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^{68}Ga-PSMA-11 PET/CT in newly diagnosed prostate cancer: diagnostic sensitivity and interobserver agreement

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Abstract

Purpose To determine the diagnostic sensitivity and interobserver agreement of Gallium 68-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA-11 PET/CT) imaging for diagnosis and staging of patients with newly diagnosed prostate cancer (PC).

Materials and methods One hundred and seventy-three men (mean age, 68 ± 7.7 years; range 46–84 years) with newly diagnosed, untreated PC were enrolled in this prospective study between January 2017 and August 2018. All patients underwent a ^{68}Ga-PSMA-11 PET/CT examination. For each patient, we determined the disease stage, the Gleason score, and the maximum standardized uptake value (SUVmax) for primary prostatic tumor and extraprostatic metastases. The diagnostic sensitivity and interobserver agreement of ^{68}Ga-PSMA-11 PET/CT for diagnosis and staging of PC were established by histopathology as the reference standard.

Results ^{68}Ga-PSMA-11 PET/CT examinations were interpreted as positive for PC in 166 of 173 patients (101 patients had primary prostatic tumor only, two patients had extraprostatic metastases only and 63 patients had combined lesions). The sensitivity of ^{68}Ga-PSMA-11 PET/CT examination in the diagnosis of PC was 96%. ^{68}Ga-PSMA-11 PET/CT produced a significant change of stage in 28.6% patients with an upstage in 17.9% patients and a downstage in 10.7% patients. The interobserver agreements were almost good to perfect ($k = 0.63$–0.89) for visual image interpretation, SUVmax measurement, and tumor staging.

Conclusion ^{68}Ga-PSMA-11 PET/CT is a valuable tool with high diagnostic sensitivity (96%) and high reproducibility for diagnosis and staging of patients with newly diagnosed PC.

Keywords ^{68}Ga-PSMA-11 · PET/CT · Newly diagnosed · Prostate cancer · Interobserver agreement

Introduction

Prostate cancer (PC) is the most commonly known malignancy in men and is a leading cause of cancer death [1]. In spite of its prevalence and the recent improvements in its management, the ability of conventional imaging techniques, such as computed tomography (CT) and technetium-99 m (^{99m}Tc) bone scintigraphy, to correctly detect PC remains a challenge in the field [2]. This issue can cause management difficulty at all stages of the disease, from early diagnosis [3] and biochemical recurrence [4] to the occurrence of metastases [5]. Correct staging of PC is an essential step for treatment decisions and patient management [6]. In patients with newly diagnosed PC, the determination of the exact tumor stage, prostate-specific antigen (PSA) value and Gleason score (GS), has significant effects for prognostic grouping and management decision [7, 8].

Studies performing cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI), or functional imaging with ^{18}F-FDG PET/CT and ^{18}F-choline PET/CT, have demonstrated unsatisfying sensitivity percentages in detecting lymph node (LN) -positive

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lesion [9, 10]. Among the newly evolved PET radiotracers, the ^{68}Ga-PSMA-11 is considered the most specific for PC diagnosis [11, 12]. PSMA is a unique membrane-bound type II glycoprotein that is overexpressed on PC tissue at all stages [13].

Over the last 4 years, several studies have been performed to prove that ^{68}Ga-PSMA-11 PET/CT is a highly accurate technique for detecting PC metastases and relapse, but few of these publications evaluated the performance of ^{68}Ga-PSMA PET/CT for diagnosis and staging of newly diagnosed PC. Accordingly, we conducted this prospective study to address the diagnostic sensitivity and interobserver agreement of ^{68}Ga-PSMA-11 PET/CT image for diagnosis and staging of patients with newly diagnosed PC.

Materials and methods

Study design and population

This is a multicentre prospective study. All centers obtained approval from their respective institutional review boards, and all participants were assured about the study and offered written informed consent. We applied the ethical concepts of the Declaration of Helsinki during planning for this study. Between January 2017 and August 2018, 178 consecutive patients with newly diagnosed, untreated PC were recruited from five institutions. Inclusion criteria included histopathologically proven PC, no prior PC treatment, male aged 18 years or over, and adequate hepatic, bone marrow, coagulation, and renal function. Exclusion criteria, included patients unable to undergo PET/CT scan owing to weight (e.g., > 180 kg) (two patients), claustrophobia, or unable to lie still throughout the scanning duration (two patients), and renal failure (one patient). This yielded a final cohort of 173 patients (mean age, 68 ± 7.7 years; range 46–84 years). The patients' data are summarized in Table 1. The flowchart of our study is illustrated in Fig. 1. Once enrolled, all patients were submitted to a ^{68}Ga-PSMA-11 PET/CT scan for primary staging of PC. For each patient, we determined the PSA value, disease stage, and Gleason score (GS). The patients in the present study were staged by applying the American Joint Committee on Cancer (AJCC) TNM staging system [14].

^{68}Ga-PSMA-11 PET/CT protocol

All ^{68}Ga-PSMA-11 PET/CT images were performed using one integrated PET/CT scanner (Ingenuity TF 128; Philips Healthcare, Cleveland, OH, USA). The complete protocol has been detailed elsewhere [15].

Table 1 Patients' data

Characteristic	Value
No. of patients	173
Age (year) mean ± SD (range)	68 ± 7.7 (46–84)
Gleason score at diagnosis	
0	7 (4)
3 + 3 = 6	36 (20.8)
3 + 4 = 7	25 (14.5)
4 + 3 = 7	26 (15)
4 + 4 = 8	40 (23.1)
4 + 5 = 9	22 (12.7)
5 + 4 = 9	10 (5.8)
5 + 5 = 10	7 (4)
Prior imaging	
CT abdomen and pelvis	101 (58.4)
MRI abdomen and pelvis	90 (52)
^{18}FDG-PET/CT	12 (6.9)
Bone scan	112 (64.7)
Any prior imaging	39 (22.5)
Stage	
IIA	19 (11)
IIB	61 (35.3)
III	21 (12.1)
IV	65 (37.6)
0	7 (4)
PSA (ng/mL)	
Mean ± SD	44.4 ± 50.5
Median (range)	17.7 (1.4–185)
^{68}Ga-PSMA-11 PET/CT	
Positive	166 (96)
Negative	7 (4)

The data are represented as numbers with the corresponding percentages given in parentheses

SD standard deviation, *PSA* prostatic specific antigen, *^{18}F-FDG PET/CT* fluorine-18 fluoro-D-glucose positron emission tomography/computed tomography, *^{68}Ga-PSMA PET/CT* 68 Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography

Image analysis

All CT images, attenuation-corrected PET images, and fused PET/CT images were transmitted and checked centrally on an interactive workstation (IntelliSpace Portal V4.0; Philips Healthcare, Cleveland, Ohio, USA). Five nuclear medicine experts from the different institutions with over 10 years of experience read independently all PET/CT images. The nuclear medicine experts were blinded to any clinical data and the reports of the biopsy, but examined PET/CT images regarding the primary prostatic tumor and extraprostatic metastases (LN, bone, and

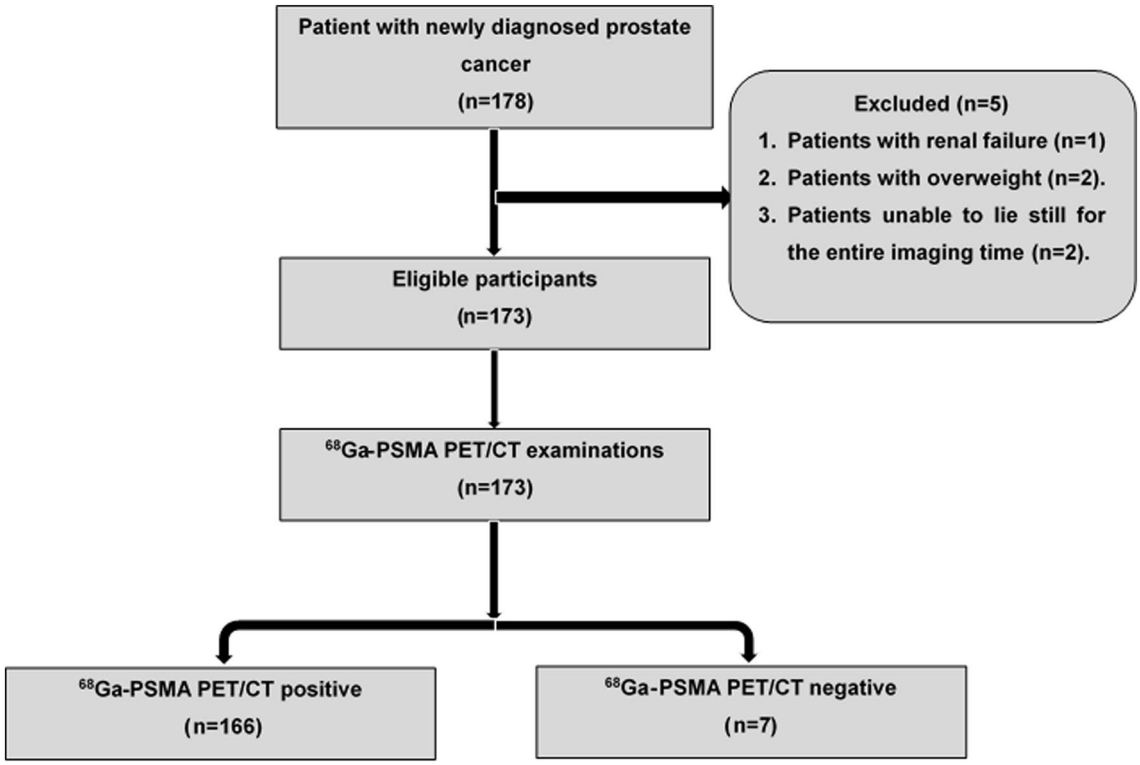

Fig. 1 Flow chart of the study population

soft tissue metastases). Disease activity was determined, both qualitatively and semi-quantitatively. Qualitative examination was based on the detection of focal ^{68}Ga-PSMA-11 uptake that was higher than the surrounding background and distinct from tracer uptake physiologic sites, whereas semi-quantitative evaluation typically based on the measurement of the maximum standardized uptake value (SUV_{max}). Each nuclear medicine expert measured for each patient the SUV_{max} of primary prostatic tumor and extraprostatic metastases. To measure SUV_{max}, a circular region of interest (ROIs) was drawn and placed on the area of the highest activity consistent with primary tumor or extraprostatic metastases, but not covering the whole lesion, with the help of combined CT and measured SUV_{max} in the ROI_S. In the patient with more than one lesion in the prostate, the SUV_{max} of the lesions was considered the highest SUV_{max} of the lesions.

Visual image interpretation was reported for the followings: Overall scan result for presence or absence of disease, number of prostatic lesions, number of regional LN metastases, number of distant LN metastases, number of bone metastases, and number of soft tissue metastases.

In order to accurately estimate the diagnostic sensitivity of ^{68}Ga-PSMA-11 PET/CT, any disagreement between the five nuclear medicine experts was reviewed until consensus was reached.

Reference standard

The definitive diagnosis was validated by histopathological results after biopsy. Biopsies were obtained by transrectal ultrasound (TRUS) guided procedure within 2 weeks before ^{68}Ga-PSMA-11 PET/CT images. All specimens were examined by two experienced pathologists, and the final results were acquired by consensus.

Statistical analysis

The data were managed and examined using the statistical software MedCalc (version 11.1; MedCalc, Mariakerke, Belgium). Correlation analysis was conducted using Spearman's rank correlation, and the outcome was documented as an *r*-value along with a *p* value. The Fleiss kappa (κ) statistics and 95% confidence intervals (CIs) were applied to assess the interobserver agreement. The κ values were interpreted as follows: poor agreement = 0.01–0.20; fair agreement = 0.21–0.40; moderate agreement = 0.41–0.60; good agreement = 0.61–0.80; and perfect agreement = 0.81–1.0. A patient-based sensitivity evaluation was also done. Unfortunately, patient-based calculation of specificity, positive predictive value (PPV), and negative predictive value (NPV) could not be determined as all our patients had histopathologically proven PC and therefore the cohort did not include

true-negative patients. A p value of ≤ 0.05 was deemed to indicate statistical significance.

Results

The current study enrolled 173 patients with newly diagnosed, untreated PC. We properly performed all ^{68}Ga-PSMA-11 PET/CT examinations without any side effects.

Distribution of ^{68}Ga-PSMA-11 PET/CT-avid lesions

^{68}Ga-PSMA-11 PET/CT examinations were interpreted as positive for PC in 166 of 173 patients. Two out of 166 patients demonstrated no tracer uptake in the prostate gland where uptake is expressed in the LNs, bone, and hepatic lesions (Fig. 2). Primary prostatic tumor was observed in 164 patients (Table 2, Fig. 3), of them 63 also had extraprostatic metastases and 101 had primary prostatic tumor only. We found single tracer uptake in the prostate gland in 126 patients and multifocal tracer uptake in 38 patients. Extraprostatic metastases were noticed in 65 patients, among whom 63 also had primary prostatic tumor and two had extraprostatic metastases only. Extraprostatic metastatic foci were noticed in many sites (Table 2, Fig. 4). LN was the most common site of extraprostatic metastases ($n=54$ patients). Fifty-two out of 54 patients with positive LNs metastases were regional (Fig. 5). Forty-seven patients had positive bony metastases (Fig. 6). The most common sites of bone metastases were the pelvic bone ($n=39$) followed by vertebrae ($n=31$).

Correlations of ^{68}Ga-PSMA-11 PET-avid lesions

Table 3 summarizes the important characters of ^{68}G-PSMA-11 PET-avid lesions. We found higher SUV_{max} in primary tumor with extraprostatic metastases (16.9 ± 10.5) than those without metastases (5.4 ± 2.8). The highest SUV_{max} was detected in distant LNs metastases (19.7 ± 17.1). The highest PSA value was found in patients with soft tissue metastases (105 ng/mL). We found a significant positive correlation between PSA level and SUV_{max} of

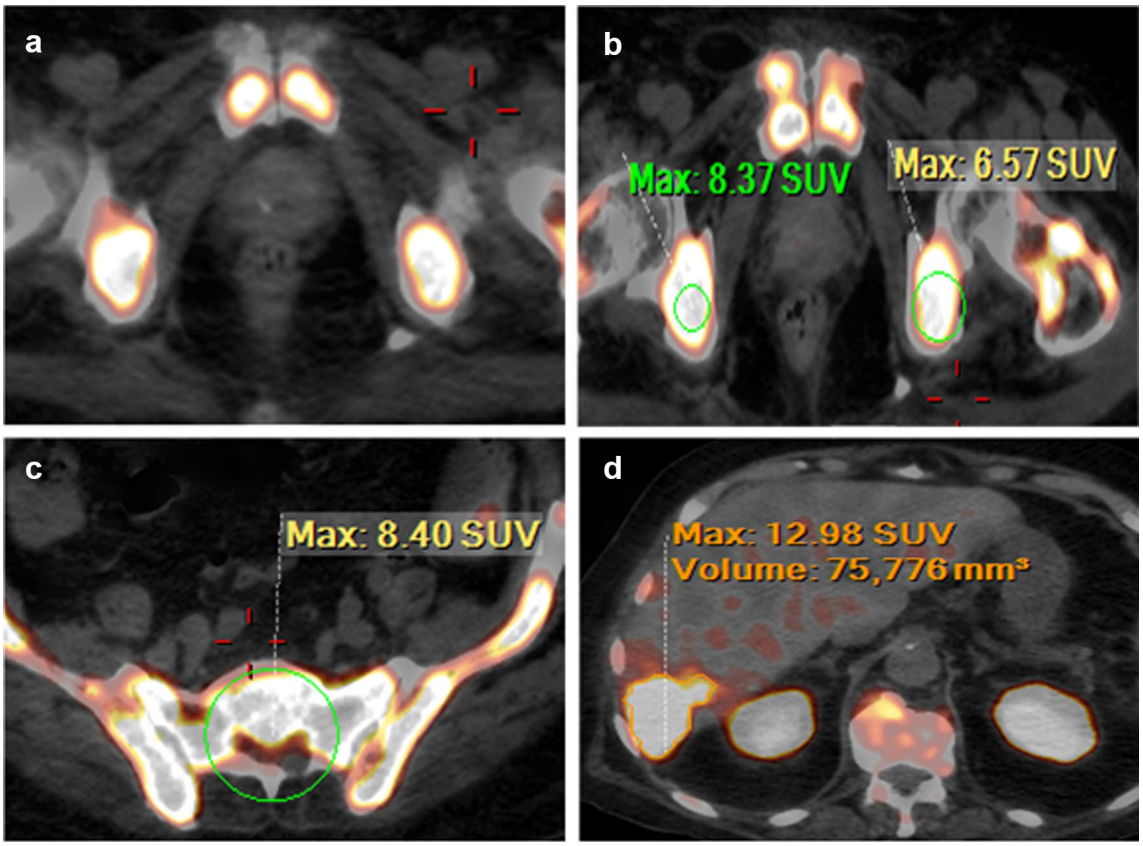

Fig. 2 A 84-year-old man with newly diagnosed PC referred for initial staging (PSA level 185 ng/mL; GS 4+4). **a** Axial ^{68}Ga-PSMA PET/CT image showing an average size prostate with no focal lesions or ^{68}Ga-PSMA-avid lesions. **b** and **c** Axial ^{68}Ga-PSMA PET/CT images show multiple active sclerotic bony lesions are seen infiltrating the pelvic bones, the most avid one is seen at the sacrum and achieves SUV_{max} of 8.4. **d** Axial ^{68}Ga-PSMA PET/CT image shows multiple ^{68}Ga-PSMA-avid hepatic focal lesions, the most avid one is seen at segment VI and achieves SUV_{max} of 12.98. The patient was staged as stage IV

Table 2 Distribution of ^{68}Ga-PSMA-11 PET/CT-avid lesions in 166 patients

Primary tumor	Number of patients (%)
Total	164 (94.8)
Single lesion	126 (72.8)
Multiple lesion	38 (22)
Site of extraprostatic metastases	**Number of patients (%)**
Total	65 (37.6)
Lymph nodes	54 (31.2)
Regional LNs	52 (30.1)
Para-aortic LNs	19 (11)
Aortocaval LNs	11 (6.4)
Mediastinal LNs	6 (3.5)
Retrocrural LNs	3 (1.7)
Bone	47 (27.2)
Pelvic bone	39 (22.5)
Vertebrae	31 (17.9)
Femur	20 (11.6)
Ribs	14 (8.1)
Humorous	11 (6.4)
Scapula	8 (4.6)
Skull	4 (2.3)
Sternum	3 (1.7)
Soft tissue	7 (4)
Lung	4 (2.3)
Liver	3 (1.7)

One patient may have more than one type of lesion

^{68}*Ga-PSMA PET/CT* 68 Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography, *LNs* lymph nodes

primary tumor ($r=0.57$; $p<0.001$; 95% CI 0.35 to 0.74). However, there was no significant correlation between PSA levels and SUV_{max} of different types of extraprostatic metastases. The PSA values of patients with non-visible ^{68}Ga-PSMA-avid primary tumors on PET/CT were significantly lower than those in patients with ^{68}Ga-PSMA-avid primary tumors (median PSA: 7.4 vs. 20.0 ng/mL; $p<0.0001$). In addition, a significant positive correlation was detected between the PSA level and the disease stage ($r=0.59$; $p<0.001$; 95% CI 0.37 to 0.75). The likelihood of ^{68}Ga-PSMA-11 PET/CT positive nodal disease appeared to increase with GS; 43 out of 54 patients (79.6%) with positive LNs metastases were GS 4 + 4 or more.

Disease staging

A subgroup of patients consisted of 112 patients had already been examined with conventional imaging modalities (CT and/or MRI) before the ^{68}Ga-PSMA-11 PET/CT. In comparison to conventional imaging, ^{68}Ga-PSMA-11 PET/CT produced 17.9% (20/112) upstaging of the patients [10.7% (12/112) in stage III and 7.1% (8/112) in stage IV] and 10.7% (12/112) downstaging of the patients [1.8% (2/112) in stage IIA, 7.1% (8/112) in stage IIB, and 1.8% (2/112) in stage III). The change in individual patient staging on account of ^{68}Ga-PSMA-11 PET/CT, compared to conventional imaging is presented in Table 4.

Diagnostic sensitivity of ^{68}Ga-PSMA-11 PET/CT

Out of 173 patients, a total of 166 patients were interpreted as positive for PC on ^{68}Ga-PSMA-11 PET/CT examinations. The patient-based analysis revealed a sensitivity of 96% (95% CI 91.84% to 98.36%). A patient-based calculation of specificity, PPV, and NPV was impossible.

Interobserver agreement

The interobserver agreement for visual image interpretation, SUV_{max} measurement, and tumor staging are shown in Table 5 and Fig. 7. The interobserver agreement was perfect for the visual detection of bone metastases ($\kappa=0.83$) and overall scan results ($\kappa=0.81$), and good for the visual detection of other lesions ($\kappa=0.63$-0.79). The interobserver agreement was perfect for SUV_{max} measurement of primary tumor ($\kappa=0.89$), and good for SUV_{max} measurement of other lesions (0.64–0.78). The interobserver agreement was perfect for tumor staging ($\kappa=0.82$).

Discussion

Accurate diagnosis and staging of patients with newly discovered PC is the cornerstone of appropriate managing decisions. In the years since ^{68}Ga-PSMA-11 PET/CT was developed, the research literature has been bulging with articles from all over the world about this emerging staging technology and its value in the diagnosis and staging of PC. The study presented here was conducted on 173 patients with newly diagnosed PC to evaluate diagnostic sensitivity and interobserver agreement of ^{68}Ga-PSMA-11 PET/CT image for diagnosis and staging of patients with newly diagnosed PC. As all patients enrolled in our study already had primary PC and our cohort did not include true-negative patients, calculating patient-based specificity, PPV, and NPP was not possible. However, regarding a patient-based analysis, the

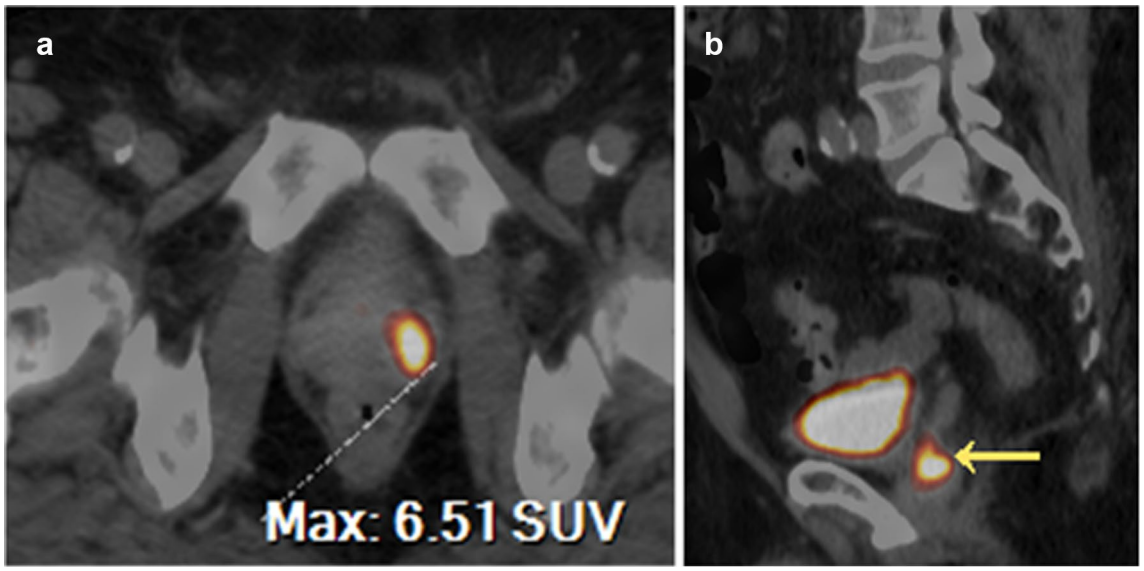

Fig. 3 A 55-year-old man with newly diagnosed PC referred for initial staging (PSA level: 5.9 ng/mL; GS: 3 + 4). **a** Axial and **b** Sagittal ^{68}Ga-PSMA PET/CT images showing an average size prostate with a ^{68}Ga-PSMA-avid lesion at the left peripheral zone. The lesion measures 16 × 10 mm and achieves SUV_{max} of 6.51

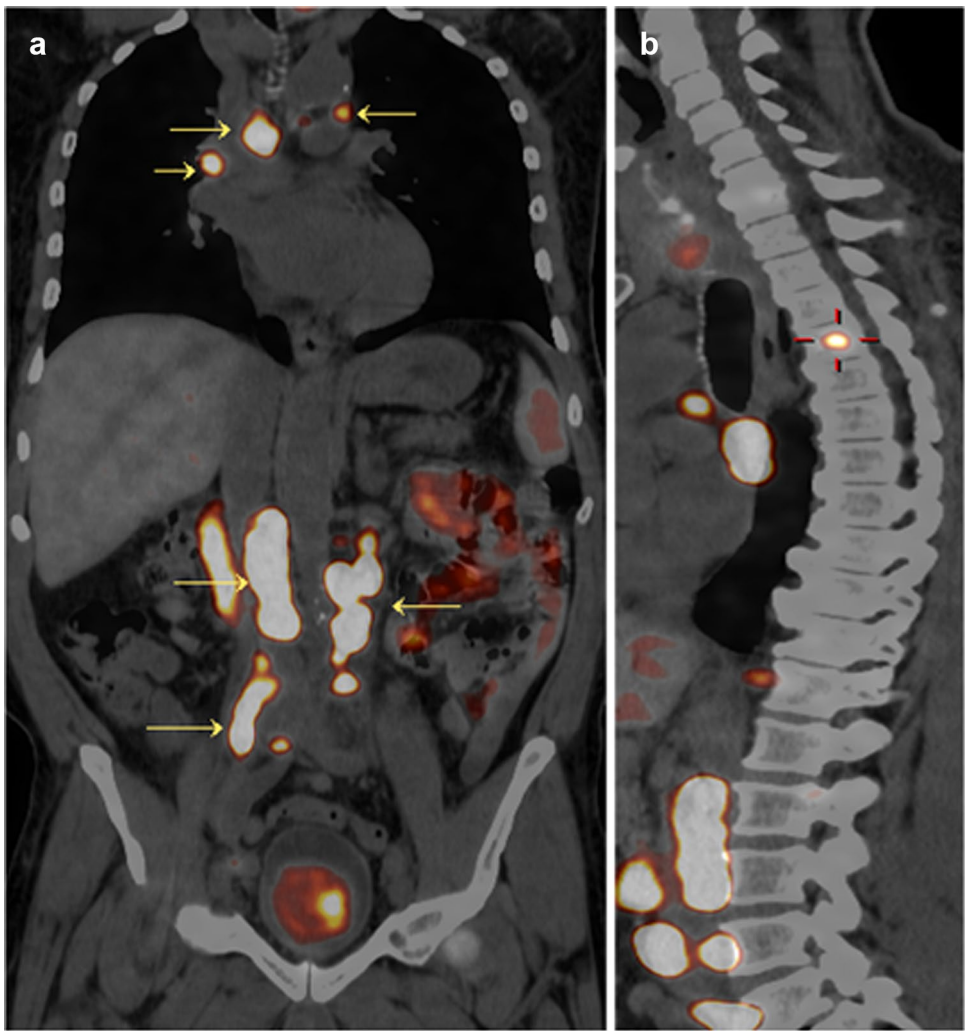

Fig. 4 A 70-year-old man with newly diagnosed PC referred for initial staging (PSA level: 100 ng/mL; GS: 4 + 4). **a** Coronal and **b** Sagittal ^{68}Ga-PSMA PET/CT images showing extensive ^{68}Ga-PSMA-avid metastatic LNs affecting almost all regional lymphatic chains and ^{68}Ga-PSMA-avid metastatic bony deposit at D4

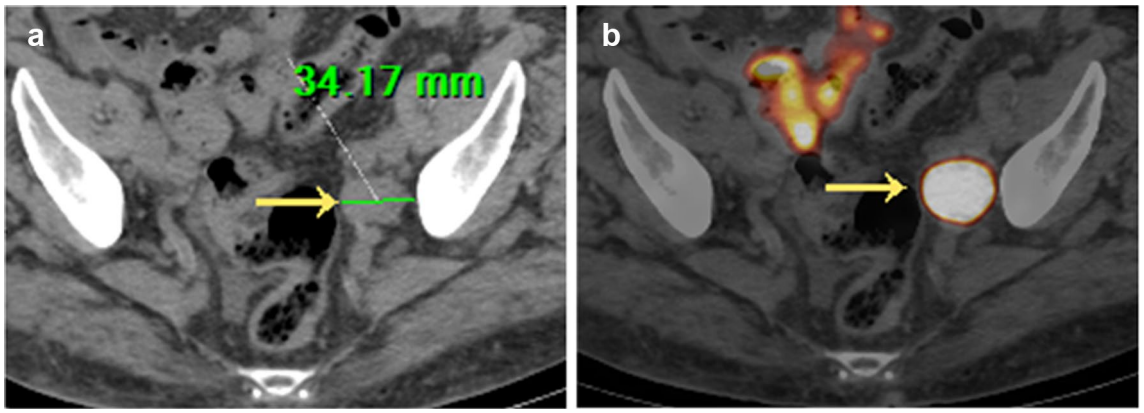

Fig. 5 A 72-year-old man with newly diagnosed PC referred for initial staging (PSA level: 5.4 ng/mL; GS: 5 + 4). **a** Axial CT and **b** Axial ^{68}Ga-PSMA PET/CT images showing a large single regional ^{68}Ga-PSMA-avid left internal iliac LN (yellow arrow), measures 34 × 20 mm and achieves SUV_{max} of 26.5

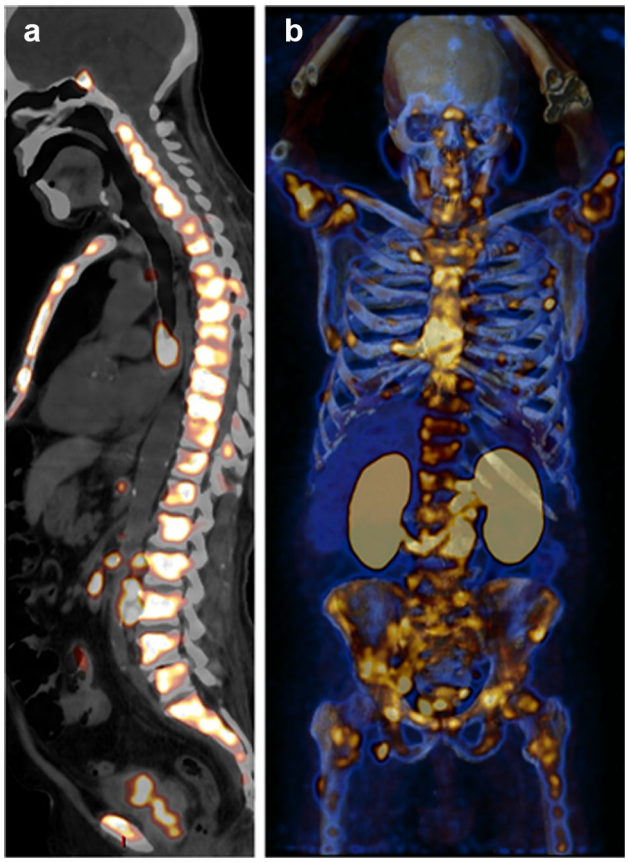

Fig. 6 A 73-year-old man with newly diagnosed PC referred for initial staging (PSA level: 145 ng/mL; GS: 5 + 5). **a** Sagittal and **b** Coronal ^{68}Ga-PSMA PET/CT images showing the axial and appendicular skeletons are totally replaced by heavily infiltrating diffuse ^{68}Ga-PSMA-avid metastatic osseous lesions, the most avid one achieves SUV_{max} of 15

overall results are encouraging and confirmed the high diagnostic sensitivity of ^{68}Ga-PSMA PET/CT in patients with newly diagnosed PC. The overall sensitivity in studies published before [16–22] ranged from 77 to 100%. Our data are congruent with these mentioned with an overall sensitivity of 96%. Notably, a recent meta-analysis published by Perera et al. [23] revealed that the per-patient sensitivity of ^{68}Ga-PSMA-11 PET/CT was high (86%). These results highlight the promising ability of ^{68}Ga-PSMA PET/CT as a diagnostic tool for patients with newly diagnosed PC.

We found that ^{68}Ga-PSMA-11 PET/CT produced a significant change of stage in 28.6% patients with an upstage in 17.9% patients and a downstage in 10.7% patients in comparison to the conventional imaging. Similarly, Wong et al. [24] found that the use of ^{68}Ga-PSMA-11 PET/CT resulted in a significant change of stage in 28% of patients with an upstage in 13% of patients and a downstage in 15% of patients. In comparison, Dewes et al. [25] demonstrated a 40% upstage and 13% downstage when ^{68}Ga-PSMA-11 PET/CT is used in initial staging. In a prospective study conducted by Hruby et al. [26], the use of ^{68}Ga-PSMA-11 PET/CT led to a change in stage in 21% of patients, of which only 2.8% of patients were downstaged. In a recent meta-analysis performed by Han et al. [27], the use of ^{68}Ga-PSMA-11 PET/CT reported highly superior detection rates over conventional imaging modalities and resulted in a change in management in 54% of patients. Considering our results, which mimic those of the aforementioned studies, we encouraged the inclusion of ^{68}Ga-PSMA-11 PET/CT during routine work-up for primary staging and diagnosis of PC, as ^{68}Ga-PSMA-11 PET/CT could potentially change in management decision. However, further work-up should be done to ascertain if these changes in management result in better impact for patients.

Table 3 Characters of ^{68}Ga-PSMA-11 PET-avid lesions

Lesions	Number of patient	SUV_{max} Mean ± SD	PSA (ng/mL) Median (range)	GS Mean ± SD	Stage Median (range)
Primary tumor					
Total	164	9.7 ± 4.5	17.6 (1.4–185)	7.4 ± 1.2	3 (0–4)
With extraprostatic metastases	101	16.9 ± 10.5	95.7 (1.4–185)	7.8 ± 1.6	4 (4–4)
No extraprostatic metastases	63	5.4 ± 2.8	13.3 (2.8–60)	6.8 ± 1.1	2 (0–4)
Regional LNs metastases	54	14.2 ± 11.8	100 (1.4–168)	7.9 ± 1.3	4 (4–4)
Distant LNs metastases	39	19.7 ± 17.1	100 (52–145)	8.3 ± 1	4 (4–4)
Bone metastases	47	17.8 ± 14.7	84 (1.4–185)	8.1 ± 1.4	4 (4–4)
Soft tissue metastases	7	5.6 ± 4.8	105 (5.6–185)	8.8 ± 1.8	4 (4–4)

^{68}Ga-PSMA PET/CT 68 Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography, *SUV_{max}* maximum standardized uptake value, *SD* standard deviation, *LNs* lymph nodes, *PSA* prostatic specific antigen, *GS* Gleason score

Table 4 Change in individual patient staging on account of ^{68}Ga-PSMA-11 PET/CT, compared to conventional imaging

^{68}Ga-PSMA PET/CT	Conventional imaging				
	Stage IIA	Stage IIB	Stage III	Stage IV	Total
Stage IIA	***9 (8)***	**2 (1.8)**	***0***	***0***	11 (9.8)
Stage IIB	***0***	***5 (4.5)***	**6 (5.4)**	**2 (1.8)**	13 (11.6)
Stage III	***0***	*12 (10.7)*	***33 (29.5)***	**2 (1.8)**	47 (42)
Stage IV	***0***	***0***	*8 (7.1)*	***33 (29.5)***	41 (36.6)
Total	9 (8)	19 (17%)	47 (42)	37 (33)	112 (100)

The data are represented as numbers with the corresponding percentages given in parentheses

The different font style indicate whether ^{68}Ga-PSMA PET/CT upstaged (italicized values), downstaged (bolded values) or kept the stage the same (bolditalicized values) as conventional imaging

^{68}Ga-PSMA PET/CT 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography

Table 5 Interobserver agreement for visual image interpretation, SUV_{max} measurements, and tumor staging by ^{68}Ga-PSMA-11 PET/CT

Parameter	*k*	95% CI
Visual image interpretation		
Overall scan result	0.81	0.61–1.00
Primary tumor	0.71	0.40–1.00
Regional LNs metastases	0.79	0.70–0.87
Distant LNs metastases	0.77	0.68–0.86
Bone metastases	0.83	0.74–0.92
Soft tissue metastases	0.63	0.47–0.80
SUV_{max} measurements		
Primary tumor	0.89	0.82–0.96
Regional LNs metastases	0.78	0.64–0.91
Distant LNs metastases	0.77	0.68–0.87
Bone metastases	0.76	0.64–0.89
Soft tissue metastases	0.64	0.51–0.77
Stage	0.82	0.70–0.94

^{68}Ga-PSMA PET/CT 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography, *SUV_{max}* maximum standardized uptake value, *LNs* lymph nodes, *k* Kappa, *CI* confidence interval

Although ^{68}Ga-PSMA-11 PET/CT has better detection rates than conventional imaging, still some of primary PC tumors do not exhibit significant PSMA expression and resulted in underestimation on PET/CT. Nine of the patients in this study had no uptake in the prostate gland on ^{68}Ga-PSMA PET/CT imaging despite proven PC. In two of these patients, ^{68}Ga-PSMA-avid LNs, bone, and hepatic lesions were detected. This finding goes in line with the finding of previous studies [18, 28–32]. Schreiter et al. [28] explained this underestimation due to a lack of soft tissue contrast of the CT at initial staging of primary PC or because of the small tumor mass or micrometastasis which does not express adequate tracer uptake to be efficiently detected by PET/CT. Meyrick et al. [29] assumed that the absence of PSMA avidity may represent a more aggressive variant of disease as very high-grade/neuroendocrine PC.

Despite the fact that interobserver agreement is an essential factor of high clinical value, to the best of our knowledge, few studies have performed the interobserver assessment for ^{68}Ga-PSMA-11 PET/CT. Without better evidence for reproducibility of the ^{68}Ga-PSMA PET/CT in the PC, the results of the study become unusable for clinical practice

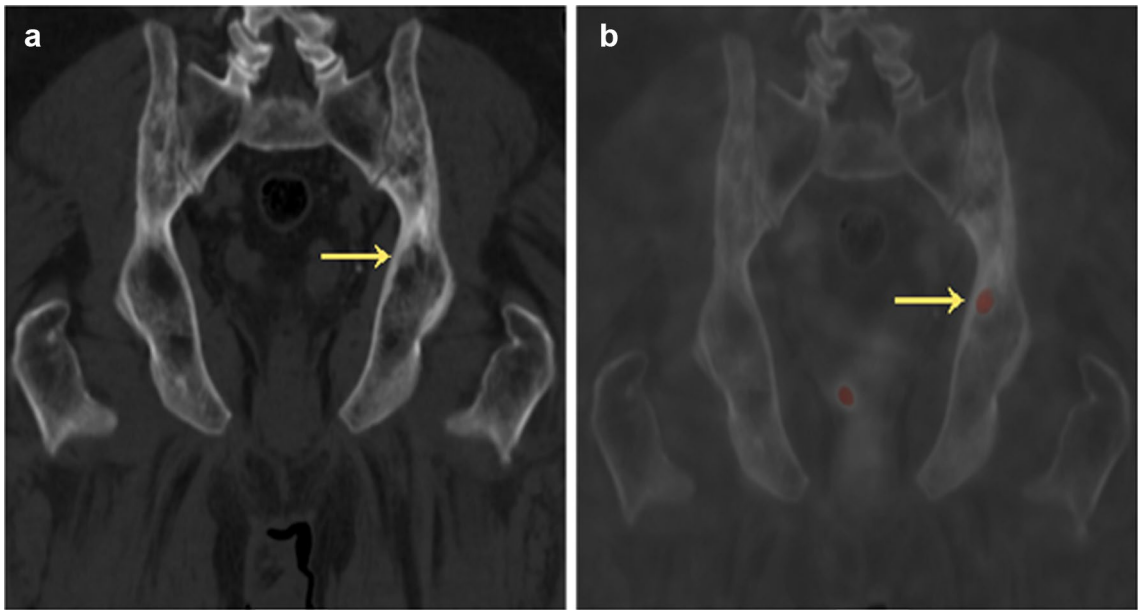

Fig. 7 A 70-year-old man with newly diagnosed PC referred for initial staging (PSA level: 13.3 ng/mL; GS: 3 + 3). **a** Coronal CT image showing small sclerotic bony lesion at left acetabular roof (yellow arrow). **b** Coronal ^{68}Ga-PSMA PET/CT image reveals faint uptake at this bony lesion (yellow arrow) with low activity (SUV_{max} 3.6). This lesion was detected by all observers but judged negative by three and positive by two. It could be of early metastatic nature versus chronic degenerative lesion

and we remain uncertain whether this is technique we should be doing or not. In our study, we performed interobserver agreements for visual image interpretation, SUV_{max} measurement, and tumor staging by five highly experienced nuclear medicine experts. We found that the interobserver agreements were almost good to perfect. These results are in keeping with the interobserver assessments by Fendler et al. [30] and Kranzbühler et al. [33] for ^{68}Ga-PSMA-11 PET/CT.

Detecting extraprostatic metastases is crucial in providing more accurate staging of newly diagnosed PC, determining the ideal treatment option, and avoiding unnecessary surgery. ^{68}Ga-PSMA-11 PET/CT is a valuable and promising technique to detect extraprostatic metastases. In our group, which consisted of 173 patients, ^{68}Ga-PSMA-11 PET/CT detected extraprostatic metastases in 65 (37.6%) patients. A remarkable finding in our study was that the most common site of extraprostatic metastases was the LNs (54 patients).

In keeping with the results published by Sachpekidis et al. [21] and Uprimny et al. [32], our study showed a statistically significant positive correlation between PSA value and SUV_{max} of primary tumors. Importantly, the PSA values of patients with non-visible ^{68}Ga-PSMA-avid primary tumors on PET/CT were significantly lower than those in patients with ^{68}Ga-PSMA-avid primary tumors. The risk of ^{68}Ga-PSMA-11 PET/CT positive LNs seemed to increase with GS. Additionally, we found a significant positive correlation between the PSA level and the disease stage. These data are matched to that of Meyrick et al. [29] who stated that high rates of metastases were detected by ^{68}Ga-PSMA-11 PET/CT in patients with high-grade primary disease (GS ≥ 9 and PSA > 10 ng/mL).

Interestingly, we found higher SUV_{max} in primary tumor with extraprostatic metastases than those without metastases. The highest SUV_{max} was detected in distant LNs metastases. The highest PSA value was found in patients with soft tissue metastases. These findings are consistent with that proved by Sathekge et al. [34] who reported that both the SUV_{max} value of the primary tumor and PSA values proved significantly higher in patients with LN and/or distant metastases when compared to those without LN and/or distant metastases.

Although the ^{68}Ga-PSMA-11 PET/CT is quite expensive than conventional imaging methods, it is relatively less expensive than systemic or surgical treatment. Hence, this imaging technique, though obviously diagnostic method only, may assist clinicians in deciding to initiate this more expensive treatment.

Our study has many strength points. We conducted a large prospective, multicentre study to avoid the selection bias of a retrospective study. We made a correlation with histopathology of primary lesions in all patients. However, our study has some limitations. First, the specificity, PPV, and NPV of ^{68}Ga-PSMA-11 PET/CT scan for PC were not established, as we did not have non-malignant patients for analysis. Second, the extraprostatic metastases (LNs, bone, and soft tissue metastases) could not be definitively confirmed in this study

due to lack of histopathological reference for these stages. It was extremely hard to get histopathological confirmation of all sites of obvious tumors owing to ethical and practical reasons. Third, our included patients were heterogeneous in form of disease severity (low, moderate, and high risk) with a wide variation in PSA values and GS. Finally, the cost of using ^{68}Ga-PSMA PET/CT examination may be a problem of this modality.

Conclusion

^{68}Ga-PSMA-11 PET/CT is a valuable tool with high diagnostic sensitivity (96%) and high reproducibility for diagnosis and staging of patients with newly diagnosed PC. ^{68}Ga-PSMA-11 PET/CT should be included during routine work-up for staging of patients with newly diagnosed PC. Nevertheless, due to its high costs, the ^{68}Ga-PSMA-11 PET/CT might be limited to suspected cases where there is still doubt after doing conventional imaging methods. Future prospective studies with a large sample size should be performed using either image-guided or targeted biopsies with histopathology from prostatectomy specimen to verify the sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA-11 PET/CT in primary PC.

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Compliance with ethical standards

Conflict of interest The authors of this manuscript declare no relevant conflicts of interest, and no relationships with any companies, whose products or services may be related to the subject matter of the article.

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