A PSMA PET/CT based risk model for prediction of concordance between targeted biopsy and combined biopsy in detecting prostate cancer

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Abstract

Backgroud

mpMRI-TB improves the clinically significant prostate cancer (csPCa) detection rate. However, there has been none consensus regarding the avoidance of systematic biopsy (SB) with more biopsy cores in patients undergoing mpMRI-TB. Thus, this study is to investigate the diagnostic value of ^{68}Ga-PSMA-11 in predicting the concordance between mpMRI-TB and combined biopsy (CB) in detecting PCa.

Methods

115 consecutive men with ^{68}Ga-PSMA-11 PET/CT prior to prostate biopsy were included for analysis. PSMA intensity, quantified as maximum standard uptake value (SUVmax), minimum apparent diffusion coefficient (ADCmin) and other clinical characteristics were evaluated relative to biopsy concordance by using univariate and multivariate logistic regression analyses. A prediction model was developed based on the identified parameters.

Results

concordance between mpMRI-TB and CB occurred in 76.5% (88/115) of the patients. Multivariate logistic regression analyses performed that SUVmax (OR = 0.952; 95% CI: 0.917–0.988; p = 0.010) and ADCmin (OR = 1.006; 95% CI: 1.003–1.010; p = 0.001) were independent risk factors for biopsy concordance. The developed model showed a sensitivity, specificity, accuracy and AUC of 0.67, 0.78, 0.81 and 0.78 in the full sample.

Conclusions

The developed prediction model based on SUVmax and ADCmin showed practical value in guiding the optimization of prostate biopsy pattern. Lower SUVmax and Higher ADCmin values are associated with greater confidence in implementing mono-TB and safely avoiding SB, effectively balancing benefits and risks.

1. Introduction

Prostate cancer (PCa) is a common malignancy in the male population and has been a major burden in almost every healthcare system[1]. For clinically suspicious patients, the definitive diagnosis is based on histopathological assessment after tissue biopsy. Systematic biopsy (SB) is the traditionally standard selection of prostate tissue biopsy. With the development and application of multiparametric magnetic resonance imaging (mpMRI) recently, MRI is recommended before prostate biopsy for biopsy-naive men,

as well as repeat biopsy. MRI-guided targeted biopsy (TB) in combination with SB defined as combined biopsy (CB) would be suggested for men with positive findings on mpMRI [2]. This approach arises a question that could the SB be avoided because the SB usually requires 12 additional biopsy cores, which increase potential harms with low detection of clinically significant PCa (csPCa)[3–5]. Despite growing evidence supporting mono-TB pathways (ie, mpMRI-TB only without SB, or when mpMRI is negative no biopsy at all) [6, 7], there has been none consensus regarding the avoidance of SB because the added value of SB has been demonstrated in several clinical trials [8–10]. Therefore, the prediction of the concordance between TB and CB is of great interesting for the decision making of implementing mono-TB in men with positive MRI.

Prostate-specific membrane antigen (PSMA)-ligand positron emission tomography/computed tomography (PET/CT) has been demonstrated to be an ideal tool for primary staging[11] and restaging[12, 13] of PCa. PSMA-ligand PET/CT has excellent efficacy in detecting tumor lesions[14–17] and predicting tumor aggressiveness[18, 19] due to its better signal-to-background ratio and uptake in target lesions, and has supplementary significance to multiparameter MRI. However, it remains unknown that whether PSMA-ligand PET/CT can play a diagnostic role in PCa of recommending mono-TB but avoiding SB for biopsy-naïve patients.

Therefore, this study was designed to investigate the role of PSMA-ligand PET/CT in predicting the concordance between TB and CB to avoid SB. Biopsy-naive men who had undergone PSMA-ligand PET/CT scanning before prostate biopsy were included in the present study. Using the biopsy pathology as the reference, clinically, MRI-derived and PSMA-ligand PET/CT imaging parameters were collected for analysis.

2. Patients and methods

2.1 Participants

207 consecutive biopsy-naive men who underwent ^{68}Ga-PSMA-11 PET/CT prior to prostate biopsy between August 2019 and August 2022 were considered for the study. Patients with negative (PI-RADS score of 1 or 2) or equivocal (PI-RADS score of 3) lesions on mpMRI were excluded. Patients with any treatments to prostate before prostate biopsy were also excluded (hormone therapy, n = 15; TURP, n = 2). Patients without TB were also excluded. Finally, a total of 115 patients were included in the analysis of this study.

2.2 Imaging

Imaging protocols have been previously described[20]. All mpMRI images were reported by experienced radiologists according to the Prostate Imaging Reporting and Date System Version 2.1 (PI-RADS v2.1). Moreover, each suspicious lesion was freehand drawn on ADC images and ADCmin was read directly from the pixel-wise ADC values within the whole-lesion volumes of interest (VOI) by using the MIStar software (Apollo Medical Imaging Technology, Australia). All PET/CT images were independently

evaluated by two double-trained board-certified experienced nuclear medicine physicians, who were blind to the pathological results of the prostate biopsy. The two nuclear medicine physicians reached consensus regarding the PSMA PET/CT assessment criteria in PCa[21]. Suspicious lesion was defined as an increased uptake in prostate regions higher than background. For each lesion, regions of interest (ROI) were delineated on continuous PET/CT fusion images by RadiAnt DICOM viewer, 4.2.1(Medixant, Poznan, Poland). The maximum standardized uptake values (SUVmax) were derived from the whole-lesion ROIs.

2.3 Multiparametric magnetic resonance imaging-targeted biopsy

All patients underwent ultrasound-guided 12-needle systematic biopsy plus mpMRI-targeted biopsy. In accordance with the protocol described previously[22], transperineal freehand mpMRI fusion targeted biopsy technique was used for TB. All biopsies were performed by the same urologist (H.F.H.).

2.4 Pathological analysis

After prostate biopsy, all biopsy cores were fixed in 10% formalin and sliced at 3-mm intervals. The slices were embedded in paraffin, stained with hematoxylin-eosin, and were then scanned by a whole-slide scanner (NanoZoomer S60; Hamamatsu, Japan). All digital slices were uniformly reviewed by a uropathologist (Y. F. over 10 years' experience) according to the 2014 ISUP modified criteria[23]. Biopsy concordance was defined that the highest Gleason score of TB was higher than or equal to that of SB.

2.5 Statistical analysis

The Mann-Whitney U test was selected for continuous variables and the $\chi 2$ test for categorical variables. And univariate and multivariate logistic regression analyses were performed for collected significant parameters to predict the biopsy concordance. SPSS software (IBM, USA) was conducted for Receiver operating characteristic (ROC) analysis for the internal discrimination validation and to derive the corresponding area under the curve (AUC) with 95% confidence interval, sensitivity, specificity, and cutoff value for differentiation. The software SPSS 26.0 was employed for statistical analysis, of which all tests were two sided with statistical significance set at $p < 0.05$.

3. Results

3.1 Patient characteristics

Patient characteristics were summarized in Table 1 and the time between ^{68}Ga-PSMA-11 PET/CT and prostate biopsy was within 30 days because ^{68}Ga-PSMA-11 PET/CT can reflect the true state of the lesions. 115 men with PI-RADS 4/5 were included, with median age of 69.0 (IQR 65.0-75.0) years, median PSA of 11.69 (IQR 7.01-24.65) ng/ml, median prostate volume of 35.15 (IQR 26.61-51.03) ml, and median PSAD of 0.37 (IQR 0.21-0.58) ng/ml/ml. The distributions of PIRADS 4/5 and ISUP GG at TB/ CB were also shown in Table 1. The concordance between TB and CB were found in 88/115 men (76.5%).

According to the status of concordance between TB and CB, patients were divided into two groups (concordance vs. discordance). As shown in Table 2, there is no significant difference in terms of PSA, prostate volume, PSAD and maximal tumor diameter on PSMA PET/CT between the concordance and discordance group (Table 2). The proportion of multifocality on mpMRI or PSMA PET/CT was found to be similar between the two groups. However, patients had a significant lower age (69.0 [IQR: 65.0–73.5] vs. 73.0 [IQR: 66.5–79.0] years, p = 0. 035), higher ADCmin level (444 [353-558] vs. 317 [219-396] um^2/s, p<0.001), and lower SUVmax level (12.78 [8.34-21.91] vs.20.85 [12.82-26.56], p=0.020) in patient with concordance between TB and CB (Table 2).

3.2 Risk factors associated with concordance between TB and CB

Clinical and imaging parameters were included in the univariable and multivariable logistic regression to investigate the predictors of the concordance between TB and CB (Table 3). In univariate analysis, age (OR = 0.929; 95% CI: 0.870–0.992; p = 0.029) and SUVmax (OR= 0.968; 95% CI: 0.942–0.995; p = 0.020) were found to be positively correlated with biopsy concordance. ADCmin (OR= 1.005; 95% CI: 1.002–1.009; p = 0.001) also showed a significantly positive correlation with biopsy concordance. In multivariable analysis, SUVmax (OR= 0.952; 95% CI: 0.917–0.988; p = 0.010) and ADCmin (OR= 1.006; 95% CI: 1.003–1.010; p = 0.001) were found to be independent risk factors significantly associated with biopsy concordance.

3.3 Diagnosis performance of developed risk model in predicting concordance between TB and CB

The diagnostic performances of the evaluated models for the prediction of biopsy concordance were summarized in Table 4 and Fig. 1. The combination of SUVmax+ADCmin features was found to have the best performance, with the sensitivity, specificity and accuracy of 0.67, 0.78 and 0.81 in the full sample, showing an AUC of o.78.

4. Discussion

The relationship between mpMRI-TB and CB has long been a subject worthy of discussion. And increasing investigations are exploring the possible approaches to reduce the systematic biopsy cores[24–27]. In our study, PSMA PET derived SUVmax and mpMRI derived ADCmin were found to be independent risk factors for the prediction of concordance between TB and CB. The biopsy concordance means mono-TB can reflect the accurate pathological grade without SB at all. Therefore, the present study revealed that undergoing ^{68}Ga-PSMA-11 PET/CT and mpMRI prior to prostate biopsy can avoid unnecessary systematic biopsy cores and potentially risky procedure. To our knowledge, this is the first study to explore the role of ^{68}Ga-PSMA-11 PET/CT and ADC value to predict the biopsy concordance between mpMRI-TB and CB to recommend mono-TB in prostate biopsy.

In this study, SUVmax was significantly decreased in patients with biopsy concordance (Table 3). PSMA is a transmembrane glycoprotein expressed on the cell membrane. Compared with normal prostate tissue or benign prostatic hyperplasia, PSMA showed a specific high expression pattern in PCa. In the

reported studies, the expression of PSMA increased with tumor lesions with higher Gleason score[28] and SUVmax was positively correlated with tumor grade[29]. Therefore, our result can be explained that the expression of PSMA is related to the malignancy degree, invasiveness and heterogeneity of the tumor, the higher the expression of SUVmax, the higher the heterogeneity of the tumor, and a few small tumor lesions do not perform on the mpMRI, so mpMRI-TB fails to reach the highest tumor grade of the specimen which is reached by extensive SB, which leads to the biopsy discordance. On the contrary, the lower the expression of SUV, the lower the heterogeneity of the tumor, and the more uniform the histopathologic grade inside the tumor lesions. In this case, the tumor grade of tumor specimen with mpMRI-TB is concordant with that with SB or higher than that of the normal tissue or hyperplastic tissue biopsied by SB, which is defined as biopsy concordance. According to our results, these patients can undergo mono-TB without SB at all.

ADCmin was also found to be an independent risk factor for prediction of biopsy concordance. The apparent diffusion coefficient (ADC), derived from diffusion-weighted MRI, is thought to be related to the cellularity and interstitial structure of pathological tissue. In PCa, normal glandular epithelial and tubular structures are damaged, proliferating, dense cancer cells replace the normal acinar structures, and the diffusion of water molecules would be limited, resulting in lower ADC values. Therefore, ADC can reflect the histopathological heterogeneity of malignant tumors[30–32]. In the reported studies, Peng, etc.[33] found ADC10 and ADCmean can distinguish prostate cancer from normal tissue. Donati et al.[34] evaluated the relation between different ADC values and Gleason scores, and found the most significant relation between ADC10 and Gleason scores, but patients in their cohort only underwent mpMRI-TB to perform the pathological findings. In our investigation, ADCmin could recommend patients underwent mono-TB by comparing the pathological findings between mpMRI-TB and CB.

Generally, our findings revealed that, for PI-RADS 4 and 5 on mpMRI, patients with lower SUVmax and higher ADCmin had the strongest probability for biopsy concordance ((Fig. 2). Therefore, ^{68}Ga-PSMA-11 PET/CT combined with mpMRI might be helpful to select the biopsy approach before prostate biopsy. Based on the results, mpMRI-TB could be considered for patients with lower SUVmax and higher ADCmin to decrease unnecessary biopsy cores, potential physical hazards.

There are also several limitations in this investigation. Firstly, this is a single-center retrospective study and the sample size is only 115 patients, the results of multivariable analysis may be affected. Therefore, our findings need to be further verified by a larger external cohort. Secondly, patients without suspicious lesion on mpMRI (PI-RADS 1,2 and 3) were not considered in this investigation due to the low cancer detection rate by mpMRI-TB. A meta-analysis revealed that the prevalence of PI-RADS 3 cases was 17.3%, with similar rates of csPCa (19%) and insignificant PCa (17%) cases. Therefore, PI-RADS 3 lesions are recognized as equivocal for the presence of csPCa and not defined as positive lesions[35–37], therefore, The guiding role of 68Ga-PSMA-11 PET/CT combined with mpMRI for these patients remains unclear. Thirdly, not all the pathological diagnosis of final radical prostatectomy specimens is known. Therefore, there is no evaluation of correlation between biopsy and final radical prostatectomy specimens.

To sum up, the biopsy concordance of findings substantiates the conclusion: 68Ga-PSMA-11 PET/CT combined with mpMRI prior to prostate biopsy can be an ideal risk factor of PCa to guide the clinicians and patients to consider the appropriate biopsy approach-mono-TB without additional SB. The prediction deserves special consideration and is a subject worthy of future evaluation. Moreover, we need more further prospective studies to validate our findings.

Declarations

- Ethics approval and consent to participate: Informed consent was obtained from all individual participants included in the study.
- Consent for publication: The authors affirm that human research participants provided informed consent for publication of the images in Figure 2.
- Availability of data and materials: All data generated or analysed during this study are included in this published article.
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- Authors' contributions:

conception and design: Chaoli An, Xuefeng Qiu, Hongqian Guo

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administrative, technical, or material support: Yao Fu, Feng Wang

supervision: Feng Wang, Xiaozhi Zhao, Hongqian Guo

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Ethics and consent

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was

approved by the institutional review board of Nanjing Drum Tower Hospital, Medical School of Nanjing University.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Baseline characteristics of included patients

Characteristics	Value
Age（years）	69.0 (65.0-75.0)
PSA（ng/ml）	11.69 (7.01-24.65)
Prostate volume（ml）	35.15 (26.61-51.03)
PSAD（ng/ml/ml）	0.37 (0.21-0.58）
PI-RADS score	
4	49 (42.6）
5	66 (57.4）
ISUP GG at TB	
1	15 (13.0)
2	21 (18.3)
3	31 (27.0)
4	33 (28.7)
5	15 (13.0)
ISUP GG at CB	
1	10 (8.7)
2	14 (12.2)
3	27 (23.5)
4	46 (40.0)
5	18 (15.7)

Continuous variables are presented as median (interquartile range; IQR), while categorical variables are presented as patients (%).

PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PI-RADS, Prostate Imaging Reporting and Data System; ISUP, International Society of Urological Pathology; TB, targeted biopsy; CB, combined biopsy

Table 2 Clinical and imaging characteristics of patients with biopsy concordance/Discordance between TB and CB

	Biopsy concordance status		
Characteristics	Concordance（n=88）	Discordance（n=27）	P
Age（years）	69.0 (65.0-73.5）	73.0 (66.5-79.0）	**0.035**
PSA（ng/ml）	11.13 (7.11-25.30)	13.47 (7.23-23.75)	0.679
Prostate volume（ml）	34.75 (26.61-50.72）	35.46 (28.32-49.97）	0.853
PSAD（ng/ml/ml）	0.36 (0.21-0.55）	0.42 (0.23-0.75）	0.359
PI-RADS score			0.825
4	37 (42.0）	12 (44.4）	
5	51 (58.0）	15 (55.6）	
Multifocality on MRI			0.099
Yes	36 (41.4）	15 (60.0）	
No	51 (58.6）	10 (40.0）	
ADCmin($\mu m^2/s$)	444 (353-558）	317 (219-396)	**<0.001**
SUVmax	12.78 (8.34-21.91）	20.85 (12.82-26.56）	**0.020**
Maximal tumor diameter on PET/CT（cm）	1.80 (1.30-2.29）	1.80 (1.49-2.32）	0.579
Multifocality on PET/CT			0.822
Yes	38 (42.6）	11 (40.7）	
No	50 (57.4）	16 (59.3）	

Continuous variables are presented as median (interquartile range; IQR), while categorical variables are presented as patients (%).

MRI, magnetic resonance imaging; PET/CT, positron emission computed tomography; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density;

PI-RADS, Prostate Imaging Reporting and Data System;

TB, targeted biopsy; CB, combined biopsy;

Significant p values were presented in bold text

Table 3 Univariable and multivariable logistic regression analysis of possible predictors for biopsy concordance between TB and CB

	Univariable logistic regression			Multivariable logistic regression		
Parameters	OR	95%CI	P	OR	95%CI	P
Age（years）	0.929	0.870-0.992	**0.029**	0.931	0.858-1.009	0.082
PSA（ng/ml）	0.998	0.976-1.020	0.832			
Prostate volume（ml）	1.003	0.981-1.025	0.789			
PSAD（ng/ml/ml）	0.799	0.423-1.507	0.488			
PI-RADS score	0.907	0.380-2.163	0.826			
Multifocality on MRI	2.125	0.858-5.262	0.103			
ADCmin($\mu m^2/s$)	1.005	1.002-1.009	**0.001**	1.006	1.003-1.010	**0.001**
SUVmax	0.968	0.942-0.995	**0.020**	0.952	0.917-0.988	**0.010**
Maximal tumor diameter on PET/CT（cm）	1.023	0.607-1.724	0.931			
Multifocality on PET/CT	0.905	0.377-2.172	0.822			

MRI, magnetic resonance imaging; PET/CT, positron emission computed tomography; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; ADC, apparent diffusion coefficient; SUV, standard uptake value; PI-RADS, Prostate Imaging Reporting and Data System; TB, targeted biopsy; CB, combined biopsy; OR, odds ratio; CI, confidence intervals. Significant P values were presented in bold text.

Table 4 Performances of the models for the classification of biopsy concordance and discordance in the full sample

Model	Sensitivity	Specificity	Accuracy	AUC
SUVmax	0.50	0.82	0.77	0.65
ADCmin	0.64	0.78	0.78	0.73
SUVmax+ADCmin	0.67	0.78	0.81	0.78

ADC, apparent diffusion coefficient; SUV, standard uptake value

Figures

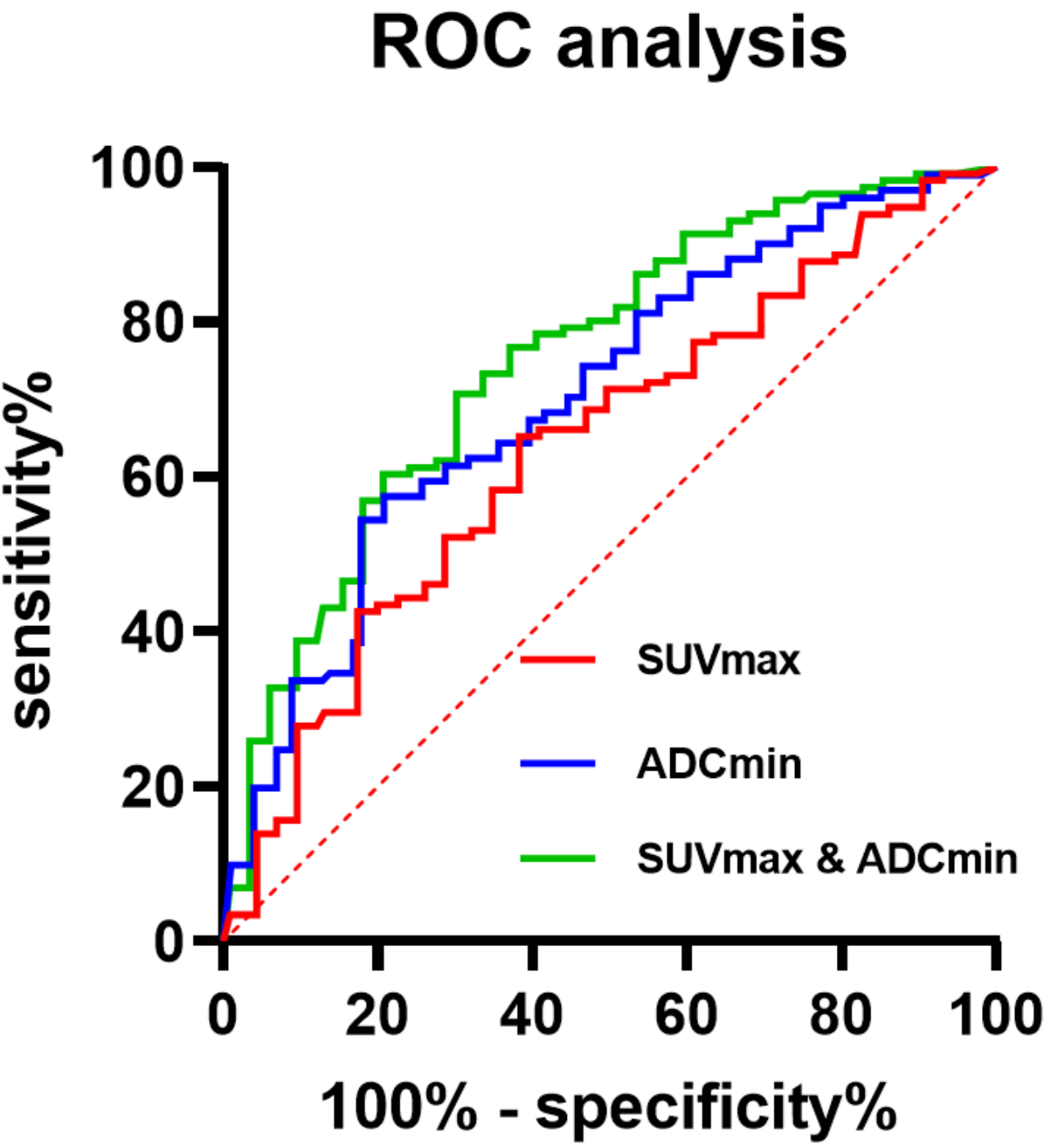

Figure 1

ROC analysis to evaluate the diagnostic accuracy of the identified parameters.

SUV, standard uptake value; ADC, apparent diffusion coefficient;

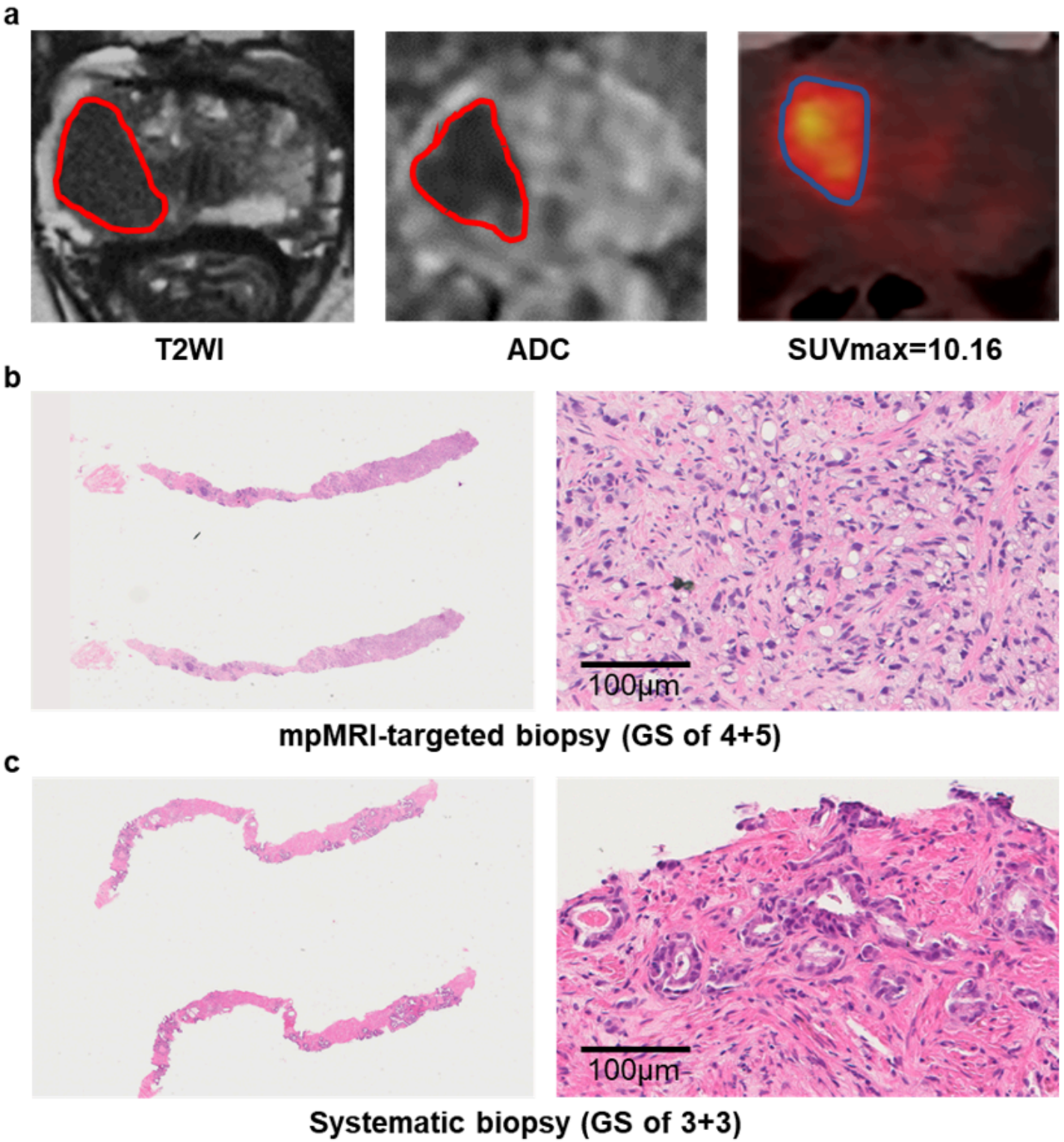

Figure 2

Representative radiopathology matching biopsy concordance case. The patient was an 83-yearold male with an intuitive PSA level of 26.7 ng/ml. (a) The suspicious lesion was detected on mpMRI (PIRADS 5; ADCmin 504) and preoperative ^{68}Ga-PSMA-11 PET/CT (SUVmax=10.16). (b) mpMRI-targeted biopsy indicated prostate cancer with GS of 4+5. (c) Systemic biopsy indicated prostate cancer with GS of 3+3.