Comparison of bone scintigraphy and ^{68}Ga-PSMA PET for skeletal staging in prostate cancer

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Abstract

Purpose The aim of our study was to compare the diagnostic performance of ^{68}Ga-PSMA PET and ^{99m}Tc bone scintigraphy (BS) for the detection of bone metastases in prostate cancer (PC) patients.

Methods One hundred twenty-six patients who received planar BS and PSMA PET within three months and without change of therapy were extracted from our database. Bone lesions were categorized into benign, metastatic, or equivocal by two experienced observers. A best valuable comparator (BVC) was defined based on BS, PET, additional imaging, and follow-up data. The cohort was further divided into clinical subgroups (primary staging, biochemical recurrence, and metastatic castration-resistant prostate cancer [mCRPC]). Additionally, subgroups of patients with less than 30 days delay between the two imaging procedures and with additional single-photon emission computed tomography (SPECT) were analyzed.

Results A total of 75 of 126 patients were diagnosed with bone metastases. Sensitivities and specificities regarding overall bone involvement were 98.7–100 % and 88.2–100 % for PET, and 86.7–89.3 % and 60.8–96.1 % ($p < 0.001$) for BS, with ranges representing results for 'optimistic' or 'pessimistic' classification of equivocal lesions. Out of 1115 examined bone regions, 410 showed metastases. Region-based analysis revealed a sensitivity and specificity of 98.8–99.0 % and 98.9–100 % for PET, and 82.4–86.6 % and 91.6–97.9 % ($p < 0.001$) for BS, respectively. PSMA PET also performed better in all subgroups, except patient-based analysis in mCRPC.

Conclusion Ga-PSMA PET outperforms planar BS for the detection of affected bone regions as well as determination of overall bone involvement in PC patients. Our results indicate that BS in patients who have received PSMA PET for staging only rarely offers additional information; however, prospective studies, including a standardized integrated x-ray computed tomography (SPECT/CT) protocol, should be performed in order to confirm the presented results.

Keywords 68Ga-PSMA · Bone scintigraphy · Prostate cancer · Bone metastasis

Introduction

Bone scintigraphy (BS) with ^{99m}Tc-labeled phosphonates is a cost-effective and widely available examination that has demonstrated high sensitivity for the detection of bone metastases, especially in tumor entities in which metastases with osteoblastic activity prevail [1]. Patients with prostate cancer (PC), the most common malignant tumor in males in Western countries, are particularly prone to osseous involvement, which occurs in about 30 % of cases [2] and is predominantly osteoblastic in nature. As a consequence, BS is commonly employed for the assessment of skeletal metastases in PC, and its use for patients at high risk of metastatic disease is recommended in several clinical guidelines [3–5]. Specificity of BS, however, is limited due to unspecific tracer uptake in benign, e.g. degenerative or

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post-traumatic lesions, and additional investigations, such as targeted x-rays, computed tomography (CT), or magnetic resonance imaging (MRI), are often necessary to clarify unclear findings [6, 7]. The accuracy of BS has been shown to be superior to x-ray and CT [8], roughly equivalent to that of ^{11}C-Choline-positron emission tomography (PET) [9], but inferior to whole-body MRI [10] and ^{18}F-Fluoride PET [7, 11], which have not yet found their way into clinical routine.

Radio-labeled prostate-specific membrane antigen (PSMA) ligands, on the other hand, are increasingly used in the workup of patients with PC. PET with ^{68}Ga-labeled PSMA inhibitors such as PSMA HBED-CC [12–14] has been shown to be of high clinical value for lymph node staging [15] and detection of local recurrence [16], and is emerging as the imaging modality of choice for PC staging. Up to now, though, it remains unclear as to how PSMA PET performs in the detection of bone metastases. Particularly, the need for additional BS in patients who have already received PSMA PET needs to be further evaluated. In this study, we compare the diagnostic accuracy of BS and PSMA PET for skeletal staging in PC patients, and investigate whether PSMA PET could replace BS for this purpose.

Material and methods

Patients

From 2297 individuals in our database who received ^{68}Ga-PSMA-HBED-CC PET/CT or PET/MR for PC staging between 11/2012 and 07/2015, 213 patients who underwent additional planar BS were extracted. Cases with a delay of more than three months between BS and PET as well as those with alteration of therapy between the two scans were excluded, resulting in 126 patients with a median interval of 20 days between PSMA PET and BS included in the final analysis (Fig. 1). No surgery or chemotherapy was performed in the interval, but 26 patients received continued anti-hormone therapy at the time of the scans. In 86 cases, PSMA PET was performed before BS, while in 40 cases, BS was performed before PSMA PET. The cohort was further divided into three groups: primary staging, biochemical recurrence (BCR), and metastatic castration-resistant prostate cancer (mCRPC), as these stages of disease progression are important clinically, and the value of BS and PSMA PET might be different in the respective settings. Mean age was 68.9 ± 7.7 (mean ± standard deviation; range 49 – 89) years, and the mean PSA level was 43.5 ± 89.8 ng/ml (2.7–500) for primary staging, 20.9 ± 74.6 ng/ml (0.3–490) for BCR, and 446 ± 740 ng/ml (0.97–3333) for mCRPC. In order to investigate whether a shorter time interval between the two imaging procedures would lead to different results, an additional subgroup of patients with a delay of less than 30 days between BS and PET (median: 12.5 days; $n = 84$) was defined and analyzed. Furthermore, we retrieved 57 patients in our cohort who had received additional single-photon emission computed tomography (SPECT) examinations.

All patients gave written informed consent for the purpose of anonymized evaluation and publication of their data. The retrospective analysis was approved by the institutional review board of the Technical University of Munich (permit 5665/13).

Synthesis and application of ^{68}Ga-PSMA ligand

Images were obtained with HBED-CC [12] that was labeled with $^{68}Ga^{3+}$ (half-life 67.6 min) from a ^{68}Ge/^{68}Ga radionuclide generator (iThemba Labs, South Africa) by means of a fully automated module (Scintomics, Germany) and good manufacturing practice-grade disposable cassettes and reagent kit (ABX, Germany), as described previously [14]. The final product was dissolved in isotonic phosphate-buffered saline (PBS) with subsequent sterile filtration.

Imaging protocol

The ^{68}Ga-PSMA-ligand complex solution was applied to patients via an intravenous bolus (mean 151 ± 26 MBq, range 95–217 MBq). Variation of injected radiotracer activity was caused by the short half-life of ^{68}Ga and variable elution efficiencies obtained during the lifetime of the ^{68}Ge/^{68}Ga radionuclide generator.

PET acquisition was scheduled to start at 60 minutes after tracer injection. In total, 111 patients underwent ^{68}Ga -PSMA PET/CT on a Biograph mCT scanner (Siemens Medical Solutions, Erlangen, Germany) and 15 patients ^{68}Ga PSMA PET/MR on a Biograph mMR scanner (Siemens Medical Solutions). PET/CT and PET/MR acquisitions were performed as previously described [16, 17]. Generally, the scanned area covered the body from the skull base to the upper thigh, but was extended to the cranium and/or the distal extremities when bone metastases in these regions were expected. All PET images were acquired in 3D mode and reconstructed by an attenuation-weighted ordered-subsets expectation maximization algorithm (four iterations, eight subsets) followed by a post-reconstruction smoothing Gaussian filter (5 mm full-width at half-maximum).

Whole-body BS was performed on a Symbia T6 SPECT camera (Siemens Medical Solutions) operated in planar imaging mode with an acquisition time of 1 minute / 10 cm body height. Activity was body weight-adjusted (9 MBq/kg; mean 669 ± 72 MBq, range 490–1085 MBq) and injected 3 hours before imaging. As mentioned above, for a subgroup of patients, additional SPECT images were obtained. SPECT imaging was performed using 90 frames with 10 sec/frame and 3D OSEM reconstruction with eight iterations and 15 subsets

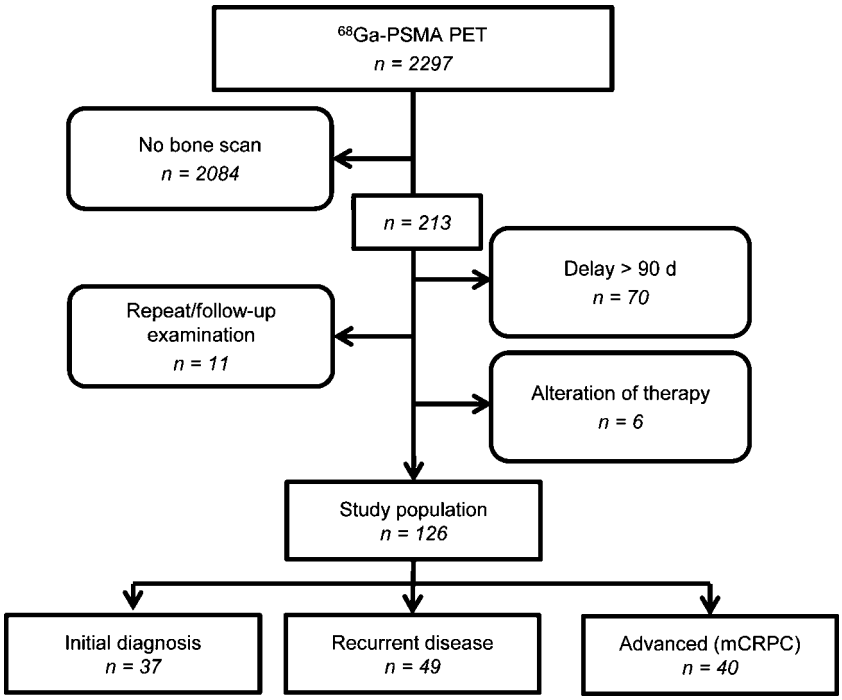

Fig. 1 Patient population

in a 128x128 matrix. In the case of integrated x-ray computed tomography (SPECT/CT), CT was performed using low-dose technique at a photon energy of 130 keV.

Best valuable comparator

As a histologic gold standard was absent for most of the cases, a best valuable comparator (BVC) was defined based on a consensus review of all available current and follow-up images (BS, SPECT, PET, CT, MR) and clinical data; this procedure has been described in earlier comparative imaging studies in PC patients [10]. The material was assessed by the specialists involved in the study (radiologists, nuclear medicine physicians and urologists) to determine the affected bone regions and overall metastatic status.

Data and statistical analysis

For both BS and PSMA PET, up to five lesions in each of nine bone regions (skull, clavicle/scapula, ribs/sternum, cervical, thoracic and lumbar spine, pelvis, upper and lower extremity) were identified and categorized into benign, metastatic, or equivocal by two independent, experienced nuclear medicine physicians. This approach was preferred to the conventional 'consensus' read, as a definitive consensus for equivocal lesions often cannot be obtained without additional data, e.g. CT or MR images; furthermore, data on equivocal findings was used to compare the accuracy of both imaging methods employing a receiver-operating characteristics (ROC) analysis (see below). For PSMA PET, judgement of lesions was consequently based only on the PET information and no additional morphologic information was used for lesion characterization. For BS, morphological images were similarly not taken into account in order to guarantee comparable analyses for all patients. As an exception, we examined CT images present at the time of the scan for the SPECT subgroup analysis, in order to estimate the benefit gained through the additional investigation.

Sensitivities and specificities for BS and PSMA PET regarding involved bone regions and overall metastatic status were calculated both for the 'optimistic' and 'pessimistic' readings, i.e. counting equivocal lesions as negative or positive. ROCs involving equivocal readings were determined using MedCalc 7.2 (MedCalc Software bvba, Ostend, Belgium), including calculation of the area under the curve (AUC) and statistical comparison of ROC curves. Tests were performed two-sided and a level of significance of $\alpha = 0.05$ was used.

Results

Detailed data on the number and distribution of bone lesions in PSMA PET, BS as well as determined by BVC are listed in Table 1.

Patient-based analysis

For PSMA PET, we determined a sensitivity regarding overall bone involvement of 98.7–100 % (see Table 2), depending on whether equivocal lesions were classified as negative or positive. Specificity for PET was 88.2–100 %. For BS, patient-based

Table 1 Number and location of bone lesions determined by PSMA PET, BS, and BVC

	PSMA PET		BS		BVC
	Pos.	Equiv.	Pos.	Equiv.	Pos.
Skull*	58	1	71	27	99
Cerv. Spine	162	2	95	20	170
Dorsal Spine	226	1	203	23	233
Lumb. Spine/Sacrum	227	2	190	20	231
Clavicle/Scapula	180	0	154	18	181
Rib/Sternum	235	9	208	17	235
Pelvic bone	235	3	202	10	236
Upper Extr.	141	0	97	5	145
Lower Extr.	159	0	134	9	165
All regions	1623	18	1354	149	1695
Patients (overall status)	74	1	65	2	75

*57 Patients showed skull lesions in BS; of these, only 38 had PET scans that included the cranium, leading to a lower lesion count in PET

pos. positive, *equiv.* equivocal

sensitivity was 86.7–89.3 %, and specificity was 60.8–96.1 %. Accuracy of the diagnostic test as measured by ROC was significantly higher for PSMA PET than for BS (AUC 0.999 vs. 0.903, $p < 0.001$).

Region-based analysis

Region-based analysis revealed a sensitivity and specificity of 98.8–99.0 % and 98.9–100 % for PET, and 82.4–86.6 % and 91.6–97.9 % for BS, respectively (Table 2). Again, accuracy as measured by ROC analysis was significantly higher for PET (AUC 0.995 vs. 0.916, $p < 0.001$). Five regions (1.2 %) with metastases were recognized in BS, but not in PET, which led to a change in the overall metastatic status in one patient with biochemical recurrence, but only if equivocal PET lesions in this patient were counted as negative. On the other hand, 72 affected bone regions (17.6 %) were correctly assessed by PET, but remained undetected by BS, changing the status of 10 patients.

Subgroup analysis

As described above, the cohort was further divided into three subgroups: primary diagnosis ($n = 37$), BCR ($n = 49$) and mCRPC ($n = 40$)—see Table 3 for details. PSMA PET performed better than BS in patient- and region-based analysis in the first two subgroups ($p < 0.001$–0.014). In mCRPC, no difference between the two modalities on a patient basis was determined, which was due to the high prevalence of disseminated bone metastases that were uniformly detected by BS as well as PSMA PET. However, PET still performed better in the identification of affected bone regions in patients with mCRPC (AUC 0.993 vs. 0.945, $p < 0.001$).

In order to investigate whether a shorter time period between the two imaging procedures would lead to different results, we analyzed a subgroup of 84 patients with a delay of less than 30 days between PSMA PET and BS. Results were similar to the 90-day group (see Table 2; AUC PET vs. BS: 0.999 vs. 0.924, $p = 0.001$).

Finally, to account for the possible benefits of SPECT imaging, we examined another subgroup of 57 patients. Of these patients, 22 had integrated SPECT/CT, 24 patients had

Table 2 Sensitivities and specificities of BS and PSMA PET

Subgroup			Patient-based		Region-based	
		equiv.	PET	BS	PET	BS
All patients	Sensitivity	–	98.7 % (92.8–100)	86.7 % (76.8–93.4)	98.8 % (97.2–99.6)	82.4 % (78.4–86.0)
		+	100 % (95.2–100)	89.3 % (80.1–95.3)	99.0 % (97.5–99.7)	86.6 % (82.9–89.7)
	Specificity	–	100 % (93.0–100)	60.8 % (46.1–74.2)	98.7 % (97.8–99.5)	97.9 % (96.5–98.8)
		+	88.2 % (76.1–95.6)	96.1 % (86.5–99.5)	100 % (99.5–100)	91.6 % (89.3–93.6)
	AUC		0.999 (0.969–1.000)	0.903 (0.837–0.948)	0.995 (0.989–0.998)	0.916 (0.899–0.932)
	p-value		<0.001		<0.001	
<30 days between PET and BS	Sensitivity	–	98.2 % (90.3–100)	87.3 % (75.5–94.7)	98.6 % (96.5–99.6)	82.2 % (77.3–86.4)
		+	100 % (93.5–100)	89.1 % (77.8–96.0)	99.0 % (97.0–99.8)	86.6 % (82.2–90.3)
	Specificity	–	100 % (88.1–100)	100 % (88.1–100)	100 % (99.2–100)	97.4 % (95.4–98.6)
		+	86.2 % (68.3–96.1)	65.5 % (45.7–82.1)	98.7 % (97.1–99.5)	91.2 % (88.2–93.6)
	AUC		0.999 (0.955–1.000)	0.924 (0.844–0.970)	0.995 (0.987–0.999)	0.914 (0.899–0.933)
	p-value		0.001		<0.001	

95 % CIs are given in parentheses; the column under 'equiv.' denotes whether equivocals are counted as negative or positive ('optimistic' or 'pessimistic' reading)

Table 3 Analysis for patients receiving additional SPECT

		Patient based			Region based		
	equ.	PET	BS	SPECT	PET	BS	SPECT
Sensit.	-	96.1 % (80.4 – 99.9)	80.8 % (60.6 – 93.4)	80.8 % (60.6 – 93.4)	99.0 % (94.5 – 100)	62.6 % (52.3 – 72.1)	61.6 % (51.3 – 71.2)
	+	100 % (86.8 – 100)	84.6 % (65.1 – 95.6)	88.5 % (69.8 – 97.6)	100 % (96.3 – 100)	70.7 % (60.7 – 79.4)	70.7 % (60.7 – 79.4)
Specif.	-	100 % (88.8 – 100)	93.6 % (78.6 – 99.2)	93.6 % (78.6 – 99.2)	100 % (99.1 – 100)	97.1 % (95.0 – 98.5)	98.8 % (97.2 – 99.6)
	+	87.1 % (70.2 – 96.4)	45.2 % (27.3 – 64.0)	51.6 % (33.1 – 69.8)	98.8 % (97.2 – 99.6)	89.9 % (86.5 – 92.6)	92.3 % (89.3 – 94.7)
AUC		0.998	0.843	0.867	1.000	0.824	0.834
p-value			0.008			<0.001	
			0.012			<0.001	
				0.389			0.220

95 % CIs are given in parentheses

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SPECT and separate CT of the examined body region available in PACS at the time of the bone scan, while in 11 patients only SPECT, but no CT was available. The scanned body regions for SPECT included the pelvis in 44, the lumbar spine in 35, dorsal spine/rib/sternum in 14, and cervical spine/skull in five individuals. Specificity was increased by SPECT imaging; however, the overall improvement in diagnostic accuracy compared to planar imaging was not significant (see Table 4; AUC 0.867 vs. 0.843, $p = 0.389$), and was still lower than that of PSMA PET (AUC 0.998; $p = 0.012$). Region-based analysis for SPECT was hampered by inconsistent imaging of body regions, but neither showed significant differences to planar scintigraphy.

Figures 2 and 3 show imaging examples of patients with underestimation of osseous involvement by BS and improved determination of bone metastatic status by PSMA PET.

Table 4 Clinical subgroup analysis

Subgroup			Patient-based		Region-based	
		equiv.	PET	BS	PET	BS
Primary staging	Sensitivity	–	100 % (76. 8–100)	57.1 % (28.9–82.3)	100 % (91.0–100)	46.2 % (30.1–62.8)
		+		71.4 % (41.9–91.6)		61.5 % (44.6–76.6)
	Specificity	–	100 % (85.2–100)	95.7 % (78.1–99.9)	100 % (98.7–100)	97.9 % (95.6–99.2)
		+	91.3 % (72.0–98.9)	65.2 % (42.7–83.6)	99.3 % (97.5–99.9)	92.1 % (88.4–94.9)
	AUC		1.000 (0.904–1.000)	0.767 (0.599–0.890)	1.000 (0.989–1.000)	0.780 (0.732–0.824)
	p-value		0.006		<0.001	
BCR	Sensitivity	–	95.8 % (78.9–99.9)	83.3 % (62.6–95.3)	98.9 % (93.9–100)	73.0 % (62.6–81.9)
		+	100 % (85.8–100)		100 % (95.9–100)	76.4 % (66.2–84.8)
	Specificity	–	100 % (86.3–100)	96.0 % (79.6–99.9)	100 % (98.9–100)	98.0 % (95.8–99.2)
		+	88.0 % (68.8–97.5)	60.0 % (38.7–78.9)	98.5 % (96.6–99.5)	93.0 % (89.7–95.4)
	AUC		0.998 (0.922–1.000)	0.867 (0.739–0.947)	1.000 (0.991–1.000)	0.865 (0.829–0.896)
	p-value		0.014		<0.001	
mCRPC	Sensitivity	–	100 % (90.5–100)	100 % (90.5–100)	98.6 % (96.4–99.6)	90.4 % (86.4–93.6)
		+				93.3 % (89.7–95.9)
	Specificity	–	100 % (29.2–100)	100 % (29.2–100)	100 % (95.0–100)	97.2 % (90.3–99.7)
		+	66.7 % (9.4–99.2)	33.3 % (0.8–90.6)	98.6 % (92.5–100)	83.3 % (72.7–91.1)
	AUC		1.000 (0.911–1.000)	1.000 (0.911–1.000)	0.993 (0.977–0.999)	0.945 (0.916–0.967)
	p-value		1.000		<0.001	

95 % CIs are given in parentheses

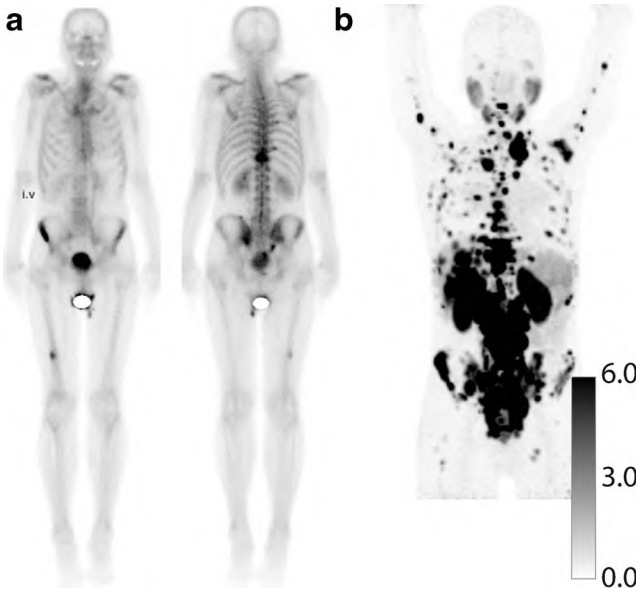

Fig. 2 Example of improved sensitivity of PSMA PET vs. BS with respect to affected bone regions. A 67-year-old patient with mCRPC under anti-androgenic therapy; PSA level was 500 ng/ml. **a**—bone scintigraphy shows only limited bone involvement of the lumbar spine, ribs, pelvis, and right femur. **b**—PSMA PET shows extensive osseous metastases in spine, pelvis, shoulder girdle, ribs, and all extremities, as well as lymph node involvement. Colorbar shows SUV

Discussion

In this study, the diagnostic value of ^{68}Ga-PSMA-HBED-CC PET for skeletal involvement in PC patients was retrospectively assessed and compared with that of BS, the current standard examination for this purpose. From our results, several important conclusions can be drawn: First, PSMA PET performed better than BS in determining the metastatic status of patients (overall presence of bone metastases), showing favorable sensitivity and specificity. Second, PSMA PET exhibited a significantly higher diagnostic accuracy for the assessment of involved bone regions. Overall, 17.6 % of affected bone regions were recognized only by PET, but not by BS; conversely, only 1.2 % of positive regions were detected by BS while remaining unrecognized by PET. Moreover, the number of equivocal lesions was substantially lower in PSMA PET, which should help to reduce additional investigations that are often necessary to clarify unclear findings in BS. In summary, the added value of BS in patients who have already undergone PSMA PET for staging is comparatively small, and the need for additional BS should therefore be questioned.

In clinical management of PC, categorizing patients into primary diagnosis, BCR, and mCRPC is of considerable therapeutic importance, and we therefore conducted separate analyses of these patient categories. PET outperformed BS in the first two subgroups; in advanced disease, defined by mCRPC, both modalities were equally able to identify the mostly disseminated lesions on a patient basis. Nevertheless, PET was still superior to BS for determination of bone regions with metastases in this last subgroup.

A higher number of skull lesions were observed in BS than in PSMA PET, a finding related to the area covered by the PET scan, which did not routinely comprise the cranium; however, these additional detected lesions in whole-body BS did not change the overall metastatic status in any of the examined patients, as metastases in the skull and the distal extremities almost exclusively occur in advanced metastatic disease. PC is a rather slowly progressive disease, which let us choose a maximum interval of 90 days (median: 20 days) for the delay between the two imaging procedures. For validation, we additionally analyzed a subgroup of patients with a delay of less than 30 days (median: 12.5 days) between PSMA PET and BS. No substantial differences were observed compared to the 90-day interval, suggesting that disease progression between the scans had no major influence on our results.

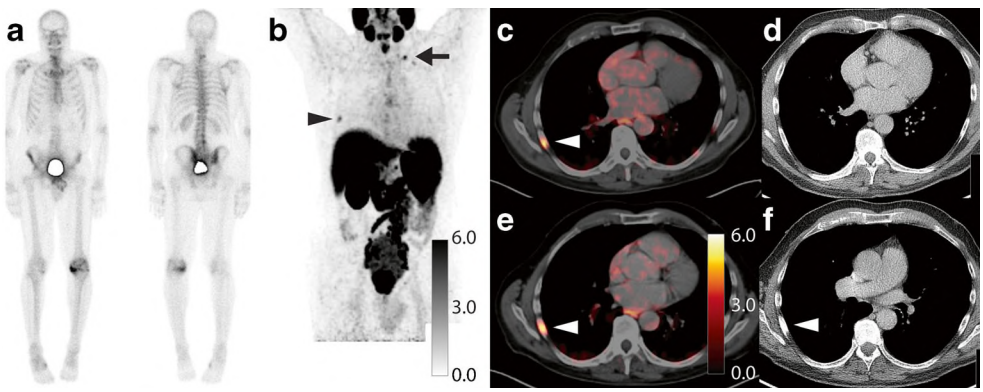

Fig. 3 Example of improved determination of bone involvement by PSMA PET. A 59-year-old patient with an initial diagnosis of PC; PSA level was 490 ng/ml. **a**—bone scintigraphy is unremarkable with degenerative changes in the left knee and the spine. **b**–**d**—PSMA PET exhibits a focal rib lesion without CT correlate (*arrowhead*); furthermore, extensive pelvic, para-aortal and cervical lymph node metastases were detected (*arrow*: Virchow's lymph node). Colorbars show SUV. e–f—during follow-up, the rib lesion shows slowly increasing uptake and becomes visibly sclerotic in CT, proving the diagnosis of osseous metastasis

Adding SPECT and SPECT/CT to plain BS has been shown to improve anatomical detail and reduce the number of equivocal lesions [11]. To investigate the benefits of SPECT imaging, we analyzed another subgroup of patients who had either additional SPECT or SPECT/CT examinations. SPECT increased specificity as it has been expected; however, the diagnostic accuracy was still significantly lower than that of PSMA PET, and the difference to planar scintigraphy was not significant. Several reasons for this discrepancy to earlier published studies [18] might apply: integrated SPECT/CT was available only inconsistently in our cohort and SPECT was limited to certain body regions, in most cases lumbar spine/pelvic. Furthermore, bone SPECT was mainly performed for difficult diagnostic questions and was able to provide clarification only in a minority of these cases: e.g. degenerative changes in the spine sometimes cannot be distinguished from metastatic lesions even with the addition of CT, while MRI would be more helpful. Another important point is that sensitivities and specificities greatly rely on the type of gold standard used; in our study, PSMA PET, which has been included in the BVC, exhibits a much higher sensitivity than BS, in turn reducing the sensitivity of BS and SPECT. Newer, prospective studies regarding the value of BS and SPECT incorporating highly sensitive methods such as 18 F-Fluoride PET or whole-body MRI [19] likewise showed considerably reduced sensitivities and specificities for SPECT compared to the enthusiastic earlier publications. Morphologic information from PET/CT or PET/MRI was not included in our analysis, but would probably have further increased the diagnostic accuracy of PSMA PET. In summary, the imaging protocols used were too inconsistent to draw definite conclusions regarding the comparison between PSMA PET and bone SPECT/CT. Although it seems plausible from our analysis and from our subjective impression that PSMA PET would prove its superiority in this setting as well, affirmative studies including a standardized integrated SPECT/CT protocol should be performed in the future to dispel any methodological doubts.

Naturally, PSMA PET allows also for the identification of extra-osseous lesions, such as lymph nodes, local recurrence, or visceral metastases, the additional value of which was not investigated in this work. Reimbursement remains a critical point, being unclear for PSMA PET and therefore limiting its widespread use in many countries, while BS is often covered by general health insurance.

Our study is limited by being retrospective. Furthermore, a major limitation consists in the absence of a histologic gold standard, as confirmatory biopsies are not routinely performed for suggestive bone lesions. Instead, the BVC approach used might have introduced substantial incorporation bias, as BVC and diagnostic tests (PET and BS) are not independent, leading to an overestimation of the diagnostic accuracy of PSMA PET. However, it represents the most practical solution to the problem of lacking histologic adjudication and has been used for this reason in PC patients in similar comparative studies [10]. Particularly, we think the bias resulting from this approach does not privilege the one or the other modality and therefore does not critically affect the main implications of our study with regard to the superiority of PSMA PET over BS for bone staging. In addition, the high specificity of PSMA PET does not seem completely unrealistic, given the low frequency of false positive results with regard to lymph node, visceral, and soft tissue metastases, as reported recently [15, 16, 20], though pitfalls remain and are in fact just beginning to be investigated [21, 22].

Finally, the influence of different kinds of treatment of bone metastases on the diagnostic accuracy was not assessed in this study. Earlier publications showed incongruent results regarding the effect of anti-androgenic therapy on the accuracy of PSMA PET [16, 20]. Similarly, problems in BS might arise from the so-called flare phenomenon that can lead to false-positive results in metastases that undergo osteoblastic healing processes after therapy [23]. Further studies might be of interest in order to disentangle a possible treatment-dependency of PSMA PET for the examination of bone metastases.

Conclusion

In this retrospective study, ^{68}Ga-PSMA-HBED-CC PET proved to be an accurate method for the assessment of bone metastases in PC patients and outperformed planar BS for the detection of affected bone regions as well as the determination of overall bone involvement. Our results indicate that BS in patients who have received PSMA PET for staging only rarely offers additional information; however, prospective studies, including a standardized integrated SPECT/CT protocol, should be performed in order to confirm the presented results.

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All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study as part of the clinical routine. The retrospective analysis was approved by the institutional review board of the Technical University of Munich (permit 5665/13).

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