

The Added Value of ¹⁸F-FDG PET/CT Compared with ⁶⁸Ga-PSMA PET/CT in Patients with Castration-Resistant Prostate Cancer

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⁶⁸Ga-prostate-specific membrane antigen (⁶⁸Ga-PSMA) PET/CT is a commonly used imaging modality in prostate cancers. However, few studies have compared the diagnostic efficiency between ⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT and evaluated whether a heterogeneous metabolic phenotype (especially ⁶⁸Ga-PSMA-negative [-], ¹⁸F-FDG-positive [+] lesions) exists in patients with castration-resistant prostate cancer (CRPC). We determined the added value of ¹⁸F-FDG PET/CT compared with ⁶⁸Ga-PSMA PET/CT in CRPC patients and identified CRPC patients who may benefit from additional ¹⁸F-FDG PET/CT. **Methods:** The data of 56 patients with CRPC who underwent both ⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT from May 2018 to February 2021 were retrospectively analyzed. The patients were classified into 2 groups: with or without ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions. The differences in patient characteristics between the 2 groups and predictors of patients who have at least 1 ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesion were analyzed. **Results:** Although both the detection rate (75.0% vs. 51.8%, $P = 0.004$) and the number of positive lesions (135 vs. 95) were higher for ⁶⁸Ga-PSMA PET/CT than for ¹⁸F-FDG PET/CT, there were still 13 of 56 (23.2%) patients with at least 1 ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesion. Prostate-specific antigen (PSA) and the Gleason score were both higher in patients with ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions than in those without ($P = 0.04$ and $P < 0.001$, respectively). Multivariate regression analysis showed that the Gleason score (≥ 8) and PSA (≥ 7.9 ng/mL) were associated with the detection rate of patients who had ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions ($P = 0.01$ and $P = 0.04$, respectively). The incidences of having ⁶⁸Ga-PSMA-, ¹⁸F-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 ($P < 0.001$). **Conclusion:** Gleason score and PSA are significant predictors of ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions, and CRPC patients with a high Gleason score and PSA may benefit from additional ¹⁸F-FDG PET/CT.

Key Words: ¹⁸F-FDG; ⁶⁸Ga-PSMA; castration-resistant prostate cancer; negative PSMA

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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 tumor 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 MRI and CT is limited (2). The application of ⁶⁸Ga-prostate-specific membrane antigen (PSMA) PET/CT can significantly improve imaging sensitivity in prostate cancer (3–6). Many studies have reported that the detection efficiency of ⁶⁸Ga-PSMA PET is higher than that of conventional imaging methods (3,7).

At the same time, the effect of ADT on the detection efficiency of ⁶⁸Ga-PSMA PET/CT has been controversial. Although some studies show that long-term use of ADT has no effect on ⁶⁸Ga-PSMA PET/CT, Afshar-Oromieh et al. and Hoberuck et al. found that use of long-term ADT could reduce ⁶⁸Ga-PSMA uptake and the visibility of tumor lesions in castration-sensitive prostate cancer (8,9). Weber et al. observed that ⁶⁸Ga-PSMA PET/CT was positive in 75% of early-CRPC patients (10). These studies show that many CRPC patients might have negative ⁶⁸Ga-PSMA PET/CT findings. Although ¹⁸F-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 upregulation of glucose transporter 1, which is positively associated with higher ¹⁸F-FDG uptake in CRPC. Several case reports have also shown that ¹⁸F-FDG PET/CT could be positive in those with negative ⁶⁸Ga-PSMA PET/CT results (13,14). These findings have proven that ¹⁸F-FDG PET/CT could be complementary to ⁶⁸Ga-PSMA PET/CT in partial-CRPC patients with the downregulation of PSMA expression. However, few studies have compared the diagnostic efficiency between ⁶⁸Ga-PSMA PET/CT and ¹⁸F-FDG PET/CT in patients with CRPC.

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

MATERIALS AND METHODS

Patients

In Renji Hospital, ⁶⁸Ga-PSMA and ¹⁸F-FDG PET/CT were routinely performed concomitantly in prostate cancer patients who were

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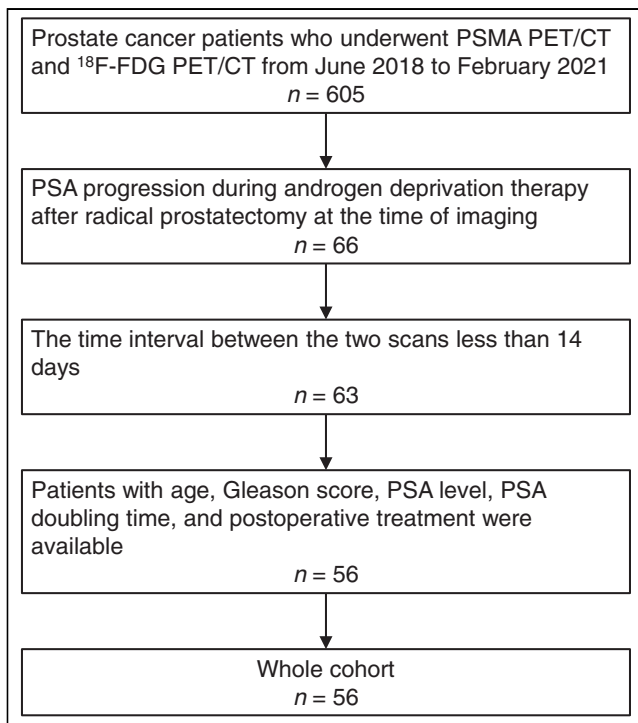


FIGURE 1. Patient recruitment flowchart.

willing to undergo PET/CT. Fifty-six patients with CRPC were identified of 605 patients with prostate cancer who underwent both ^{68}Ga -PSMA and ^{18}F -FDG PET/CT from May 2018 to February 2021 (Fig. 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 underwent radical prostatectomy, had histopathologically proven prostate cancer, showed prostate-specific antigen (PSA) progression during ADT therapy, underwent ^{68}Ga -PSMA and ^{18}F -FDG PET/CT at an interval of less than 14 d, and had available data on 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

The patients fasted for 6 h before receiving the ^{18}F -FDG injection, at a dose of 3.7 MBq/kg, and then remained quiet for 1 h before undergoing ^{18}F -FDG PET/CT. The dose of ^{68}Ga -PSMA was 1.85 MBq/kg, and the PSMA ligand was ^{68}Ga -PSMA-11, which was synthesized as previously described (15). A PET/CT scan (Biograph mCT; Siemens) was obtained 50–60 min after injection of the ^{68}Ga -PSMA. CT images (section thickness, 3 mm; automatic milliamp current, 120 kV) were obtained from the upper thigh to the skull. The PET scanning time for every bed position was 3 min. For better detection of local recurrence, forced diuresis with additional late imaging was performed to reduce retention of radioactive urine in the bladder. Additional late imaging was performed 1.5 h after early imaging. The patients received 20 mg of furosemide, drank at least 500 mL of water, and were asked to void frequently. Additional late imaging covered a range of 2 bed positions centered on the bladder.

Image Evaluation

Two nuclear medicine physicians with 8 and 12 y of PET/CT interpretation experience evaluated the images independently. When discrepancies occurred, they reached a consensus. In accord with interpretation guidelines (16–19), the experts evaluated the presence of positive lesions in local recurrence, lymph node metastasis, and

TABLE 1
Patient and Tumor Characteristics ($n = 56$)

Characteristic	Data
Age (y)	
Mean \pm SD	69.6 \pm 7.0
Median	70.0 (IQR, 63.0–75.0)
PSA doubling time (mo)	
Mean \pm SD	7.9 \pm 6.4
Median	5.8 (IQR, 3.3–9.6)
PSA level (ng/mL)	
Mean \pm SD	12.5 \pm 4.6
Median	5.0 (IQR, 1.5–14.5)
ADT duration time (mo)	
Mean \pm SD	25.5 \pm 4.0
Median	16.5 (IQR, 8.0–33.0)
Two-scan interval (d)	
Mean \pm SD	7.3 \pm 0.7
Median	7.0 (IQR, 1.0–12.0)
Gleason score	
6	4
7	20
8	9
9	23

IQR = interquartile range.

distant metastasis. After excluding physiologic uptake and other important pitfalls, ^{68}Ga -PSMA or ^{18}F -FDG positivity was defined as focal avidity greater than the background mediastinal blood pool. Patients were considered to have positive PET/CT results if positive lesions were seen in cases of local recurrence, lymph node metastasis, or distant metastasis. PSA measurements, imaging examinations, and biopsies were used for follow-up. We used composite validation to verify these positive results.

Statistical Analysis

t testing or χ^2 testing was used to evaluate the statistical significance of the correlation between clinicopathologic characteristics in patients with or without ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions. Univariate and multivariate regression analyses were used to predict the detection rate of patients who had at least 1 ^{68}Ga -PSMA-, ^{18}F -FDG+ lesion. All data were analyzed by SPSS (version 13.0; IBM).

RESULTS

Characteristics of Enrolled Patients with CRPC

The mean age was 70 y (interquartile range, 63–75 y), and the mean duration of ADT was 16.5 mo; 57.1% (32/56) of patients had a Gleason score of at least 8. The average PSA was 5.0 ng/mL (interquartile range, 1.5–14.5 ng/mL). The average interval between ^{68}Ga -PSMA PET/CT and ^{18}F -FDG PET/CT was 7.0 d (interquartile range, 1.0–12.0 d).

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

There was perfect agreement between the 2 nuclear medicine physicians for ^{68}Ga -PSMA PET/CT and ^{18}F -FDG PET/CT

TABLE 2
Absolute Numbers and Percentages of Lesions Detected by ⁶⁸Ga-PSMA or ¹⁸F-FDG PET/CT

Parameter	Tracer		P
	⁶⁸ Ga-PSMA	¹⁸ F-FDG	
Absolute numbers of positive lesions	135	95	0.020
Percentages of positive or negative findings			
Positive findings	42 (75%)	29 (51.8%)	0.004
Negative findings	14 (25%)	27 (48.2%)	

(both, $\kappa = 0.97$). ⁶⁸Ga-PSMA PET/CT detected 135 lesions in 42 of the 56 patients, and ¹⁸F-FDG PET/CT detected 95 lesions in 29 of the 56 patients (Table 2). Overall, 169 lesions were detected in 48 of the 56 patients by ⁶⁸Ga-PSMA PET/CT, ¹⁸F-FDG PET/CT, or both. The detection rate of CRPC per patient was significantly higher with ⁶⁸Ga-PSMA PET/CT than with ¹⁸F-FDG PET/CT (75.0% vs. 51.8%, $P = 0.004$) (Table 2). Using a head-to-head comparison of PSMA uptake and ¹⁸F-FDG uptake, we were able to classify every lesion into the ⁶⁸Ga-PSMA+, ¹⁸F-FDG+/- (⁶⁸Ga-PSMA+, ¹⁸F-FDG+ or ⁶⁸Ga-PSMA+, ¹⁸F-FDG-) group or the ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ group. Of the 169 lesions detected in 48 patients, 135 were ⁶⁸Ga-PSMA+, ¹⁸F-FDG+/- and 34 lesions were ⁶⁸Ga-PSMA-, ¹⁸F-FDG+. Among the 56 patients, 14.3% (8/56) patients had double-negative results, 62.5% (35/56) patients had only ⁶⁸Ga-PSMA+, ¹⁸F-FDG+/- lesions, and 23.2% (13/56) patients had at least 1 ⁶⁸Ga-PSMA-,

¹⁸F-FDG+ lesion. 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 (range, 7–8). The representative images of ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions and ⁶⁸Ga-PSMA+, ¹⁸F-FDG- lesions are shown in Supplemental Figure 1 (supplemental materials are available at <http://jnm.snmjournals.org>).

We verified the ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions with composite validation (Table 3). Among the 13 CRPC patients with ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions, 2 were verified by histopathology, 2 by decreasing PSA levels after radiotherapy, and 9 by imaging. All ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ lesions were verified as true-positive.

The Relationship Between Clinical Characteristics and Patients With or Without ⁶⁸Ga-PSMA-, ¹⁸F-FDG+ Lesions

Although both the detection rate (75.0% vs. 51.8%, $P = 0.004$) and the number of positive lesions (135 vs. 95) for ⁶⁸Ga-PSMA

TABLE 3
⁶⁸Ga-PSMA-, ¹⁸F-FDG+ Lesion Validation

Patients	Gleason score	PSA (ng/mL)	Lesions (n)	Lesions with ⁶⁸ Ga-PSMA-, ¹⁸ F-FDG+ findings	Validated lesion	Validation method
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	Pathologic confirmation
13	9	15.9	2	Pelvic lymph nodes and bone	Bone	Pathologic confirmation

Conventional imaging = CT, MRI, or bone scintigraphy; SBRT = stereotactic body radiotherapy.

PET/CT were higher than those for ^{18}F -FDG PET/CT, there were still 13 of 56 (23.2%) patients with at least 1 ^{68}Ga -PSMA-, ^{18}F -FDG+ lesion. We then divided patients into 2 groups according to those with at least 1 ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions ($n = 13$) and those without ($n = 43$). Table 4 describes the association between clinical characteristics and patients with or without ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions. There were no significant differences in age, scan interval, PSA doubling time, or ADT duration between the 2 groups. However, there were significant differences in PSA and Gleason score between the 2 groups. Namely, patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions had a higher PSA than those without (20.8 ± 8.3 vs. 7.5 ± 2.5 ng/mL; $P = 0.04$; Fig. 2A), and patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions had a higher Gleason score than those without (9 [range, 8–9] vs. 7 [range, 7–9]; $P < 0.001$; Fig. 2B).

We then determined the optimal PSA threshold to predict at least 1 ^{68}Ga -PSMA-, ^{18}F -FDG+ lesion in patients by using receiver-operating-characteristic curve analysis. The highest accuracy (75.0%) was obtained when PSA was 7.9 ng/mL (Fig. 3). We classified patients into low- or high-PSA groups (i.e., PSA < 7.9 vs. PSA \geq 7.9 ng/mL). The detection rate of patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions was higher in the high-PSA group than in the low-PSA group (12.8% vs. 47.1%, respectively; $P < 0.001$; Fig. 2C).

We also found that Gleason score was positively associated with patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions ($P = 0.006$). The detection rates of patients having ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions with Gleason scores of 6, 7, 8, and 9 were 0%, 0%, 33.3%, and 43.5%, respectively. We classified patients into groups with a low or high Gleason score (Gleason score < 8 vs. \geq 8). The detection rate of patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesion was higher in the high group than in the low group (38.2% vs. 0%, respectively; $P < 0.001$; Fig. 2D).

Predictors of Patients with at Least One ^{68}Ga -PSMA-, ^{18}F -FDG+ Lesion

A multivariate regression analysis showed that PSA (odds ratio, 4.7; 95% CI, 1.1–20.8; $P = 0.04$) and Gleason score (odds ratio, 3.2; 95% CI, 1.3–7.7; $P = 0.01$) were significant predictors of patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions (Table 5). According to

Gleason score and PSA, we classified patients for their probability of having ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions: a low-probability group (low Gleason score and low PSA), a medium-probability group (low Gleason score and high PSA, or high Gleason score and low PSA), and a high-probability group (high Gleason score and high PSA). The incidences of patients with ^{68}Ga -PSMA-, ^{18}F -FDG+ lesions in the low-, medium-, and high-probability groups were 0%, 21.7%, and 61.5%, respectively ($P < 0.001$).

Added Value of Staging by Incorporating ^{18}F -FDG PET/CT with ^{68}Ga -PSMA PET/CT

For staging (Table 6), 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%, from 42.9% to 55.4%, from 35.7% to 39.3%, and from 75.0% to 85.7%, respectively, when compared with ^{68}Ga -PSMA PET/CT alone. When patients were in a low-probability group, the addition of ^{18}F -FDG PET/CT could not increase the detection rate regardless of local recurrence, lymph node metastasis, distant metastasis, or any location, compared with ^{68}Ga -PSMA PET/CT alone. However, when patients were in a high-probability group, 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 0% to 7.7%, from 30.8% to 61.5%, from 53.8% to 61.5%, and from 69.2% to 100%, respectively, when compared with ^{68}Ga -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). ^{18}F -FDG positivity has been used as an exclusion criterion before radioligand therapy or as an indicator of 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

TABLE 4
Relationship Between Clinicopathologic Characteristics and Patients With or Without ^{68}Ga -PSMA-, ^{18}F -FDG+ Lesions

Variable	Total (n)	^{68}Ga -PSMA-, ^{18}F -FDG+ lesions		P
		No	Yes	
Age (y)				
<70	31	23	8	0.609
\geq 70	25	20	5	
PSA doubling time (mo)				
<6	29	22	7	0.203
\geq 6	27	24	3	
PSA level (ng/mL)	56	7.5 ± 2.5	20.8 ± 8.3	0.040
ADT duration time (mo)	56	16.8 ± 2.5	28.0 ± 5.1	0.238
Two-scan interval (d)	56	7.4 ± 0.8	6.9 ± 2.0	0.806
Median Gleason score	56	7 (IQR, 7–9)	9 (IQR, 8–9)	<0.001

IQR = interquartile range.

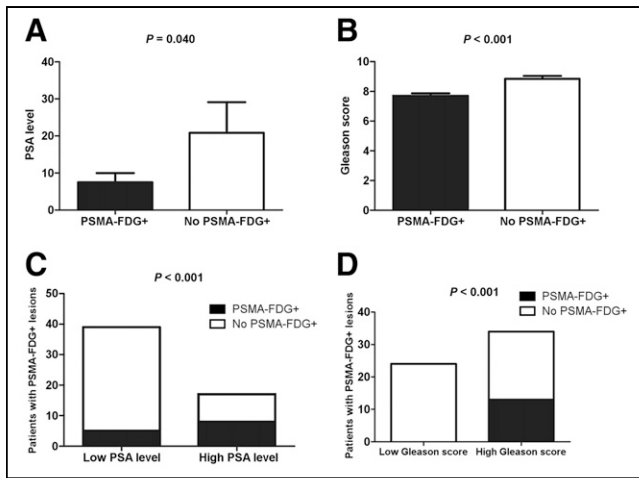


FIGURE 2. Analysis of ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions according to PSA and Gleason score. (A) Patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions had higher PSA than patients without ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions (20.8 ± 8.3 vs. 7.5 ± 2.5 ng/mL; $P = 0.04$). (B) Patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions had higher Gleason score than those without ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions (8.8 ± 0.2 vs. 7.7 ± 0.2 ; $P < 0.001$). (C) Detection rate for patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions was higher in high-PSA than low-PSA group (12.8% vs. 47.1%, respectively; $P < 0.001$). (D) Detection rate for patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesion was higher in high-Gleason score group than low-Gleason score group (38.2% vs. 0%, respectively; $P < 0.001$).

retrospectively compared 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 a higher detection rate and a higher number of positive lesions than ^{18}F -FDG PET/CT, we also identified patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -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 a high PSA and a high Gleason score.

Although both the detection rate (75.0% vs. 51.8%, $P = 0.004$) and the number of positive lesions (135 vs. 95) were higher for ^{68}Ga -PSMA PET/CT than for ^{18}F -FDG PET/CT, there were still 13 of 56 (23.2%) patients with at least 1 ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. We identified 34 ^{68}Ga -PSMA $^{-}$, ^{18}F -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%, from 42.9% to 55.4%, from 35.7% to 39.3%, and from 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 ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. For locally recurrent or solitary bone metastases, salvage radiotherapy (22) may be feasible for the ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. For recurrent lymph node metastases, salvage radiotherapy or salvage node dissection (23) could be used for these ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. For patients with multiple lesions involved, systemic therapy may be the most appropriate treatment. However, only 23.2% of patients had at least 1 ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesion. Therefore, identification of the most appropriate patients for ^{18}F -FDG PET/CT is essential to optimize its use and avoid expensive and possibly unnecessary staging in low-risk patients.

We studied the correlation between clinicopathologic characteristics and the presence or absence of ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$

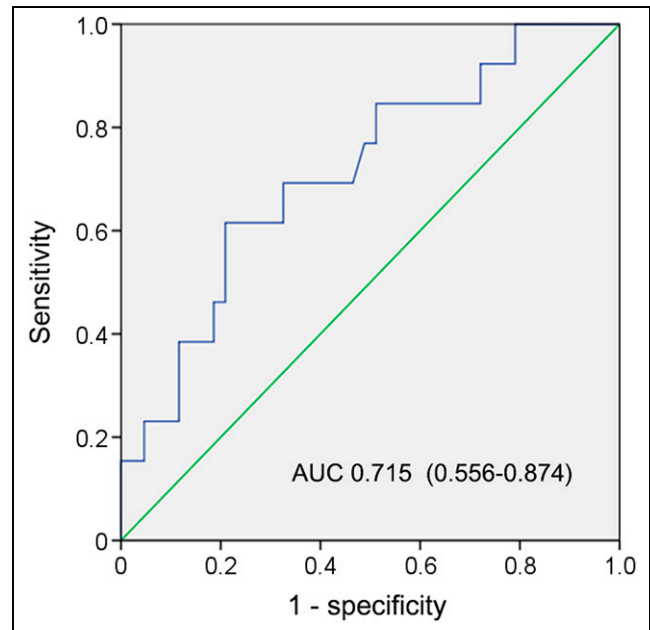


FIGURE 3. PSA for predicting ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions in CRPC patients. Area under curve (AUC) was 0.715 (95% CI, 0.556–0.874; $P = 0.02$), and PSA of 7.9 ng/mL was determined for predicting patients with at least 1 ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesion. Sensitivity and specificity for predicting at least 1 ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesion were 61.5% (8/13) and 79.1% (34/43), respectively.

lesions and found an excellent correlation between PSA and ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. Patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions had a higher PSA than did patients without. The receiver-operating-characteristic analysis suggested that PSA could be used to predict ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. Previous results have shown that the rate of ^{18}F -FDG PET/CT positivity was associated with PSA level in the diagnosis of prostate cancer (11). Our study further demonstrated a positive correlation between PSA and detection rate in patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. Aside from PSA, we also found that there was a good association between Gleason score and detection rate in patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. The group with a high Gleason score had a significantly higher detection rate of ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions than did the group with a low score in CRPC. Previous studies have shown that ^{18}F -FDG PET/CT has diagnostic value in prostate cancer with a high Gleason score (11,24). Consistent with these previous results, our results further suggest that Gleason score is an important predictor of patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions. Our previous study (25) showed that ^{18}F -FDG PET/CT has added value in patients with biochemical recurrence, who were different from the patients in this study, which included CRPC patients. In addition, the PSA level in ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ patients tended to be lower in CRPC patients than in patients with biochemically recurrent prostate cancer (25). This finding may be because the PSA level in patients with ^{68}Ga -PSMA $^{-}$, ^{18}F -FDG $^{+}$ lesions was 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. Bakht et al. (26) found that PSMA inhibition is associated with upregulation of glucose uptake-related genes and is positively associated with higher

TABLE 5
Univariate and Multivariate Regression to Predict ⁶⁸Ga-PSMA⁻, ¹⁸F-FDG⁺ Lesions

Variable and intercept	Univariate logistic regression		Multivariate logistic regression	
	OR	P	OR	P
Age (y)	1.333 (0.396–4.484)	0.642	NA	NA
PSA doubling time (≥6 mo vs. <6 mo)	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-scan interval (d)	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 multivariate logistic regression model, so odds ratio and P values were not available.

Data in parentheses are 95% CIs.

¹⁸F-FDG uptake in PSMA-inhibited prostate cancer. Therefore, the added value of ¹⁸F-FDG could be attributed to the amplification of glucose uptake-related genes after long-time ADT.

We classified CRPC patients according to their incidence of having ⁶⁸Ga-PSMA⁻, ¹⁸F-FDG⁺ lesions, based on Gleason score and PSA, into low-, medium-, and high-probability groups. The probability that patients would have ⁶⁸Ga-PSMA⁻, ¹⁸F-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 ¹⁸F-FDG PET/CT could not increase the detection rate at any location, when compared with ⁶⁸Ga-PSMA PET/CT alone. However, when patients were in a high-probability group, the

addition of ¹⁸F-FDG PET/CT could increase the detection rate of local recurrence, lymph node metastasis, distant metastasis, and any location from 0% to 7.7%, from 30.8% to 61.5%, from 53.8% to 61.5%, and from 69.2% to 100%, respectively, compared with ⁶⁸Ga-PSMA PET/CT alone. These results suggest that ¹⁸F-FDG PET/CT is not appropriate for those with a low probability of having ⁶⁸Ga-PSMA⁻, ¹⁸F-FDG⁺ lesions but is feasible for those with a high probability of having ⁶⁸Ga-PSMA⁻, ¹⁸F-FDG⁺ lesions. For those with a low probability of having ⁶⁸Ga-PSMA⁻, ¹⁸F-FDG⁺ lesions, other imaging tracers should be further explored.

The current study had some limitations, including its retrospective design and small sample size. The fact that the number of

TABLE 6
Detection Rate of Local Recurrence, Lymph Node Metastasis, and Distant Metastasis by ⁶⁸Ga-PSMA PET/CT and ¹⁸F-FDG PET/CT

TNM stage	Patients (n)	Location	⁶⁸ Ga-PSMA PET/CT		¹⁸ F-FDG PET/CT		⁶⁸ Ga-PSMA and ¹⁸ F-FDG PET/CT	
			n	%	n	%	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%

patients with ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesions was small may reduce the power of the multivariate regression analysis. In addition, though we found that when PSA 7.9 ng/mL was used as the threshold, PSA could predict ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesions, the area under the curve was not particularly high. Therefore, the association between PSA level and patients with ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesion should be interpreted carefully, and prospective studies with a larger 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%) than in other studies (27) should also be interpreted carefully. The dose of PSMA-11 in our study was on the lower end of the recommended spectrum (18) and may have influenced the sensitivity.

CONCLUSION

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

DISCLOSURE

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KEY POINTS

QUESTION: Does a heterogeneous metabolic phenotype (especially ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesions) exist in patients with CRPC, and does ^{18}F -FDG PET/CT have added value compared with ^{68}Ga -PSMA PET/CT in CRPC patient?

PERTINENT FINDINGS: Although both the detection rate and the number of positive lesions were higher for ^{68}Ga -PSMA PET/CT than for ^{18}F -FDG PET/CT, there were still 13 of 56 patients with at least 1 ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesion. The incidences of having ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesions in low-, medium-, and high-probability groups were 0%, 21.7%, and 61.5%, respectively ($P < 0.001$).

IMPLICATIONS FOR PATIENT CARE: Gleason score and PSA are significant predictors of ^{68}Ga -PSMA $-$, ^{18}F -FDG $+$ lesions, and CRPC patients with a high Gleason score and a high PSA may benefit from additional ^{18}F -FDG PET/CT.

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