Journal of Nuclear Medicine, published on July 5, 2018 as doi:10.2967/jnumed.118.211086

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

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Running title: PSMA-11: implications for RT management

Total words: 4368
Word count abstract: 200

ABSTRACT

The present study analyzed the impact of Gallium-68 (^{68}Ga)-labeled prostate-specific membrane antigen-HBED-CC (^{68}Ga-PSMA-11) positron-emission tomography (PET)/computed tomography (CT) on radiotherapeutic management in a large cohort of men with primary or recurrent disease. **Methods**: This study investigated 121 men with carcinoma of the prostate who underwent ^{68}Ga-PSMA-11 PET/CT as well as conventional imaging. 50 patients were treatment naive, 11 had persistent prostate-specific antigen (PSA) soon after surgery and 60 presented with recurrent PSA following definitive therapy. Changes in TNM classification of malignant tumors (TNM) stage and radiotherapeutic management after ^{68}Ga-PSMA-11 imaging were compared to 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**: ^{68}Ga-PSMA-11 PET/CT may shortly become an indispensable tool for detecting prostate cancer lesions in treatment-naïve patients as well as in men with recurrent disease or persistent PSA and seems to be very helpful in personalizing radiotherapeutic management to the individual patients' distribution of disease.

Key words: prostate cancer, PSMA, PET/CT, radiotherapy, staging

INTRODUCTION

Since the development of ^{68}Ga-PSMA-11 PET/CT about seven years ago, the ability to accurately stage prostate cancer has improved dramatically. ^{68}Ga-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 which would otherwise remain undetected using conventional imaging such as magnetic resonance imaging (MRI) or computed tomography 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 for a cohort of 248 patients after surgery (*5*). Detection rates with ^{68}Ga-PSMA-11 are superior to other PET probes such as ^{18}F-Fluorocholine PET/CT, especially in patients with low PSA-values (*6*). Therefore, as it becomes more available, ^{68}Ga-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. Since histologic confirmation of PSMA imaging results in patients undergoing radiation therapy has trailed behind surgical series in which histologic validation is routine, there has been less data to report. However, data supporting the accuracy of PSMA imaging based on surgery has improved confidence in using the results to guide radiotherapy. Using ^{68}Ga-PSMA-11 PET/CT to guide radiation could lead to a more individualized and precise delivery of radiotherapy improving effectiveness while decreasing side effects. While several studies have discussed the impact of ^{68}Ga-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 ^{68}Ga-PSMA-11 PET/CT in a large cohort of patients with treatment naïve 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, ^{68}Ga-PSMA-11 PET/CT was performed in 2186 patients with prostate carcinoma at initial diagnosis or with PSA persistence/recurrence after primary treatment. Of this cohort, 2065 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 four months prior to or after ^{68}Ga-PSMA-11 PET/CT (median: 28 days, range: 0 – 124 days). In this study, conventional imaging was performed either by MRI or CT according to national guidelines. 110 patients (90.9%) received CT and 44 (36.4%) MRI scan. Bone scan was performed for all symptomatic patients and for men with ^{68}Ga-PSMA-11 PET/CT-positive bone lesions without CT-correlate. Eleven patients had only bone scan due to the detection of multiple bone metastases.

^{68}Ga-PSMA-11 PET/CT Imaging

53 patients underwent imaging on a Biograph mCT Flow scanner (*Siemens, Erlangen, Germany*) using the following parameters: PET in 3D mode (matrix 200 × 200) was acquired using FlowMotion. For the emission data, correction for randoms, scatter and decay was performed. Reconstruction of the images was done with an ordered subset expectation maximization algorithm with 2 iterations/21 subsets and Gauss-filtered to a trans axial resolution of 5 mm at 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, Erlangen, Germany*) and examinations were performed using the following parameters: a whole-body PET in 3D mode (matrix 168 × 168) was acquired. A four-minute 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. Reconstruction of the images was done with an ordered subset expectation maximization algorithm with 2 iterations/8 subsets and Gauss-filtered to a transaxial resolution of 5 mm at 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) ^{68}Ga-PSMA-11. Synthesis of ^{68}Ga-PSMA-11 was performed according to sterile methods as previously described (*15-17*).

Image Evaluation

Image analysis was performed using Syngo TrueD (*Siemens, Erlangen, Germany*) and an appropriate workstation. ^{68}Ga-PSMA-11 PET/CT scans were evaluated retrospectively by two board-certified nuclear medicine physicians and one board-certified radiation oncologist. Any tracer-accumulation that was not related to physiological tracer-uptake with relevant difference to the background, was considered tumor-positive. All findings on ^{68}Ga-PSMA-11 PET/CT were interpreted in consensus. Evaluation of conventional imaging was done by two board-certified radiologists in consensus without knowledge of ^{68}Ga-PSMA-11 PET/CT results thus establishing the pre-^{68}Ga-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. On MRI, focal contrast-enhancement in a lesion or suggestive findings on diffusion weighted imaging were considered positive for tumor. On bone scan activity not related to degenerative processes was considered tumor-positive. According to clinical routine, physicians were not blinded to patient history. Stage and radiotherapeutic management was documented before and after ^{68}Ga-PSMA-11 PET/CT imaging by two nuclear medicine physicians and one radiation oncologist.

Statistical Analysis

For statistical analysis Microsoft Excel for Mac Version 15.41 (*Microsoft Corporation, Redmond/ Washington, USA*) and SPSS Statistics Version 24 (*IBM Corp., Armonk/ NY, USA*) were used. Descriptive

analyses were performed for patients and their tumor characteristics. Normality was tested using the Kolmogorov-Smirnov-test and mean and standard deviation are given where normality was observed. In all other cases, median and range are used. The correlation of TNM change was determined by using McNemar test. A p-value of < 0.05 was considered statistically significant.

RESULTS

In total, 121 men (median age: 71 years, range: 50 – 84) with prostate carcinoma underwent ^{68}Ga-PSMA-11 PET/CT. Fifty patients (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 ± bone scan) was performed in all patients. Using conventional imaging, lymph node metastasis was diagnosed in 5 of 50 (10.0%) treatment-naïve 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 extra-pelvic lymph nodes, bone metastases and/ or soft tissue metastases) on conventional imaging. ^{68}Ga-PSMA-11 PET/CT detected lymph node metastases in 39 out of 121 patients (32.2%) including 16.0% of the treatment-naïve 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 ^{68}Ga-PSMA-11 PET/CT imaging. For men with recurrent or persistent PSA, CT and/ or MRI lead to inconclusive findings in 46.5% regarding local relapse, while PSMA-imaging was able to exclude recurrent disease in the prostate bed in 74.6% (**Table 2**). Overall, ^{68}Ga-PSMA-11 PET/CT resulted in a change in TNM staging in 49 patients (40.5%), including 26.0% in the treatment naïve 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-naïve: 8.0%; persistence/recurrence: 19.7%) following ^{68}Ga-PSMA-11 PET/CT imaging. By focusing on patients with a TNM change, 11 of 13 (84.6%) treatment naïve patients and 36 of 36 patients (100%) with persistence/recurrence were upstaged after ^{68}Ga-PSMA-11 PET/CT. The changes in TNM classification often lead to a different radiotherapeutic approach. Comparing radiotherapeutic management with and without consideration of PSMA-data for all patients, in total, for 62 of 121 men (51.2%) a change occurred after ^{68}Ga-PSMA-11 PET/CT (**Fig. 1**).

In subgroup analyses, there was an alteration in the treatment plan in 44.0% of treatment-naïve patients and 56.3% of patients with persistence/recurrence (**Table 3**). In general terms, ^{68}Ga-PSMA-11 PET/CT data resulted in a reduction of the target volume (de-escalation of radiotherapy) in the treatment naïve group (68.2%) while de-escalation occurred in only 2.5% of the persistence/recurrence group. However, ^{68}Ga-PSMA-11 PET/CT also resulted in substantive changes in the treatment plan without de-escalation in 10% of treatment naïve patients and 52% of persistence/recurrence patients (**Fig. 1 and 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 noninvolved tissues, thus improving the therapeutic index. Due to its high sensitivity for prostate cancer, ^{68}Ga-PSMA-11 PET/CT is very 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 50.7% of patients after ^{68}Ga-PSMA-11 PET/CT. This is comparable to the findings of other studies such as a study of 57 patients in which ^{68}Ga-PSMA-11 PET/CT resulted in a change in TNM classification in 50.8% (*14*). Schiller et al. reported that ^{68}Ga-PSMA-11 PET/CT changed TNM stage in 45.2% of patients with recurrent disease (*19*). ^{68}Ga-PSMA-11 PET/CT seems to produce TNM changes in fewer treatment naïve patients. In our cohort, 26% of such patients had a TNM stage change after ^{68}Ga-PSMA-11 PET/CT. Confirmatory studies in this population are scarce, however, one prospective study of 431 patients, of whom 108 were treatment naïve 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-naïve prostate cancer patients with comparable patient characteristics to our study, TNM change was reported in 53.3% of treatment naïve patients after ^{68}Ga-PSMA-11 PET/CT (*13*). This wide range of TNM stage alteration in treatment naïve 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. In the current study, the radiotherapeutic management was altered in 44.0% of all treatment naïve patients. This contrasts with the results of Dewes et al. (33.3% treatment plan change) and Roach et al. (21% treatment plan change) (*13*,*20*). In recurrent or persistent disease ^{68}Ga-PSMA-11 PET/CT lead 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 ^{68}Ga-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 ^{68}Ga-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 ^{68}Ga-PSMA-11 PET/CT in this setting (*11*,*12*,*23*,*24*). ^{68}Ga-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 ^{68}Ga-PSMA-11 PET/CT-guided radiotherapy. Other studies in patients with recurrent disease confirm these findings and demonstrate superior PSA response rates (*25*). Similarly, for treatment naïve patients ^{68}Ga-PSMA-11 PET/CT offers the ability to provide an individualized radiotherapeutic treatment approach which boosts radiation to the dominant intraprostatic lesion, hopefully resulting in better local control and clinical outcome (*26*). Interestingly, in as many as 30% of the patients in our cohort, ^{68}Ga-PSMA-11 PET/CT results allowed de-escalation of radiotherapy in treatment naïve patients by, for instance, reducing the target volume (usually in the pelvic 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 ^{68}Ga-PSMA-11 PET/CT on radiation treatment planning, it has several limitations. The major limitation is the retrospective nature the study which makes it prone to patient selection biases. This can only be overcome by prospective randomized trials in which one arm employs ^{68}Ga-PSMA-11 PET/CT to guide therapy and the other arm does not. As PSMA 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 ^{68}Ga-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 ^{68}Ga-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 towards the realization of individualized radiation oncology for patients with advanced prostate carcinoma.

DECLARATION

List of Abbreviations

^{68}Ga-PSMA-11	Gallium-68 (^{68}Ga)-labeled prostate-specific membrane antigen-HBED-CC
PET	positron-emission tomography
CT	computed tomography
PSA	prostate-specific antigen
TNM	TNM classification of malignant tumors
MRI	magnetic resonance imaging

Conflicts of Interests

No potential conflicts of interest relevant to this article exist.

Acknowledgments

None.

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FIGURES

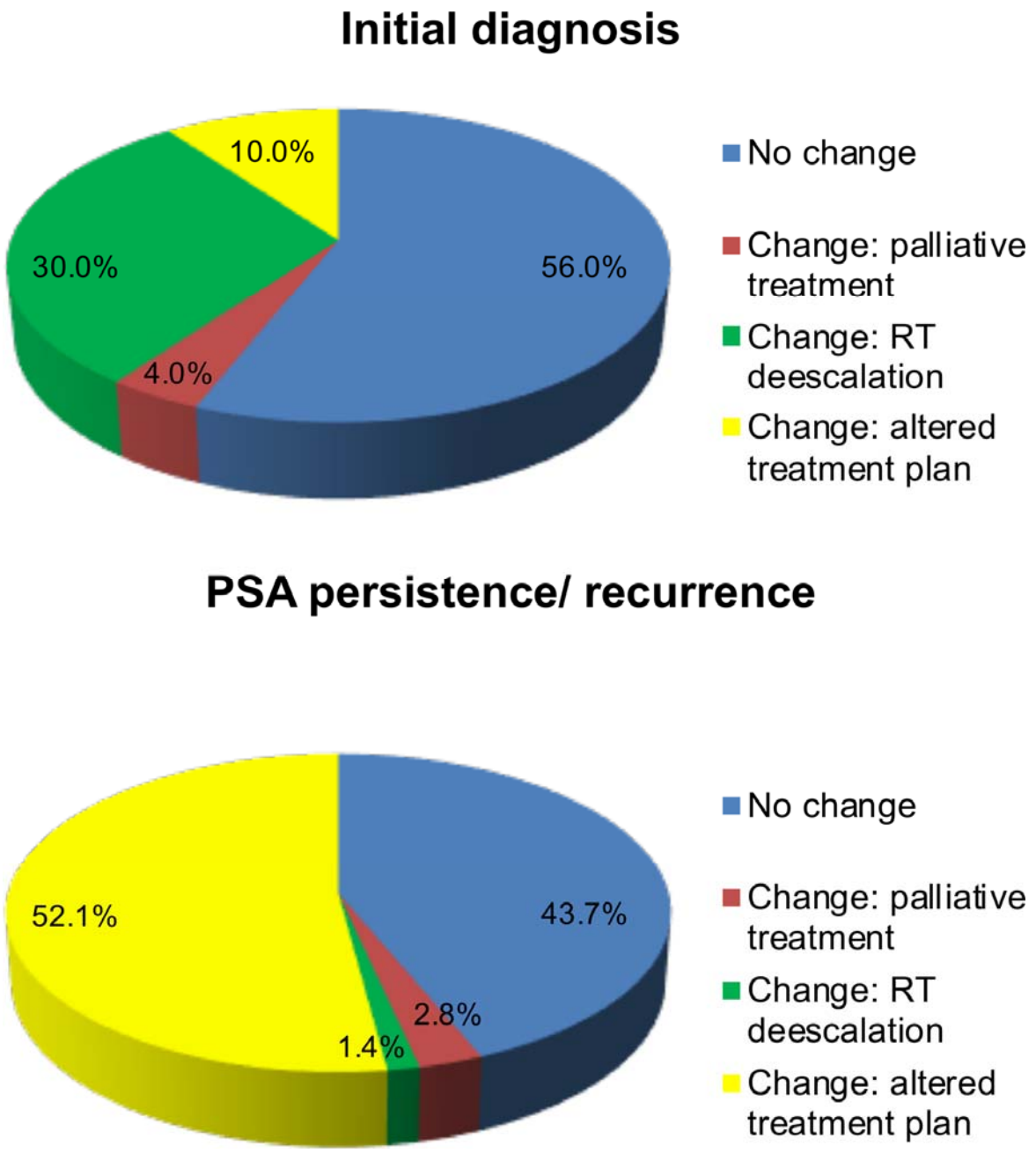

FIGURE 1. Impact of ^{68}Ga-PSMA-11 PET/CT imaging on radiotherapeutic management. (RT = radiation therapy)

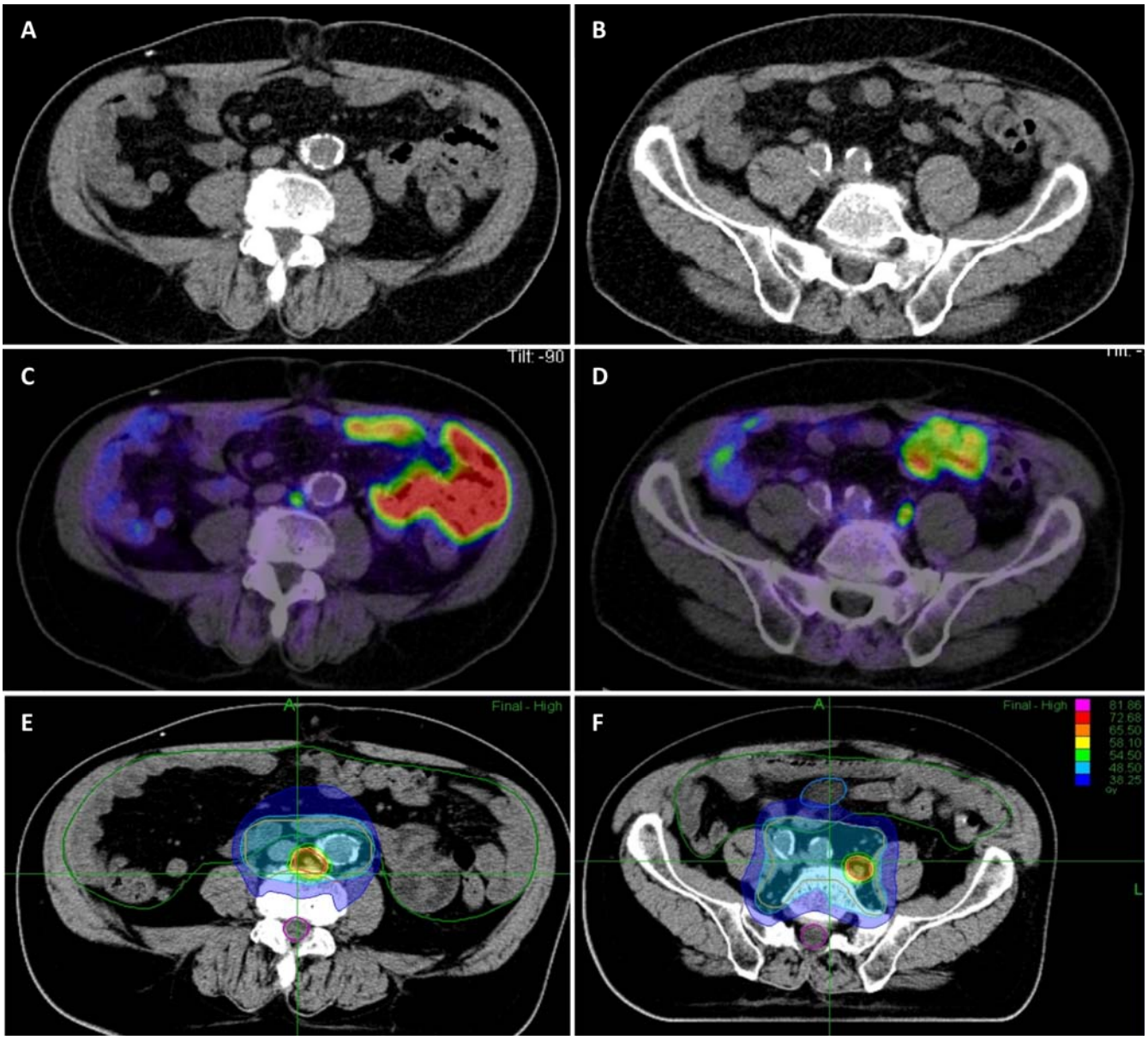

FIGURE 2. ^{68}Ga-PSMA-11 PET/CT (C and D) guided radiotherapy (E and F) with SIB of two lymph node metastases for a high-risk prostate cancer patient with negative CT-scan (A and B).

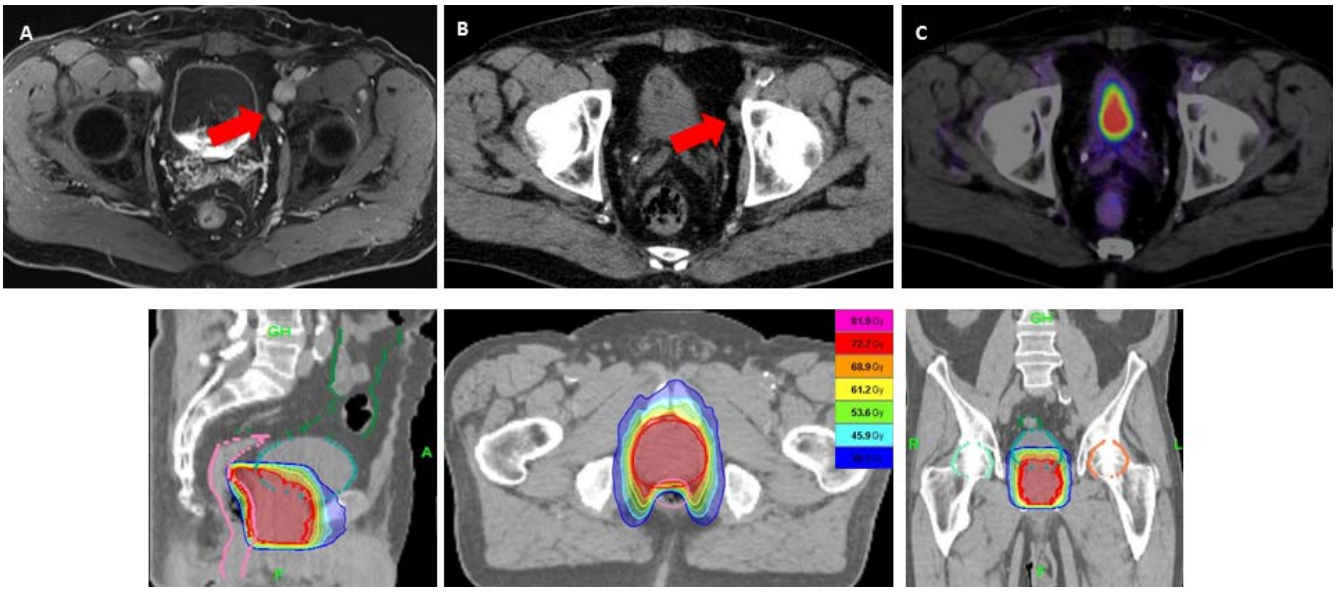

FIGURE 3. ^{68}Ga-PSMA-11 PET/CT guided radiotherapy de-escalated after ^{68}Ga-PSMA-11 PET/CT. Whereas MRI and CT demonstrated suspicious nodes (A and B), ^{68}Ga-PSMA-11 PET/CT showed no increased activity in the nodes (C): Thus, treatment could be planned for the prostate itself with reduced doses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

TABLES

TABLE 1: Patient characteristics.

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

Characteristic	All patients	Initial diagnosis	PSA persistence after surgery	PSA recurrence
Patient number	121	50	11	60
Age [years], median (range)	71 (50-84)	72 (50-84)	67 (53-75)	69 (50-84)
Gleason score, n (%)				
≤6	6 (5.0%)	4 (8.0%)	-	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%)
iPSA [ng/mL], median (range)	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%)	-	-	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%)

TABLE 2: Comparison of conventional and ^{68}Ga-PSMA-11 PET/CT imaging.

*some patients with multiple forms of lymphatic/ distant spread

†also, some patients with change in T-staging

Characteristic		Conventional imaging	^{68}Ga-PSMA-11 PET/CT	Change	
Local relapse, n (%)					
PSA recurrence/ persistence	Total			**30/71 (42.3%)**	**p < 0.001**
	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%)**†	**p < 0.001**
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%)**†	**p < 0.001**
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%)*		

TABLE 3: Overview of changes in radiotherapeutic management according to ^{68}Ga-PSMA-11 PET/CT.

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

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%)**

TABLE 4: Changes in radiotherapeutic management after additional ^{68}Ga-PSMA-11 PET/CT imaging in detail [n, (%)].

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

		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 chemo-therapy**
Planned RT prior to ^{68}Ga-PSMA-11 PET/CT imaging	**RT prostate only**	X	-	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	-	-	-	-	-	X	2/62 (3.2%)	-
	BSC	-	-	-	1/62 (1.6%)	-	-	-	-