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[^{18}F]Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) in Suspected Recurrent Breast Cancer: A Prospective Comparative Study of Dual-Time-Point FDG-PET/CT, Contrast-Enhanced CT, and Bone Scintigraphy

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ABSTRACT

Purpose
To prospectively investigate the diagnostic accuracy of [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) with dual-time-point imaging, contrast-enhanced CT (ceCT), and bone scintigraphy (BS) in patients with suspected breast cancer recurrence.

Patients and Methods
One hundred women with suspected recurrence of breast cancer underwent 1-hour and 3-hour FDG-PET/CT, ceCT, and BS within approximately 10 days. The study was powered to estimate the precision of the individual imaging tests. Images were visually interpreted using a four-point assessment scale, and readers were blinded to other test results. The reference standard was biopsy along with treatment decisions and clinical follow-up (median, 17 months).

Results
FDG-PET/CT resulted in no false negatives and fewer false positives than the other imaging techniques. Accuracy of results were similar for 1-hour and 3-hour FDG-PET/CT. For distant recurrence, the area under the receiver operating curve was 0.99 (95% CI, 0.97 to 1) for FDG-PET/CT, 0.84 (95% CI, 0.73 to 0.94) for ceCT, and 0.86 (95% CI, 0.77 to 0.94) for the combined ceCT+BS. Of 100 patients, 22 (22%) were verified with distant recurrence, and 18 of these had bone involvement. Nineteen patients (19%) had local recurrence only. In exploratory analyses, diagnostic accuracy of FDG-PET/CT was better than ceCT alone or ceCT combined with BS in diagnosing distant, bone, and local recurrence, shown by a greater area under the receiver operating curve and higher sensitivity, specificity, and superior likelihood ratios.

Conclusion
FDG-PET/CT was accurate in diagnosing recurrence in breast cancer patients. It allowed for distant recurrence to be correctly ruled out and resulted in only a small number of false-positive cases. Exploratory findings suggest that FDG-PET/CT has greater accuracy than conventional imaging technologies in this patient group.

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INTRODUCTION

Breast cancer is the most frequent malignant disease in women and, after lung cancer, the second leading cause of death in women in the United States.[1] The 5-year survival rate exceeds 95% for localized breast cancer and 25% for patients with distant disease.[1] After breast-conserving surgery and adjuvant treatment of early primary breast cancer, the 10-year risk of recurrence reaches 20% to 35%,[2] with bone being the most frequent site of distant recurrence.[3]

Current American and European guidelines regarding follow-up after primary treatment of breast cancer include clinical examination and

mammography without other imaging or medical testing in asymptomatic patients.[4,5] Diagnostic work-up is recommended when clinically indicated, but no clear recommendations exist for a specific imaging modality in recurrence detection. Conventional investigations other than laboratory testing often comprise symptom-oriented imaging, such as contrast-enhanced computed tomography (ceCT) and bone scintigraphy (BS). Functional imaging, such as [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT), is generally used sporadically or when conventional imaging is inconclusive.[4,5]

Table 1. Characteristics of 100 Danish Patients With Breast Cancer

Characteristic	No. of Patients
Primary site	
Left	55
Right	42
Bilateral	3
Type of surgery	
Breast-conserving	59
Mastectomy	41
Adjuvant chemotherapy and/or radiotherapy	
Yes	92
No	8
Histology of the primary tumor	
Invasive ductal carcinoma	73
Invasive lobular carcinoma	13
Ductal carcinoma in situ	5
Other	8
Missing	1
Stage of disease at diagnosis*	
I	16
II	44
III	23
Missing	17
Estrogen receptor status	
Positive	79
Negative	15
Missing	6
Progesterone receptor status	
Positive	37
Negative	57
Missing	6
HER2 status	
Positive	13
Negative	81
Missing	6
Sentinel node procedure	
Yes	54
No	42
Missing	4
Axillary dissection	
Yes	69
No	29
Missing	2
Years since treatment of primary breast cancer, median (range)	4 (0-30)
Tumor size in mm, median (range)†	17 (5-110)
Total No. of lymph nodes removed, median (range)‡	14 (1-32)
No. of positive lymph nodes, median (range)§	1 (0-23)

Abbreviation: HER2, human epidermal growth factor receptor 2.
*Stage of the disease was defined according to the Bloom-Richardson grading system.
†No. missing = 7.
‡No. missing = 6.
§No. missing = 5.

Recent meta-analyses of the diagnostic work-up for breast cancer recurrence indicate high accuracy and the superiority of FDG-PET/CT over conventional imaging techniques.[6-9] In addition, increased accuracy of FDG-PET/CT could be expected from taking images at a delayed scan time because of the increasing FDG uptake in malignant cells over time, along with decreasing FDG uptake in benign cells.[10,11] Existing meta-analyses of FDG-PET/CT for breast cancer recurrence are largely based on retrospective accuracy studies, which have methodological limitations.[12-26] Therefore, the need for prospective studies comparing FDG-PET/CT with conventional imaging techniques has been emphasized.[8,27,28]

The aim of this study was to investigate the diagnostic accuracy of dual-time-point FDG-PET/CT versus ceCT and BS in patients with suspected recurrent breast cancer and to evaluate whether FDG/PET-CT could serve as a stand-alone investigation for suspected recurrent breast cancer.

PATIENTS AND METHODS

We performed a prospective study at a single institution (Odense University Hospital, Denmark) from December 2011 to September 2014 in a collaborative effort between the Departments of Nuclear Medicine, Radiology, Oncology, Breast Surgery, and Clinical Pathology. Patients with suspected breast cancer recurrence or with verified local recurrence and potential distant disease were invited to participate when they were referred for FDG-PET/CT, ceCT, or BS. Exclusion criteria were a history of other malignancy, age younger than 18 years, whether currently pregnant or breast-feeding, diagnosed with diabetes mellitus, or considered unable to cooperate. Patients who accepted participation were asked to undergo all three imaging modalities within 14 days.

FDG-PET/CT

Patients were required to fast for at least 6 hours before the FDG-PET/CT scan. The blood glucose level was determined before tracer injection, and a maximum value of 144 mg/dL was allowed. The tracer FDG was administered intravenously in a dose of 4 MBq/kg. Thereafter, the patient rested and rehydrated with 800 mL of water. The first scan was performed after 60 minutes (± 5 minutes) from the skull to the proximal femur, applying a low-dose CT scan, and was immediately followed by a PET scan of the same area. The second scan was performed after 180 minutes (± 5 minutes) and was carried out in the same manner as the first.

FDG-PET/CT scanning was performed using either GE Discovery STE or Discovery RX (GE Medical Systems, Milwaukee, WI) with the

Table 2. Sites of Recurrence and Number of Verifying Biopsies by Location

Sites of Recurrence	No. of Patients	No. of Biopsies
Distant recurrence	22	20*
Local recurrence	19	19
Breast	23	21
Bone	18	7
Lymph nodes	13	8
Lungs	6	1
Liver	5	3
Brain	1	1
Other (eg, skin, subcutis, or muscle)	5	5

NOTE. Patients with metastasis in more than one distant site typically had only one biopsy taken; additional metastatic sites were confirmed by imaging or (retrospectively) by progressive lesions on later scans.
*Two patients with distant recurrence were verified by local biopsy and strong clinical confidence of distant metastases.

following settings: CT scan, 140 kV and 30-110 mA (Smart mA, GE Medical Systems); rotation time, 0.8 seconds; pitch, 1.375:1; noise index, 25; and detector coverage, 40 mm. Transverse images were reconstructed using standard filtered back-projection, a slice thickness of 3.75 mm, and an interval of 3.27 mm. PET scans were performed in 3D, with a scan time of 2.5 min/frame for 1-hour images and 3.5 min/frame for 3-hour images. Images were reconstructed iteratively, with ordered subset expectation maximization, two iterations, 21 or 28 subsets, and a slice thickness of 3.3 mm.

Contrast-Enhanced Computed Tomography

Diagnostic ceCT of the thorax and upper abdomen was performed at the Department of Radiology according to their current guidelines. The patients were scanned from the seventh cervical vertebra to the upper abdomen, including the liver. One hundred milliliters of Optiray (ioversol; Mallinckrodt, St Louis, MO), at 300 mg/mL, was administered, with a flow of 3.0 mL/s and a delay of 60 seconds. The scan was performed on Discovery 750HD or Lightspeed VCT (GE Medical Systems) with the following settings: 120 kV and up to 700 mA (Smart mA); rotation time, 0.5 seconds; noise index, 30; pitch, 0.984:1; table feed, 39 mm/rotation; and slice, 0.625 mm. Coronal, sagittal, and transverse images of 5-mm thickness were reconstructed using three different algorithms (standard, soft, and lung).

Bone Scintigraphy

The patients were injected with 700 MBq of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid 3 to 4 hours before whole-body imaging. In the

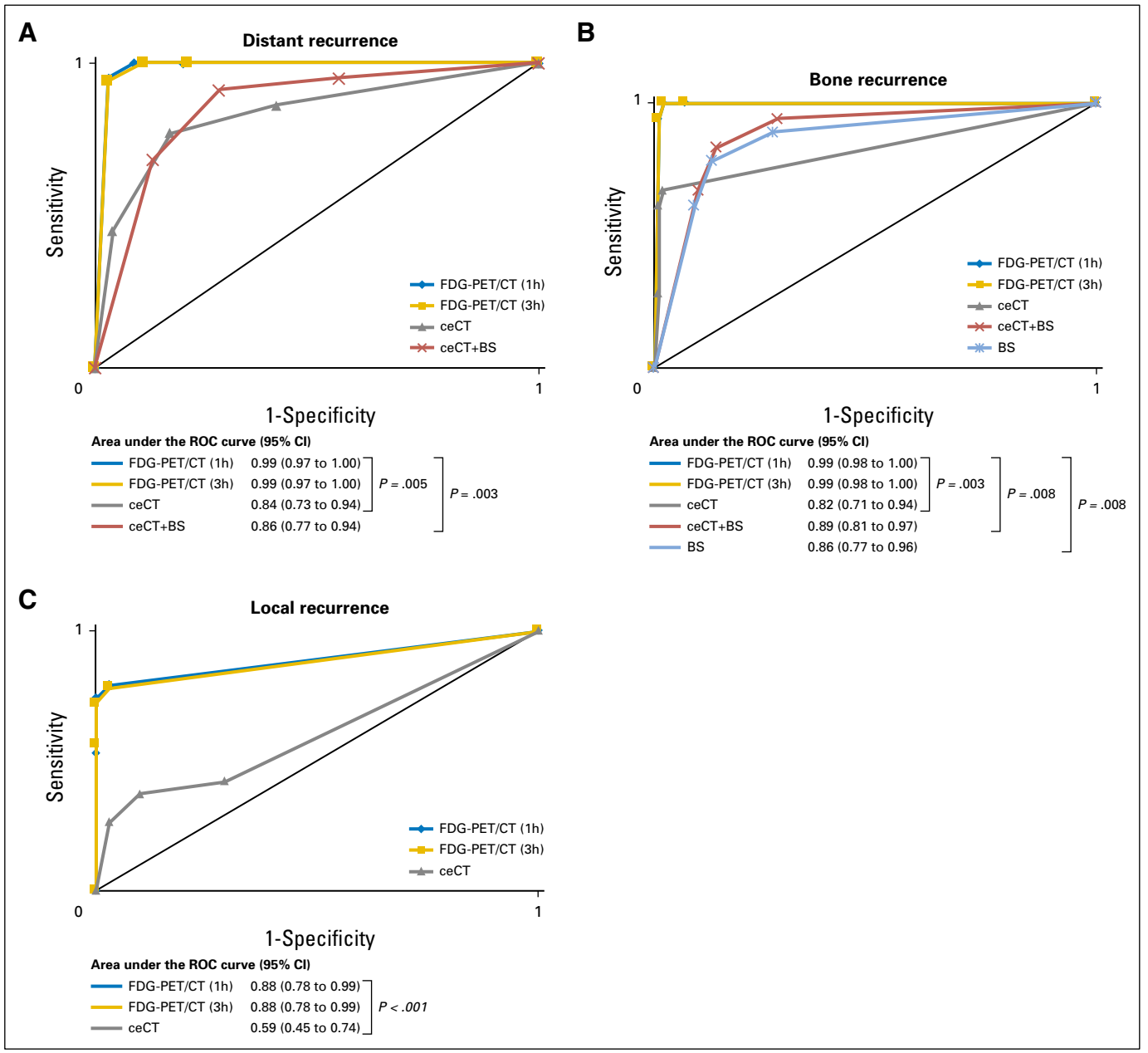

Fig 1. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC-ROC) for three imaging modalities in the diagnosis of (A) distant recurrence (n = 100), (B) bone recurrence (n = 100), and (C) local recurrence (n = 77). The AUC-ROC was statistically significantly different between the imaging modalities (global hypothesis of equality of all AUC-ROCs): (A) $P = .019$, (B) $P = .004$, (C) $P < .001$). 1h, 1 hour after injection; 3h, 3 hours after injection; BS, bone scintigraphy; ceCT, contrast-enhanced computed tomography; FDG-PET/CT, [^{18}F]fluorodeoxyglucose-positron emission tomography/computed tomography.

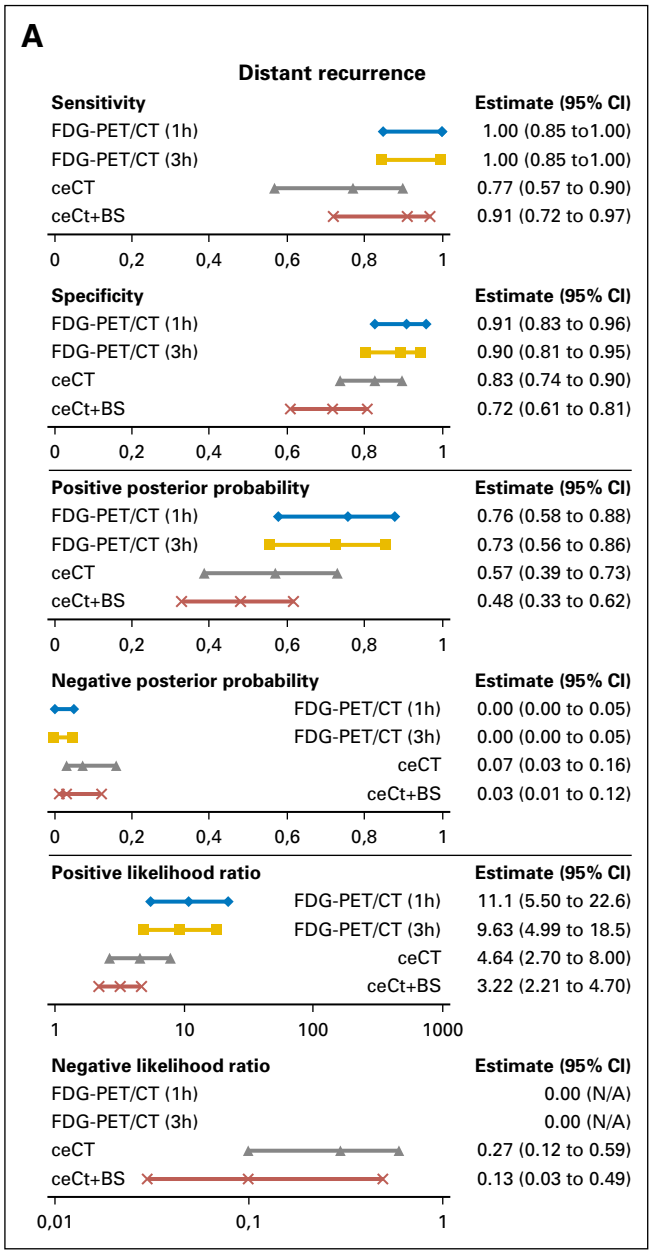

Fig 2. Estimates for sensitivity, specificity, positive and negative posterior probabilities, and positive and negative likelihood ratios are illustrated for diagnosis of (A) distant recurrence (n = 100), (B) bone recurrence (n = 100), and (C) local recurrence (n = 77). 1h, 1 hour after injection; 3h, 3 hours after injection; BS, bone scintigraphy; ceCT, contrast-enhanced computed tomography; FDG-PET/CT, [^{18}F] fluorodeoxyglucose-positron emission tomography/computed tomography.

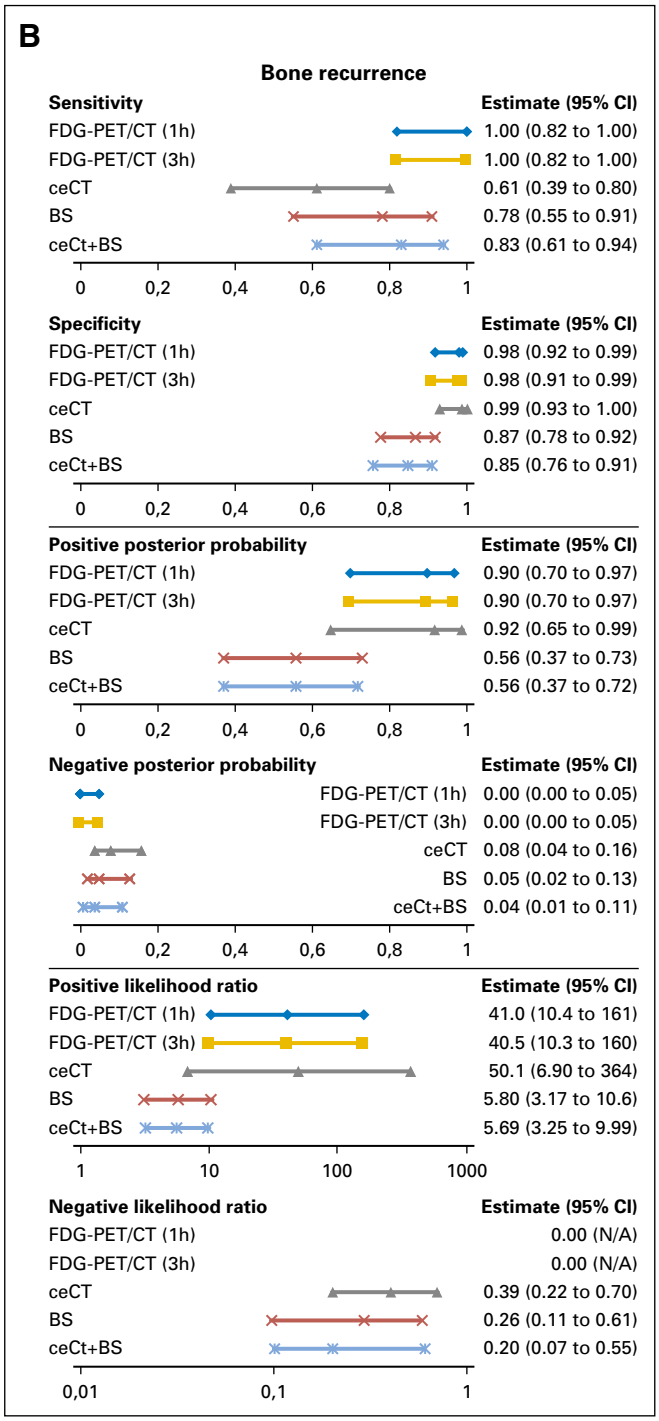

Fig 2. (Continued).

waiting period, the patients were asked to drink approximately 1 L of clear liquids. The scan was performed on Skylight or PRISM XP2000 (Philips Medical, Surrey, UK), with the following parameters: low-energy high-resolution collimator; energy window, 140 keV ± 20%; matrix, 256 × 1,024; and scan speed, 14 cm/min.

Image Interpretation

The scans were visually interpreted using a four-point graded assessment (0 = no sign of metastases, 1 = probably none, 2 = probable, 3 = definite signs of metastasis). Readings were made by two experienced specialists in nuclear medicine and four experienced radiologists who were aware of the referral text but were blinded to the other imaging results. Each scan was interpreted by a single reader. One nuclear medicine physician read the BS scans, and the other read the FDG-PET/CT scans; the 1-hour and 3-hour images were read independently in a first and second round, with random selection of the order in which the two scans were read. The ceCT scans were distributed between the four radiologists, with each radiologist interpreting one quarter of the scans.

Reference Standard

Verification of suspected recurrence was performed using a biopsy as the reference standard. Additional information on the pathohistologic

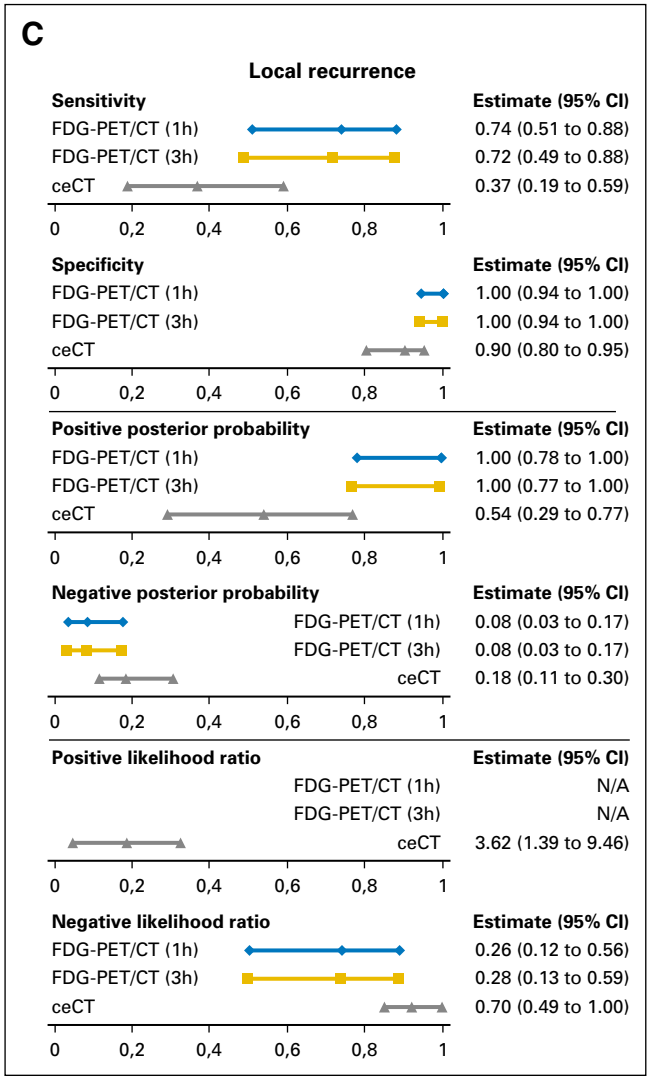

Fig 2. (Continued).

methodology of the biopsies is described in the Appendix (online only). The categorization into "distant recurrence," "local recurrence," or "no recurrence" was in accordance with the treatment decision and clinical follow-up. In the latter two groups, any clinical distant recurrence within a period of 6 months after the end of diagnostic work-up would lead to a change in category to distant recurrence. All patients treated explicitly for bone metastasis, typically with bisphosphonates, were categorized as having "bone recurrence."

Clinical follow-up was performed by reading the patients' medical files. Follow-up time was defined as the time interval between the date of the first scan and the date of the latest registered clinical contact with the Departments of Oncology or Breast Surgery.

Statistical Analysis

Analyses were conducted for 1-hour and 3-hour FDG-PET/CT, ceCT, BS (only for bone metastases), and combined BS and ceCT. When BS and ceCT were combined, higher values overruled lower values.

Receiver operating characteristic (ROC) curves were constructed on the basis of four-point visual assessments, resulting in estimates of the area under the ROC curve (AUC-ROC) with 95% CIs. The imaging modality with the largest AUC-ROC would thus be considered the most accurate test. The global hypothesis of equality of AUC-ROC for the imaging modalities was tested and supplemented by pairwise comparisons with 1-hour FDG-PET/CT if the global hypothesis could be rejected. However, the study was powered on the basis of precise estimates (and 95% CIs) of the FDG-PET/CT and not on the superiority of one imaging test over another.

Accuracy analyses were performed with regard to sensitivity, specificity, positive and negative likelihood ratios, and positive and negative posterior probabilities.[29] These estimates were supplemented by 95% CIs. The Wilson score method[30] was used to compare the sensitivity, specificity, and posterior probabilities of the modalities. The log method[31] was applied for the likelihood ratios.

For the sample size, we assumed a prevalence of recurrence of 20% and based our calculations on a total sample size of 150 patients. With a true (but unknown) sensitivity of 95% (90%), the expected width of a 95% Wilson score–based CI for the sensitivity of FDG-PET/CT was 17.9% (22.2%). With a true (but unknown) specificity of 95% (90%), the expected width of a 95% Wilson score–based CI for the specificity of FDG-PET/CT was 8.2% (10.9%). The duration of the inclusion period was intended to be 2 years, but because of slower-than-expected recruitment, the number of patients included after 3 years (December 2014) was 102. The chief reason for closure of the study was that the time allotted had been exceeded.

Missing values remained missing and were not imputed. The level of significance was 5% without adjustment for multiple testing. Data were stored electronically using Statistical Package for the Social Sciences (version 21.0, SPSS, Chicago, IL) and analyzed with STATA/MP software (version 13.1, STATA, College Station, TX).

Ethics and Disclosures

This study was conducted in compliance with good clinical practice and the Declaration of Helsinki. Permission was granted from the local ethics committee, and informed consent was obtained from all included patients. The project was implemented without the involvement of private organizations or companies.

RESULTS

Of the 102 patients who initially agreed to participate in the study, one patient changed her mind before FDG-PET/CT was performed, and another was excluded due to a previous biopsy-verified bone metastasis, leaving 100 women available for analysis. The median age was 60 years (range, 37 to 83); characteristics of the participants' primary breast cancer are listed in Table 1.

The reason for referral was suspected bone metastases in 66 patients (66%), biopsy-verified local recurrence and a subsequent risk of distant metastases in 20 patients (20%), and miscellaneous reasons in 14 patients (14%). Except for one, all patients had the three scans performed (in any order) within a median time interval of 10 days (range, 0 to 35), but for one outlier, the interval was 110 days. The ceCT was canceled for one patient; thus, the low-dose CT scan performed for the FDG-PET was used for the CT evaluation. This patient was categorized as having distant (including bone) recurrence on all modalities. Another patient was not able to complete the 3-hour scan; thus, only the 1-hour FDG-PET/CT was included.

Twenty-two patients (22%) were diagnosed with distant recurrence; 20 were verified by distant biopsy and two by local biopsy and strong clinical confidence of distant metastasis. Sites of distant recurrence and associated biopsies are listed in Table 2. Five of these 22 patients (23%) had metastases in only one distant site, eight (36%) had metastases in two sites, and nine (41%) had

Table 3. Number of Patients With False-Positive and False-Negative Diagnoses

Modality	No.	No. and Site	Description
FDG-PET/CT			
False-positive	7	4 lymph	3 mediastinal, 1 parasternal; regression at follow-up
		2 bone	1 sternum, fracture; recent car accident
			1 sternum and lumbar spine; Tietze syndrome?
		1 lung	Lung nodule with FDG uptake
False-negative	0	—	—
ceCT			
False-positive	13	8 liver	Primarily benign cysts
		4 lymph	All axillary, 1 also mediastinal
		1 bone	Sternum, fracture; recent car accident
False-negative	5	2 bone	1 femur; positive bone biopsy (femur)
			1 clavicle; positive bone biopsy (clavicle)
		2 bone and soft tissue	1 rib and pelvis, 1 sternum; positive soft tissue biopsies and confirmation at follow-up scans
		1 brain and lymph	Positive biopsies (brain and mediastinal lymph nodes)
BS and ceCT			
False-positive	22*	8 liver	Same as for ceCT
		4 lymph	Same as for ceCT
		11 bone	1 same as for ceCT; 10 positive on BS
False-negative	2	1 bone and soft tissue	Rib and pelvis; same as for ceCT
		1 brain, lymph	Same as for ceCT

Abbreviations: BS, bone scintigraphy; ceCT, contrast-enhanced computed tomography; FDG, [^{18}F]fluorodeoxyglucose; FDG-PET/CT, FDG-positron emission tomography/computed tomography.
*One patient was false positive for both bone on BS and liver on ceCT.

metastases in three or more sites. After a median follow-up period of 19 months (range, 1 to 35), 12 patients (55%) were still receiving treatment. Ten (45%) died within a median of 17 months after detection of recurrence (range, 1 to 35); in nine cases, the death could have been related directly to breast cancer, and one patient died of sepsis. Of the 22 patients with distant recurrence, 18 (82%) were classified as having bone metastases (seven bone biopsies and 11 biopsies from other sites, with confirmation of bone involvement by further imaging or by retrospectively observed progression in bone lesions on later scans).

Nineteen patients (19%) were classified as having local recurrence only and 59 patients (59%) as having no recurrence. The median follow-up period in these patients was 16 months (range, 0 to 36). Two patients who developed distant recurrence after 21 and 32 months, respectively, were not changed to the distant recurrence category.

Diagnostic Accuracy of Imaging Modalities

The AUC-ROC curves in Figure 1 show that the AUCs of FDG-PET/CT were significantly closer to the upper left corner or coordinate (0,1) of the ROC space (indicating 100% sensitivity [zero false negatives] and 100% specificity [zero false positives]) than were those of ceCT and BS in the diagnosis of distant, bone, and local recurrence.

As shown in Figure 2, the sensitivity of FDG-PET/CT in diagnosing distant, bone, and local recurrences was higher than that of the conventional techniques, either alone or combined, although this difference was not statistically significant. Similarly, the specificity of FDG-PET/CT was nonsignificantly higher than that of ceCT and BS combined. No difference was observed between the 1-hour and 3-hour FDG-PET/CT accuracy results.

FDG-PET/CT resulted in seven patients being falsely diagnosed with disease recurrence (Table 3). The ceCT resulted in 18 false test results; four of these were due to overlooked bone metastases. In two of those, the metastases were localized in the bone marrow in proximal long bones and might be explained by the reduced field of view in the ceCT. The combination of BS and ceCT resulted in three of the four false-negative bone lesions being correctly categorized by the BS; however, 10 new false-positive bone lesions were identified. Two metastatic lesions were not detected by either BS or ceCT; one is illustrated in Figure 3. Additional examples are shown in Appendix Figures A1 and A2.

DISCUSSION

In the current study, the accuracy of FDG-PET/CT was significantly higher than that of conventional imaging techniques for diagnosing distant recurrence. A recent systematic review and two meta-analyses reported sensitivities of 0.88 to 0.95 and specificities of 0.69 to 0.93 for FDG-PET/CT.[6-8] The varying levels of accuracy may partly be explained by major quality issues raised about the studies reviewed. The original study designs were mostly retrospective, and many studies have been performed without comparative tests; yet, when present, the time delay between tests could be up to several months. In addition, there are methodological issues regarding various technologies (eg, FDG-PET *v* FDG-PET/CT), blinding, and reference standards.

Regarding the diagnosis of bone recurrence, our results were in agreement with previous research demonstrating the superiority of FDG-PET/CT.[28,32] In a retrospective study, reports of FDG-PET/CT and BS in 163 women with suspected metastatic breast cancer were examined and showed 31 occurrences of discordant reports; 12 of these had pathology confirming osseous metastases. Nine were FDG-PET/CT positive and BS negative, one was FDG-PET/CT positive and BS equivocal, and two were FDG-PET/CT

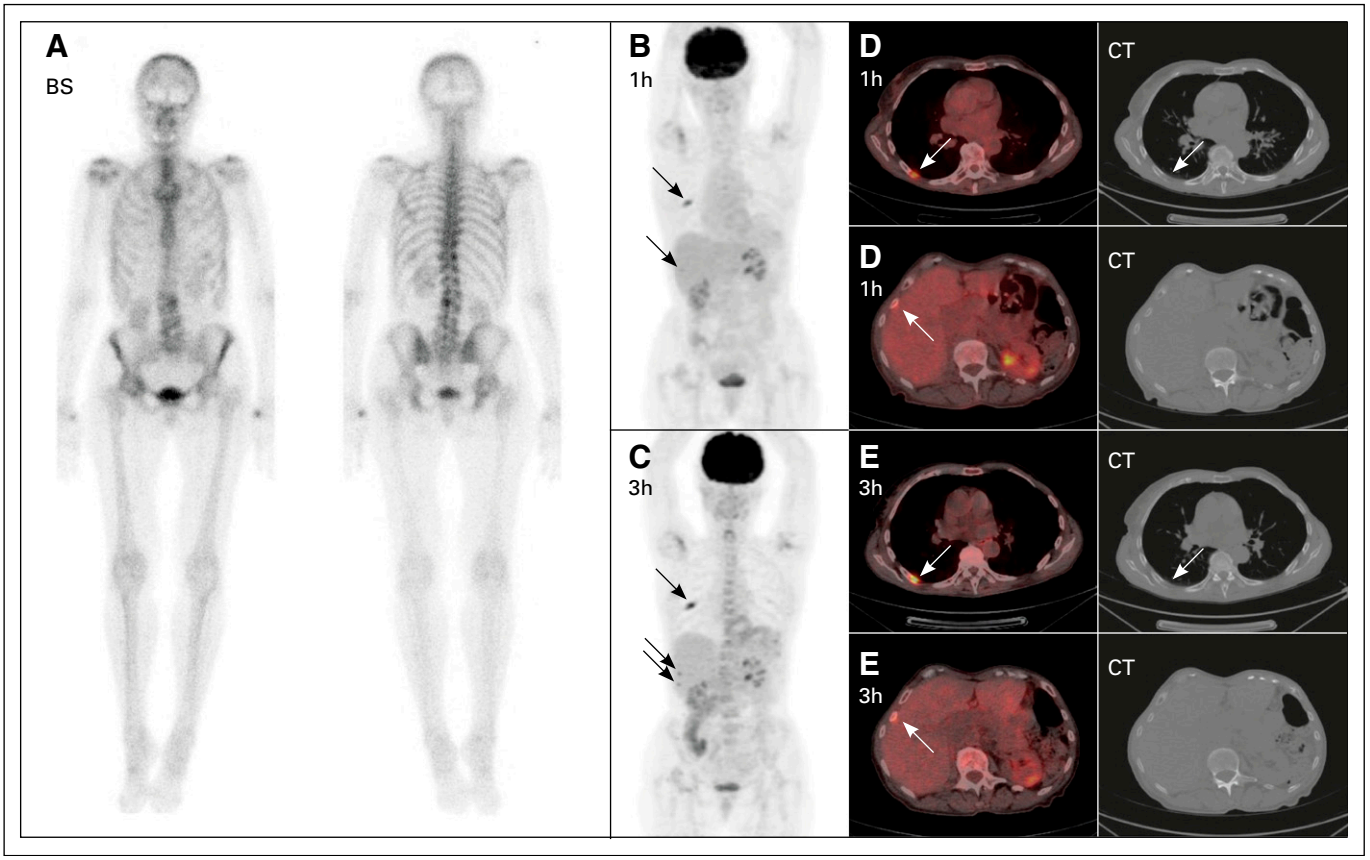

Fig 3. Example of a patient with verified bone metastases detected by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) only. The arrows show lesions in the costae categorized as bone recurrence on FDG-PET/CT. The bone scintigraphy (BS) and the contrast-enhanced CT were both false negative. The patient was confirmed to have bone metastases on follow-up with further imaging that showed progression of bone metastases. (A) BS in anterior and posterior projection. Maximum intensity projection images of FDG-PET/CT at (B) 1 hour (1h) and (C) 3 hours (3h) after injection. Transaxial images of at (D) 1 hour after injection, (E) 3 hours after injection, and low-dose CT scans.

equivocal and BS negative.[28] A possible explanation for the discordance between imaging test results may be that bone-related metastases show heterogeneity representing a variety of bone marrow lesions and osteosclerotic, osteolytic, and mixed bone lesions.[32,33] The importance of correct and early diagnosis of bone metastases seems obvious because, when associated with skeletal-related events, bone involvement can compromise quality of life and reduce survival.[33] Our results indicate that FDG-PET/CT may improve early detection of bone and bone marrow metastases; with early diagnosis and treatment, the skeletal-related events may be more easily addressed.

FDG-PET/CT was significantly better than conventional ceCT at correctly identifying local recurrence. As expected, both modalities resulted in some false negatives for local recurrence. The analyses of local recurrence should be interpreted with some caution because this diagnosis was often included in the referral text and thus known by the physicians and radiologists interpreting the scans.

Regarding dual-time-point imaging, we observed higher FDG uptake in metastatic lesions on delayed images than in earlier ones. In addition to the lower FDG uptake in background tissue, this gave the clear impression of a higher tumor-to-background ratio in delayed images but with no clear diagnostic advantage. Unexpectedly, we found no difference in accuracy between the 1-hour and 3-hour FDG-PET/CT imaging. In malignant cells, FDG activity increases with time, whereas it decreases with time in benign cells.[10,11] A delayed scan time was expected to further improve visualization of metastases; hence, increased sensitivity and specificity were expected. However, this could not be substantiated by our results.

The strengths of our study were that it was prospective, it included consecutive patients over a 3-year period, each patient acted as her own control with respect to the imaging modalities, the time between the imaging modalities was short (median of 10 days), and up-to-date technology was used for all scan types, including delayed scan time for the FDG-PET/CT. The assessments were made by experienced readers blinded to the results of the other imaging modalities, and a high-quality reference standard was used, with a focus on the importance of all patients being verified by biopsy.[34,35] Hence, in this prognostic study, a high-quality comparative methodology was used in a diagnostic design. This may be considered an advantage or a disadvantage, depending on whether the proven higher accuracy translates into improved patient outcomes. The randomized clinical trial reporting patient and patient-centered outcomes will probably always be considered the optimal study design for drawing evidence-based medical conclusions because the difference in patient-relevant outcomes is measured directly. The impact of a diagnostic test is indirect and

does not necessarily translate into a changed patient outcome because it is influenced by multiple downstream procedures.[36] With these methodological considerations in mind, a recent commentary pointed to the need for high-quality nonrandomized studies that compare test performance among alternative PET-based strategies and competing modalities.[37]

Limitations of our study included the fact that it was performed only at a single institution, which restricts generalizing the results. Furthermore, assessment was made on the basis of 95% CIs for sensitivity and specificity of FDG-PET/CT alone, and the study was closed before reaching the intended patient population. In addition, the BS was performed without single-photon emission computed tomography/CT, and the more novel fluoride-PET/CT was not included for analysis. For the ceCT, the field of view was defined as the thorax and upper abdomen, according to current guidelines, which was limited compared with the field of view of the FDG-PET/CT.

Current guidelines do not provide clear recommendations for the specific choice of imaging modality to be used for diagnostic work-up in patients with clinical indications of disease recurrence.[4,5] Future prospective multicenter studies on accurate testing and patient outcomes are needed to optimize guidelines for the specific choice of imaging in this patient group. Trials investigating the benefit of functional imaging in surveillance should be considered for future research as well.

The cost-effectiveness of performing FDG-PET/CT compared with conventional imaging techniques plays an important role in clinical practice. Data are sparse in this field,[38] and FDG-PET/CT in breast cancer recurrence has not yet been shown to be cost-effective.[39] Efforts regarding the clinical impact and economic modeling of this prospective set-up are subject to separate considerations.

In conclusion, FDG-PET/CT was shown to be accurate in diagnosing patients with suspected breast cancer recurrence. Exploratory findings further suggested that FDG-PET/CT is more accurate than conventional imaging technologies in this patient group.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

[^{18}F]Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) in Suspected Recurrent Breast Cancer: A Prospective Comparative Study of Dual-Time-Point FDG-PET/CT, Contrast-Enhanced CT, and Bone Scintigraphy

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Appendix

The needle biopsies were fixed in neutral buffered formalin for 12 to 24 hours. Larger specimens were formalin fixed for approximately 24 hours. If needed, bone biopsies were decalcificated with EDTA, 25 g/175 mL (pH, 7.0 to 7.4). For one specimen, formic acid (4 mol/L) was used. Afterward, all specimens were conventionally dehydrated, clarified, and paraffinated. The paraffin-embedded tissue was then cut into 2- to 3-mm-thick slices and routinely stained with hematoxylin and eosin. After primary examination, supplementary immunohistochemical stainings were ordered. If the primary origin was in doubt, breast cancer markers, that is, GATA3, mammaglobin, and GCDFP15, were examined, and all specimens were analyzed for estrogen receptor, human epidermal growth factor receptor 2, and Ki-67 status. All immunohistochemical procedures were quality secured according to NordiQC.

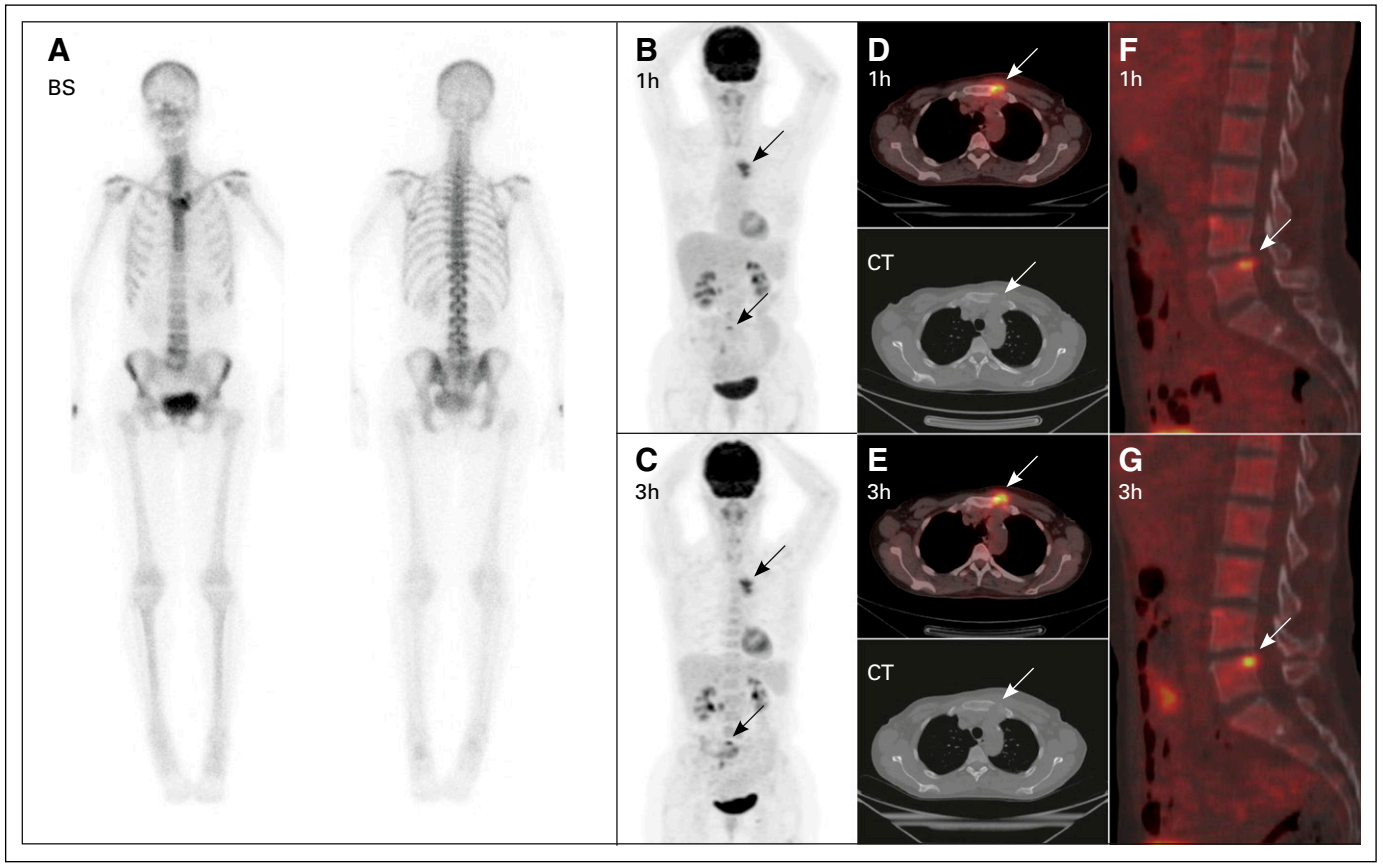

Fig A1. Example of a patient falsely categorized by [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) as having bone recurrence in the sternum and lumbar spine. After these images were taken, a biopsy was taken from the patient's sternum. The biopsy was inconclusive, and the patient was diagnosed with Tietze syndrome. She did not start treatment of any kind. Clinical follow-up without further imaging revealed no recurrence. (A) Bone scintigraphy (BS) in the anterior and posterior projection. Maximum intensity projection images of FDG-PET/CT at (B) 1 hour (1h) and (C) 3 hours (3h) after FDG injection. Transaxial images at (D) 1 hour and (E) 3 hours after injection and low-dose CT scans showing a lesion in the sternum (arrow), categorized as bone recurrence on FDG-PET/CT. Sagittal images at (F) 1 hour and (G) 3 hours after injection of a lesion in L5 in the lumbar spine (arrow), categorized as false positive on FDG-PET/CT.

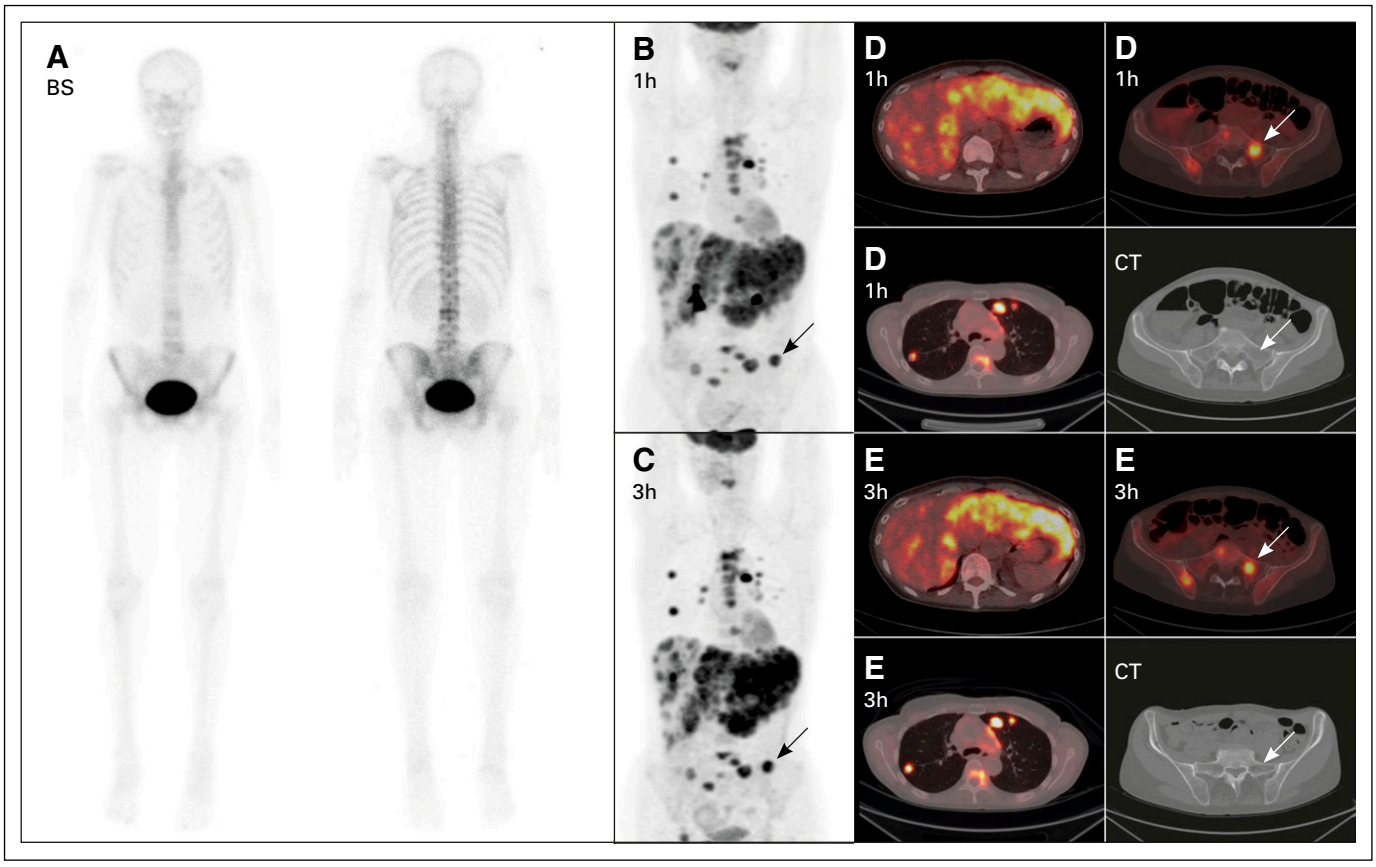

Fig A2. Example of a patient with multiple metastases, including bone, as visualized by the three modalities. Little is seen on the bone scintigraphy (BS), whereas several [^{18}F]fluorodeoxyglucose (FDG)-avid lesions are shown on FDG-positron emission tomography(PET)/computed tomography (CT). An example of this is the lesion on the right side of the sacrum (arrow). The CT scan did not detect this lesion. Notice also the difference between the 1-hour (1h) and 3-hour (3h) scans. For clinical interpretation, we hardly noticed a difference. With regard to the imaging quality, the delayed image showed higher uptake in the lesions and lower uptake in background tissue. This issue may be important in a clinical situation with the differentiation between limited or nonrecurrent disease. (A) BS in anterior and posterior projection. Maximum intensity projection images of FDG-PET/CT at (B) 1 hour after FDG injection (1h) and (C) 3 hours after FDG injection (3h). Transaxial images at (D) 1 hour after injection and (E) 3 hours after injection, and low-dose CT scans showing lesions in the liver, lung, and bone (arrow).