scapula, ribs, pelvis, and lower limbs) and the presence or non-presence of FDG was analyzed in each area (even if multiple metastatic foci were located only in vertebra, it was defined as solitary area bone metastasis). Next, the two physicians had a discussion and made a final diagnosis on each area in a 5-point-scale, as follows; 0: definitely negative, 1: probably negative, 2: equivocal, 3: probably positive, and 4: definitely positive for bone metastasis. Then, two physicians were shown all available clinical information, previous PET scan imaging and correlative conventional imaging except for bone scintigraphy and then made a final diagnosis on each area.

BS images were interpreted first by two independent experienced nuclear medicine physicians without any available clinical or other information in the same manner as that in PET images, using the 5-point-scale. Then, the two physicians were shown all available clinical information, previous BS scan imaging and correlative conventional imaging except for PET images and then made a final diagnosis on each area.

Score 0–2 in the 5-point-scale for confirmed bone metastases was defined as false negative, while score 3–4 in the 5-point-scale for benign bone lesions was defined as false positive.

Statistical analysis was performed using McNemar's test. A value of $p < 0.05$ was considered statistically significant.

## RESULTS

*—Detection of bone metastases—*

Table 1 summarizes the characteristics of patients with malignant bone lesions in the present study. Twenty-one of 95 patients (22.1%) with 43 of 760 areas (5.7%) of bone metastases were finally confirmed. Confirmation of bone metastases was performed by pathological examination (n = 3), MRI (n = 13), CT (n = 2), and clinical follow-up

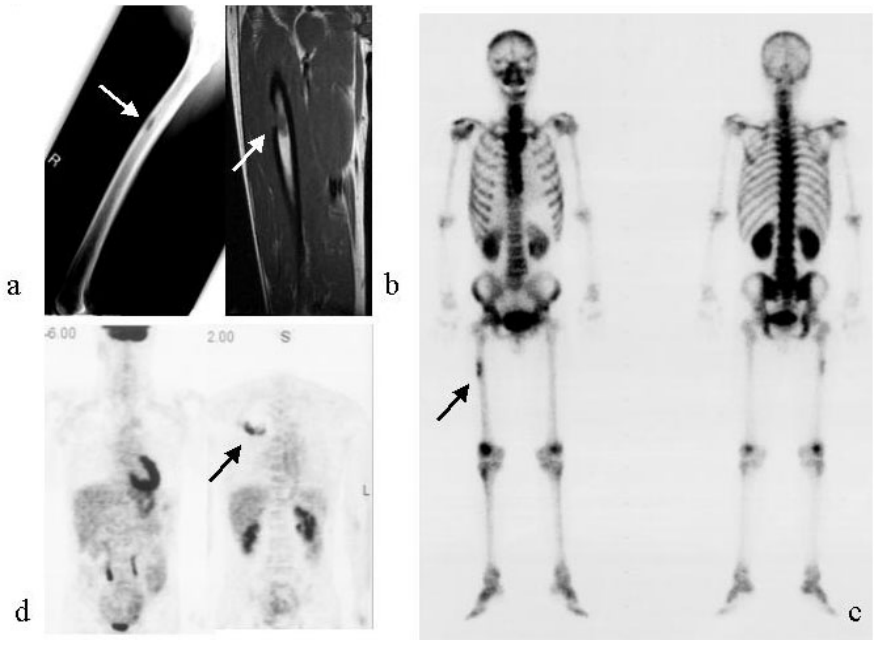


**Fig. 1** A case of bone metastasis located in the middle of femur (patient #1). Fifty-year-old male patient with lung cancer. At first, the lesion was suspected to be a primary femoral bone tumor. Then the diagnosis was changed to metastatic tumor based on the result of biopsy, which showed a poorly-differentiated carcinoma. Plain X-ray and MRI (T1WI) showed an excentric bone tumor in the right femoral diaphysis (a, b). BS showed high accumulation of $^{99m}$Tc-HMDP in the corresponding area (c). FDG-PET was performed to detect the primary tumor, and therefore, FOV of PET scan did not include full-length of the femur. Whole-body scan from inguinal area to face showed high accumulation of FDG in the right upper lobe which was diagnosed as lung cancer later (d).

(n = 3). Primary malignancies for bone metastasis were lung cancers (n = 8), bone & soft tissue tumors (n = 2), breast cancers (n = 3), esophageal cancers (n = 2), and others (gall bladder cancer, hypopharyngeal cancer, renal cell carcinoma, rectal cancer, prostate cancer and neuroblastoma, each n = 1). In eight cases, the primary tumor itself was not treated and distant metastases including bone metastases were detected. In 6 cases, the primary tumor was resected and in the follow-up period newly-developed bone metastases were detected. In 7 cases, metastatic bone lesions with and without primary lesions were under treatment (chemotherapy: n = 6, local radiation: n = 1) and therapeutic effect was diagnosed by PET and BS.

In the untreated cases with patient-based diagnosis, PET with and without clinical information showed better sensitivity than BS (not significant). One case (patient #1: lung cancer) with solitary bone metastasis located in the middle of femur, outside of FOV of PET scan, showed false negative in PET and true positive in BS (Fig. 1). In this case, however, the purpose of the PET study was the detection of the primary site of this already-known metastatic bone lesion in the femur. This lesion was at first believed to be a primary bone tumor, and then biopsy revealed metastatic tumor with poorly differentiated adenocarcinoma origin. Therefore, in the present study, this case was counted as false negative for PET, but negative result in PET was no problem clinically. Three cases (patient #2, 6, 14) showed true positive in PET and false negative in BS due to osteolytic type bone metastases. In patient #2, BS showed false negative, but turned to be true positive with clinical information (Fig. 2). This was the only case with a so-called "pure osteolytic" bone metastasis in the present study. In patient #4, PET and BS were negative for bone metastasis, but 5 months later the patient developed lower half body paralysis by bone metastasis in the thoracic vertebrae. Thus, in the untreated cases, PET with and without clinical information showed better sensitivity than BS in patient-based diagnosis.

In the 7 cases of therapeutic effect evaluation, PET showed positive in about half of the cases, while BS showed positive in most of the cases (Fig. 3). These PET-negative/BS-positive results were clinically diagnosed as typical post-chemotherapeutic state with flare phenomenon in BS according to the clinical information (improved symptom or decreased tumor markers, etc). Therefore, we believed that PET negative results were not false negative, but true negative. Thus, for the purpose of treatment effect evaluation, PET showed better results because of its ability in the evaluation of rapid response of

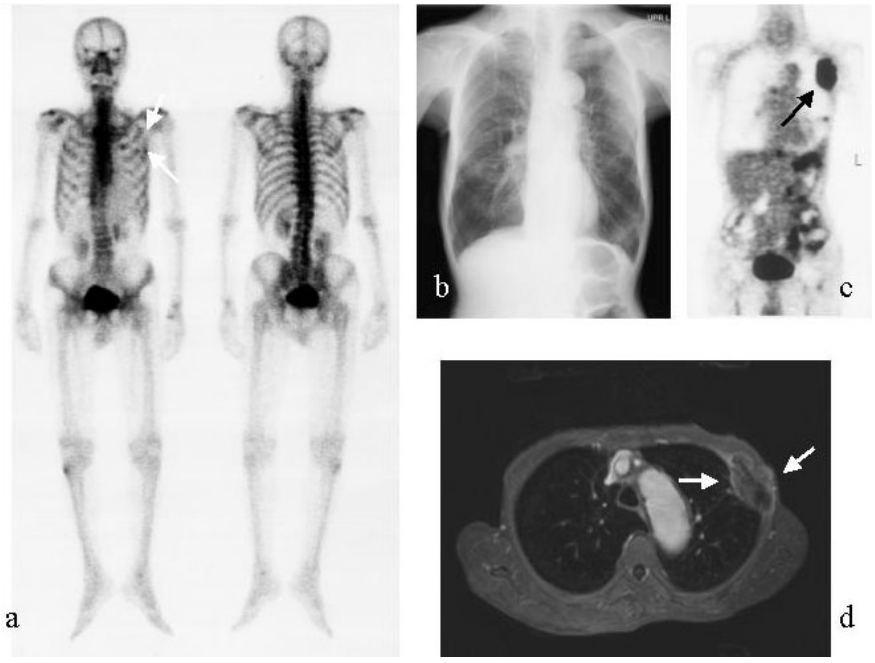


**Fig. 2** A case of osteolytic-type bone metastasis (patient #2). Eighty-year-old male patient with a chest wall tumor. BS showed heterogeneous uptake in bilateral ribs (a). BS diagnosis without clinical information could not detect osteolytic lesion in the left upper rib, whereas BS diagnosis with clinical information was able to detect the osteolysis. Chest X-ray revealed chest wall tumor, but no osteolytic lesion (b). FDG-PET showed high accumulation of FDG in the left upper chest wall (c). MRI: Gd enhanced 3D-VIBE (fat-suppressed 3D gradient-echo technique with a volumetric interpolated breath-hold examination). Gd enhanced MRI showed poorly enhanced left rib tumor surrounded by well enhanced capsule (d). Further evaluation including biopsy and immunohistochemical analysis suggested that a primary bone tumor was negative and metastasis from a poorly differentiated lung cancer was highly suspected. This patient was treated by localized radiotherapy against the chest wall tumor; however, he died of multiple mediastinal lymph node, bone and liver metastases. According to the clinical course, the final diagnosis of this patient was established as lung cancer.

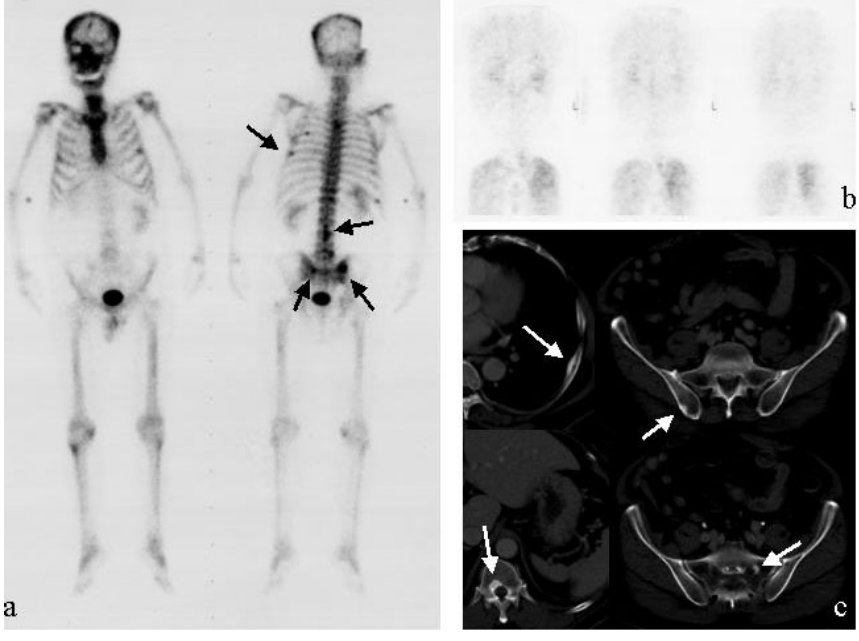


**Fig. 3** A case of chemotherapeutic effect evaluation (patient #18). Seventy-year-old male patient with prostate cancer. In the follow-up period after operation of the primary lesion, he was diagnosed as having multiple bone metastases (PET and BS showed positive before treatment), and chemotherapy was performed. BS and FDG-PET were performed to evaluate the therapeutic effect (a, b). BS showed multiple uptake in bilateral ribs, lower vertebrae, sacrum and ilium (a). FDG-PET was performed, but whole-body scan showed no uptake of FDG (b). CT scan showed multiple increased densities in the corresponding lesions (c). Clinical data supported the results of FDG-PET as therapeutic effect.

**Table 2** Area-based diagnosis of confirmed metastatic bone lesions. False negative/negative findings by PET and BS

| | | PET | | BS | |
|---|---|---|---|---|---|
| | | clinical information | | clinical information | |
| | | without | with | without | with |
| Untreated cases: 14 cases | | | | | |
| | | False negative areas | | | |
| Total | n = 24 | 11/24 | 6/24 | 10/24 | 10/24 |
| skull | n = 3 | 3* | 2* | 2 | 2 |
| vertebra | n = 9 | 3 | 2 | 5 | 5 |
| upper limb | n = 1 | 0 | 0 | 0 | 0 |
| sternum/clavicles | n = 2 | 1 | 0 | 1 | 2 |
| scapula | n = 0 | 0 | 0 | 0 | 0 |
| ribs | n = 3 | 2 | 0 | 1 | 1 |
| pelvis | n = 2 | 0 | 0 | 1 | 0 |
| lower limbs | n = 4 | 2** | 2** | 0 | 0 |
| Evaluation of treatment effect (during treatment): 7 cases | | | | | |
| | | Negative areas | | | |
| Total | n = 19 | 15/19 | 13/19 | 6/19 | 6/19 |
| skull | n = 2 | 2 | 2 | 0 | 0 |
| vertebra | n = 6 | 4 | 3 | 2 | 2 |
| upper limb | n = 0 | 0 | 0 | 0 | 0 |
| sternum/clavicles | n = 1 | 1 | 1 | 1 | 1 |
| scapula | n = 0 | 0 | 0 | 0 | 0 |
| ribs | n = 3 | 3 | 2 | 1 | 1 |
| pelvis | n = 5 | 5 | 5 | 1 | 2 |
| lower limbs | n = 2 | 0 | 0 | 1 | 0 |

*: including one false negative lesion out of scan range of PET
**: all of them were false negative lesions out of scan range of PET

**Table 3** False positive findings in PET and bone scan

| | PET | | Bone scan | |
|---|---|---|---|---|
| Clinical information | without | with | without | with |
| Patient-basis | 18/74 cases<br>24.0% | 1/74 case<br>1.3% | 2/74 cases<br>2.6% | 1/74 case<br>1.3% |
| Area-basis | 24/592 areas<br>4.1% | 1/592 area<br>0.2% | 2/592 areas<br>0.3% | 1/592 area<br>0.2% |
| detailed location | | | | |
| skull | 0 case | 0 case | 0 case | 0 case |
| vertebra | 13 cases* | 1 case* | 0 case | 1 case* |
| upper limbs | 1 case | 0 case | 0 case | 0 case |
| sternum/clavicles | 0 case | 0 case | 0 case | 0 case |
| scapula | 1 case | 0 case | 0 case | 0 case |
| ribs | 5 cases | 0 case | 1 case | 0 case |
| pelvis | 4 cases | 0 case | 1 case | 0 case |
| lower limbs | 0 case | 0 case | 0 case | 0 case |

* false positive results in PET and BS were observed in the same patients

tumor cells against chemotherapy.

Table 2 summarizes the characteristics of area-based diagnostic results of malignant bone lesions in the present study. Solitary-area bone metastases were found in 11 patients, while 10 patients showed multiple-area bone metastases. Solitary-area metastases were detected mainly in vertebrae (n = 6), followed by lower limbs (n = 3), ribs (n = 1), pelvis (n = 1). Out of 10 cases of multiple-area metastases, 9 cases included vertebrae. There were only three lesions in two patients located outside of FOV in

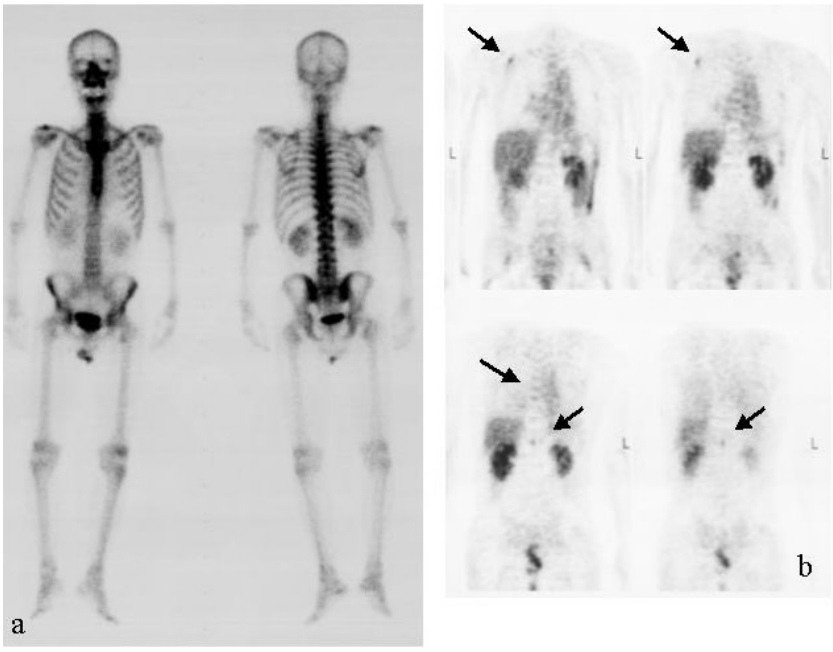


**Fig. 4** A false positive case of FDG-PET. Sixty-one-year-old male patient with hepatocellular carcinoma, post-treatment. In the follow-up period after transarterial-embolization (TAE) of the primary lesion, he received BS and FDG-PET without any evident sign of recurrence (a, b). BS showed a normal uptake pattern of $^{99m}$Tc-HMDP, but whole-body PET scan showed increased uptake of FDG in right chest wall and vertebrae (b). Multiple bone metastases were diagnosed by PET without clinical information, whereas PET diagnosis with clinical information did not suspect these lesions as bone metastases because of low tumor marker value. Follow-up clinical information confirmed that these were not metastatic lesions.

PET scan. Two lesions in one patient were located in the top of skull bone and in the middle of the femur, but more bone metastatic lesions were detected in this case (patient #10: lung cancer). The other solitary lesion located in the femur (patient #1) was outside of FOV of PET scan, but clinically represented no problem, as mentioned above.

In the untreated cases, total 24 areas in 14 patients were diagnosed as bone metastases. Vertebra (n = 9) was the most frequent invaded area, followed by lower limbs (n = 4), skull bone (n = 3), and ribs (n = 3). PET with clinical information showed the most sensitive detection rate in the present study. Excluding the lesions outside of FOV of PET scan (mentioned above), only 1 area was false negative in PET with clinical information. Most of the false negative lesions in BS were osteolytic-type bone metastases in vertebral bones. (In most of these cases, however, BS was not false negative in patient-based diagnosis, because BS detected osteoplastic type bone metastasis in other areas.)

In the cases of treatment effect evaluation, vertebrae (n = 6) was the most frequently invaded area, followed by pelvic bone (n = 5), and ribs (n = 3). There was no evident difference between PET and BS.

*—False positive results—*

Table 3 summarizes the diagnostic results of PET and BS in patient-based and area-based diagnoses of non-malignant bone lesions in the present study. Total 74 patients with 592 areas were diagnosed as true negative for bone metastasis by other imaging modalities, including MRI, and clinical follow-up for 12 months or more. PET study with clinical information, BS with and without clinical information showed accurate diagnosis with specificity of 97% or more in patient-basis and 99.7% or more in area-basis, while PET without clinical information showed relatively low specificity of 76% in patient-basis ($p < 0.05$) and 95.9% in area-basis. False positive areas in the PET study without clinical information were vertebra (n = 13), followed by ribs (n = 5), and pelvic bones (n = 4), where moderate uptake in bone and surrounding area was observed in PET scan due to benign lesions (mainly deformity due to aging or bruise). In most of these cases, clinical information had an important role in reducing the 5-point-scale. Figure 4 showed a typical false positive case of PET without clinical information.

In untreated 14 cases with confirmed bone metastases, where there were total 88 true negative areas, PET without clinical information also showed 9 false positive areas (over-diagnosis). On the other hand, PET study with clinical information and BS with and without clinical information showed no false positive area.

## DISCUSSION

FDG-PET has been described as an important method for preoperative staging and detection of recurrence in a variety of malignant diseases.[1,6–9] In addition, FDG-PET has been known as a useful method in detecting bone metastasis in pre-operative patients or in post-operative follow-up patients.[1,5] On the other hand, conventional BS is an established imaging modality as a first choice for detecting bone metastasis, but also known for its drawback in detecting pure osteolytic bone metastases.[1,4,19] In the present study, the patient-based results showed that detectability of bone metastasis was comparable in PET and BS. In untreated patients, 12 of 14 bone metastasis-positive patients were detected by PET, while 9 of 14 were detected by BS. Area-based diagnosis was also comparable in PET and BS. Osteolytic bone metastases were difficult to detect in BS, but easy to detect in PET scan in the present study, which was similar to previous studies.[1,4,16,17,19] However, the number of osteolytic lesions were limited in the present study. On the other hand, the number of osteoblastic bone metastases was also small in the present study, and therefore, there was no false negative in PET/true positive in BS lesion, except for the patients with lesions out of FOV in PET.

Direct comparisons between BS and PET have been already reported in a variety of cancers.[14–19] In breast cancer patients with known skeletal metastases, Cook et al. showed that FDG-PET detected more lesions than BS except in a subgroup of patients with osteoblastic metastases.[22] On the other hand, Uematsu et al. and Abe et al. showed that BS detected more osteoblastic metastatic lesions than PET did.[16,19] Eubank et al. in their review article stated that these data clearly show the complementary nature of BS and FDG-PET in the evaluation of skeletal metastases in breast cancer patients.[1] They suggest that FDG-PET and BS should not be considered substitutes for each other for bone metastasis staging in breast cancer. In prostate cancers, it is already established that FDG-PET is less sensitive than BS.[5] Shreve et al. reported that FDG identified only 131 of 202 untreated metastases in 22 patients with a sensitivity of 65%.[23] Morris et al. showed in their report with 134 bone metastases that BS was more sensitive (94%) than FDG (77%).[24] FDG appears to be less useful due to osteoblastic-type metastases in prostate cancers. In lung cancers, FDG appears to be more useful in the detection of bone metastases.[5] Several comparative studies revealed that PET showed better accuracy in detecting bone metastases than BS did.[25,26] These data imply that in detection of bone metastases diagnostic results of PET and BS would be different according to the type of primary cancers.

In the present study, hepatobiliary cancers were the most frequent, with only a limited number of breast and prostate cancers enrolled. Lung and prostate cancers are known for their high incidence rate of bone metastasis (up to 20–40%) in the preoperative staging, whereas the incidence ratio of hepatobiliary cancers is less than 3% in the preoperative staging.[26–28] These facts suggest that our patient population may have influenced the diagnostic accuracy of PET and BS. Osteoblastic bone lesions are quite common in breast and prostate cancers, although osteolytic lesions are quite common in hepatobiliary cancers.[1,5,29] Osteolytic lesions confined to the marrow cavity are difficult to detect on BS because of a lack of sufficient osteoblastic response.[30] Therefore, pure osteolytic bone metastasis is supposed to be a good indication for FDG-PET. In the present study, there was only one lesion with "pure osteolytic" change (patient #2). It should be noted that BS without clinical information missed the lesion, while BS with clinical information clearly detected it. Thus, we can conclude in the present study that the diagnostic accuracy of bone metastases was comparable in PET and BS, and that PET could be a substitute for BS in the evaluation of bone metastasis, except for high risk cases with breast and prostate cancers, which are known for their high incidence rate of osteoblastic bone metastasis.

BS is known for its high false positive rate because benign bone lesions can also show reactive change with osteoblastic change, particularly in the elderly, with the most common causes of degenerative disease, fractures, and inflammatory changes.[5] Such problems may arise much more frequently when reading test without clinical information is performed. Our data, however, revealed that false positive results of BS were low, probably because of the high diagnostic skill of the experienced physicians in the present study. On the other hand, PET without clinical information showed a relatively high incidence rate of false positive. In addition, it was implied that knowledge of the clinical information could reduce the rate of false positive results in PET study. This result is compatible with a previous study.[31] Nakamoto et al. mentioned that in their study of 403 patients with various cancers, PET consistently revealed more metastatic foci than did the bone scan on a lesion basis, but also that PET yielded more false positive lesions in a specific case. FDG-PET sometimes shows false positive in vertebrae because of the reactive hyper glucose metabolism in bone marrow due to chemotherapeutic reaction or therapy using bone marrow stimulating factors.[31] Knowledge of this clinical information is mandatory for accurate PET diagnosis.

As for the treatment effect on bone metastases, BS is not supposed to be useful in monitoring treatment in malignancy due to a flare response, typically observed in the first few months after successful treatment.[22,33] On the other hand, PET can evaluate the true representation of pathologic response of tumor tissue to treatment by examining the change of glucose metabolism. Stafford et al. showed that change in FDG uptake correlated well with clinical assessment of response and changes in tumor

marker levels.[34] In the 7 cases of therapeutic effect evaluation in the present study, BS showed positive in most of the cases, whereas PET showed negative in about half of the cases. According to the clinical information, PET negative results were clinically assumed to be true negative due to the chemotherapeutic effect. Therefore, PET was supposed to be a better imaging modality than BS, because of its ability in the evaluation of rapid response of tumor cells against chemotherapy.

Limited field of view (FOV) in PET scan should be discussed. Conventional whole-body PET does not usually include the lower extremities or top of the skull bone, mainly because of relatively slow output of the PET machine. In cancer patient management, the number of bone metastases is one of the most important points for the choice of treatment, and choice of treatment method including extra-corporeal radiation therapy or systemic chemotherapy depends on the number of bone metastases. Therefore, presence of solitary bone metastasis in the top of the skull bone or in the lower extremities would be clinically critical because of the difference in FOV between PET and BS. In the present study, there were 11 cases with solitary-area bone metastasis, while there were only three lesions in two patients located outside of FOV in PET scan. However, although the diagnosis of FDG-PET was negative for those peripheral bone metastases, it was clinically no problem, as mentioned in the results. Thus, there was no problematic case located outside of PET FOV in the present study.

Corcoran et al. reported in their study of more than one thousand consecutive patients with extraskeletal primary malignancies that solitary metastatic lesions were detected only in 58 cases (4.3%).[34] Vertebrae and pelvic bones were the most common sites of spread (2.9%), followed by long bones (0.9%), skull bone (0.3%), and ribs & clavicles (0.1%). In their study, solitary peripheral bone metastasis accounted for 7% of metastatic cases, which means only 0.6% in total cases. According to these data, because of this extremely low incidence rate of solitary peripheral bone metastasis, limited FOV in PET scan may be clinically no problem in cancer patient management. Thus, limited FOV in PET scan may not be a great drawback in the detection of bone metastatic lesion(s).

On the other hand, patients with diabetes mellitus and patients whose serum glucose level just before $^{18}$F-FDG injection were more than 140 mg/d*l* were excluded in the present study. Glucose metabolic disorders are not supposed to affect BS results, while in the case of patients with diabetes mellitus or high serum glucose level, false negative lesions might happen in FDG-PET. We need to be careful about this disadvantage of FDG-PET.

## CONCLUSIONS

Diagnostic accuracy of bone metastases was comparable in PET and BS in the present study. PET could be a substitute for BS in the evaluation of bone metastasis, except for high risk cases with breast and prostate cancers or diabetic patients. In a usual clinical condition, limited FOV (from face to upper thigh) of PET scan may not be a major drawback in the detection of bone metastases because of the relatively low risk of solitary bone metastasis in skull bone and lower limbs.

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