68Ga-PSMA-11 PET/CT combining ADC value of MRI in the diagnosis of naive prostate cancer

Perspective of radiologist

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Abstract

68Ga-PSMA-11 positron emission computed tomography /computed tomography (PET/CT) is more sensitive than magnetic resonance imaging (MRI) in detecting prostate cancer (PCa). We evaluated the value of 68Ga-PSMA-11 PET/CT with MRI in treatment-naive PCa.

This retrospective study was approved by the hospital ethics committee. The MRI and 68Ga-PSMA-11 PET/CT imaging data of 63 cases of highly suspected PCa were enrolled in this study. The SUVmax, and apparent diffusion coefficient (ADC), and their ratio, were assessed as diagnostic markers to distinguish PCa from benign disease.

There were 107 prostate lesions detected in 63 cases. Forty cases with 64 malignant primary lesions were confirmed PCa, whereas 23 cases had 43 benign lesions. PSMA-avid lesions correlated with hypointense signal on ADC maps and hyperintense signal on diffusion-weighted imaging. The ADC of PCa was lower than that of benign lesions, and SUVmax and SUVmax/ADC of PCa was higher than that of benign lesions (P<0.01). ADC had significant negative correlation with Gleason score (GS) and SUVmax, SUVmax, and SUVmax/ADC positively correlated with GS. From ROC analysis, we established cutoff values of ADC, SUVmax, and SUVmax/ADC at 1.02 × 10−3mm²/s, 11.72, and 12.35, respectively, to differentiate PCa from benign lesions. The sensitivity, specificity, and AUC were 90.6%, 58.1%, and 0.816 for ADC, 67.2%, 97.7%, and 0.905 for SUVmax, and 81.2%, 88.4%, and 0.929 for SUVmax/ADC, respectively.

68Ga-PSMA-11 PET/CT combined with MRI offers higher diagnostic efficacy in the detection of PCa than either modality alone.

Abbreviations: ADC = apparent diffusion coefficient, AUC = area under the curve, BPH = benign prostatic hyperplasia, DWI = diffusion-weighted imaging, GS = Gleason score, MRI = magnetic resonance imaging, PCa = prostate cancer, PET = positron emission computed tomography, PSMA = prostate-specific membrane antigen, TR = repetition time. T1WI = T1-weighted imaging, T2WI = T2-weighted imaging.

Keywords: magnetic resonance imaging (MRI), positron emission computed tomography (PET), prostate cancer, prostate-specific membrane antigen (PSMA)

1. Introduction

Magnetic resonance imaging (MRI) is recommended for the diagnosis of prostate cancer (PCa) in patients with a high pretest likelihood.1,2 Multiparametric MRI can reveal histopathological characteristics.3 MRI tends to detect high-risk lesions or clinically significant PCa, which leads to prompt treatment. The apparent diffusion coefficient (ADC) generated by diffusion-weighted imaging (DWI) is a parameter for quantitative analysis of malignant lesions.4,5 Though ADC is helpful for tumor characterization, false-positive and false-negative findings are common.6 Therefore, ADC alone has...
not become the single parameter with which to decide on biopsy.

Prostate-specific membrane antigen (PSMA) is an intrinsic transmembrane protein, which is highly expressed in 95% of PCa; its expression corresponds positively with the degree of malignancy.[7,8] The improved efficacy of [68Ga]-labeled PSMA with a ligand, such as PSMA-11 (also known as HBED-CC) and PSMA-617, has been well documented in the diagnosis of PCa.[9,10] Our previous studies further demonstrated that it had higher sensitivity in the diagnosis of treatment-naive PCa and primary staging, especially for lymphadenopathy.[11–14] This technique allows prediction of biochemical recurrence and of lymphadenopathy, which has great impact on the clinical management.

The objective of this study was to evaluate the diagnostic value of 68Ga-PSMA-11 positron emission computed tomography (PET/CT) and MRI in treatment-naive PCa and investigate the feasibility of combining ADC from MRI and SUVmax from PET/CT in differentiation of PCa from benign disease.

2. Methods

2.1. Patients

Between December 2016 and September 2019, 428 patients with suspected PCa underwent 68Ga-PSMA-11 PET/CT. A total of 95 patients underwent both 68Ga-PSMA-11 PET/CT and MRI. Inclusion criteria for case data were: No treatment prior to examinations. PET/CT and MRI were performed within 2 weeks. Patients underwent radical prostatectomy or biopsy after imaging, with the final diagnosis confirmed by histopathology. Exclusion criteria: patients diagnosed with PCa previously; >14 days between the 2 examinations; previous surgery or biopsy; disease not confirmed by pathology. A total of 63 cases met the inclusion criteria. Mean age was 69.56 ± 11.56 years. A detailed flowchart is shown in Fig. 1. The prostate-specific antigen (PSA) levels ranged from 4.15 to 1298 ng/mL. This retrospective study was approved by the review board of our hospital. All patients signed written consents.

2.2. MRI acquisition protocol

MRI was performed with a high-field system (Intera Achieva 3.0T TX, Philips, The Netherlands). The sequences were as follows: transverse T1-weighted imaging (T1WI, repetition time [TR] = 400 ms, echo time [TE] = 10 ms, field-of-view [FOV] = 35 × 30 cm, matrix = 192 × 200); T2-weighted imaging (T2WI) (TR = 3500 ms, TE = 90 ms, FOV = 20 × 20 cm, matrix = 240 × 230); fat-suppression spectral presaturation attenuated inversion recovery-T2WI (TR = 2800 ms, TE = 100 ms, FOV = 25 × 40 cm, matrix = 270 × 200); DWI (TR = 6200 ms, TE = 2000 ms, FOV = 20 × 30 cm, matrix = 80 × 142, b = 1500 s/mm²). The section thickness of each sequence was 3 mm; the section interval was 0.3 mm. Transverse DWI was obtained by single-shot echo planar imaging.

2.3. 68Ga-PSMA-11 PET/CT

PSMA-11 (HBED-CC) was purchased from ABX (Germany). 68Ga-PSMA-11 was radiolabeled using the automated labeling module produced by ITM (Germany). The radiochemical purity was > 99%. The synthesis procedure was reported previously.[11] Whole-body PET/CT (uMI780, United Imaging, China) was performed from the vertex to the proximal legs 1 hour postinjection of 68Ga-PSMA-11 (111–185 MBq). Attenuation-corrected images were assessed clinically by certified nuclear medicine physicians.

Figure 1. The flow chart of eligible case data inclusion.
2.4. Image interpretation

All MR images were interpreted by 1 certified radiologist (with 5 years of experience in prostate MRI) while blinded to PET images. Both interpreters reviewed all imaging data in a single session blinded to all clinical and pathologic data. Regions of interest were placed around lesions with diameters > 5mm. The mean ADC and maximum SUVmax were measured. For ADC values, an ROI was drawn around the lesion on DWI according to hypointense signal on T2WI. The SUVmax/ADC ratio was manually calculated to express both PSMA expression and ADC.

2.5. Statistical analysis

Continuous variables with abnormal distribution are expressed as median (interquartile range). The correlation between SUVmax and ADC and correlation between GS and SUVmax, ADC, and SUVmax/ADC were evaluated by Spearman correlation analysis. The Wilcoxon rank-sum test was used to compare the difference in SUVmax, ADC, and SUVmax/ADC among different groups. Additionally, receiver operating characteristic curve (ROC) analysis was performed to evaluate the sensitivity, specificity, area under the curve (AUC), and cutoff value of each parameter. AUCs of the 3 parameters were compared by the z test. R (version 3.6.1) and MedCalc (version 15.0) statistical software programs were employed for all analysis. *P* < .05 was considered statistically significant.

3. Results

Out of 63 cases enrolled in this retrospective study (40 with PCa, 23 with benign prostatic disease), 32 cases were confirmed by postoperation pathology, and 31 cases were confirmed by needle biopsy. A total of 107 primary prostate lesions were found among the 63 cases. There were 2 to 4 lesions in 27 cases, and 36 solitary lesions. Eighteen cases with PCa had lymph node metastasis (28.57%) and 6 cases had bone metastasis (9.52%). All pelvic lymph node metastases were detected by PET/CT and MRI while all extraprostatic bone metastases were only detected by PET/CT.

PCa presented as hypointense signal in the peripheral zone or the central gland on T2WI, hypointense signal on ADC maps, and hyperintense signal on DWI. These findings corresponded to focal increased uptake in 68Ga-PSMA-11-PET images (Fig. 2). Benign prostatic hyperplasia (BPH) presented as increased volumes in the transition zone and central zone with compression and thinning of the peripheral zone (Fig. 3). Mixed hypointense and hyperintense signals were observed on T2WI, and no obvious hypointense or hyperintense signals appeared on DWI and ADC maps. No significantly increased uptake was observed on 68Ga-PSMA-11 PET/CT. Characteristics of prostatitis were hypointense signals in the central and peripheral zone on T2WI, isointense or hyperintense signal on DWI, and isointense or hypointense signal on ADC maps. 68Ga-PSMA-11-PET/CT showed no or mildly diffuse uptake (Fig. 4).

Figure 2. 68Ga-PSMA-11 PET/CT and MRI in a case with progressive dysuria (male, age 83, PSA: 87.18 ng/mL). Hypointense signals were shown on T2WI (A, white and red arrows), and hyperintense signals on DWI (B, white and red arrows) in both lobes of prostate. ADC map showed hypointense signal in all lesions (C, white and red arrows). A PSMA-avid lesion occupies the right peripheral zone (SUVmax = 33.19, SUVmax/ADC = 68.37; D and E, white, black and red arrows). All of left and right lesions were confirmed pathologically as prostate cancer (HE staining, 100 × magnification; GS 4 + 5 = 9; F), ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, GS = Gleason score, MRI = magnetic resonance imaging, PET = positron emission computed tomography, PSMA = prostate-specific membrane antigen, SUV = standard uptake value, T2WI = T2-weighted imaging, PSA = prostate-specific antigen, CT = computed tomography.
5.49 (3.27–8.64) in benign disease, and ADC value alone showed high sensitivity in detecting PCa. However, the specificity of MRI for PCa is limited, and MRI likely missed some prostatic and extraprostatic lesions.

Transrectal ultrasound-guided percutaneous biopsy is a routine method in the diagnosis of PCa. However, the false-negative rate of biopsy is as high as 15% to 35%. MRI has improved the detection rate of clinically significant PCa, which avoids unnecessary biopsy. The ADC from DWI reflects the degree of diffusion of water molecules in the tissue. Current studies have shown that ADC maps illustrate the histopathological features of the lesion, and ADC values were significantly lower in the PCa group than that in prostatitis, and ADC value alone showed high sensitivity in detecting PCa. However, the specificity of MRI for PCa is limited, and MRI likely missed some prostatic and extraprostatic lesions.

56Ga-PSMA-11 PET has been validated to be more sensitive than MRI in the detection of PCa. SUV$_\text{max}$ represents PSMA expression, which correlates with tumor differentiation.
and prognosis. The aim of this study was to investigate the diagnostic value of $^{68}$Ga-PSMA-11 in treatment-naive prostate cancer compared with that of MRI, and the feasibility of using the SUVmax/ADC was further explored. To our knowledge, this is the first head-to-head comparison study between MRI and $^{68}$Ga-PSMA-11 PET in the detection of primary prostatic lesions in China.

In this study, the ADC value negatively correlated with SUVmax, which was consistent with previous studies. The SUVmax/ADC ratio has been utilized to evaluate the combined advantages of MRI and PET/CT and showed great sensitivity and specificity for the detection of lymphadenopathy in PCa. This study demonstrated PCa was associated with lower ADC, and higher SUVmax and SUVmax/ADC. The GS negatively correlated with ADC values, and positively correlated with SUVmax and the SUVmax/ADC. These findings were consistent with other studies. SUVmax/ADC may be used as a predictive parameter for PCa, to help distinguish benign from malignant prostatic lesions.

ROC curve analysis showed that ADC had high sensitivity but lower specificity in the detection of PCa. The sensitivity of SUVmax in this study (67.2%) was less than that reported in other studies, which may be attributed to differences among the populations and the different cutoff values. The ratio of SUVmax/ADC integrates the degree of water molecule diffusion and PSMS expression. In this study, the diagnostic efficacy of the SUVmax/ADC ratio was better than that of SUVmax or ADC alone. SUVmax/ADC might be an alternative parameter in the detection of treatment-naive prostatic lesions.

MRI has been well documented in the detection of treatment-naive prostate cancer, recent studies validated that MRI might improve the detection rate of clinical significantly PCa. However, MRI missed the lesion located in the transitional and ventral zone, especially patients combining with prostate hyperplasia. $^{68}$Ga-PSMA-11 PET/CT had higher sensitivity in the detection of biochemical recurrence, several studies further validated that it improved the detection rate of primary prostatic lesion, especially in the peripheral and translational zone even with low PSA level. However, PSMA PET/CT missed some primary lesions in patients with higher Gleason Score or poor differentiated PCa and special rare PCa. Some false-positive or false-negative results existed in the clinical when SUVmax and ADC valued are used separately. Therefore, as a radiologist, we supposed that SUVmax combining with ADC value might improve the detection rate of primary prostatic lesion. Combination of the SUVmax and ADC will decrease the deviation and improve the diagnostic accuracy.

In cases of high-GS primary PCa, $^{68}$Ga-PSMA-11 PET/CT not only improved the detection rate of prostatic primary lesions but also of extra-prostatic spread, which had great impacts on staging and clinical management. To our great interest, 27 cases with multiple primary lesions were discovered in this study. MRI with $^{68}$Ga-PSMA-11 PET/CT detected all lesions. From a radiology perspective, MRI is valuable in the detection of primary prostatic lesions in the peripheral and translational zone, and identification of seminal vesicle involvement. $^{68}$Ga-PSMA-11 PET/CT has the advantage in the detection of multiple lesions and lesions in the central zone. ADC integration with $^{68}$Ga-PSMA-11 PET/CT

Figure 4. $^{68}$Ga-PSMA-11 PET/CT and MR in a patient with prostatitis (male, age 65, PSA: 10.93 ng/mL). An irregular lesion with blurred borders in the left peripheral and transitional zones shown on T2WI (A, white arrow), slightly higher signal on DWI (B, white arrow), and low signal on ADC (C, white arrow). No obvious uptake in prostate gland (SUVmax = 4.66, SUVmax/ADC = 5.18; D and E). Benign prostatic hyperplasia with prostatitis was confirmed by pathology (HE staining, 100 x magnification; F). ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, PET = positron emission computed tomography, PSMA = prostate-specific membrane antigen, SUV = standard uptake value, T2WI = T2-weighted imaging, PSA = prostate-specific antigen, CT = computed tomography.
Figure 5. $^{68}$Ga-PSMA-11 PET/CT detected a primary prostatic lesion, missed by MRI, in a case of suspected PCa (male, age 63, PSA: 17.57 ng/mL). Slightly hypointense signal in the right peripheral zone and transition zone are shown on T2WI (A, white arrow), isointense signal on DWI (B, white arrow), and slightly hypointense signal on ADC (C, white arrow). In $^{68}$Ga-PSMA-11 PET/CT, obvious focal uptake in the right transition zone is shown (SUV$_{\text{max}}$ = 15.03, SUV$_{\text{max}}$/ADC = 17.68; D and E, white arrow). Prostate cancer confirmed by pathology (HE staining, 100 x magnification; GS 3 + 4 = 7; F). ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, PET = positron emission computed tomography, PSMA = prostate-specific membrane antigen, SUV = standard uptake value, T2WI = T2-weighted imaging, PSA = prostate-specific antigen, CT = computed tomography, PCa = prostate cancer, GS = Gleason score.

Figure 6. Scatter plots of the different parameters and GS. Correlation among SUV$_{\text{max}}$ and ADC (A), benign lesions (B), and PCa lesions (C). Correlation among ADC and GS in PCa lesions (D), correlation between SUV$_{\text{max}}$ and GS in PCa lesions (E), and correlation between SUV$_{\text{max}}$/ADC and GS in PCa lesions (F). ADC = apparent diffusion coefficient, SUV = standard uptake value, PCa = prostate cancer, GS = Gleason score.
Table 1
The difference of the 3 diagnostic parameters.

| Parameter | Benign lesion | PCa lesion | W   | P     |
|-----------|---------------|------------|------|-------|
| ADC       | 1.04 (0.75, 1.29) | 0.69 (0.55, 0.85) | 2246 | 3.27 × 10⁻⁶ |
| SUV_{max} | 4.02 (3.00, 7.86)  | 14.86 (9.54, 19.80) | 262  | 1.49 × 10⁻¹² |
| SUV_{max}/ADC | 3.51 (2.67, 6.15) | 19.64 (13.12, 33.16) | 195  | 6.33 × 10⁻¹⁴ |

ADC = apparent diffusion coefficient, SUV_{max} = standard uptake value.

Table 2
The difference of the 3 diagnostic parameters between PCAs with high (≥7) and low (<6) GS.

| Parameter | GS(≤6) | GS(≥7) | W | P     |
|-----------|--------|--------|---|-------|
| ADC       | 0.92 (0.69, 0.97)  | 0.63 (0.51, 0.77) | 484 | 1.12 × 10⁻² |
| SUV_{max} | 8.69 (7.90, 9.56)  | 17.37 (12.69, 24.79) | 93  | 7.14 × 10⁻⁵ |
| SUV_{max}/ADC | 10.32 (9.00, 12.47) | 23.17 (17.80, 44.17) | 62  | 7.16 × 10⁻⁶ |

ADC = apparent diffusion coefficient, SUV_{max} = standard uptake value, GS = Gleason score.

This study provides some insights into the evaluation of tumor behavior and aggressiveness, with GS correlating positively with SUV_{max}/ADC. This study will pave the way for future investigations into the molecular phenotyping of prostate cancer.

The limitation of this study is that this was a small-scale retrospective study. Large-scale prospective studies between MRI and {sup}-Ga-PSMA-11 PET/CT in the detection of prostatic primary lesions are warranted in China. Second, this study was not performed with hybrid PET/MRI but with the modalities separated. A well-designed study with hybrid PET/MRI is underway. Third, we did not evaluate the role of SUV_{max}/ADC in predicting metastatic behavior on follow-up. In the future study, further study will be performed with simultaneous PET/MRI, which has been used in my department, SUV_{max}/ADC parameter will be further evaluated not only in prostatic primary lesion but also in metastatic lesion. We will validate if SUV_{max}/ADC can be served as a useful parameter for the evaluation of tumor biology and prognosis, which may have great impact of treatment strategy selection.

5. Conclusion
MRI combined with {sup}-Ga-PSMA-11 PET/CT has higher sensitivity and specificity for the diagnosis of treatment-naive PCAs, which has great merits in the detection of multiple primary prostatic lesions and confirmation of seminal vesicle involvement. The SUV_{max}/ADC ratio may serve as a valuable parameter for the diagnosis of PCAs and evaluation of biological behavior.

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