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ORIGINAL ARTICLE

Diagnostic performance of ^{68}Ga-PSMA PET/CT in the detection of prostate cancer prior to initial biopsy: comparison with cancer-predicting nomograms

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Abstract

Purpose To assess the diagnostic performance of ^{68}Ga-PSMA PET/CT for detecting suspected prostate cancer (PCa) and to compare it with that of two cancer-predicting nomograms.

Methods We performed a retrospective analysis of 146 consecutive patients with suspected PCa based on symptoms or elevated total prostate-specific antigen (tPSA) levels who underwent ^{68}Ga-PSMA PET/CT and histopathologic examinations from April 2017 to April 2018 in a large tertiary care hospital in China. The ^{68}Ga-PSMA PET/CT results (PCa or benignancy) were evaluated by two experienced nuclear medicine specialists. The risk of positive PCa was evaluated using ERSPC and PCPT nomograms. The diagnostic performances of ^{68}Ga-PSMA PET/CT and that of the two nomograms were compared via receiver operating characteristic (ROC) curve analysis, decision curve analysis, and logistic regression.

Results A total of 58 patients with tPSA of 0.4–50 ng/ml were included in the final analysis; PCa diagnosis was confirmed in 37 patients and excluded in 21 patients. ROC analysis showed that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ^{68}Ga-PSMA PET/CT were 91.67, 81.82, 89.19, and 85.71%, respectively, in per-patient analyses. ^{68}Ga-PSMA PET/CT exhibited a higher AUC (0.867) than those of ERSPC-RC3 (0.855) and PCPT-RC (0.770). The net benefit of ^{68}Ga-PSMA PET/CT was greatest for patients within threshold probabilities of 15–90%. Among the 58 patients, 11 (19%) biopsies suggested by ERSPC-RC3 were unnecessary and could have been avoided if judged by the ^{68}Ga-PSMA PET/CT results. Multivariate analysis revealed that the maximum standardised uptake value (SUV_{max}) and prostate volume were significant predictive factors for positive PCa results.

Conclusion In suspected PCa patients with tPSA of 0.4–50 ng/ml, ^{68}Ga-PSMA PET/CT outperformed the nomograms in predicting cancer and reducing unnecessary biopsies. In addition, the risk of PCa was positively correlated with a higher SUV_{max} and lower prostate volume, which could help clinicians in making preliminary estimates of individual cancer risk, monitoring ^{68}Ga-PSMA PET/CT false-positive results and making biopsy decisions in daily medical practice.

Keywords ^{68}Ga-PSMA PET/CT · Prostate cancer · Biopsy · Nomogram · Multivariate analysis · Decision curve analysis

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Introduction

Prostate cancer (PCa) is the most common type of malignant tumour and the third leading cause of cancer-associated mortality among men worldwide [1]. Currently, total prostate-specific antigen (tPSA) is the most widely used biomarker for screening and early detection of PCa. When it increases to greater than 50 ng/ml, tPSA is 98.5% accurate in predicting PCa [2]. However, the benefit of tPSA remains debatable owing to its organ specificity rather than tumour specificity and its low specificity in the detection of PCa patients with tPSA less than 50 ng/ml [2]. This issue has led to overdiagnosis and unnecessary prostate biopsies, which are invasive examinations associated with higher costs and adverse effects, such as infection and bleeding. Statistically, the overdiagnosis rate was as high as 16.4% in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, 33.2% in the European Randomized Study of Screening for Prostate Cancer (ERSPC) Trial, and 40.7% in the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) [3].

To reduce unnecessary prostate biopsy, multiple nomograms incorporating tPSA and other clinical predictors have been developed to predict the likelihood of a positive biopsy result [4–6]. Among established nomograms, the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator (RC) and the American Prostate Cancer Prevention Trial (PCPT) RC are currently the most used and can help to reduce the complications and costs incurred by unnecessary biopsy [7, 8].

In recent years, in addition to cancer nomograms, ^{68}Ga prostate-specific membrane antigen positron emission tomography/computerized tomography (^{68}Ga-PSMA PET/CT) has earned widespread attention as a novel imaging modality based on molecular-level analysis, rather than morphological or physiological analysis, to assist in PCa diagnosis and tumour burden evaluation. Accumulating evidence has proved the advantage of ^{68}Ga-PSMA PET/CT in detecting primary PCa and biochemical recurrence, even with low tPSA levels [9, 10]. Hence, ^{68}Ga-PSMA PET/CT has been used to aid decision making by confirming or eliminating the need for biopsies [11].

A previous study showed that ^{11}C-choline PET/CT outperformed PCa nomograms in diagnosing lymph node metastasis [12]. However, to our knowledge, no previous studies have compared ^{68}Ga-PSMA PET/CT with PCa nomograms in the detection of PCa with tPSA of 0.4–50 ng/ml. Therefore, the purpose of the present study was to assess the diagnostic performance of ^{68}Ga-PSMA PET/CT in the detection of suspected treatment-naïve PCa with tPSA of 0.4–50 ng/ml, to compare its efficacy with that of the ERSPC-RC3 and PCPT-RC nomograms in avoiding unnecessary biopsies, and to determine the significant factors leading to performance discrepancies among the three diagnostic tests via receiver operating characteristic (ROC) curve analysis, decision curve analysis, and logistic regression analysis.

Materials and methods

Patients

We retrospectively analysed our data from 146 consecutive patients who were evaluated with ^{68}Ga-PSMA PET/CT from April 2017 to April 2018. This study was conducted in the Urology Department and Nuclear Medicine Department of the Fourth Military Medical University Affiliated Hospital (Xijing Hospital, Xi'an, Shaanxi, China). Patients were included in the analysis if they met the aggregated requirements of ERSPC-RC3 and PCPT-RC: (1) age between 55 and 90 years old; (2) tPSA between 0.4 and 50 ng/ml; and (3) prostate volume between 10 and 110 ml [13, 14]. Patients were excluded due to: (1) lack of histological examination-proven diagnosis of PCa; and (2) ^{68}Ga-PSMA PET/CT being performed after pharmacotherapy or surgery for PCa since PSMA-targeted imaging can be disturbed by previous therapies [15, 16]. Finally, a total of 58 patients were eligible for the analysis. Owing to suspected PCa, in addition to having undergone ^{68}Ga-PSMA PET/CT, all 58 patients had referrals for either or both transabdominal ultrasound (TAUS) and magnetic resonance imaging (MRI) for initial diagnosis and staging. The conclusive results were pathologically confirmed by transrectal ultrasound (TRUS)-guided biopsy for all 58 patients. Two nomograms—ERSPC-RC3 and PCPT-RC—for predicting biopsy results based on age, tPSA, family history of PCa, digital rectal examination, prior biopsy, prostate volume, and TRUS were used to evaluate the risk of positive biopsy results in each patient [7, 8]. The prostate volumes of 58 patients were measured using at least one imaging method, including TAUS, MRI, or TURS. For the sake of comparison, values of prostate volume measured by TAUS or MRI were converted according to previously described algorithms [17, 18]. Written informed consent for ^{68}Ga-PSMA PET/CT and biopsy, as well as anonymous publication of examination data, was obtained from all of the individual participants included in the study.

^{68}Ga-PSMA PET/CT acquisition and image reconstruction

All image acquisition was performed with a Biograph 40 system (Siemens Medical Solutions, Erlangen, Germany). The ^{68}Ge/^{68}Ga generator system was produced by ITG GmbH (Munich, Germany), and the DOTA-PSMA-617 ligand was obtained from ABX GmbH (Radeberg, Germany). The ^{68}Ga PSMA-617 was synthesized according to a previously

described protocol [19]. The patients were intravenously injected with 1.8–2.2 MBq/kg body weight ^{68}Ga PSMA-617. Low-dose CT scans (pitch 0.8, 50 mA, 120 kV [peak]) for PET attenuation were acquired (automatic mA, 120 keV, 512 × 512 matrix, 5-mm slice thickness, 1.0-s rotation time, and 0.8 pitch), followed by a PET scan with 5 bed positions (3 min/bed, from head to the proximal thighs) performed 60 min later. The PET/CT images were transferred to a multimodal workstation (Syngo TrueD and HD Truepoint Siemens Medical Solutions) for data analysis.

Evaluation of imaging data

^{68}Ga-PSMA PET/CT scans were reviewed by consensus of two experienced board-certified nuclear medicine specialists (F. K. and D. L.), using the Siemens MIWP workstation (Syngo MIWP; Siemens Medical Solutions, Erlangen, Germany). Positive tumour lesions on PET/CT images were defined as having a higher uptake than the local background and not associated with physiologic uptake, according to the Joint EANM and SNMMI Procedure Guideline and the previous literature [20, 21]. To calculate standardised uptake values (SUVs), three-dimensional (3D) spherical regions of interest (ROIs) were manually delineated in PCa lesions and normal prostate glands, as performed previously in a similar manner [22]. Within all of the volumes of interest, maximum SUVs (SUV were measured. Background activity was determined by drawing circular ROIs on gluteal muscle tissue, sparing intramuscular vessels (= background SUV_{mean}), and target-to-background (T/B) ratios were calculated for each lesion to assist physicians in the comprehensive judgement of malignancy. Indeterminate results were incorporated into the final analysis and resolved by consensus.

Histological examination

A 12-core, TRUS-guided prostate biopsy with necessary additional target biopsy was performed for each patient's prostate biopsy. Subsequently, the tissues were formalin-fixed and routinely processed. Haematoxylin-eosin (HE) staining and immunohistochemistry (IHC) analysis were performed as needed, as previously reported in our study [23]. Microscopic histological examination was conducted by senior uropathologists. The histopathological result served as a reference, which was stratified in accordance with the 7th edition of the AJCC staging system for PCa. In cases of missed diagnosis with the initial biopsy, negative cases were further confirmed by follow-up for at

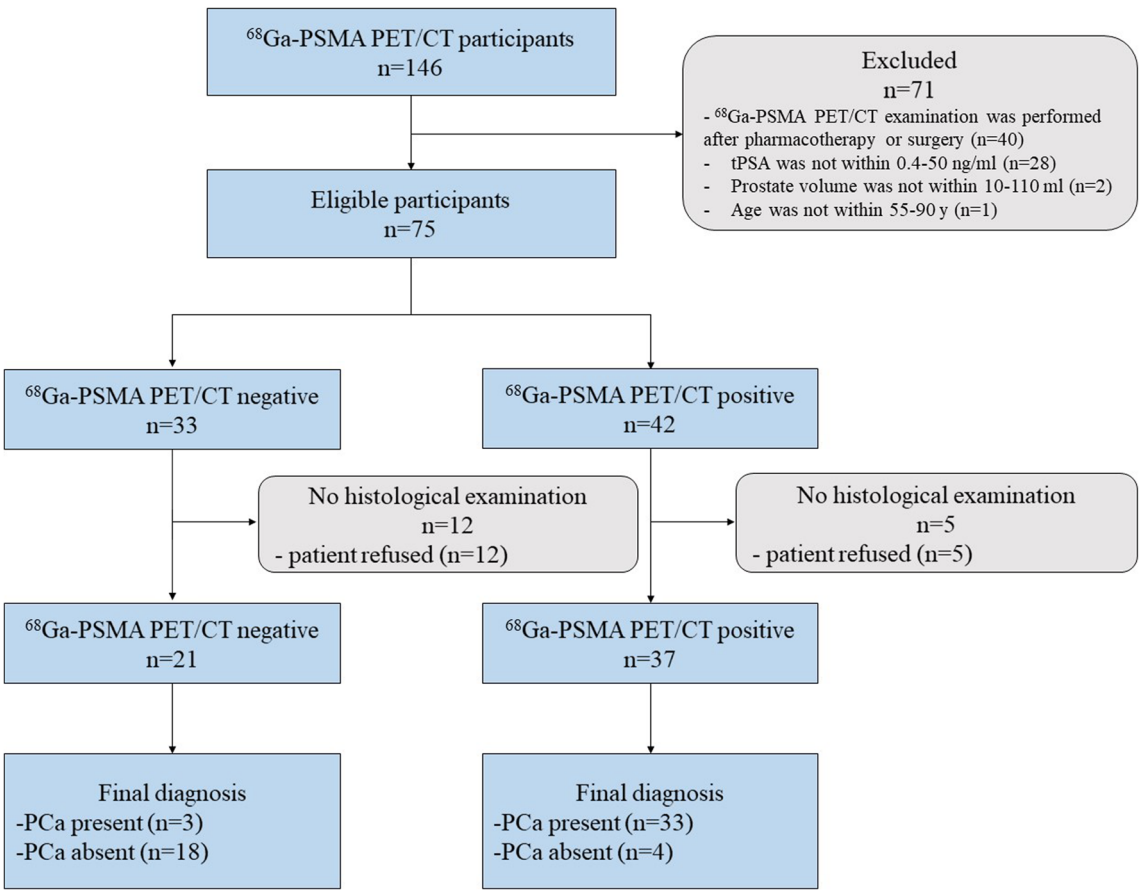


Fig. 1 Flow diagram of patients through the study

least 6 months by PSA screening, MRI, second biopsy, or trans-urethral resection prostate (TURP) with histopathologic examination.

Statistical analysis

Continuous variables are presented as the means ± standard deviations or medians (interquartile ranges). Categorical variables are presented as frequencies (percentages). Correlations of variables were evaluated with Spearman's rank correlation. The diagnostic performances of ^{68}Ga-PSMA PET/CT and prediction models of ERSPC and PCPT were assessed using ROC curve analysis and compared using the areas under the ROC curves (AUC), as well as decision analysis curves. Logistic regression was used to identify independent predictors in analysing the biopsy results, which were binary dependent variables. Variables with P values <0.05 in univariate analysis were finally incorporated into the multivariate analysis. The data were analysed by IBM SPSS statistics software, version 23.0 (IBM, Inc., Chicago, IL, USA), GraphPad Prism software, version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA), and R software, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

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

According to the inclusion and exclusion criteria depicted on the flowchart (Fig. 1), 146 men underwent ^{68}Ga-PSMA PET/CT, among whom 58 patients were included in the final analysis. The overall characteristics of the 58 patients are presented in Table 1. The mean time between ^{68}Ga-PSMA PET/CT examination and histopathological examination was 16.6 days (range, 1–69 days). Table 2 shows the ^{68}Ga-PSMA PET/CT in relation to PCa diagnoses. To investigate the diagnostic performance of ^{68}Ga-PSMA PET/CT, we calculated the sensitivity, specificity, PPV, and NPV (Table 3) and performed ROC analysis (Fig. 2) of the examinations, based on biopsy and histopathological diagnosis, which proved good diagnostic performance of ^{68}Ga-PSMA PET/CT. In addition, no significant adverse events occurred as a result of ^{68}Ga-PSMA PET/CT examinations. Five (8.6%) patients had slight pain and minor bleeding associated with TRUS-guided prostate biopsy, which was controlled by symptomatic approaches.*SD* standard deviation, *tPSA* total prostate-specific antigen, *SUV*$_{max}$ maximum standardised uptake value, *DRE* digital rectal examination, *TRUS* transrectal ultrasound,

In total, 37 (63.79%) of 58 patients showed positive results on ^{68}Ga-PSMA PET/CT. As shown in Fig. 3, detailed analysis of the ^{68}Ga-PSMA PET/CT results showed that the positive results were significantly ($P < 0.05$) more likely to be correlated with increasing values of tPSA, as well as SUV$_{max}$ and decreasing values of prostate volume. Regarding age, the correlation was not significant ($P = 0.9668$; Table 4). These findings showed that tPSA, SUV$_{max}$, and prostate volume were significant predictors of ^{68}Ga-PSMA PET/CT results (Fig. 3).

Table 1 Demographic and clinical characteristics of the 58 patients investigated in this study

Characteristic	Value
Age (years)	
Mean ± SD	69 (±8.03)
Median (range)	70 (55–85)
tPSA at PET/CT (ng/ml)	
Mean ± SD	17.99 (±11.01)
Median (range)	15.46 (1.31–49.07)
Prostate volume (ml)	
Mean ± SD	41.06 (±23.99)
Median (range)	32.89 (12.42–105.97)
SUV$_{max}$	
Mean ± SD	8.76 (±10.53)
Median (range)	4.67 (0–54)
Previous negative prostate biopsy	
Yes	3 (5.2)
No	55 (94.8)
DRE	
Abnormal	36 (62.1)
Normal	22 (37.9)
TRUS	
Abnormal	15 (25.9)
Normal	43 (74.1)
Clinical Gleason score (%)	
0	22 (37.9)
6	3 (5.2)
7	15 (25.9)
8	13 (22.4)
9	4 (6.9)
10	1 (1.7)

Table 2 ^{68}Ga-PSMA PET/CT in relation to the diagnosis of prostate cancer

^{68}Ga-PSMA PET/CT	Prostate cancer		Total
	Positive	Negative	
Positive	33	4	37
Negative	3	18	21
Total	36	22	58

Table 3 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) analysis with ^{68}Ga-PSMA PET/CT in the detection of PCa

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
^{68}Ga-PSMA PET/CT	91.67% (76.41–97.82)	81.82% (58.99–94.01)	89.19% (73.64–96.48)	85.71% (62.64–96.24)	0.867 (0.773–0.962)

CI confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the curve,

Comparison of the discriminative ability between ^{68}Ga-PSMA PET/CT and nomograms

To determine which modality had better discriminative ability in detecting suspected PCa, we plotted the ROC curves (Fig. 4) of ^{68}Ga-PSMA PET/CT and the two nomograms to compare the accuracy of ^{68}Ga-PSMA PET/CT in the diagnosis of primary PCa and the accuracy of the nomograms in predicting positive biopsy results; for each nomogram, a cut-off value corresponding to the highest level of accuracy was utilized. We found that the sensitivity, specificity, PPV, NPV, and AUC of ^{68}Ga-PSMA PET/CT were significantly better than those of PCPT-RC and slightly higher than those of ERSPC-RC3 (Table 5). Conclusively, the discriminative ability of ^{68}Ga-PSMA PET/CT was superior to that of PCPT-RC and ERSPC-RC3.

Comparison of the clinical utility between ^{68}Ga-PSMA PET/CT and nomograms

To determine which modality had better clinical utility in assisting biopsy decisions, we performed decision curve analysis of these diagnostic methods (Fig. 5). The grey line (leftmost) represents the 'biopsy all patients' strategy, and the horizontal black line indicates the 'biopsy none' strategy. Curves representing each diagnostic method are indicated. As expected, all of the methods were superior to the 'prostate biopsy for all' strategy, and the net benefit of PCPT was the lowest (Fig. 5). A previous study conducted by Sternberg et al. preliminarily proposed threshold probabilities of 10–40% as a reasonable risk range for PCa biopsy, and they recommended performing biopsy if the risk was greater than 40%, avoiding biopsy if the risk was less than 10%, and consulting doctors individually if the risk fell between these ranges [6, 24]. As shown in Fig. 5, the net benefit of ^{68}Ga-PSMA PET/CT was the greatest for patients within threshold probabilities of 15–90%, suggesting that the clinical utility of ^{68}Ga-PSMA PET/CT was superior to that of ERSPC-RC3 and PCPT-RC on most occasions. Hence, decision curve analysis showed that ^{68}Ga-PSMA PET/CT is the preferred diagnostic method in the detection of PCa over ERSPC-RC3 and PCPT-RC.

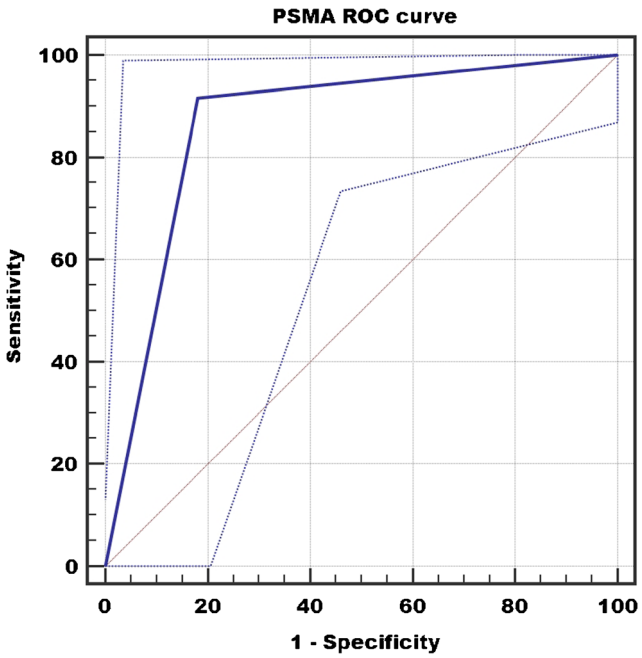


Fig. 2 Receiver operating characteristic (ROC) curve of ^{68}Ga-PSMA PET/CT for detecting prostate cancer with tPSA of 0.4–50 ng/ml

Impact of ^{68}Ga-PSMA PET/CT on biopsy decisions

Next, we sought to retrospectively explore the practical impact of ^{68}Ga-PSMA PET/CT in reducing unnecessary biopsies. We found among all 22 patients with negative biopsy results that 11 cases showed negative results of ^{68}Ga-PSMA PET/CT, but their probabilities of positive biopsy results were greater than 20% based on ERSPC-RC3. According to the ERSPC-RC3 guidelines, prostate biopsy should be performed as long as the probability of positive results exceeds 20% [8]. Finally, these 11 patients agreed to undergo prostate biopsy, yet the results of both pathological examination and subsequent follow-up proved that they were cancer-free. Conclusively, in this study, with 58 samples, 11 (19%) biopsies suggested by ERSPC-RC3 were unnecessary and could have been avoided according to the ^{68}Ga-PSMA PET/CT examination results.

Factors affecting the outperformance of ^{68}Ga-PSMA PET/CT

To determine the factors leading to the performance discrepancies between ^{68}Ga-PSMA PET/CT and the two nomograms, we performed correlation analysis and further logistic regression analysis. As shown in Fig. 6, the results

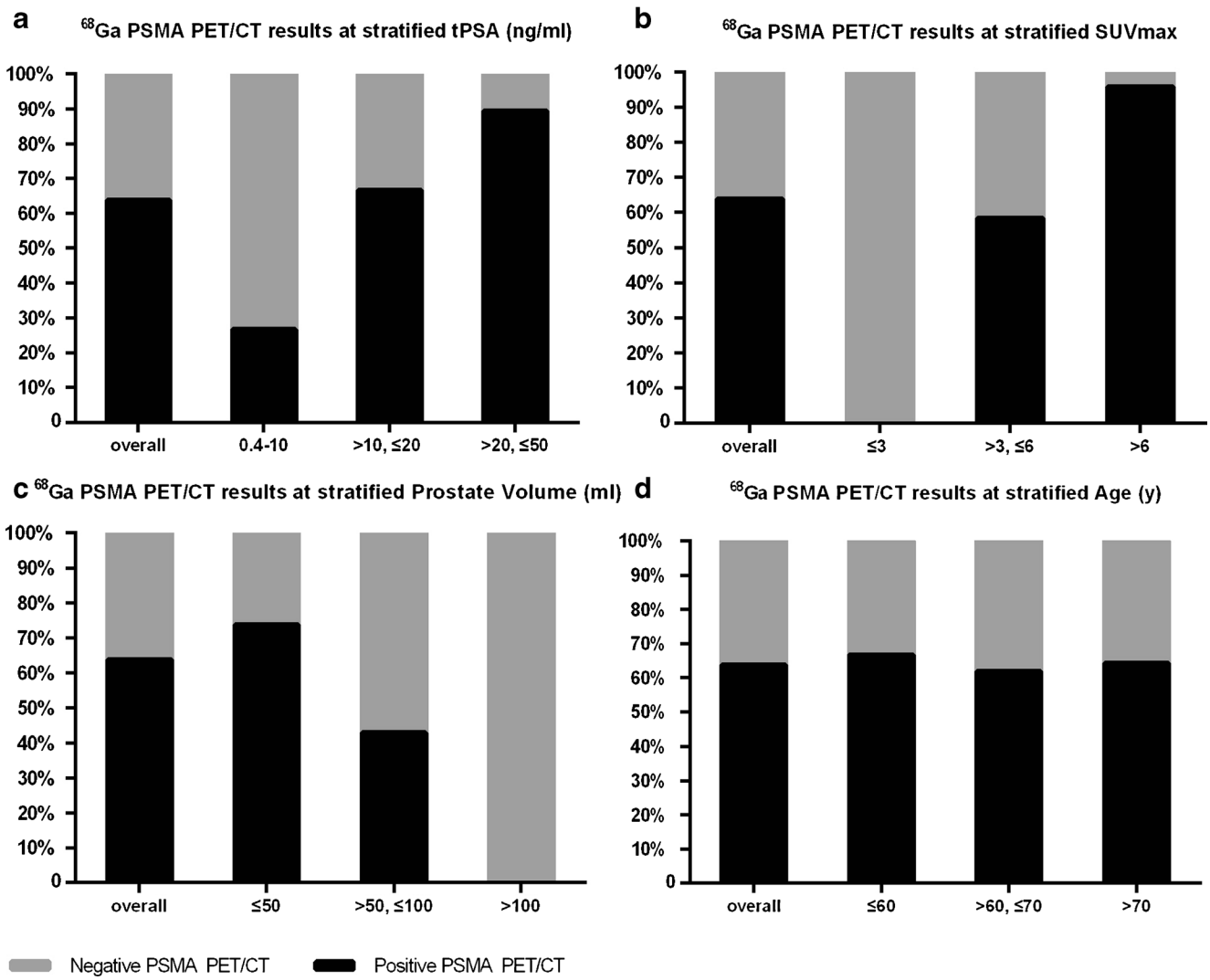


Fig. 3 Proportions of positive ^{68}Ga-PSMA PET/CT at stratified PSA levels ($P < 0.05$) (**a**). Proportions of positive ^{68}Ga-PSMA PET/CT at stratified SUV_{max} levels ($P < 0.05$) (**b**). Proportions of positive ^{68}Ga-PSMA PET/CT at stratified prostate volume ($P < 0.05$) (**c**). Proportions of positive ^{68}Ga-PSMA PET/CT at stratified age. No significant associations are shown ($P = 0.9668$) (**d**)

of correlation analysis demonstrated that the biopsy results were significantly ($P < 0.05$) positively correlated with SUV_{max}, tPSA, the results of ^{68}Ga-PSMA PET/CT, digital rectal examination (DRE), and TRUS and were negatively correlated with prostate volume (Fig. 6). Further, logistic regression analysis was performed to identify the predictive factors for biopsy results. As shown in Table 6, the univariate analysis revealed that all of the factors reached significance except for age ($P = 0.657$, OR [odds ratio]: 1.015, 95% CI: 0.950–1.085; Table 6). Subsequently, multivariate analysis showed that only SUV_{max} ($P = 0.005$, OR: 2.177, 95% CI: 1.263–3.755) and prostate volume ($P = 0.041$, OR: 0.945, 95% CI: 0.895–0.998) were significant predictive factors.

Conclusively, these findings indicated that SUV_{max} and prostate volume were significant predictive factors, leading to the performance discrepancies among the three tests.

Reasons for ^{68}Ga-PSMA PET/CT false-positive and false-negative results

We finally sought to determine the reasons for the false results of ^{68}Ga-PSMA PET/CT in this study. Specimens of the four false-positive, as well as three false-negative patients obtained from biopsy or surgery, were histopathologically examined (Fig. 7) using HE staining and PSMA-IHC.

In the four false-positive cases, we observed that the HE staining and PSMA-IHC, respectively, confirmed the absence of prostate tumour tissues and the presence of PSMA expression. These results suggested that the reason for false positives was overexpression of PSMA in benign prostatic cells.

In the three false-negative patients (Fig. 7a, d, g), we observed different reasons for the three false-negative results. For the first patient, HE staining and PSMA-IHC, respectively, confirmed the presence of prostate adenocarcinoma (Fig.

Table 4 Proportions of positive ^{68}Ga-PSMA PET/CT results at stratified levels

Stratified values	Number of positive results (%)	Number of negative results (%)	*P* value
Stratified tPSA (ng/ml)			
0.4–10	4 (26.67)	11 (73.33)	< 0.05
> 10, ≤ 20	16 (66.67)	8 (33.33)	
> 20, ≤ 50	17 (89.47)	2 (10.53)	
Total	37 (63.79)	21 (36.21)	
Stratified SUV_{max}			
≤ 3	0 (0)	10 (100)	< 0.05
> 3, ≤ 6	14 (58.33)	10 (41.67)	
> 6	23 (95.83)	1 (4.17)	
Total	37 (63.79)	21 (36.21)	
Stratified prostate volume (ml)			
≤ 50	31 (73.81)	11 (26.19)	< 0.05
> 50, ≤ 100	6 (42.86)	8 (57.14)	
> 100	0 (0)	2 (100)	
Total	37 (63.79)	21 (36.21)	
Stratified age (y)			
≤ 60	6 (66.67)	3 (33.33)	0.9668
> 60, ≤ 70	13 (61.90)	8 (38.10)	
> 70	18 (64.29)	10 (35.71)	
Total	37 (63.79)	21 (36.21)	

7b) and overexpression of PSMA (Fig. 7c). However, the ratio of tumour tissue to all radical prostatectomy specimens was only 3%, and the maximum diameter of the tumour in radical prostatectomy specimens was 5 mm. For the second patient, HE staining and PSMA-IHC, respectively, showed the presence of acinar prostate adenocarcinoma (Fig. 7e) and extremely low expression of PSMA (Fig. 7f). By HE staining, the third patient was diagnosed with a mixed adenocarcinoma, including 98% ductal prostate adenocarcinoma and 2% acinar prostate adenocarcinoma (Fig. 7h). PSMA-IHC showed moderate PSMA expression in the acinar prostate adenocarcinoma, but extremely faint PSMA expression in the ductal prostate adenocarcinoma (Fig. 7i). Considered together, the reasons for the false-negative results were small size of the tumour or extremely low expression of PSMA.

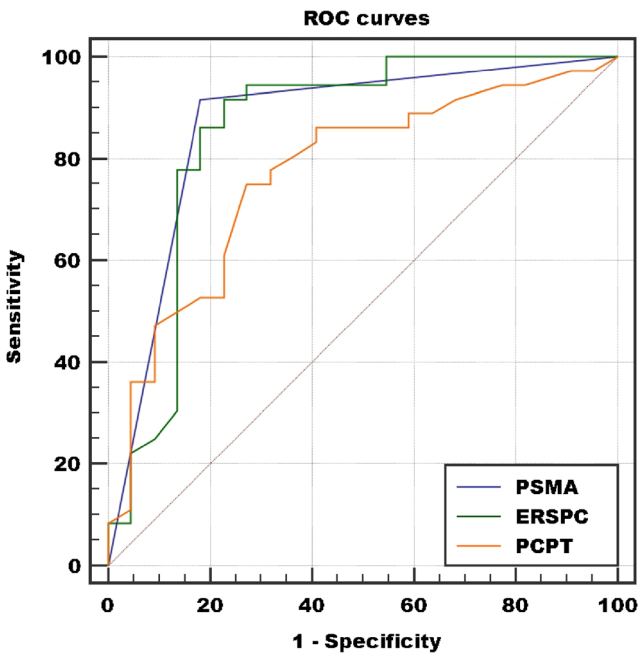


Fig. 4 Receiver operating characteristic (ROC) curves of ^{68}Ga-PSMA PET/CT for detecting PCa with tPSA of 0.4–50 ng/ml and of the two nomograms for predicting PCa with tPSA of 0.4–50 ng/ml

Discussion

In a cohort of suspected PCa patients, we primarily found that ^{68}Ga-PSMA PET/CT outperformed the two nomograms in predicting PCa and reducing unnecessary biopsies owing to better discriminative ability and clinical utility, SUV_{max}, and prostate volume being the significant predictive factors. The current study, for the first time, compared the diagnostic performance of ^{68}Ga-PSMA PET/CT with that of ERSPC-RC3 and PCPT-RC nomograms in the detection of PCa within a tPSA of 0.4–50 ng/ml. Our findings could help clinicians in the preliminary estimation of individual cancer risk, the monitoring of ^{68}Ga-PSMA PET/CT false-positive results, and the biopsy decision making in daily medical practice.

In the setting of primary PCa, several previous studies have suggested that ^{68}Ga-PSMA PET could detect the location and extent of intraprostatic lesions and promote diagnostic efficacy in detecting lymph node lesions [10, 25]. A previous study

Table 5 Sensitivity, specificity, PPV, NPV, and AUC analysis of ^{68}Ga-PSMA PET/CT in the detection of prostate cancer and RCs in the prediction of cancer risk

	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%)	NPV (%)	AUC (95% CI)
^{68}Ga-PSMA PET/CT	91.67 (76.41–97.82)	81.82 (58.99–94.01)	89.19	85.71	0.867 (0.773–0.962)
ERSPC RC3 (*cut-off >62%)	91.67 (76.41–97.82)	77.27 (54.18–91.31)	86.84	85.00	0.855 (0.735–0.976)
PCPT RC (*cut-off >46%)	75.00 (57.46–87.27)	72.72 (49.56–88.39)	81.82	64.00	0.770 (0.643–0.898)

PPV positive predictive value, *NPV* negative predictive value, *AUC* area under the curve, *RC* risk calculator, *CI* confidence interval

*Cut-off value corresponding to the highest level of accuracy (minimal false-negative and false-positive results) for each risk calculator

based on histopathology segments analysis reported that the sensitivity and specificity of ^{68}Ga-PSMA PET/CT for detecting primary intraprostatic lesions were 67% and 92%, respectively [26]. Consistent with these previous studies, our results also suggested excellent diagnostic performance of ^{68}Ga-PSMA PET/CT. However, our results exhibited higher sensitivity of 91.67% than specificity of 81.82%. Nevertheless, it is worth noting that our study only included patients with tPSA of 0.4–50 ng/ml. In this range, compared with greater than 50 ng/ml, there would be a lower prevalence of PCa and greater prevalence of false-positive cases [27], which could partially explain the relatively low specificity in our study, compared to previous studies [28].

To further understand the reasons for the better diagnostic performance of ^{68}Ga-PSMA PET/CT than the two nomograms, we performed correlation analysis and logistic regression analysis with predicting factors. As shown in Table 4, all of the factors except for age were significantly correlated with biopsy results. In addition, consistent with previous studies suggesting the significant role of SUV_{max} [29] and prostate volume [30, 31], our study demonstrated that only SUV_{max} and prostate volume were significant in multivariate logistic regression analysis, which might partially explain the better diagnostic performance of ^{68}Ga-PSMA PET/CT compared to the two nomograms. Future studies could incorporate SUV_{max} as a factor to develop new nomograms.

Although the excellent diagnostic ability of ^{68}Ga-PSMA PET/CT has been proved, there always exist false results. Hence, we subsequently detected the reasons for the four false-positive results and three false-negative results with ^{68}Ga-PSMA PET/CT in the present study. Histopathological

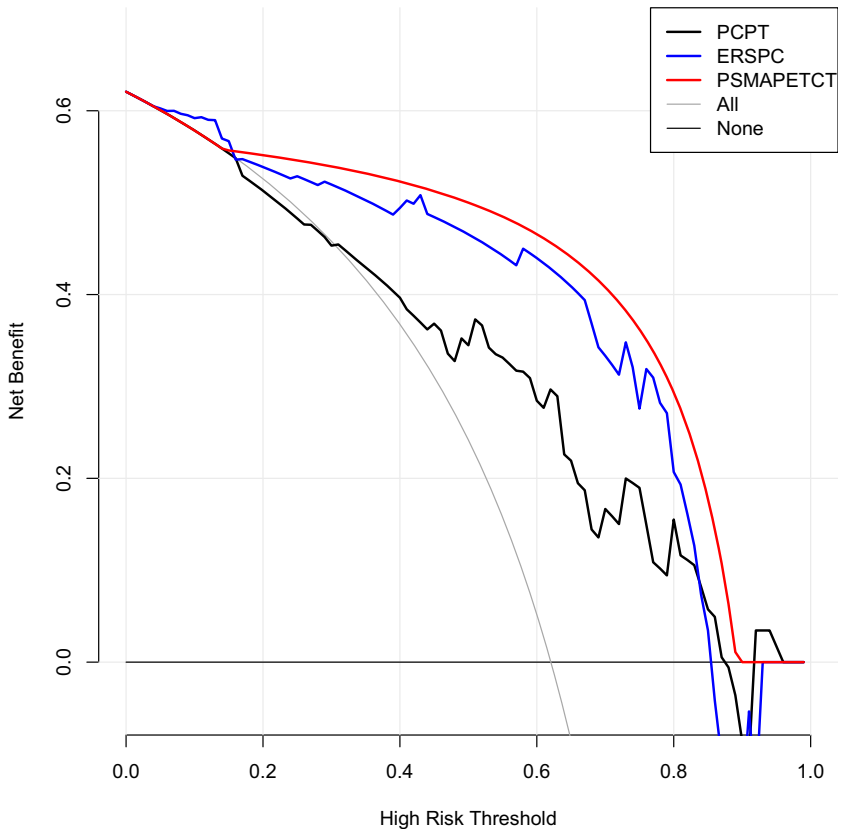


Fig. 5 Decision curve analysis of the clinical utility of ^{68}Ga-PSMA PET/CT and risk calculators for the detection of prostate cancer with tPSA of 0.4–50 ng/ml. Net benefit was plotted, and decision curves for all methods are shown, accompanied by the reference strategies of treating none or treating all. The net benefit of ^{68}Ga-PSMA PET/CT was greatest for patients within the threshold probabilities of 15–90%

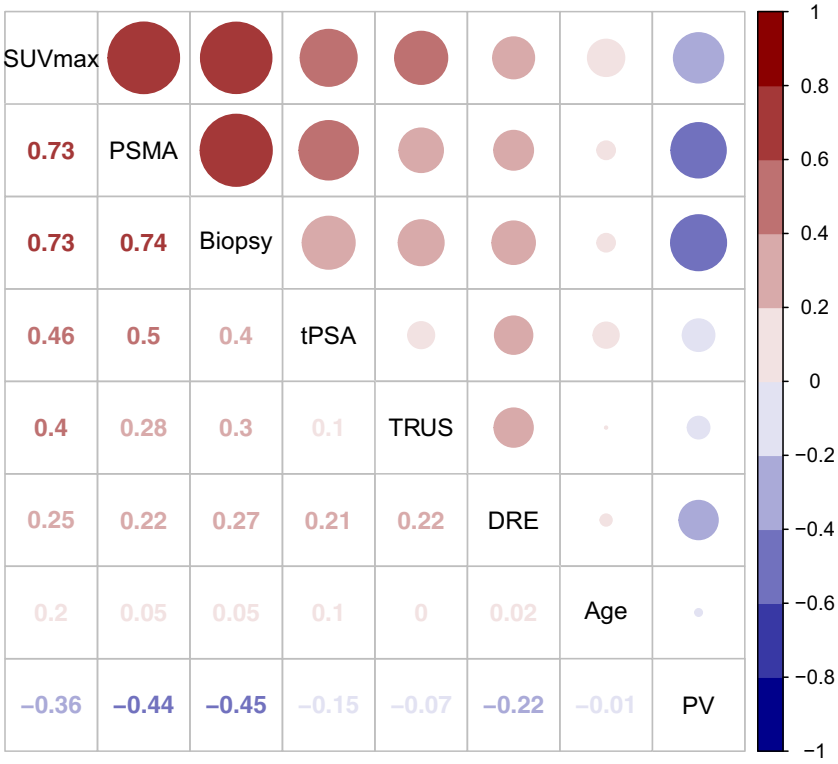


Fig. 6 The correlation coefficients between biopsy results and other clinical factors (*tPSA* total PSA, *PV* prostate volume, *DRE* digital rectal examination, *TRUS* transrectal ultrasound, *PSMA* prostate-specific membrane antigen)

examination results of HE staining and PSMA-IHC demonstrated that the false positives were due to the overexpression of PSMA in benign prostatic cells, similar to a previous study showing that PSMA was also expressed in prostatic epithelial cells in benign prostatic hyperplasia (BPH) patients [32].

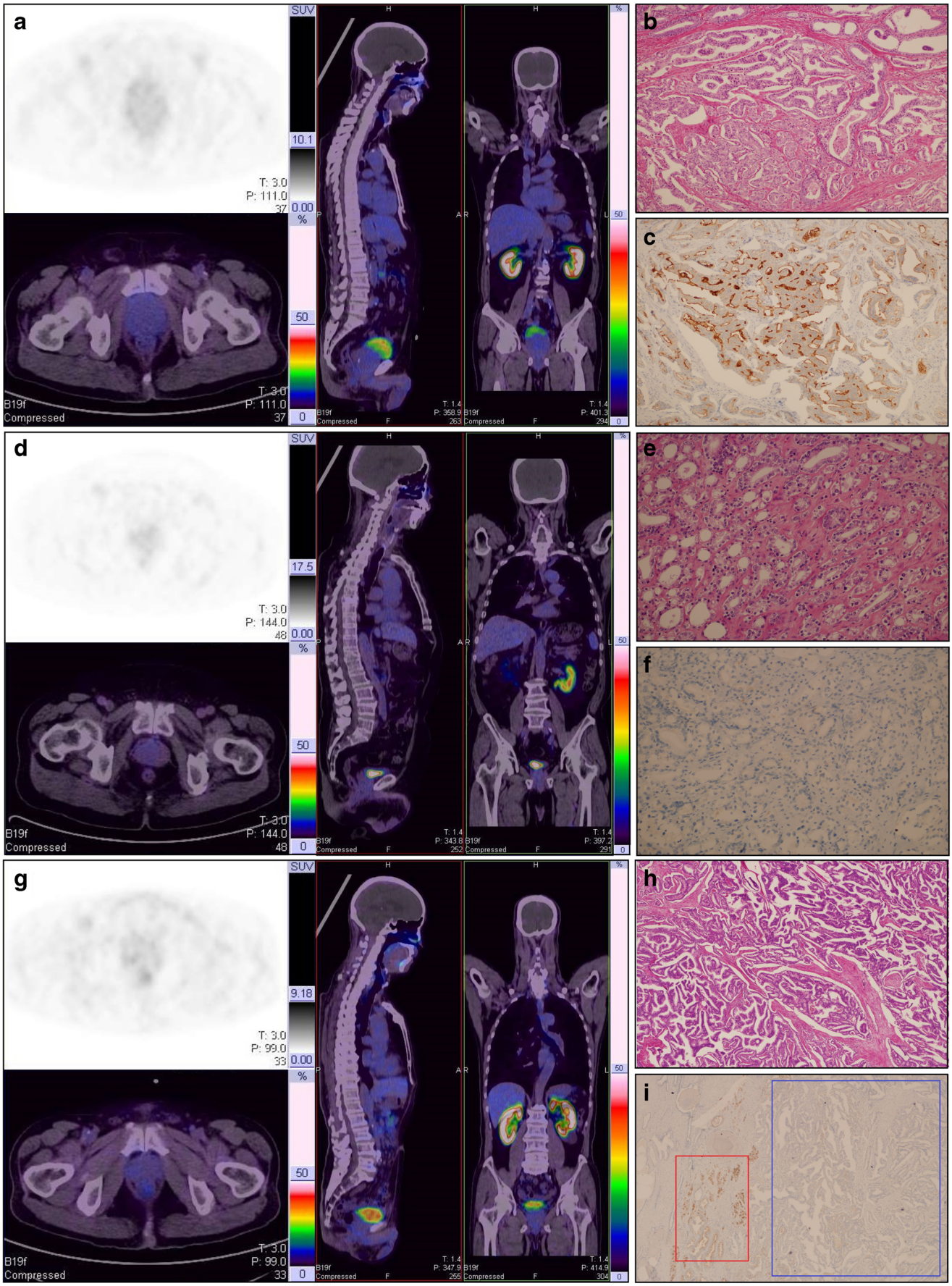
Notably, there was a false-positive case excluded from the final analysis because his prostate volume was as large as 153 ml, exceeding the upper limit of the ERSPC-RC3 requirement for prostate volume. This case, along with the aforementioned inverse correlation between prostate volume and malignant results, suggests that doctors should be extremely cautious about positive ^{68}Ga-PSMA PET/CT results accompanied by overly large prostate volumes because it is presumably a false-positive result.

Regarding the false-negative results, according to previous studies, they are prone to be present in neuroendocrine-dedifferentiated PCa patients [33, 34]. However, the histopathological examination of the three false-negative cases confirmed that all of them were non-neuroendocrine-dedifferentiated. Thus, in the present study, the reason was not PCa neuroendocrine dedifferentiation. Through HE staining and PSMA-IHC, we eventually proved that the reasons for the false-negative results were small size of the tumour, no expression of PSMA in acinar prostate adenocarcinoma, and no expression of PSMA in ductal prostate adenocarcinoma. Similarly, a previous study analysed 30 PCa patients and found that ^{68}Ga-PSMA PET/CT presented false-negative results of PCa lymph node (LN) metastases with sizes from 1.0 to 10.8 mm [35]. Another previous study reported that the reason for false-negative results was no PSMA expression in acinar prostate adenocarcinoma [36]. All of these findings suggest that the diagnosis of ^{68}Ga-PSMA PET/CT can be

Table 6 Univariate and multivariate analyses of factors associated with prostate cancer prediction

Categorical variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per year increase)	1.015	0.950–1.085	0.657			
tPSA (per ng/ml increase)	1.092	1.021–1.168	0.010			
SUV_{max}	2.650	1.407–4.992	0.003	2.177	1.263–3.755	0.005
PV	0.959	0.932–0.987	0.004	0.945	0.895–0.998	0.041
TRUS	5.652	1.136–28.130	0.034			
DRE	3.120	1.026–9.485	0.045			

tPSA total PSA, *PV* prostate volume, *TRUS* transrectal ultrasound, *DRE* digital rectal examination, *OR* odds ratio, *CI* confidence interval


a
SUV
10.1
0.00
%
50
0
T: 3.0
P: 111.0
37
B19f
Compressed
b
c
d
SUV
17.5
0.00
%
50
0
T: 3.0
P: 144.0
48
B19f
Compressed
e
f
g
SUV
9.18
0.00
%
50
0
T: 3.0
P: 99.0
33
B19f
Compressed
h
i

◀ **Fig. 7** ^{68}Ga-PSMA PET/CT results (**a, d, g**), HE staining (**b, e, h**), and PSMA staining (**c, f, i**) of three patients with pathology-proven prostate cancer (Gleason score 4 + 4 = 8, 4 + 3 = 7, and 4 + 3 = 7; PSA 9.33, 9.53, and 15.65 ng/ml). The three-prostate cancer was negative on ^{68}Ga-PSMA PET/CT, but positive on HE staining. PSMA staining was positive in the first patient (**c**), but negative in the second patient (**f**). In the third patient, PSMA staining showed no expression in ductal prostate adenocarcinoma (**i**, blue square), but moderate expression in acinar prostate adenocarcinoma (**i**, red square)

affected by the size of tumour lesions and the expression level of PSMA, which call for awareness in interpreting ^{68}Ga-PSMA PET/CT images. In addition, we observed that the proportion of false-negative results was 8.3% (3/36), consistent with a previous study conducted by Maurer et al., who reported 8.4% primary PCa patients showing false-negative results with ^{68}Ga-PSMA PET/CT [37].

Moreover, ^{68}Ga-PSMA PET/CT in the present study was conducted using the compound PSMA-617 rather than PSMA-11. There is no denying that the compound PSMA-11 is currently the most widely used and investigated agent for PCa PSMA-PET/CT imaging, and studies focusing on the newly developed radiotracer PSMA-617 have been limited [38]. However, PSMA-617 was developed based on PSMA-11 by replacing the chelator NOTA with DOTA and by introducing a p-iodo phenyl substitution in the linker between the DUPA motif and DOTA, ensuring the required lipophilicity in the side chain [10, 39]. In preclinical studies, this ligand showed significantly improved binding affinity to PSMA and highly efficient internalization into PCa cells [40]. The application value of ^{68}Ga-PSMA-617 PET/CT in detecting primary PCa has already been confirmed in clinical studies and guidelines [21, 39, 41].

Our study had some limitations. First, despite the significance of the prostate volume agreeing with previous studies [30, 31, 42], the data on prostate volume in the present retrospective study were obtained using different methods, including MRI, TRUS, and TAUS. To homogenize the value of prostate volume, values obtained from MRI and TAUS were finally transformed into corresponding TRUS values via previously defined algorithms [17, 18]. Additional prospective studies are necessary to acquire high-quality data to confirm and validate these results. Second, the present study only focused on ^{68}Ga-PSMA PET combined with low-dose CT. Analysis of PET/MRI and other imaging modalities was not performed. In fact, PSMA PET/MRI shows advantages in prostate biopsy, and Eiber et al. successfully applied ^{68}Ga-PSMA PET/MRI in fusion biopsy of the prostate, suggesting that MRI can provide additional morphological information to help with the evaluation of suspected prostate tumour lesions [43–46]. Further studies focusing on PET/MRI are warranted.

Conclusion

In suspected PCa patients with low tPSA (0.4–50 ng/ml), ^{68}Ga-PSMA PET/CT outperformed the risk calculators ERSPC-RC3 and PCPT-RC in predicting cancer risk and reducing unnecessary biopsies. In addition, biopsy results were significantly more likely to be positive with higher SUV_{max} and lower prostate volume, which could help clinicians with preliminary estimation of individual cancer risk and biopsy decision making in daily medical practice. In addition, clinicians should pay additional attention to positive ^{68}Ga-PSMA PET/CT result with overly large prostate volume because it presumably is false positive.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All of the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this study type, formal consent is not required.

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