⁶⁸Ga-PSMA-11 PET/CT in Primary and Recurrent Prostate Carcinoma: Implications for Radiotherapeutic Management in 121 Patients

Stefan A. Koerber^{1–3}, Leon Will⁴, Clemens Kratochwil^{4,5}, Matthias F. Haefner^{1–3}, Hendrik Rathke⁴, Christophe Kremer⁴, Jonas Merkle⁴, Klaus Herfarth^{1–3}, Klaus Kopka^{6,7}, Peter L. Choyke⁸, Tim Holland-Letz⁹, Uwe Haberkorn^{4,5}, Juergen Debus^{1–3}, and Frederik L. Giesel^{4,5,7}

¹Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; ²Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; ³National Center of Radiation Oncology (NCRO), Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany; ⁴Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; ⁵Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany; ⁶Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ), Heidelberg, Germany; ⁷German Cancer Consortium (DKTK), Heidelberg, Germany; ⁸Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and ⁹Department of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

The present study analyzed the impact of 68Ga-labeled prostatespecific membrane antigen-HBED-CC (68Ga-PSMA-11) PET/CT on radiotherapeutic management in a large cohort of men with primary or recurrent prostate cancer. Methods: This study investigated 121 men with carcinoma of the prostate who underwent ⁶⁸Ga-PSMA-11 PET/CT as well as conventional imaging. Fifty patients were treatment-naive, 11 had persistent prostate-specific antigen (PSA) soon after surgery, and 60 presented with recurrent PSA after definitive therapy. Changes in TNM classification of malignant tumor stage (TNM) and radiotherapeutic management after ⁶⁸Ga-PSMA-11 imaging were compared with results achieved with conventional imaging. Results: In total, a change in TNM stage and radiotherapeutic management was observed for 49 patients (40.5%) and 62 patients (51.2%), respectively. In treatment-naive patients, a change in TNM stage and radiotherapeutic plan occurred in 26.0% and 44.0% of the cohort, respectively. For patients with PSA persistence or recurrence, TNM and radiotherapeutic management changed in 50.7% and 56.3%, respectively. Conclusion: ⁶⁸Ga-PSMA-11 PET/ CT may shortly become an indispensable tool for detecting prostate cancer lesions in treatment-naive patients as well as in men with recurrent disease or persistent PSA and seems to be helpful in personalizing radiotherapeutic management to the individual patients' distribution of disease.

Key Words: prostate cancer; PSMA; PET/CT; radiotherapy; staging

J Nucl Med 2019; 60:234–240DOI: 10.2967/jnumed.118.211086

Received Mar. 8, 2018; revision accepted Jun. 12, 2018. For correspondence or reprints contact: Frederik L. Giesel, Department of Nuclear Medicine, University Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany.

E-mail: frederik@egiesel.de Published online Jul. 5, 2018.

COPYRIGHT © 2019 by the Society of Nuclear Medicine and Molecular Imaging.

Dince the development of ⁶⁸Ga-labeled prostate-specific membrane antigen-HBED-CC (68Ga-PSMA-11) PET/CT about 7 y ago, the ability to accurately stage prostate cancer has improved dramatically. ⁶⁸Ga-PSMA-11 PET/CT enables a highly accurate identification of prostate cancer both within and outside the prostate. With a sensitivity and specificity for prostate cancer of up to 80% and 95%, respectively, in higher grade disease, the detection of lymph node metastases or bone lesions that would otherwise remain undetected using conventional imaging such as MRI or CT and bone scan is allowed. This is especially true for patients with high-risk disease but low prostate-specific antigen (PSA) levels (1-4). Eiber et al. demonstrated detection rates of 72.7% and 57.9% at PSA levels of 0.5-1 and 0.2-0.5 ng/mL, respectively, for a cohort of 248 patients after surgery (5). Detection rates with ⁶⁸Ga-PSMA-11 are superior to other PET probes such as ¹⁸Ffluorocholine PET/CT, especially in patients with low PSA values (6). Therefore, as it becomes more available, ⁶⁸Ga-PSMA-11 PET/ CT is increasingly used to stage high- or intermediate-risk patients with newly diagnosed or recurrent prostate cancer (7).

The role of PSMA imaging in radiation oncology has not been widely discussed. Because histologic confirmation of PSMA imaging results in patients undergoing radiation therapy has trailed behind surgical series in which histologic validation is routine, there have been less data to report. However, data supporting the accuracy of PSMA imaging based on surgery have improved confidence in using the results to guide radiotherapy. Using ⁶⁸Ga-PSMA-11 PET/CT to guide radiation could lead to a more individualized and precise delivery of radiotherapy, improving effectiveness while decreasing side effects. Although several studies have discussed the impact of ⁶⁸Ga-PSMA-11 PET/CT on prostate cancer management, most of them are focused on recurrent disease (8-12) or have included only a small number of patients (13,14). Thus, the purpose of this study was to evaluate the role of ⁶⁸Ga-PSMA-11 PET/CT in a large cohort of patients with treatment-naive or recurrent prostate cancer in altering TNM stage and radiotherapy planning.

MATERIALS AND METHODS

Study Design and Patient Characteristics

This retrospective single-center exploratory study was approved by the local institutional review board (S-636/2017) and conducted in agreement with the Declaration of Helsinki and its later amendments. Between July 2011 and August 2017, ⁶⁸Ga-PSMA-11 PET/CT was performed in 2,186 patients with prostate carcinoma at initial diagnosis or with PSA persistence/recurrence after primary treatment. Of this cohort, 2,065 patients were excluded because no comparable conventional imaging or insufficient clinical data were available for evaluation. In the remaining 121 men, conventional imaging for staging was available at a maximum of 4 mo before or after ⁶⁸Ga-PSMA-11 PET/CT (median, 28 d; range, 0–124 d). In this study, conventional imaging was performed either by MRI or CT according to national guidelines. One hundred ten patients (90.9%) underwent CT and 44 (36.4%) MRI scanning. Bone scanning was performed for all symptomatic patients and for men with 68Ga-PSMA-11 PET/CTpositive bone lesions without CT correlate. Eleven patients underwent only bone scanning due to the detection of multiple bone metastases.

⁶⁸Ga-PSMA-11 PET/CT Imaging

Fifty-three patients underwent imaging on a Biograph mCT Flow scanner (Siemens) using the following parameters: PET in 3-dimensional

mode (matrix, 200×200) was acquired using FlowMotion. For the emission data, correction for randoms, scatter, and decay was performed. Images were reconstructed with an ordered-subset expectation maximization algorithm with 2 iterations/21 subsets and Gauss-filtered to a transaxial resolution of 5 mm in full width at half maximum. An unenhanced low-dose CT reconstructed to a slice thickness of 5 mm with an increment of 3–4 mm was used for attenuation correction.

The remaining 68 patients underwent imaging on a Biograph 6 PET/CT scanner (Siemens), and examinations were performed using the following parameters: a whole-body PET image in 3-dimensional mode (matrix, 168×168) was acquired. A 4-min acquisition time with a 15.5-cm field of view was used for each bed position (16.2 cm, 4.2 cm overlapping scale). For the emission data, correction for randoms, scatter, and decay was performed. The images were reconstructed with an ordered-subset expectation maximization algorithm with 2 iterations/8 subsets and Gauss-filtered to a transaxial resolution of 5 mm in full width at half maximum. An unenhanced low-dose CT reconstructed to a slice thickness of 5 mm with an increment of 1.5 mm was used for attenuation correction.

PET imaging was acquired 63 ± 9 min after injection of a median activity of 231 MBq (range, 77–361 MBq) of 68 Ga-PSMA-11. 68 Ga-PSMA-11 was synthesized according to sterile methods as previously described (15–17).

TABLE 1
Patient Characteristics

		r ationt onaraoton			
Characteristic	All patients	Initial diagnosis	PSA persistence after surgery	PSA recurrence	
No. of patients	121	50	11	60	
Median age (y)	71 (50–84)	72 (50–84)	67 (53–75)	69 (50–84)	
Gleason score (n)					
≤6	6 (5.0%)	4 (8.0%)	<u> </u>	2 (3.3%)	
7	59 (48.8%)	18 (36.0%)	2 (18.2%)	39 (65.0%)	
≥8	55 (45.5%)	28 (56.0%)	9 (81.8%)	18 (30.0%)	
Unknown	1 (0.8%)	_	-	1 (1.7%)	
Median iPSA (ng/mL)	9.95 (1.40–520.00)	11.9 (3.50–313.13)	18.58 (5.20–87.55)	9.14 (1.40–520.00	
Nadir PSA (ng/mL)	0.09 (<0.01-9.70)	_	1.36 (0.53–9.70)	0.07 (<0.01–3.00	
PSA at PET (ng/mL)	3.06 (0.03-41.24)	9.76 (0.06-37.10)	1.27 (0.03–9.70)	1.10 (0.10-41-24	
Risk group according to D'Amico (n)					
Low	3 (2.5%)	3 (6.0%)	_	_	
Intermediate	12 (9.9%)	9 (18.0%)	_	3 (5.0%)	
High	106 (87.6%)	38 (76.0%)	11 (100.0%)	57 (95.0%)	
Ongoing ADT (n)					
Yes	26 (21.5%)	12 (24.0%)	5 (45.5%)	9 (15.0%)	
No	95 (78.5%)	38 (76.0%)	6 (54.5%)	51 (85.0%)	
Prior RP only	34 (28.1%)	_	11 (100.0%)	23 (38.3%)	
Prior RT only	5 (4.1%)	_	<u> </u>	5 (8.3%)	
Prior RP and RT	32 (26.4%)	_		32 (53.3%)	
Surgery margin					
R0	40 (33.1%)	_	2 (18.2%)	38 (69.1%)	
R1	24 (19.8%)	_	9 (81.8%)	15 (27.3%)	
Rx	2 (1.7%)	_	_	2 (3.6%)	

iPSA = initial prostate-specific antigen serum level; ADT = androgen deprivation therapy; RP = radical prostatectomy; RT = radiotherapy.

Data in parentheses are ranges unless otherwise indicated.

TABLE 2Comparison of Conventional and ⁶⁸Ga-PSMA-11 PET/CT Imaging

Characteristic	Conventional imaging	⁶⁸ Ga-PSMA-11 PET/CT	Change	P
Local relapse (n)				
PSA recurrence/persistence			30/71 (42.3%)	< 0.00
Total				
rcTx	33/71 (46.5%)	8/71 (11.3%)		
rcT0	33/71 (46.5%)	53/71 (74.6%)		
rcT+	5/71 (7.0%)	10/71 (14.1%)		
Lymph node spread (n)				
All patients	15/121 (12.4%)	39/121 (32.2%)	25/121 (20.7%)*	< 0.00
Initial diagnosis	5/50 (10.0%)	8/50 (16.0%)	5/50 (10.0%)	
Intern iliac vessels	_	2/50 (4.0%)†		
Extern iliac vessels	5/50 (10.0%)†	5/50 (10.0%)†		
Presacral	1/50 (2.0%)†	2/50 (4.0%)†		
Obturatoric vessels	_	2/50 (4.0%)†		
Other	_	1/50 (2.0%)†		
PSA recurrence/persistence	10/71 (14.1%)	31/71 (43.7%)	20/71 (28.2%)	
Intern iliac vessels	3/71 (4.2%)†	10/71 (14.1%)†		
Extern iliac vessels	3/71 (4.2%)†	13/71 (18.3%)†		
Presacral	3/71 (4.2%)†	12/71 (16.9%)†		
Obturatoric vessels	_	2/71 (2.8%)*		
Other	2/71 (2.8%)†	8/71 (11.3%)†		
Distant metastases (n)				
All patients	26/121 (21.5%)	41/121 (33.9%)	23/121 (19.0%)*	< 0.00
Initial diagnosis	3/50 (6.0%)	5/50 (10.0%)	7/50 (14.0%)	
Lymph nodes	2/50 (4.0%)	3/50 (6.0%)†		
Bone	1/50 (2.0%)	3/50 (6.0%)†		
Other	_	_		
PSA recurrence/persistence	23/71 (32.4%)	36/71 (50.7%)	16/71 (22.5%)	
Lymph nodes	2/71 (2.8%)	8/71 (11.3%)†		
Bone	18/71 (25.4%)	27/71 (38.0%)†		
Other	3/71 (4.2%)	3/71 (4.2%)†		

^{*}Also, some patients with change in T staging.

Image Evaluation

Images were analyzed using Syngo TrueD (Siemens) and an appropriate workstation. ⁶⁸Ga-PSMA-11 PET/CT scans were evaluated retrospectively by 2 board-certified nuclear medicine physicians and 1 board-certified radiation oncologist. Any tracer accumulation that was not related to physiologic tracer-uptake with relevant difference to the background was considered tumor-positive. All findings on ⁶⁸Ga-PSMA-11 PET/CT were interpreted in consensus. Conventional imaging was evaluated by 2 board-certified radiologists in consensus without knowledge of ⁶⁸Ga-PSMA-11 PET/CT results, thus establishing the pre-⁶⁸Ga-PSMA-11 PET/CT TNM classification. Lymph nodes were considered tumor-positive on CT and MRI when they had a short-axis diameter 8 mm or greater. On MRI, focal contrast-enhancement in a lesion or suggestive findings on diffusion-weighted imaging were considered positive for tumor. On the bone scan, activity not related to degenerative or traumatic processes was considered tumor-positive. According to clinical routine, physicians were not masked to patient history. Stage and radiotherapeutic management were documented before and after ⁶⁸Ga-PSMA-11 PET/CT imaging by 2 nuclear medicine physicians and 1 radiation oncologist.

Statistical Analysis

For statistical analysis Microsoft Excel for Mac, version 15.41 (Microsoft Corp.) and SPSS Statistics, version 24 (IBM Corp.) were used. Descriptive analyses were performed for patients and their tumor characteristics. Normality was tested using the Kolmogorov–Smirnov test, and mean and SD are given where normality was observed. In all other cases, median and range are used. The correlation of TNM change was determined using the McNemar test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

In total, 121 men (median age, 71 y; range, 50–84 y) with prostate carcinoma underwent ⁶⁸Ga-PSMA-11 PET/CT. Fifty patients

[†]Some patients with multiple forms of lymphatic/distant spread.

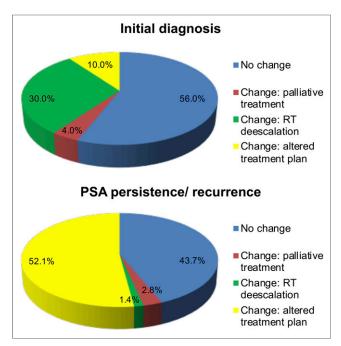


FIGURE 1. Impact of 68 Ga-PSMA-11 PET/CT imaging on radiotherapeutic management. RT = radiation therapy.

(41.3%) were scanned at initial diagnosis, 11 patients (9.1%) presented with PSA persistence after surgery and were scanned soon thereafter, and 60 men (49.6%) presented with recurrent disease at variable times after initial definitive therapy. Overall, 100 patients (87.6%) had high-risk disease at diagnosis according to D'Amico risk classification (18) (Table 1).

Conventional imaging (CT or MRI \pm bone scan) was performed in all patients. Using conventional imaging, lymph node metastases were diagnosed in 5 of 50 (10.0%) treatment-naive patients and 10 of 71 men (13.2%) after definitive treatment. Three patients (6.0%) at initial diagnosis and 23 men (32.4%) with persistence or recurrence had distant metastases (defined as extrapelvic lymph nodes, bone metastases, or soft-tissue metastases) on conventional imaging. ⁶⁸Ga-PSMA-11 PET/CT detected lymph node metastases in 39 of 121 patients (32.2%) including 16.0% of the treatment-naive group and 43.7% of the persistence/recurrence group. Five patients (10.0%) at initial diagnosis and 36 men

(50.7%) with persistence or recurrence had distant metastases on ⁶⁸Ga-PSMA-11 PET/CT imaging. For men with recurrent or persistent PSA, CT or MRI led to inconclusive findings in 46.5% regarding local relapse, whereas ⁶⁸Ga-PSMA-11 PET/CT was able to exclude recurrent disease in the prostate bed in 74.6% (Table 2). Overall, ⁶⁸Ga-PSMA-11 PET/CT resulted in a change in TNM staging in 49 patients (40.5%), including 26.0% in the treatmentnaive group and 50.7% in the persistence/recurrence group. In addition to the previously described changes in nodal and distant metastases status, T classification also changed in 14.9% of the entire cohort (treatment-naive, 8.0%; persistence/recurrence, 19.7%) after ⁶⁸Ga-PSMA-11 PET/CT imaging. By focusing on patients with a TNM change, 11 of 13 (84.6%) treatment-naive patients and 36 of 36 patients (100%) with persistence/recurrence were upstaged after ⁶⁸Ga-PSMA-11 PET/CT. The changes in TNM classification often led to a different radiotherapeutic approach. Comparing radiotherapeutic management with and without consideration of ⁶⁸Ga-PSMA-11 PET/CT data in total, a change after ⁶⁸Ga-PSMA-11 PET/CT occurred in 62 out of 121 men (51.2%) (Fig. 1).

In subgroup analyses, there was an alteration in the treatment plan in 44.0% of treatment-naive patients and 56.3% of patients with persistence/recurrence (Table 3). In general terms, ⁶⁸Ga-PSMA-11 PET/CT data resulted in a reduction of the target volume (deescalation of radiotherapy) in the treatment-naive group (in 68.2%) whereas de-escalation occurred in only 2.5% of the persistence/recurrence group. However, ⁶⁸Ga-PSMA-11 PET/CT also resulted in substantive changes in the treatment plan without de-escalation in 10.0% of treatment-naive patients and 52.0% of persistence/recurrence patients (Fig. 1; Table 4).

DISCUSSION

Radiation therapy usually benefits from more accurate depiction of the anatomic distribution of disease; for a fixed radiation dose, therapy can be directed to areas of higher risk, sparing non-involved tissues, thus improving the therapeutic index. Because of its high sensitivity for prostate cancer, ⁶⁸Ga-PSMA-11 PET/CT is helpful in individualizing treatment plans, thereby overcoming the limitations of existing conventional imaging, which is quite insensitive for extraprostatic and recurrent disease. Our study showed that TNM stage changed in 40.5% of patients after ⁶⁸Ga-PSMA-11 PET/CT. This is comparable to the findings of other studies such as a study of 57 patients in which ⁶⁸Ga-PSMA-11

TABLE 3Overview of Changes in Radiotherapeutic Management According to ⁶⁸Ga-PSMA-11 PET/CT

Characteristic	All patients	Initial diagnosis	PSA persistence/recurrence
Individual RT concept (n)		5/22 (22.7%)	37/40 (92.5%)
SIB lymph node	26/62 (41.9%)	4/22 (18.2%)	22/40 (55.0%)
SBRT lymph node	5/62 (8.1%)	1/22 (4.6%)	4/40 (10.0%)
SBRT bone lesion	6/62 (9.7%)	_	6/40 (15.0%)
Other	5/62 (8.1%)	_	5/40 (12.5%)
RT de-escalation (n)	16/62 (25.8%)	15/22 (68.2%)	1/40 (2.5%)
Palliative treatment (n)	4/62 (6.5%)	2/22 (9.1%)	2/40 (5.0%)

RT = radiotherapy; SIB = simultaneous integrated boost; SBRT = stereotactic body irradiation.

TABLE 4Changes in Radiotherapeutic Management After Additional ⁶⁸Ga-PSMA-11 PET/CT Imaging in Detail [n, (%)]

Planned RT before ⁶⁸ Ga-PSMA-11 PET/CT imaging	RT after ⁶⁸ Ga-PSMA-11 PET/CT imaging							
	RT prostate only	RT prostate and pLN	RT prostate, pLN and SIB	SBRT only	ADT	Other, individual RT concept	RT pLN and SIB	Systemic chemotherapy
RT prostate only	Х	_	4/62 (6.5%)	2/62 (3.2%)	1/62 (1.6%)	1/62 (1.6%)	_	_
RT prostate and pLN	15/62 (24.2%)	X	8/62 (12.9%)	_	_	1/62 (1.6%)	_	_
RT prostate, pLN, and SIB	_	1/62 (1.6%)	X	1/62 (1.6%)	2/62 (3.2%)	3/62 (4.8%)	_	_
SBRT only	_	_	_	X	_	3/62 (4.8%)	1/62 (1.6%)	1/62 (1.6%)
ADT	_	_	_	5/62 (8.1%)	X	4/62 (6.5%)	6/62 (9.7%)	_
Individual RT concept	_	_	_	_	_	Х	2/62 (3.2%)	_
BSC	_	_	_	1/62 (1.6%)	_	_	_	_

RT = radiotherapy; pLN = pelvic lymph nodes; SIB = simultaneous integrated boost; SBRT = stereotactic body radiotherapy, ADT = androgen deprivation therapy; BSC = best supportive care.

PET/CT resulted in a change in TNM classification in 50.8% (14). Schiller et al. reported that ⁶⁸Ga-PSMA-11 PET/CT changed TNM stage in 45.2% of patients with recurrent disease (19). ⁶⁸Ga-PSMA-11 PET/CT seems to produce TNM changes in fewer treatmentnaive patients. In our cohort, 26.0% of such patients had a TNM stage change after ⁶⁸Ga-PSMA-11 PET/CT. Confirmatory studies in this population are scarce, however, one prospective study of 431 patients, of whom 108 were treatment-naive and the remainder were recurrent, confirmed that the rate of TNM change was much higher in the latter group (20). In contrast, in a smaller study of 15

treatment-naive prostate cancer patients with patient characteristics comparable to those in our study, TNM change was reported in 53.3% of treatment-naive patients after ⁶⁸Ga-PSMA-11 PET/CT (*13*). This wide range of TNM stage alteration in treatment-naive patients may be explained by differences in the aggregate risk of each patient population and by the quality and thoroughness of conventional imaging at different institutions.

The degree to which TNM stage is altered influences the degree of changes in radiotherapeutic management. Lower rates of TNM change have commensurately lower rates of treatment plan changes.

CT-guided radiotherapy. Other studies in

In the current study, the radiotherapeutic management was altered in 44.0% of all treatment-naive patients. This contrasts with the results of Dewes et al. (33.3% treatment plan change) and Roach et al. (21.0% treatment plan change) (13,20). In recurrent or persistent disease, ⁶⁸Ga-PSMA-11 PET/CT led to a change in the radiotherapy plan in 56.3% in this study, which is in accordance with the results of a study of 100 men with recurrent disease in which 68Ga-PSMA-11 PET/CT resulted in a change of radiotherapy planning in 59.0% of cases (21). Schmidt-Hegemann et al. reported 129 men with recurrent prostate carcinoma scanned with ⁶⁸Ga-PSMA-11 PET/CT and showed changes in the radiotherapy plan in 56.6% (22). These consistent results are also supported by numerous other studies supporting the role of ⁶⁸Ga-PSMA-11 PET/CT in this setting (11,12,23,24). 68Ga-PSMA-11 PET/CT imaging identification of isolated bone metastases has led to an increase in the use of stereotactic body radiation therapy, and the detection of small nodes often leads to increased use of simultaneous integrated boost to affected areas (Fig. 2). These treatment modifications can be achieved without increased acute toxicity. For instance, Zschaeck et al. reported a low rate of acute toxicity in 21 men treated with ⁶⁸Ga-PSMA-11 PET/

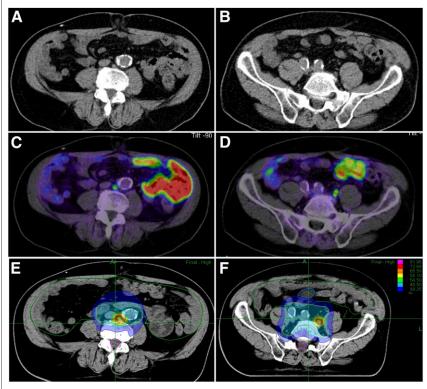


FIGURE 2. ⁶⁸Ga-PSMA-11 PET/CT (C and D) guided radiotherapy (E and F) with simultaneous integrated boost of 2 lymph node metastases for a high-risk prostate cancer patient with negative CT scan (A and B).

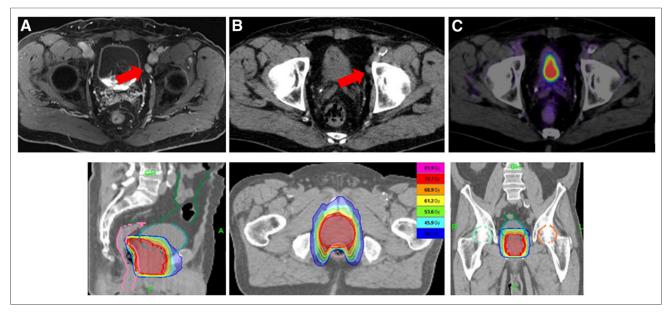


FIGURE 3. ⁶⁸Ga-PSMA-11 PET/CT-guided radiotherapy de-escalated after ⁶⁸Ga-PSMA-11 PET/CT. Whereas MRI and CT demonstrated suspicious nodes (A and B), ⁶⁸Ga-PSMA-11 PET/CT showed no increased activity in nodes (C). Thus, treatment could be planned for prostate itself with reduced doses to pelvic side walls.

patients with recurrent disease confirm these findings and demonstrate superior PSA response rates (25). Similarly, for treatment-naive patients ⁶⁸Ga-PSMA-11 PET/CT offers the ability to provide an individualized radiotherapeutic treatment approach that boosts radiation to the dominant intraprostatic lesion, with hope resulting in better local control and clinical outcome (26). Interestingly, in as many as 30.0% of the patients in our cohort, ⁶⁸Ga-PSMA-11 PET/CT results allowed de-escalation of radiotherapy in treatment-naive patients by, for instance, reducing the target volume (usually in pelvic lymph nodes), thus reducing side effects, particularly grade 3+ gastrointestinal adverse events (Fig. 3) (27).

Although this is one of the largest studies exploring the effect of ⁶⁸Ga-PSMA-11 PET/CT on radiation treatment planning, it has several limitations. The major limitation is the retrospective nature of the study, which makes it prone to patient-selection biases. This can be overcome only by prospective randomized trials in which one arm uses ⁶⁸Ga-PSMA-11 PET/CT to guide therapy and the other arm does not. As ⁶⁸Ga-PSMA-11 imaging becomes more widely available, such trials will likely be conducted. Also, there was a relatively small number of patients with PSA persistence, although persistence may simply be considered as part of the spectrum of recurrent disease and it may not be necessary to subclassify this group.

CONCLUSION

This study confirms that ⁶⁸Ga-PSMA-11 PET/CT is well suited to detect intra- and extraprostatic prostate cancer in men with high-risk disease, both at initial diagnosis and at the time of PSA persistence/recurrence. In clinical terms, the use of ⁶⁸Ga-PSMA-11 PET/CT often results in a change in TNM staging and therefore, radiotherapeutic management. Even when considering that the impact might be greater for men with recurrent disease, this innovative new technology can be seen as a first step toward the realization of individualized radiation oncology for patients with advanced prostate carcinoma.

DISCLOSURE

No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ⁶⁸Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42:197–209.
- Hijazi S, Meller B, Leitsmann C, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by ⁶⁸Ga-PSMA-positron emission tomography/computerized tomography. *Prostate*. 2015;75:1934–1940.
- Giesel FL, Sterzing F, Schlemmer HP, et al. Intra-individual comparison of ⁶⁸Ga-PSMA-11-PET/CT and multi-parametric MR for imaging of primary prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43:1400–1406.
- Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive ⁶⁸Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2016;70:926–937.
- Bluemel C, Krebs M, Polat B, et al. ⁶⁸Ga-PSMA-PET/CT in patients with biochemical prostate cancer recurrence and negative ¹⁸F-choline-PET/CT. Clin Nucl Med. 2016;41:515–521.
- Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid ⁶⁸Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med.* 2015;56:668–674.
- Calais J, Cao M, Nickols NG. The utility of PET/CT in the planning of external radiation therapy for prostate cancer. J Nucl Med. 2018;59:557–567.
- Bluemel C, Linke F, Herrmann K, et al. Impact of ⁶⁸Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer and persisting PSA values or biochemical relapse after prostatectomy. *EJNMMI Res.* 2016;6:78.
- Verburg FA, Pfister D, Heidenreich A, et al. Extent of disease in recurrent prostate cancer determined by [68Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. Eur J Nucl Med Mol Imaging. 2016;43:397–403.
- Calais J, Czernin J, Cao M, et al. ⁶⁸Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence after radical prostatectomy in 270 patients with a PSA level of less than 1.0 ng/mL: impact on salvage radiotherapy planning. J Nucl Med. 2018;59:230–237.
- Afaq A, Alahmed S, Chen SH, et al. Impact of ⁶⁸Ga-prostate-specific membrane antigen PET/CT on prostate cancer management. J Nucl Med. 2018;59:89–92.

- Grubmüller B, Baltzer P, D'Andrea D, et al. ⁶⁸Ga-PSMA 11 ligand PET imaging in patients with biochemical recurrence after radical prostatectomy: diagnostic performance and impact on therapeutic decision-making. *Eur J Nucl Med Mol Imaging*. 2018;45:235–242.
- Dewes S, Schiller K, Sauter K, et al. Integration of ⁶⁸Ga-PSMA-PET imaging in planning of primary definitive radiotherapy in prostate cancer: a retrospective study. *Radiat Oncol.* 2016:11:73.
- Sterzing F, Kratochwil C, Fiedler H, et al. ⁶⁸Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. *Eur J Nucl Med Mol Imaging*. 2016;43:34–41.
- Eder M, Schafer M, Bauder-Wust U, et al. ⁶⁸Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconjug Chem.* 2012;23:688–697.
- Schäfer M, Bauder-Wust U, Leotta K, et al. A dimerized urea-based inhibitor of the prostate-specific membrane antigen for ⁶⁸Ga-PET imaging of prostate cancer. *EJNMMI Res.* 2012;2:23.
- Eder M, Neels O, Muller M, et al. Novel Preclinical and radiopharmaceutical aspects of [68Ga]Ga-PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer. *Pharmaceuticals (Basel)*. 2014;7:779–796.
- D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969–974.
- Schiller K, Sauter K, Dewes S, et al. Patterns of failure after radical prostatectomy in prostate cancer: implications for radiation therapy planning after ⁶⁸Ga-PSMA-PET imaging. Eur J Nucl Med Mol Imaging. 2017;44:1656–1662

- Roach PJ, Francis R, Emmett L, et al. The impact of ⁶⁸Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. J Nucl Med. 2018;59:82–88.
- Habl G, Sauter K, Schiller K, et al. 68 Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: individualized medicine or new standard in salvage treatment. *Prostate*. 2017;77:920–927.
- Schmidt-Hegemann NS, Fendler WP, Buchner A, et al. Detection level and pattern of positive lesions using PSMA PET/CT for staging prior to radiation therapy. *Radiat Oncol.* 2017;12:176.
- Gupta SK, Watson T, Denham J, et al. Prostate-specific membrane antigen positron emission tomography-computed tomography for prostate cancer: distribution of disease and implications for radiation therapy planning. *Int J Radiat Oncol Biol Phys.* 2017;99:701–709.
- Kabasakal L, Demirci E, Nematyazar J, et al. The role of PSMA PET/CT imaging in restaging of prostate cancer patients with low prostate-specific antigen levels. *Nucl Med Commun.* 2017;38:149–155.
- Zschaeck S, Wust P, Beck M, et al. Intermediate-term outcome after PSMA-PET guided high-dose radiotherapy of recurrent high-risk prostate cancer patients. *Radiat Oncol.* 2017;12:140.
- Koerber SA, Utzinger MT, Kratochwil C, et al. ⁶⁸Ga-PSMA-11 PET/CT in newly diagnosed carcinoma of the prostate: correlation of intraprostatic PSMA uptake with several clinical parameters. *J Nucl Med.* 2017;58:1943–1948.
- Roach M, 3rd, DeSilvio M, Valicenti R, et al. Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. Int J Radiat Oncol Biol Phys. 2006;66:647–653.