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Description of FDG and Prostate-Specific Membrane Antigen PET/CT Findings in Korean Patients With Advanced Metastatic Castration-Resistant Prostate Cancer

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Objective: We aimed to describe the [^{18}F]fluorodeoxyglucose (FDG) and prostate-specific membrane antigen (PSMA) PET/CT findings in Korean men with advanced metastatic castration-resistant prostate cancer (mCRPC).
Materials and Methods: The results of paired FDG and PSMA PET/CT examinations performed in 42 consecutive men with prostate cancer for treatment planning after failure of anti-androgen therapy and chemotherapy were studied. Tumor lesions with FDG or PSMA uptake intensity higher than that of the liver on visual review were considered positive and noted per patient and tumor site (prostate bed, lymph node, bone, and visceral organ). The presence of unequivocally discordant FDG and PSMA uptake patterns in tumor lesions was assessed. Patients were grouped according to the total tumor volume as seen on each PET/CT scan, and the clinical findings between the patient groups were compared using the Mann-Whitney U test.
Results: On patient-based analysis, the image findings were PSMA+/FDG- in 2 patients, PSMA-/FDG+ in one, and PSMA+/FDG+ in 39 patients. On site-based analysis, the discordance (PSMA+/FDG- or PSMA-/FDG+) rate was 9.5% (4/42) for prostate/bed, 11.9% (5/42) for lymph nodes, 9.5% (4/42) for bones, and 11.9% (5/42) for visceral organs. FDG uptake was higher than PSMA uptake in at least one tumor site in 54.8% (23/42) of patients. Patients with greater total tumor volume on FDG PET/CT than that on PSMA PET/CT ("FDG-dominant pattern") accounted for 28.6% (12/42), and they had significantly shorter time from diagnosis (median 25 months vs. 62 months, $P = 0.049$), and higher aspartate aminotransferase (median 28.5 vs. 22.5, $P = 0.027$) and lactate dehydrogenase (median 341.5 vs. 224.5, $P = 0.010$) levels.
Conclusion: Most patients with advanced mCRPC had tumors with positive findings on both FDG and PSMA PET/CT. However, the uptake patterns varied; 54.8% of the patients had tumor(s) with FDG uptake greater than PSMA uptake, and FDG-dominant pattern was noted in 28.6% of the patients.
Keywords: Metastatic castration-resistant prostate cancer; PSMA; FDG; PET/CT

INTRODUCTION

Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer cells and has been a much-

studied target in prostate cancer [1]. Radiopharmaceuticals that bind to PSMA for diagnostic and therapeutic purposes have been developed, and clinical trials have shown remarkable results [2-4], leading to their rapid implementation in daily practice [5]. In contrast, [^{18}F]fluorodeoxyglucose (FDG) PET/CT with its wide-range of application in oncology had limited use in diagnosis of prostate cancer as malignant lesions can exhibit low FDG uptake because of their inherent biological properties [6,7]. Nonetheless, FDG uptake in prostate cancer is correlated with cancer aggressiveness and the overall prognosis [8]. Bauckneht et al. [9] demonstrated that metabolic tumor volume measured using FDG PET/CT serves as an independent predictor of overall survival in patients with prostate

cancer. At the cellular level, one study showed that an increase in the proliferation rate and migratory potential of primary prostate cancer cells is associated with enhanced FDG uptake and decreased PSMA retention [10].

Prostate cancer demonstrates a heterogeneous array of biological and clinical characteristics [11]. Although the incidence of prostate cancer is relatively low in Asia [12], it has been increasing recently in China, Japan, and Korea [13]. A significant proportion of 604 Korean men who underwent radical prostatectomy showed poor differentiation regardless of serum prostate-specific antigen (PSA) level or clinical stage and a greater rate of PSA failure in a multicenter study [14]. In addition, the incidence of high-grade or advanced-stage prostate cancer is reportedly higher in Korean men than in Caucasian men [15,16]. Black men with prostate cancer have shown worse outcomes for various reasons [17]. Although different clinical manifestations among racial groups have been studied, studies comparing the imaging findings of prostate cancer among Asians are scarce, especially in the field of molecular imaging.

Limited coverage issues of FDG PET/CT prevent its routine utilization for decision-making in patients with prostate cancer in Korea despite its prognostic potential; no study has compared FDG and PSMA uptake patterns in Asian men with advanced prostate cancer. PSMA PET/CT is a prerequisite prior to PSMA-targeting radioligand therapy (RLT); however, no current international consensus exists on the use of FDG PET/CT. The VISION trial did not require FDG PET/CT to be eligible for the study [3], and the supplementary data reported a relatively poor response in the Asian group. Owing to the few Asian participants (n = 15) in the VISION trial and insufficient information regarding ethnicity in other trials, it is unknown whether there is a true disparity in the response to RLT in Asian men. FDG and PSMA are two clinically available imaging biomarkers of prostate cancer that can guide treatment decisions; however, data regarding their dynamics in Korean men at advanced stages is unavailable. In this study, we aimed to describe the FDG and PSMA PET/CT findings in Korean men with advanced metastatic castration-resistant prostate cancer (mCRPC).

MATERIALS AND METHODS

Patients

Paired FDG and PSMA PET/CT images, collected consecutively between October 2022 and July 2023, were retrospectively reviewed. PET/CT studies assessed the

eligibility for PSMA-targeting RLT with [^{177}Lu]Ludotadipep [18] through clinical trials or expanded access programs in men with mCRPC who had evidence of progression after exhausting all therapeutic options, including anti-androgens and chemotherapy. Clinical data (age, time from initial diagnosis to PSMA PET/CT imaging, Gleason score, PSA level at the time of imaging, complete blood count, and blood chemistry profile) were collected from medical records. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (IRB Nos. KC20MDSF0483, KC22MDSS0440, and KC23MOSC0134).

FDG and PSMA PET/CT

After 6 hours of fasting, 284 ± 36 MBq of FDG was injected. No intravenous contrast agents were administered. Images were acquired using PET/CT scanner, Discovery 710 (GE Healthcare, Chicago, IL, USA) or Biograph TruePoint (Siemens Medical Solutions, Knoxville, TN, USA). CT began at the vertex and progressed to the upper thigh using the following standard protocol: 120 kV, 50 mA, 5 mm slice thickness (Biograph TruePoint); 120 kVp, variable mAs adjusted by topographic image, 2.5 mm slice thickness (Discovery 710). PET followed immediately over the same body region. The acquisition time was 2–3 minutes per bed position. CT data were used for attenuation correction, and PET images were reconstructed using standard ordered-subset expectation maximization. The same method was used to obtain PSMA PET/CT 90 minutes after the intravenous injection of 185 ± 19 MBq of [^{18}F]Florastamin (FutureChem, Seoul, Korea), a PSMA targeting diagnostic radiopharmaceutical [19].

Image Analysis

Lesions with FDG or PSMA uptake intensity higher than that of the liver on visual assessment were considered positive and noted for each patient and tumor site. Tumor sites were categorized as prostate bed, lymph nodes, bone, and visceral organ. The site was considered positive with at least one lesion with uptake higher than that of the liver at that site. The readers independently looked for lesions with FDG uptake intensity unequivocally higher than that of the PSMA uptake. Visual assessments were performed using the liver as the reference organ. Two readers reviewed the images together to reach a consensus in case of disagreement for uncertain lesions. The total tumor volumes from the FDG and PSMA PET/CT images were manually measured with a fixed threshold of SUV 4.0 using Mirada XD3 software (Mirada Medical, Oxford, UK). A

case was considered to be "FDG-dominant" when the total tumor volume computed from FDG PET/CT was greater than the volume computed from PSMA PET/CT by either 1) an absolute difference ≥50 mL, or 2) a factor ≥2. Guidelines on how to compute and compare tumor volumes using FDG and PSMA PET/CT remain nonexistent. The authors borrowed an arbitrary 50 mL absolute value from the threshold used to define a large prostate volume [20], and the relative volume factor was adapted from the PSA doubling time used in clinical practice to express tumor aggressiveness [21]. Additionally, the time from the initial diagnosis to PSMA PET/CT imaging (disease duration), Gleason score at staging, and laboratory parameters (PSA level, complete blood count, and blood chemistry profile) obtained within a week of PSMA PET/CT were retrieved. We compared the clinical findings between FDG-dominant patients and other patients using the Mann–Whitney U test. The statistically significant threshold was set at $P < 0.05$.

RESULTS

A total of 42 pairs of FDG- and PSMA-PET/CT studies were reviewed. Patient characteristics are shown in Table 1.

Of the 42 patients, 41 and 40 showed positive lesions on PSMA PET/CT and FDG PET/CT, respectively. On patient-based analysis, two patients revealed PSMA+/FDG- findings (no tumor with positive FDG uptake), one patient showed PSMA-/FDG+ (no tumor with PSMA uptake), and 39 patients showed PSMA+/FDG+ (one or more lesions positive on both images). On site-based analysis, the discordance (PSMA+/FDG- or PSMA-/FDG+) rates were 9.5% (4/42) for prostate beds, 11.9% (5/42) for LNs, 9.5% (4/42) for bones, and 11.9% (5/42) for visceral organs (Fig. 1).

Unequivocally higher FDG uptake than PSMA uptake in at least one tumor site was observed in 54.8% (23/42) of patients. Patients with a greater total tumor volume on FDG PET/CT than that on PSMA PET/CT, that is, FDG-dominant patients, accounted for 28.6% (12/42). The FDG-dominant group showed significantly shorter disease duration (median 25 months vs. 62 months, $P = 0.049$), higher AST (median 28.5 U/L vs. 22.5 U/L, $P = 0.027$), and higher LDH levels than their counter group (median 341.5 U/L vs.

Table 1. Patient characteristics

Characteristic	Value
Age, yrs	71.3 ± 8.9 (51–88)
Disease duration, mos*	63.6 ± 43.5 (9–162)
Prostate-specific antigen, mg/mL	363.5 ± 651.1 (2.4–3570)
Gleason score[†]	
7	8 (21)
8	8 (21)
9	18 (47)
10	4 (11)
Time between FDG and PSMA PET/CT, days	6.7 ± 8.4 (2–31)

Data are mean ± standard deviation (range) or number (%) of patients.
Available in 41* and 38[†] patients.
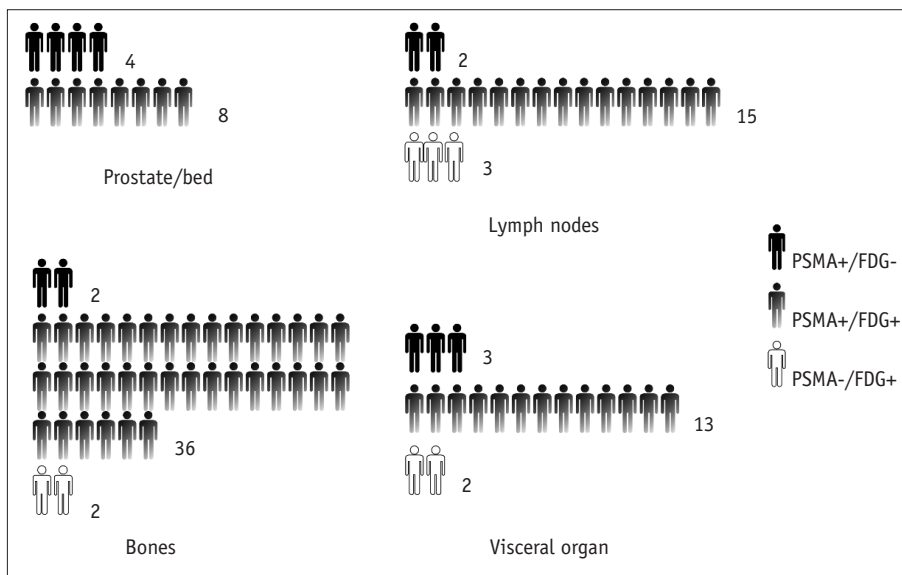FDG = [18F]fluorodeoxyglucose, PSMA = prostate-specific membrane antigen

Fig. 1. PSMA and FDG positivity per tumor site. PSMA = prostate-specific membrane antigen, FDG = [18F]fluorodeoxyglucose
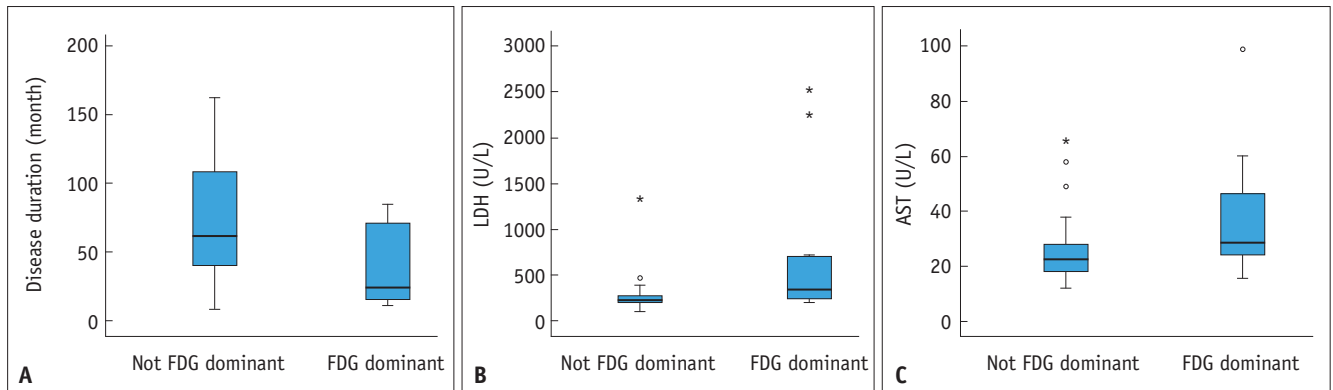
Fig. 2. Comparison of clinical findings between FDG-dominant and non-FDG-dominant patient groups. The FDG-dominant group shows a significantly shorter disease duration (**A**, $P = 0.049$) higher serum LDH (**B**, $P = 0.010$) and AST (**C**, $P = 0.027$) levels than non-FDG-dominant group (Mann–Whitney U, $P < 0.05$). °Outlier, *Extreme outlier. FDG = [^{18}F]fluorodeoxyglucose, LDH = lactate dehydrogenase, AST = aspartate aminotransferase
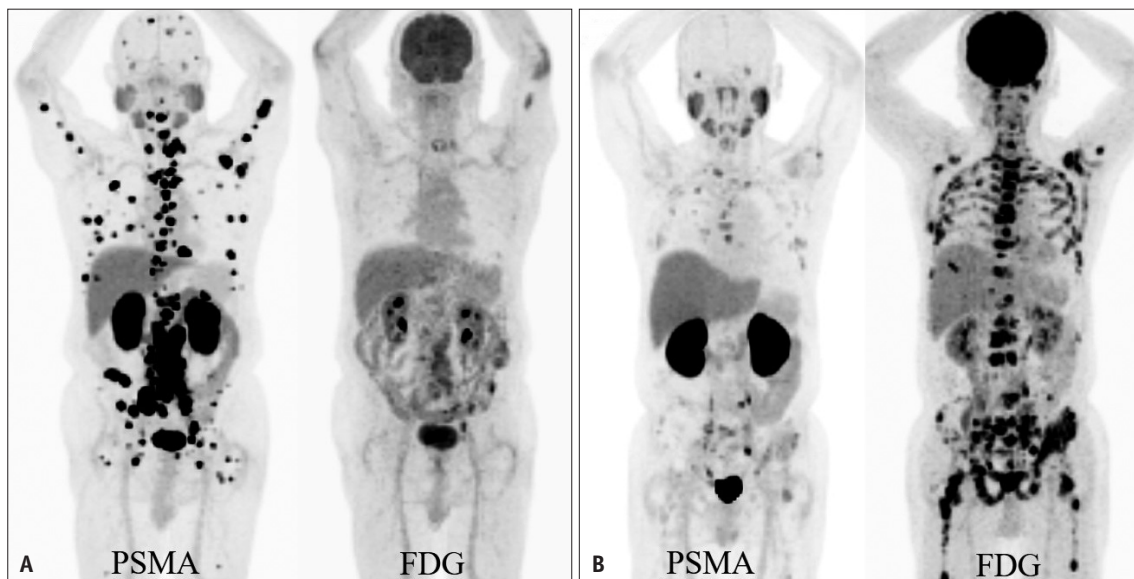

Fig. 3. Representative PSMA and FDG discordant cases. **A:** A 75-year-old prostate cancer patient with PSA 94 ng/mL shows multiple sites of positive uptakes in abdominopelvic lymph nodes and bones on both PSMA and FDG PET/CT images. The tumor volume was greater in PSMA PET/CT. The disease duration was 51 months, LDH 180 U/L and AST 20 U/L. **B:** A 59-year-old prostate cancer patient with PSA 106 ng/mL is positive on both PSMA and FDG PET/CT, but shows FDG-dominant tumor volume. Multiple bone lesions show low uptake on PSMA PET/CT. Intense uptake is noted in the pelvic lymph nodes, bones and lung nodule on FDG PET/CT. The disease duration was 17 months, LDH 718 U/L and AST 51 U/L. PSMA = prostate-specific membrane antigen, FDG = [^{18}F]fluorodeoxyglucose, PSA = prostate-specific antigen, LDH = lactate dehydrogenase, AST = aspartate aminotransferase

224.5 U/L, $P = 0.010$) (Fig. 2). Representative cases are shown in Figure 3.

DISCUSSION

In the current study of Korean patients with advanced mCRPC that progressed after standard anti-androgen and chemotherapy regimens, most patients exhibited positive findings on both PSMA and FDG PET/CT images. Upon analysis by tumor site, discordant PSMA and FDG positivity was observed in approximately 10% of patients. Comparing individual lesions, over half (23/42) of the patients included in this study cohort had at least one lesion that exhibited higher FDG uptake than PSMA uptake. Furthermore, considering the overall tumor volume, 12 of the 42 patients (28.6%) demonstrated predominance on FDG PET/CT.

While a few studies have compared the diagnostic performance of FDG and PSMA PET/CT for the staging or biochemical recurrence of prostate cancer [22,23], the patterns of uptake in the two PET/CT modalities in mCRPC

remain unclear. For decades, FDG PET/CT has been widely utilized to characterize various solid tumors; however, its role has been relatively limited in prostate cancer in Asian men. We aimed to fill this gap in the literature by examining the FDG uptake pattern, a known surrogate for tumor aggressiveness, and PSMA expression in Koreans. As demonstrated in our study, while most patients exhibited positive findings on both PSMA and FDG PET/CT, the patterns of uptake varied per individual and tumor site, which has implications for treatment planning.

PSMA-targeting RLT has been approved for adult patients with PSMA-positive mCRPC who progress from androgen receptor pathway inhibition to taxane-based chemotherapy [24]. In the VISION trial, FDG PET/CT was not required to select patients for treatment [3]. However, in the TheraP trial, PSMA and FDG PET/CT were used to assess treatment eligibility [2]. Although some patients who did not meet the eligibility criteria of the TheraP trial also showed response, patient selection using this criteria resulted in better treatment outcomes [25]. Despite its importance in the patient selection process, imaging criteria for PSMA-targeting RLT have not been studied in Korean men.

Reports have indicated the poor prognosis associated with GLUT expression in prostate cancer specimens obtained through surgery [26]. A recent study showed that patients with a metabolic tumor volume greater than 200 mL on FDG PET/CT had lower odds of PSA response after PSMA-targeting RLT [27]. In another study of patients with mCRPC undergoing RLT, those with at least one FDG+/PSMA- lesion at baseline had a significantly lower overall survival than patients without any discordant lesions [28]. In theory, a tumor lesion that is PSMA- will not respond to PSMA RLT, and FDG+ lesions have the potential to drive disease progression. These studies suggested that evaluating FDG uptake may be as important as examining PSMA overexpression before RLT.

In our study, patients with higher tumor volumes on FDG PET/CT had elevated levels of AST and LDH, and a shorter time from the diagnosis of prostate cancer to disease progression. In a previous study, elevated baseline LDH levels were associated with an increased risk of disease progression after RLT [29]. If the FDG-dominant pattern demonstrates biologically aggressive tumors, targeting PSMA alone may be insufficient to effectuate clinical benefits in approximately 29% of patients who are RLT candidates, as seen in this study cohort. This rate is somewhat higher than the 18% reported previously from Germany [30]; however,

a direct comparison is not possible because the definition of mismatch was different. Further studies are required to determine the true rate of discordance and whether the FDG-dominant group exhibits differences at the molecular and genetic levels.

The first limitation of this study is its single-center design with a small sample size. Second, as a surrogate for PSMA expression, we utilized Florastamin, a novel PSMA-targeting tracer with no in vivo data on its compatibility with the more widely used [^{68}Ga]Ga-PSMA-11 or [^{18}F]DCFPyL. However, direct comparison studies among various PSMA-targeting tracers are scarce, and it is generally agreed that a readily available PMSA-targeting tracer can be used to determine the feasibility of PSMA-targeted therapy [31]. Third, while we examined the associations between FDG and PSMA uptake patterns and certain clinical features, we did not directly correlate the imaging findings with actual patient treatment responses or survival outcomes at this stage. However, given the scarcity of reports on the imaging patterns in Korean patients with advanced mCRPC, our findings may serve as a basis for future prospective diagnostic and therapeutic studies.

In conclusion, most patients with advanced mCRPC in our study were positive on both PSMA and FDG PET/CT, and approximately half of the patients had tumor lesion(s) with higher FDG uptake than PSMA uptake. Approximately 29% of the patients exhibited a predominantly higher FDG volume overall, which may be associated with more aggressive clinical features. Therefore, it may be beneficial to conduct both PSMA- and FDG-PET/CT for treatment planning in Korean patients with advanced mCRPC.

Availability of Data and Material
The datasets generated or analyzed during the study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest
Joo Hyun O, who holds respective positions on the Editorial Board Member of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. Seunggyun Ha has consultant agreement with FutureChem. Joo Hyun O has consultant agreements with FutureChem and Novartis. The remaining authors have declared no conflicts of interest.

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Conceptualization: Joo Hyun O, Seunggyun Ha, In-Ho Kim. Data curation: Ji Youl Lee, Seunggyun Ha, Sae Jung Na. Formal analysis: Sae Jung Na. Funding acquisition: Joo Hyun O. Investigation: Sae Jung Na. Methodology: Sae Jung Na, Joo Hyun O. Project administration: Joo Hyun O. Resources: Ji Youl Lee, Seunggyun Ha, In-Ho Kim. Supervision: Joo Hyun O. Validation: Joo Hyun O. Visualization: Sae Jung Na. Writing—original draft: Sae Jung Na. Writing—review & editing: all authors.

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