The added value of ^{18}F-FDG PET/CT compared to ^{68}Ga-PSMA PET/CT in patients with castration-resistant prostate cancer

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Disclosure

No potential conflict of interest was reported.

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ABSTRACT

Purpose: The ^{68}Ga-prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is a commonly used imaging modality in prostate cancers. However, few studies have compared the diagnostic efficiency between ^{68}Ga-PSMA and ^{18}F-FDG PET/CT and evaluated whether a heterogeneous metabolic phenotype (especially PSMA-FDG+ lesions) exists in patients with castration-resistant prostate cancer (CRPC). We determined the added value of ^{18}F-FDG PET/CT compared to ^{68}Ga-PSMA PET/CT in CRPC patients and identified CRPC patients who may benefit from additional ^{18}F-FDG PET/CT.

Methods: Data of 56 patients with CRPC who underwent both ^{68}Ga-PSMA and ^{18}F-FDG PET/CT from May 2018 to February 2021 were retrospectively analysed. Patients were classified into two groups with or without PSMA-FDG+ lesions. The differences in patient characteristics between the two groups and predictors of patients who having at least one PSMA-FDG+ lesion were analysed.

Results: Although both the detection rate (75.0% vs. 51.8%, P=0.004) and positive lesion number (135 vs. 95) of ^{68}Ga-PSMA PET/CT were higher than ^{18}F-FDG PET/CT, there were still 13/56 (23.2%) patients with at least one PSMA-FDG+ lesion. The prostate-specific antigen (PSA) and Gleason score were both higher in the patients with PSMA-FDG+ lesions than in those without PSMA-FDG+ lesions (P=0.04 and P<0.001, respectively). Multivariate regression analysis showed that the Gleason score (≥8) and prostate specific antigen (PSA, ≥7.9 ng/mL) were associated with the detection rate of patients who had PSMA-FDG+ lesions (P=0.01 and P=0.04, respectively). The incidences of having PSMA-FDG+ lesions in low-probability (Gleason score<8 and PSA<7.9 ng/mL), medium-probability (Gleason score≥8 and PSA<7.9 ng/mL or Gleason score<8 and PSA≥7.9 ng/mL), and high-probability (Gleason score≥8 and

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PSA≥7.9 ng/mL) groups were 0%, 21.7%, and 61.5%, respectively (P<0.001).

Conclusion: Gleason score and PSA are significant predictors for PSMA-FDG+ lesions, and CRPC patients with high Gleason score and PSA may benefit from additional ^{18}F-FDG PET/CT.

Keywords: ^{18}F-FDG; ^{68}Ga-PSMA; castration-resistant prostate cancer; negative PSMA

INTRODUCTION

Biochemical recurrence is a difficult problem after radical prostatectomy in prostate cancer (*1*). Androgen deprivation therapy (ADT) is the main treatment for biochemical recurrence. Despite inhibition of serum androgens, many patients develop castration-resistant prostate cancer (CRPC), and the tumour continues to grow, requiring multidrug therapy. Therefore, determining the location and degree of castration resistance is important to guide relevant treatment. However, the sensitivity of conventional imaging techniques such as magnetic resonance imaging and computed tomography (CT) (*2*) are limited. The application of ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) can significantly improve the imaging sensitivity in prostate cancer (*3-6*). Many studies have reported that the detection efficiency of ^{68}Ga-PSMA PET is higher than that of conventional imaging methods (*3,7*).

At the same time, the effect of ADT on detection efficiency of ^{68}Ga-prostate specific membrane antigen (PSMA) PET/CT has been controversial. Although some studies show that long-term use of ADT has no effect on ^{68}Ga-PSMA PET/CT, Afshar-Oromieh et al. found that use of long-term ADT could reduce the PSMA uptake and the visibility of tumour lesions in castration-sensitive prostate cancer (*8,9*). Weber et al. observed that ^{68}Ga-PSMA PET/CT were positive in 75% of early CRPC patients (*10*). These studies show that many CRPC patients might have negative ^{68}Ga-PSMA PET/CT findings. Although ^{18}F-FDG is not commonly used in prostate cancer because of its low diagnostic efficiency (*11*), Wang et al. (*12*) found that PSMA inhibition is associated with the up-regulation of glucose transporter 1 which is positively associated with higher ^{18}F-FDG uptake in CRPC. Several case reports have also shown that ^{18}F-FDG PET/CT could be positive in those with negative ^{68}Ga-PSMA PET/CT results (*13,14*). These findings have proven that ^{18}F-FDG PET/CT could be complementary to ^{68}Ga-PSMA PET/CT in partial CRPC patients

with the down-regulation of PSMA expression. However, few studies have compared the diagnostic efficiency between ^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET/CT in patients with CRPC.

Therefore, by incorporating dual-tracer (^{68}Ga-PSMA and ^{18}F-FDG) PET/CT, we conducted this retrospective study to evaluate whether a heterogeneous metabolic phenotype (especially PSMA-FDG+ disease) exists and whether incorporating ^{18}F-FDG PET/CT with ^{68}Ga-PSMA PET/CT has added value in diagnosis of CRPC patients.

MATERIALS AND METHODS

Patients

In Renji Hospital ^{68}Ga-PSMA and ^{18}F-FDG PET/CT were routinely concomitant performed in prostate cancer patients who were willing to undergo PET/CT. Fifty-six patients with CRPC were identified out of 605 patients with prostate cancer who received both ^{68}Ga-PSMA and ^{18}F-FDG PET/CT from May 2018 to February 2021 (Figure 1). Of these, 549 were excluded and 56 patients were finally included in this study. Table 1 shows the patient characteristics. The inclusion criteria were: Patients who (a) underwent radical prostatectomy and histopathologically proven prostate cancer; (b) showed PSA progression during ADT therapy; (c) underwent ^{68}Ga-PSMA and ^{18}F-FDG PET/CT at an interval of <14 days; and (d) those with available data of age, PSA, Gleason score, and ADT treatment. This retrospective study was approved by the Ethics Committee of Renji Hospital, and the requirement to obtain informed consent was waived.

^{68}Ga-PSMA and ^{18}F-FDG PET/CT

Patients were fasted for 6 h before receiving the ^{18}F-FDG injection. The dosage of ^{18}F-FDG injection was 3.7 MBq/kg. Patients need to keep quiet for 1 hour before ^{18}F-FDG PET/CT. The dosage

of ^{68}Ga-PSMA was 1.85 MBq/kg and the ligand of PSMA was ^{68}Ga-PSMA-11. ^{68}Ga-PSMA-11

synthesis was performed as previously described (*15*). PET/CT (Biograph mCT; Siemens) scan was

performed 50–60 min after injecting ^{68}Ga-PSMA. CT images (section thickness, 3 mm; automatic

milliamp current, 120 kV) were scanned from the upper thigh skull to skull. The scan time of

every bed position was 3 min for PET. For the better detection of local recurrence, forced diuresis with

additional late imaging was performed to reduce the retention of active urine in the bladder. Additional

late imaging was performed after 1.5 h of early imaging. Patients received 20 mg of furosemide and

an extra oral intake of at least 500 mL water. Patients were asked to void frequently. Additional late

imaging covered a range of two bed positions centered at the location of the bladder.

Image Evaluation

Two nuclear medicine physicians with 8 years (RC) and 12 years (JL) of PET/CT interpretation experience

evaluated the images. They evaluated the images independently. When discrepancies occurred, they

reached a consensus. According to interpretation guidelines (*16-19*), the experts evaluated the presence of

positive lesions in local recurrence, lymph node metastasis, and distant metastasis. After excluding

physiological uptake and other important pitfalls, ^{68}Ga-PSMA or ^{18}F-FDG positivity was defined as focal

avidity greater than the background of the mediastinal blood pool. Patients were considered to have

positive PET/CT results if local recurrence, lymph node metastasis, or distant metastasis had positive

lesions. PSA measurements, imaging examination, and biopsies were used for follow-up. We used

composite validation to verify these positive results.

Statistical Analysis

T-test or chi-squared test was used to evaluate the statistical significance of the correlation between

clinicopathologic characteristics in patients with or without PSMA-FDG+ lesion. Univariate and multivariate regression analyses were used to predict the detection rate of patients who had at least one PSMA-FDG+ lesion. All the data were analyzed by SPSS (version 13.0)

RESULTS

Characteristics of Enrolled Patients with CRPC

The mean age was 70 years (interquartile range [IQR]: 63–75 years), and the mean duration of ADT was 16.5 months. 57.1% (32/56) of patients had a Gleason score ≥8. The average PSA was 5.0 ng/mL (IQR: 1.5–14.5). The average interval between ^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET/CT was 7.0 days (IQR 1.0–12.0).

Detection Rate of ^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET/CT

There was perfect agreement between the two nuclear medicine physicians for ^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET/CT (both k coefficient = 0.97). 135 lesions were detected in 42 of the 56 patients by ^{68}Ga-PSMA PET/CT and 95 lesions were detected in 29 of the 56 patients by ^{18}F-FDG PET/CT (Table 2). Overall, 169 lesions were detected in 48 of the 56 patients by either ^{68}Ga-PSMA PET/CT, ^{18}F-FDG PET/CT, or both. The detection rate of CRPC per patient was significantly higher with ^{68}Ga-PSMA PET/CT than with ^{18}F-FDG PET/CT (75.0% vs. 51.8%, P=0.004) (Table 2). Using a head-to-head comparison of PSMA uptake and FDG uptake, we were able to classify every lesion into the PSMA+FDG+/- (PSMA+FDG+ or PSMA+FDG-) group or the PSMA-FDG+ group. Of the 169 lesions detected in 48 patients, 135 were PSMA+FDG+/- and 34 lesions were PSMA-FDG+. Among the 56 patients, 14.3% (8/56) patients had double negative results, 62.5% (35/56) patients had only PSMA+FDG+/-lesions, and 23.2% (13/56) patients had at least one PSMA-FDG+ lesions. Of the 8 patients with double negative results, the mean

PSA was 0.5 ± 0.3 ng/ml and the median Gleason score was 7 (7-8). The representative images of PSMA-FDG+ lesions and PSMA+FDG- lesions were shown in Supplemental Figure 1.

We validated the PSMA-FDG+ lesions with composite validation (Table 3). Among the 13 CRPC patients with PSMA-FDG+ lesions, two were verified by histopathology, two were verified by decreasing PSA levels after radiotherapy, and nine were verified by imaging. All the PSMA-FDG+ lesions were verified as being true positives.

The Relationship between Clinical Characteristics and Patients with or without PSMA-FDG+ Lesions

According to the above results, we found that although both the detection rate (75.0% vs. 51.8%, P=0.004) and positive lesion number (135 vs. 95) of ^{68}Ga-PSMA PET/CT were higher than those of ^{18}F-FDG PET/CT, there were still 13/56 (23.2%) patients with at least one PSMA-FDG+ lesion. We then divided patients into two groups according to those with at least one PSMA-FDG+ lesions (n=13) and those without (n=43). Table 4 describes the association between clinical characteristics and patients with or without PSMA-FDG+ lesions. There were no significant differences in age, scan interval, PSA doubling time, or ADT duration between the two groups. However, there were significant differences in PSA and Gleason scores between the two groups. Namely, patients with PSMA-FDG+ lesions had higher PSA than those without (20.8±8.3 vs. 7.5±2.5 ng/mL; P=0.04; Figure 2A); and patients with PSMA-FDG+ lesions had higher Gleason score than those without (9 [8-9] vs. 7 [7-9]; P<0.001; Figure 2B).

We then determined the optimal PSA threshold to predict at least one PSMA-FDG+ lesion in patients by using the ROC curve analysis. The highest accuracy (75.0%) was obtained when PSA was 7.9 ng/mL (Figure 3). We classified patients into low or high PSA groups (i.e., PSA<7.9 vs. PSA≥7.9 ng/mL).

The detection rate of patients with PSMA-FDG+ lesions was higher in the high PSA group than in the low PSA group (12.8% vs. 47.1%, respectively; P<0.001; Figure 2C).

We also found that the Gleason score was positively associated with patients with PSMA-FDG+ lesions (P=0.006). The detection rates of patients having PSMA-FDG+ lesions with Gleason scores of 6, 7, 8, and 9 were 0%, 0%, 33.3%, and 43.5%, respectively. We classified patients into a low or high Gleason score group (Gleason score <8 vs. ≥8). The detection rate of patients with PSMA-FDG+ lesion was higher in the high Gleason score group than in the low group (38.2% vs. 0%, respectively; P<0.001; Figure 2D).

Predictors of Patients with at Least One PSMA-FDG+ lesions

A multivariate regression analysis showed that PSA (OR, 4.7; 95%CI, 1.1–20.8; P=0.04) and Gleason score (OR, 3.2; 95%CI, 1.3–7.7; P=0.01) were significant predictors of patients with PSMA-FDG+ lesions (Table 5). According to Gleason score and PSA, we classified patients according to the incidences of having PSMA-FDG+ lesions: low-probability group (low Gleason score and low PSA), medium-probability group (low Gleason score and high PSA, or high Gleason score and low PSA), and high-probability group (high Gleason score and high PSA). The incidences of patients with PSMA-FDG+ lesions in the low-probability, medium-probability, and high-probability groups were 0%, 21.7%, and 61.5%, respectively (P<0.001).

Added Value of Staging by Incorporating FDG PET/CT with PSMA PET/CT

For staging (Table 6), the addition of FDG PET/CT could increase the detection rate of local recurrence, lymph node metastasis, distant metastasis, and any location from 14.3% to 19.6%, 42.9% to 55.4%, 35.7% to 39.3%, and 75.0% to 85.7%, respectively when compared with PSMA PET/CT alone. When patients were in a low-probability group, the addition of FDG PET/CT was unable to increase the

detection rate regardless of the local recurrence, lymph node metastasis, distant metastasis, or any location compared with PSMA PET/CT alone. However, when patients were in a high-probability group, the addition of FDG PET/CT could increase the detection rate of local recurrence, lymph node metastasis, distant metastasis, and any location from 0% to 7.7%, 30.8% to 61.5%, 53.8% to 61.5%, and 69,2% to 100%, respectively, when compared with PSMA PET/CT alone.

DISCUSSION

^{68}Ga-PSMA PET/CT has been widely used in the diagnosis and biochemical recurrence of prostate cancer. However, partial CRPC might have negative ^{68}Ga-PSMA PET/CT findings (*10,20*). For these patients, ^{18}F-FDG PET/CT may be a compensatory diagnostic method. Combined ^{68}Ga-PSMA and ^{18}F-FDG scanning has been reported in the later phase of CRPC (*21*). FDG-positivity has been used as an exclusion criterion prior to radioligand therapy or as an indicator for a poorer outcome after radioligand therapy (*21*). However, the patients scheduled for radioligand therapy are examined at a later stage of their carcinoma disease. In our study, using dual-tracer PET/CT (^{68}Ga-PSMA and ^{18}F-FDG), we retrospectively compared the diagnostic efficiency between ^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET/CT and evaluated the metabolic heterogeneity in patients who have just developed castration resistance. Although ^{68}Ga-PSMA PET/CT showed both higher detection rate and positive lesion number than ^{18}F-FDG PET/CT, we also identified patients with PSMA-FDG+ lesions, and incorporating ^{18}F-FDG PET/CT with ^{68}Ga-PSMA PET/CT had added value in the case of partial CRPC patients, especially in those with high PSA and high Gleason score.

Although both the detection rate (75.0% vs. 51.8%, P=0.004) and positive lesion number (135 vs. 95) of ^{68}Ga-PSMA PET/CT were higher than that of ^{18}F-FDG PET/CT, there were still 13/56 (23.2%) patients with at least one PSMA-FDG+ lesions. We identified 34 PSMA-FDG+ lesions from 13 patients. The

addition of ^{18}F-FDG PET/CT could increase the detection rate of local recurrence, lymph node metastasis, distant metastasis, and any location from 14.3% to 19.6%, 42.9% to 55.4%, 35.7% to 39.3%, and 75.0% to 85.7%, respectively compared with ^{68}Ga-PSMA PET/CT alone. These findings show that treatment could accordingly be administered for the PSMA-FDG+ lesions. For the local recurrent or solitary bone metastases, salvage radiotherapy (22) may be feasible for the PSMA-FDG+ lesions. For the recurrent lymph node metastases, salvage radiotherapy or salvage node dissection (23) could be taken for these PSMA-FDG+ lesions. For the patients with multiple lesions involved, systemic therapy may be the most appropriate treatment. However, the proportion of patients who had at least one PSMA-FDG+ lesion was only 23.2%. Therefore, identification of the most appropriate patients for ^{18}F-FDG PET/CT is essential to optimise its use and avoid expensive and possibly unnecessary staging in low-risk patients.

We studied the correlation between clinicopathologic characteristics and patients with or without PSMA-FDG+ lesions and found an excellent correlation between PSA and patients with PSMA-FDG+ lesions. Patients with PSMA-FDG+ lesions had higher PSA than those without PSMA-FDG+ lesions. The ROC analysis suggested that PSA could be used to predict PSMA-FDG+ lesions. Previous results have shown that the positive rate of ^{18}F-FDG PET/CT was associated with PSA value in the diagnosis of prostate cancer (11). Our study further demonstrated a positive correlation between PSA value and detection rate of patients with PSMA-FDG+ lesions. Except for PSA, we also found that there was a good association between Gleason score and the detection rate of patients with PSMA-FDG+ lesions. The high Gleason score group had a significantly higher detection rate of patients with PSMA-FDG+ lesions than those with low group in CRPC. Previous studies have shown that ^{18}F-FDG PET/CT has diagnostic value in prostate cancer with high Gleason score (11,24). Consistent with these previous results, our results further

suggest that Gleason score is an important predictor of patients with PSMA-FDG+ lesions. Our previous study (*25*) showed that ^{18}F-FDG PET/CT has added value in biochemical recurrent patients, which were different from this study including CRPC patients. In addition, the PSA level in PSMA-FDG+ patients was tendentially lower in CRPC patients when compared to the biochemical recurrent prostate cancer (*25*). This may be because the PSA level in patients with PSMA-FDG+ lesions were affected in the initial stage of ADT treatment, though these patients later developed resistance.

Although ^{18}F-FDG PET/CT has potential value in CRPC, its value-added mechanism is unclear. Porter et al. (*26*) found that PSMA inhibition is associated with up-regulation of glucose uptake-related genes, and is positively associated with higher ^{18}F-FDG uptake in PSMA-inhibited prostate cancer. Therefore, the added value of ^{18}F-FDG could be attributed to the amplification of glucose uptake-related genes after long-time ADT.

We classified CRPC patients according to their incidences of having PSMA-FDG+ lesions, based on Gleason score and PSA into low-, medium-, and high-probability groups. The probability of patients having PSMA-FDG+ lesions was 0% in the low-probability group but 61.5% in the high-probability group. When patients were in a low-probability group, the addition of FDG PET/CT was unable to increase the detection rate in any location when compared with PSMA PET/CT alone. However, when patients were in a high-probability group, the addition of FDG PET/CT could increase the detection rate of local recurrence, lymph node metastasis, distant metastasis, and any location from 0% to 7.7%, 30.8% to 61.5%, 53.8% to 61.5%, and 69.2% to 100%, respectively compared with PSMA PET/CT alone. These results suggest that ^{18}F-FDG PET/CT was not appropriate for those with low probability of having PSMA-FDG+ lesions, but was feasible for those with high probability of having PSMA-FDG+ lesions. For those with low probability

of having PSMA-FDG+ lesions, other imaging tracers should be further exploited.

The current study has some limitations including its retrospective design and small sample size. The number of patients with PSMA-FDG+ lesions was small, which may reduce the power of the multivariate regression analysis. In addition, though we found when PSA 7.9 ng/ml was used as the threshold, PSA could be used to predict PSMA-FDG+ lesions; the area under the curve was not particular high. So the association between PSA level and patients with PSMA-FDG+ lesion should be interpreted carefully. Therefore, prospective studies with a greater sample size are needed to further validate our findings. Furthermore, the lower detection rate of ^{68}Ga-PSMA PET/CT in our study (75.0%) compared to other studies (27) should also be interpreted carefully. This is possibly because the dosage of PSMA-11 in our study was on the lower end of the recommended spectrum (18), so the sensitivity may be influenced by relatively low dosage.

CONCLUSION

Our study assessed the added value of ^{18}F-FDG PET/CT compared to ^{68}Ga-PSMA PET/CT in CRPC patients. This study showed that ^{18}F-FDG PET/CT has additional value in 23.2% of CRPC patients, and Gleason score and PSA were significant predictors of PSMA-FDG+ lesions. CRPC patients with high Gleason score ($\geq$8) and PSA ($\geq$7.9 ng/mL) may benefit from ^{18}F-FDG PET/CT.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

KEY POINTS：

QUESTION： Did a heterogeneous metabolic phenotype (especially PSMA-FDG+ lesions) exist in patients with castration-resistant prostate cancer (CRPC) and ^{18}F-FDG PET/CT have the added value compared to ^{68}Ga-PSMA PET/CT in CRPC patient？

PERTINENT FINDINGS： Although both the detection rate (P=0.004) and positive lesion number of ^{68}Ga-PSMA PET/CT were higher than ^{18}F-FDG PET/CT, there were still 13/56 (23.2%) patients with at least one PSMA-FDG+ lesion. The incidences of having PSMA-FDG+ lesions in low-probability (Gleason score<8 and PSA<7.9 ng/mL), medium-probability (Gleason score≥8 and PSA<7.9 ng/mL or Gleason score<8 and PSA≥7.9 ng/mL), and high-probability (Gleason score≥8 and PSA≥7.9 ng/mL) groups were 0%, 21.7%, and 61.5%, respectively (P<0.001).

IMPLICATIONS FOR PATIENT CARE: Gleason score and PSA are significant predictors for PSMA-FDG+ lesions, and CRPC patients with high Gleason score and PSA may benefit from additional ^{18}F-FDG PET/CT.

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Figure and Figure Legends

Fig. 1 Patient recruitment flowchart

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┌─────────────────────────────────────────────────┐
│ Prostate cancer patients who underwent PSMA      │
│ PET/CT and ¹⁸F-FDG PET/CT from June 2018  to     │
│ February 2021.                                    │
│                    n = 605                        │
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┌─────────────────────────────────────────────────┐
│ PSA progression during androgen deprivation      │
│ therapy after radical prostatectomy at the time of│
│ imaging                                           │
│                    n = 66                         │
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┌─────────────────────────────────────────────────┐
│ The time interval between the two scans less than 14│
│ days                                              │
│                    n = 63                         │
└─────────────────────────────────────────────────┘
                         │
                         ▼
┌─────────────────────────────────────────────────┐
│ Patients with age, Gleason score, PSA  level, PSA │
│ doubling time, and postoperative treatment  were  │
│ available                                         │
│                    n = 56                         │
└─────────────────────────────────────────────────┘
                         │
                         ▼
┌─────────────────────────────────────────────────┐
│                   Whole cohort                    │
│                    n = 56                         │
└─────────────────────────────────────────────────┘
```
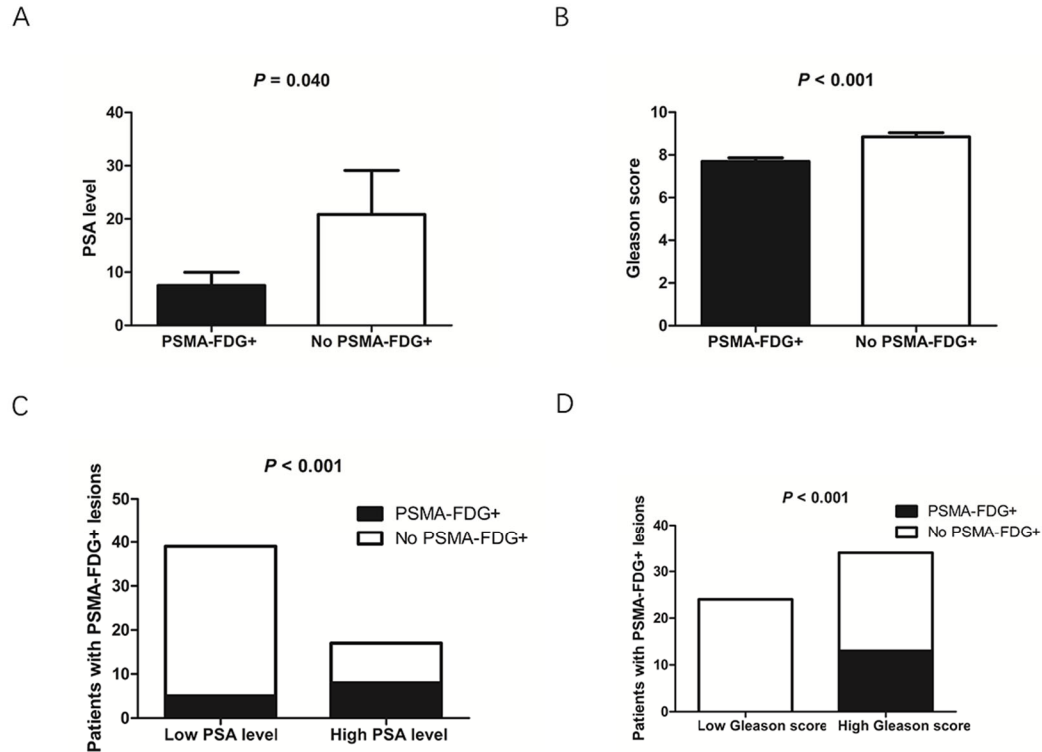
Fig. 2 Analysis of the PSMA-FDG+ lesions according to PSA and Gleason score.

(A) Patients with PSMA-FDG+ lesions had higher PSA than patients without PSMA-FDG+ lesions (20.8±8.3 vs. 7.5±2.5 ng/mL; P=0.04).

(B) Patients with PSMA-FDG+ lesions had higher Gleason score than those without PSMA-FDG+ lesions (8.8±0.2 vs. 7.7±0.2; P<0.001).
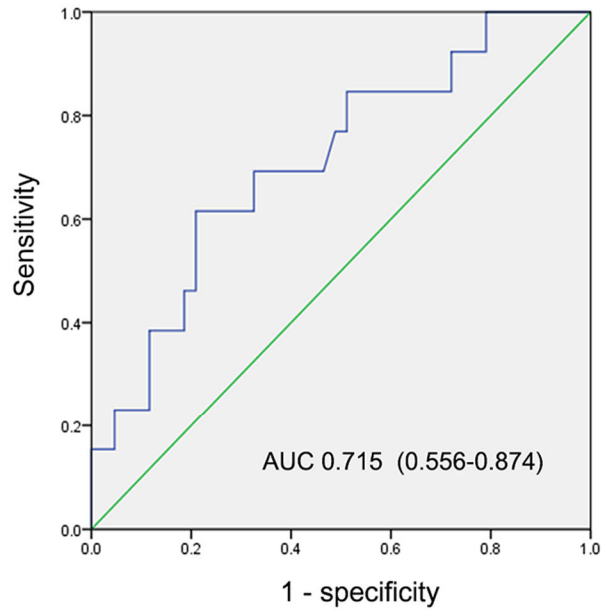
(C) The detection rate of patients with PSMA-FDG+ lesions was higher in the high PSA than the low PSA group (12.8% vs. 47.1%, respectively; P<0.001).

(D) The detection rate of patients with PSMA-FDG+ lesion was higher in the high Gleason score group than the low group (38.2% vs. 0%, respectively; P<0.001).

Fig. 3 PSA for predicting patients with PSMA-FDG+ lesions in CRPC patients.

The area under curve was 0.715 (95% CI, 0.556–0.874; P = 0.02), and a PSA of 7.9ng/mL was determined for predicting patients who having at least one PSMA-FDG+ lesion. The sensitivity and specificity for predicting at least one PSMA-FDG+ lesion were 61.5% (8/13) and 79.1% (34/43), respectively.

Table

Table 1. Patients and tumour characteristics (n=56)

Characteristics	
Age (y)	
Mean ± SD	69.6±7.0
Median （IQR）	70.0 (63.0-75.0)
PSA doubling time （months）	
Mean ± SD	7.9±6.4
Median （IQR）	5.8 (3.3-9.6)
PSA level （ng/ml)	
Mean ± SD	12.5±4.6
Median （IQR）	5.0 (1.5-14.5)
ADT duration time （months）	
Mean ± SD	25.5±4.0
Median （IQR）	16.5 （8.0-33.0）
Two scans interval (days)	
Mean ± SD	7.3±0.7
Median （IQR）	7.0 (1.0-12.0)
Gleason score	
6	4
7	20
8	9
9	23

Table 2. The absolute numbers and percentages of lesions detected by PSMA or FDG PET/CT

The absolute numbers and percentages of lesions	Tracer		P value
	^{68}Ga-PSMA	^{18}F-FDG	
The absolute numbers of positive lesions	135	95	0.020
The percentages of positive or negative findings			
Positive findings	42 (75%)	29 (51.8%)	0.004
Negative findings	14 (25%)	27 (48.2%)	

Table 3. PSMA-FDG+ lesions validation

Patients	Gleason score	PSA (ng/ml)	Number of lesions	Lesions with PSMA-FDG+ findings	Validated lesion	Validation methods
1	9	0.4	1	Bone	Bone	Conventional imaging
2	9	2.0	2	Pelvic lymph nodes	Pelvic lymph nodes	Conventional imaging
3	8	8.0	1	Bone	Bone	Conventional imaging
4	9	4.6	3	Pelvic lymph nodes	Pelvic lymph nodes	Conventional imaging
5	9	31.0	1	Bone	Bone	Conventional imaging
6	8	0.9	1	Bone	Bone	Conventional imaging
7	9	86.0	2	Pelvic lymph nodes	Pelvic lymph nodes	Conventional imaging
8	9	8.9	7	Pelvic lymph nodes, bone	Pelvic lymph nodes	[18]F-FDG PET/CT
9	9	18.4	1	Extrapelvic lymph nodes	Extrapelvic lymph nodes	[18]F-FDG PET/CT
10	8	2.1	1	Pelvic lymph nodes	Pelvic lymph nodes	PSA response after SBRT
11	9	84.7	2	Pelvic lymph nodes	Pelvic lymph nodes	PSA response after SBRT
12	8	8.0	10	Local recurrence, pelvic lymph nodes, inguinal lymph nodes, bone	Inguinal lymph nodes	Pathological confirmation
13	9	15.9	2	Pelvic lymph nodes and bone	Bone	Pathological confirmation

SBRT:stereotactic body radiotherapy; Conventional imaging: including CT, MRI or bone scintigraphy

Table 4. Relationship between clinicopathologic characteristics and patients with or without PSMA-FDG+ lesions

Variable	Total (n)	PSMA-FDG+ lesions		P value
		No	Yes	
Age （years）				
＜70	31	23	8	0.609
≥70	25	20	5	
PSA doubling time （months）				
＜6	29	22	7	0.203
≥6	27	24	3	
PSA level （ng/mL)	56	7.5 ± 2.5	20.8 ± 8.3	0.040
ADT duration time （months）	56	16.8±2.5	28.0±5.1	0.238
Two scans interval （days）	56	7.4±0.8	6.9±2.0	0.806
Median Gleason score (IQR)	56	7 (7-9)	9 (8-9)	＜0.001

**Table 5 Univariate and multivariate regression to predict PSMA-FDG+ lesions**

Variable and Intercept	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	P	OR (95% CI)	P
Age （years）	1.333(0.396-4.484)	0.642	NA	NA
PSA doubling time （months） （≥6 vs. ＜6）	0.721 （0.345-1.507）	0.416	NA	NA
PSA level (high vs. low)	6.0(1.6-23.0)	0.008	4.7(1.1-20.8)	0.04
ADT duration time	0.985(0.952-1.019)	0.375	NA	NA
Two scans interval （days）	0.986 （0.883-1.101）	0.802	NA	NA
Gleason score （High vs.low）	3.3(1.5-7.5)	0.004	3.2(1.3-7.7)	0.01

NA = not available. These variables were eliminated in the multivariate logistic regression model, so the odds ratio and P values were not available.

Table 6 Detection rate of local recurrence, lymph node metastasis and distant metastasis by PSMA PET/CT and FDG PET/CT

TNM stage	Number of patients (N)	Location	PSMA PET/CT N	%	FDG PET/CT N	%	PSMA&FDG PET/CT N	%
Total	56	Local recurrence	8	14.3%	5	8.9%	11	19.6%
		Lymph node metastasis	24	42.9%	14	25.0%	31	55.4%
		Distant metastasis	20	35.7%	17	30.4%	22	39.3%
		Any location	42	75.0%	29	51.8%	48	85.7%
Low risk	20	Local recurrence	3	15.0%	1	5.0%	3	15.0%
		Lymph node metastasis	11	55.0%	2	10.0%	11	55.0%
		Distant metastasis	6	30.0%	1	5.0%	6	30.0%
		Any location	16	80.0%	4	20.0%	16	80.0%
Moderate risk	23	Local recurrence	5	21.7%	3	13.0%	7	30.4%
		Lymph node metastasis	9	39.1%	6	26.1%	12	52.2%
		Distant metastasis	7	30.4%	7	30.4%	8	34.8%
		Any location	17	73.9%	14	60.9%	19	82.6%
High risk	13	Local recurrence	0	0.0%	1	7.7%	1	7.7%
		Lymph node metastasis	4	30.8%	6	46.2%	8	61.5%
		Distant metastasis	7	53.8%	8	61.5%	8	61.5%
		Any location	9	69.2%	11	84.6%	13	100%

Graphical Abstract
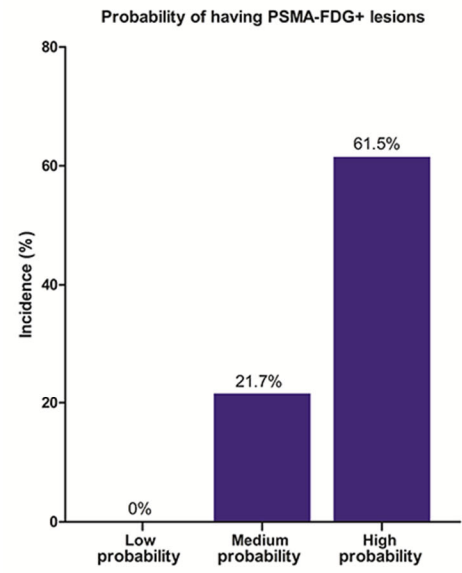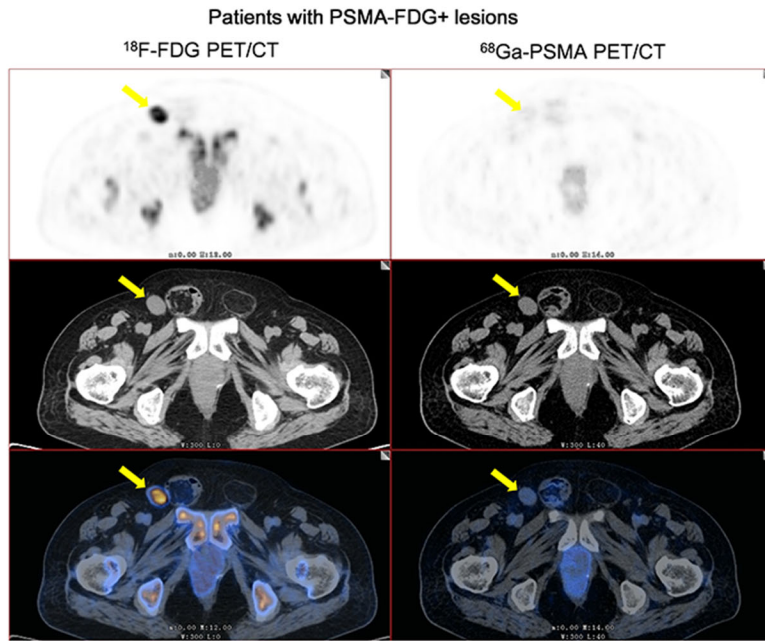
SUPPLEMENTAL FIGURE 1.

(A). The CRPC patients (Gleason score, 8) had a PSA of 8.0 at the time of imaging. Dual-tracer PET/CT detected PSMA-FDG+ lymph node (yellow arrow) on the right inguinal area. Lymph node dissection confirmed that this PSMA-FDG+ lesion was lymph node metastasis by histopathology.
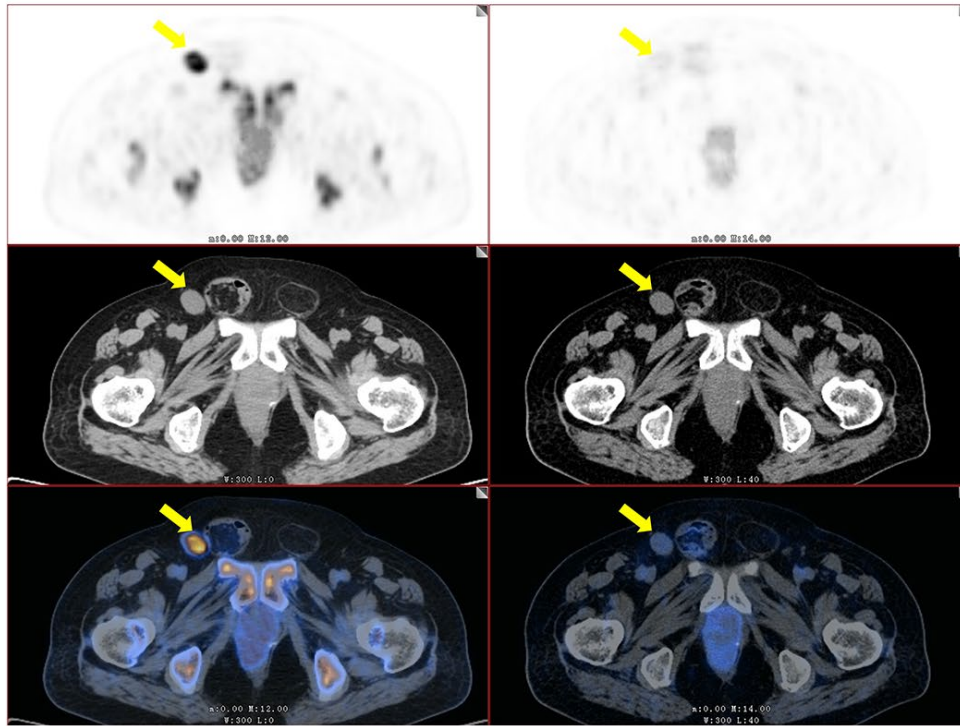
(B) The CRPC patients (Gleason score, 7) had a PSA of 0.3 at the time of imaging. Dual-tracer PET/CT detected PSMA+FDG- lymph node (yellow arrow) on the parailiac vessels. Lymph node dissection confirmed that this PSMA+FDG- lesion was lymph node metastasis by histopathology.

A   Patients with PSMA-FDG+ lesions

¹⁸F-FDG PET/CT   ⁶⁸Ga-PSMA PET/CT

B   Patients with PSMA+FDG- lesions

¹⁸F-FDG PET/CT   ⁶⁸Ga-PSMA PET/CT