Original article

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Comparison of bone scintigraphy and Ga-68 prostate-specific membrane antigen positron emission tomography/computed tomography in the detection of bone metastases of prostate carcinoma

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Aim **This study aims to assess the diagnostic performance of Ga-68 prostate-specific membrane antigen PET/computed tomography in the comparison of planar bone scintigraphy in the detection of bone metastases. Another purpose is to define the additional benefit of bone scintigraphy subsequent to prostate-specific membrane antigen PET/computed tomography and the role of prostate-specific membrane antigen PET/computed tomography in the treatment planning.**

Material and method **Forty-six patients with a median interval of 19 (range: 3–90) days between prostate-specific membrane antigen PET/computed tomography and bone scintigraphy included in the analysis. Diagnostic performance of both modalities was calculated and compared.**

Results **Prostate-specific membrane antigen PET/computed tomography and bone scintigraphy were performed for initial staging in 25 (54%), for evaluation of biochemical recurrence in 11 (24%) and metastatic castration-resistant prostate carcinoma in 10 (22%) patients. In the patient-based analysis sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for bone scintigraphy for detection of bone metastases were calculated as 50%, 19–29%, 32–39%, 32–39%, and 33–39%, respectively, based on whether equivocal findings were classified as positive or negative. For prostate-specific membrane antigen PET/computed tomography, these values were found significantly higher as 100%, 95–100%, 98–100%, 96–100%, and 100%, respectively. The diagnostic performance of bone scintigraphy and PET/computed tomography in clinical subgroups was analyzed, prostate-specific membrane antigen PET/computed tomography was superior to bone scintigraphy in three groups.**

Conclusion **In this retrospective study, prostate-specific membrane antigen PET/computed tomography was found to be superior to planar bone scintigraphy in the detection of bone metastases. Additional bone scintigraphy seems to be unnecessary in patients who underwent prostate-specific membrane antigen PET/computed tomography within three months period without additional treatment.** ***Nucl Med Commun*** **40:1243–1249** **Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: bone scintigraphy, prostate carcinoma, prostate-specific membrane antigen PET/computed tomography

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Introduction

Prostate cancer is the most common cancer in men worldwide [1]. The most frequent metastasis sites are pelvic lymph nodes and bones. Bone metastases develop in about 30% of prostate cancer patients throughout the disease [2]. One of the most common symptoms of bone metastases is pain, and pain is the primary cause for worsening the quality of life. Moreover, the extent of bone metastasis is one of the most important prognostic factors in prostate cancer patients [3]. In the case of first staging or biochemical recurrence (BCR), detection of bone metastases leads to change the treatment strategy [4].

Bone scintigraphy (BS) with Tc-99 m-labeled phosphonates is a highly sensitive, cost-effective, and widely available method to detect osteoblastic bone metastases [5]. Since bone metastases of prostate cancer are mostly in osteoblastic nature, BS is the first-line imaging technique to evaluate bone involvement of prostate cancer [6–8]. However, the specificity of BS is limited since the radiotracer uptake does not have a unique mechanism for metastases. Benign lesions or conditions such as traumatic or degenerative changes usually show tracer uptake. Further evaluation is often needed to clarify equivocal findings [9,10]. BS has been found superior to X-ray or CT and equal to ^{11}C-choline PET and inferior to whole-body MRI and F-18 Flouride PET in the detection of bone metastases [11–14]. In the last decade, PET imaging with Gallium (Ga)-68 prostate-specific membrane

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antigen (PSMA) ligands have been widely performed for staging and restaging of prostate cancer patients [15–17]. The accuracy of Ga-68 PSMA PET/CT in the evaluation of prostatic bed and lymph nodes has been reported to be high [18,19]. However, its sensitivity for the detection of bone metastases is still unclear.

The aim of this study is to assess (1) the diagnostic performance of Ga-68 PSMA PET/CT in the comparison of planar BS in the detection of bone metastases, (2) additional benefit of BS in the patients who already underwent Ga-68 PSMA PET/CT, and (3) the role of further data from Ga-68 PSMA PET/CT in the treatment strategy planning.

Material and methods

Patients

Total 676 patients who underwent Ga-68 PSMA PET/CT for staging, BCR or evaluation of castration-resistant prostate cancer (CRPC) between January 2014 and January 2018 were searched from the hospital database. Totally 214 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 46 patients with a median interval of 19 (range: 3–90) days between PSMA PET and BS included in the final analysis. In 40 cases, PSMA PET was performed after BS, while in 6 cases, BS was performed after PSMA PET. Mean age was 68.4 ± 6.4 (range: 51–81) years, and the median prostate specific antigen (PSA) level was 7.65 (range: 1.0–329) ng/ml for primary staging, 23.4 (range: 2–1658) ng/ml for BCR, and 61.2 (range: 49–1011) ng/ml for metastatic castration-resistant prostate carcinoma (mCRPC) groups. 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 fewer than 30 days between BS and PET (median: 12.5 days; n = 30) was defined and analyzed.

Image analyses

Informed consent was taken from all patients for both modalities. PSMA 11 peptide (abx, Radeberg, Germany) kit was labeled with Ga-68 an automated synthesis system (mini AIO, Trasis, Belgium) integrated with Ge-68/Ga-68 generator (ITG, GMBH, Munich, Germany). After quality control of the radiopharmaceutical by HPLC and radioactive impurity control, approximately 111–185 MBq ^{68}Ga-PSMA 11 was injected intravenously. Whole-body PET/CT images were acquired with a Discovery PET/CT 710 series scanner (General Electric, Milwaukee, USA) 45–60 minutes after the tracer injection. Images from the vertex to the proximal femur were obtained while patients were in the supine position. PET images were acquired for 2 minutes per bed position. PET images were reconstructed with noncontrast low-dose CT images that were obtained with the use of a standardized protocol of 120 kV, 70 mA, tube rotation time of 0.5 seconds per rotation, a pitch of 1.375, and a slice thickness of 3.3 mm. Patients were allowed to breathe normally during the procedure.

Whole-body BS was performed with an Optima NM/CT 640 single photon emission tomography (SPECT)/CT camera (General Electric, Milwaukee, USA) operated in planar imaging mode with an acquisition time of 15 cm body height/160 second 3 hours after intravenous injection of approximately 370–490 MBq Tc-99 m methylene diphosphonate. In case of suspicious findings, additional planar images from different views were obtained from corresponding parts of the skeleton.

Two experienced readers performed image analyses with consensus by focusing on bone lesions. First, BS and PET images were examined separately; then, images were interpreted concomitantly. In comparison to the healthy bone activity, increased Tc-99 m methylene diphosphonate tracer uptake indicated increased osteoblastic activity. Focal or diffuse increased osseous uptake was assessed by comparison with the contralateral bone. If the location was compatible, osteodegenerative, or trauma-related uptake was taken into consideration. To perform the one-to-one comparison, uptakes located on the distal part of extremities excluded from the analysis because these parts of the skeleton are not within the acquisition area of PET imaging. The location and number of abnormal findings were described. During the evaluation of PET/CT images, first, the maximum intensity projection PET images were reviewed then attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal, and sagittal) using Advance Workstation Volumeshare 5 (GE Medical Systems). Focal or diffuse ^{68}Ga-PSMA osseous uptake higher than surrounding bone tissue was accepted as pathological. Location, intensity, and number of the bone lesions were noted. The osseous lesions were divided into eight regions: cranium, cervical spine, thoracal spine, lumbar spine, sternum/costa, pelvic bone, lower extremities, and upper extremities. Osseous uptake that did not meet the described pathological criteria was accepted equivocal. For statistical analysis, the equivocal lesions were counted as negative (optimistic reading) or positive (pessimistic reading) in all imaging modalities. The data were collected for region-by-region and a patient-by-patient analysis.

Best valuable comparator

Since histologic gold standard was absent for most of the cases, best valuable comparator (BVC) was defined based on the consensus review of all available current and follow-up clinical data and imaging studies. Serial serum PSA measurements, response to treatment and complementary imaging studies such as ceCT or MRI was considered for BVC.

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Statistical analysis

Descriptive data were expressed as median (range) or mean ± SD. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of each modality in the detection of bone metastases were calculated for optimistic and pessimistic readings for different patient groups. The patient subgroups were the reason for referral for imaging and time interval between two modalities. Tests were performed 2-sided, and a level of significance of $P = 0.05$ was used. SPSS version 20.0 software (IBM, Chicago, Illinois, USA) was used for statistical analysis.

Results

PSMA PET/CT and BS were performed for initial staging in 25 (54%), for evaluation of BCR in 11 (24%) and mCRPC in 10 (22%) patients. Details of the descriptive data of patients were summarized in Table 1.

Although the accepted time interval between two studies was three months, they were performed within the 30 days in the majority (n = 30) of the patients. While BS was positive for bone metastases in 31 (67%) patients, PSMA PET/CT was positive in 24 (52%) patients. BVC has been found positive in 25 (53%) of patients. Equivocal findings were found in 17 (37%) of BS and 4 (8%) of PSMA PET/CT. Details of locations for positive and equivocal findings were listed in Table 2.

Patient and region-based analysis

On patient-based analysis, based on the classification of equivocal findings as positive or negative, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for BS for detection of bone metastases were calculated as 50%, 19–29%, 32–39%, 32–39%, and 33–39%, respectively. For PSMA PET/CT, these values have been found significantly higher as 100%, 95–100%, 98–100%, 96–100%, and 100%, respectively. Diagnostic performance for both modalities on patient-based analysis is summarized in Table 3.

In the region-based analysis, sensitivity and specificity of BS for the detection of bone metastases were calculated about 70–80% and 15–80%, depending on whether equivocal findings were classified as positive or negative. For PSMA PET/CT, these values have been found significantly higher as around 100%, and 100%, region-based diagnostic performance analysis for both modalities are summed in Table 4. Examples for patients with equivocal findings in BS were given in Figs. 1 and 2.

Table 1 Descriptive data of patients

Parameter	
Age (mean ± SD)	68.4 ± 6.4
PSA level (median, range) (ng/ml)	11.6, 1.0–1658
ALP level (median, range) (U/L)	72, 22–998
Gleason scores (median, range)	8, 6–10
6	8 (17%)
7	13 (28%)
8	9 (20%)
9	12 (26%)
10	1 (2%)
Unknown	3 (7%)
Indication, n (%)	
Staging	25 (54)
BCR	11 (24)
mCRPC	10 (22)
Interval between imaging modalities (median, range) (days)	19, 3–126
< 30	30 (65%)
31–60	10 (22%)
61–90	6 (13%)
Follow-up period (median, range) (days)	438, 55–1626

ALP, alkaline phosphatase; BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate carcinoma; PSA, prostate specific antigen.

Subgroup analysis

When investigated whether the different period between the two imaging procedures would lead to different results, the diagnostic performance of BS remained similar in the subgroup of patients with the period less than 30 days between two procedures. Further analysis of the distinguishing performance of BS and PET/CT were based on clinical subgroups. Summary of the diagnostic performance of both methods is provided in Table 5. PSMA PET/CT was superior to BS in three groups. BS had higher sensitivity in staging and mCRPC subgroups than BCR subgroup. However, its specificity was lower in the same subgroups. BS seems to have the highest accuracy in the mCRPC group.

In the staging group, BS was positive or equivocal, and PSMA PET/CT was negative for bone metastases in 13/25 patients. PSMA PET/CT detected lymph node and lung metastases in 1/13 and 1/13 patients in this group. Finally, treatment strategy remained the same in these two patients while it was changed from systemic to local therapy in 11/25 patients. Mean serum PSA and alkaline phosphatase levels of patients with Ga-68 PSMA positive and negative bone metastases were calculated as 63 ± 13.5 vs. 9.3 ± 2.3 ($P = 0.001$) and 74.7 ± 20.6 vs. 67.5 ± 22.7 ($P = 0.865$). In BCR group, BS was positive or equivocal in 3/11 patients while PSMA PET/CT was negative for bone metastases. However, PSMA PET/CT

Table 2 Distribution of lesions in patients for bone scintigraphy and prostate-specific membrane antigen PET/computed tomography

	PSMA PET/CT		BS	
Regions	Positivity (no. of patients)	Equivalent (no. of patients)	Positivity (no. of patients)	Equivalent (no. of patients)
Cranium	8	0	12	1
Cervical vertebrae	12	0	15	4
Thoracal vertebrae	14	0	19	0
Lumbar vertebrae	13	0	19	3
Costae/sternum	16	1	26	2
Pelvis	20	2	29	3
Upper extremities	10	1	16	5
Lower extremities	14	0	16	4
Patients	24	4	31	17

BS, bone scintigraphy; CT, computed tomography; PSMA, prostate-specific membrane antigen.

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Table 3 Diagnostic performance of prostate-specific membrane antigen PET/computed tomography and bone scintigraphy to detect bone metastases for different time intervals according to patient-based analysis

		<90 days		<30 days	
	Equivalent	BS	PSMA PET/CT	BS	PSMA PET/CT
Sensitivity	+	50	100	53.8	100
	–	50	100	51.5	100
Specificity	+	19.2	95.7	17.6	92.3
	–	29.2	100	46.2	100
Accuracy	+	32.6	97.8	33.3	96.7
	–	39.1	100	48.6	100
PPV	+	32.3	95.8	33.3	94.1
	–	39.3	100	44.7	100
NPV	+	33.3	100	33.3	100
	–	38.9	100	52.9	100

BS, bone scintigraphy; CT, computed tomography; NPV, negative predictive value; PPV, positive predictive value; PSMA, prostate specific membrane antigen.

Table 4 Diagnostic performance of prostate-specific membrane antigen PET/computed tomography and bone scintigraphy to detect bone metastases for according to region-based analysis

	Equivalent	BS	PSMA PET/CT
Sensitivity	+	79.8	100
	–	68.5	100
Specificity	+	79.8	100
	–	14.7	NA
Accuracy	+	82.6	72.3
	–	77	72.3

BS, bone scintigraphy; CT, computed tomography; PSMA, prostate-specific membrane antigen.

detected recurrence in prostatic bed in three of them. Treatment strategy changed from systemic to local in all of them. One example of patients in BCR group was given in Fig. 3. In the mCRPC group, BS was equivocal, and PSMA PET/CT was negative for bone metastases in only one patient.

On the other hand, bone metastases of 11 patients were correctly detected by PSMA PET/CT but were undetectable in BS. The reasons for PET-CT referral of these patients were staging, BCR, and mCRPC in 6, 3, and 2 patients. Treatment strategy was changed from local to systemic in 9 patients of staging and BCR groups.

Discussion

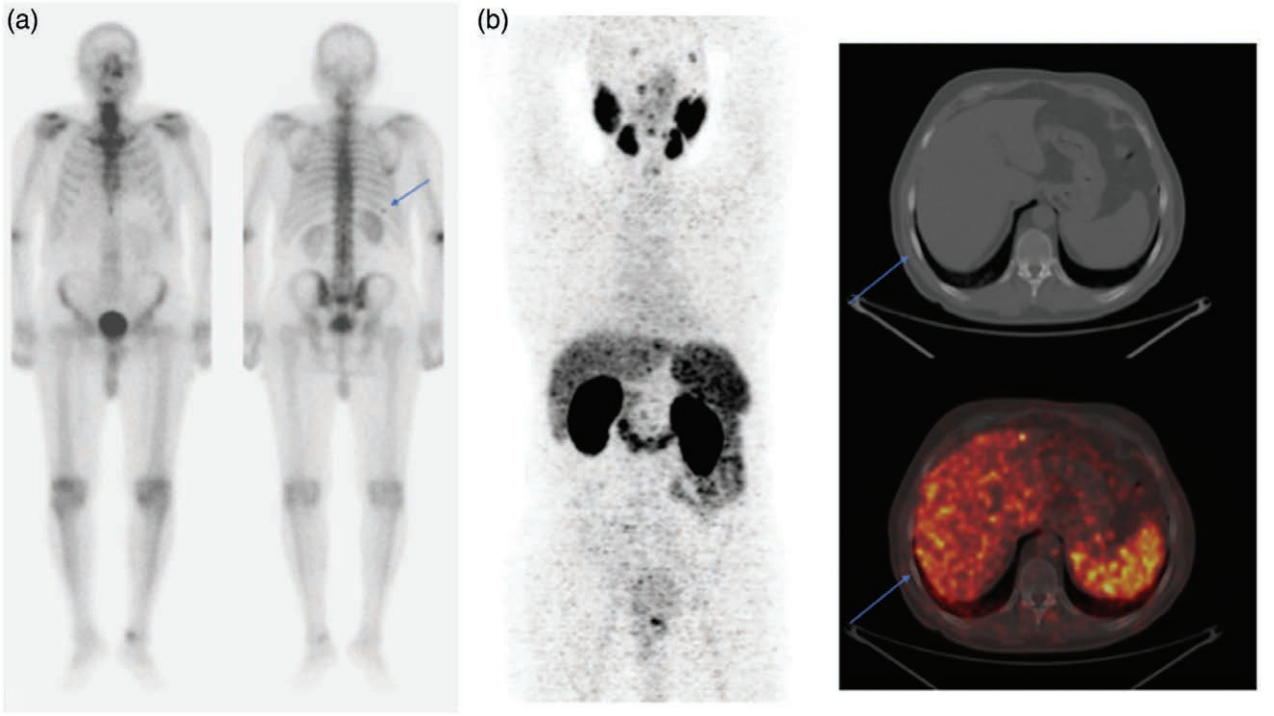
This single-center retrospective study compared BS and Ga-68 PSMA PET/CT in the detection of bone metastases of prostate cancer patients. The first aim of this study was to evaluate the diagnostic performance of Ga-68 PSMA PET/CT in the comparison of planar BS in the detection of bone metastases. Ga-68 PSMA PET/CT was found superior to BS in all indications and both interval periods. BS is known with high false positive findings due to nonspecific uptake mechanism. Therefore, in the case of staging or BCR recurrence, single and equivocal findings have to be confirmed with other modalities. In the mCRPC group, BS had the highest sensitivity, possibly due to the high rate of disseminated bone metastases in that stage. In this study, the diagnostic performance of BS had lower diagnostic accuracy than similar studies in the literature [20,21]. One possible explanation for these results might be the absence of SPECT or SPECT/CT imaging for the bone scan. SPECT imaging, mainly performed with fused CT, increases the specificity of BS. Janssen *et al.*[21] reported that data from low-dose CT reduces the equivocal findings for both modalities. However, in the previous two studies where BS was performed with SPECT/CT imaging Ga-68 PSMA PET/CT still have been reported superior to BS [20,21].

The second aim was to determine if there was an additional benefit of BS in the patients who already underwent Ga-68 PSMA PET/CT. In this study, PSMA PET/BT was performed after BS in the majority of patients (n = 40) which reflects the trend of using PSMA PET/CT to clarify the presence or absence of bone metastases in case of equivocal findings in BS. Moreover, in case of high clinical suspicion of metastatic or recurrent disease, a typical BS cannot be satisfactory to eliminate the possibility without confirmation with Ga-68 PSMA PET/CT. Fitting to this hypothesis in this study, BS could not detect any bone metastases that could not be detected by Ga-68 PSMA PET/CT. Considering the availability and cost of both modalities, BS still seems to remain as the first step in the evaluation of bone metastases of prostate cancer. Additionally, data on the diagnostic performance of Ga-68 PSMA PET/CT in the detection of bone metastases are limited with retrospective cohorts. It can be concluded that there is no additional effect of the BS in the patient management for patients who already underwent Ga-68 PSMA PET/CT for any indication within 3-months period. It can be beneficial in the case of administering treatments such as newly initiated androgen deprivation treatment or radiation therapy that can affect the sensitivity of Ga-68 PSMA PET/CT. However, this present data should be supported by prospective randomized studies.

The ultimate aim was to define the role of additional information from Ga-68 PSMA PET/CT in the treatment strategy planning. In staging group, Ga-68 PSMA PET/CT revealed extra-osseous metastases in two patients. Bone metastasis was excluded from 13/25 patients with positive or equivocal findings in BS. A vital treatment

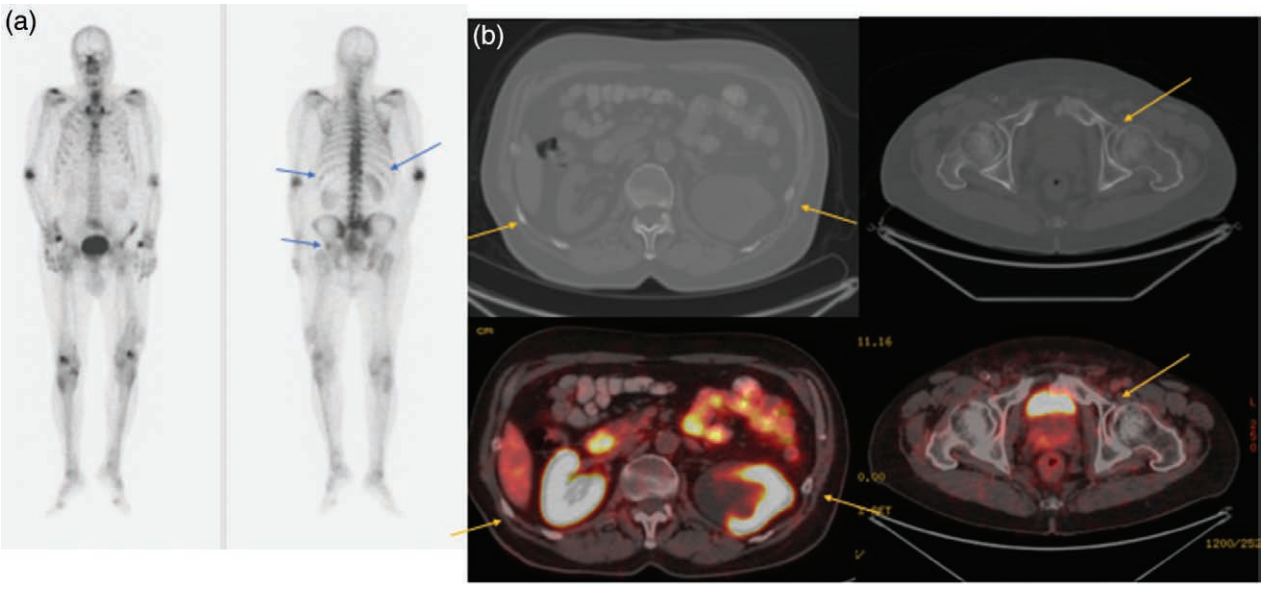
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Fig 1



A 51-years-old male patient underwent BS for the staging of his newly diagnosed Gleason Score 8 prostatic adenocarcinoma. An equivocal uptake was seen on the posterior 11th costa on the right side (a). However, corresponding Ga-68 PSMA PET/CT and CT images did not show any abnormalities (b). The patient underwent radical prostatectomy and postoperative serum PSA level decreased to undetectable levels. BS, bone scintigraphy; CT, computed tomography; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen.

Fig. 2



A 67-years-old male patient with newly diagnosed Gleason Score 9 prostatic carcinoma underwent BS for the staging of his disease. Equivocal uptakes were detected on both 11th costa and left acetabular region (a). There were no uptake on Ga-68 PSMA PET/CT and no CT changes in the same locations. The patient underwent additional MRI which did not reveal any abnormality (b). The patient underwent radical prostatectomy and serum PSA levels decreased to < 0.1 ng/ml. BS, bone scintigraphy; CT, computed tomography; PSMA, prostate-specific membrane antigen.

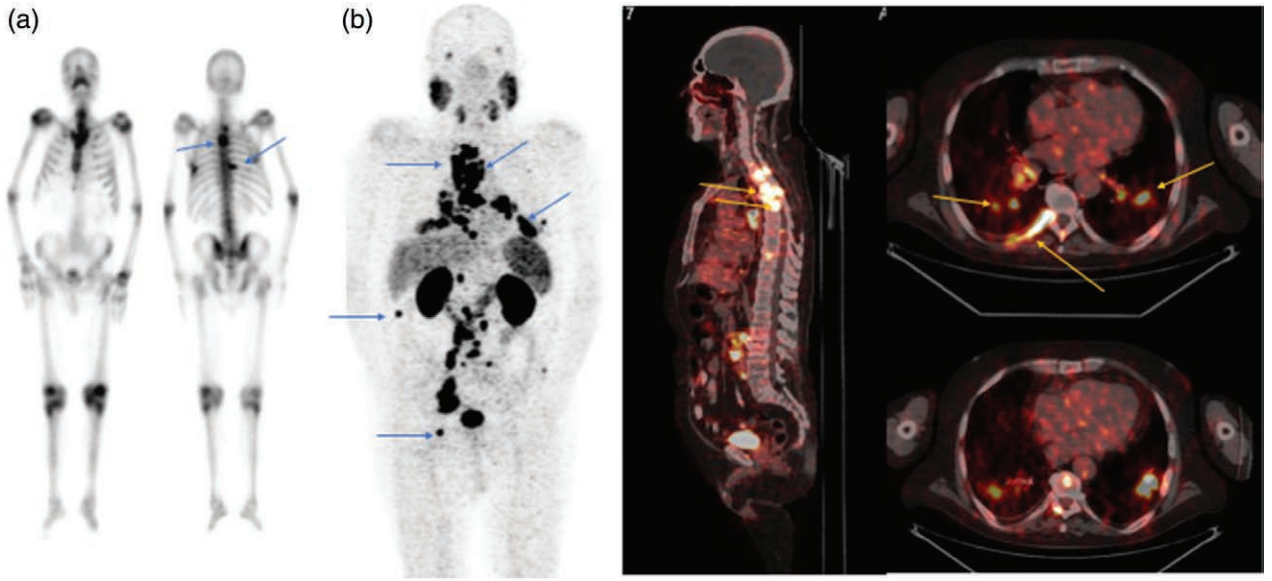
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Table 5 Diagnostic performance of prostate-specific membrane antigen PET/computed tomography and bone scintigraphy according to clinical subgroup analysis

		Staging		BCR		mCRPC	
	Equivalent	BS	PSMA PET/CT	BS	PSMA PET/CT	BS	PSMA PET/CT
Sensitivity	Positive	50	90.9	33.3	100	60	100
	Negative	43	100	33.3	100	73.3	93.3
Specificity	Positive	19.2	94.7	40	100	33.3	100
	Negative	38.1	100	60	100	33.3	100
Accuracy	Positive	33.3	93.3	37.5	100	55.6	100
	Negative	36.7	100	50	100	66.7	94.4
PPV	Positive	15.8	90.9	25	100	81.8	100
	Negative	18.8	100	33.3	100	84.6	100
NPV	Positive	63.6	94.7	50	100	14.3	100
	Negative	57.1	100	60	100	20	75

BCR, biochemical recurrence; BS, bone scintigraphy; CT, computed tomography; mCRPC, metastatic castration-resistant prostate carcinoma; NPV, negative predictive value; PPV, positive predictive value; PSMA, prostate-specific membrane antigen.

Fig. 3



A 71-years-old male patient with BCR underwent BS in which pathological uptakes were detected 8th costae on the right side and upper thoracic vertebras (a). In Ga-68 PSMA PET/CT additional bone lesions were detected. Moreover, multiple lymph nodes and lung metastases were revealed (b). BCR, biochemical recurrence; BS, bone scintigraphy; CT, computed tomography; PSMA, prostate-specific membrane antigen.

strategy change rate was observed in this group, but this rate difference is not realistic since the majority of these patients would not be treated based on the BS findings only. If Ga-68 PSMA PET/CT was not available different imaging tools would be performed to confirm the findings of BS. Moreover, bone metastasis of 6/25 patients could be detected by only Ga-68 PSMA PET/CT. If PET/CT was not performed, these patients might be treated only locally. Thus, additional information from Ga-68 PSMA PET/CT seems to be reliable and crucial in the staging group. In BCR group, BS was positive or equivocal in 3/11 patients while PSMA PET/CT was negative for bone metastases. Ga-68 PSMA PET/CT detected bone metastases of another 3 patients while BS was negative. As a result, the treatment strategy was changed in more than half of the patients in the BCR group. In the mCRPC group, Ga-68 PSMA PET/CT did not cause a change in the treatment plan of any patients. Ga-68 PSMA PET/CT seems to be useful in the planning of the treatment strategy of patients with BCR. In newly diagnosed patients, Ga-68 PSMA PET/CT can be considered for patients with high serum PSA levels due to the high probability of bone metastasis [22,23]. Establishing this point, in this research, mean serum PSA levels were significantly higher for patients with Ga-68 PSMA positive bone metastases than those with negative.

This study has several limitations; it had a retrospective design and a limited number of patients. Furthermore, the lack of the SPECT/CT imaging for BS and the absence

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of histopathological confirmation as a gold standard can be accounted for as other limitations. Since a biopsy is not performed routinely for bone lesions, BVC approach was used as in similar studies [20,21]. Since BVC is not independent of BS and PET results, an overestimation of diagnostic performance for PET imaging might be seen. However, high accuracy of PSMA PET/CT have been reported for extra-osseous metastases [18,19]. Therefore, the superiority of PSMA PET/CT is predicted for bone metastases.

Conclusion

In this retrospective study, PSMA PET/CT proved to be superior to planar BS for the assessment of bone metastases in patients with prostate cancer. Additional BS seems to be unnecessary in patients who underwent PSMA PET/CT within three months period without additional treatment. Additional information from PSMA PET/CT changes the treatment strategy in patients with BCR. PSMA PET/CT should be considered for patients with high serum PSA levels at the initial diagnosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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