Original Article

Biphasic GA 68-labeled prostate specific membrane antigen-11 positron emission tomography/computed tomography scans in the differential diagnosis and risk stratification of initial primary prostate cancer

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Background: This study aimed to assess the value of biphasic GA 68-labeled prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) positron emission tomography/computed tomography (PET/CT) scan in the differential diagnosis and risk stratification of initial primary prostate cancer (PCa).

Methods: A total of 51 patients with PCa (8 low- and intermediate-risk PCa patients and 43 high-risk PCa patients) and 36 patients with benign prostate lesions, who underwent standard whole-body imaging and delayed pelvic imaging of ^{68}Ga-PSMA-11 PET/CT, were enrolled in this prospective study. The PET parameters, such as maximum and mean standard uptake value (SUVmax and SUVmean), and maximum and mean standard retention index of PET images were calculated and compared in different prostate lesions. The diagnostic performances of the PET parameters were evaluated by receiver operating characteristic (ROC) curves.

Results: All the PET parameters of PCa participants were significantly higher than those of participants with benign prostate lesions (P<0.001). The SUVmean of delayed imaging had the best performance in the diagnosis of PCa with an area under the curve (AUC) of 0.918 (95% CI: 0.858 to 0.977), the sensitivity of 90.0%, and specificity of 83.3%. The SUVmax and SUVmean of high-risk PCa participants were significantly higher than those of low- and intermediate-risk PCa participants (P<0.005). The SUVmax of standard imaging had the best performance in predicting high-risk PCa with an AUC of 0.890 (95% CI: 0.799 to 0.980), a sensitivity of 76.7%, and a specificity of 100.0%.

Conclusions: The biphasic ^{68}Ga-PSMA-11 PET/CT scan had good performance in discriminating prostate cancer from benign prostate diseases. The SUVmean of the prostate lesion at delayed imaging of ^{68}Ga-PSMA-11 PET/CT had the best value in the differential diagnosis of PCa, and the SUVmax at standard imaging was most valuable in predicting the risk stratification of PCa.

Keywords: Initial prostate cancer; ^{68}Ga-PSMA-11; diphase; differential diagnosis; risk stratification

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Introduction

Prostate cancer (PCa) is the second most frequent cancer and the fifth leading cause of cancer death in men. There were approximately 1.3 million new cases and 359,000 deaths associated with PCa worldwide in 2018 (1). The incidence and burden of global PCa are steadily increasing, resulting in further challenges in allocating limited health care resources (2). The diagnosis and staging of PCa mainly rely on morphologic imaging with computed tomography (CT) and magnetic resonance imaging (MRI), and evaluation of bone metastases by whole-body bone scan. In recent years, prostate-specific membrane antigen (PSMA)-targeted molecular imaging has shown a good prospect of clinical application in PCa, including disease diagnosis, staging, biochemical recurrence, and therapeutic management (3,4).

The GA 68-labeled prostate-specific membrane antigen-11 (^{68}Ga-PSMA-11) is one of the most widespread agents for PSMA-targeted imaging, particularly in Europe and Asia (5). After injection of tracer according to guideline recommendations, ^{68}Ga-PSMA positron emission tomography (PET)/CT scan is routinely performed for 60 min (an acceptable range of 50 to 100 min) as a standard imaging protocol (6). Several studies (7-14) have applied dual-time-points or multiple time-points PSMA-targeted PET/CT, mainly to evaluate patients with recurrent PCa. Little attention has been focused on the value of PSMA-targeted PET/CT imaging in initial PCa, and studies are still scarce.

Expression of PSMA was first confirmed in the cells of PCa; meanwhile, the expression of this molecule has been found in a range of normal tissues, as well as other benign and malignant pathologies, because of selective expression in the endothelium of some benign proliferative tissues or tumor angiogenesis (5). Some benign prostate lesions, such as prostatic hyperplasia or prostatitis, may also express PSMA and excrete a high level of serum prostate-specific antigen (PSA), which needs to be distinguished from PCa in clinical work. To date, some studies have shown that PSMA-targeted PET/CT had a satisfactory diagnostic performance in detecting primary PCa at 60 min post-injection (p.i.) of agent (15-17). However, little is known about the clinical value of dual-time points of PSMA-targeted PET/CT in discriminating PCa from benign prostate diseases and the risk stratification of initial PCa.

Therefore, the present study aimed to evaluate the value of the differential diagnosis and risk stratification of initial PCa in ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging.

Methods

Study population

This was a single-center prospective study. Data acquisition under separate but clinically identical PET/CT protocols was defined at baseline. 94 patients with newly suspected PCa were recruited at The Third Affiliated Hospital of Sun Yat-sen University between February 2019 and June 2020. Patients were excluded if no pathological results or a Gleason score for PCa were not available or had not been collected. Finally, a total of 87 patients were eligible for the analysis, who had detailed pathological findings after PET/CT scans, including 42 cases from prostatectomy and 45 cases from the biopsy. The serum prostate-specific antigens (PSA) of participants were tested within 2 weeks before their PET/CT scans. According to prostate pathology, 36 participants had a benign prostate lesion (prostatic hyperplasia or/and prostatitis), and 51 had PCa, including 8 with low- and intermediate-risk, and 43 with high-risk as defined by the D'Amico Risk Classification System (18). Cases of benign prostate lesions that were detected at the initial biopsy were further confirmed by follow-up for at least 6 months by PSA screening, MRI, or even second biopsy. The simple research sketch for participants is shown in *Figure 1*. The baseline characteristics of participants are shown in *Table 1*.

This study was conducted following the Declaration of Helsinki (as revised in 2013). Institutional Review Board approved this study at our Hospital {[2019]02-012-01}. All participants provided written informed consent.

Preparation of ^{68}Ga-PSMA-11

The Precursor of PSMA-11 {Glu-NH-CO-NH-Lys(Ahx)-HBED-CC;HBED= N,N′-bis[2-hydroxy-5-(carboxyethyl) benzyl]ethylenediamine-N,N′-diacetic acid} was purchased from ABX advanced biochemical compounds GmbH (ABX GmbH, Radeberg, Germany), which met Good Manufacturing Practice (GMP) quality standards. The ^{68}Ga3+ was produced from a ^{68}Ge/^{68}Ga radionuclide generator system (Modular-Lab PharmTracer; Eckert & Ziegler, Berlin, Germany) and mingled with the PSMA-11 conjugate according to a previously described protocol (19,20). The final product was dissolved in isotonic phosphate-

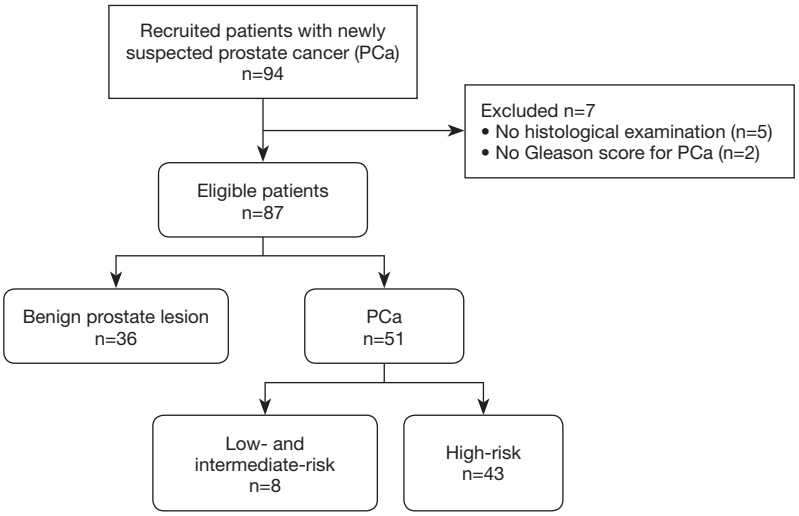

Figure 1 Research flow chart of participants. PCa, prostate cancer.

Table 1 Details of participant data

Characteristics	Percent	Number
All patients		87
Prostate benign lesion	41.4%	36
PCa	58.6%	51
PSA of PCa patients		51
≤10	19.6%	10
10.1–20	11.8%	6
>20	68.6%	35
Gleason score		51
≤6	11.8%	6
7	19.6%	10
≥8	68.6%	35
T stage		51
≤T2a	19.6%	10
T2b	2.0%	1
≥T2c	78.4%	40
Risk stratification		51
Low	9.8%	5
Intermediate	5.9%	3
High	84.3%	43

PCa, prostate cancer; PSA, prostate specific antigen.

buffered saline (PBS) with subsequent sterile filtration. The radiochemical purity of the agent was >99% as determined by reversed-phase high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) analysis. The solution of ^{68}Ga-PSMA-11 was applied to the patient via an intravenous bolus injection mean ± standard deviation [$\bar{x}$±SD], 149.5±49.4 MBq; 62.2–278.2 MBq. The recommended dose was 1.8–2.2 MBq per kilogram of body weight (6).

PET/CT scans

The PET/CT images of all patients were obtained on a dedicated PET/CT scanner (GE Discovery Elite, Wauwatosa, WI, USA) with the same protocol. A standard whole-body PET/CT scan was acquired at about 60 min after intravenous injection of the radiopharmaceutical, each with 9–11 bed positions from the top of the skull to mid-thigh. After completing the whole-body scan, each patient received 0.5 mg of furosemide per kilogram of body weight (maximum, 30 mg) followed by oral hydration with 1,000 mL of water, and then urinated actively to reduce radiation. Then, a delayed pelvic PET/CT scan was acquired at about 180 min post-injection (p.i.) of an agent with 2 bed positions from the iliac crest to the pubic symphysis. The CT data were acquired with 120 kV, 90–250 mA and modulated using the GE Auto mA technique with a noise index of 13.0,

Table 2 Comparison of different parameters between prostate benign lesion and PCa

Parameters	Prostate benign lesion (n=36)	PCa (n=51)	P value
PSA (ng/mL)	8.6 (6.2, 15.5)	32.1 (15.1, 82.2)	<0.001
Standard imaging			
SUVmax	5.1 (3.9, 6.5)	14.3 (8.2, 22.0)	<0.001
SUVmean	2.7 (2.0, 3.4)	7.2 (4.4, 13.2)	<0.001
Delayed imaging			
SUVmax	4.1 (3.1, 6.0)	15.4 (8.5, 26.8)	<0.001
SUVmean	2.3 (1.6, 3.1)	8.4 (4.5, 15.9)	<0.001
RImax	–8.2%±26.2%	14.7%±31.3%	<0.001
RImean	–9.4%±25.7%	14.6%±28.8%	<0.001

PCa, prostate cancer; PSA, prostate specific antigen; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value; RImax, maximum retention index; RImean, mean retention index.

slice thickness of 3.75 mm, slice interval of 3.27 mm, matrix size of 512×512, and scan field of vision (FOV) of 50 cm. The PET data were obtained in 3-dimensional (3D) time-of-flight (TOF) mode with a 3 min scan per bed position, slice thickness of 3.27 mm, slice interval of 3.75 mm, matrix size of 192×192, and scan FOV of 70 cm. The PET data were attenuation-corrected (AC) by the integrated CT AC technology. The CT data were reconstructed in standard mode, window width/window level 400/40. The PET data were then reconstructed in the light of VUE point FX TOF, with adaptive statistical iterative reconstruction (ASiR) 30%.

PET image analysis

All PET/CT datasets were processed and analyzed using the PET/CT review application at GE Advance Workstation (AW version. 4.6, GE, USA). The SUVmax and SUVmean of each prostate lesion were determined in the region of interest (ROI) with isocontours set at 40% of the maximum uptake. According to a previous report of retention index (RI) (21), maximum and mean RI (RImax and RImean) were respectively defined as: RImax (%) =100%× {SUVmax[delayed] – SUVmax[standard]}/SUVmax[standard] and RImean (%) = 100% × {SUVmean[delayed] – SUVmean[standard]}/SUVmean[standard].

Statistical analysis

Quantitative data consistent with the skewed distribution using the median and interquartile {M [P25, P75]} met the normal distribution with $\bar{x}$±SD. The semi-quantitative PET parameters among the different prostate lesions were compared using Mann-Whitney-U Test. Spearman rank correlation analysis was used to describe the relationship between 2 variables. The pairwise comparisons at different imaging time points were used by paired t-test or Wilcoxon signed ranks test. The patient-based diagnostic sensitivity, specificity, and area under the curve (AUC) were calculated according to receiver operating characteristic (ROC) curves. All statistical significance was established for P values of ≤0.05. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA) and SPSS 23.0 (IBM Corp., Armonk, NY, USA).

Results

The PSA and all the PET parameters of PCa participants, such as SUVmax, SUVmean, RImax, and RImean, were significantly higher than those of participants with benign prostate lesions (P<0.001, *Table 2*). The ROC analysis showed that all the PET-parameters at ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging had good performances in the diagnosis of PCa (*Table 3*), in which the SUVmean of delayed imaging had the best performance with an AUC of 0.918 (95% CI: 0.858 to 0.977), the sensitivity of 90.0%, and specificity of 83.3% (*Figure 2A*).

There were 43 high-risk and 8 low- and intermediate-risk PCa participants in this research, according to the D'Amico Risk Classification System. The PSA values in high-risk PCa participants were significantly higher than those in low- and intermediate-risk participants (P<0.001). The

Table 3 Efficiencies of different parameters for diagnosing PCa

Indices	Cutoff value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P value
PSA (ng/mL)	16.5	0.797 (0.701, 0.893)	74.0	80.6	<0.001
Standard imaging					
SUVmax	7.6	0.912 (0.852, 0.973)	84.0	88.9	<0.001
SUVmean	3.8	0.899 (0.834, 0.963)	82.0	86.1	<0.001
Delayed imaging					
SUVmax	6.7	0.914 (0.853, 0.976)	88.0	86.1	<0.001
SUVmean	3.3	0.918 (0.858, 0.977)	90.0	83.3	<0.001
RImax	1.5%	0.728 (0.619, 0.837)	74.0	74.2	<0.001
RImean	0.8%	0.757 (0.653, 0.862)	74.0	75.0	<0.001

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; PCa, prostate cancer; PSA, prostate specific antigens; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value; RImax, maximum retention index; RImean, mean retention index.

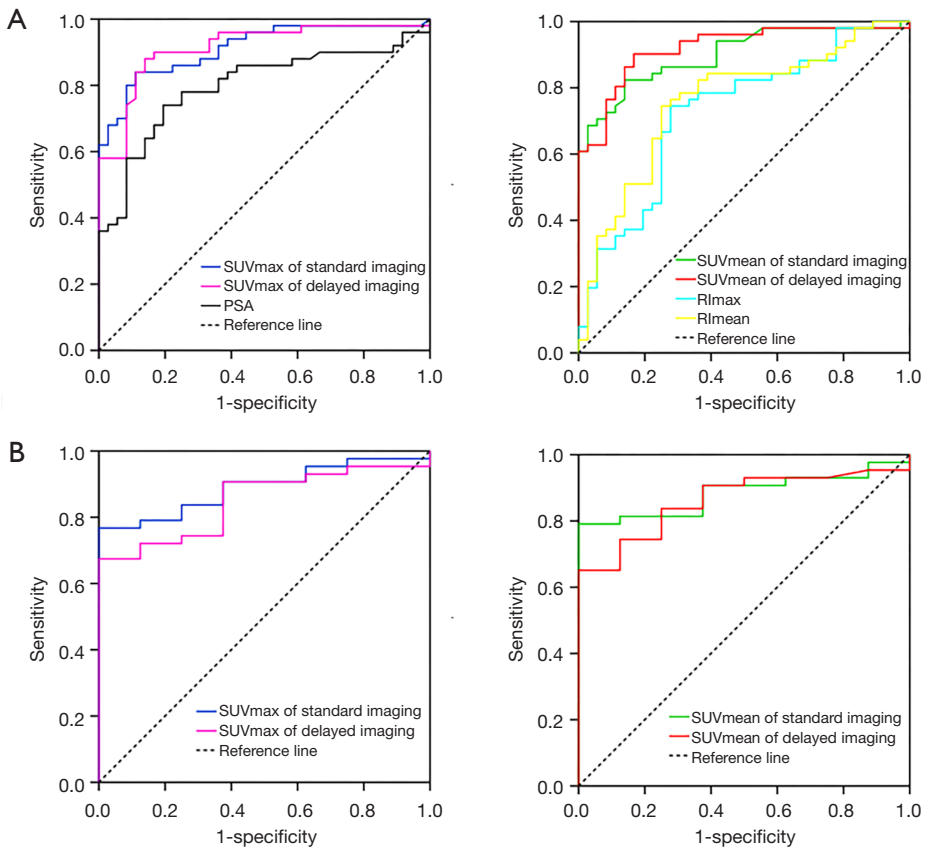

Figure 2 The ROC curves of PET-parameters and PSA. (A) The ROC curves of the SUVmax and SUVmean at standard or delayed imaging, PSA, RImax, and RImean parameters for diagnosis of PCa. (B) The ROC curves of the SUVmax and SUVmean at standard or delayed imaging for predicting high-risk PCa. ROC, receiver operating characteristic; PCa, prostate cancer; PSA, prostate specific antigen; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value; RImax, maximum retention index; RImean, mean retention index.

Table 4 Comparison of different parameters between low- and intermediate-risk PCa and high-risk PCa

Parameters	Low- and intermediate-risk (n=8)	High-risk (n=43)	P value
PSA (ng/mL)	9.7 (5.0, 15.1)	44.3 (25.4, 138.4)	<0.001
Standard imaging			
SUVmax	7.2 (5.3, 9.1)	14.8 (9.8, 25.9)	<0.001
SUVmean	3.7 (2.9, 4.8)	8.2 (5.2, 14.1)	<0.001
Delayed imaging			
SUVmax	7.3 (5.4, 9.8)	17.2 (8.9, 29.3)	0.002
SUVmean	3.8 (3.0, 5.1)	9.7 (4.9, 16.8)	0.001
RImax	10.6%±27.1%	15.5%±32.2%	0.688
RImean	8.3%±19.3%	15.8%±30.2%	0.505

PCa, prostate cancer; PSA, prostate specific antigens; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value; RImax, maximum retention index; RImean, mean retention index.

Table 5 Efficiencies of different parameters for predicting high-risk PCa

Indices	Cutoff value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P value
Standard imaging					
SUVmax	9.8	0.890 (0.799, 0.980)	76.7	100.0	0.001
SUVmean	5.0	0.884 (0.792, 0.975)	79.1	100.0	0.001
Delayed imaging					
SUVmax	12. 8	0.849 (0.737, 0.960)	67.4	100.0	0.002
SUVmean	6.7	0.862 (0.755, 0.969)	65.1	100.0	0.001

AUC, area under the curve; CI, confidence interval; PCa, prostate cancer; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value.

SUVmax and SUVmean of high-risk PCa participants were significantly higher than those of low- and intermediate-risk PCa participants at standard and delayed imaging (P<0.005). However, the RImax and RImean had no statistical significance between high-risk and low- and intermediate-risk PCa participants (P>0.05, *Table 4*). The ROC analysis demonstrated that the SUVmax and SUVmean of PCa participants at ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging had good performances in predicting high-risk PCa, in which the SUVmax of standard imaging had the best performance with an AUC of 0.890 (95% CI: 0.799 to 0.980), the sensitivity of 76.7%, and specificity of 100.0% (*Figure 2B*), their detailed performances are listed in *Table 5*. An example of a patient with high-risk PCa visible on ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging is presented in *Figure 3*.

In addition, the correlations between the PET parameters and risk stratification or Gleason score of PCa were briefly analyzed in this study. There were low or moderate correlations between SUVmax or SUVmean of biphasic imaging and risk stratification of PCa [range of correlation coefficient (r): 0.45 to 0.50, P<0.001]. There were weak correlations between SUVmax or SUVmean of biphasic imaging and Gleason score of PCa (range of r: 0.30 to 0.37, P=0.007–0.030). There were no significant correlations between RImax or RImean and risk stratification or Gleason score of PCa (P>0.05).

Discussion

In recent years, PSMA-targeted PET/CT, as a promising imaging tool, has been widely used in PCa. A procedure guideline of ^{68}Ga-PSMA PET/CT for PCa imaging was published online in 2017 (6). A routine 60 min interval is

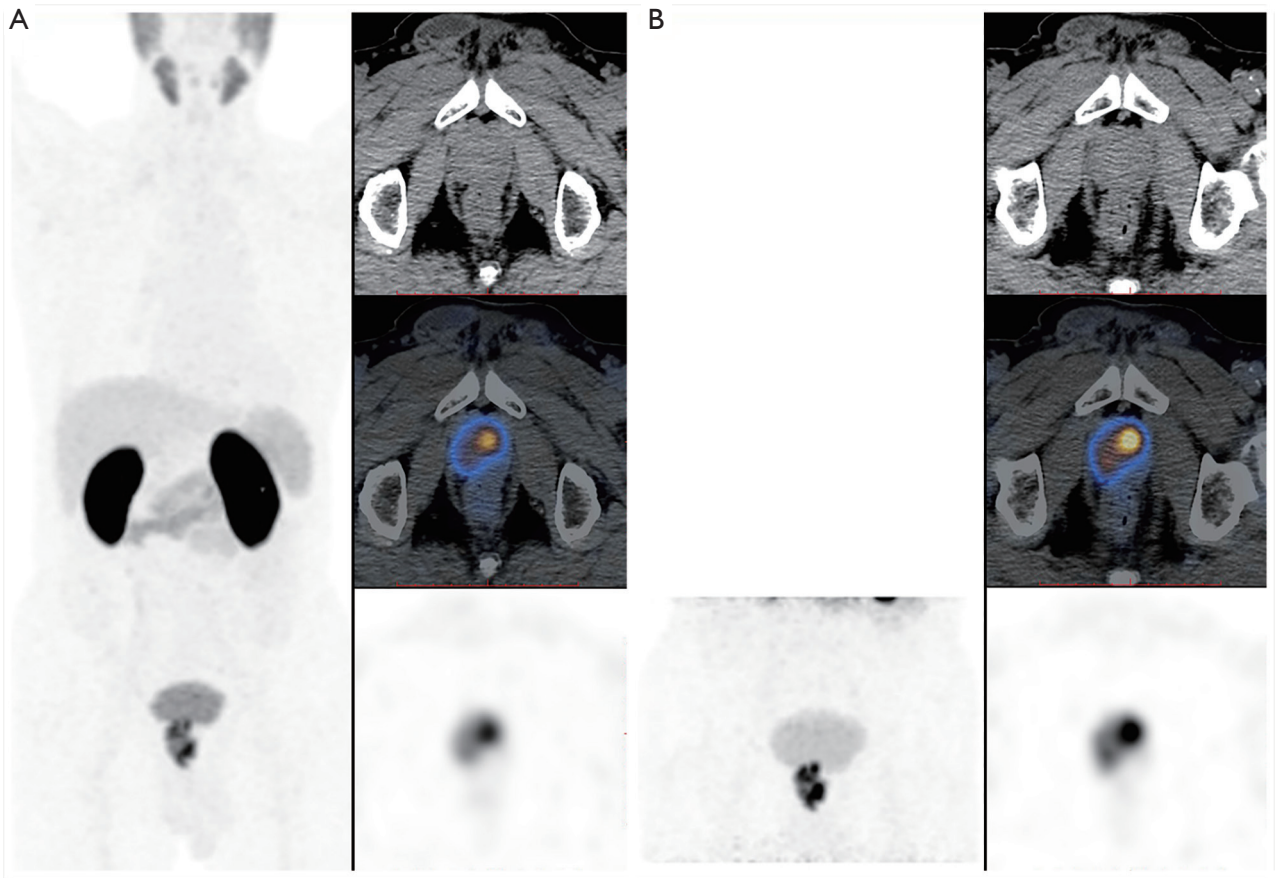

Figure 3 ^{68}Ga-PSMA-11 PET/CT in a 76-year-old man with high-risk PCa (T2c, Gleason score =8, PSA =0.9 ng/mL). (A) The standard ^{68}Ga-PSMA-11 PET/CT imaging, the SUVmax and SUVmean of prostate were 25.4 and 14.1, respectively, at standard image; (B) The delayed ^{68}Ga-PSMA-11 PET/CT imaging, the SUVmax and SUVmean of prostate were 34.1 and 19.2, respectively, at delayed image. The RImax and RImean of prostate was 34.2% and 35.7%, respectively. ^{68}Ga-PSMA-11 PET/CT, GA 68-labeled prostate specific membrane antigen-11 positron emission tomography/computed tomography; PCa, prostate cancer; PSA, prostate specific antigens; SUVmax, maximum standard uptake value; SUVmean, mean standard uptake value; RImax, maximum retention index; RImean, mean retention index.

recommended for uptake time in ^{68}Ga-PSMA PET/CT. Aspects worthy of further discussion include when delayed imaging techniques in ^{68}Ga-PSMA PET/CT should be used, or the value of ^{68}Ga-PSMA PET/CT delayed imaging. The previous studies (7-14) of PSMA-targeted PET/CT delayed imaging have mainly focused on patients with recurrent of PCa. In the present study, we investigated the power of biphasic ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging in the diagnosis and risk stratification of PCa.

Some studies (9,13,14) have shown increased PSMA uptake for PCa lesions and deceased uptake for benign prostate tissues at 180 min p.i. compared with that at 60 min p.i. The analogous consequence was observed in our present study. Our results also demonstrated that PCa had higher PSMA uptake than benign prostate lesions at biphasic ^{68}Ga-PSMA-11 PET/CT imaging, similar to the previous multi-time point study (14). However, we found that both the SUVmax and SUVmean of prostate lesions at the dual-time point had good performance in the diagnosis of PCa, and especially the SUVmean at 180 min p.i had the best performance with an AUC of 0.918, the sensitivity of 90.0%, and specificity of 83.3%. These results were also superior to the results (0.867, 91.67%, and 81.82%, respectively, at 60 min p.i.) reported by Zhang *et al.* (16).

The RI has long been used as the preferred indicator of malignancy, and RI >10% or RI >0% are commonly used criteria to indicate malignancy (21). We had found that the

average RImax (–8.2%) or RImean (–9.4%) of the benign prostate lesion was less 0%, while the average RImax (14.7%) or RImean (14.6%) of PCa was more than 10%. The cutoff of RImax and RImean were 1.5% and 0.8%, respectively, for discriminating PCa from benign prostate lesions in the biphasic ^{68}Ga-PSMA-11 PET/CT imaging. However, our results indicated that the RImax or RImean was inferior to the SUVmax or SUVmean in diagnostic performance for PCa at standard imaging or delayed imaging. The data in *Table 2* showed that the diagnostic performance of SUVmean at delayed imaging was still best among the PET parameters in our study.

Risk stratification of PCa has been widely applied to clinical practice, which is very conducive to selecting treatment and prognosis of PCa (22). Therefore, it is particularly important to assess the risk stratification of PCa accurately. As we know, risk stratification of PCa has mainly been based on tumor T staging, Gleason score, and serum PSA, which usually require invasive examinations. A previous study (14) demonstrated that the PSMA uptake for PCa with a Gleason score ≥8 was higher than that for PCa with a Gleason score ≤7 at multi-time point imaging. In our study, not all PCa patients with a Gleason score ≤7 had relatively low PSMA uptake and some PCa participants with a Gleason score =7 had relatively high PSMA uptake with SUVmax as high as 22.0, which defined the high-risk group. We attempted to noninvasively predict high-risk PCa by PET-parameters in biphasic ^{68}Ga-PSMA-11 PET/CT, and found that high-risk PCa had higher PSMA uptake than low- and intermediate-risk PCa at biphasic imaging. We found that the correlations between PSMA uptake and risk stratification were superior to those between PSMA uptake and Gleason score. The SUVmax and SUVmean had good performances for predicting high-risk PCa with prominent specificity and relatively poor sensitivity. The PSMA uptake in participants with low- and intermediate-risk PCa was almost always relatively low, responsible for high specificity in the study. It was reported that ^{68}Ga-PSMA PET could produce false negatives in up to 5% of patients with PCa (6). We also observed that low PSMA uptake was present in some participants with high-risk PCa, leading to relatively poor sensitivity in the study. Compared with delayed imaging, the SUVmax and SUVmean of standard imaging had better performances in predicting high-risk PCa, in which the SUVmax of standard imaging showed the best performance with an AUC of 0.890, the sensitivity of 76.7%, and specificity of 100.0%. However, the RImax and RImean had no statistical significance between high-risk and low- and intermediate-risk PCa patients (10.6% and 8.3% *vs.* 15.5% and 15.8%, respectively), and had a little value in predicting risk stratification of PCa. In other words, it meant that delayed imaging might not provide an additional benefit in predicting high-risk PCa.

In the present study, the final diagnosis of some patients was made via histologic biopsy. A recent study (23) showed that biopsy histology outcomes were similar to radical prostatectomy specimens. Therefore, the use of biopsy in our study was acceptable and trustworthy. At the same time, the negative cases diagnosed as benign prostate lesions by the initial biopsy were further confirmed by follow-up for at least 6 months which can minimize the chance of misdiagnosis.

Limitations

There were some limitations in this study. First, the patient cohort of biphasic ^{68}Ga-PSMA-11 PET/CT was relatively small. In particular, there were only 8 participants of low- and intermediate PCa. Even so, this was presently the largest population-based study for dual-time point PSMA ligand imaging in diagnosis and risk stratification of primary PCa. Second, due to the missing part of the MRI information, no further comparative study between ^{68}Ga-PSMA-11 PET/CT and MR was conducted in this study. Further research is required to elucidate whether patients will benefit financially from delayed imaging in PSMA-target PET/CT.

Conclusions

The findings from this study demonstrated that all the PET-parameters, such as SUVmax and SUVmean, maximum and mean standard retention index (RImax and RImean) of ^{68}Ga-PSMA-11 PET/CT standard and delayed imaging helped discriminate PCa from benign prostate lesions. In the PET-parameters, the SUVmean of the prostate lesion at delayed imaging of ^{68}Ga-PSMA-11 PET/CT had the best value in diagnosing PCa, and the SUVmax at standard imaging was the most valuable in predicting the risk stratification of PCa. Additional studies with a larger sample size are necessary to verify the findings from this study.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1312). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted following the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board at The Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was provided by all participants.

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