Optimized application of 68Ga-prostate-specific membrane antigen-617 whole-body PET/CT and pelvic PET/MR in prostate cancer initial diagnosis and staging

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Abstract

Purpose To analyze 68Ga-PSMA-617 PET/CT or PET/MR and delayed PET/MR images in patients diagnosed with or suspected of prostate cancer, and to explore the optimal use of PET/CT and PET/MR for initial diagnosis and staging in prostate diseases.

Methods Images from conventional scan by 68Ga-PSMA whole-body PET/CT or PET/MR followed by delayed pelvic PET/MR were retrospectively analyzed. Prostatic 68Ga-PSMA uptake was measured as SUVmax1 (conventional scan 1 h post injection) and SUVmax2 (delayed scan 3 h post injection). Age, PSA levels, and SUVmax were compared between benign and malignant cases. The correlation of SUVmax1 and SUVmax 2 was analyzed. Diagnostic performance was evaluated by ROC analysis.

Results We enrolled 56 patients with 41 malignant and 15 benign prostate lesions. Fifty-three patients had paired conventional and delayed scans. Age, PSA levels, and SUVmax were significantly different between benign and malignant cases. A good correlation was found between SUVmax1 and SUVmax2. There was significant difference between SUVmax1 and SUVmax2 in the malignant group ($p = 0.001$). SUVmax1 had superior diagnostic performance than SUVmax2, SUVmax difference and PSA levels, with a sensitivity of 85.4%, a specificity of 100% and an AUC of 0.956. A combination of SUVmax1 with nodal and/or distant metastases and MR PIRADS V2 score had a sensitivity and specificity of 100%. Delayed pelvic PET/MR imaging in 33 patients were found to be redundant because these patients had nodal and/or distant metastases which can be easily detected by PET/CT.

Conclusion Combined 68Ga-PSMA whole-body PET/CT and pelvic PET/MR can accurately differentiate benign prostate diseases from prostate cancer and accurately stage prostate cancer. Whole-body PET/CT is sufficient for advanced prostate cancer, and more economic and time-saving than PET/MR. Pelvic PET/MR contributes to diagnosis and accurate staging in early prostate cancer. Imaging at about 1 hour after injection is sufficient in most patients.

Trial registration: NCT03756077. Registered 27 November 2018 - Retrospectively registered, <https://clinicaltrials.gov/show/NCT03756077>

Introduction

Prostate cancer is a common malignancy harmful to health of old males. The incidence ranks second (13.5%) and it is the fifth leading cause of cancer death (6.7%) among males worldwide ¹. Accurate diagnosis and staging are very important to choose the most suitable treatment.

Serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) are the most commonly used initial screening methods for prostate gland disease². The limitations of PSA level as a prostate cancer biomarker are well known because false positive and false negative results are common, and screening for prostate cancer with PSA is generally no longer recommended³. The value of DRE is limited in the early stages of the disease. Systematic transrectal ultrasound (TRUS)-guided biopsy is regarded as a standard, but it has frequent false-negative results and underestimates the final Gleason score of the tumor compared with histologic examination after radical prostatectomy ⁴.

Imaging technologies play an important role in the management of prostate cancer. Conventional imaging modalities, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and bone scan are commonly used in the diagnosis, staging, and restaging of prostate cancer⁵. However, these conventional imaging modalities are usually regional imaging, or have limited accuracy in small lymph node metastases and small-volume bone metastases. Molecular imaging is regarded as a promising approach to improve prostate cancer diagnosis and staging⁶. Several positron emission tomographic (PET) tracers, like 18F-FDG, 18F-fluorocholine, 11C-choline, and 11C-acetate, have been studied in patients with prostate cancer, but the performance of most PET radiotracers has so far remained limited^{7,8}.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein which is obviously overexpressed in prostate cancer^{9,10}. It becomes a promising target for specific imaging of prostate cancer¹¹. In recent years, gallium 68 (68 Ga) has been used to label PSMA ligands for PET imaging¹². Initial experience using 68 Ga-PSMA PET/CT indicates that 68 Ga-PSMA PET can visualize relapses and metastases of prostate cancer with high contrast through binding to the extracellular domain of PSMA and internalization¹³. Studies have described the superior value of 68 Ga-PSMA ligand PET imaging to conventional imaging in different clinical scenarios, including differential diagnosis; guiding biopsy, surgery and radiotherapy; initial staging and restaging; recurrence detection and selecting patients who may benefit from systemic targeted radionuclide therapy^{14–16}.

PET/MR is a hybrid technology that can provide both biologic and morphologic information. Recently introduced 68 Ga-PSMA-11 PET/MR combines multiparametric MRI (mpMRI) along with molecular information of PSMA expression into a “one-stop shopping” procedure for better anatomic localization and characterization of prostate lesions. Compared with PET/CT, simultaneous PET/MR has the advantages of reduced radiation exposure and inherent higher soft-tissue contrast resolution^{17,18}. PSMA PET/MR is particularly important for accurate localization and assessment of the extent of pelvic disease in the initial staging of prostate cancer. Some PET centers have both PET/CT and PET/MR, and PET/MR has been used increasingly widely. Choosing the right scan is important. Despite the advantages of PSMA PET/MR over PSMA PET/CT, cost, scanning time, and patient comfort should also be considered. Domachevsky¹⁹ demonstrated that although early PET/MRI has very good agreement compared to same-day PET/CT, PET/CT and early PET/MRI cannot be used interchangeably. They further demonstrated that pelvic PSMA PET/MR is better than whole-body PSMA PET/CT for detecting extensions of localized disease, and may be useful for initial evaluation of prostate cancer²⁰.

Does every patient need to undergo both PET/CT and PET/MR? The purpose of this study was to retrospectively analyze the images of whole-body PSMA PET/CT or PET/MR followed by delayed limited pelvic PSMA PET/MR in patients diagnosed with or suspected to have prostate cancer, and to explore how to rationally use PET/CT and PET/MR in prostate diseases.

Materials And Methods

Patients

This study was approved by Institutional Review Board. Patient data involved in a study that was registered on ClinicalTrials.gov (NCT03756077) were retrospectively analysed. Patients diagnosed with or suspected of having prostate diseases who underwent whole-body ⁶⁸Ga-PSMA PET/CT or PET/MR followed by delayed pelvic PET/MR

in our PET Center were included between May 2018 and January 2020. All the patients were divided into a “malignant group” or a “benign group” according to the histological or follow-up results.

Imaging Protocol

No special preparation was needed prior to PET scanning. ^{68}Ga was produced from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (ITG GmbH, Munich Germany) by eluting with 0.05N hydrochloric acid. ^{68}Ga -PSMA-617 was synthesized using an ITG manual synthesis module as described previously²¹. Briefly, 4 mL of $^{68}\text{GaCl}_3$ was reacted with 20 μg (20 nmol) PSMA-617 ligand (Jiangsu Huayi Technology Company, Changshu, China) in 1 mL of 0.25M sodium acetate buffer for 5 min at 105 °C. The production was purified in a C18 cartridge and collected through a 0.22- μm -pore filter.

All patients were injected with a dose of 173.53 ± 50.69 MBq (4.69 ± 1.37 mCi) of ^{68}Ga -PSMA-617 intravenously. Patients were encouraged to drink water after injection and required to urinate before imaging. Conventional imaging from vertex to proximal legs began at 70.0 ± 16.9 min (PET/CT) or 74.3 ± 12.5 min (PET/MR) [$p = 0.357$] after injection using a hybrid PET/CT scanner (Discovery VCT; GE Healthcare, Waukesha WI, USA) or a time-of-flight hybrid PET/MR scanner (SIGNA PET/MR; GE Healthcare). Delayed pelvic PET/MR images were acquired at 171.2 ± 37.9 min after injection.

PET/CT acquisition followed our standard protocol. A CT scan (120 kV, 110 mAs) was acquired after a scout image with a scanning thickness of 3.75 mm, followed by whole-body emission static PET imaging in a three-dimensional (3D) mode at 3 minutes per bed position. PET images were attenuation-corrected using CT images, and reconstructed using an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (28 subsets and 2 iterations) and coregistered with CT images (Xeleris; GE Healthcare).

For PET/MR, MR attenuation images were acquired using ZTE technology after acquisition of localization images. The PET acquisition of PET/MR was performed in 3D mode for 6 minutes per bed position (89 sections per bed) in five bed positions. MR imaging of the brain [axial T2-weighted, T1-weighted, and fluid-attenuated inversion recovery (FLAIR)] was performed along with the PET scan, then whole-body imaging (from skull base to mid thigh in four bed positions, a high-resolution axial T1-weighted LAVA-Flex sequence and a coronal T2-weighted fast recovery fast spin echo [FRFSE] sequence in two planes were included) were acquired during the PET scan. Next, dedicated mpMRI images of the prostate [transverse, coronal, and sagittal T2-weighted images and diffusion-weighted spin-echo echo-planar images (b-factor, 0/1000/1,400 s/mm^2)] were acquired. Other MR protocols were included when clinically required. The delayed pelvic PET/MR imaging was the same to the previous. All PET data were reconstructed with TOF information, using the system's default 3D OSEM protocol iterative reconstruction algorithms with 2 iterations and 28 subsets and coregistered to MR images on a workstation (AW, GE Healthcare).

Image Analysis

PET/CT and PET/MR images were interpreted by two experienced nuclear medicine physicians using dedicated software on the AW workstation. Visual assessment was used for characterizing PSMA-avid lesions in axial, coronal and sagittal reconstructions. Lymph nodes, bone lesions and other foci suspected of being distant metastases were evaluated first. Intra-prostatic PSMA-avid foci were defined as PSMA uptake greater than the adjacent prostate gland or background on PET/CT or PET/MR, and regions of interest (ROIs) were drawn on PSMA-avid area or prostate bed if presented with a diffuse pattern of uptake, and maximum standard uptake value (SUVmax) were measured, the SUVmax in the conventional scan was defined as “SUVmax1”, and the

SUVmax in the delayed scan was defined as “SUVmax2”. Capsular invasion; seminal vesicle, bladder or other adjacent organ involvement; and involvement of small pelvic lymph nodes were identified if PSMA uptake and abnormal MR signal were seen outside the boundaries of the prostate gland or corresponded to sites on PET/MR images. Version 2 of the Prostate Imaging Reporting and Data System (PI-RADS V2) was used to score prostatic regions with abnormal signal on MR images²². Patients with prostate cancer were staged according to AJCC Prognostic Groups by combination of TNM, PSA level and Gleason score²³.

Statistical Analysis

Independent samples *t*-tests were performed to compare the mean values between the malignant group and the benign group cases. Paired samples *t*-tests were performed to compare SUVmax1 and SUVmax2. All the correlations were analyzed using Spearman’s rank correlation test, and a scatter diagram was drawn with the regression line. Bland–Altman plots were used to assess the agreement between SUVmax1 and SUVmax2. ROC curves were generated to assess the diagnostic performance of each parameter, and to calculate a cutoff value. The sensitivity and specificity were calculated on a per-patient basis imaging diagnosis against the final clinical diagnosis. All statistical analyses were performed using SPSS Statistics, version 22 (IBM, Armonk, NY, USA). A $p < 0.05$ was considered to indicate significant difference.

Results

1. Scanner usage, characteristics of patients, and prostatic features in benign and malignant groups

Of the 56 patients enrolled between May 2018 and January 2020, 40 patients underwent whole-body PET/CT and delayed pelvic PET/MR, 13 patients underwent whole-body PET/MR and delayed pelvic PET/MR, 3 patients underwent only whole-body PET/MR. Finally, forty-one patients were diagnosed as malignant and 15 were benign. In the malignant group, 32 patients were confirmed by histopathology, including 19 acinar adenocarcinoma, 1 ductal adenocarcinoma, 5 adenocarcinoma, and 7 prostate cancers of unknown type. The other 9 patients were confirmed by treatment and at least half a year followup results. The benign group included benign prostatic hyperplasia (BPH) and/or prostatitis, 6 patients with biopsy results, and 9 patients confirmed by treatment and follow-up at least half a year. The patient characteristics are listed in Table 1.

Table 1
Patient characteristics and prostatic features in benign group and malignant group

	Benign group	Malignant group	p Value
Age (y)	61.93 ± 7.41(47–75)	71.02 ± 8.58(52–91)	p = 0.001
tPSA (ng/ml)	15.67 ± 18.43(n = 15)	135.98 ± 232.92 (n = 37) *	p = 0.004
fPSA (ng/ml)	2.82 ± 4.45(n = 14)	11.18 ± 11.49 (n = 35) #	p = 0.001
fPSA/tPSA	0.164 ± 0.086(n = 14)	0.132 ± 0.840(n = 27)	p = 0.247
Prostatic SUVmax1	4.09 ± 0.96	20.31 ± 15.74	p < 0.001
Prostatic SUVmax2	4.63 ± 1.34	24.53 ± 16.38	P < 0.001
Location of lesion in prostate			
Peripheral zone	7(46.7%)	12(29.3%)	p = 0.006
Central zone	5(33.3%)	3(7.3%)	
Peripheral zone + Central zone	3(20.0%)	26(63.4%)	
*6 patients have tPSA > 100 ng/ml, 2 > 1000 ng/ml; #5 patients have fPSA > 30 ng/ml. The limit values were used in statistics.			

The differences in age, tPSA, fPSA, and prostatic SUVmax between the benign group and the malignant group were statistically significant. Intra-prostatic PSMA-avid foci were found in 6 patients in the benign group (40.0%) and 35 in malignant group (85.4%). In the benign group, three of six presented with symmetrical accumulation in posterior peripheral bands at the base of prostate. In six prostate cancer patients without intra-prostatic PSMA-avid foci, one had bone metastases, two had lymph node metastases, two had both lymph node and bone metastases. Representative images are shown in Fig. 1 and Fig. 2. The locations of the lesions in prostate are shown in Table 1; most were in the peripheral or central zone in the benign group. In the malignant group, most involved both the peripheral zone and central zone (Fig. 2).

2. Characteristics of prostatic 68 Ga-PSMA-617 uptake and its correlation with Gleason score and PSA level

In the 53 of the 56 patients with paired conventional and delayed scans, 68 Ga-PSMA-617 uptake in the two phases was compared. In the benign group, the mean prostatic SUVmax values in the conventional and delayed scans were 3.95 ± 0.88 and 4.64 ± 1.34 (n = 13), respectively. No significant difference was found between the two phases (t = - 1.642, p = 0.127). In the malignant group, the mean prostatic SUVmax in the conventional and delayed scans were 20.31 ± 15.74 and 24.53 ± 16.38 (n = 40), respectively, with a significant difference between the two phases (t = - 3.695, p = 0.001). The scatter diagram of SUVmax from different scanners at different time point is shown in Fig. 3A. Bland–Altman plots reveal a scatter diagram of the differences plotted against the means of SUVmax values from conventional whole-body PET/CT or PET/MR with delayed pelvic PET/MRI. In the benign group, the mean SUVmax has a narrow range at low levels, and the mean difference is 0.68, with the limits of agreement (LOA) between - 2.26 and 3.63. In the malignant group, mean SUVmax had a wide range, and the mean difference was 4.22, with LOA between - 10.32 and 18.75 (Fig. 3B). Good correlation was found between SUVmax1 and SUVmax2 (r = 0.932, p < 0.001, Fig. 3C, $Y(\text{SUVmax1}) = - 0.41 + 0.85 \cdot X(\text{SUVmax2})$). No significant

correlation was found between SUVmax and Gleason score, tPSA, and fPSA. There was a significant negative correlation between SUVmax and fPSA/tPSA ($r = 0.674$, $p = 0.039$). The scatter diagram shown in Fig. 3D expresses Y (SUVmax1) as the result of $20.45 - 47.99 \times X$ (SUVmax2).

3. Gleason score, AJCC prognostic stage and primary lesion, involvement of surrounding tissues, and distant metastasis in patients with prostate cancer

Because this was a retrospective study, only 30 patients had available Gleason scores. The numbers of patients with different Gleason scores and AJCC prognostic stage are listed in Table 2. No significant differences were found in SUVmax among different groups according to Gleason score and AJCC prognostic stage. The higher Gleason score, the higher incidence of nodal and distant metastases. However, nodal and distant metastases also occurred even in patients with low Gleason score.

Table 2
clinical and imaging characteristics in patients with prostate cancer

Characteristic	No.	Prostatic SUVmax	Seminal vesicle involvement	Other adjacent organ involvement*	Lymph node metastasis	Bone metastasis	Other metastases#
Gleason score	30	$p = 0.550$	16	8	23	13	4
1 (≤ 6)	4	24.3 ± 22.6	0	1 (12.5%)	2 (8.7%)	3 (23.1%)	2 (50%)
2(3 + 4 = 7)	3		2 (12.5%)	0	2 (8.7%)	2 (15.4%)	1 (25%)
3(4 + 3 = 7)	2		0	0	0	0	0
4(4 + 4 = 8)	9	17.3 ± 12.4	6 (37.5%)	4 (50%)	8(34.8%)	2 (15.4%)	0
5(9 or 10)	12	21.3 ± 15.9	8 (50%)	3 (37.5%)	11(47.8%)	6 (46.2%)	1 (25%)
AJCC prognostic stage	41	$p = 0.700$	23	11	29	19	7
2A	5	20.1 ± 14.8	0	0	0	0	0
2B	3		0	0	0	0	0
4A	14	19.3 ± 12.1	10 (43.5%)	3 (37.5%)	14 (48.3%)	0	0
4B	19	21.1 ± 18.9	13 (56.5%)	8 (62.5%)	15 (51.7%)	19 (100%)	7 (100%)
*Other adjacent organ involvement include 11 bladder involvement, 1 combined with urethra and corpus spongiosum penis involvement, 1 right ureter and rectum involvement, 1 right ureter involvement, and 1 rectum involvement.							
#Other distant metastases include 4 bilateral lung metastasis, 1 bilateral lung metastasis and liver metastasis, 2 muscle metastases (1 right obturator, 1 right psoas major).							

4. Diagnostic Performance

ROC analysis was performed to evaluate the diagnostic performance of tPSA, fPSA, and fPSA/tPSA (Fig. 4A), SUVmax1 SUVmax2, and the difference between SUVmax1 and SUVmax2 (Δ SUVmax) (Fig. 4B) for differentiating malignant from benign lesions. Cutoff values, sensitivity, specificity, AUC, 95% confidence interval (CI) and P values are shown in Table 3. SUVmax1 from the conventional PET/CT or PET/MR revealed the best diagnostic performance with an AUC of 0.956, cutoff value of 5.25 (sensitivity, 85.4%; specificity, 100%; $p < 0.001$). When combining SUVmax1 with nodal/distant metastases, the sensitivity improved to 95.1%. If we combine SUVmax1, nodal/distant metastases and MR PIRADS V2, sensitivity and specificity both reached 100%.

Table 3
Diagnostic performance of several indices and its combination

	Cut-off	sensitivity	specificity	AUC	95% CI	P
tPSA	7.73	88.9%	57.1%	0.786	0.637–0.934	0.003
fPSA	1.58	85.2%	64.3%	0.751	0.583–0.920	0.009
SUVmax1	5.25	85.4%	100%	0.956	0.907–1.000	< 0.001
SUVmax2	7.85	82.9%	100%	0.919	0.848–0.991	< 0.001
Δ SUVmax	0.90	70.7%	69.2%	0.742	0.614–0.870	0.009
LN/Distant metastasis + SUVmax1		95.1%	100%			
LN/Distant metastasis + SUVmax1 + mpMR		100%	100%			

5. Diagnostic Overview Of All Patients In This Study

A diagnostic overview of all patients is shown in Fig. 5. Thirty-three patients at advanced stages were diagnosed and staged by conventional whole-body PET/CT or PET/MR due to detection of bone metastases and involved lymph nodes, so pelvic PET/MR imaging of these patients would be redundant. Among the rest of the patients, delayed pelvic PET/MR was used for further evaluation. Seven had prostatic foci with SUVmax > 5.25 (Fig. 2B), and 1 had a PIRADS score > 3 (Fig. 2B), which were diagnosed as malignant. The remaining 15 patients were diagnosed with benign disease.

Discussion

This retrospective study confirmed the value of PSMA PET/CT and PET/MR in prostate disease diagnosing and staging. In this study, whole-body PET/CT (PET/MR) and delayed pelvic PET/MR accurately diagnosed and staged all of the patients. When the SUVmax from a conventional scan was used as the only criterion, sensitivity and specificity reached 85.4% and 100%, respectively. Our optimal cutoff value is 5.25, which is close to literature reports of 5.94²³. However, PSMA uptake in the prostate is not significantly elevated in some patients; fortunately,

nodal or bone metastases were observed on PET/CT or PET/MR imaging (Fig. 1), so combination of SUVmax with nodal or bone metastases further improved the sensitivity to 95.1%. There are still a few cases with neither bone, nodal metastasis nor positive prostatic PSMA uptake. In this situation, mpMRI may improve detection (Fig. 2B). Combination use of nodal metastases, bone metastases, SUVmax of primary lesions, and MR PIRAS score from whole-body PET/CT and PET/MR made the sensitivity and specificity reach 100% for prostate diseases diagnosis in this study.

Because it has been proven that the FDG SUV measured by PET/CT and PET/MR has clinically acceptable repeatability^{24,25}, we ignored the influence of SUV from different instrument in conventional scans for statistics. Our results showed that SUVmax values from delayed scans were significantly higher than those from conventional scans in patients with prostate cancer, indicating tracer accumulation increased overtime. Park, S. Y. reported similar results²⁶. Our results revealed SUVmax values from conventional scanning at about 1 h post injection and those from delayed scan at about 3 h are linearly correlated, which is consistent with the results reported by Ringheim, et al²⁷. However, they also found a mean 20% difference between PET/CT than on PET/MR (higher on PET/CT), which cannot be used interchangeably in followup²⁷. Therefore, a more detailed study is needed to evaluate the quantitative accuracy of PET/MR and the factors governing it.

As for the optimal timing for prostate PSMA imaging, ROC analysis shows that SUVmax1 from conventional imaging has relatively good diagnostic performance compared with delayed imaging, so we believe that conventional imaging at about 1 h is sufficient for most patients. Delayed imaging takes up time, increases patient anxiety, and may make patients with urinary retention uncomfortable, so it is not necessary on a routine basis. However, for those patients who are difficult to diagnose and whose pelvic images were affected by urine in the bladder, it is necessary to perform delayed imaging after drinking plenty of water and urinating. Some studies have analyzed multiple time-point ⁶⁸Ga-PSMA imaging, including early dynamic images, static scans after 60 min (conventional scan) and 180 min (delayed scan) post-injection. Kabasakal et al.²⁸ and Uprimny et al.²⁹ demonstrated that early PET/CT pelvic imaging has better lesion detectability of lesions in the pelvis than in late images because of the low incidence of halo artifact in the bladder. Another study showed that PET/MR early acquisition has high lesion contrast with very good agreement for lesion detectability with same-day whole-body PET/CT. However, 95% LOAs in SUVpeak and MTV are far beyond the clinically acceptable range. Therefore, they suggested whole-body PET/CT and early PET/MR should not be used interchangeably¹⁹. Some studies compared conventional and delayed scans, and reported that detection rates were the same between 60 and 180 min, although improved contrast and an additional cancer focus was found, they concluded that delayed imaging has limited impact^{26,30}. However, Afshar-Oromieh et al.³¹ reported different results: compared with 1 h after injection, 3-h images revealed higher detection rates and more lesions, but these PET-positive lesions were not confirmed by histopathology.

PSA has a certain value for the identification of benign and malignant prostate lesions³. This study showed that the difference of fPSA/tPSA between benign and malignant groups is not statistically significant, while the differences of tPSA and fPSA between the two groups are statistically significant, but there are false positive and false negative results and the sensitivity and specificity are not as good as PSMA PET imaging. One study confirmed that SUVmax correlated significantly with PSA level²⁶. However, our results detected no correlation between tPSA, fPSA and SUVmax, while fPSA/tPSA was negatively correlated with SUVmax. Incomplete data maybe one reason and further study is needed.

Gleason score is a commonly used grading method for prostate cancer. However, we could not find any correlation between SUVmax of primary tumor and Gleason scores. The same results were also reported in two studies, due to inherent bias of the limited range of Gleason scores^{23,32}. Our results also showed lymph node and distant metastases presented in patients with low Gleason scores, so Gleason score cannot reflect clinical stage, the possible reason may due to underestimate of the actual Gleason score from biopsy in some patients. These results suggest that imaging techniques have better performance in the detection of prostate cancer than screening techniques such as PSA, DRE, and TRUS-guided biopsy.

Despite many studies reporting the advantages of PET/MR^{26,33–35}, its limitations include expense, a relatively long whole-body scanning time, low visibility of lung lesions, and challenges in patients with claustrophobia and metal implants. For patients in advanced stages of disease, PET/CT is enough because these patients have nodal and/or distant metastases which can be easily diagnosed by PET/CT only, and PET/CT is better for lung lesion detection, and more time-saving and economic than PET/MR. However, to accurately stage those patients without obvious lymph node or bone involvement, to differentiate BPH or prostatitis from early stage or PSMA-negative prostate cancer, pelvic PET/MR is required mainly because of the high soft tissue resolution of MR²⁰. PI-RADS 3 lesions are difficult to diagnose by MR only; PET/MR improves the detection of these patients through PET³⁶. Therefore, whole-body PET/CT with or without pelvic PET/MR would be a sufficient, time-saving method for initial diagnosis and accurate staging of prostate cancer, rational use of pelvic PET/MR for proper patients is important. In centers with both PET/CT and PET/MR, we recommend that all patients undergo PET/CT scanning first, and if lymph node and/or bone metastases are found, the patient can be diagnosed as advanced prostate cancer and PET/MR is not necessary. Otherwise, according to whether the image quality and prostatic lesion detectability were affected by activity of ⁶⁸Ga-PSMA from urine in bladder, pelvic PET/MR should be performed subsequently or at about 3 h post injection to further evaluate the prostate, surrounding tissue involvement, and small lymph nodes, if the patient has no contraindications. Undoubtedly, PET/MR provides superior diagnostic performance in local prostate cancer recurrence, especially biochemical failure, compared with ⁶⁸Ga-PSMA-617 PET/CT^{37–39}.

There are some limitations to the present study. First, the number of cases is relatively limited. Second, due to it being a retrospective study, some patients did not have a histopathology confirmation and Gleason score, they were diagnosed through comprehensive clinical evaluation and followup after treatment. Third, some data are not suitable for statistical analysis, such as the results of tPSA > 100 ng/L, fPSA > 30 ng/L in some patients. Fourth, the high proportion of advanced prostate cancer in this study may have affected the final results. Therefore, more patients with early prostate cancer should be included for prospective studies to further verify our conclusions.

Conclusion

This study confirmed that a combination application of PSMA whole-body PET/CT and pelvic PET/MR can accurately distinguish BPH/prostatitis from prostate cancer and accurately stage prostate cancer. Whole-body PET/CT is sufficient to diagnose advanced prostate cancer, and more economic and time-saving than PET/MR. The value of pelvic PET/MR is in the diagnosis and accurate staging of early prostate cancer. Conventional imaging at about 1 h is recommended with no need to perform delayed imaging for most patients. Further study with more early-stage prostate cancer patients and a prospective design is needed.

Declarations

Conflict of Interest Statement We declare that we have no conflict of interest to this work.

Ethics approval and consent to participate The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Union hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from individual participants.

Consent for publication Written informed consent for publication was obtained from all participants.

Not applicable.

Availability of data and material The datasets used in the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions

Chunxia Qin conducted the analyses and was a major contributor in writing the manuscript; Yongkang Gai and Qingyao Liu synthesized the radiopharmaceuticals and performed quality control; Weiwei Ruan and Fan Hu acquired PET/CT and PET/MR images; Fang Liu analyzed the images; Xiaoping Zhang provided clinical information of all patients; Xiaoli Lan conceived the idea and contributed to analysis and revision. All authors read and approved the final manuscript.

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Figures

Figure 1

A. A 65-year-old man with a total PSA level of > 1000 ng/L and free PSA > 30 ng/L underwent 68Ga-PSMA PET/MR, which revealed extensive bone metastases but negative uptake of PSMA in the prostate. B. A 64-year-old man with a total PSA level of 13.9 ng/L and free PSA of 2.15 ng/L underwent 68Ga-PSMA PET/CT, which showed uptake in multiple lymph nodes in the left supraclavicular area, retroperitoneum, and the left iliac chain. Prostate acinar adenocarcinoma with left iliac lymph node metastases (6/6) were histopathologically proven.

Figure 2

A. A 72-year-old man with a PSA level of 21.26 ng/L underwent 68Ga-PSMA PET/CT and delayed pelvic PET/MR. Positive PSMA uptake was revealed in the left peripheral zone, consistent with the signal change in mpMR. B. A 68-year-old man with proven prostate cancer in the right lobe underwent PET/MR for staging. Axial T2-weighted image shows an ill-defined hypointense lesion in the right peripheral zone with corresponding hypointensity on the apparent diffusion coefficient map. No significant hyperintense signal was observed on DW images ($b = 1000$ s/mm²). This was assigned a PI-RADS score of 4, but negative PSMA uptake was observed with diffuse 68Ga-PSMA uptake in the prostate (SUV_{max}, 4.10). C. A 71-year-old man with proven prostate cancer after prostate transurethral resection, 68Ga-PSMA PET/CT and pelvic PET/MR were performed for staging. PET/CT revealed only one small lymph node in the left pelvic cavity, which was revealed more clearly on PET/MR, and more lesions were revealed on PET/MR, which were proved to be metastases after surgery.

Figure 3

A. Scatter diagram of SUVmax from different scanner at different time point. B. Bland–Altman plots of the differences against the means of SUVmax1 with SUVmax2. C. Scatter plot and correlation of SUVmax1 and SUVmax2. D. Scatter plot and correlation of SUVmax1 and fPSA/tPSA.

Figure 4

ROC curves evaluating diagnostic performance of PSA levels and 68Ga-PSMA SUVmax

Figure 5

Diagnostic overview of all patients in this study.