ORIGINAL ARTICLE

Detection efficacy of PET/CT with ^{18}F-FSU-880 in patients with suspected recurrent prostate cancer: a prospective single-center study

Tomoaki Otani[1] · Tsuneo Saga[1] · Takayoshi Ishimori[1,2] · Eitaro Kidera[1] · Yoichi Shimizu[1] · Rihito Aizawa[3] · Kiyonao Nakamura[3] · Takayuki Goto[4] · Shusuke Akamatsu[4] · Takashi Mizowaki[3] · Yuji Nakamoto[1]

Abstract

Purpose Our objective was to investigate the efficacy of PET/CT with a novel prostate-specific membrane antigen (PSMA)-targeted PET probe, ^{18}F-FSU-880, for detection and localization of recurrent disease in prostate cancer patients in whom recurrence was suspected based on an increase in plasma prostate-specific antigen (PSA) levels after initial treatment.

Methods This study was a prospective institutional review board-approved study of 72 patients (age 56–84 years, PSA level 0.22–40.00 ng/ml) with suspected relapse of prostate cancer after primary therapy, including radical prostatectomy (RP) ($n = 35$) or radiation therapy (RT) ($n = 37$). Patients underwent PET/CT approximately 1 h and 3 h after injection of ^{18}F-FSU-880 (101.8–380 MBq). The correlation between patient-based detection rate and Gleason score (GS) of the primary tumor and plasma PSA levels at the time of PET/CT was evaluated. Maximum standardized uptake values (SUVmax) of the positive uptakes at 1 h post-injection were compared with those at 3 h post-injection.

Results In total, 51 patients (71%) showed at least one positive PSMA PET result. The PSA-stratified detection rates were 22% (2/9), 36% (4/11), 89% (16/18) and 85% (29/34) for PSA levels of 0.2 to < 0.5, 0.5 to < 1.0, 1.0 to < 2.0 and ≥ 2.0 ng/ml, respectively. The GS-stratified detection rates were 33% (2/6), 67% (16/24), 70% (16/23) and 89% (17/19) for GS 6, 7, 8 and 9, respectively. In lesion-based analysis, 157 positive lesions were detected at 3 h post-injection, 18 in the prostate or prostate bed, 65 in lymph nodes, 71 in the bone and 3 in the lung. Two local recurrences, eight pelvic lymph nodes and one distant lymph node were depicted only at 3 h post-injection. SUV max at 3 h post-injection was significantly higher than SUVmax at 1 h post-injection ($p < 0.001$).

Conclusion Our preliminary data suggest that ^{18}F-FSU-880 might be a promising new PSMA-targeting tracer for detecting recurrence after initial treatment in patients with prostate cancer.

Keywords Prostate cancer · PSMA · ^{18}F-FSU-880

Introduction

Prostate cancer is one of the most common cancers in men worldwide, and the number of newly diagnosed patients is increasing [1]. Despite initial therapy, biochemical recurrence (BCR) remains a commonly encountered sequel, occurring in up to 50% of cases within 10 years [2]. Early detection of recurrent disease might provide a chance for salvage therapy and improve prognosis. However, it is difficult to detect sites of recurrence by conventional imaging modalities, especially in patients with low plasma levels of prostate-specific antigen (PSA) [3]. Hence, there is need for improved diagnostic modalities.

✉ Yuji Nakamoto
ynakamo1@kuhp.kyoto-u.ac.jp

1. Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoinkawahara-cho, Sakyo-Ku, Kyoto 606-8507, Japan

2. Department of Radiology, Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan

3. Department of Radiation Oncology Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

4. Department of Urology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

The prostate-specific membrane antigen (PSMA) has received attention owing to its high levels of expression in prostate cancer cells [4], and the fact that the degree of PSMA expression increases with increasing tumor malignancy grade [5, 6]. A variety of PET/CT using ^{68}Ga- and ^{18}F-labeled PSMA inhibitors have been developed and achieved high detection rates in prostate cancer patients with BCR [7–16]. Recently, our group developed ^{18}F-FSU-880, a novel PET probe based on a PSMA-inhibitor labeled with ^{18}F [17]. Preclinical studies indicated that ^{18}F-FSU-880 possesses a seven times higher binding affinity for PSMA than ^{18}F-DCFPyL and shows a favorable pharmacokinetic profile with high accumulation in PSMA-expressing tumors [17]. In addition, we conducted PET/CT with ^{18}F-FSU-880 in six patients with metastatic prostate cancer. PET/CT with ^{18}F-FSU-880 could visualize metastatic lesions detected by conventional diagnostic tools, such as CT and bone scintigraphy, with no significant adverse effects [18]; however, its clinical efficacy is still to be investigated.

Therefore, the aim of this study was to investigate the efficacy of PET/CT with ^{18}F-FSU-880 for detection and localization of recurrent disease in more patients who were suspected to have recurrence based on an increase in plasma PSA levels after receiving initial treatment of prostate cancer.

Materials and methods

Patients

This study received the approval of the ethics committee of our institute (approval no. CRB5180002) and was registered in the Japan Registry of Clinical Trials (registration number jRCTs051180037). All patients provided written informed consent for participation in the study. All reported investigations were conducted in accordance with the Declaration of Helsinki and with national regulations.

The present study was conducted as a phase 2 clinical study of ^{18}F-FSU-880. We prospectively analyzed 72 patients (age 56–84 years, PSA level 0.22–40.00 ng/ml) who were referred for PET/CT with ^{18}F-FSU-880 from February 2019 to March 2021. Inclusion criteria were patients with prostate cancer (20–85 years) who were suspected as having recurrence due to an increase in plasma PSA levels after receiving initial definitive treatment. Patients were excluded if they had communication difficulty, severely compromised general condition or severe renal dysfunction that might alter the biodistribution of ^{18}F-FSU-880 (eGFR < 30 ml/min/1.73 m^2). The patients' characteristics are summarized in Table 1.

Table 1 Patients' characteristics

Characteristic	Data
No. of patients (n)	72
Primary therapy	
Radical prostatectomy	35
Radiation	37
Age (years)	56–84, median 71
Gleason score of the primary tumor	
Gleason 6	6
Gleason 7	24
Gleason 8	23
Gleason 9	19
PSA (ng/ml)	0.22–40.0, median 1.84

^{18}F-FSU-880 PET/CT

^{18}F-FSU-880 was prepared on a COSMiC-Compact 24XX automated synthesis module (NMP Business Support Co., Ltd., Hyogo, Japan), following previously published methods [17], and was filter-sterilized. The PET/CT studies were performed with an integrated PET/CT scanner (Discovery IQ; GE Healthcare, Waukesha, WI, USA) with a bismuth germanate scintillator arranged in five rings, and a 16-detector-row CT scanner. Low-dose CT was performed for attenuation correction and anatomic correlation without oral/intravenous (iv) contrast. Whole-body PET images were acquired from mid-thigh to the skull vertex at 1 h and 3 h after iv injection of ^{18}F-FSU-880 (101.8–380.0 MBq) as has been conducted by Afshar-Oromieh et al. [19] The acquisition time was 2 min per bed for 1 h post-injection and 3 min per bed for 3 h post-injection scans. Images were reconstructed using VuePoint HD, an ordered-subset expectation maximization (OSEM)-based algorithm (four iterations and 12 subsets).

Image analysis

All PET/CT images were reviewed on a dedicated workstation (Advantage Workstation v.4.6; GE Healthcare) by two board-certified nuclear medicine physicians (YN and TO). Any abnormal uptake greater than that of the surrounding background and not associated with physiologic uptake was considered positive, although positive lesions finally diagnosed as other disease by histology or additional imaging modalities were considered negative. In cases with equivocal findings or discrepancies, the final interpretation was decided at a consensus meeting. PET positive lesions were classified as local recurrence, lymph node metastases, bone metastases and metastases to other

organs. Lymph nodes located below the common iliac artery bifurcation were defined as pelvic lymph nodes, and those located above the common iliac artery bifurcation were defined as distant lymph nodes. For quantitative analysis, a volume of interest (VOI) was manually placed on a PET positive lesion to include the entire lesion and exclude any surrounding structures. Maximum standardized uptake value (SUVmax), defined as the highest regional uptake in each VOI, was calculated for each VOI. Up to five highest uptake lesions per organ were chosen for reliable analysis when there were six or more lesions in each organ.

Statistical analysis

All statistical analyses were performed with JMP version 14.0.0 software (SAS Institute, Cary, NC). A p value of less than 0.05 was considered statistically significant. For subgroup analysis, patients were divided into four groups depending on their PSA level: 0.2 to < 0.5, 0.5 to < 1.0, 1.0 to < 2.0 and ≥ 2.0 ng/ml. The correlations between patient-based detection rate and Gleason score of the primary tumor and PSA levels measured at the time of PET/CT were assessed. SUVmax values of the prostate cancer lesions at 1 h post-injection and 3 h post-injection were compared using the Wilcoxon signed rank test. Mann–Whitney U test was used to evaluate differences in plasma PSA levels between groups with and without pathologic positive uptake and between radical prostatectomy and radiation therapy cases. The Chi-squared test was used to determine whether the detection rate was dependent on initial treatment, PSA levels or GS.

Results

Comparison of SUVmax between the two phases

One hundred and fifty-seven positive lesions were detected at 3 h post-injection, while 146 lesions were detected at 1 h post-injection. Two local recurrences, eight pelvic lymph nodes and one distant lymph node were depicted only in the 3 h post-injection scan. Table 2 demonstrates comparisons of SUVmax between the two phases, excluding two unmeasurable lesions due to their location being too close to the bladder. SUVmax was higher at 3 h post-injection than at 1 h post-injection at all sites, with statistical significance ($p < 0.001$). Figure 1 shows the case with local recurrence depicted only at 3 h post-injection.

Table 2 SUVmax of the detected lesions at each phase

	n	1 h	3 h	p value*
Total	144	10.1 ± 10.6	16.7 ± 15.9	< 0.001
Local recurrence	14	6.5 ± 3.3	10.6 ± 5.4	< 0.001
Lymph node				
Pelvic	31	8.1 ± 8.0	13.3 ± 13.8	< 0.001
Distant	25	19.3 ± 17.1	29.7 ± 23.7	< 0.001
Bone	71	8.3 ± 7.5	15.2 ± 12.1	< 0.001
Other organ	3	10.2 ± 5.6	17.3 ± 9.4	0.125

*Wilcoxon signed rank test

Patient-based analysis

One case of positive uptake in the thoracic vertebra was later diagnosed as hemangioma based on the findings of MRI performed after PET/CT, and was hence considered negative. In total, 51 patients (71%) showed positive PSMA PET/CT results at 3 h post-injection. Local recurrences, pelvic lymph node metastases, distant lymph node metastases, bone metastases and other organ metastases were identified in 17 patients (24%), 18 patients (25%), 9 patients (13%), 13 patients (18%) and 3 patients (4%), respectively. Representative images of bone metastasis and pelvic lymph node metastasis are illustrated in Figs. 2 and 3, respectively.

The PSA-stratified detection rates were 22% (2/9), 36% (4/11), 89% (16/18) and 85% (29/34) for PSA levels of 0.2 to < 0.5, 0.5 to < 1.0, 1.0 to < 2.0 and ≥ 2.0 ng/ml, respectively (Fig. 4). When patients were divided into two groups by a cut-off value of plasma PSA of 1.0 ng/ml, there was a significant difference in the detection rates between the two groups: 87% (45/52) in patients with PSA levels above 1.0 ng/mL vs. 30% (6/20) in patients with PSA levels below 1.0 ng/ml ($p < 0.001$). In addition, the PSA value was significantly higher in patients with positive PET results than those with negative results [2.25 (0.25–40.00) vs. 0.85 (0.22–12.90), mean (range), $p < 0.001$].

The GS-stratified detection rates were 33% (2/6), 67% (16/24), 70% (16/23) and 89% (17/19) for GS 6, 7, 8 and 9, respectively (Fig. 5). When patients were divided into two groups according to GS, the detection rate in patients with GS of 8 and 9 tended to be higher than that in patients with GS of 6 and 7 [79% (33/42) vs. 60% (18/30)], although this difference was not statistically significant ($p=0.087$).

Lesion-based analysis

In total, 157 positive lesions were detected at 3 h post-injection, 18 in the prostate or prostate bed, 65 in lymph nodes, 71 in bones and three in the lungs. The distribution of positive lesions stratified by PSA levels is listed in Table 3. Local recurrences were not detected in patients with PSA levels
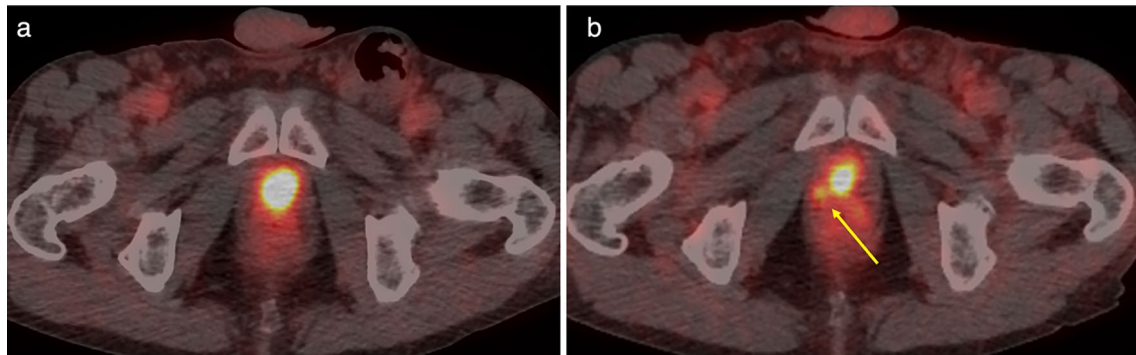
Fig. 1 ^{18}F-FSU-880 PET/CT scan images in a 79-year-old man with suspected recurrence after radical prostatectomy (RP) (Gleason score (GS) 4+4, PSA 1.00 ng/ml). ^{18}F-FSU-880 PET/CT showed focal uptake on the right side of the prostate bed only at 3 h post-injection (yellow arrow in b, SUVmax, 6.8). Radiation therapy (RT) was sub-sequently administered, which resulted in a decrease in PSA levels to 0.01 ng/ml. **a** Transaxial PET/CT fusion images at 1 h after injection; **b** transaxial PET/CT fusion images at 3 h after injection (color figure online)
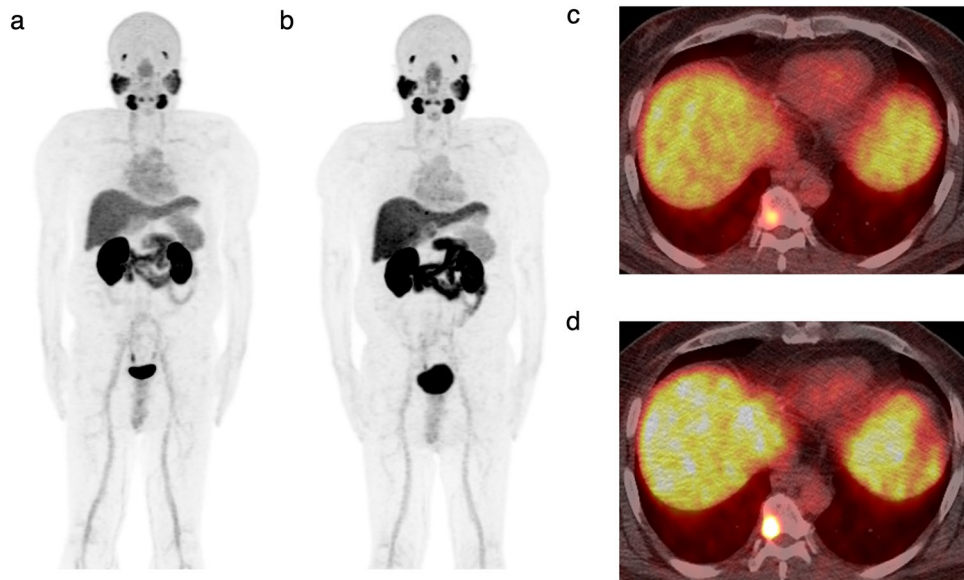

Fig. 2 ^{18}F-FSU-880 PET/CT scan images in a 64-year-old man with suspected recurrence after radiation therapy (RT) for prostate cancer (Gleason score (GS) 4+5, PSA 2.84 ng/ml). ^{18}F-FSU-880 PET/CT showed focal uptake in the thoracic spine, suggesting bone metasta-sis. SUVmax was 5.5 and 16.2 at 1 h and 3 h post-injection, respectively. The patient proceeded with salvage RT for the bone lesion, which resulted in his plasma PSA level decreasing to 0.76 ng/ml. **a** Maximum intensity projection image 1 h after injection; **b** maximum intensity projection image 3 h after injection; **c** transaxial PET/CT fusion image at 1 h after injection; **d** transaxial PET/CT fusion images at 3 h after injection

less than 1.0 ng/ml. In patients with PSA levels less than 0.5 ng/ml, only pelvic lymph nodes were detected. All but one case of distant lymph node metastases were present in patients with PSA levels greater than 2.0 ng/ml.

Diagnostic performance according to initial treatment methods

The PSA level at the time of PET/CT was significantly lower in patients initially treated with radical prostatectomy (RP) than in those initially treated with radiation therapy (RT) [1.00 (0.22–12.9) vs. 2.33 (0.75–40.0), median (range), respectively, $p < 0.001$]. The overall detection rate of recur-rence tended to be higher in patients who received RT than those underwent RP, although [81% (30/37) vs. 60% (21/35), $p = 0.049$]. In patients with PSA levels greater than 0.5 ng/ml, no significant difference in the detection rate was observed between patients who underwent RP and those who received RT [73% (19/26) vs. 81% (30/37), $p = 0.452$]. After stratification of patients who underwent RP by PSA, the detection rates were 22% (2/9), 38% (3/8), 100% (8/8) and 80% (8/10) for PSA levels of 0.2 to < 0.5, 0.5 to < 1.0,

Fig. 3 ^{18}F-FSU-880 PET/CT scan images in a 78-year-old man suspected to have recurrence after radiation therapy (RT) for prostate cancer (GS 3 + 4, PSA 5.13 ng/ml). Focal uptake was observed in **a** 6 mm lymph node behind the left external iliac vein (red arrow in **c**) (SUVmax, 10.7, 26.4 at 1 h post-injection and 3 h post-injection, respectively). Salvage RT was performed, which resulted in his plasma PSA level decreasing to 0.01 ng/ml. **a** Transaxial PET/CT fusion images at 1 h after injection; **b** transaxial PET/CT fusion images at 3 h after injection; **c** transaxial CT (color figure online)
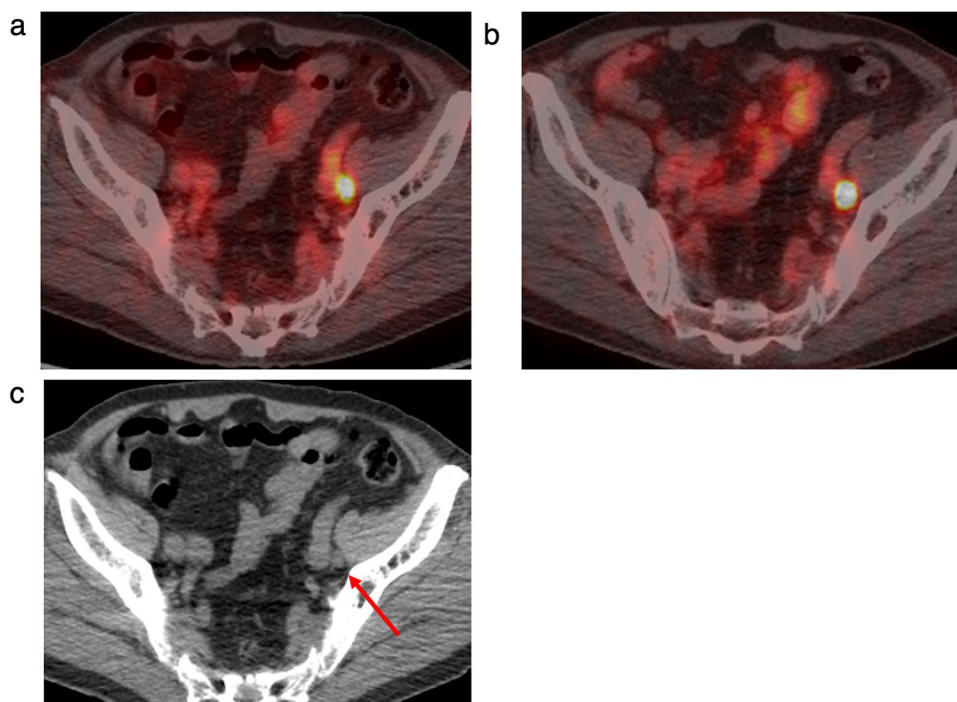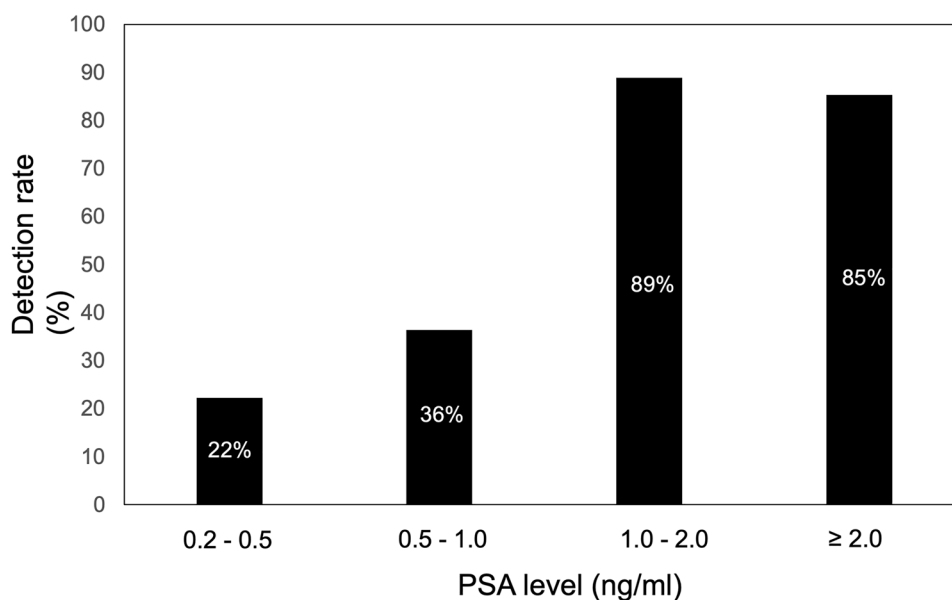


Fig. 4 Detection rate according to PSA levels

1.0 to < 2.0 and ≥ 2.0 ng/ml, respectively. For patients who received RT, the detection rates were 33% (1/3), 80% (8/10) and 88% (21/24) for PSA levels of 0.5 to < 1.0, 1.0 to < 2.0 and ≥ 2.0 ng/ml, respectively. None of the patients who received RT had a PSA level of less than 0.5 ng/ml.

Table 4 shows a comparison of the detection rates of recurrence between the two treatment methods stratified by tumor location. The frequency of local recurrence was significantly higher in patients who received RT than those who

underwent RP ($p = 0.018$). No significant differences were observed between the two groups for the other locations.

Discussion

This was a prospective study assessing the clinical efficacy of PET/CT with ^{18}F-FSU-880 in prostate cancer patients with suspected recurrence after initial treatment. ^{18}F-FSU-880 PET/CT scans of 72 patients referred for localization of

Fig. 5 Detection rate according to Gleason scores
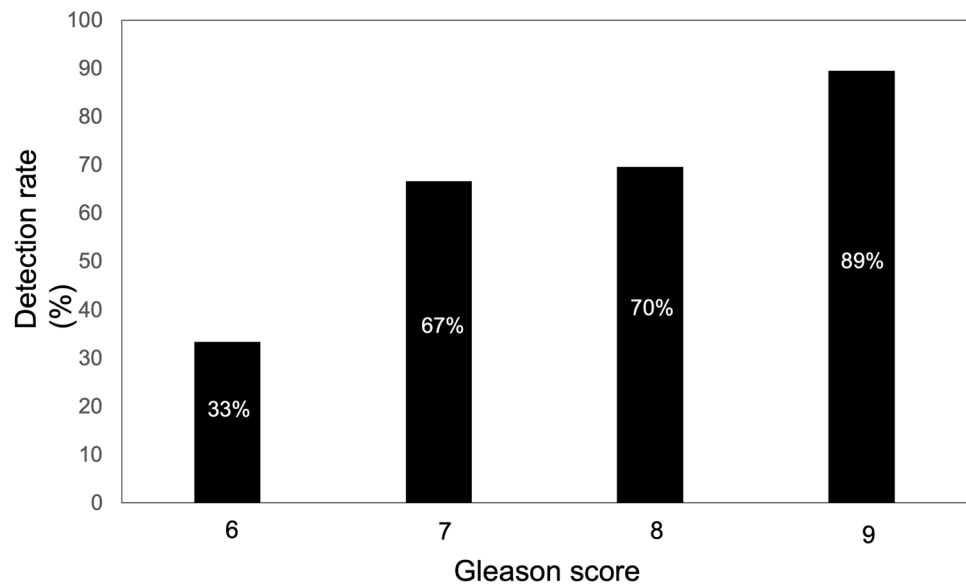
Table 3 Distribution of positive lesions stratified by PSA levels (3 h post-injection)

PSA levels (ng/ml)	0.2– < 0.5	0.5– < 1.0	1.0– < 2.0	≥ 2.0
Total	3	7	27	120
Local recurrence	0	0	8	10
Lymph node				
Pelvic	3	2	10	24
Distant	0	1	0	25
Bone	0	3	9	59
Other organ	0	1	0	2

Table 4 Comparison of patient-based detection rates between the treatment methods stratified by tumor location (3 h post-injection)

	RP (n = 35) (%)	RT (n = 37) (%)	p value*
Total	21 (60)	30 (81)	0.049
Local recurrence	4 (11)	13 (35)	0.018
Lymph node			
Pelvic	9 (26)	9 (24)	0.892
Distant	2 (6)	7 (19)	0.090
Bone	5 (14)	8 (22)	0.419
Other organ	2 (6)	1 (3)	0.523

RP radical prostatectomy, *RT* radiation therapy

*Chi-squared test

relapse sites were analyzed. We found a significant correlation between higher PSA levels at PET/CT and higher PET/CT positivity, which was considered consistent with other previous reports [9, 12, 13]. Higher PET/CT positivity also correlated with higher GS. We consider that these findings were reasonable, based on several basic studies employing surgical specimens of prostate cancer, in which positive relationships between GS and PSMA expression were shown [20, 21]. In addition, in the recent study including big cohort of patients with recurrent prostate cancer after prostatectomy, the significant association between GS and detection rate was described [22].

PET/CT with ^{18}F-FSU-880 achieved a high detection rate (87%) in patients with plasma PSA levels greater than 1.0 ng/ml. A meta-analysis demonstrated that the detection rate of ^{18}F-labeled PSMA-targeted PET/CT in patients with PSA greater than 1.0 ng/ml was approximately 90% [23]. In the present patient group, the performance of ^{18}F-FSU-880 was comparable to that of other ^{18}F labeled PSMA PET agents. On the other hand, in patients with PSA levels below 1.0 ng/ml, the detection rate was only 30% (6/20), which was lower than those reported for other PSMA-targeted imaging probes, especially for ^{18}F-labeled probes [23]. The reason for the low detection rate in patients with PSA levels below 1.0 ng/ml might be that local recurrences were not detected in this patient group. In a previous study using ^{18}F-PSMA-1007, local recurrences were detected in 18.5% and 21.3% of patients with PSA levels of 0.2 to < 0.5 ng/ml and 0.5 to < 1.0 ng/ml, respectively [9]. However, in the current study, local recurrence was not identified in any of the cases with PSA levels below 1.0 ng/ml. Physiological urinary excretion might impair detection of small local recurrences at the early stage of recurrence by ^{18}F-FSU-880 PET/CT. To resolve this problem, injection of furosemide or early dynamic scans commencing at the first minute after injection were considered. Although furosemide injection caused reduction of bladder activity, which led to better assessment of the prostate region [24], the routine use of diuretics needs to be carefully considered because of the potential side effects, such as dehydration. In other studies,

dynamic imaging also achieved better detection of local recurrence [25, 26], although Chevalme et al. reported that early dynamic imaging added value in only 5% of all cases [27].

PSMA-targeted PET radiotracer uptake is seen in ganglia, most commonly in celiac and stellate ganglia, which could be misinterpreted as metastatic lesions [28]. In previous reports, 89–97% of patients demonstrated uptake in at least one ganglion [28, 29]. However, in our study, uptake in ganglia was hardly noticeable and there were only few cases in which differentiation between physiological uptake in ganglia and pathological uptake in metastatic nodes was considered problematic.

We compared the detection rate and site of recurrence between RT and RP groups. The detection rate tended to be higher in patients who received RT than those who underwent RP. However, in patients with PSA levels higher than 0.5 ng/ml, there was no significant difference between the two groups. This tendency was considered to be due to the absence of cases with PSA levels below 0.5 ng/ml in the RT group. Following stratification by PSA levels, there were no significant differences in detection rates between the two groups. As for the site of recurrence, the frequency of local recurrence was significantly higher in patients who received RT than those who underwent RP. Aizawa et al. reported that of 268 patients with high-risk prostate cancer treated with intensity-modulated radiation therapy (IMRT), 97 patients developed BCR, and among them, clinical failure was detected by CT or bone scintigraphy in only 45 patients [30]. Local recurrences might explain some of these cases where the site of recurrence could not be identified.

In this study, ^{18}F-FSU-880 uptake was analyzed at 1 h and 3 h post-injection, which showed that more lesions were detected and SUVmax was significantly higher at 3 h post-injection. A previous study on ^{18}F-PSMA-1007 demonstrated that SUVmax at 2 h post-injection was significantly higher than that at 1 h post-injection, and recommended that ^{18}F-PSMA-1007 PET-CT scans should be performed at 2 h post-injection [31], which is in accordance with our results showing that delayed images are superior to images obtained 1 h post-injection. In addition, some reports proved that images at 3 h post-injection sometimes provided additional information as compared to inconclusive uptakes in the prostate bed at 1 h post-injection in ^{68}Ga-labeled PSMA targeting images [19, 25]. Therefore, PSMA-targeted PET/CT at dual time points might be useful.

There are several limitations to this study. First, the sample size was small and lack of histopathological confirmation in most cases is a major limitation of this study, similar to most previous investigations about PSMA-targeted PET/CT. However, pathological confirmation of all lesions for research purposes is not realistic from an ethical point of view, and some lesions were too small and/or too deeply seated to perform biopsy. However, when histopathologic validation was available, the results confirmed the high positive predictive value of ^{18}F-FSU-880 PET-CT scans. Additionally, previous studies have revealed that histopathologic confirmation indicated a high correlation between PSMA positive lesions and histopathologic findings [32, 33]. Second, the impact of ^{18}F-FSU-880 PET/CT on treatment decision was not evaluated because this was a preliminary study focusing on the detection rate of ^{18}F-FSU-880 PET/CT. PSMA-targeted imaging was previously reported to lead to a change in treatment in approximately 60% of BCR cases [14, 34]. In future, we need to investigate this PSMA-compound from the point of view of clinical impact. Third, we only analyzed 1 h and 3 h post-injection images. Therefore, it remains unknown whether waiting for 3 h after administration is the most optimal timing.

Conclusion

Our preliminary data suggest that ^{18}F-FSU-880 might be a promising new PSMA-targeting tracer for detecting recurrence after primary treatment in patients with prostate cancer. However, small local recurrence and metastatic nodes close to the bladder might have been masked due to the urinary excretion characteristics of this tracer, which remains an issue to be overcome to improve the detection rate.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30.
2. Briganti A, Karnes RJ, Gandaglia G, Spahn M, Gontero P, Tosco L, et al. Natural history of surgically treated high-risk prostate cancer. Urol Oncol. 2015;33(4):163.e7-13.
3. Bott SR. Management of recurrent disease after radical prostatectomy. Prostate Cancer Prostatic Dis. 2004;7(3):211–6.
4. Evans JC, Malhotra M, Cryan JF, O'Driscoll CM. The therapeutic and diagnostic potential of the prostate specific membrane antigen/glutamate carboxypeptidase II (PSMA/GCPII) in cancer and neurological disease. Br J Pharmacol. 2016;173(21):3041–79.
5. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology. 1998;52(4):637–40.
6. Israeli RS, Powell CT, Corr JG, Fair WR, Heston WD. Expression of the prostate-specific membrane antigen. Cancer Res. 1994;54(7):1807–11.

7. Eiber M, Kroenke M, Wurzer A, Ulbrich L, Jooß L, Maurer T, et al. (18)F-rhPSMA-7 PET for the detection of biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med. 2020;61(5):696–701.

8. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56(5):668–74.

9. Giesel FL, Knorr K, Spohn F, Will L, Maurer T, Flechsig P, et al. Detection efficacy of (18)F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med. 2019;60(3):362–8.

10. Watabe T, Uemura M, Soeda F, Naka S, Ujike T, Hatano K, et al. High detection rate in [(18)F]PSMA-1007 PET: interim results focusing on biochemical recurrence in prostate cancer patients. Ann Nucl Med. 2021;35(4):523–8.

11. Mena E, Lindenberg ML, Turkbey IB, Shih JH, Harmon SA, Lim I, et al. (18)F-DCFPyL PET/CT imaging in patients with biochemically recurrent prostate cancer after primary local therapy. J Nucl Med. 2020;61(6):881–9.

12. Afshar-Oromieh A, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging. 2017;44(8):1258–68.

13. Rahbar K, Afshar-Oromieh A, Seifert R, Wagner S, Schäfers M, Bögemann M, et al. Diagnostic performance of (18)F-PSMA-1007 PET/CT in patients with biochemical recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2018;45(12):2055–61.

14. Song H, Harrison C, Duan H, Guja K, Hatami N, Franc BL, et al. Prospective evaluation of (18)F-DCFPyL PET/CT in biochemically recurrent prostate cancer in an academic center: a focus on disease localization and changes in management. J Nucl Med. 2020;61(4):546–51.

15. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(2):197–209.

16. Rowe SP, Campbell SP, Mana-Ay M, Szabo Z, Allaf ME, Pienta KJ, et al. Prospective evaluation of PSMA-targeted (18)F-DCFPyL PET/CT in men with biochemical failure after radical prostatectomy for prostate cancer. J Nucl Med. 2020;61(1):58–61.

17. Harada N, Kimura H, Onoe S, Watanabe H, Matsuoka D, Arimitsu K, et al. Synthesis and biologic evaluation of novel 18F-labeled probes targeting prostate-specific membrane antigen for PET of prostate cancer. J Nucl Med. 2016;57(12):1978–84.

18. Saga T, Nakamoto Y, Ishimori T, Inoue T, Shimizu Y, Kimura H, et al. Initial evaluation of PET/CT with (18) F-FSU-880 targeting prostate-specific membrane antigen in prostate cancer patients. Cancer Sci. 2019;110(2):742–50.

19. Afshar-Oromieh A, Sattler LP, Mier W, Hadaschik BA, Debus J, Holland-Letz T, et al. The clinical impact of additional late PET/CT imaging with (68)Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. J Nucl Med. 2017;58(5):750–5.

20. Minner S, Wittmer C, Graefen M, Salomon G, Steuber T, Haese A, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate. 2011;71(3):281–8.

21. Kasperzyk JL, Finn SP, Flavin R, Fiorentino M, Lis R, Hendrickson WK, et al. Prostate-specific membrane antigen protein expression in tumor tissue and risk of lethal prostate cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(12):2354–63.

22. Afshar-Oromieh A, da Cunha ML, Wagner J, Haberkorn U, Debus N, Weber W, et al. Performance of [(68)Ga]Ga-PSMA-11 PET/CT in patients with recurrent prostate cancer after prostatectomy-a multi-centre evaluation of 2533 patients. Eur J Nucl Med Mol Imaging. 2021;48(9):2925–34.

23. Treglia G, Annunziata S, Pizzuto DA, Giovanella L, Prior JO, Ceriani L. Detection rate of (18)F-labeled PSMA PET/CT in biochemical recurrent prostate cancer: a systematic review and a meta-analysis. Cancers (Basel). 2019. https://doi.org/10.3390/cancers110 50710.

24. Derlin T, Weiberg D, von Klot C, Wester HJ, Henkenberens C, Ross TL, et al. (68)Ga-PSMA I&T PET/CT for assessment of prostate cancer: evaluation of image quality after forced diuresis and delayed imaging. Eur Radiol. 2016;26(12):4345–53.

25. Beheshti M, Manafi-Farid R, Geinitz H, Vali R, Loidl W, Mottaghy FM, et al. Multiphasic (68)Ga-PSMA PET/CT in the detection of early recurrence in prostate cancer patients with a PSA level of less than 1 ng/mL: a prospective study of 135 patients. J Nucl Med. 2020;61(10):1484–90.

26. Uprimny C, Kroiss AS, Decristoforo C, Fritz J, Warwitz B, Scarpa L, et al. Early dynamic imaging in (68)Ga- PSMA-11 PET/CT allows discrimination of urinary bladder activity and prostate cancer lesions. Eur J Nucl Med Mol Imaging. 2017;44(5):765–75.

27. Chevalme YM, Boudali L, Gauthé M, Rousseau C, Skanjeti A, Merlin C, et al. Survey by the French Medicine Agency (ANSM) of the imaging protocol, detection rate, and safety of (68)Ga-PSMA-11 PET/CT in the biochemical recurrence of prostate cancer in case of negative or equivocal (18)F-fluorocholine PET/CT: 1084 examinations. Eur J Nucl Med Mol Imaging. 2021;48(9):2935–50.

28. Krohn T, Verburg FA, Pufe T, Neuhuber W, Vogg A, Heinzel A, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. Eur J Nucl Med Mol Imaging. 2015;42(2):210–4.

29. Werner RA, Sheikhbahaei S, Jones KM, Javadi MS, Solnes LB, Ross AE, et al. Patterns of uptake of prostate-specific membrane antigen (PSMA)-targeted (1w8)F-DCFPyL in peripheral ganglia. Ann Nucl Med. 2017;31(9):696–702.

30. Aizawa R, Takayama K, Nakamura K, Inoue T, Yamasaki T, Kobayashi T, et al. Ten-year outcomes of high-dose intensity-modulated radiation therapy for nonmetastatic prostate cancer with unfavorable risk: early initiation of salvage therapy may replace long-term adjuvant androgen deprivation. Int J Clin Oncol. 2019;24(10):1247–55.

31. Rahbar K, Afshar-Oromieh A, Bögemann M, Wagner S, Schäfers M, Stegger L, et al. (18)F-PSMA-1007 PET/CT at 60 and 120 minutes in patients with prostate cancer: biodistribution, tumour detection and activity kinetics. Eur J Nucl Med Mol Imaging. 2018;45(8):1329–34.

32. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2017;44(4):678–88.

33. Liu C, Liu T, Zhang Z, Zhang N, Du P, Yang Y, et al. (68)Ga-PSMA PET/CT combined with PET/Ultrasound-guided prostate biopsy can diagnose clinically significant prostate cancer in men with previous negative biopsy results. J Nucl Med. 2020;61(9):1314–9.

34. Rousseau E, Wilson D, Lacroix-Poisson F, Krauze A, Chi K, Gleave M, et al. A prospective study on (18)F-DCFPyL PSMA PET/CT imaging in biochemical recurrence of prostate cancer. J Nucl Med. 2019;60(11):1587–93.