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Original Article

Diagnostic test accuracy study of ^{18}F-sodium fluoride PET/CT, ^{99m}Tc-labelled diphosphonate SPECT/CT, and planar bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer

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Abstract: The aim of this study was to prospectively compare planar, bone scan (BS) versus SPECT/CT and NaF PET/CT in detecting bone metastases in prostate cancer. Thirty-seven consecutive, newly diagnosed, prostate cancer patients with prostate specific antigen (PSA) levels ≥ 50 ng/mL and who were considered eligible for androgen-deprivation therapy (ADT) were included in this study. BS, SPECT/CT, and NaF PET/CT, were performed prior to treatment and were repeated after six months of ADT. Baseline images from each index test were independently read by two experienced readers. The reference standard was based on a consensus decision made by a multidisciplinary team on the basis of baseline and follow-up images of the index tests, the findings of the baseline index tests by the experienced readers, and any available imaging, biochemical, and clinical data, including the response to ADT. Twenty-seven (73%) of the 37 patients had bone metastases according to the reference standard. The sensitivities for BS, SPECT/CT and NaF PET/CT were 78%, 89%, and 89%, respectively, and the specificities were 90%, 100%, and 90%, respectively. The positive predictive values of BS, SPECT/CT and NaF PET/CT were 96%, 100%, and 96%, respectively, and the negative predictive values were 60%, 77% and 75%, respectively. No statistically significant difference among the three imaging modalities was observed. All three imaging modalities showed high sensitivity and specificity. NaF PET/CT and SPECT/CT showed numerically improved, but not statistically superior, sensitivity compared with BS in this limited and selected patient cohort.

Keywords: Diagnostic test accuracy, NaF PET/CT, SPECT/CT, bone scan, prostate cancer, bone metastases

Introduction

Prostate cancer is one of the most frequently occurring cancers in men. It often metastasizes to the skeleton and thus causes significant morbidity [1]. Reliable detection of bone metastases is important in patient management. Across clinical guidelines, planar whole-body bone scintigraphy (BS) remains the internationally recommended method for the detection of bone metastases in prostate cancer [2-4]. Technical refinements of BS such as single-photon emission computed tomography (SPECT) with computed tomography (CT) using ^{99}mTc-labelled diphosphonate are commonly applied, and improved accuracy has been reported in many studies. However, neither SPECT/CT nor positron emission tomography (PET) with CT is recommended in the international guidelines for the initial staging of prostate cancer [2-4].

Studies of the diagnostic performance of bone SPECT/CT and PET/CT are small, often retro-

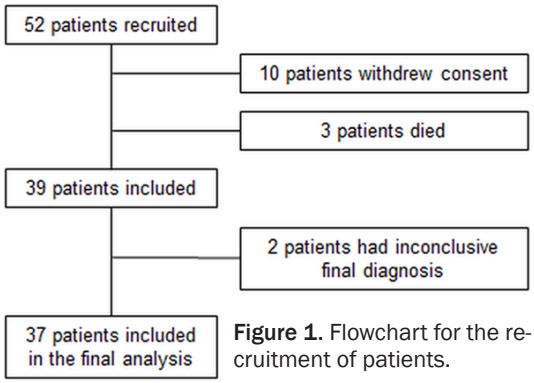

Figure 1. Flowchart for the recruitment of patients.

spective, and based on heterogeneous patient populations [5]. However, the main drawback in these studies has been the lack of a well-defined reference standard. Histopathology is rarely used as a reference. Thus, the reference largely relies on clinical follow up and/or supplementary or follow-up imaging. The criteria used for clinical follow-up and decision analyses are often vaguely described, and the methods for supplementary imaging may include methods with low diagnostic characteristics (such as x-ray) or imaging modalities with the same mode of action as the test being investigated. The reference standard may have been based entirely or predominantly on consensus evaluations of the index test, which might artificially boost the performance of the index test in a circular reasoning [5-8]. Thus, in the absence of histological verification, a firm definition of the presence or absence of bone metastases is essential to evaluate the diagnostic performance of any imaging modality [6].

The purpose of the present study was to prospectively compare the diagnostic performances of conventional BS, SPECT/CT, and ^{18}F-sodium fluoride (NaF) PET/CT. We aimed to establish a well-defined reference standard based on consensus decisions in a multidisciplinary team of experts with access to all available clinical, biochemical, and imaging information, including images at baseline and follow-up images after androgendeprivation therapy (ADT).

Materials and methods

Study design

This was a prospective, multi-center, diagnostic test accuracy (DTA) study comparing the diagnostic accuracy of NaF PET/CT and SPECT/CT versus BS for the diagnosis of bone metastases. The study protocol has been published separately [9]. This study was fully compliant with the Standards for Reporting of Diagnostic Accuracy (STARD) guideline for DTA studies [8]. The study was approved by the Regional Research Ethics committee (N-20130068) and the Danish Data Protection Agency, and it followed the Helsinki Declaration. All patients received oral and written information and provided written informed consent for participation in this study.

Patients

Consecutive patients with newly diagnosed, high-risk prostate cancer were recruited from two departments of urology in Denmark, namely, at Regional Hospital West, Herning and Holstebro, and at Aalborg University Hospital, Aalborg from February 2014 to December 2015. Eligibility criteria comprised the following: 1) histologically confirmed adenocarcinoma of the prostate; 2) prostatespecific antigen (PSA) blood levels ≥ 50 ng/mL; 3) eligible for ADT; 4) no current or prior cancer (5 years); and 5) no investigational drugs. The PSA cut-off value of ≥ 50 ng/mL was chosen because the estimated prevalence of bone metastases in this group was approximately 50% according to previous research [10]. A metastasis-enriched population was selected to optimize sample size and statistical power [9]. The patients had not have any other bone imaging prior to inclusion in this study.

Sample size

Sample size calculations were based on the recommendations by Hayen et al. for sample size calculations in DTA studies [11] They were based on a prevalence of 50% bone metastases in a bone-metastasis-enriched population (PSA > 50 ng/ml) and weighted means of sensitivity and specificity of BS, SPECT/CT and NaF PET/CT calculated from values in previously published clinical trials [9]. This resulted in 114 patients being required to show a significant difference between the specificities of the index tests. Accounting for dropouts, we aimed to recruit 140 patients. However, despite persistent efforts towards increasing recruitment across centers, only 39/52 recruited patients completed the study (**Figure 1**).

Imaging and related procedures

Planar whole-body BS, SPECT/CT, and NaF PET/CT were performed within a timeframe of 14

Table 1. Reference standard - List of all information that were available to the consensus review committee

Routine Procedures
Diagnostic information; PSA, Gleason Score, T-stage
Treatment; type, duration, and response
Routine PSA measurements; up to 1 year after inclusion
Baseline BS
Clinical questionnaire filled out by the patients with BS
Any existing routine imaging; x-ray, CT, MRI, and non-study-related BS and SPECT/CT
Study-related procedures
Baseline performance status
Blood levels of testosterone (baseline and after 6 months)
Follow-up PSA after 6 months
Baseline imaging; SPECT/CT and NaF PET/CT
Follow-up imaging after 6 months; BS, SPECT/CT, and NaF PET/CT
Consensus classification of index imaging test results as reported by expert readers

PSA, prostate-specific antigen; CT, computed tomography; MRI, magnetic resonance imaging; BS, planar whole-body bone scintigraphy; SPECT, single photon emission computed tomography; NaF PET/CT, ^{18}F-sodium fluoride positron emission tomography/computed tomography.

days and no later than seven days after the initiation of ADT treatment. Imaging by all three modalities was repeated after six months of treatment to assist in the determination of the final diagnosis (see the reference standard below). A clinical questionnaire was, as per routine, filled out by the patients with each BS, containing information about artificial joint replacements, prior joint and bone surgery or infections, known degenerative or inflammatory bone diseases, recent trauma to the skeleton, and the location and duration of unexplained bone pain [12]. The blood levels of PSA and testosterone were measured at baseline and after six months of treatment.

BS and SPECT/CT were conducted in accordance with current institutional recommendations, which are in line with international guidelines [13]. All BS procedures were performed using Symbia dual-head gamma cameras with multi-purpose, low-energy, high-resolution collimators (Symbia T16, Siemens Medical Solutions, Erlangen, Germany, in Aalborg and Symbia T2 and T16 in Herning). Scans were performed two to three hours after the intravenous administration of 750-1000 MBq ^{99m}Tc-labelled diphosphonate in Aalborg and 10 MBq/kg in Herning. The scan speed was 10 cm/min in Herning and 24 cm/min in Aalborg, with 30% alpha blending.

In Aalborg, a three-bed position SPECT/CT scan, from the vertex to mid-thigh, was performed immediately following planar imaging using the following parameters: matrix: 128 × 128; zoom factor: 1; 20 s per view; 32 views; and rotation of the detectors by 180 degrees in a non-circular orbit using the step-and-shoot mode. A similar protocol was used in Herning but with 10 s per view, and 64 views, in a continuous mode. At both sites, low-dose CT without intravenous contrast was acquired and used for attenuation correction and anatomical co-registration: 30 mA: 130 kV, 3-mm slice thickness (Aalborg); reference mA: 100 (CARE dose), 130 kV, and 5-mm slice thickness (Herning).

NaF PET/CT scans were performed using two different PET/CT scanners in Aalborg and Herning, respectively: 1) VCT discovery True 64 PET/CT (GE Healthcare) and 2) Biograph mCT 64, 4R (Siemens Medical Solutions). All scans were performed 30 min after the intravenous administration of approximately 200 MBq NaF in 3D mode from the vertex to mid-thigh, encompassing 7-9 bed positions (150 s per bed position for GE VCT discovery True and 120-180 s per bed position according to the body mass index for Siemens Biograph). PET images were reconstructed by iterative construction and using low-dose CT images for attenuation correction and anatomical co-registration. The CT parameters were 70-200 mA smart mA, 120 kV for GE VCT discovery True and 30 mAs, 120 kV for Siemens Biograph. Both protocols had a slice thickness of 0.625 mm.

Image interpretation

Images from each index test were independently read by two trained experts. The readers were blinded to all clinical and biochemical information, except the prostate cancer diagnosis and the high level of PSA. Two experienced

Table 2. Patient demographics and baseline characteristics (n=37 patients)

Age (years), mean (range)	71 (46-87)
Baseline PSA (ng/mL), median (range)	180 (53-9,708)
Gleason score, median (range)	9 (7-10)
T-stage	
T1, n (%)	1 (2.7)
T2, n (%)	6 (16.2)
T3, n (%)	22 (59.4)
T4, n (%)	8 (21.6)
Performance status	
0, n (%)	26 (70.2)
1, n (%)	8 (21.6)
2, n (%)	3 (8.1)
Unexplained bone pain, n (%)	10 (27.0)
Chronic degenerative bone disorder, n (%)	6 (16.2)
Treatment	
Primary ADT treatment, n (%)	35 (94.6)
Radical prostatectomy, n (%)	1 (2.7)
No treatment, n (%)	1 (2.7)

PSA, prostate-specific antigen; ADT, androgen-deprivation therapy.

nuclear medicine physicians with more than 10 years of experience in bone imaging (JF and JAE) read the BS and SPECT/CT separately without knowledge of prior findings. Likewise, NaF PET/CT scans were evaluated by two experienced nuclear medicine physicians (CH and HWH), who had 5 and 10 years of experience, respectively, with NaF PET/CT.

Each reader was asked to assess the baseline image on a three-point scale (non-metastatic (M0), equivocal (Me), or malignant (M1)) and on a dichotomous scale (M0 or M1). After completing the individual readings, the readers were asked to reach a consensus on the patient level.

Reference standard

In the absence of a histologic gold standard, the reference standard consisted of a consensus review of all available imaging, including results of index tests, and all clinical, and biochemical information (**Table 1**). The consensus review was conducted by a multidisciplinary team consisting of three board-certified specialists who did not participate in the initial expert consensus readings. The team consisted of a nuclear medicine physician (HDZ), a radiologist (MBL), and a urologist (NCL) (7-20 years of experience with prostate cancer and bone imaging). The consensus review was conducted as follows: Each patient was presented with diagnostic information, treatment type and response to treatment, biochemical response, and the results of the independent expert readings of baseline images. Furthermore, schematic drawings of the skeleton filled out by the expert readers were presented for patients with fewer than 10 bone lesions to identify suspicious lesions and the clinical questionnaire filled out by the patient was reviewed for unexplained bone pain or other relevant information. The baseline and follow-up images from all three imaging modalities were then evaluated side-by-side. Suspicious lesions identified on baseline images were traced to follow-up images for the assessment of changes following treatment. Any additional imaging was included if required (n=2). The multidisciplinary team discussed the available information and reached a final consensus for each patient regarding the presence of bone metastases.

Due to logistical reasons, we changed parts of the image analysis procedure after the protocol was published [9]. The protocol largely relied on the imaging-based response of ADT to clarify malignant lesions from benign findings; i.e., in responding patients (PSA decrease > 80%), the bone lesions became invisible or significantly decreased in intensity at follow-up, but the preliminary analysis showed inconsistencies in the treatment-induced responses. We therefore changed the reference standard to include an evaluation by a multidisciplinary team with access to all available information, as described above.

Statistical analyses

Data are presented on a patient basis and are presented with 95% confidence intervals (95% CIs). The sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV) were calculated on the basis of the results of the reference standard. The sensitivities and specificities for BS, SPECT/CT and NaF PET/CT were compared using the McNemar test with $p<0.05$ considered statistically significant. All statistical analyses were performed using StataIC version 13, StataCorp LCC, TX, USA.

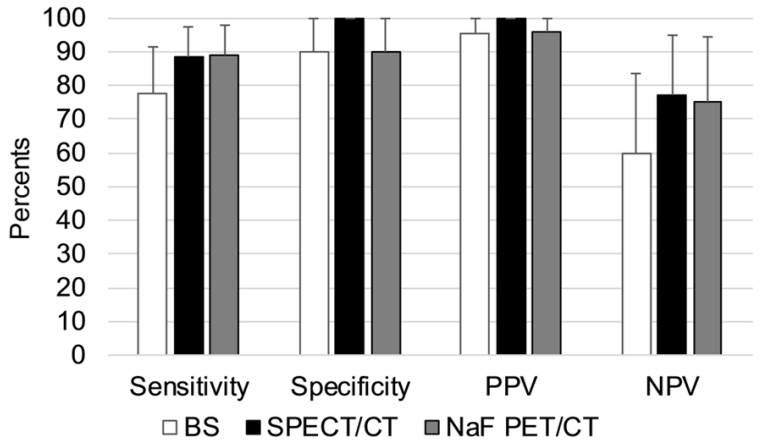

Figure 2. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values of bone scan (BS), SPECT/CT and NaF PET/CT. Error bars indicate the upper 95% confidence interval.

Table 3. Assessment of bone metastases on a three point-scale and subsequent dichotomous classification according to imaging modality and the reference standard

	M1 by reference standard (n=27)			M0 by reference standard (n=10)		
Modality	M1	Me	M0	M1	Me	M0
BS	21	3	3	0	1	9
Dichotomous reading	*21*	-	*6*	*1*	-	*9*
SPECT/CT[a]	21	3	2	0	1	9
Dichotomous reading	*23*	-	*3*	*0*	-	*10*
^{18}F-NaF PET/CT	24	2	1	1	0	9
Dichotomous reading	*24*	-	*3*	*1*	-	*9*

[a]Baseline SPECT/CT was missing in one patient M1, malignant bone lesions; M0, non-metastatic; Me, equivocal; BS, planar whole-body bone scintigraphy; SPECT/CT, single photon emission computed tomography/computed tomography; ^{18}F-NaF PET/CT, ^{18}F-fluoride positron emission tomography/computed tomography.

Results

Thirty-nine patients completed the study. However, the multidisciplinary team found it impossible to reach a consensus on the reference standard in two patients: One patient was suspected suffering from osteopoikilosis, a sclerosing bony dysplasia characterized by numerous bony islands, but a final diagnosis could not be made. Another patient showed equivocal lesions on both BS and NaF PET/CT, and neither CT nor follow-up BS or NaF PET/CT could verify these as bone metastases. Thus, 37 patients were included in the final analysis (**Table 2**). Baseline SPECT/CT data were missing in one patient.

The reference standard classified bone metastasis in 27 patients (73%). In 20/27 patients (74%) with bone metastases, at least one of the imaging modalities detected > 10 suspicious bone lesions. Using the dichotomous classification, bone metastases (M1 disease) were correctly diagnosed in 20 of 27 patients (74%) by all three imaging modalities. Similarly, bone metastases were correctly identified as absent in 8 of 10 patients (80%) by all three imaging modalities.

The diagnostic properties of BS, SPECT/CT and NaF PET/CT are shown in **Figure 2**. The sensitivities of the three index tests were 78% (95% CI: 58-91%) for BS, 89% (95% CI: 70-98%) for SPECT/CT, and 89% (95% CI: 71-98%) for NaF PET/CT. SPECT/CT correctly classified all patients without bone metastases, thus demonstrating a specificity of 100% (95% CI: 69-100%), whereas the specificity of both BS and NaF PET/CT was 90% (95% CI: 56-100%). The PPV was 96% (95% CI: 77-100%) for BS, 100% (95% CI: 85-100%) for SPECT/CT, and 96% (95% CI: 80100%) for NaF PET/CT. The NPV for SPECT/CT was 77% (95% CI: 46-95%) and 75% (95% CI: 43-95%) for NaF PET/CT; consequently, both SPECT/CT and NaF PET/CT outperformed BS in this regard (NPV=60%; 95% CI: 32-84%). The overall accuracies for the three index tests were 81% for BS, 92% for SPECT/CT, and 89% for NaF PET/CT. No statistically significant differences among the sensitivities and specificities of BS, SPECT/CT and NaF PET/CT were observed on a patient level.

In the initial evaluation of images, the readers were allowed an equivocal rating option. The proportion of equivocal results were 11% for BS, 11% for SPECT/CT and 5% for NaF PET/CT. **Table 3** shows the distribution of patients as malignant, equivocal, or nonmetastatic and their subsequent dichotomous classifications according to imaging modality and their final

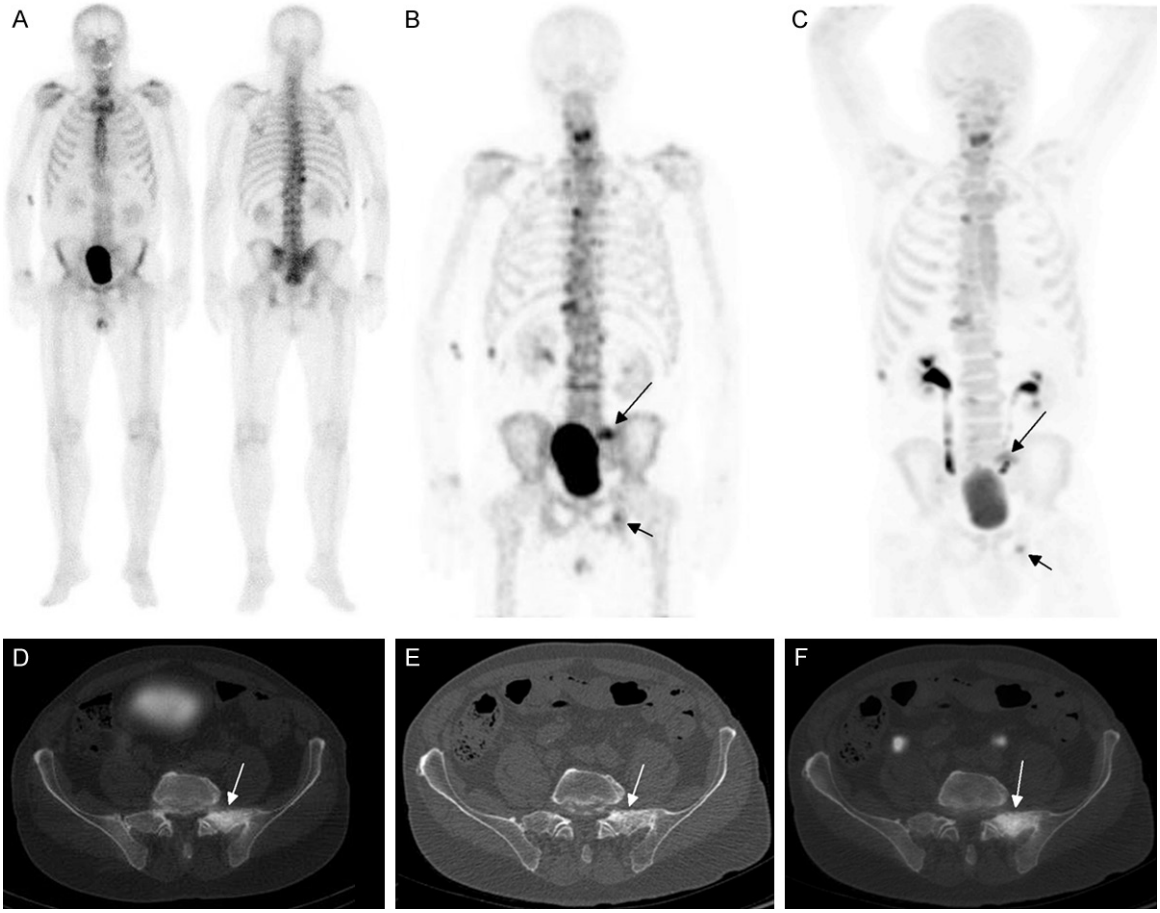

Figure 3. An illustrative example of baseline imaging of a 74-year-old patient classified as true positive for bone metastases by both SPECT/CT and NaF PET/CT, but false negative by planar whole-body bone scan. Anterior and posterior projections of the bone scan (A) were interpreted as non-metastatic on the dichotomous scale (with equivocal uptake in the pelvic region noted on the three-point scale). Both SPECT (B) and NaF PET (C) showed metastatic lesions on the maximum intensity projection images (long and short black arrows). These lesions were confirmed by fused SPECT/CT and PET/CT: Axial images corresponding to the lesion indicated by a long black arrow on (B and C) are shown on the fused SPECT/CT (D), on the corresponding CT from the NaF PET/CT scan showing sclerosis at the site of the lesion (E), and finally on (F), which shows the fused NaF PET/CT image (white arrows).

diagnosis of malignant or non-metastatic. For BS, three equivocal patients were incorrectly down-staged, and one was incorrectly up-staged on the dichotomous scale. Two patients were correctly up-staged, and was one correctly down-staged by SPECT/CT; one patient was incorrectly down-staged. Two patients were classified as equivocal by NaF PET/CT; they were both incorrectly down-staged.

All imaging modalities misclassified one or more patients. Three patients were false negative by BS; these patients were correctly diagnosed with bone metastases by SPECT/CT and NaF PET/CT, **Figure 3**. One patient was incorrectly classified as negative for bone metastases by all three imaging modalities using the dichotomous scale, although BS and NaF PET/CT both identified a single equivocal lesion in a rib when evaluating the images on the three-point scale with the possibility of an equivocal status. Bone scintigraphy and NaF PET/CT each identified one patient as false positive. In addition, three more patients were incorrectly classified by two of the three index tests.

The expert consensus evaluations showed a high level of agreement between readers (JAE vs. JF and HWH vs. CHN), and the crude agreements on the dichotomous scale were 95% for BS, 86% for SPECT/CT, and 100% for NaF PET/CT. On the three-point scale, they were 78% for BS, 84% for SPECT/CT, and 97% for NaF PET/CT.

Discussion

When NaF was introduced in the 1970s, the logistical and technical requirements for the investigation of bone metastases by this tracer were very high. Additionally, due to the low costs and availability of BS, it remained the standard imaging modality for the identification of bone metastases. In recent years, PET scanners have become increasingly available, and this has spiked the interest in using NaF PET/CT for molecular skeletal imaging. Although guidelines have refrained from recommending the use of NaF PET/CT [4], it is used routinely in clinics worldwide. Compared with BS, NaF PET/CT has the advantages of faster blood clearance, an improved target-to-background ratio, high spatial resolution, attenuation correction, and the inherent hybrid PET/CT imaging. Furthermore, previous research has shown the advantages of NaF PET/CT over BS. However, despite these apparent advantages, the existing evidence has methodological flaws, and there is a lack of consistent evidence showing the clinical benefits of NaF PET/CT versus BS. Therefore, recent guidelines continue to recommend BS for bone metastases staging [5, 14].

In this prospective, fully STARD-compliant study, we performed a patient-based, head-to-head comparison of planar BS, SPECT/CT, and NaF PET/CT. Our results showed that BS, with a sensitivity of 78%, was numerically outperformed by both SPECT/CT and NaF PET/CT, both of which showed sensitivities of 89%. These differences did not reach statistical significance, which is likely caused by the limited sample size and resulting broad and overlapping confidence intervals. Our results are supported by previous studies demonstrating that the sensitivity of NaF PET/CT is superior to that of BS [15-17]. Likewise, studies comparing the diagnostic properties of BS vs. SPECT/CT have shown that the sensitivity of BS is improved by adding SPECT/CT [16, 18]. It is generally considered that the sensitivity of BS is sufficiently high to exclude any clinically relevant bone metastases [18].

In contrast to the sensitivity, the specificity of BS is considered quite low, and this has been a challenge in clinical practice. The reported specificity of planar BS ranged from 39% to 82% in previous studies [18]. Our data showed excellent specificity with BS. The specificity did not improve NaF PET/CT, which, similar to BS, showed a specificity of 90%. These findings contrast research showing the improved specificity of NaF PET/CT over BS. Damle et al. showed a markedly lower specificity of BS (41%) than that of NaF PET/CT (71%) [15]. Additionally, Even-Sapir et al. showed a specificity of BS at 57% and 100% for NaF PET/CT but with an unclear distinction between NaF PET/CT and the reference standard [16]. The high specificity of BS, as found in the current study, might reflect that the readers of BS had clinical experience with BS before the possibility of add-on SPECT/CT, thus making them likely to provide confident and unequivocal answers to BS.

Compared with previous studies with highly heterogeneous study populations [5, 15-18], we focused on high-risk, newly diagnosed patients. Based on previous research, we expected a prevalence of bone metastases of 50% [10]. A metastasis-enriched population was selected in this study to optimize the sample size and statistical power [9]. However, our observed prevalence was much higher than expected (73%). In general, the prevalence is a trade-off between the PPV and the NPV; i.e., a high prevalence is associated with a high PPV and a low NPV. This corresponded to the observed results in this study, and we realized that any conclusions drawn by the NPV should be viewed in the context of the actual and not the planned recruitment and prevalence of bone metastases.

We showed that the addition of tomography and CT, numerically improved the specificity of SPECT/CT over planar BS, causing an improvement in the specificity from 90 to 100% (not statistically significant). We are well aware of the low statistical power of the comparisons; however, the improved specificity of SPECT/CT over BS is in line with previous research showing that adding SPECT/CT improved the specificity of BS [16, 18].

A major drawback of BS is the apparent large proportion of equivocal imaging results. The proportion of equivocal cases has been reported to account for approximately 20% of all patients in large, prospective trials [10, 19]. The proportion of equivocal scan results in this study was low across all three imaging modalities, with the proportion for NaF PET/CT (5%) being half that of BS and SPECT/CT (11%). It

should be noted, however, that the observers were more likely to make the right decision based on the presence of bone metastases when using SPECT/CT compared with BS and NaF PET/CT (**Table 3**). Our results indicated that when having the option of adding SPECT/CT to BS to evaluate equivocal lesions, this seems to be equal to using NaF PET/CT and is superior to using BS alone. We did not investigate whether upfront 3-bed SPECT/CT was superior to add-on SPECT/CT in the case of equivocal BS.

A major limitation of this study was the low patient number and, thus, the impaired power. There were several explanations for this. First, some centers withdrew from their initial interest to participate due to logistic issues, competing protocols, lack of willingness to share data, and unacceptable cost for scans. Second, the proportion of newly diagnosed patients with high-risk prostate cancer has diminished in the past decade [20-22]. Additionally, high-risk patients (PSA > 50 ng/mL) might have more symptoms of morbidity, making them less willing to participate in studies that require extra visits and procedures. Thus, we realized that the recruitment of 114 evaluable patients was unlikely within a realistic timeframe, and recruitment was prematurely ceased. However, the current study is still quite large among similar comparable studies [15-18, 23].

An important aspect to consider is that patients in this study were required to have PSA blood levels ≥ 50 ng/mL at diagnosis. These patients are unlikely to undergo radical treatment, even if imaging excludes the presence of bone metastases. Most likely, the diagnostic performances of the index tests will be different in an unselected population of newly diagnosed prostate cancer patients or in patients with biochemical recurrence after radical prostatectomy. In particular, when considering that most of the patients in the current study showed more than ten bone metastases, it can be expected that these patients will be correctly classified by all three index tests.

The index tests in the current study were part of the reference standard, causing a slight risk of biased decisions based on the presence of bone metastases, i.e., circular reasoning. We found that in bone metastases imaging studies, it is difficult to obtain a reference test without including the results of the index test(s), although the STARD guidelines recommend otherwise [8]. However, the multidisciplinary team worked independent of the original reviewers and used a combination of imaging, biochemical and clinical information to support a final decision, which was reached in the vast majority of patients.

Data have shown that patient management is changed after performing NaF PET/CT, but there is no evidence that this actually leads to improved patient outcome [24] (no data exist for SPECT/CT). Therefore, it remains to be shown in properly conducted, large comparative studies that SPECT/CT and NaF PET/CT have a clinical impact on patient management that significantly outperforms BS [8, 25]. In summary, with reservations concerning the limited study population, we found no significant differences in the diagnostic performance among BS, SPECT/CT and NaF PET/CT in the detection of bone metastases on the patient level. Despite the lack of statistical significance, we found that SPECT/CT and NaF PET/CT numerically outperformed BS. We conclude that NaF PET/CT and SPECT/CT can be used due to logistic or capacity issues without compromising the results of the examinations. The scan time is notably reduced for NaF PET/CT versus BS. With SPECT/CT, which we found to be diagnostically equal to NaF PET/CT in high-risk prostate cancer patients, the scans can also be performed with a low acquisition time (<5 minutes) [26]. Thus, even if BS ought to remain the standard of care due to the low costs and satisfactory diagnostic performance, it might be time for the guidelines in prostate cancer to reconsider the consistent recommendation of planar BS, and include SPECT/CT and NaF PET/CT as equal or apparently improved modalities.

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Disclosure of conflict of interest

None.

Abbreviations

ADT, androgendeprivation therapy; BS, planar wholebody bone scintigraphy; CT, computed tomography; DTA, diagnostic test accuracy; M0, non-metastatic; Me, equivocal; M1, malignant; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PSA, prostatespecific antigen; SPECT, singlephoton emission tomography; STARD, Standards for Reporting of Diagnostic Accuracy.

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References

[1] Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group. Bone health in cancer patients: ESMO clinical practice guidelines. Ann Oncol 2014; 25 Suppl 3: iii124-137.

[2] Graham J, Kirkbride P, Cann K, Hasler E and Prettyjohns M. Prostate cancer: summary of updated NICE guidance. BMJ 2014; 348: f7524.

[3] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F and Mottet N. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014; 65: 124-137.

[4] Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Kane CJ, Kawachi MH, Kuettel M, Lee RJ, Meeks JJ, Penson DF, Plimack ER, Pow-Sang JM, Raben D, Richey S, Roach M 3rd, Rosenfeld S, Schaeffer E, Skolarus TA, Small EJ, Sonpavde G, Srinivas S, Strope SA, Tward J, Shead DA and Freedman-Cass DA. Prostate cancer, version 1.2016. J Natl Compr Canc Netw 2016; 14: 19-30.

[5] Wondergem M, van der Zant FM, van der PT and Knol RJ. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun 2013; 34: 935-945.

[6] Naaktgeboren CA, de Groot JA, Rutjes AW, Bossuyt PM, Reitsma JB and Moons KG. Anticipating missing reference standard data when planning diagnostic accuracy studies. Bmj 2016; 352: i402.

[7] Bertens LC, Broekhuizen BD, Naaktgeboren CA, Rutten FH, Hoes AW, van Mourik Y, Moons KG and Reitsma JB. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. PLoS Med 2013; 10: e1001531.

[8] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC; Standards for Reporting of Diagnostic Accuracy. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Clin Radiol 2003; 58: 575-580.

[9] Fonager RF, Zacho HD, Langkilde NC and Petersen LJ. (18)F-fluoride positron emission tomography/computed tomography and bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer patients: study protocol for a multicentre, diagnostic test accuracy study. BMC Cancer 2016; 16: 10.

[10] Zacho HD, Barsi T, Mortensen JC, Mogensen MK, Bertelsen H, Josephsen N and Petersen LJ. Prospective multicenter study of bone scintigraphy in consecutive patients with newly diagnosed prostate cancer. Clin Nucl Med 2014; 39: 26-31.

[11] Hayen A, Macaskill P, Irwig L and Bossuyt P. Appropriate statistical methods are required to assess diagnostic tests for replacement, add-on, and triage. J Clin Epidemiol 2010; 63: 883-891.

[12] Zacho HD, Mørch CD, Barsi T, Mortensen JC, Bertelsen H, Petersen LJ. Unexplained bone pain is an independent risk factor for bone metastases in newly diagnosed prostate cancer: a prospective study. Urology 2017; 99: 148-154.

[13] Van den Wyngaert T, Strobel K, Kampen WU, Kuwert T, van der Bruggen W, Mohan HK, Gnanasegaran G, Delgado-Bolton R, Weber WA, Beheshti M, Langsteger W, Giammarile F, Mottaghy FM, Paycha F; EANM Bone & Joint Committee and the Oncology Committee. The EANM practice guidelines for bone scintigraphy. Eur J Nucl Med Mol Imaging 2016; 43: 1723-1738.

[14] Wong KK and Piert M. Dynamic bone imaging with 99mTc-labeled diphosphonates and ^{18}F-NaF: mechanisms and applications. J Nucl Med 2013; 54: 590-599.

[15] Damle NA, Bal C, Bandopadhyaya GP, Kumar L, Kumar P, Malhotra A and Lata S. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. Jpn J Radiol 2013; 31: 262-269.

[16] Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H and Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 2006; 47: 287-297.

[17] Iagaru A, Mittra E, Dick DW and Gambhir SS. Prospective evaluation of (99m)Tc MDP scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 2012; 14: 252-259.

[18] Palmedo H, Marx C, Ebert A, Kreft B, Ko Y, Turler A, Vorreuther R, Gohring U, Schild HH, Gerhardt T, Poge U, Ezziddin S, Biersack HJ and Ahmadzadehfar H. Whole-body SPECT/CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients. Eur J Nucl Med Mol Imaging 2014; 41: 59-67.

[19] Briganti A, Passoni N, Ferrari M, Capitanio U, Suardi N, Gallina A, Da Pozzo LF, Picchio M, Di Girolamo V, Salonia A, Gianolli L, Messa C, Rigatti P and Montorsi F. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. Eur Urol 2010; 57: 551-558.

[20] Hoffman RM, Meisner AL, Arap W, Barry M, Shah SK, Zeliadt SB and Wiggins CL. Trends in United States prostate cancer incidence rates by age and stage, 1995-2012. Cancer Epidemiol Biomark Prev 2016; 25: 259-263.

[21] Outzen M, Brasso K, Martinussen N, Christensen J, Tjonneland A, Friis S and Olsen A. Prostate cancer in Denmark 1978-2009--trends in incidence and mortality. Acta Oncol 2013; 52: 831-836.

[22] Buzzoni C, Auvinen A, Roobol MJ, Carlsson S, Moss SM, Puliti D, de Koning HJ, Bangma CH, Denis LJ, Kwiatkowski M, Lujan M, Nelen V, Paez A, Randazzo M, Rebillard X, Tammela TL, Villers A, Hugosson J, Schroder FH and Zappa M. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the european randomized study of screening for prostate cancer. Eur Urol 2015; 68: 885-890.

[23] Withofs N, Grayet B, Tancredi T, Rorive A, Mella C, Giacomelli F, Mievis F, Aerts J, Waltregny D, Jerusalem G and Hustinx R. (1)(8)F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. Nucl Med Commun 2011; 32: 168-176.

[24] Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF and Coleman RE. Impact of 18F-fluoride PET in patients with known prostate cancer: initial results from the National oncologic PET registry. J Nucl Med 2014; 55: 574-581.

[25] Lijmer JG and Bossuyt PM. Various randomized designs can be used to evaluate medical tests. J Clin Epidemiol 2009; 62: 364-373.

[26] Zacho HD, Manresa JAB, Aleksyniene R, Ejlersen JA, Fledelius J, Bertelsen H, Petersen LJ. Three-minute SPECT/CT is sufficient for the assessment of bone metastasis as add-on to planar bone scintigraphy: prospective head-to-head comparison to 11-min SPECT/CT. EJNMMI Res 2017; 7: 1.