Original Article

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Molecular Imaging of Prostate Cancer with PSMA-Targeted Probes: Comparison of ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T PET/CT

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Abstract

Objective: Positron emission tomography (PET) probes targeting prostate-specific membrane antigen (PSMA) have gained increasing interest, while the use of PSMA PET/computed tomography (CT) for prostate cancer (PCa) has rapidly and widely expanded over the last 5 years. The most preferred radiotracers available at many European PET centers, including those in Turkey, are ^{68}Gallium (^{68}Ga)-PSMA-11 and ^{68}Ga-PSMA-I&T. The aim of this study is to compare ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T PET/CT in patient groups with similar characteristics.

Methods: PSMA PET/CT images of 81 patients with biopsy-proven PCa were retrospectively analyzed. Physiological distribution, tumor-to-background ratios, positivity rates, uptakes, and visual score classifications of primary tumors, lymph nodes, and bone metastases were analyzed for comparison. Additionally, PET/CT findings were compared according to the proposed molecular imaging tumor, node, and metastasis (miTNM) classification.

Results: There was no significant difference between PSMA-11 and PSMA-I&T in terms of overall positivity rates, bone metastases, recurrent tumors, and overall detection rates of recurrent disease. Blood pool as well as bone marrow and muscle uptake of PSMA-I&T were slightly higher than those of PSMA-11. There was no significant difference between uptake values, tumor-to-background ratios, and visual scores of lymph node and bone metastasis. Average maximum standardized uptake values (SUVmax) and visual scores of primary tumors with PSMA-I&T were slightly higher than those of PSMA-11; however, the variance was minor, and there was no statistically significant difference between tumor-to-background ratios of primary tumors. Pelvic lymph node mapping according to the miTNM template showed similar results with both tracers.

Conclusion: ^{68}Ga-PMSA-I&T may have an advantage with slightly higher uptake in primary tumors and slightly lower blood pool and bone marrow uptake. However, ^{68}Ga-PMSA-I&T and ^{68}Ga-PSMA-11 showed similar clinical performance for staging and restaging of PCa in terms of detection rates, visual scores, tumor uptakes, and comparable physiological distribution.

Keywords: Positron emission tomography, prostate cancer, prostate specific membrane antigen

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in Turkey and a leading cause of cancer-related deaths (1, 2). Unfortunately, conventional imaging methods still have limited sensitivity and specificity for PCa (3, 4). Multiparametric magnetic resonance imaging (MRI) of the prostate gland has shown excellent results in imaging of primary tumors with accurate T-staging. However, MRI has limited sensitivity in cases of nodal disease and is usually limited to the pelvic area (5). In positron emission tomography (PET) imaging, two metabolic tracers, ^{18}Fluorine (^{18}F)-fluoride and ^{18}F-choline, were the only widely available alternatives for the imaging of PCa until recently. The former is a bone-seeking tracer that shows metastatic lesions indirectly by mapping osteoblastic activity. The

latter is a radiolabeled choline that accumulates in tumor cells at a much higher rate than it accumulates in normal cells due to increased proliferation rates (6, 7). However, both tracers are limited by the nonspecific nature of using metabolic pathways (6).

Positron emission tomography (PET) probes targeting prostate specific membrane antigen (PSMA) have gained increasing interest and the use of PSMA PET/computed tomography (CT) for PCa has rapidly and widely expanded over the last 5 years (8). PSMA is increased in various tissues but is significantly higher in PCa cells, and the level of expression is directly associated with tumor aggressiveness (9, 10). PSMA is an excellent and well-established target for PCa imaging. Because of these advantages, PSMA PET/CT has high clinical impact in the management of PCa. In a recent meta-analysis involving 1309 patients, Perrara et al. (11) reported 54% pooled proportion of management changes with PSMA PET/CT. On a per lesion analysis, the sensitivity and specificity were 80% and 97%, respectively (11). PSMA PET/CT imaging is recommended for the staging of intermediate and high risk PCa and recurrent disease after prostatectomy/radiotherapy (9, 12-14).

To date, various radionuclides, such as ^{68}Gallium (^{68}Ga), ^{18}F, ^{44}Scandium (^{44}Sc), ^{111}Indium (^{111}In), and ^{99m}Technetium (^{99m}Tc), have been used to prepare PSMA targeting radiopharmaceuticals by labeling various small molecules or antibodies (15-17). Among these, ^{68}Ga, which is commercially available through ^{68}Germanium(^{68}Ge)/^{68}Ga generators, is the most preferred radionuclide and is available at several European PET centers, including those in Turkey (15). ^{68}Ga can be labeled with small molecule PSMA inhibitors, mostly PSMA-11 or PSMA-I&T (Figure 1), to prepare the final radiopharmaceutical (15, 18, 19). However, so far only one study has compared both tracers head-to-head with limited number of patients (n=20) (20). Therefore, we conducted a retrospective study to compare ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T PET/CT in patient groups with similar characteristics.

METHODS

Patient Selection

Probes targeting prostate specific membrane antigen (PSMA)/Positron emission tomography (PET)/CT images of 81 patients (mean age, 68±10.6 years; range, 33-89 years) were retrospectively analyzed. Of these patients, 42 underwent PSMA-I&T PET/CT and 39 underwent PSMA-11 PET/CT. All patients had biopsy-proven PCa and provided informed written consent. PET/CT images with technical issues affecting the calculation of standardized uptake values, such as motion artifacts, significant extravasation of radiotracer, reconstruction, or scatter correction artifacts, were excluded to avoid possible quantification errors. This study was approved by the local research ethics committee in accordance with Turkish regulations and was performed in compliance with the Declaration of Helsinki.

Preparation of ^{68}Ga-PSMA-11 and PSMA ^{68}Ga-PSMA-I&T

^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T were prepared with a fully automated radiopharmaceutical synthesis device based on a modular concept (SCINTOMICS GmbH, Fürstenfeldbruck, Germany). Briefly, the ligand was labeled with $^{68}Ga^{+3}$ (half-life, 67.6 min) from a SnO2-based ^{68}Germanium/^{68}Ga radionuclide generator (a iThemba LABS)) by means of a fully automated module (SCINTOMICS GmbH), good manufacturing practice-grade disposable cassettes, and reagent kits (ABX Advanced Biochemical Compounds, Dresden, Germany). The final product was dissolved in phosphate-buffered saline and filtered through a 0.2-µm sterile filter. Radiochemical purity, determined by high-performance liquid chromatography, exceeded 95% in all cases.

Image Acquisitions

After preparation and quality control of the radiotracer, all patients received approximately 191±47 MBq (range, 111-333 MBq, <2 nmol PSMA-11 and PSMA-I&T) of radiopharmaceutical intravenously. Average injected activities of ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T were 200±53 and 184±44 MBq, respectively. Whole body images were acquired using an integrated PET/CT scanner (Discovery PET/CT 710; GE Healthcare, Milwaukee, WI, USA). The patients were placed on the scanner table in a supine position, and a low dose CT transmission scan was acquired with low tube current. Then, PET emission scanning was performed with the identical transverse field of view in the caudocranial direction with a duration of 3 min per bed position and 53±15 min after injection of radiopharmaceutical. Reconstruction was performed with an ordered-sub-

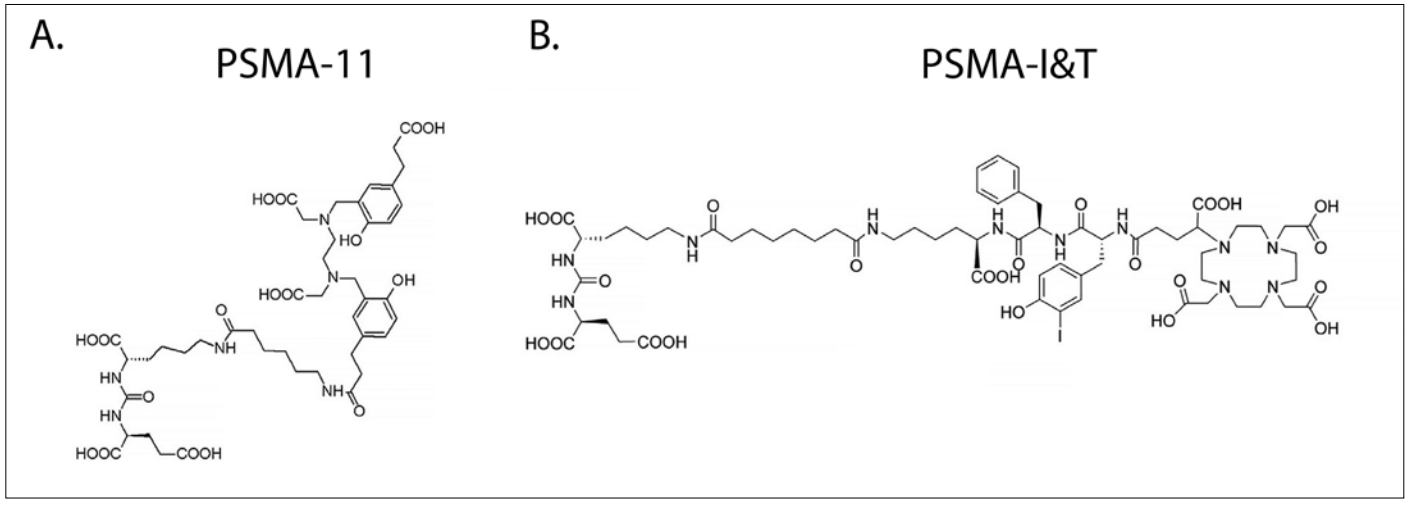


Figure 1. a, b. Chemical structures of PSMA-11 (a) and PSMA-I&T (b) (19). PSMA, prostate-specific membrane antigen

sets expectation-maximization algorithm with four iterations/eight subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width at half-maximum. PET images were corrected for attenuation by CT transmission images and for randoms, scatter, decay, and dead time.

Image Analysis

A nuclear medicine physician with 5-year PSMA PET experience analyzed all images. PET images were reviewed using a workstation (Advantage Workstation Version: 4.7, GE Healthcare, Milwaukee, USA). Volumes of interests (VOIs) were drawn by auto-contour function for tumors, lacrimal glands, parotid, submandibular glands, and kidneys. VOIs were drawn manually for mediastinal blood pool, liver, spleen, lumbar vertebras, and gluteal muscles. Maximum (SUVmax) and mean (SUVmean) SUV values were calculated from VOIs. SUVmax values of primary tumors in the prostate gland, local recurrence in the prostate bed, and lymph node and bone metastases were calculated. For multiple lesions, five index lesions with highest SUVmax were noted for primary, lymph node, and bone metastases.

Statistical Analysis

Statistical analysis of the difference between physiological distribution, primary tumors, local recurrence, and lymph node and bone metastases were compared with independent sample t-test or Mann-Whitney U tests according to the distribution of sample groups. PET positivity rates, indications, Gleason scores, and other patient characteristics of two groups (PSMA-11 and PSMA-I&T) were compared with the chi-square test.

RESULTS

Patients underwent PSMA PET/CT for initial staging (n=39, 48.1%), restaging after biochemical recurrence (n=18, 22.2%), or to assess treatment response (n=24, 29.6%). Mean and median prostate-specific antigen (PSA) levels were 54.9 and 10 ng/dL, respectively (range, 0.024-1187 ng/dL; standard error, 17.49). PSMA PET scan was performed with ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-I&T in 39 (48.1%) and 42 (51.9%) patients, respectively. There was no statistically significant difference between the groups in terms of the World Health Organization (WHO) Gleason Grade Groups, indication of PET, amount of injected pharmaceutical, or PSA levels except age. The mean age of the PSMA-I&T patient group was slightly higher than that of the PSMA-11 group. Patient characteristics are reported for both groups in Table 1.

The overall positivity rates of PET/CT imaging groups were 88.1% (n=37/42) for PSMA-I&T and 87.2% for PSMA-11 (n=34/39), without significant difference (p=0.9). Mean PSA in patients referred for staging (n=18) was 7.1±12.5. In the staging subgroup, both tracers had similar overall positivity rates: 95% (n=19/20) for PSMA-I&T and 89.5% (n=17/19) for PSMA-11. There was no statistically significant difference between the groups (p>0.05). In patients who underwent PSMA PET for restaging of recurrent disease, median PSA was 2.06 (0.48-50) and 1.5 (0.24-11.4) ng/mL for PSMA-I&T and PSMA-11, respectively (not significantly different, p=0.24). Detection rates of recurrent disease were similar in both groups despite the low sample size: 60% (n=6/10) for PSMA-I&T and 62.5% (n=5/8) for PSMA-11 (p>0.05).

There was a statistically significant difference between the average SUVmax values of primary tumors with PSMA-I&T and PSMA-11 (13.9±10.7 and 10.3±7.75, respectively; p=0.035). However, the variance was minor. There was no statistically significant difference between tumor-to-background ratios of primary tumors (7.4±6 for PSMA-I&T and 7.2±7.9 for PSMA-11), or between the uptakes of tumor-to-background ratios of lymph node and bone metastases and recurrent tumors (Figure 2).

All lesions included in the SUV quantification were also classified according to prostate cancer molecular imaging standardized evaluation (PROMISE) criteria (21). There was a statistically significant difference (higher with PSMA-I&T) between the average

Table 1. Patient characteristics of two groups

	PSMA-11	PSMA-I&T	Statistics
Total number of patients	n=39	n=42	N/A
Gleason Groups (n of valid cases:76)	Group 1 (3+3): 10.8% (n=4)	Group 1 (3+3): 15.4% (n=6)	Chi-square Likelihood Ratio: 0.741
	Group 2 (3+4): 21.6% (n=8)	Group 2 (3+4): 25.6% (n=10)	p=0.946*
	Group 3 (4+3): 16.2% (n=6)	Group 3 (4+3): 12.8% (n=5)	
	Group 4 (4+4): 18.9% (n=7)	Group 4 (4+4): 15.4% (n=6)	
	Group 5 (4+5 or 5+4): 32.4% (n=12)	Group 5 (4+5 or 5+4): 30.8% (n=12)	
Indication of PET/CT imaging	Staging: 48.7% (n=19)	Staging: 47.6% (n=20)	Chi-square Likelihood Ratio: 0.137
	Restaging 20.5% (n=8)	Restaging 23.8% (n=10)	p=0.934*
	Response Assessment to treatment 30.8% (n=12)	Response Assessment to treatment 28.6% (n=12)	
PSA values (n of valid cases:80)	Median=10 ng/mL (0.07-480)	Median=10.47 ng/mL (0.024-1187)	p=0.623*
Age	65±0.8	70±8.8	p=0.037**

*Difference between group is statistically nonsignificant
**Difference between group is statistically significant
n: number; ng: nanogram; mL: milliliter

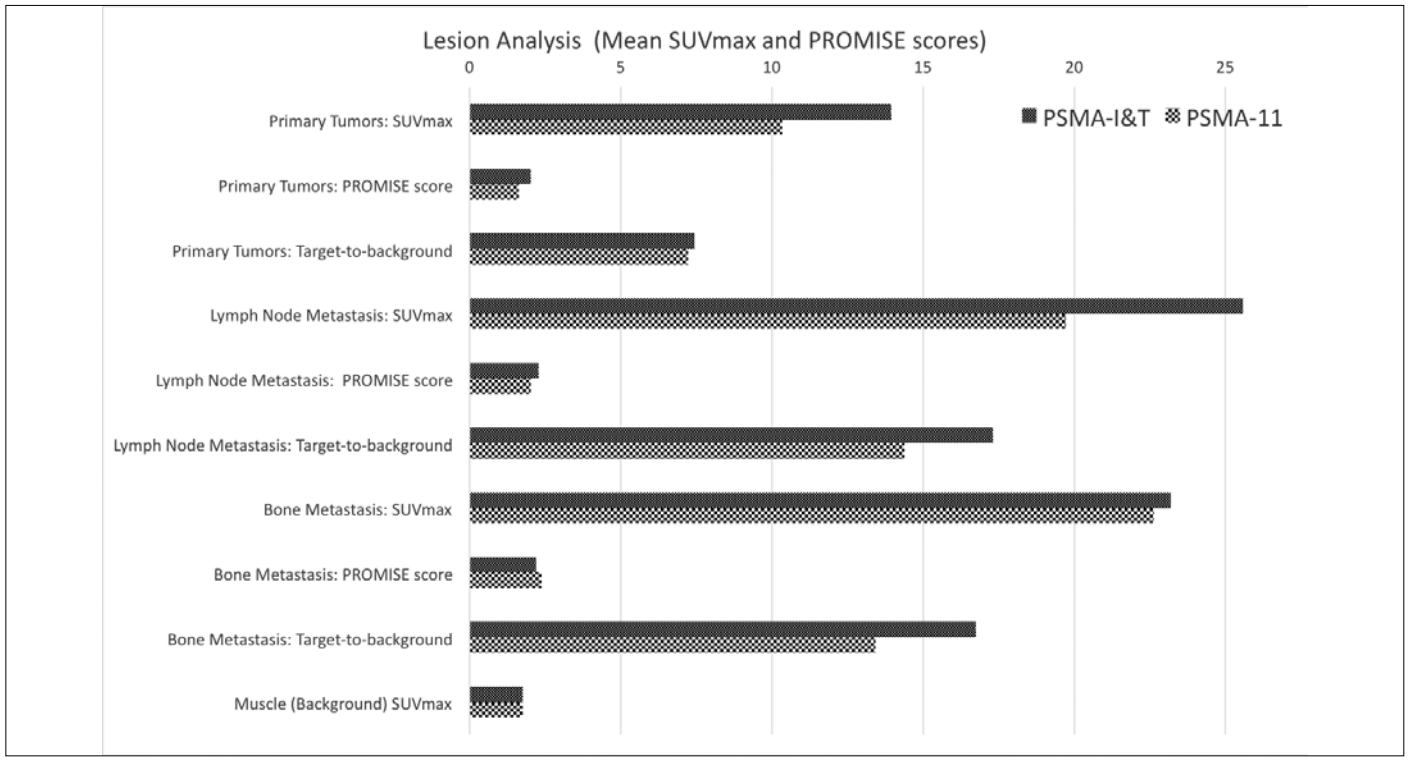


Figure 2. Comparison of tumor-to-background ratios and semiquantitative uptake values of tumoral lesions. SUVmax, maximum standard uptake value (X-axis)

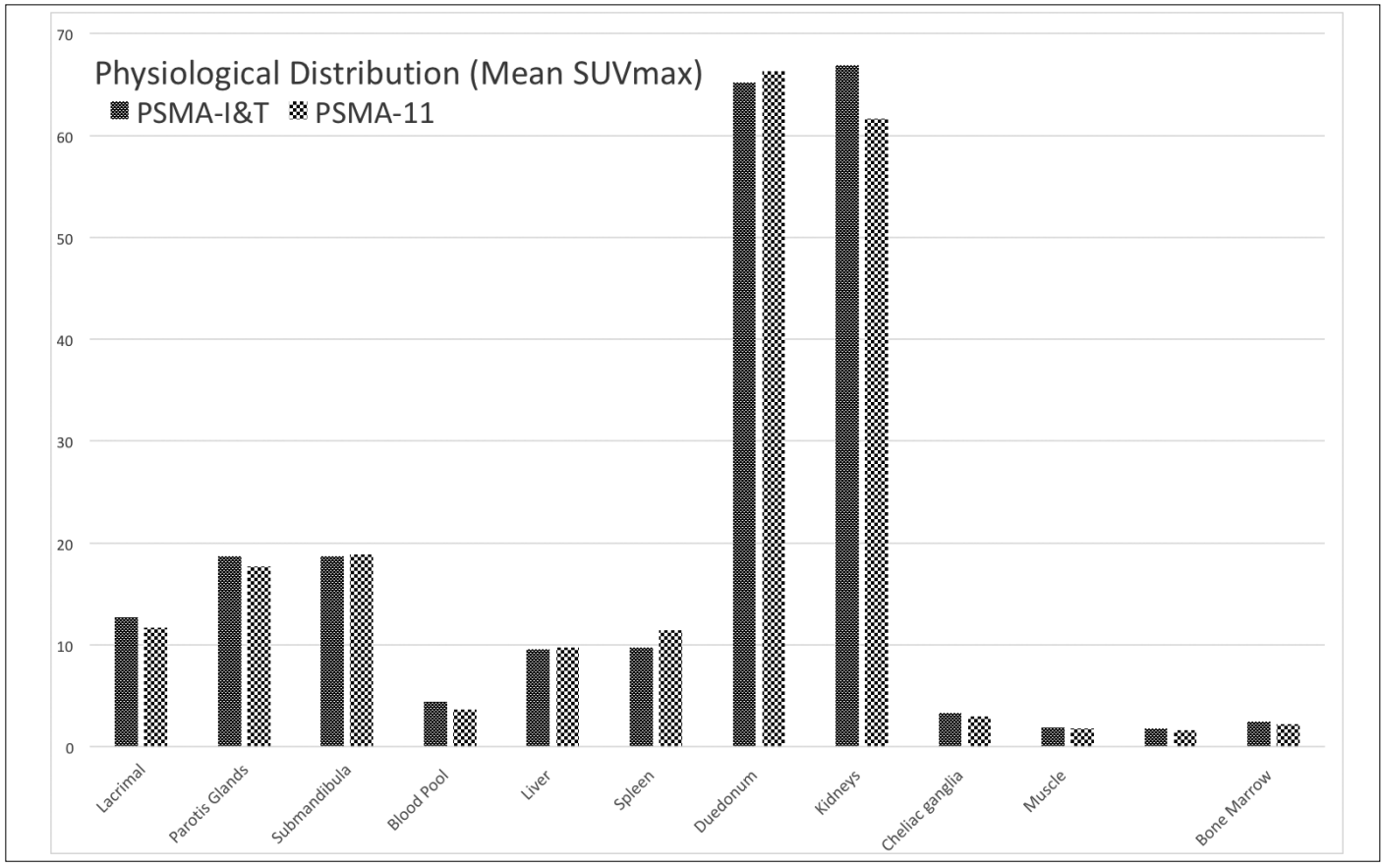


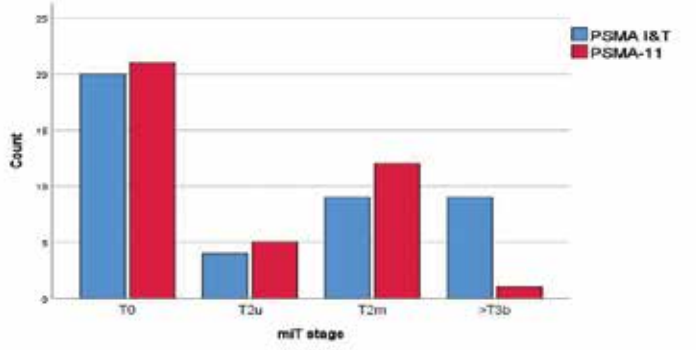
Figure 3. Comparison of basic physiological distribution of 68Ga-PSMA-11 and 68Ga-PSMA-I&T: SUVmean, mean standard uptake value (Y-axis)

SUVmax values of primary tumors in the PSMA-I&T and PSMA-11 groups (2.02±0.8 and 1.62±0.79, respectively; p=0.014). Similar to SUVmax values of local recurrence and lymph node and bone metastases, there were no statistically significant differences in PROMISE uptake scores (p>0.05).

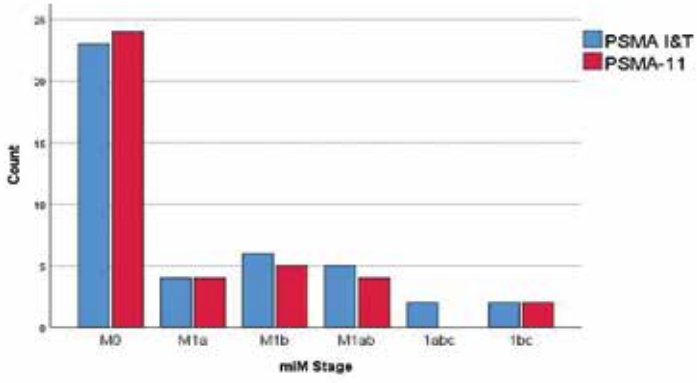
Physiologic distribution of both radiotracers was similar in terms of SUVmax and SUVmean values of lacrimal glands, submandibular and parotid glands, spleen, duodenum, and kidneys p>0.05). Average SUVmean values of liver is slightly higher with PSMA-11 than those of PSMA-I&T (p=0.004), however the difference of average SUVmax values was not significant (p>0.05): Average SUVmean and Average SUVmax values were 4.58±1.12 and 9.55±5.97 for PSMA-I&T; 5.12±2.14 and 9.74±3.13 for PSMA-11. Blood pool, bone marrow, and muscle uptakes of PSMA-I&T were slightly higher than those of PSMA-11; however, the difference was not statistically significant (p>0.05, Figure 3). Celiac ganglia, which is a common pitfall of PSMA imaging due to its physiologic uptake and adjacent location to lymph nodes, showed similar uptake of both radiotracers: 3.28±1.1 for PSMA-I&T and 2.9±0.9 for PSMA-11 (p=0.29, Figure 3).

In the evaluation of pelvic lymph nodes, PSMA-I&T PET detected 4.8% (n=2) stage N1a disease and 33.3% (n=14) stage N1b disease, compared to 5.1% (n=2) and 28.2% (n=11), respectively, for PSMA-11 PET. The difference was not statistically significant. PET results according to proposed molecular imaging tumor, node, metastasis (miTNM) staging are shown in Figure 4.

		Grup		
miT Staging		PSMA-I&T	PSMA-11	Total
T0	Count	20	21	41
	% within Grup	47.6%	53.8%	50.6%
T2u	Count	4	5	9
	% within Grup	9.5%	12.8%	11.1%
T2m	Count	9	12	21
	% within Grup	21.4%	30.8%	25.9%
T3b	Count	9	1	10
	% within miT_SPSS	90.0%	10.0%	100.0%
	% within Grup	21.4%	2.6%	12.3%
	Count	42	39	81
	% within miT_SPSS	51.9%	48.1%	100.0%
	% within Grup	100.0%	100.0%	100.0%



		Grup		
miN Staging		PSMA-I&T	PSMA-11	Total
N0	Count	26	26	52
	% within Grup	61.9%	66.7%	64.2%
N1a	Count	2	2	4
	% within Grup	4.8%	5.1%	4.9%
N1b	Count	14	11	25
	% within Grup	33.3%	28.2%	30.9%
	Count	42	39	81
	% within Grup	100.0%	100.0%	100.0%



		Grup		
miM Staging		PSMA-I&T	PSMA-11	Total
M0	Count	23	24	47
	% within Grup	54.8%	61.5%	58.0%
M1a	Count	4	4	8
	% within Grup	9.5%	10.3%	9.9%
M1b	Count	6	5	11
	% within Grup	14.3%	12.8%	13.6%
M1ab	Count	5	4	9
	% within Grup	11.9%	10.3%	11.1%
1abc	Count	2	0	2
	% within Grup	4.8%	0.0%	2.5%
	% within Grup	4.8%	5.1%	4.9%
	Count	42	39	81
	% within Grup	100.0%	100.0%	100.0%

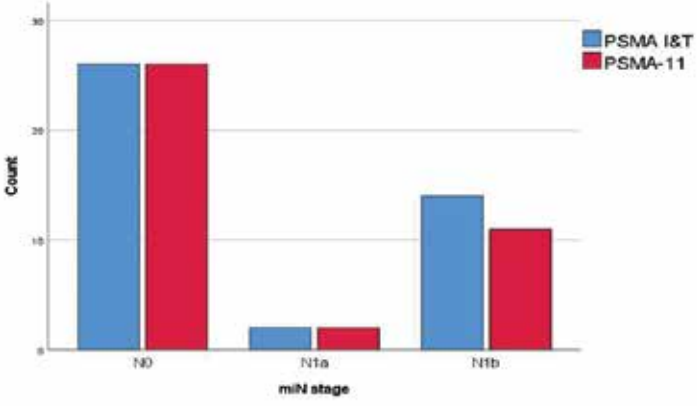


Figure 4. Positron emission tomography/computed tomography findings described and organized in molecular imaging tumor, node, metastasis framework for both groups

DISCUSSION

Patients underwent PSMA PET/CT is a novel imaging method applying targeted imaging to the personalized medicine of PCa. With high success rates, PSMA imaging is rapidly and widely expanding with various radiopharmaceuticals (15, 16). To date, ^{68}Ga, ^{18}F, ^{44}Sc, ^{111}In, and ^{99m}Tc have been used to prepare PSMA targeting radiopharmaceuticals (15-17). Among these, ^{68}Ga is the most preferred radionuclide because of its availability at many European PET centers (15). ^{68}Ga can be labeled with small molecule PSMA ligands, PSMA-11, PSMA-I&T, or PSMA-617, to prepare the final radiopharmaceutical. ^{68}Ga-PSMA-617 requires late imaging at approximately 4 h after injection for an optimal tumor uptake, which is not feasible due to the short half-life of ^{68}Ga (68 min). Therefore, PSMA-I&T or PSMA-11 is mostly used for ^{68}Ga labeling (15,18). Our study compared these two PSMA targeting radioligands for physiologic distribution, tumor-to-background ratios, positivity rates, uptakes, visual scores of primary tumors, and lymph node and bone metastases.

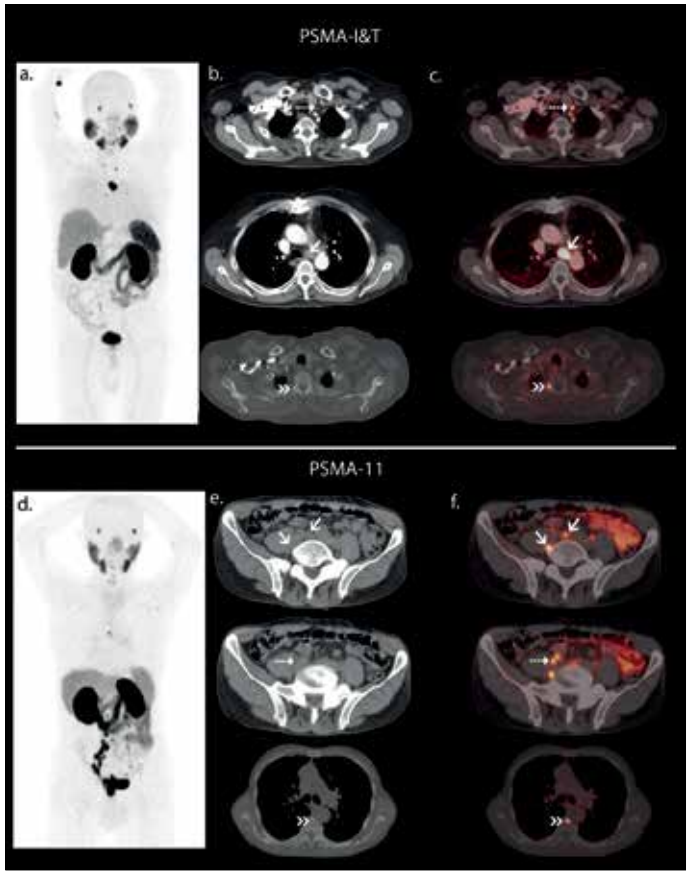


Figure 5. a-f. PSMA positron emission tomography/computed tomography images of two patients with recurrent prostate cancer showing metastatic lymph nodes (dotted and dashed arrows) and single bone metastasis (chevron arrows). Both tracers were able to show lymph nodes as small as 5mm (dashed arrows). Figure labels: maximum intensity projection (a), axial CT slices (b), PET and CT fusion slices (c) of 68Ga-PSMA-I&T; Maximum intensity projection (d), axial CT slices (e), PET and CT fusion slices (f) of 68Ga-PSMA-11

Probes targeting prostate specific membrane antigen (PSMA) also known as glutamate carboxypeptidase 2 or folate hydrolase, is expressed in various normal tissues and limits tumor detectability by decreasing tumor-to-background ratios in specific organs (22, 23). However, the binding of radiotracers to a target is affected not only by the carrier molecule and their binding affinity to the target, but also by other factors affecting pharmacokinetics, such as lipophilicity, negative charge, binding to plasma proteins, and the amount of the carrier molecule used during synthesis (24, 25). Because of the aforementioned factors, the uptake of PSMA-I&T and PSMA-11 in organs with significant PSMA expression were compared and both radiotracers showed a similar physiological distribution, with a high uptake in the kidneys, spleen, and lacrimal and salivary glands. However, PSMA-11 has slightly lower average SUVmean and SUVmax values for blood pool, bone marrow, and background (muscle uptake), which is a slight advantage over PSMA-I&T. This finding can be explained by slower clearance of ^{68}Ga-PSMA-I&T (20). In the liver, the SUVmax difference of two groups was not significant, whereas the average SUVmean of PSMA-11 was slightly higher than that of PSMA-I&T. McCarth et al. (20) also reported a slightly higher average SUVmean with PSMA-11 than with PSMA-I&T, and they calculated ΔSUVmean of 0.88±0.27 between the groups. While the difference is probably too low to affect lesion detection rates (ΔSUVmean of 0.54 according to study and 0.88 according to McCarth et al. (20), it may affect the PROMISE scoring system which uses liver uptake as a reference (21).

Recurrent disease after prostatectomy or initial radiotherapy is an important problem in clinical management of PCa, and the early detection of recurrent disease is a key factor for the success of salvage therapies (26, 27). PSMA PET imaging has the highest sensitivity and specificity in restaging of recurrent PCa among all imaging modalities, PSMA can detect recurrent disease even with low PSA levels down to 0.2 ng/mL (9, 12, 26) PSMA imaging is also recommended for restaging in clinical guidelines (13). In agreement with these data, both radiotracers performed well despite low PSA levels with a median of 1.6 (0.024-50) ng/mL. Detection rates of recurrent disease were similar with PSMA-I&T and PSMA-11 (60% and 62.5%, respectively). Two exemplary cases of recurrent prostate cancer are shown in Figure 5. Unfortunately, the low sample group number did not allow detailed comparison according to PSA ranges. In a previous study by Berliner et al. (28), PSMA-I&T detection rates were compared with data published on PSMA-11 and PSMA-I&T, and detection rates were similar. Our study confirms this conclusion using similar patient groups with the advantage of eliminating the negative effects of using various types of PET scanners. However, further studies with larger cohorts are needed to support these results.

In addition to semiquantitative comparison, PET/CT images acquired with both tracers were also evaluated according to the PROMISE reporting criteria (21). According to this criteria, PSMA-ligand PET/CT findings were described and organized in an miTNM framework, designed in analogy to clinicopathological TNM to aid the clinician in defining tumor extent, tailoring therapy management, and assessing prognosis (21). In this study, there were no statistically significant differences in overall miTNM results of PMSA-I&T and PSMA-11 (Figure 4, $p>0.05$). Among those, N-staging is one of the most important aspects

of PSMA imaging due to superior sensitivity and specificity over conventional imaging. Possessing precise information about the presence or absence of lymph node metastases as well as accurate location have a major impact on treatment planning (29). Compared within the miTNM framework, results of N staging with both tracers were in line with detection rates of 4.8% stage N1a and 33.3% stage N1b disease by PSMA-I&T versus 5.1% and 28.2%, respectively, by PSMA-11 ($p>0.05$).

Sensitivity and specificity of radiotracers were not compared due to lack of histopathologic confirmation of the PET findings. Because specificity of the PSMA PET/CT was very high with both radiotracers, one can assume that the low amount of false-positive lesions had little effect on the comparison (30-32). The small number of patients (n=81) is another limitation of the study, and this did not allow further analysis of the performance of radiotracers in different clinical scenarios, such as staging in high-risk disease, biochemical recurrence, and biopsy guidance.

CONCLUSION

This study demonstrated similar detection rates, visual scores, tumor uptakes, and physiologic distribution with ^{68}Ga-PMSA-I&T and ^{68}Ga-PSMA-11, which are used for PSMA PET/CT imaging. Both radiotracers showed comparable clinical performance for staging and restaging of PCa. However, ^{68}Ga-PMSA-I&T has an advantage over its direct theragnostic counterpart ^{177}Lutetium (Lu)-PSMA-I&T, whereas ^{68}Ga-PSMA-11 was coupled with ^{177}Lu-PSMA-617.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yeditepe University Clinical Research (Decision Date: 31/05/2018/Decision No: 857).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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