Journal of Nuclear Medicine, published on August 10, 2017 as doi:10.2967/jnumed.116.189183

A prospective study comparing ^{99m}Tc-HDP planar bone scintigraphy and whole-body SPECT/CT with ^{18}F-fluoride PET/CT and ^{18}F-fluoride PET/MRI for diagnosing bone metastases

Johan Löfgren[1], Jann Mortensen[1], Sine H Rasmussen[1], Claus Madsen[2], Annika Loft[1], Adam E Hansen[1], Peter Oturai[1], Karl Erik Jensen[3], Mette Louise Mørk[1], Michala Reichkendler[1], Liselotte Højgaard[1], Barbara M Fischer[1]

[1]Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, University of Copenhagen, Denmark.

[2]Department of Clinical Physiology and Nuclear Medicine, Herlev hospital, University of Copenhagen, Denmark

[3]Department of Radiology, Rigshospitalet, University of Copenhagen, Denmark.

Corresponding Author: Johan Löfgren, MD.

Department of Clinical Physiology, Nuclear Medicine & PET

Rigshospitalet, University of Copenhagen,

Blegdamsvej 9

2100 Copenhagen, Denmark

johan.olof.loefgren@regionh.dk

Phone: +45-35459823, fax: +45-35453898

Word count: 4999 (< 5000)

Financial Support: No funding received for this work.

Running Title: Comparing pBS, SPECT/CT, NaF-PET/CT/MRI

ABSTRACT

We prospectively evaluated and compared the diagnostic performance of ^{99m}Tc-HDP planar bone scintigraphy (pBS), ^{99m}Tc-HDP Single-photon emission computed tomography/computed tomography (SPECT/CT), ^{18}F-NaF Positron emission tomography/computed tomography (PET/CT) and ^{18}F-NaF PET/Magnetic resonance imaging (PET/MRI) for the detection of bone metastases. **Methods**: 117 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 days. ^{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 were significantly higher for pBS than for SPECT/CT and PET/CT (18 vs 5 and 6 respectively, p=0.004 resp. p=0.01). When equivocal readings were excluded no statistically significant difference in sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) 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 percentage of misdiagnosed patient for the "pessimistic analysis" were 21%, 15%, 9% and 7% for pBS, SPECT/CT, PET/CT and PET/MR respectively. Corresponding figures for the "optimistic analysis" were 9%, 12%, 5% and 7%. In those patients identified to have bone metastases according to reference standard; SPECT/CT, ^{18}F-NaF PET/CT and PET/MR detected additional lesions compared to 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 to pBS which implies an improved diagnostic confidence. However, the clinical benefit of using e.g. ^{18}F-NaF PET/CT or PET/MR as compared to 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, PET/MR compared to pBS, but a larger patient population or a patient population with a higher prevalence of bone metastases would have to be studied in order to demonstrate this.

Abstract word count: 342 (<350) words

Keywords: ^{99m}Tc-HDP, SPECT/CT, ^{18}F-NaF-PET/CT, PET/MRI, bone metastases

INTRODUCTION

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 a pBS improves the specificity and 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% makes ^{18}F-NaF an excellent bone imaging agent *(7)*. In the 1970s it was replaced by ^{99}Tc-labeled diphosphonate compounds with physical characteristics more suitable for conventional gamma cameras *(8)*.

The more widespread availability of PET/CT scanners and cyclotrons and a more recent global shortage of ^{99}Mo/^{99m}Tc generators in the late '00s 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: While pBS is performed after a 2-5 hours uptake time *(9),* high quality PET/CT images can be obtained as soon as 30-45 minutes after administration of ^{18}F-NaF *(10)*.

Recent meta-analyses 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 for Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R2), December 2015), after reviewing the last 5 years' worth of data, they concluded that there is still not enough evidence to support coverage of ^{18}F-NaF-PET to identify bone metastases. 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 compared to 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 to 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: 1) patients with histologically proven malignancy referred for pBS under the clinical suspicion of bone metastases; and 2) patients able to have a ^{18}F-NaF-PET/CT performed within 9 days, which were considered justifiable to minimize disparity between scans due to potential progression. Exclusion criteria were: 1) known or history of bone metastases; 2) age <18; 3) pregnant or lactating women. When no contraindications to MRI were identified and there was an available timeslot a whole-body ^{18}F-NaF-PET/MRI was performed on the same day as PET/CT in the first 50 patients.

Planar Bone Scintigraphy and SPECT/CT

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

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

PET/CT

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

PET/MRI

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

Attenuation correction was performed using Siemens standard four-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 1.25x1.25 mm^2; scan time 1:25-3:12 minutes/bed), coronal whole-body short tau inversion recovery (TR/TE 5000/84 ms; Flip angle 125°, slice thickness/gap 5/1.5 mm, matrix 186 × 384, in-plane resolution 1.17x1.17 mm^2; scan time 1:47-2:50 minutes/bed) and sagittal short tau inversion recovery covering the spine (TR/TE 2110/8.6 ms; Flip angle 150°, slice thickness/gap 3/0.6 mm, matrix 224×320, in-plane resolution 1.3x0.9 mm^2; scan time 2:28-5:14 minutes/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 1.0x1.0 mm^2; scan time 1:03 minutes/bed) was acquired subsequent to PET at 3 bed positions. 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. Approximate scan time 60-65 minutes.

Image Interpretation

All exams were read on standard workstations. pBS and SPECT/CT were interpreted separately by 2 experienced nuclear medicine specialists with assistance of a radiologist and discrepancies were solved in consensus. ^{18}F-NaF-PET/CT were read by 2 other experienced nuclear medicine specialists with assistance of 2 radiologists and discrepancies were solved in consensus with a third nuclear medicine specialist. ^{18}F-NaF-

PET/MRI were read by a nuclear medicine specialist together with a MR-radiologist specialized in musculoskeletal MRI. All readers were blinded 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. Based on these data three 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" *(15,18)*.

Reference Standard

Results from the interpretations were held up against final diagnoses as confirmed by histological evaluation, clinical follow-up, or other imaging studies. At least 6-month clinical follow-up, including review of all regional hospitals' medical records, biopsies, laboratory reports and all subsequent imaging were used. 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 were strong evidence of bone metastases. Scans were considered false-negative if follow-up revealed bone metastases within 6 months.

Statistical Analysis

The sample size calculation was prospectively determined to be 120 (power of 80%, alpha 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., Armonk, NY). A patient-based data analysis was performed. Sensitivity, specificity, accuracy, PPV and NPV for pBS, SPECT/CT, PET/CT and PET/MRI were compared using McNemar test. Two-sided p-values were calculated and a p-value <0.05 was considered statistical significant. Frequency of equivocal readings was compared with 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 ^{18}F-NaF-PET/CT was performed 5.3±2.3 days after pBS and SPECT/CT. 46 patients had a supplemental ^{18}F-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 exam. Effective dose from ^{18}F-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 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 days (range 130-1090). 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 days after the initial pBS. 66 patients (56%) had relevant imaging within the follow-up period and 45 (38%) within six months.

Patient-based Analysis

91 out of 117 (true positive and true negative cases) patients were correctly diagnosed with pBS including 9 out of 16 with bone metastases and 82 out of 101 without bone metastases. 18 pBS readings were equivocal (2 with bone metastases and 16 without), Table 5. 99/117 patients were correctly diagnosed with SPECT/CT including 9/16 with bone metastases and 90/101 without. 5 SPECT/CT readings were equivocal (1 with bone metastases and 4 without). 102/117 patients were correctly diagnosed with PET/CT including 12/16 with bone metastases and 94/101 without. 6 PET/CT readings were equivocal (1 with bone metastases and 5 without). 43/46 patients were correctly diagnosed with PET/MRI including 6/7 with bone metastases and 37/39 without. No PET/MRI readings were equivocal. All modalities missed the same 2 patients diagnosed with bone metastases 4.5 and 5 months after the initial pBS.

The number of equivocal pBS, 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 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, NPV or overall accuracy were found when comparing the different techniques. Table 6 summarizes the diagnostic performance when applying "optimistic analysis" and "pessimistic analysis".

Imaging Findings

Among the 16 patients with bone metastases, three patients were categorized by PET/CT to have widespread metastases (>20 lesions) while SPECT/CT showed >20 lesions in two of them and pBS only characterized one of them to have widespread bone metastases. Compared to pBS, SPECT/CT showed additional lesions in 5 out of these 16 patients (31%) and PET/CT in 10 (63%). Seven of the 16 patients with bone metastases performed PET/MRI. PET/MRI revealed additional lesions in 5 out of 7 these patients (71%) compared to pBS, and in two (28%) of them also lesions not identified on SPECT/CT and PET/CT (example in Fig. 3 and Supplemental Fig. 1). In two cases, PET/MRI indicated in contradiction to the other modalities presence of single bone metastases 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 to 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 relative high percentage of those patient identified to have bone metastases, 31%, 63% and 71% respectively. But on a patient level, despite the technological advantages of SPECT/CT, PET/CT and PET/MR, they only correctly changed the tumor stage in a relatively small fraction of patients compared to 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, summarised in several meta-analyses *(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 contradictive to prior meta-analyses where pooled sensitivity for pBS is 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 where 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.

Standard of reference were clinical follow-up, including other imaging examinations and histological evaluation. Histology evaluation were in our study performed on two patients. The definition of false negative scans could be debateable 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 months 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 should 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 histological proof is of course impractical and unethical. In lesion-based analysis the number of lesions included in each patient must also be limited because otherwise patients with lots of true positive lesions detected only on PET/CT will have too strong influence on the result. As a consequence of this bias, the problem with verification and the fact 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 two methods highly sensitive for changes in respectively bone and bone marrow. Thus, we expected an increased diagnostic sensitivity of PET/MRI compared to standard imaging in this setting. However even though PET/MRI in two patients could reveal additional lesions not seen neither with SPECT/CT nor ^{18}F-NaF-PET/CT, we couldn't 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 *(19,20)*, the promising results with new PET-tracers, especially ^{68}Ga-PSMA for imaging both osseous and non-osseous prostate cancer metastases *(21)* 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 in order to confirm or disprove this. ^{18}F-NaF-PET/CT and SPECT/CT however produces significantly lower number of equivocal readings compared to pBS, most likely due to the structural information available with corresponding CT. No significantly improved diagnostic performance was found in the subgroup of 46 patients with PET/MRI.

Conflict of Interest: The Authors declare no conflicts of interest to report. The authors confirm that there is no funding received for this work.

ACKNOWLEDGEMENTS

The authors wish to thank K Stahr, M Federspiel, J Poulsen, E Abrahamnsson, T Lundby, M C H Albers, and M H B Frederiksen for all their work in conjunction with scanning of the patients and John and Birthe Meyer foundation for donation of the PET/MRI system.

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FIGURE LEGENDS

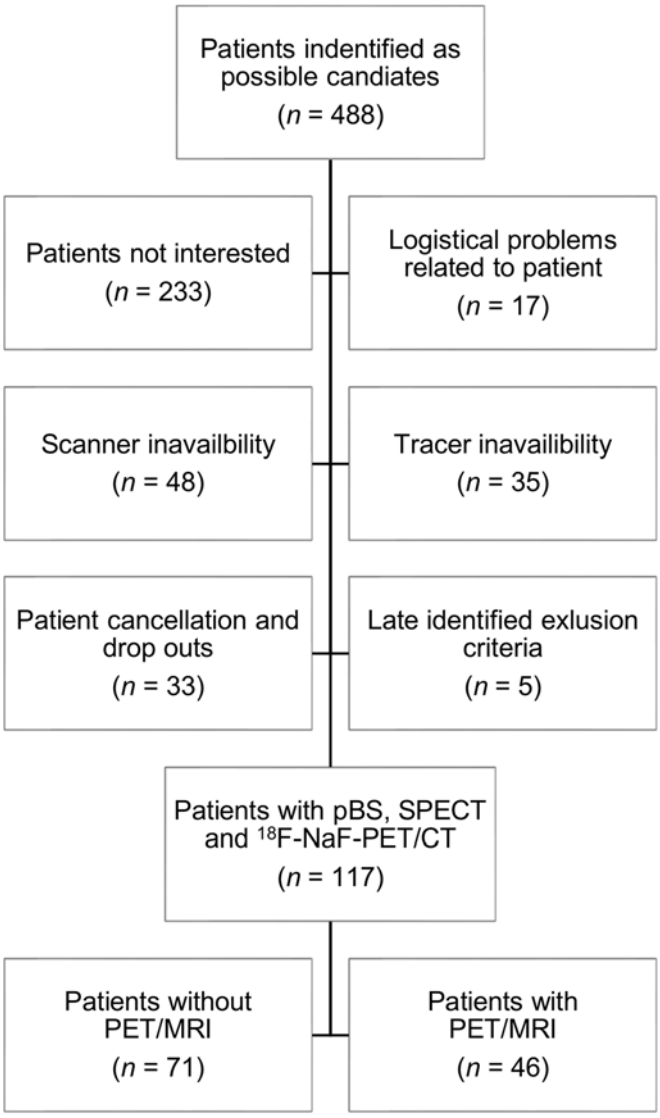


FIGURE 1. Flowchart illustrating patient inclusion and exclusion

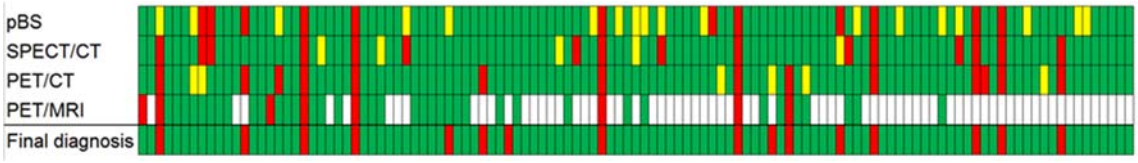


FIGURE 2. Illustrates all scans with one patient in each column. Red – positive scan or final diagnosis, green – negative scan or final diagnosis, yellow – equivocal scan, white – not performed

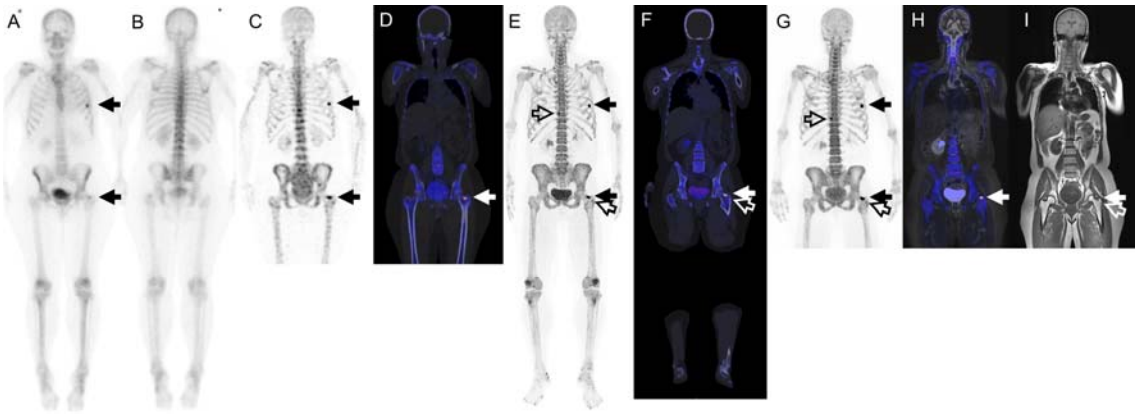


FIGURE 3. 51-year-old woman treated for locally advanced breast cancer. A+B) pBS, anterior and posterior view, C+D) SPECT/CT, maximum intensity projection image (MIP) and fused image, E+F) PET/CT, MIP and fused image, G+H+I) PET/MRI, MIP, fused image and T1 turbo spin echo. All modalities identified uptake in the left rib and in the 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 the lesion in the left hip. The lesion in the rib represented a fracture on CT. PET/CT and PET/MRI identified addition lesions, two are marked with hollow arrows, see also more details and follow-up images in Supplemental Figure 1.

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/view (s)	6	8			
Time/bed (min)			2	2	5
Axial FOV/bed (cm)	38.7	38.1	21.8	21.8	25.8
Matrix	128x128	128x128	336x336	400x400	344x344
Slice thickness (mm)			3	2	2
Energy window (keV)	140±15%	140±15%	435-650	435-650	430-610
Reconstruction method	5iter 10subs	4iter 16subs Astonish	3iter 21subs 4mm	3iter 21subs 4mm	3iter 21subs 4mm
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	

TABLE 2

Patient characteristics

Characteristics	Study population	Subgroup with PET/MRI
Number of patients	117	46
Gender n (%)		
Female	55 (47%)	22 (48%)
Male	62 (53%)	24 (52%)
Age, mean (SD)	62.3 (10.7)	61.0 (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.

†The average Gleason score, for the 19 prostate cancer patient having the bone scan for initial staging, was 7.7

TABLE 3

Clinical indication for requesting bone scan overall and stratified by cancer type.

	Prostate	Breast	Renal	Combined
Number of patients (% of cohort)	62 (53.0)	54 (46.2)	1 (0.9)	117 (100)
Main reason for ordering bone scan (%)				
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 one patient with metastases to testes, one with elevated alkaline phosphatase and one with weight loss as a signs of progression.

TABLE 4

Patients with confirmed bone metastases based on reference standard

Gender	Age	pBS	SPECT/CT	PET/CT	PET/MRI	Cancer type	Follow-up imaging	Final diagnosis based on
Woman	51	Eq	Pos	Pos	Pos	Breast	CTx3	Change from lytic to sclerotic during treatment
Woman	51	Pos	Neg	Pos	-	Breast	CTx11	Change from lytic to sclerotic during treatment
Male	70	Pos	Pos	Pos	Pos	Prostate	MRIx4, CTx5, pBSx4	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	CTx3, pBSx5	Bone metastases diagnosed on follow-up imaging approx. 5 month after initial scans*
Male	66	Neg	Neg	Pos	-	Prostate	MRI, CT	Follow-up imaging
Male	79	Neg	Neg	Neg	-	Prostate	CTx4, pBSx4, MRI	Bone metastases diagnosed on follow-up imaging approx. 4 month 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	CTx2, pBSx3	Progression of index lesion and increased lesion number over time.
Woman	48	Neg	Neg	Eq	-	Breast	MRI, CTx8, FDG-PET	Change from lytic to sclerotic during treatment
Male	64	Neg	Neg	Pos	Pos	Prostate	MRIx2, 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	CTx4, pBSx4	Typical appearance of multifocal disease and increased lesion number over time.
Woman	44	Pos	Pos	Pos	-	Breast	FDG-PET, CTx6, MRIx2	Change from lytic to sclerotic during treatment
Male	69	Pos	Pos	Pos	-	Prostate	CTx2, pBSx2, MRI	Progression of index lesion and change from lytic to sclerotic during treatment
Woman	56	Neg	Pos	Pos	-	Breast	MRIx5, CTx9, FDG-PET	Biopsy and follow-up imaging

* bone metastases first diagnosed during follow-up, within 6 months. Eq: equivocal, Neg: Negative, Pos: Positive.

TABLE 5

Patient-based analysis

	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

TP: true positive, FP: false positive, TN: true negative, FN: false negative.

* pBS different from SPECT/CT (p=0.004) and PET/CT (p=0.01).

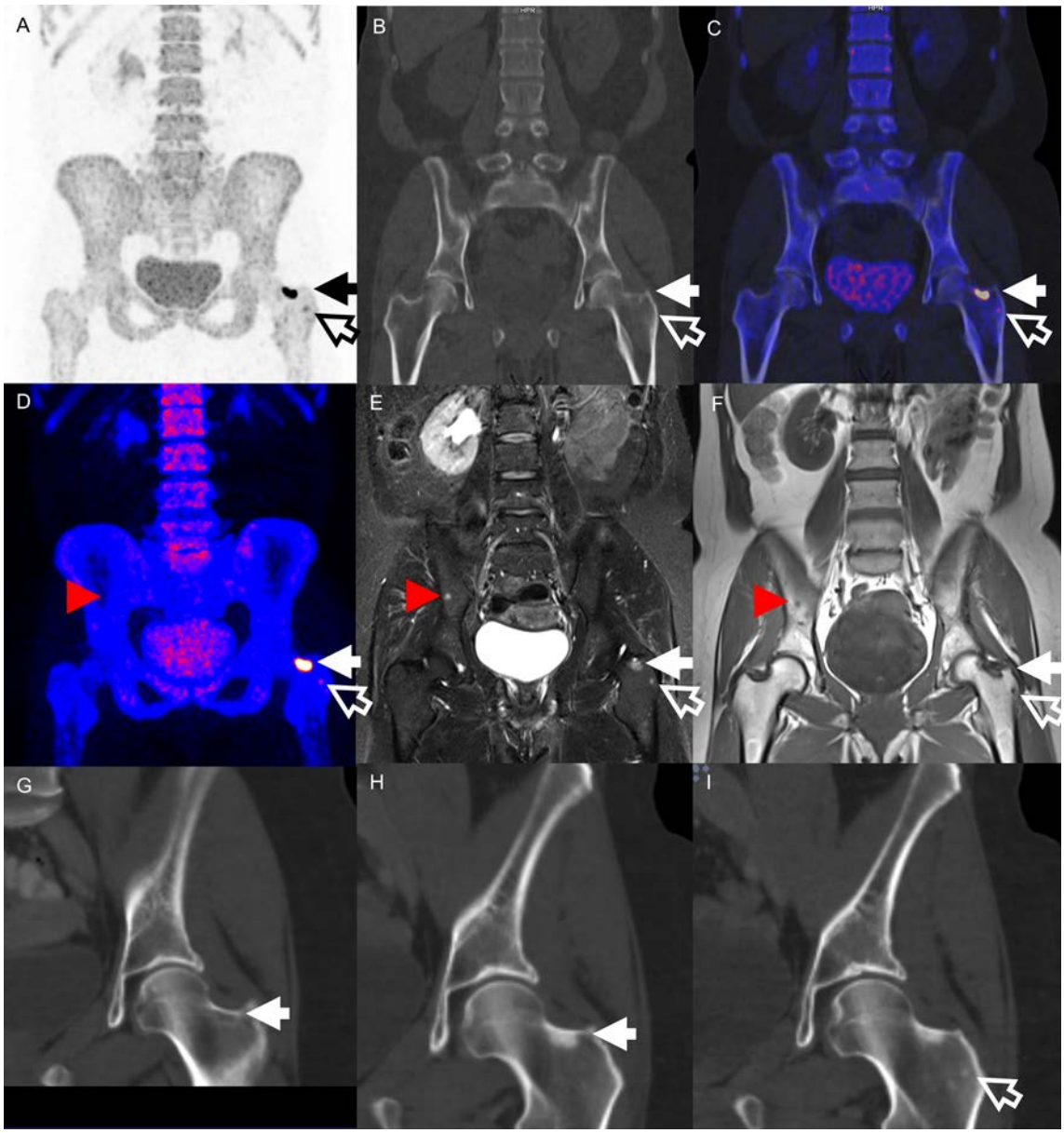
TABLE 6

Patient-based analysis

	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, PPV: positive predictive value, NPV: negative predictive value, ACC: accuracy. PET/CT showed significantly higher overall accuracy than SPECT/CT with the "optimistic analysis" (*p=0.039). PET/CT showed significantly higher specificity (†p=0.012), and overall accuracy (‡p=0.011) than pBS with the "pessimistic analysis". All other comparisons were non-significant, p>0.05.

SUPPLEMENTAL FIGURE LEGENDS



SUPPLEMENTAL FIGURE 1. Same patient as in Figure 3. A-C) PET/CT, D-F) PET/MRI. Two lesions in the left hip were identified on both PET and MR (solid and hallow arrow). G) The bigger lesion could retrospectively be found on a diagnostic CT one month prior to PET. H) CT 2 months after treatment shows a sclerotic transformation of the lesion. I) The smaller lesion has also turned sclerotic. MRI showed an additional lesion in the pelvic bone (red arrowheads) not identified on PET.