

A Prospective Study Comparing ^{99m}Tc -Hydroxyethylene-Diphosphonate Planar Bone Scintigraphy and Whole-Body SPECT/CT with ^{18}F -Fluoride PET/CT and ^{18}F -Fluoride PET/MRI for Diagnosing Bone Metastases

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We prospectively evaluated and compared the diagnostic performance of ^{99m}Tc -hydroxyethylene-diphosphonate (^{99m}Tc -HDP) planar bone scintigraphy (pBS), ^{99m}Tc -HDP SPECT/CT, ^{18}F -NaF PET/CT, and ^{18}F -NaF PET/MRI for the detection of bone metastases.

Methods: One hundred seventeen patients with histologically proven malignancy referred for clinical pBS were prospectively enrolled. pBS and whole-body SPECT/CT were performed followed by ^{18}F -NaF PET/CT within 9 d. ^{18}F -NaF PET/MRI was also performed in 46 patients. **Results:** Bone metastases were confirmed in 16 patients and excluded in 101, which was lower than expected. The number of equivocal scans was significantly higher for pBS than for SPECT/CT and PET/CT (18 vs. 5 and 6, respectively; $P = 0.004$ and 0.01 , respectively). When equivocal readings were excluded, no statistically significant difference in sensitivity, specificity, positive predictive value, negative predictive value, or overall accuracy were found when comparing the different imaging techniques. In the per-patient analysis, equivocal scans were either assumed positive for metastases ("pessimistic analysis") or assumed negative for metastases ("optimistic analysis"). The percentages of misdiagnosed patients for the pessimistic analysis were 21%, 15%, 9%, and 7% for pBS, SPECT/CT, PET/CT, and PET/MRI, respectively. Corresponding figures for the optimistic analysis were 9%, 12%, 5%, and 7%. In those patients identified as having bone metastases according to the reference standard, SPECT/CT, ^{18}F -NaF PET/CT, and PET/MRI detected additional lesions compared with pBS in 31%, 63%, and 71%, respectively. **Conclusion:** ^{18}F -NaF PET/CT and whole-body SPECT/CT resulted in a significant reduction of equivocal readings compared with pBS, which implies an improved diagnostic confidence. However, the clinical benefit of using, for example, ^{18}F -NaF PET/CT or PET/MRI as compared with SPECT/CT and pBS in this patient population with a relatively low prevalence of bone metastases (14%) is likely limited. This conclusion is influenced by the low prevalence of patients with osseous metastases. There may well be significant differences in the sensitivity of SPECT/CT, PET/CT, and PET/MRI compared with pBS, but a larger patient

population or a patient population with a higher prevalence of bone metastases would have to be studied to demonstrate this.

Key Words: ^{99m}Tc -HDP; SPECT/CT; ^{18}F -NaF-PET/CT; PET/MRI; bone metastases

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Bone metastases are frequent in advanced cancers, especially in patients with breast or prostate cancer, and the presence of bone metastases often implies a change of treatment (1,2) and indicates shortened patient survival. Conventional planar bone scintigraphy (pBS) with ^{99m}Tc -labeled radiopharmaceuticals, such as hydroxyethylene-diphosphonate (^{99m}Tc -HDP), is still the most frequently used modality for diagnosing bone metastases (3). Studies have shown that adding SPECT/CT to pBS improves the specificity and positive predictive value (PPV) as well as the diagnostic confidence of the reader, thereby reducing the number of equivocal study reports (4,5).

^{18}F -sodium fluoride (^{18}F -NaF) was introduced in 1962 by Blau et al. (6). Low affinity to protein, rapid clearance from the plasma, and a first-pass extraction to bone approaching 100% make ^{18}F -NaF an excellent bone-imaging agent (7). In the 1970s, ^{18}F -NaF was replaced by ^{99m}Tc -labeled diphosphonate compounds with physical characteristics more suitable for conventional γ -cameras (8).

The more widespread availability of PET/CT scanners and cyclotrons and a more recent global shortage of $^{99}\text{Mo}/^{99m}\text{Tc}$ generators in the late 2000s initiated a renewed interest for ^{18}F -NaF as an alternative to pBS. Furthermore, ^{18}F -NaF PET is more time efficient for the patient: although pBS is performed after a 2- to 5-h uptake time (9), high-quality PET/CT images can be obtained as soon as 30–45 min after administration of ^{18}F -NaF (10).

Recent metaanalyses have indicated that ^{18}F -NaF PET/CT is more accurate than pBS but the question of whether there is an incremental diagnostic improvement on a patient basis with ^{18}F -NaF PET or PET/CT for bone metastases is not settled (11–13).

The Centers for Medicare & Medicaid Services has covered ^{18}F -NaF PET under the coverage with "an evidence development process" since 2010. In their final decision (Decision Memo

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TABLE 1
Scanning and Reconstruction Specifications

Scanner	Symbia T16 SPECT/CT	Precedence SPECT/CT	Biograph TrueV 40 PET/CT	Biograph mCT PET/CT	Biograph mMR PET/MRI
Emission data					
Views	180	128			
Time per view (s)	6	8			
Time per bed position (min)			2	2	5
Axial field of view per bed position (cm)	38.7	38.1	21.8	21.8	25.8
Matrix	128 × 128	128 × 128	336 × 336	400 × 400	344 × 344
Slice thickness (mm)			3	2	2
Energy window (keV)	140% ± 15%	140% ± 15%	435–650	435–650	430–610
Reconstruction method	5 iterations	4 iterations	3 iterations	3 iterations	3 iterations
	10 subsets	16 subsets	21 subsets	21 subsets	21 subsets
		Astonish	4 mm	4 mm	4 mm
CT acquisition					
Voltage (kV)	130	140	120	120	
Tube current	Weight adapted (dynamic)	Weight adapted (dynamic)	40 mAs (dynamic)	40 mAs (dynamic)	
Rotation (s/rotation)	0.6	0.5	0.5	0.5	
Pitch	1.5	0.938	0.8	0.8	
Slice thickness (mm)	5	5	3	2	

for PET (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R2), December 2015), after reviewing the last 5 y worth of data, they concluded that there is still not enough evidence to support coverage of ^{18}F -NaF PET to identify bone metastases. The Society of Nuclear Medicine and Molecular Imaging, American College of Nuclear Medicine, and American College of Radiology have pointed out that they strongly disagree with this conclusion.

Meanwhile, whole-body MRI has emerged as an alternative method to detect bone metastases. MRI is more sensitive at detecting early bone marrow lesions than CT. Comparative studies have indicated that MRI is more sensitive and specific than pBS (14–17).

We wanted to test the hypothesis that there is an improved diagnostic performance of ^{18}F -NaF PET/CT compared with conventional pBS and SPECT/CT for the detection of bone metastases on a per-patient basis by conducting, to this date, the largest prospective study on this topic. We also wanted to investigate if there is an added value of combining ^{18}F -NaF PET with MRI using a combined PET/MRI scanner.

MATERIALS AND METHODS

Patients

This study was performed as a prospective clinical study, approved by the local ethics committee (H-4-2012-024). Written, informed consent was obtained from all patients. The inclusion criteria were patients with histologically proven malignancy referred for pBS under the clinical suspicion of bone metastases; and patients able to undergo ^{18}F -NaF PET/CT within 9 d, which was considered justifiable to minimize disparity between scans due to potential progression. Exclusion criteria were known or history of bone metastases, age younger than 18, and pregnant or lactating women. When no contraindications to MRI were identified and there was an available timeslot, whole-body ^{18}F -NaF PET/MRI was performed on the same day as PET/CT in the first 50 patients.

pBS and SPECT/CT

Standard pBS followed by whole-body $^{99\text{m}}\text{Tc}$ -HDP SPECT/CT were acquired in one session using a hybrid SPECT/CT (Symbia [Siemens Medical Solutions] or Precedence [Philips]) consisting of a dual-head, variable-angle γ -camera combined with a 16-slice helical CT scanner. Anterior and posterior views covering the whole skeleton with the patient supine were obtained 3 h after injection of $^{99\text{m}}\text{Tc}$ -HDP (mean activity, 586 ± 27 MBq; range, 523–655 MBq; low-energy high-resolution collimators, 10 cm/min). The approximate scan time was 20–25 min.

Whole-body SPECT/CT was performed, without repositioning of the patient, using a whole-body SPECT software option covering 3 bed positions from the tip of the head to the mid thighs. SPECT, low-dose CT, and reconstructions parameters are specified in Table 1. The approximate scan time was 30–35 min.

PET/CT

Whole-body PET/CT from head to toe with the patient supine was performed on either a 128-slice or 64-slice Biograph mCT or a 40-slice Biograph TrueV scanner (Siemens Medical Solutions). The scan was obtained 45 min (mean, 49 ± 10 min; range, 30–83 min) after injection of ^{18}F -NaF (mean activity, 210 ± 13 MBq; range, 151–239 MBq). The approximate scan time was 30–35 min. A rough estimation of the effective dose from the low-dose CT component was made on the basis of dose–length product and conversion factors described in International Commission on Radiological Protection publication 102 (18).

PET/MRI

Simultaneous PET/MRI from tip of the head to mid thigh was performed after completion of the PET/CT on a 3-T Biograph mMR scanner (Siemens Medical Solutions) using a head and neck coil and 4 body surface coils. The mean time from injection to scan was 124 ± 23 min (range, 89–181 min).

Attenuation correction was performed using a Siemens standard 4-compartment-attenuation map. Noncontrast sequences for all bed positions (in most cases 5) included coronal whole-body T1 turbo spin echo (repetition time/echo time [TR/TE], 600/8.7 ms; flip angle, 140°; slice thickness/gap, 5/1 mm; matrix, 186 × 384; in-plane resolution, 1.25 × 1.25 mm²; scan time, 1:25–3:12 min/bed), coronal whole-body short tau inversion recovery (TR/TE, 5,000/84 ms; flip angle, 125°; slice thickness/gap, 5/1.5 mm; matrix, 186 × 384; in-plane resolution, 1.17 × 1.17 mm²; scan time, 1:47–2:50 min/bed), and sagittal short tau inversion recovery covering the spine (TR/TE, 2,110/8.6 ms; flip angle, 150°; slice thickness/gap, 3/0.6 mm; matrix, 224 × 320; in-plane resolution, 1.3 × 0.9 mm²; scan time, 2:28–5:14 min/bed). In addition, sagittal T1 turbo spin echo also covering the spine (TR/TE, 600/9.1 ms; flip angle, 150°; slice thickness/gap, 3.0/0.6 mm; matrix, 288 × 384; in-plane resolution, 1.0 × 1.0 mm²; scan time, 1:03 min/bed) was acquired subsequent to PET at 3 bed positions. The sequence scan time could vary with bed position due to variations in number of slices needed for patient coverage and prolongation due to restrictions on specific absorption rate of radiofrequency radiation. The approximate scan time was 60–65 min.

Image Interpretation

All examinations were read on standard workstations. pBS and SPECT/CT were interpreted separately by 2 experienced nuclear medicine specialists with the assistance of a radiologist, and discrepancies were solved in consensus. ¹⁸F-NaF PET/CT were read by 2 other experienced nuclear medicine specialists with the assistance of 2 radiologists, and discrepancies were solved in consensus with a third nuclear medicine specialist. ¹⁸F-NaF PET/MRI were read by a nuclear medicine specialist together with a MR radiologist specialized in musculoskeletal MRI. All readers were masked to the other imaging modalities. Each scan was categorized on a per-patient basis as bone metastases present, widespread metastases (>20 bone metastases present), benign (bone metastases absent), or equivocal. On the basis of these data, 3 analyses were performed: first, excluding all equivocal readings—consensus reading; second, categorizing equivocal readings as benign—optimistic analysis; and third, categorizing equivocal readings as suggestive of malignancy—pessimistic analysis (15,19).

Reference Standard

Results from the interpretations were held up against final diagnoses as confirmed by histologic evaluation, clinical follow-up, or other imaging studies. At least 6-mo clinical follow-up, including review of all regional hospitals' medical records, biopsies, laboratory reports, and all subsequent imaging, was used. The progression of index lesion on subsequent imaging or lytic lesion changing to blastic lesion during treatment, but also typical appearance of multifocal disease and increased lesion number over time, was strong evidence of bone metastases. Scans were considered false-negative if follow-up revealed bone metastases within 6 mo.

Statistical Analysis

The sample size calculation was prospectively determined to be 120 (power of 80%, α of 5%) to detect a difference of 13%, as we estimated that approximately 30% of patients would have bone metastases.

Data analysis was performed using SPSS (version 19; IBM Corp.). A patient-based data analysis was performed. Sensitivity, specificity, accuracy, PPV, and negative predictive value for pBS, SPECT/CT, PET/CT, and PET/MRI were compared using the McNemar test. Two-sided *P* values were calculated, and a *P* value of less than 0.05 was

considered statistically significant. Frequency of equivocal readings was compared with the χ^2 test.

RESULTS

Between June 2012 and January 2015, 488 patients referred for a clinical pBS met the inclusion criteria and were invited to participate. Figure 1 shows patient inclusion leading to a total of 117 patients available for study evaluation: 62 men with prostate cancer, 54 women with breast cancer, and 1 woman with renal cancer. Patient characteristics are listed in Table 2, and reasons for patient referral are listed in Table 3.

The ¹⁸F-NaF PET/CT was performed 5.3 ± 2.3 d after pBS and SPECT/CT. Forty-six patients underwent a supplemental ¹⁸F-NaF PET/MRI (on the same day as the PET/CT). The approximate effective dose was 4 mSv from the pBS and an additional 4–5 mSv from the low-dose CT incorporated in the SPECT/CT examination. The effective dose from ¹⁸F-NaF PET/CT was approximately 6 mSv from the tracer and an additional 4–5 mSv from the low-dose CT, resulting in a total dose of

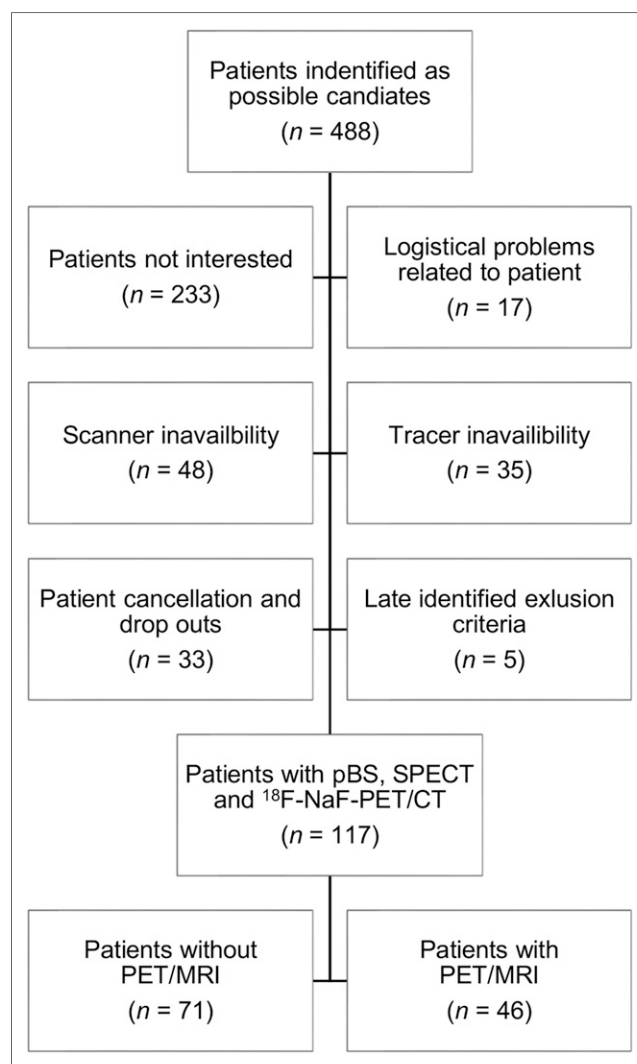


FIGURE 1. Flowchart illustrating patient inclusion and exclusion criteria.

TABLE 2
Patient Characteristics

Characteristic	Study population	Subgroup with PET/MRI
No. of patients	117	46
Sex (n)		
Female	55 (47%)	22 (48%)
Male	62 (53%)	24 (52%)
Mean age \pm SD	62.3 \pm 10.7	61.0 \pm 12.4
Cancer type (n)		
Breast*	54 (46)	21 (46)
Prostate†	62 (53)	24 (52)
Renal	1 (1)	1 (2)

*83% were estrogen receptor-positive.

†Average Gleason score, for 19 prostate cancer patients undergoing bone scanning for initial staging, was 7.7.

Data in parentheses are percentages.

10–11 mSv. The PET/MRI did not cause any additional radiation dose to the patient.

Follow-up

The average follow-up period was 652 ± 217 d (range, 130–1,090). Bone metastases were confirmed in 16 patients (14%) (4 breast cancer patients and 12 prostate cancer patients) based on the reference standard (Table 4). Bone metastases were excluded in the remaining 101 patients (86%). Four patients died during follow-up, 130, 140, 669, and 705 d after the initial pBS. Sixty-six patients (56%) underwent relevant imaging within the follow-up period and 45 (38%) within 6 mo.

Patient-Based Analysis

Ninety-one of 117 (true-positive and true-negative cases) patients were correctly diagnosed with pBS including 9 of 16

with bone metastases and 82 of 101 without bone metastases. Eighteen pBS readings were equivocal (2 with bone metastases and 16 without) (Table 5). Ninety-nine of 117 patients were correctly diagnosed with SPECT/CT including 9 of 16 with bone metastases and 90 of 101 without. Five SPECT/CT readings were equivocal (1 with bone metastases and 4 without). One hundred two of 117 patients were correctly diagnosed with PET/CT including 12 of 16 with bone metastases and 94 of 101 without. Six PET/CT readings were equivocal (1 with bone metastases and 5 without). Forty-three of 46 patients were correctly diagnosed with PET/MRI including 6 of 7 with bone metastases and 37 of 39 without. No PET/MRI readings were equivocal. All modalities missed the same 2 patients diagnosed with bone metastases 4.5 and 5 mo after the initial pBS.

The number of equivocal pBS scans, 18, was significantly higher than for SPECT/CT (5 scans, $P = 0.004$) and PET/CT (6 scans, $P = 0.01$) (Table 5). None of the 46 PET/MRI scans was classified as equivocal. Figure 2 illustrates interpretations and the final diagnosis for all patients.

When equivocal readings were categorized as malignant (pessimistic analysis), pBS misdiagnosed 24 (21%) patients, SPECT/CT 17 (15%) patients, and PET/CT 10 (9%) patients. The corresponding figures for optimistic analysis were 10 (9%) misdiagnosed by pBS, 14 (12%) by SPECT/CT, and 6 (5%) by PET/CT. PET/MRI misdiagnosed 3 (7%) patients in both cases.

Diagnostic Accuracy

When equivocal readings were excluded, no statistically significant difference in sensitivity, specificity, PPV, negative predictive value, or overall accuracy were found when the different techniques were compared. Table 6 summarizes the diagnostic performance when optimistic analysis and pessimistic analysis are applied.

Imaging Findings

Among the 16 patients with bone metastases, 3 patients were categorized by PET/CT to have widespread metastases (>20 lesions) whereas SPECT/CT showed more than 20 lesions in two of them and pBS only characterized one of them

TABLE 3
Clinical Indication for Requesting Bone Scanning Overall and Stratified by Cancer Type

Reason for patient referral	Prostate	Breast	Renal	Combined
No. of patients (% of cohort)	62 (53.0)	54 (46.2)	1 (0.9)	117 (100)
Main reason for ordering bone scanning				
Initial staging	19 (30.6)	1 (1.8)	0 (0.0)	20 (17.1)
Rising tumor markers	25 (40.3)	0 (0.0)	0 (0.0)	25 (21.4)
Bone pain	1 (1.6)	52 (96.3)	1 (100)	54 (46.2)
Bone pain and rising tumor markers	5 (8.1)	0 (0.0)	0 (0.0)	5 (4.3)
Other imaging findings	2 (3.2)	1 (1.8)	0 (0.0)	3 (2.6)
Participating in clinical trial	7 (11.3)	0 (0.0)	0 (0.0)	7 (6.0)
Other reason*	3 (4.8)	0 (0.0)	0 (0.0)	3 (2.6)

*Including 1 patient with metastases to testes, 1 with elevated alkaline phosphatase, and 1 with weight loss as a sign of progression. Data in parentheses are percentages.

TABLE 4
Patients with Confirmed Bone Metastases Based on Reference Standard

Sex	Age	pBS	SPECT/CT	PET/CT	PET/MRI	Cancer type	Follow-up imaging	Final diagnosis based on
Female	51	Eq	Pos	Pos	Pos	Breast	CT × 3	Change from lytic to sclerotic during treatment
Female	51	Pos	Neg	Pos	—	Breast	CT × 11	Change from lytic to sclerotic during treatment
Male	70	Pos	Pos	Pos	Pos	Prostate	MRI × 4, CT × 5, pBS × 4	Typical appearance of multifocal disease and increased lesion number over time
Male	66	Pos	Pos	Pos	Pos	Prostate	—	Typical appearance of multifocal disease
Male	73	Eq	Neg	Neg	Neg	Prostate	CT × 3, pBS × 5	Bone metastases diagnosed on follow-up imaging approximately 5 mo after initial scans*
Male	66	Neg	Neg	Pos	—	Prostate	MRI, CT	Follow-up imaging
Male	79	Neg	Neg	Neg	—	Prostate	CT × 4, pBS × 4, MRI	Bone metastases diagnosed on follow-up imaging approximately 4 mo after initial scans*
Male	62	Pos	Pos	Pos	Pos	Prostate	—	Typical appearance of multifocal disease and clinical follow-up
Male	69	Pos	Pos	Pos	Pos	Prostate	CT × 2, pBS × 3	Progression of index lesion and increased lesion number over time
Female	48	Neg	Neg	Eq	—	Breast	MRI, CT × 8, ¹⁸ F-FDG PET	Change from lytic to sclerotic during treatment
Male	64	Neg	Neg	Pos	Pos	Prostate	MRI × 2, CT	Change from lytic to sclerotic during treatment
Male	67	Pos	Eq	Neg	—	Prostate	CT	Typical appearance of multifocal disease and clinical follow-up
Male	70	Pos	Pos	Pos	—	Prostate	CT × 4, pBS × 4	Typical appearance of multifocal disease and increased lesion number over time
Female	44	Pos	Pos	Pos	—	Breast	¹⁸ F-FDG PET, CT × 6, MRI × 2	Change from lytic to sclerotic during treatment
Male	69	Pos	Pos	Pos	—	Prostate	CT × 2, pBS × 2, MRI	Progression of index lesion and change from lytic to sclerotic during treatment
Female	56	Neg	Pos	Pos	—	Breast	MRI × 5, CT × 9, ¹⁸ F-FDG PET	Biopsy and follow-up imaging

*Bone metastases first diagnosed during follow-up, within 6 mo.
Eq = equivocal; Pos = positive; neg = negative.

to have widespread bone metastases. Compared with pBS, SPECT/CT showed additional lesions in 5 of these 16 patients (31%) and PET/CT in 10 (63%). Seven of the 16 patients with bone metastases underwent PET/MRI. PET/MRI revealed additional lesions in 5 of 7 of these patients (71%) compared

with pBS, and in 2 (28%) of them also lesions not identified on SPECT/CT and PET/CT (example in Fig. 3 and Supplemental Fig. 1 [supplemental materials are available at <http://jnm.snmjournals.org>]). In 2 cases, PET/MRI indicated in contradiction to the other modalities presence of single bone metastases

TABLE 5
Patient-Based Analysis

Modality	Consensus reading						Optimistic analysis				Pessimistic analysis			
	TP	FP	TN	FN	# equivocal	Total	TP	FP	TN	FN	TP	FP	TN	FN
pBS	9	3	82	5	18 (15%)*	117	9	3	98	7	11	19	82	5
SPECT/CT	9	7	90	6	5 (4%)*	117	9	7	94	7	10	11	90	6
PET/CT	12	2	94	3	6 (5%)*	117	12	2	99	4	13	7	94	3
PET/MRI	6	2	37	1	0 (0%)	46	6	2	37	1	6	2	37	1

*pBS different from SPECT/CT ($P = 0.004$) and PET/CT ($P = 0.01$).
TP = true positive; FP = false positive; TN = true negative; FN = false negative.

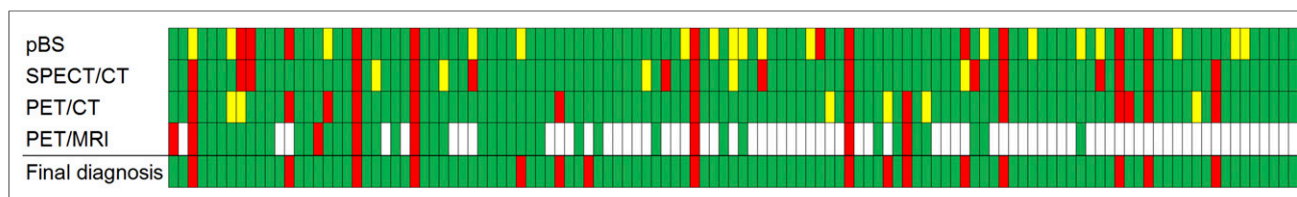


FIGURE 2. All scans with 1 patient in each column. Red = positive scan finding or final diagnosis; green = negative scan finding or final diagnosis; yellow = equivocal scan finding; white = not performed.

but in both cases follow-up could not verify the metastatic lesions.

DISCUSSION

To our knowledge, this study is the largest prospective study on the diagnostic performance of ^{18}F -NaF PET/CT compared with conventional pBS and SPECT/CT for the detection of bone metastases. It is also the first to include ^{18}F -NaF PET/MRI.

In the studied patient population, SPECT/CT, PET/CT, and PET/MR detected additional lesions in a relatively high percentage of those patients identified as having bone metastases, 31%, 63%, and 71%, respectively. But on a patient level, despite the technologic advantages of SPECT/CT, PET/CT, and PET/MR, they correctly changed only the tumor stage in a relatively small fraction of patients compared with pBS. The percentage of misdiagnosed patient for the optimistic analysis were 9%, 12%, 5%, and 7% for pBS, SPECT/CT, ^{18}F -NaF PET/CT, and ^{18}F -NaF PET/MR, respectively.

These results are not completely in line with the last 2 decades of studies on diagnostic accuracy of ^{18}F -NaF PET, summarized in several metaanalyses (11–13). In 2013, Palmedo et al. published a large study comparing whole-body SPECT/CT and pBS in 308 patients with either prostate or breast cancer (5). There was no significant difference in per-patient sensitivity, which was 93%, 94%, and 97% for pBS, SPECT, and SPECT/CT, respectively. Specificity was, on the other hand, significantly better with SPECT/CT. These results are contradictory to prior metaanalyses in which pooled sensitivity for pBS was as low as 47% but more in line with our results.

The lack of significance in our study could be partly explained by the relatively low prevalence of patients with osseous

metastases in the study population. The observed prevalence of 14% is lower than expected from our clinical practice and does imply that even after inclusion of 117 patients, we have to conclude that this study was underpowered.

A possible reason for this low prevalence of osseous metastases could be that patients with severe pain, caused by widespread metastatic disease, would be less willing to participate in a study in which they should undergo multiple scans on different days. On the other hand, in patients with widespread metastatic disease it seems even less likely to find a significant difference in sensitivity on patient-based analysis.

The standard of reference was clinical follow-up, including other imaging examinations and histologic evaluation. In our study, histology evaluations were performed on 2 patients. The definition of false-negative scans could be debatable especially if all modalities are negative. What acceptable and reasonable time period should pass after an initial negative scan, before you should consider a scan on a patient, later being diagnosed with bone metastases, as being false-negative? We chose 6 mo, which in some sense could be considered a long time but is a relevant time period in relation to normal imaging frequency.

The nature and verification of small lesions detected by ^{18}F -NaF PET is cumbersome; therefore, follow-up including repetitive imaging is essential if the true diagnostic performance is going to be established. We believe this lack of reference standard in many studies is a weakness, especially in lesion-based analysis. To verify all lesions by obtaining histologic proof is of course impractical and unethical. In lesion-based analysis, the number of lesions included in each patient must also be limited because patients with many true-positive lesions detected only on PET/CT will have too strong an influence on the result. As a consequence of this bias, the problem with verification and the fact

TABLE 6
Diagnostic Accuracy

Modality	Consensus reading					Optimistic analysis					Pessimistic analysis				
	Sens	Spec	PPV	NPV	ACC	Sens	Spec	PPV	NPV	ACC	Sens	Spec	PPV	NPV	ACC
pBS	64.3	96.5	75.0	94.3	91.9	56.3	97.0	75.0	93.3	91.5	68.8	81.2 [†]	36.7	94.3	79.5 [‡]
SPECT/CT	60.0	92.8	56.3	93.8	88.4	56.3	93.1	56.3	93.1	88.0 [*]	62.5	89.1	47.6	93.8	85.5
PET/CT	80.0	97.9	85.7	96.9	95.5	75.0	98.0	86.7	96.1	94.9 [*]	81.3	93.1 [†]	65.0	96.9	91.5 [‡]
PET/MRI	85.7	94.9	75.0	97.4	93.5	85.7	94.9	75.0	97.4	93.5	85.7	94.9	75.9	97.4	93.5

Sens = sensitivity; Spec = specificity; NPV = negative predictive value; ACC = accuracy.

PET/CT showed significantly higher overall accuracy than SPECT/CT with optimistic analysis ($^*P = 0.039$). PET/CT showed significantly higher specificity ($^†P = 0.012$) and overall accuracy ($^‡P = 0.011$) than pBS with pessimistic analysis. All other comparisons were nonsignificant ($P > 0.05$).

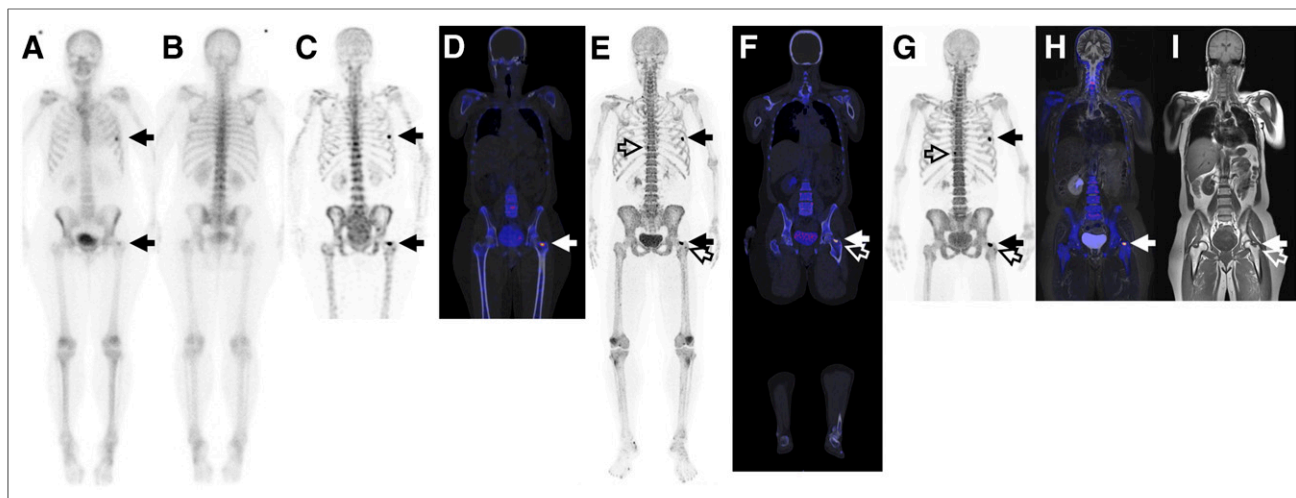


FIGURE 3. A 51-y-old woman treated for locally advanced breast cancer. (A and B) pBS; anterior and posterior views. (C and D) SPECT/CT; maximum-intensity-projection (MIP) and fused image. (E and F) PET/CT; MIP and fused image. (G–I) PET/MR; MIP, fused, and T1 turbo spin echo image. All modalities identified uptake in left rib and in left femoral neck (solid arrows). pBS was interpreted as equivocal. SPECT/CT, PET/CT, and PET/MRI were all interpreted as positive for bone metastases based on lesion in left hip. Lesion in rib represented fracture on CT. PET/CT and PET/MRI identified additional lesions; 2 are marked with hollow arrows. More details and follow-up images are provided in Supplemental Figure 1.

that the exact number of bone metastases is of negligible clinical importance, we chose to perform patient-based analysis in our study.

^{18}F -NaF PET/MRI combines 2 methods highly sensitive for changes in, respectively, bone and bone marrow. Thus, we expected an increased diagnostic sensitivity of PET/MRI compared with standard imaging in this setting. However even though PET/MRI in 2 patients could reveal additional lesions not seen with either SPECT/CT or ^{18}F -NaF PET/CT, we could not demonstrate any significant improved diagnostic performance for PET/MRI in our subgroup of 46 patients. Thus, routine diagnosis of bone metastases by ^{18}F -NaF PET/MRI is not likely to prove cost-effective. Instead, future development of the different imaging modalities will influence the modality of choice: the newly introduced improved image reconstructions for bone on SPECT/CT by integrating CT data in the SPECT image reconstruction (20,21); the promising results with new PET tracers, especially ^{68}Ga -PSMA, for imaging both osseous and nonosseous prostate cancer metastases (22); and the continuing development of faster and optimized whole-body MR imaging sequences.

CONCLUSION

In this prospective study, designed to reflect the patient population that routinely undergoes bone scans at our institution, the clinical benefit of using ^{18}F -NaF PET/CT or PET/MR is likely limited. However, this conclusion is influenced by the lower than expected prevalence of patients with osseous metastases. There may well be significant differences in the sensitivity of SPECT/CT, PET/CT, PET/MR, and pBS, but a larger patient population or a patient population with a higher prevalence of bone metastases would have to be studied to confirm or disprove this. ^{18}F -NaF PET/CT and SPECT/CT, however, produces a significantly lower number of equivocal readings than pBS, most likely because of the structural information

available with corresponding CT. No significantly improved diagnostic performance was found in the subgroup of 46 patients with PET/MRI.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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