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Evaluation of ^{18}F-PSMA-1007 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy

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ABSTRACT

Purpose: Prostate-specific membrane antigen (PSMA) ligands targeting has shown promising results in staging of prostate cancer (PCa). The aim of present study was to evaluate the value of ^{18}F-PSMA-1007 PET/CT in PCa patients with biochemical recurrence.

Methods: 71 patients with PCa after radical prostatectomy (RP) were included in the present study. Median prostate-specific antigen (PSA) level was 1.27 ng/mL (range 0.01–67.40 ng/mL, $n = 69$). All patients underwent whole-body PET/CT imaging after injection of 333±38 MBq ^{18}F-PSMA-1007. The distribution of PSMA-positive lesions was assessed. The influence of PSA level, androgen deprivation therapy and primary Gleason score on PSMA-positive finding and uptake of ^{18}F-PSMA-1007 were evaluated.

Results: 56 (79%) patients showed at least one pathological finding on ^{18}F-PSMA-1007 PET/CT. The rates of positive scans were 50%, 80%, 100%, 100% among patients with PSA levels ≤0.5, 0.51–1.0, 1.1–2.0 and >2.0 ng/mL, respectively. The median Gleason score was 8 (range 7–10), and higher Gleason score (≤7 vs. ≥8) leads to higher detection rates (58.3% (14/24) vs. 88.9% (32/36), $P = 0.006$). The median SUVmax of positive findings in patients with PSA levels ≤0.5, 0.51–1.0, 1.1–2.0 and >2.0 ng/mL were 4.51, 4.27, 11.50 and 14.08, respectively. The median SUVmax in patients with PSA level >2.0 ng/mL was significantly higher than that in patients with PSA ≤2.0 ng/mL (14.08 vs. 6.13, $P<0.001$).

Conclusion: ^{18}F-PSMA-1007 PET/CT demonstrated a high detection rate for patients with a raised PSA level after radical prostatectomy even in patients with extremely low PSA level (eg. PSA level ≤0.5 ng/mL), which was essential for further clinical management for PCa patients.

Introduction

Prostate cancer (PCa) is a common malignancy in men. Up to 53% men with prostate cancer have raised prostate-specific antigen (PSA) levels after radical treatments [1]. Some of these patients may develop to castration-resistant prostate cancer (CRPC) or nonmetastatic castration-resistant prostate cancer (nmCRPC) [2,3]. Early detection of recurrent disease provides possibility of a salvage treatment with curative intent. An increase of PSA-level may indicate the progression of PCa, but it cannot localize the clinical recurrence.

Morphological imaging modalities (e.g. computed tomography (CT), magnetic resonance imaging (MRI)) have limited value in detection of PCa lesions (metastases or recurrences) due to their low sensitivity and specificity [4]. Molecular imaging with ^{11}C-choline which was used to detect recurrent PCa exhibited superior sensitivity compared with conventional imaging modalities. However, the detection rates of

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recurrence in patients with PSA level <1 ng/ml was only 36% [5].

Thus, a new molecular probe targeting prostate-specific membrane antigen (PSMA) had been developed. Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein that is strongly overexpressed in PCa cells and barely expressed in benign prostate tissue [6, 7]. PSMA targeting positron emission tomography (PET) imaging was applied in PCa managements and suggested impressive results in detection of recurrent PCa and nmCRPC [8]. Imaging with the ^{68}Ga-labeled PSMA radioligand had significantly improved PCa diagnosis with the detection rates of 72.7% and 57.9% for patients with low (>0.5–1.0 ng/mL) and very low (0.2–0.5 ng/mL) PSAvalues [9].

However, ^{68}Ga ($t_{1/2}$ = 68 min) derived from ^{68}Ge/^{68}Ga generator elution has limited production batch yield compared to fluorine-18 (^{18}F, ($t_{1/2}$ = 109 min)) produced by cyclotron, which enable radiofluorinated PSMA tracers further distribution to satellite-centers. Radiofluorinated PSMA tracers might have more practical advantages in clinically settings of PCa biochemical relapse (BCR). ^{18}F- labeled PSMA compounds is becoming more and more popular in clinic [10,11].

Recently, ^{18}F-PSMA-1007 was reported a lot in PCa diagnosis. ^{18}F-PSMA-1007 is not metabolized through urine making it highly interesting for the differentiation of recurrent PCa from bladder urinalysis activity [12]. In the present study, we report the clinical value of ^{18}F-PSMA-1007 PET/CT in the setting of BCR.

Materials and methods

Patients

From October 2018 to December 2020, 125 PCa patients were examined with ^{18}F-PSMA-1007 PET/CT. Of these patients, 71 (median age 67 y, range, 51–80 y) were referred for the detection of recurrent PCa. All these patients presenting with rising serum PSA levels after radical prostatectomy (RP) were examined with ^{18}F-PSMA-1007 PET/CT. The study was conducted in accordance to the local regulations of China and was ethically approved by Ethics Committee of Sichuan Cancer Hospital (JS-2017–01–02). All patients signed a written informed consent form.

Radiosynthesis and quality control

^{18}F-PSMA-1007 was produced in an automated radiosynthesizer (Sumitomo corporation, Tokyo, Japan) according to the one-step procedure described previously [13]. PSMA-1007 precursor, dimethyl sulfoxide (DSMO) was obtained from ABX (Advanced Biochemical Compounds GmbH, Radeberg, Germany). PSMA-1007 precursor (2 mg, 1.2 mL) dissolved in anhydrous DSMO was then added into reactor and radiolabeling was performed at 85 °C for 10 min, then loaded the liquid onto PS-*H*+ and C18ec. Final product was eluted with 4 mL of 30% ethanol and sterile filtration yielded by 0.22 μm filter (Millipore, MA). High-performance liquid chromatography (HPLC, Shimadzu, Tokyo, Japan) and thin-layer chromatography (TLC, Eckert & Ziegler, MA) were performed to test radiochemical purity. Final product quality control including appearance, color, clarity and radionuclide purity was done and in compliance with acceptance criteria.

Imaging procedures

The patients received intravenously injection with a mean activity of 333±38 MBq (range 266–433 MBq). Scanning was performed 180 min after injection. Images were acquired by a PET/CT scanner (Biograph mCT-64, Siemens, Erlangen, Germany) from the lower limbs to the skull. First, low-dose (1.3–1.5 mSv) CT scan was performed for attenuation correction of PET emission data with tube voltage of 140 keV, pitch of 0.8. Following CT and three-dimensional (3-D) PET was acquired with an acquisition time of 2 min per bed position. Reconstruction method was ordered-subset expectation-maximization iterative reconstruction algorithm with 3 iterations/ 21 subsets.

Image analysis and quantification

All images were analyzed by two board-certified nuclear medicine physicians independently. Lesions with morphologic changes meanwhile high radiotracer uptake above normal surroundings were defined as positive lesions. Typical pitfalls in PSMA-PET imaging, such as ganglia, fractures, and degenerative changes, were observed but were not considered as positive lesions [14]. Lesions show high focal radiotracer uptake but without morphological changes were considered as pitfalls in PSMA ligand PET imaging. Identified positive lesions were grouped into: (a) local recurrences, (b) lymph nodes (LN) metastases, (c) bone metastases, (d) soft tissue metastases. Volumes of interest (VOI) were drawn using an maximum standardized uptake values (SUVmax) threshold of 42% [15]. VOI were placed on the region with highest uptake, and SUVmax for each region were measured and documented. A maximum of 5 regions were analyzed per patient.

Definition of ^{18}F-PSMA-1007 PET/CT disease

According to ^{18}F-PSMA-1007 PET/CT results, patients were found to have an isolated local recurrence or ≤3 non-visceral oligorecurrent lesions (either bone or nodal) were defined as low-volume disease. Conversely, the remaining patients with any distant metastasis were defined as high-volume disease [16].

Statistical analysis

Statistical analysis was performed through SPSS software, version 24.0 (IBM Corp.). Descriptive analysis was expressed by median, mean ±standard deviation. PSA and SUVmax between single groups were compared by Mann-Whitney U test for 2 independent samples. Pearson Chi-squared were used to compare percentage variables. $P<0.05$ was considered significant

Results

Patient findings

Among the 71 patients, none of them show adverse effects after injection of ^{18}F-PSMA-1007. The median time from RP to PSMA-PET of these patients was 15.0 months (range 1.0–131.0 months, n = 66). The minimum baseline PSA was 0.001 ng/mL. The median PSA level before treatments was 34.24 ng/mL (range 4.03–186.90 ng/mL, n = 60). The median lowest PSA level after treatments was 0.09 ng/mL (range 0.00–4.04 ng/mL, n = 51), and the median PSA level before PSMA-PET was 1.27 ng/mL (range 0.01–67.40 ng/mL, n = 69). The treatments were as follows. 1 (1/71, 1%) patient's treatment after RP was not clear. 24 (24/71, 34%) patients only received RP, while 39 (39/71, 55%) patients were treated with androgen deprivation therapy (ADT) after RP. 3 (3/71, 4%) patients received RP plus radiation beam therapy (1 patient was treated with radiation therapy from iliac crest metastasis, for others, salvage radiation therapy was given to the prostatic bed), and 4 (4/71, 6%) patients were treated with ADT and radiation therapy after RP. Patients' characteristics were listed in Table 1.

^{18}F-PSMA-1007 PET/CT findings

In total, PSMA-PET revealed 183 positive lesions. The median SUVmax for all lesions was 9.68 (range 1.83–106.18, n = 183). These lesions were composed by 18 (18/183, 10%) lesions of local relapse (Fig. 1 shows representative local recurrence) and 165 (165/183, 90%) metastases. The median SUVmax for lesions of local relapse was 15.67 (range 2.70–106.18, n = 18). Among these metastases, 100 (100/183, 54%) lesions attributed to lymph node metastases (Fig. 2 shows

Table. 1
Patients Characteristics.

Characteristic	Median (range)	No. of patients
Median age at PET/CT (y)	67 (51-80)years	71
Administered activity	333 (266-433) MBq	71
Time from RP to PSMA-PET	15.0 (1.0-131.0) months	66
PSA level before treatment	34.24 (4.03-186.90)	60
lowest PSA level after treatment	0.09 (0.001-4.04)	51
PSA level before PSMA PET/CT	1.27 (0.01-67.40)	69
Further treatment		
radical prostatectomy(RP)		24(24/71, 34%)
androgen deprivation therapy after RP		39(39/71, 55%)
radiation therapy after RP		3(3/71, 4%)
others		4(4/71, 6%)
Unknown		1(1/71, 1%)
Gleason(GS) score		
≤7		24(24/71, 34%)
≥8		36 (36/71, 51%)
Unknown		11 (11/71, 15%)

representative lymph node metastases), 60 (60/183, 33%) attributed to bone metastases (Fig. 3 shows representative bone metastases) and 5 (5/183, 3%) for soft tissue metastases. The corresponding median SUVmax was 9.95 (range 2.08–55.78, $n = 100$), 6.85 (range 1.83–63.10, $n = 60$) and 8.54 (range 4.46–19.84, $n = 5$), respectively. The median short diameter for lymph node metastases was 10 mm (range 5–30 mm).

All positive lesions were detected in 56 patients. Among them, 5 patients showed only local recurrence, 9 patients appeared exclusively lymph node metastases and 6 patients appeared exclusively bone metastases. Others detected metastases in more than two locations. ^{18}F-PSMA-1007 PET/CT detected 21 patients with low-volume disease, 35 patients with high-volume disease. The median PSA in patients with high-volume disease was significantly higher than that in patients with low-volume disease, 4.39 ng/mL (range 0.18–67.40 mg/mL) and 0.76 ng/mL (range 0.13–5.66 ng/mL), respectively ($P<0.001$). The SUVmax between the two groups showed significantly different, median SUVmax in low-volume disease group was 5.60 (range 1.83–55.70, $n = 33$), median SUVmax in high-volume disease group was 12.00 (range 2.11–106.18, $n = 150$), $P = 0.002$.

Influence of prostate-specific antigen

PSMA-positive lesions were detected in 56 (79%) patients. 2 patients' PSA level before PSMA-PET was not available. The detection efficacy for patients with PSA level >2.0 ng/mL, 1.1 to ≤2.0 ng/mL, 0.51 ng/mL to ≤1.0 ng/mL and ≤0.5 ng/mL was 100% (28/28), 100% (8/8), 80% (4/5) and 50% (14/28), respectively (Fig. 4). All patients with PSA

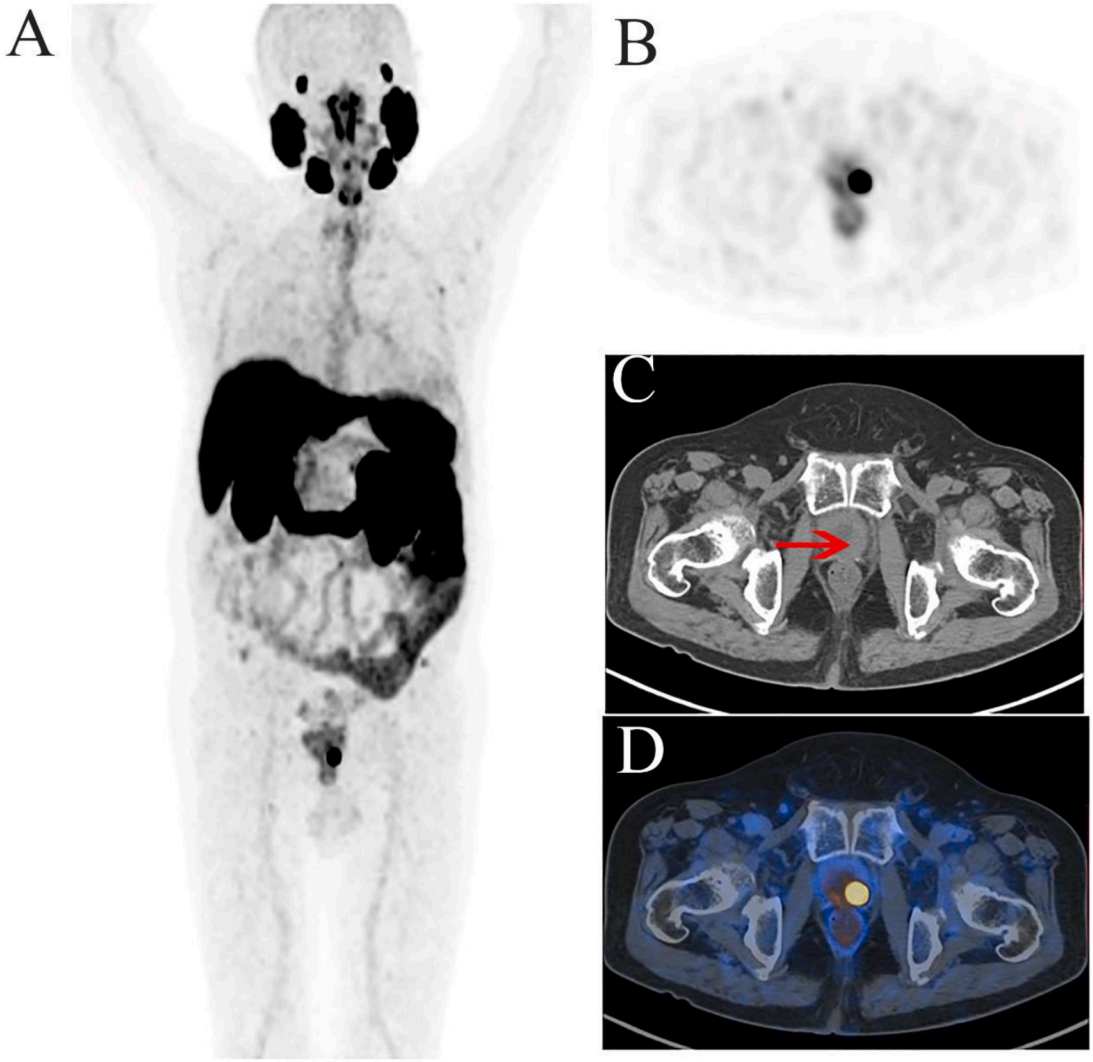

Fig. 1. Images from a 73-year-old patient after radical prostatectomy (2019; pT4), after antiandrogen therapy, and with PSA level rising to 0.45 ng/ml (July 2020). Patient underwent 18F-PSMA-1007 PET/CT, which suggested of local recurrence. (A) Maximum-intensity projection of 18F-PSMA-1007 PET/CT. It could be located in the posterior wall of bladder by CT image (C) and fused PET/CT images (D), and corresponding PET (B) show there is intense uptake.

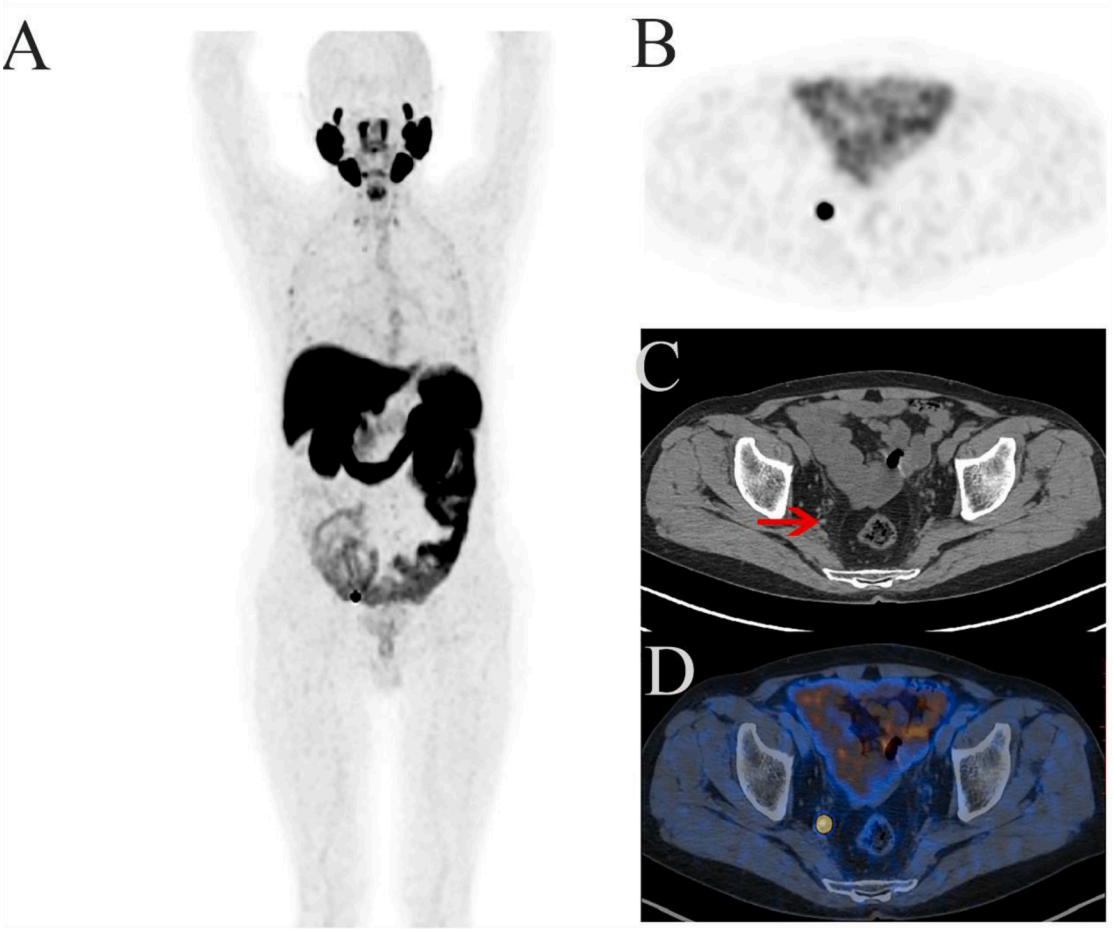

Fig. 2. Images from a 70-year-old patient after radical prostatectomy (2018; Gleason score of 9; pT3b), after antiandrogen therapy, and with PSA level rising to 0.18 ng/ml (November 2019). (A) Maximum-intensity projection of 18F-PSMA-1007 PET/CT shows intense tracer-associated uptake in the right pelvis. CT images (C) reveal lymph node metastases in region of right pelvis. Corresponding PET (B) and fused PET/CT images (D) show intense uptake.

>1.0 ng/mL (n = 36, 36/69, 52%) had positive PET/CT scans. In total, ^{18}F-PSMA-1007 PET/CT was negative in 15 patients, 1 patient with PSA level 0.51 ng/mL to ≤1.0 ng/mL and 14 patients with PSA level ≤0.5 ng/mL. The median PSA in patients with PSMA-positive findings was significantly higher than those patients with negative findings, median 2.16 ng/mL (range 0.13–67.40 ng/mL, n = 54) for patients with positive-PSMA scans, median 0.15 ng/mL (range 0.01–0.77 ng/mL, n = 15) for patients with negative findings (P = 0.002).

The median SUVmax of positive lesions in patients with PSA level ≤0.5, 0.51–1.0, 1.1–2.0 and >2.0 ng/mL was 4.51 (range 2.08–55.78), 4.27 (range 2.24–15.71),11.5 (range 2.64–106.18) and 14.08 (range 1.83–63.10), respectively. The median SUVmax in patients with PSA level >2.0 ng/mL was significantly higher than that in patients with PSA ≤2.0 ng/mL (14.08 (range 1.83–63.10) vs. 6.13 (2.08–106.18), P<0.001).

Influence of antiandrogen therapy and primary histologic differentiation

After RP, 24 patients did not receive another therapy while 39 patients received only ADT. The detection rates in patients with ADT was higher than that in patients without another therapy, 84.6% (33/39) vs. 66.7% (16/24), but this finding was not statistically significant, P = 0.096. The SUVmax between the two groups have significantly difference, median SUVmax in patients without another therapy was 6.15 (range 2.08–31.36, n = 38), median SUVmax in patients with ADT was 13.81 (range 1.83–106.18, n = 159), P = 0.007. PSA levels in patients with ADT was significantly higher than that in patients without another therapy, the median PSA was 2.49 (range 0.09–67.40, n = 38) and 0.34 (range 0.09–16.50, n = 23), respectively, P = 0.002.

11 patients without Gleason score (GS score) available, the others had a median GS score of 8 (range 7–10, n = 60). The detection rates in patients with GS score ≥8 was statistically higher than in patients with GS score ≤7 (58.3%(14/24) vs. 88.9%(32/36), P = 0.006). The SUVmax between the two groups have significant difference, median SUVmax in GS score ≥8 group was 10.36 (range 2.11–106.18, n = 111), median SUVmax in GS score ≤7 group was 6.58 (range 1.83–35.12, n = 38), P = 0.041. The corresponding PSA in the two groups was significantly different, with an median PSA of 0.35 (range 0.01–5.34, n = 23) in group of GS score ≤7 and an median PSA of 1.75 (range 0.09–67.40, n = 36) in group of GS score ≥8, P = 0.009 (Fig. 4).

Discussion

Recently, PSMA-PET becomes indispensable part in the management of PCa patients with overcoming the challenges of low sensitivity and specificity of conventional imaging modalities. This retrospective study mainly focused on evaluating the diagnosis value of ^{18}F-PSMA-1007 PET/CT in prostate cancer patients with biochemical recurrence.

In the present study, we found that ^{18}F-PSMA-1007 PET/CT exhibited a high sensitivity in detecting PSMA positive lesions. We successfully localized the recurrence for 56 patients, with the detection rates of 79% (56/71). These results were consistent with previous studies, indicating the sensitivity of ^{18}F-PSMA-1007 PET/CT in detecting patients with PSMA-positive lesions were 75–81% [17,18]. While ^{18}F-Choline and

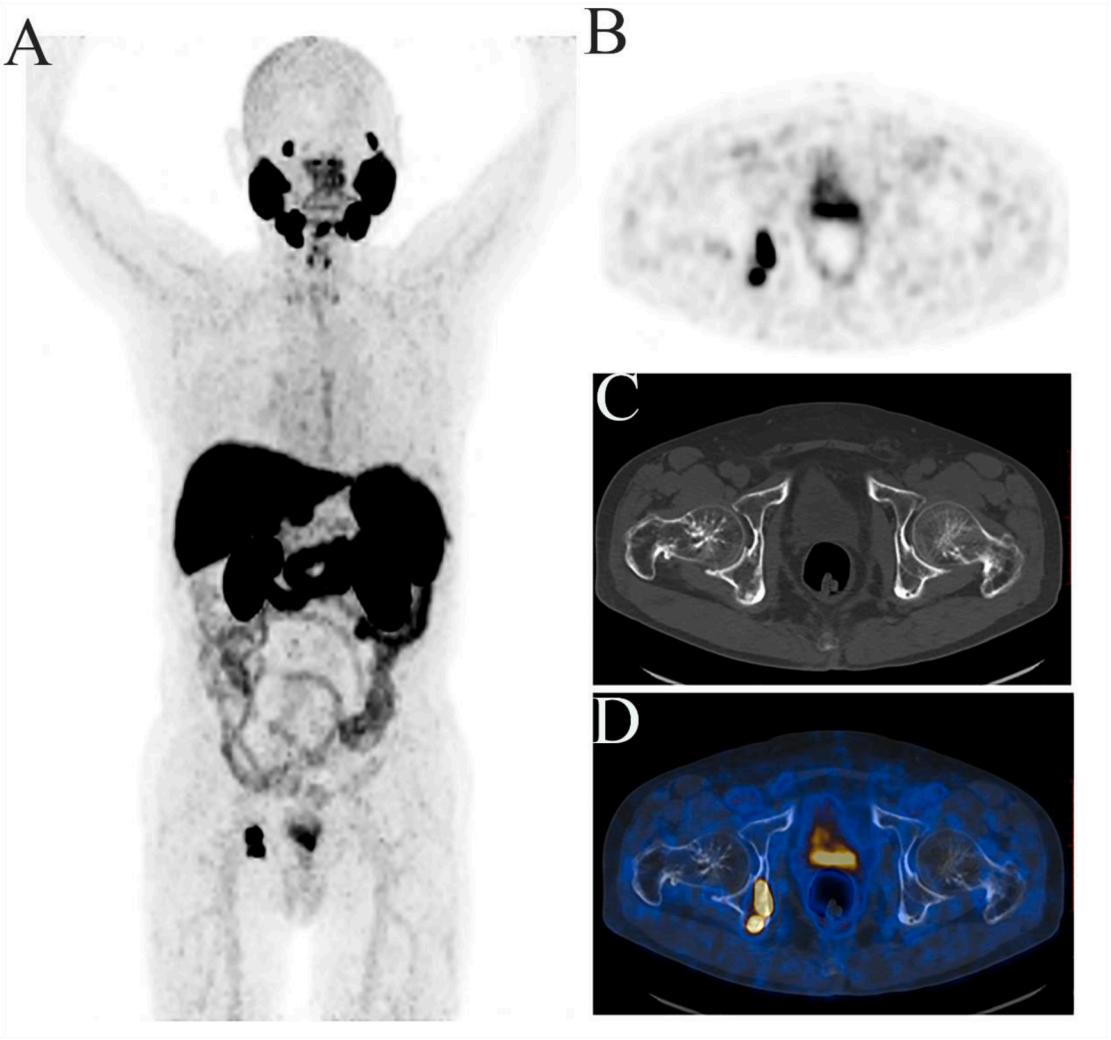

Fig. 3. Images from a 69-year-old patient after radical prostatectomy with PSA level rising to 0.34 ng/ml. (A) Maximum-intensity projection of 18F-PSMA-1007 PET/CT shows intense tracer-associated uptake in the right pelvis. CT images (C) reveal bone metastases in region of right ischium. Corresponding PET(B) and fused PET/CT images (D) show intense uptake.

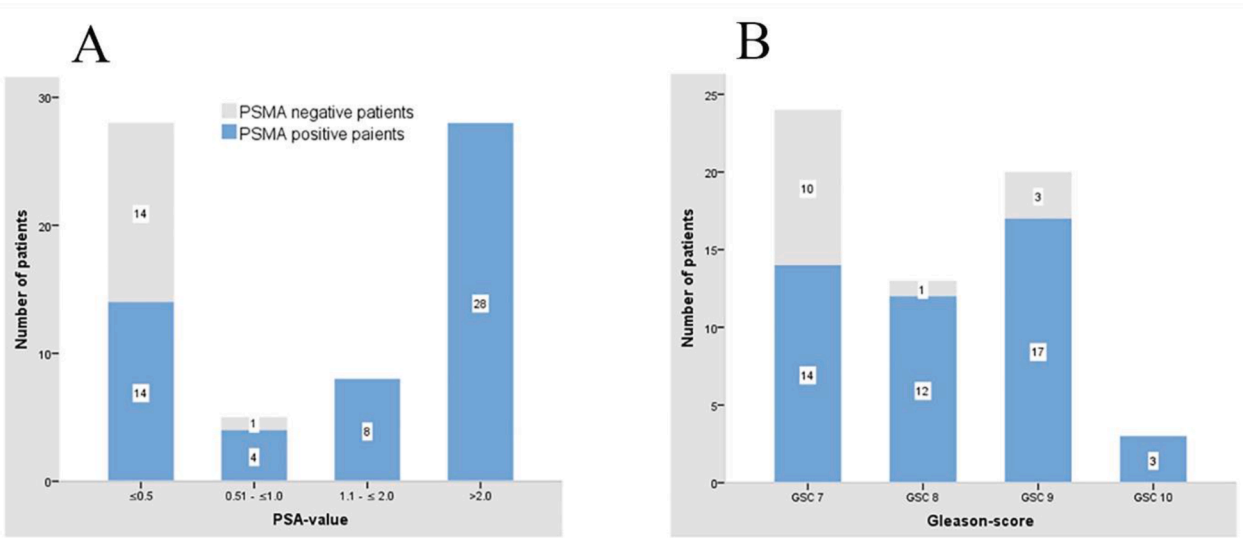

Fig. 4. (A) 18F-PSMA-1007 PET/CT scan in relation to PSA level in 69 patients. (B) 18F-PSMA-1007 PET/CT scan in relation to Gleason score in 60 patients. Blue columns show the number of patients with a positive 18F-PSMA-1007 PET/CT scan. gray columns show the number of patients with a negative PET scan (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

^{11}C-Acetate, radiotracers which were widely used in the localization of recurrence for PCa patients, were reported with the detection rates of 43%−79% and 59%−80%, respectively [19,20]

Furthermore, in our study postive lesions were found in all patients with PSA >1.0 ng/mL. However, a study involved 251 patients with biochemical relapse suggested that the detection rate for ^{18}F-PSMA-1007 PET/CT in patients with PSA>1.0 ng/mL was 93% (129/139) [18]. Other PSMA ligand radiotracer such as ^{68}Ga-PSMA-11 was reported to detect 95% (187/196) positive patients with PSA>1.0 ng/mL [9]. In the present study, we found the detection rate in patients with PSA 0.51 ng/mL to ≤1.0 ng/mL was 80%, which was higher than previous studies. Giesel et al. reported that the detection rate was 75% (35/47) for patients with PSA levels 0.51 ng/mL to ≤1.0 ng/mL in ^{18}F-PSMA-1007 [18]. Another study suggested for patients with PSA levels 0.51 ng/mL to ≤1.0 ng/mL in ^{68}Ga-PSMA-11 the detection rate was 73% (24/33) [9]. In the present study, we found 50% (14/28) patients with PSA ≤0.5 ng/mL showed more than 1 localized areas suggestive for recurrent PCa, meanwhile previous studies indicated that the detection rates in patients with PSA 0.21 ng/mL to ≤0.50 ng/mL was 62–86% [12,18], which were higher than our result. The relatively low detection rate in our study may correlate to relatively low PSA levels, and other study indicated that the higher PSA level leads to higher odds for a positive PSMA-PET scan [12]. The PSA level in our study was lower than that mentioned studies (≤ 0.50 ng/mL vs. 0.21–0.5 ng/mL), therefore, the corresponding detection rate in our study was lower. European Association of Urology suggested that biochemically recurrent prostate cancer patients after RP with PSA levels <0.5 ng/mL can be treated with salvage radiation therapy [1]. In the present study, the finding that ^{18}F-PSMA-1007 PET/CT detected 50% PCa patients with PSA ≤0.5 ng/mL for relapse provides the possibility of early salvage therapies.

In the present study, we found 183 lesions. The most frequent locations were as follows, 54% lesions attribute to lymph node metastases, 33% of lesions attribute to bone metastases, 10% lesions were local relapses and 3% were soft tissue metastases. These results were along with previous studies. Rahbar et al. suggested that when imaging with ^{18}F-PSMA-1007 local relapse was detected in 37% PCa patients [12]. While in the present study we found only 25% (18/71) patients with local relapse. The reason might due to fewer cases included in the present study. Localizing the recurrence, especially the detection of distant metastases, was crucial for further therapy. Local relapse can be treated with salvage radiation therapy, and patients with distant metastases may require systemic therapies. The using of ^{18}F-PSMA-1007 PET/CT in patients with rising PSA makes localizing the recurrence more convenient.

Consistent with previous studies, we found the median PSA value in patients with antiandrogen therapy was significantly higher than patients without another therapy. Furthermore, our study shows a trend that higher detection rate was found in patients with ADT exposure after radical prostatectomy. The reasons were as follows, it seems that patients who received antiandrogen therapy likely to have more advanced disease than patients without another therapy as they showed rising PSA levels despite antiandrogen therapy. Besides, higher PSA levels may lead to higher detection rates. It's not surprising to found the lower detection rates in patients without another therapy which had lower PSA levels.

Our study showed the detection rate and SUVmax in patients with GS score ≥8 were statistically higher than in patients with GS score ≤7. Similarity, Eiber et al. conducted a study about ^{68}Ga-PSMA-11 PET/CT scan in 248 patients and found higher GS score (≥8) may lead to higher PSMA-positive findings [9]. According to some preclinical studies, we found that the expression of PSMA was positively correlated with GS score [21,22]. In addition, a recent study indicated that lesions with higher Gleason score were more likely to be found higher immunohistochemically PSMA expressions [23]. In contrast to our group, Patena et al. found there seems to have no correlations between Gleason scores and ^{18}F-PSMA-1007 positive findings [12]. This phenomenon may be explained by the reason of only 40 patients were included in the mentioned study.

In the present study, we found that the median SUVmax in patients with PSA level >2.0 ng/mL was significantly higher than that in patients with PSA ≤2.0 ng/mL, which was consistent with Witkowska-Patena et al. [12]. Furthermore, we found the SUVmax between patients with ADT and patients without another therapy was significantly different. But the conclusion of ADT leads to higher SUVmax was controversial, some studies indicated that antihormonal treatment can increase the expression of PSMA, others believe ADT increasing PSMA expression excisted only initially [24,25]. Ongoing treatment can lead to decrease of tumor cells meanwhile ADT can increase the expression of PSMA, thus it's hard to say the final effect of ADT in the uptake of PSMA.

Recent studies show that PSMA-PET has a high potential in the diagnosis, staging and re-staging of prostate cancer, providing imaging basis for clinical management of prostate cancer patients [17,18,26]. Considering their similarity to PSMA-617, the overexpression of PSMA in recurrent PCa provides a possibility for the treatment of recurrent PCa with PSMA-617.

The lack of histopathologic confirmation of the detected lesions is the major limitation of this study, therefore, we cannot exclude false-positive lesions. The main reason is that many detected lesions were attribute to pelvic lymph node metastasis, which is difficult to biopsy. However, recent studies included histopathologic confirmation indicated that there seems to be a high correlation between PSMA-positive lesions and pathologically confirmed metastatic lesions. Giesel et al. showed that ^{18}F-PSMA-1007 PET/CT detected 18 of 19 metastatic lymph nodes confirmed by pathology with the sensitivity of 94.7%, which even metastases with a diameter as small as 1 mm was included [11]. Another limitation is that small patients was included in the present study, larger group of subjects will be include in the future.

The comparison between conventional scans and ^{18}F-PSMA-1007 PET/CT, and how does ^{18}F-PSMA-1007 PET/CT influence subsequent therapies of recurrent prostate cancer patients were both interesting topics. We will discuss them in future studies.

Conclusions

^{18}F-PSMA-1007 PET/CT demonstrated a high detection rate for patients with a raised PSA level after radical prostatectomy even in patients with extremely low PSA level. There seems to be a high correlation between PSA level, GS score and detection rate. PSA level, GS score and ADT may be important factors for the uptake of ^{18}F-PSMA-1007, however, this conclusion needs further verification.

CRediT authorship contribution statement

Xing Zhou: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Xiao Jiang:** Writing – review & editing, Funding acquisition. **Luzhou Liu:** Methodology, Data curation, Visualization. **Xiaoxiong Wang:** . **Chuan Li:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Yutang Yao:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Ying Kou:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Jiaqi Shen:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Taipeng Shen:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Zeng Li:** Funding acquisition, Data curation, Visualization. **Shengke Yang:** Funding acquisition, Data curation, Visualization. **Shukui Zhou:** Funding acquisition, Data curation, Visualization. **Hong Liao:** Funding acquisition, Data curation, Visualization. **Zhifu Luo:** . **Xiaoai Wu:** . **Shirong Chen:** Funding acquisition, Visualization. **Zhuzhong Cheng:** Supervision, Project administration, Writing – review & editing, Methodology.

CRediT authorship contribution statement

Xing Zhou: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Xiao Jiang:** Writing – review & editing, Funding acquisition. **Luzhou Liu:** Methodology, Data curation, Visualization. **Xiaoxiong Wang:** . **Chuan Li:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Yutang Yao:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Ying Kou:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Jiaqi Shen:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Taipeng Shen:** Funding acquisition, Data curation, Software, Visualization, Methodology. **Zeng Li:** Funding acquisition, Data curation, Visualization. **Shengke Yang:** Funding acquisition, Data curation, Visualization. **Shukui Zhou:** Funding acquisition, Data curation, Visualization. **Hong Liao:** Funding acquisition, Data curation, Visualization. **Zhifu Luo:** . **Xiaoai Wu:** . **Shirong Chen:** Funding acquisition, Visualization. **Zhuzhong Cheng:** Supervision, Project administration, Writing – review & editing, Methodology.

Declaration of Competing Interest

The authors have declared that no competing interest exists.

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