(1) PSMA PET/CT and standard plus PET/CT-Ultrasound fusion targeted prostate biopsy can diagnose clinically significant prostate cancer in men with previous negative biopsies

(2) PSMA PET/CT-Ultrasound prostate biopsy

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ABSTRACT

The purpose of this study was to investigate the feasibility and diagnostic efficacy of ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) combined with PET-ultrasound image-guided biopsy in the diagnosis of prostate cancer. **Methods:** A total of 31 patients with previously negative prostate biopsy, but persistent elevated serum prostate specific antigen (PSA), were imaged with a ^{68}Ga-labeled prostate-specific membrane antigen (PSMA) PET/CT ligand prior to undergoing repeat prostate biopsy. Based on the proposed PROMISE criteria, PSMA PET/CT results were interpreted as negative (miPSMA-ES 0-1) or positive (miPSMA-ES 2-3). All patients underwent standard template systematic biopsy with up to four additional PSMA PET-ultrasound fusion image-guided biopsy cores. The sensitivity, specificity, positive and negative predictive values, and accuracy of PSMA PET/CT were determined. In addition, the correlation between miPSMA-ES and detection rate of prostate cancer was also analyzed. Univariate logistic regression models were established using PSMA PET/CT semi-quantitative analysis parameters to predict the outcome of repeat prostate biopsy. **Results:** The median age of patients was 65 years (range 53-81), and the median PSA level was 18.0 ng/ml (range 5.48-49.77 ng/ml). Prostate cancer was detected in 15/31 patients (48.4%) and 12/31 patients (38.7%) had clinically significant disease. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{68}Ga-PSMA PET/CT in the diagnosis of clinically significant prostate cancer were 100.0%, 68.4%, 66.7%, 100.0% and 80.6%, respectively. The detection rate of prostate cancer increased with the increase of miPSMA-ES score. The detection rate of clinically significant prostate cancer in miPSMA-ES 0-1, 2 and 3 groups were 0%, 54.5% and 85.7% respectively. Semi-quantitative analysis of ^{68}Ga-PSMA PET/CT images showed that predictive models based on maximum standardized uptake value (SUV_{max}), tumor-to-background normal prostate SUV ($SUV_{T/BGp}$) and tumor-to-background normal liver SUV (SUV_{ratio}) could effectively predict clinically significant prostate cancer; area under the curves were 0.930, 0.877, and 0.956, respectively. **Conclusion:** This study preliminarily confirmed that ^{68}Ga-PSMA PET/CT imaging combined with PET-ultrasound fusion image-guided prostate biopsy can effectively detect clinically significant prostate cancer. Prebiopsy ^{68}Ga-PSMA PET/CT has predictive value for clinically significant cancer in the studied patient population.

Key Words: PSMA, PET/CT, biopsy, prostate cancer

INTRODUCTION

For patients with suspected prostate cancer (PCa) because of serum prostate specific antigen (PSA) elevation or digital rectal examination abnormality, transrectal ultrasound-guided biopsy (TRUS-biopsy) is currently a standard method for definitive diagnosis. However, traditional 10-core or 12-core systematic biopsy can lead to over-diagnosis of patients with non-clinically significant cancers. On the other hand, it cannot avoid missed detection of some clinically significant PCa (csPCa) (*1*). These limitations persist in patients with suspected PCa who have had a negative prostate biopsy but persistently elevated PSA. It is a challenging issue for clinicians to determine whether these patients need repeat biopsy and how to improve the detection of clinically significant cancer through biopsy.

A series of studies has suggested that multi-parametric magnetic resonance imaging (mpMRI) prior to biopsy, followed by targeted biopsy of suspected sites of PCa, can improve the detection of csPCa (*2-5*). In addition, some studies suggested that, given the high sensitivity and negative predictive value of mpMRI in the diagnosis of csPCa, patients with negative mpMRI results may avoid unnecessary biopsy (*6,7*). Indeed, both American Urological Association (AUA) and European Association of Urology (EAU) guidelines recommend mpMRI before repeat biopsy, and targeted biopsy of suspected lesions based on mpMRI findings can provide a basis for subsequent clinical decision making (*8,9*). However, the PROMIS trial (*1*) found that 24% of patients with negative mpMRI findings had csPCa, and it remains controversial whether mpMRI-negative patients need repeat biopsy (*2*). Furthermore, the interpretation of prostate mpMRI is mainly based on the Prostate Imaging Reporting and Data System (PI-RADS) 2.0 system. The image interpretation rules of PI-RADS 2.0 are relatively complicated, and the experience of different readers and their understanding of the standards may lead to high inter-reader variability(*10*).

^{68}Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) can be used for positron emission tomography/computed tomography (PET/CT) and have demonstrated excellent sensitivity and specificity in the diagnosis of PCa (*11*). Multiple studies have shown that PSMA-targeted PET/CT and PET/MRI can accurately determine the location and extent of primary prostate cancer, and some studies have demonstrated that this novel imaging technique is superior to traditional mpMRI in terms of diagnostic efficacy (*12-14*). Zamboglou et al. (*14*) compared the volume of primary prostate cancer depicted by ^{68}Ga-PSMA PET/CT and mpMRI and found that the PSMA PET/CT findings were highly consistent with postoperative pathological results. In addition, unlike complex image interpretation standards of mpMRI, the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria (*15*) that were recently proposed for the interpretation of PSMA PET/CT and PET/MRI image reports are relatively simple and may have less intrinsic inter-reader variability.

This prospective study was designed to preliminarily investigate the following aspects in patients with prior negative prostate biopsy previously but persistently elevated PSA: diagnostic efficacy of ^{68}Ga-PSMA PET/CT based on molecular imaging for PSMA (miPSMA) scoring criteria in the detection of csPCa and the feasibility and clinical value of PSMA PET/TRUS fusion biopsy.

MATERIALS AND METHODS

Patients Population and Study Protocol

Patients with clinically suspected PCa but negative prostate biopsy results were scheduled to undergo repeat prostate biopsy. These patients were included between August 2016 and September 2018. Inclusion criteria: age < 90 years, at least 1 negative prostate biopsy in the past, PSA level 4 - 50 ng/ml, and/or digital rectal examination abnormality, ability to understand study procedures, and volunteering to participate in this study. Exclusion criteria were acute prostatitis or the presence of any other cancers besides basal cell carcinoma or squamous cell skin cancer. All patients received ^{68}Ga-PSMA PET/CT imaging and related laboratory examinations prior to biopsy, followed by PSMA PET/CT-ultrasound fusion-guided targeted biopsy and standard 12-core template biopsy of the prostate (Figure 1).

^{68}Ga-PSMA PET/CT

^{68}Ga-PSMA-617 (^{68}Ga-PSMA) was produced as described previously (*16*). Each patient received an intravenous injection of ^{68}Ga-PSMA-617 (median dose: 206.09 MBq; range: 121.73-361.12 MBq), followed by PET and CT scans at 60±10 min using a Gemini TF scanner (Philips Medical Systems, The Netherlands). Scanning range was from skull base to middle thigh. CT acquisition and reconstruction parameters: voltage 120 keV, current 100 mAs, pitch 0.8 mm, and tube-rotation time 0.5 s. CT reconstruction employed the standard reconstruction method supplied by the vendor, matrix was 512 x 512, reconstructed slice thickness was 3 - 5 mm. PET acquisition and reconstruction parameters: 3D emission mode acquisition was used, a total of 9 - 10 bed positions were scanned; the acquisition time for each bed position was 90 seconds; ordered-subsets expectation maximization (OSEM) method was used for PET image reconstruction. Attenuation correction was with CT. Fusion Viewer software of Extended Brilliance Workstation (EBW, Philips, The Netherlands) was used to fuse and analyze all ^{68}Ga-PSMA-617 PET/CT images.

PET/CT Image Analysis

^{68}Ga-PSMA PET/CT images of all patients were jointly read by 2 nuclear medicine specialists with more than 10 years of experience. They conducted visual and semi-quantitative analysis of PET/CT images blinded to any knowledge of patients' clinical data. Whole body CT images, PET images and PET/CT fusion images were viewed in the axial, coronal and sagittal planes. The potential systematic and targeted biopsy areas were judged positive when lesion-related focal radiotracer uptake was higher than liver. ^{68}Ga-PSMA uptake in biopsy areas were scored according to PROMISE criteria (version 1.0) (*15*). The PROMISE scores of each biopsy were summarized, and the highest score of miPSMA-ES was determined. miPSMA Score 0-1 was considered to be negative, while miPSMA Score 2 - 3 points was considered to be positive. SUV_{max} of prostate lesion, as well as normal prostate background and liver background (SUV_{BGp} and SUV_{L}, respectively), were determined. The calculated uptake ratio of prostate lesion versus normal prostate background was $SUV_{T/BGp}$, while the calculated uptake ratio of prostate lesion versus liver background was SUV_{ratio}.

PSMA PET/CT-Ultrasound Fusion Biopsy

Transrectal Ultrasound (TRUS)-guided prostate biopsy was performed in conjunction with a fusion biopsy using the pre-biopsy PSMA PET/CT images. DICOM data of PSMA PET/CT images were first imported into a navigated 3D ultrasound system (General Electric

Logiq E9, Aurora, OH, U.S.). According to previous studies (*17*), PSMA PET/CT and ultrasound image registration was carried out using 1-plane, 1-point method at first. Briefly, the 1-plane was the puborectalis plane, and the 1-point was internal urethral orifice, cyst or calcification, which could be corrected at any time. After initial image registration finished, real-time ultrasound was performed from apex to base of prostate to evaluate the coincidence between ultrasonography and PET/CT. When the registration was not satisfied, an additional point was used to modify the registration. For patients with negative PSMA imaging, only 2-core targeted biopsy passes were conducted in the highest ^{68}Ga-PSMA uptake area of the prostate; for patients with positive PSMA imaging, up to 4-core targeted biopsy passes were conducted. All targeted biopsy procedures were conducted by an experienced urologist (> 20 years), while systematic biopsy was conducted by another experienced sonologist (> 8 years) without any knowledge of the PET/CT results. The process of obtaining a PSMA PET/US fusion-guided biopsy from image acquisition to biopsy was outlined in supplemental Figure 1.

Pathology

A dedicated genitourinary pathologist was responsible for preparing the sections of biopsy samples and reporting the results according to International Society of Urological Pathology (ISUP) 2015 Revision Standards. In addition to Gleason scores of each biopsy, the overall Gleason score of the patient was provided on basis of systematic and targeted biopsy. In our study, csPCa on standard biopsy was defined by previously published studies (Gleason Score ≥ 3+4) (*17,18*). If pathological examination showed normal prostate or benign prostatic lesions, the patients were followed for at least 6 months. Follow-up examination indices included PSA levels, imaging examinations, and/or trans-urethral resection of the prostate (TURP).

Statistics

Descriptive statistics were utilized and data were expressed as either percentages or medians (with ranges). Depending on the specific case, chi-square or Fisher exact test was used to compare categorical data, while Wilcoxon–Mann–Whitney U-test and the Kruskal-Wallis test were used to compare continuous data. The sensitivity, specificity, accuracy, and positive and negative predictive values of PSMA PET/CT were calculated for detection of csPCa. Detection rates of systematic biopsy versus targeted biopsy were compared using the McNemar mid-p test. A semi-quantitative index of PSMA PET/CT was used to construct a univariate logistic prediction model for csPCa. Diagnostic efficacy of this model was analyzed using a receiver-operating-characteristic (ROC) curve, and the optimal cut-off value was obtained with Yoden index. All statistical analysis was carried out using SPSS version 22.0 software (IBM Corp., Armonk, NY). $P < 0.05$ was considered to have statistical significance.

RESULTS

Demographics and Clinical Characteristics

This study was approved by the Ethics Committee of Beijing Cancer Hospital. All patients were informed of the study procedures in detail, and all signed informed consent. This study screened a total of 217 patients with suspected PCa treated in our hospital, among them, 34 patients who met the inclusion criteria without meeting any of the exclusion criteria were initially included. Among the enrolled patients, 2 were excluded due to failure to complete PSMA PET/CT and 1 was excluded due to failure to complete biopsy. As such, 31 patients were

included in the final analysis. Median age of the 31 patients was 65 years (range: 53 - 81). 24 patients had one prior biopsy, five patients had two, and two patients had three. The median PSA of all patients was 18.0 ng/ml (range: 5.48 - 49.77 ng/ml).

A total of 31 subjects underwent PSMA PET/TRUS fusion biopsy. Overall, PCa was detected in 15 of 31 patients (48.4%), including 12 patients with Gleason Score ≥ 3+4 and 3 patients with Gleason score 3+3. The remaining 16 patients were negative for PCa. The patients (n=12) with GS≥ 3+4 were defined as csPCa. The patients (n=19) with GS 3+3 (n=3), normal prostate and benign prostatic disease (n=16) were defined as non-clinically significant prostate cancer (non-csPC).

When the 2 groups of patients with csPCA and non-csPCA were compared, there were significant differences in PSA level, prostate volume, and PSA density. There was no statistical difference in the number of previous biopsies and free-to-total PSA ratio. See Table 1 for details.

Diagnostic Performance of ^{68}Ga-PSMA-PET/CT for PCa Detection

On a patient-by-patient basis, PSMA PET/CT imaging was positive (miPSMA ES 2-3) in 18 patients (58%) and negative in the remaining 13 patients (42%) (The typical cases were illustrated in supplemental Figures 2 and 3). The detection rate of csPCa was 0% (0/13), 54.5% (6/11), and 85.7% (6/7), respectively in each group with miPSMA-ES 0-1, 2, and 3; that difference was statistically significant ($P < 0.001$). The sensitivity, specificity, and accuracy of ^{68}Ga-PSMA PET/CT in the diagnosis of PCa were 93.3%, 75.0%, and 83.9%, respectively. The sensitivity, specificity and accuracy in the diagnosis of csPCa were 100.0%, 68.4%, and 80.6%, respectively. The positive predictive value of ^{68}Ga-PSMA PET/CT imaging (mPSMA-ES 2-3) was 77.8% in determining the presence of PCa and 66.7% in identifying csPCa. The main causes of false positives were believed to be prostate hyperplasia (2 cases) and chronic prostatitis (2 cases); miPSMA-ES was 2 in all cases. All patients with a miPSMA-ES of 3 had PCa, and most of them (85.7%) had csPCa. The negative predictive value of miPSMA-ES 0 - 1 was 92.3% in ruling out PCa and 100.0% in ruling out csPCa. Among patients with negative ^{68}Ga-PSMA PET/CT imaging, there was one case of PCa (Gleason score 6), six cases of benign prostatic hyperplasia, two cases of chronic inflammation, two cases of prostatic intraepithelial neoplasia (*9*), and one case of atypical hyperplasia.

From the 31 patients enrolled in this study, a total of 440 prostate biopsy cores were obtained, among which 105 cores (23.8%) detected PCa and 75 cores (17.0%) detected csPCa. The detection rate of clinically significant cancer gradually increased with miPSMA-ES 0 to 3 in each group; the detection rate was 0.0%, 6.7%, 44.9%, and 78.6%, respectively. The intergroup differences had statistical significance ($P < 0.001$). A total of 88 cores detected PCa (69.8%) in 126 PSMA PET/CT-positive lesions, among which 66 cores (52.4%) detected csPCa. A total of 314 biopsy cores were obtained from PSMA PET/CT-negative areas (miPSMA-ES 0-1), among which 297cores（94.6%） were normal prostate tissues or benign prostatic lesions, and 17 cores were false negative lesions (GS 6 was 8 cores, GS 7 was 7 cores, and GS 8 was 2 cores), however, none of the above false negative results affected the patient's final GS.

Semi-quantitative Analysis of ^{68}Ga-PSMA PET/CT and Its Predictive Value for Prostate Biopsy Outcomes

The median highest uptake in prostate lesion areas of interest was SUV_{max} 5.61 (range 2.90 - 30.95) in all patients. The median background radioactivity uptake in normal prostate

tissues was SUV_{max} 3.40 (range 2.00 - 4.40). The median uptake in the liver was SUV_{max} 5.47 (range 3.05 - 9.74). The median SUV_{ratio} of prostate lesion versus prostate background was 1.62 (range 1.12 - 10.32). The median SUV_{ratio} of prostate lesion versus the liver was 1.02 (range 0.64 - 6.03). When the pathological results were used for grouping, SUV_{max}, $SUV_{T/BGp}$ and SUV_{ratio} were significantly higher in csPCa (GS ≥ 7) than in non-csPCa ($P < 0.001$). There was no statistical difference in SUV_{max} and liver background between the 2 groups (P values were 0.13 and 0.484, respectively), see Table 2 for details.

Univariate logistic regression analysis suggested that SUV_{max}, $SUV_{T/BGp}$ and SUV_{ratio} could all be used as predictors of csPCa in patients undergoing repeat biopsy. The predictive model based on SUV_{max}, $SUV_{T/BGp}$ and SUV_{ratio} demonstrated an excellent diagnostic efficacy. The results of ROC curve analysis showed that the area under the curve value of PSMA PET/CT semi-quantitative parameters in the prediction of csPCa was 0.93 (SUV_{max}), 0.877 ($SUV_{T/BGp}$) and 0.956 (SUV_{ratio}), respectively (Fig. 2). When calculated by Yoden index, the optimal cutoff value of SUV_{max} was 5.27, the diagnostic sensitivity was 100%, and the specificity was 73.7% (0.93). The optimal cutoff value of SUV_{ratio} was 1.19, with sensitivity and specificity of 91.7% and 94.7%, respectively (0.956). The optimal cutoff value of $SUV_{T/BGp}$ was 1.81, and the sensitivity and specificity were 83.3% and 78.9%, respectively (0.956).

Comparison between Systematic Biopsy and ^{68}Ga-PSMA PET-US Fusion Image-Guided Targeted Biopsy

PSMA PET/TRUS fusion-guided targeted biopsy detected 12 cases of csPCa, while systematic biopsy detected 10 cases. The detection rate of targeted biopsy was slightly higher, 38.7% versus 32.3%, but the difference had no statistical significance ($P = 0.25$). The PPV and NPV were 50.0% and 96.9% for systematic biopsy, 57.1% and 100% for targeted biopsy, respectively. Two patients with systematic biopsy of GS 6 were confirmed to have csPCa (Gleason score 3+4) by targeted biopsy, and 1 patient with negative targeted biopsy was confirmed to have GS 6 prostate cancer by systematic biopsy. The detection rate of csPCa using PSMA PET/TRUS targeted biopsy increased to 66.7% in patients with positive imaging. Neither targeted biopsy nor systematic biopsy detected csPCa in patients with negative PSMA PET/CT imaging, but targeted biopsy detected more PIN (2 vs 0) and dysplasia (1 vs 0) than systematic biopsy. In addition, in the case of similar cancer detection rate, the number of cores was significantly lower with targeted biopsy than with systemic biopsy. For each patient, the median cores of the 2 biopsy methods were 2 and 12, respectively ($P < 0.001$). Overall, the percentages of total positive cores of targeted biopsy and systematic biopsy were 47.0% (31/68) and 19.4% (72/372), respectively. Extrapolating from these findings, the diagnosis of a single case would require 36 cores of systematic biopsy and only 5.5 cores of targeted biopsy.

DISCUSSION

The study described in this manuscript preliminarily confirms the following findings: for patients with previous negative prostate biopsy but elevated PSA, miPSMA-ES helped predict csPCa; the SUV_{max}, $SUV_{T/BGp}$ and SUV_{ratio} of ^{68}Ga-PSMA PET/CT were all useful predictors of csPCa. PSMA PET/TRUS fusion-guided prostate biopsy was clinically feasible and improved the detection of csPCa. This is the first prospective study of ^{68}Ga-PSMA PET/CT combined with PET/TRUS fusion biopsy based on miPSMA score for the diagnosis of patients with negative biopsy findings but suspected of harboring PCa.

Prior studies have suggested that PSMA PET may be a valuable alternative or adjunct in patients with suspected primary PCa. In recent years, some case reports and small-scale studies have successively confirmed that ^{68}Ga-PSMA PET combined with PET-CT/TRUS or PET-MRI/TRUS guided prostate biopsy can effectively improve the detection of csPCa. Simopoulos et al. (*19*) first reported the successful case of ^{68}Ga-PSMA/CT and MRI/TRUS fusion-guided prostate biopsy. Subsequently, Westenfelder et al. (*20*) successfully detected csPCa (GS 4+3) using ^{68}Ga-PSMA PET/MR and ultrasound image fusion-guided biopsy in a patient with previous negative prostate biopsy and MRI. Lopci et al. (*18*) included 45 patients with negative prostate biopsy and negative/equivocal MRI findings or MRI contraindications. All patients underwent ^{68}Ga-PSMA PET/CT. Among them, 25 patients with confirmed positive lesions immediately received PSMA PET/TRUS fusion-guided targeted prostate biopsy, and the detection rate of prostate cancer was 44%.

In our study, PSMA PET demonstrated high sensitivity (85.7% - 100%) and high specificity (75% - 100%) in the detection of PCa, with similar performance characteristics for the detection of csPCa. That imaging performance is based on miPSMA expression scoring from the PROMISE criteria (*15*), a different approach than has generally been used in other studies which have focused on using the uptake value of normal prostate for reference (*12,13,18,21*). Utilizing the liver as a reference uptake be a superior methodology, as prostate tissues are often may have associated hyperplasia, inflammation, and even glandular fibrosis caused by repeated biopsy, which could potentially cause false positive PSMA PET uptake. When the above lesions are present with prostate cancer, plus the impact of volume effect, it is possible that it may be more difficulty to interpretation PET images and increase observer error between different readers. Based on our results, during the diagnosis of patients with complicated suspected prostate cancer, miPSMA-ES criteria are more appropriate, stable and objective for the determination of positive lesions.

As shown by the results of this study, when miPSMA score 0-1 is used as negative ^{68}Ga-PSMA-PET/CT imaging criteria, it provides higher negative predictive value for the diagnosis and suggests a higher probability to obtain a negative result following a repeat biopsy. This concords with a recent report by Zhang et al. (*22*); among patients requiring prostate biopsy according to ERSPC-RC3 criteria (European Randomized Study of Screening for Prostate Cancer risk calculator-level 3). 19% of these patients could potentially avoid unnecessary biopsy if negative ^{68}Ga-PSMA PET/CT imaging results were followed. On the other hand, positive PSMA PET results with a miPSMA score of 2-3 provided high accuracy in the diagnosis of csPCa. In a recent retrospective study, Chen et al. (*23*) proposed that prostate cancer should be considered when mpMRI score was PI RADS 3 but miPSMA score was higher than 2. If miPSMA $\geq$ 2 alone was used as the criterion for the diagnosis of csPCa in our study, the sensitivity and specificity were 89% and 71%, respectively, which were similar to the results we obtained. In summary, PSMA PET/CT examination based on miPSMA-ES scoring criteria has a high diagnostic value for patients with suspected PCa who previously had negative biopsy but a persistently elevated PSA.

Previous studies on ^{68}Ga-PSMA PET/CT have mostly been based on ^{68}Ga-PSMA-11, while studies focusing on the newly developed radiotracer ^{68}Ga-PSMA-617 have been less numerous. In preclinical studies, PSMA-617 showed improved affinity that could further increase tumor uptake, and improved internalization that may keep tumor uptake stable until late time points (*24*). Furthermore, ^{68}Ga-PSMA-617 has become a valuable diagnostic agent in detecting primary PCa and in predicting risk stratification of PCa (*16,25*).

Moreover, several ^{18}F-labeled PSMA ligands have recently been introduced clinically. ^{18}F-DCFPyL and ^{18}F-PSMA-1007 are among the most promising candidates. On the basis of the physical properties of ^{18}F, radiotracers labeled with that nuclide should show a spatial resolution equal to or better than that of ^{68}Ga (*26*). In addition, delayed imaging is more feasible due to the longer half-life of ^{18}F, which could reduce urinary excreted ^{18}F-PSMA in the bladder. Therefore, ^{18}F-PSMA targeting radiotracers may have advantages in detecting small lesions in prostate.

This study showed that liver could be used as an appropriate reference tissue for thresholding images when assessing the PSMA PET/CT scans. However, liver is not always suitable serving as a reference, as the biodistribution of ^{18}F-PSMA-1007 is different from other PSMA-related radiotracers (specifically, ^{18}F-PSMA-1007 has significant hepatobiliary clearance, while other radiotracers (e.g. ^{18}F-DCFPyL, ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, etc.) have predominantly renal clearance). For agents such as ^{18}F-PSMA-1007, the SUV_{ratio} may not be suitable serving as a semi-quantitative analysis parameter.

This study does have limitations. Although it is currently the largest prospective PSMA PET diagnostic study in patients with negative biopsy previously but persistently elevated PSA, the overall sample size is still small. Considering the total number of patients in this study and the limited number of cases for grouping analysis, we were unable to analyze the potential correlation between miPSMA-ES score and GS. As limited by the sample size, we were unable to conduct multi-parametric regression analysis of semi-quantitative indices. In addition, this study did not compare radical prostatectomy with the pathological results of biopsy because a large proportion of patients included in this study did not undergo surgical operation due to advanced age, high-risk grading, and other factors. It should also be pointed out that this study only included patients visiting the Peking university cancer hospital, which may cause a bias in patient composition. As a result, our patient population may not represent a more general patient composition.

CONCLUSION

This study confirmed the feasibility of PSMA PET imaging combined with PET-ultrasound fusion imaging-guided prostate biopsy in patients with prior negative prostate biopsy. This technique can effectively detect PCa. Prebiopsy PSMA PET/CT imaging based on miPSMA-ES criteria can aid in the diagnosis of csPCa.

DISCLOSURE

The authors declare that they have no potential conflict of interests.

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KEY POINTS:

Question: Can PSMA PET/CT and standard plus PET/CT-Ultrasound fusion targeted prostate biopsy diagnose clinically significant prostate cancer(csPCa) in men with previous negative biopsies?

Pertinent Findings: In this prospective study, a total of 31 patients with previously negative prostate biopsy, but persistent elevated PSA, underwent ^{68}Ga-PSMA PET/CT and standard plus PET/CT-Ultrasound fusion targeted prostate biopsy. ^{68}Ga-PSMA PET/CT helped predict csPCa, and PSMA PET/TRUS fusion-guided prostate biopsy was clinically feasible and improved the detection of csPCa.

Implications for Patient Care: PSMA PET imaging combined with PET-ultrasound fusion imaging-guided prostate biopsy has a high diagnostic value for patients with suspected PCa who previously had negative biopsy but a persistently elevated PSA.

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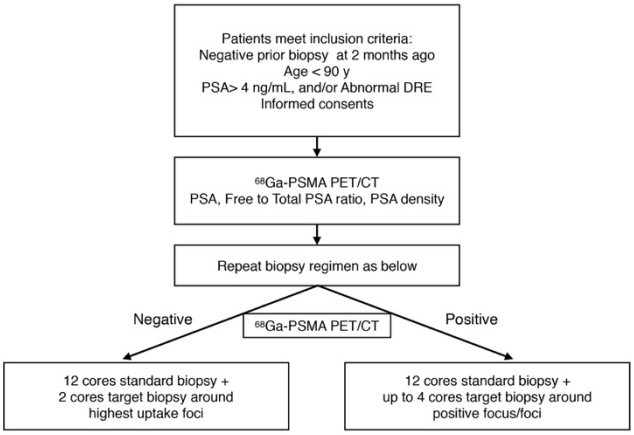


FIGURE 1. Prostate biopsy algorithm of study subjects

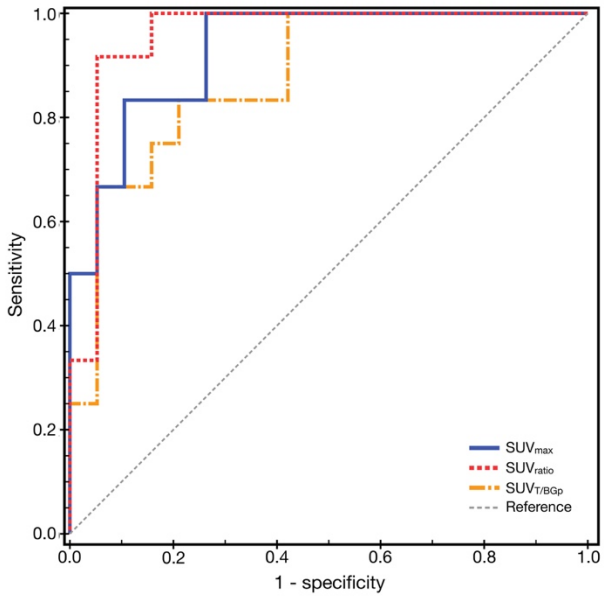


FIGURE 2. ROC curve analysis of ^{68}Ga-PSMA PET/CT semi-quantitative analysis index for the prediction of clinically significant cancer(csPCa).

TABLE 1. Patient's clinical characteristics

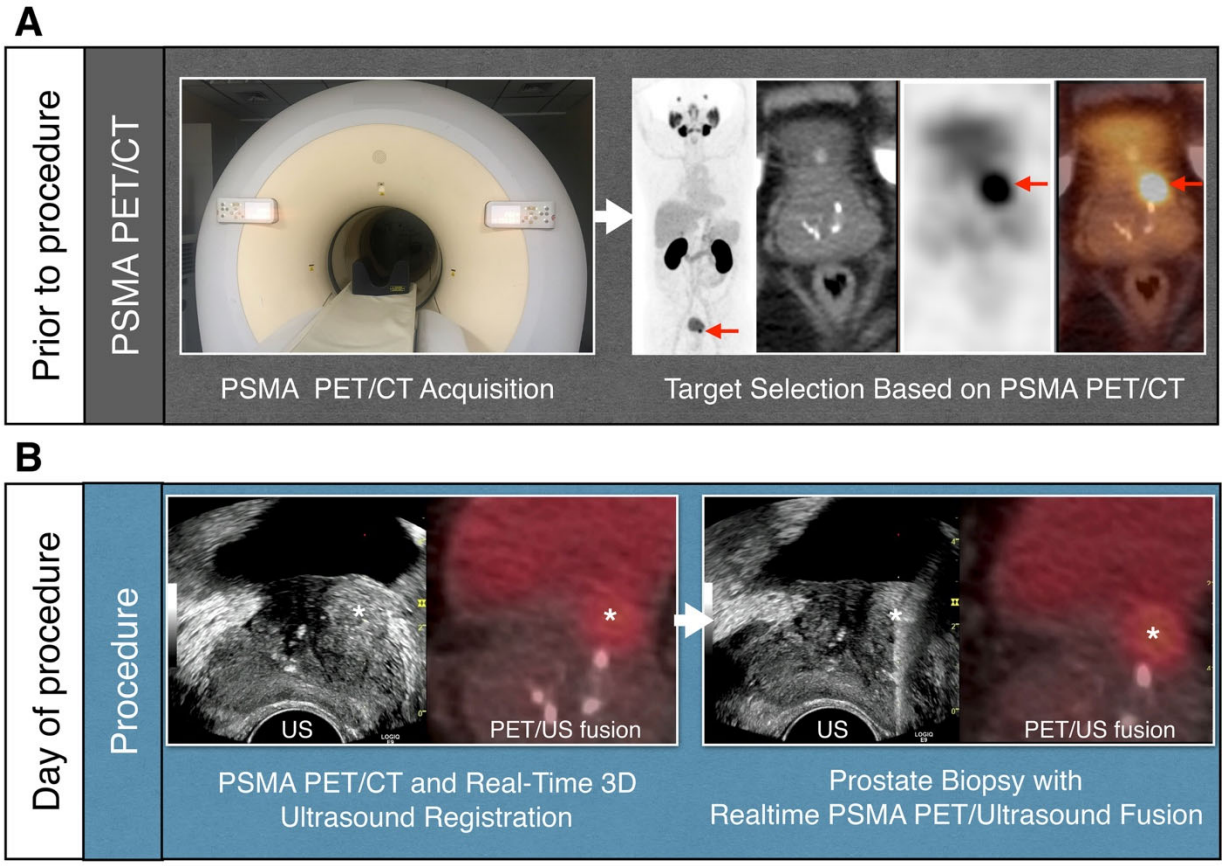
	Non-csPCa Median (Range)	csPCa Median (Range)	p Value (Wilcoxon–Mann–Whitney U-test)
No. pts	19	12	
Age	63(53-81)	70.5(57-81)	0.152
No. Prior Biopsy	1(1-3)	1(1-3)	0.857
Total PSA(ng/ml)	10.63(5.48-46.88)	37.58(8.96-49.77)	0.002*
Free/total PSA	0.15(0.07-0.47)	0.13 (0.02-0.74)	0.562
Prostate volume	56.22(22.39-108.63)	33.69(7.79-74.36)	0.023*
PSA density (ng/ml/ml)	0.16(0.09-1.75)	0.81 (0.29-2.31)	<0.001*

***significant differences (p < 0.05)**
csPCa = clinically significant prostate cancers (GS ≥ 7);
Non-csPCa = Non-clinically significant prostate cancers (GS = 6, normal prostate and benign prostatic disease);
pts = patients.

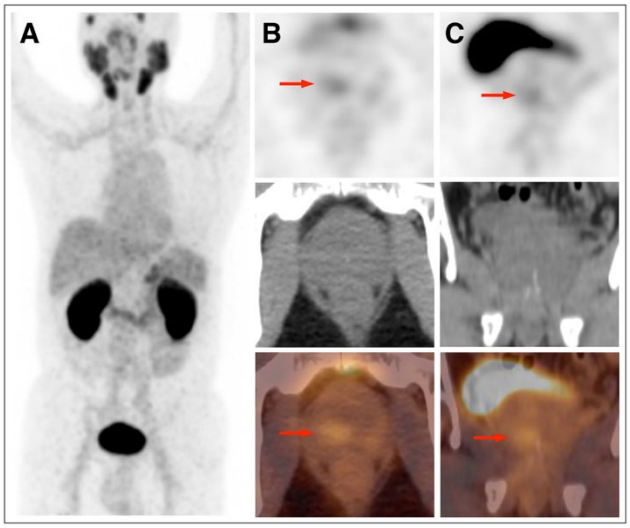
TABLE 2. Comparison of semi-quantitative analysis parameters of ^{68}Ga-PSMA PET/CT between clinically significant cancer(csPCa) and non-clinically significant cancer(non-csPCa)

	Non-csPCa Median(range)	csPCa Median(range)	p Value (Wilcoxon–Mann–Whitney U-test)
SUV_{max}	4.63(2.90-9.87)	10.15 (5.45-30.95)	<0.001*
SUV_{L}	5.47 (3.05-9.74)	5.42 (4.62-8.60)	0.484
SUV_{BGp}	3.3 （2.00-4.40）	3.5 （2.70-4.20）	0.130
$SUV_{T/BGp}$	1.43 （1.12-4.94）	3.36 （1.44-10.32）	<0.001*
SUV_{ratio}	0.91 (0.64-2.12)	1.48 (1.03-6.03)	<0.001*

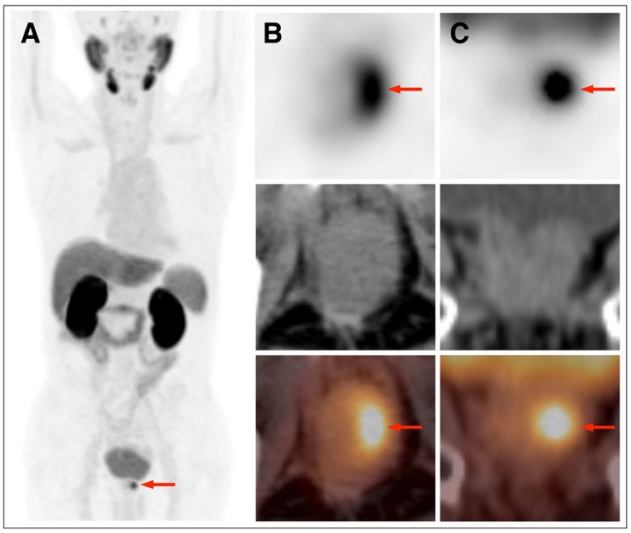
***significant differences (p < 0.05)**
csPCa = clinically significant prostate cancers (GS ≥ 7);
Non-csPCa = Non-clinically significant prostate cancers (GS = 6, normal prostate and benign prostatic disease);
SUV_{max} = maximum standard uptake of prostate lesions; SUV_{L} = maximum standard uptake of liver background; SUV_{BGp} = maximum standard uptake of prostate background; $SUV_{T/BGp}$ = maximum standard uptake ratio of prostate lesions versus prostate background; SUV_{ratio} =maximum standard uptake ratio of prostate lesions versus liver background.



Supplemental Figure 1. Schematic demonstrating steps to obtaining a PSMA PET/ultrasound fusion guided biopsy.



Supplemental Figure 2. A 61-year-old patient with prostate-specific antigen of 23.65ng/ml. ^{68}Ga-PSMA PET maximum-intensity projection (A) and axial PET/CT (B) demonstrates low PSMA expression, which is lower than liver (miPSMA-ES 1) in prostate gland (red arrow). Histopathology of prostate biopsy proven that the lesion corresponding to PET/CT is benign prostate hyperplasia (BPH).



Supplemental Figure 3. A 60-year-old patient with prostate-specific antigen of 13.29ng/ml. ^{68}Ga-PSMA PET maximum-intensity projection (A) and axial PET/CT (B) demonstrates high PSMA expression, which is higher than liver (miPSMA-ES 3) in prostate gland (red arrow). Histopathology of prostate biopsy proven that the lesion corresponding to PET/CT is a clinically significant prostate cancer with GS 4+3.