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ORIGINAL REPORT

Integrated Positron Emission Tomography/Computed Tomography May Render Bone Scintigraphy Unnecessary to Investigate Suspected Metastatic Breast Cancer

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ABSTRACT

Purpose
Although the accurate detection of osseous metastases in the evaluation of patients with suspected metastatic breast cancer (MBC) has significant prognostic and therapeutic implications, the ideal diagnostic approach is uncertain. In this retrospective, single-institution study, we compare the diagnostic performance of integrated positron emission tomography/computed tomography (PET/CT) and bone scintigraphy (BSc) in women with suspected MBC.

Patients and Methods
Women with suspected MBC evaluated with PET/CT and BSc (within 30 days) between January 1, 2003 and June 30, 2008, were identified through institutional databases. Electronic medical records were reviewed, and radiology reports were classified as positive/negative/equivocal for osseous metastases. A nuclear medicine radiologist (blinded to correlative and clinical end points) reviewed all equivocal PET/CT and BSc images and reclassified some reports. Final PET/CT and BSc classifications were compared. Baseline patient/tumor characteristics and bone pathology were recorded and compared to the final imaging results.

Results
We identified 163 women who had a median age of 52 years (range, 30 to 90 years); 32% had locally advanced breast cancer, 42% had been diagnosed with breast cancer less than 12 weeks before identification. Twenty studies were originally deemed equivocal (five with PET/CT, and 15 with BSc), and 13 (65%) of these studies were reclassified after radiology review. Overall, PET/CT and BSc were highly concordant for reporting osseous metastases with 132 paired studies (81%); 32 (20%) were positive, and 100 (61%) were negative. Thirty-one occurrences (19%) were discordant. Twelve of these (39%) had pathology confirming osseous metastases: nine (of 18) were PET/CT positive and BSc negative; one (of three) was PET/CT positive and BSc equivocal; and two (of two) were PET/CT equivocal and BSc negative.

Conclusion
This study supports the use of PET/CT in detecting osseous metastases for suspected MBC. Whether PET/CT may supplant BSc in this setting is unknown.

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INTRODUCTION

Almost 5% of the 200,000 incident breast cancers in the United States each year are metastatic, and approximately one third of women with early-stage disease ultimately experience a distant recurrence.[1] When metastatic breast cancer (MBC) is diagnosed, bone is not only the most common site but also the first site of metastases in up to 50% of patients.[2] The detection of osseous metastases has significant prognostic and therapeutic implications. However, a simple, accurate, noninvasive paradigm for the diagnosis of osseous metastases in women undergoing evaluation for suspected MBC has not yet been identified. The recent integration of positron emission tomography (PET) with computed tomography (CT) permits anatomic and metabolic assessment in a single test. It is possible that an efficient strategy, such as integrated PET/CT, may supplant historic (and often multitest) strategies for the diagnosis of suspected MBC to bone.

Radionuclide bone scan (or skeletal scintigraphy, BSc) is a commonly employed functional imaging modality for detecting bone metastases. This technique utilizes technetium-99m methylene diphosphonate (Tc-99m MDP), a

radiopharmaceutical that accumulates in areas of osteoblastic activity and therefore provides information about host response to tumor (ie, indirect information about tumor activity).[2] However, because approximately one half of breast cancer bone metastases are predominantly osteolytic, there is significant potential for false negative results.[2] False negative results can also occur with metastases to poorly vascularized areas or indolent tumor growth.[2] Consequently, the reported sensitivity of BSc is highly variable (62% to 100%).[2] BSc can also be limited by false-positive results with trauma and/or inflammation, resulting in variable specificity of 78% to 100%.[2]

PET, like BSc, is a functional imaging technique, but it uses 2-deoxy-2-[^{18}F] fluorodeoxyglucose (FDG) to assess cellular metabolism. Because cancers typically demonstrate greater than physiologic metabolic activity with high glucose uptake, PET offers direct information about tumor activity. False positive results can occur with infection, inflammation, trauma, and/or acute fractures, whereas false negative results can occur with small lesions. PET, like BSc, has variable sensitivity (57% to 100%) but superior specificity (96% to 100%) for detecting breast cancer metastases to bone.[2,3]

The variable sensitivity of PET has been largely ameliorated by the incorporation of anatomic imaging with CT. Because integrated PET/CT provides both functional and anatomic information, it may be superior at detecting bone metastases than conventional imaging modalities.[4] Furthermore, because PET/CT also detects nonosseous metastases, the need for additional visceral imaging is often obviated.

It is unknown whether the use of both PET/CT and BSc are redundant in the extent of disease evaluation for women with suspected MBC. However, PET/CT alone could be more efficient than multiple conventional studies, even in the palliative setting. To compare the diagnostic performance of integrated PET/CT with BSc, we conducted a retrospective, single-institution study of women undergoing evaluation for suspected MBC with both modalities at Memorial Sloan-Kettering Cancer Center (MSKCC), and we compared reports with bone biopsy/fine-needle aspiration (FNA) results when available.

PATIENTS AND METHODS

At MSKCC, integrated PET/CT replaced conventional PET in 2002. In this study, institutional databases were screened to identify all women undergoing evaluation for suspected MBC with integrated PET/CT and BSc between January 1, 2003 and June 30, 2008. Women with PET/CT and BSc completed within a 30-day period were included. Women with a prior history of MBC or an active second malignancy were excluded.

PET/CT images from the mid-skull to the upper thighs were obtained 60 minutes after administration of 15 mCi of FDG on one of four hybrid PET/CT systems. All patients had blood glucose less than 200 mg/dL at time of injection and were given oral contrast. BSc images were obtained with whole-body planar imaging performed by a dual-headed gamma camera, with spot views of the head and chest, at 2 to 4 hours after administration of 25 mCi Tc-99m MDP, per standard institutional policy.

Electronic BSc and PET/CT reports were reviewed by a clinical investigator and were classified as positive, negative, or equivocal for the presence of osseous metastases. All equivocal reports were reviewed by two additional clinical investigators, and consensus was reached regarding the classification. To reflect real-world practice, in which treating physicians frequently ask radiologists to re-review images when a MBC diagnosis is uncertain, the PET/CT and BSc images of all patients with persistently equivocal reports were reviewed by a nuclear medicine radiologist (J.F.) who was blinded to all radiology reports and clinical notes. PET/CT and BSc results were reclassified as appropriate, and all paired study results were compared.

Patient and tumor characteristics, including the clinical indication for PET/CT and BSc evaluation when available, were recorded from electronic medical records. Results of all bone biopsy and FNA procedures completed within 30 days of PET/CT or BSc were recorded. For patients with discordant or persistently equivocal results who did not undergo bone biopsy or FNA, reports were classified as follows. Clinical notes were reviewed by the unblinded clinician from the time of the PET/CT and BSc to the present (June 30, 2009). Correlative imaging (including x-ray, CT, and magnetic resonance imaging) studies completed within 30 days of PET/CT or BSc were reviewed by an unblinded radiologist (J.F.). A consensus between investigators was then reached, and reports were reclassified as indicated.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients (N = 163) No.	%
Age, years		
Median	52	
Range	30-90	
Estrogen receptor status		
Positive	89	55
Negative	69	42
Unknown	5	3
Progesterone receptor status		
Positive	66	41
Negative	89	55
Unknown	8	5
HER2 status*		
Positive	39	24
Negative	92	56
Unknown	32	20
Stages I to III breast cancer diagnosed > 12 weeks prior to PET/CT or BSc[5]	95	58

Abbreviations: HER2, human epidermal growth factor receptor 2; PET/CT, integrated positron emission tomography/computed tomography; BSc, bone scintigraphy.

*HER2-positive status was defined as 3+ by immunohistochemistry and/or ≥ 2 (HER2 to chromosome 17 centromere signals) by fluorescent in situ hybridization.

RESULTS

The median age of the 163 eligible patients was 52 years (range, 30 to 90 years). Baseline characteristics are outlined in Table 1. Twenty patients had equivocal studies (five with PET/CT, and 15 with BSc) after consensus review by three clinical investigators. After additional radiology review, 13 of the 20 equivocal reports were reclassified (Fig 1). The final report classifications are shown in Table 2.

Overall, PET/CT and BSc demonstrated a high degree of concordance (81%); 32 studies (20%) and 100 studies (61%) were reported as positive and negative for osseous metastases, respectively (Table 2). Of the patients with concordant positive results, 14 underwent bone biopsy or FNA within 30 days, and one underwent bone biopsy or FNA within 75 days of PET/CT or BSc, confirming osseous metastases in 14 patients (44%). In addition, 17 patients (53%) had at least one subsequent imaging study consistent with osseous metastases. These 31 patients were all treated clinically as having bone metastases. One patient, with biopsy-proven liver metastases at the time of concordant

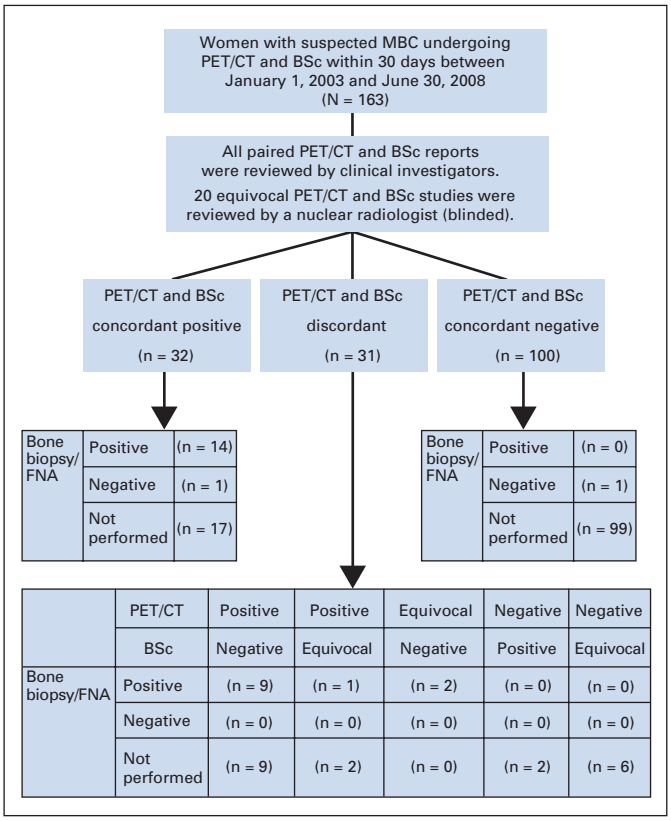

Fig 1. Study flow diagram. MBC, metastatic breast cancer; PET/CT, integrated positron emission tomography/computed tomography; BSc, bone scintigraphy; FNA, fine-needle aspiration.

positive PET/CT and BSc (sacral lesion), received a single dose of zoledronic acid; repeat BSc 4 months later showed no evidence of osseous metastases, and bisphosphonate therapy was stopped, with no additional suggestion of bone metastases on multiple subsequent imaging studies. She is alive with MBC 20 months after concordant positive PET/CT and BSc. Overall, at a median follow-up of 39 months (range, 4 to 77 months), 13 (41%) from this group have died as a result of MBC.

As outlined in Table 3, the most common indications for suspected MBC evaluation in this cohort were suspicious symptoms (84%), suspicious clinical exam (68%), or abnormal findings on other radiology modalities (58%). Among the 53 patients with PET/CT positive for bone metastases, 33 (62%) had evidence of nonosseous metastases. Of these 33 patients, 17 (52%) also had positive BSc, two (6%) had equivocal BSc, and 14 (42%) had negative BSc for osseous metastases.

Table 2. PET/CT and BSc Concordance for Women Undergoing Evaluation for Suspected MBC: Final Results After Clinical and Radiology Review

	No. of Patients by PET/CT Result (N = 163)		
BSc Result	Positive	Equivocal	Negative
Positive	32	0	2
Equivocal	3	0	6
Negative	18	2	100

Abbreviations: PET/CT, integrated positron emission tomography/computed tomography; BSc, bone scintigraphy; MBC, metastatic breast cancer.

Table 3. Indication for PET/CT and BSc Imaging in Women Undergoing Evaluation for Suspected Metastatic Breast Cancer

	Patients (N = 163)	
Indication	No.	%
Symptoms	137	84
Suspicious clinical exam	111	68
Locoregional or supraclavicular clinical findings	102	63
Abnormal radiology	94	58
Locally advanced breast cancer	52	32
Abnormal laboratory test	85	52
Elevated tumor markers*	44	27
Abnormal liver enzymes/function test†	32	20
Elevated alkaline phosphatase	22	14
Abnormal complete blood count	13	8
Indication not determined	8	5

Abbreviations: PET/CT, integrated positron emission tomography/computed tomography; BSc, bone scintigraphy.
*Tumor markers: carcinoembryonic antigen, CA 15-3, or CA-125.
†AST, ALT, lactate dehydrogenase, total/unconjugated/conjugated bilirubin, or albumin.

PET/CT Positive, BSc Negative

Eighteen (58%) of the 31 discordant occurrences had a positive PET/CT and a negative BSc (Table 2). Of these, eight underwent bone biopsy or FNA within 30 days, and one underwent biopsy 2 months after PET/CT and BSc. All nine reports confirmed breast metastases to bone (Figs 1 and 2). For the nine patients who did not undergo bone biopsy/FNA, six had clinical or radiographic evidence of MBC to bone, and three did not. Of the three without supporting evidence of metastases, one is alive 60 months later with no evidence of bone metastases; one died as a result of MBC 16 months later with no evidence of osseous metastases; and one had CT and magnetic resonance imaging evidence of MBC to bone 13 months later and died shortly thereafter.

PET/CT Positive, BSc Equivocal

Of the three patients with positive PET/CT and equivocal BSc, one underwent bone biopsy 34 days after the PET/CT, and osseous metastases were confirmed (Fig 1). One patient had correlative clinical and radiographic data supporting a diagnosis of MBC to bone; and one had no pathology or clinical/radiographic correlates.

PET/CT Equivocal, BSc Negative

Of the two patients with equivocal PET/CT and negative BSc, both (100%) underwent bone biopsy/FNA. Both had osseous metastases.

PET/CT Negative, BSc Positive

Neither of the two patients with negative PET/CT and positive BSc underwent bone biopsy. Both had locally advanced breast cancer with no definitive clinical or radiographic evidence of MBC. Both women were treated with preoperative chemotherapy and definitive locoregional therapy. One of these women had invasive lobular carcinoma and underwent repeat PET/CT and BSc 5 months later, with no evidence of osseous metastases by either modality. However, a dedicated CT scan at that time showed multiple sclerotic bony lesions consistent with healing osseous metastases that were not biopsied. She was treated

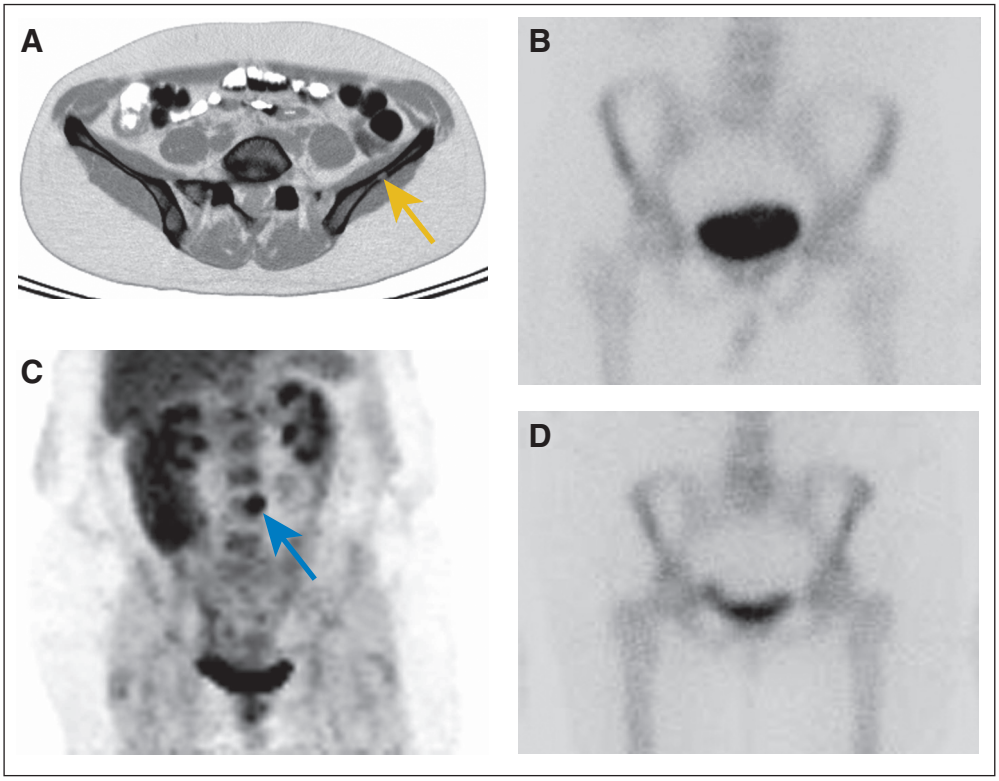

Fig 2. Example of discordant positron emission tomography (PET)/computed tomography (CT) and bone scintigraphy results. A 45-year-old woman with biopsy-proven left iliac osseous metastasis detected on (A) axial PET/CT image (gold arrow), but (B) not bone scintigraphy. A 58-year-old woman with biopsy-proven metastatic breast cancer to (C) L4 on coronal PET image (blue arrow), but (D) not bone scintigraphy.

empirically with palliative therapy, experienced clear disease progression 4 months later, and ultimately died as a result of MBC-related complications 6 months thereafter. The other patient had an equivocal single calvarium lesion on BSc but not on PET/CT at baseline that was unchanged by both modalities 14 months later and was not biopsied; however, at 25 months, lymph node metastases were proven by biopsy.

PET/CT Negative, BSc Equivocal

None of the six patients with negative PET/CT and equivocal BSc underwent bone biopsy/FNA. On review of the correlative clinical data and imaging, none of these patients had clinical or radiologic evidence of osseous metastases. Hence, in the total group of 31 patients with discordant PET/CT and BSc reports, osseous metastases were confirmed in 12 patients (39%) on histology, and there were no negative biopsies (Fig 1).

Bone Biopsy/FNA in All Patients

Overall, bone biopsies and/or FNAs were performed in 28 (17%) of the 163 study patients: 25 were biopsied within 30 days, and three were biopsied within 75 days, of PET/CT or BSc (Fig 1). The pathology was consistent with MBC to bone in 26 reports (93%): 14 were PET/CT and BSc positive; nine were PET/CT positive, BSc negative; two were PET/CT equivocal, BSc-negative; and one was PET/CT positive, BSc equivocal.

DISCUSSION

In patients with suspected MBC, the optimal strategy for detecting osseous metastases is unknown. For example, the National Comprehensive Cancer Network guidelines recommend radiologic evaluation in the setting of clinical suspicion and/or high risk of metastases, but they do not recommend specific imaging modalities.[6] Similarly, the American Society of Clinical Oncology guidelines indicate that CT, PET, PET/CT, BSc, and/or magnetic resonance imaging may play a role in evaluating the patient with suspected MBC, but, again, they do not recommend a specific imaging paradigm.[6,7]

The absence of consensus recommendations in this setting likely reflects, in part, the limitations of the imaging modalities themselves. For example, BSc provides only indirect information about tumor activity, does not detect osteolytic metastases, and poorly detects indolent metastases or metastases to poorly vascularized areas.[2] PET (without CT) provides direct information about tumor activity and detects osteolytic metastases but is insensitive to small lesions, poorly detects osteoblastic metastases, and is limited by false positive results with inflammatory processes.[2,3,8-10]

It is also likely that the absence of consensus recommendations in this setting reflects significant deficiencies in the existing data. For example, several studies have compared the diagnostic performance of BSc and PET (without CT) in detecting breast cancer metastases to bone. However, these studies have been largely limited by modest sample sizes and low rates of gold-standard pathologic correlates.[8-14] Studies without pathologic correlates have a significant potential for investigator bias and are complicated by reliance on multiple diagnostic tests with variable sensitivity and specificity. To our knowledge, we report the largest study to date comparing BSc with integrated PET/CT (as opposed to PET alone) for the detection of osseous metastases in women undergoing evaluation for suspected MBC. Furthermore, this study has the largest proportion of pathologic correlates in the published literature to date. Specifically, 28 patients (17%) underwent bone biopsy in our study, which compares favorably to the 6.7% of pathologic correlates in the largest reported series of PET (without CT) versus BSc.[10] Almost all patients (93%) who underwent bone biopsy had pathology consistent

with breast cancer to bone. Moreover 12 (29%) of the 31 patients with discordant PET/CT and BSc results underwent bone biopsy/FNA, and osseous metastases were confirmed in all occurrences.

In our study, the observed concordance between PET/CT and BSc was not only high (81%) but also superior to reported concordance between BSc (or other conventional imaging techniques) and PET (without CT) in several comparable studies.[8,9,13] Thus, these data suggest that PET/CT and BSc provide largely redundant information about the presence or absence of osseous metastases in the majority of instances for which MBC is suspected. However, PET/CT confers the additional advantage of identifying nonosseous metastases, thereby potentially obviating the need for additional imaging. In this study, for example, 62% of patients with positive PET/CT had evidence of nonosseous metastases; of these patients, 6% had equivocal BSc, and 42% had negative BSc.

We did not include data on all patients undergoing either only a PET/CT or a BSc for suspected MBC; rather, we sought to correlate results from patients undergoing both imaging modalities. Additionally, because PET/CT has not routinely been performed at MSKCC on all patients with suspected MBC but has mainly been used in instances of diagnostic uncertainty, our cohort is likely enriched for such occurrences. Given that our occurrences may have represented those with higher degrees of clinician uncertainty, it is worth noting that osseous metastases were detected on biopsy in nine patients, and the metastases were seen on PET/CT and not BSc, whereas correlative clinical and radiologic findings in the two patients with positive BSc and negative PET/CT suggest that these were, in fact, true negatives on PET/CT. In these instances, the combined anatomic and functional imaging of PET/CT may have lowered the rate of false negatives, possibly by detecting osteoblastic metastases on CT. However, it should be noted that the anatomic images obtained with PET/CT have historically been less detailed than those obtained with dedicated CT, as demonstrated by one of our patients, for whom bone metastases from invasive lobular carcinoma were seen subsequently on CT. This patient represents a subgroup of breast cancer associated with strong expression of estrogen and progesterone receptors, which tends to be less metabolically active and thus leads to potentially lower standard uptake values on PET.[15] Therefore, this may be a subgroup in whom PET/CT should be used cautiously.

An additional theoretical disadvantage of PET/CT compared with BSc is that limited views of the long bones are obtained. However, isolated breast cancer metastases to the distal skeleton are extremely rare; whether this represents a clinically relevant limitation for PET/CT is unknown. Although BSc allows imaging of the entire skeleton, use is currently being curtailed by an impending shortage of technetium. Therefore, there is a need to explore other tracers, such as fluorine-18-fluoride, which can be detected on PET/CT and may be more sensitive for osseous metastases than BSc with Tc-99m MDP.[16] The limitation of fluorine-18-fluoride compared with FDG is that visceral metastases do not accumulate the tracer. Other radiotracers, such as isotopes of gallium and copper, have been bound to monoclonal antibodies, and the resultant conjugate can be detected on PET/CT.[17] These novel approaches may have a future role in imaging patients with subgroups of breast cancer, such as tumors that overexpress the human epidermal growth factor receptor 2.[18-20] Notably, our study was limited to patients with suspected MBC and did not include women undergoing surveillance after an early-stage or locally advanced breast cancer diagnosis. Although it is unknown whether early confirmation of MBC in women undergoing evaluation for suspected MBC translates into improved patient-specific outcomes, efficiency in the accurate confirmation of MBC is clinically useful in all settings. Timely and efficient evaluation of suspected MBC with a single test read by a single, experienced radiologist could reduce patient (and physician) anxiety in confirming or refuting the diagnosis, decrease the need for additional radiologic testing, minimize the time spent by clinicians in distilling discordant reports from different tests reported by different radiologists (often working at different imaging centers and without access to prior imaging), prevent unnecessary delays in therapy initiation, and likely improve patient quality of life. Timely institution of bisphosphonate therapy when MBC to bone is confirmed might also potentially decrease the early risk of skeletal-related events. In addition, because the gold standard for confirming MBC(ie, bone biopsy/FNA) is not universally recommended and/or available, a single study conferring both anatomic and metabolic information with high bone biopsy concordance, as demonstrated in our study, can increase clinician confidence in initiating palliative therapy. Furthermore, it is possible that an efficient, single-study strategy with integrated PET/CT is ultimately cost effective compared with conventional strategies; however, a formal analysis is warranted.

In conclusion, our study represents, to our knowledge, the largest experience comparing integrated PET/CT and BSc for the diagnosis of osseous metastases from suspected MBC and the largest series to evaluate PET/CT with pathologic correlates. We have demonstrated a high degree of concordance between these imaging modalities, which suggests redundancy for detecting osseous metastases with both modalities. Furthermore, these results suggest that PET/CT may be superior in evaluating women with suspected MBC, as evidenced by the high rate of pathologically confirmed osseous metastases in women with positive PET/CT and negative BSc results. PET/CT also detected nonosseous metastases in 62% of patients with positive PET/CT in our study. Consequently, BSc may potentially be avoided in most patients undergoing PET/CT for suspected skeletal metastases. These results indicate that a prospectively conducted study evaluating the sensitivity and specificity of PET/CT in women with suspected MBC is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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