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Mapping prostate cancer lesions pre/post unsuccessful salvage lymph node dissection using repeat PSMA-PET

Title Page

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Mapping prostate cancer lesions pre/post unsuccessful salvage lymph node dissection using repeat PSMA-PET

Short running title

PSMA PET **pre/post** SLND

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ABSTRACT

Introduction: The aim of this study was **to analyze patterns of persistent versus recurrent or new PET lesions in a selected patient cohort** with PSA persistence following salvage lymph node dissection (SLND) **and pre/post procedure prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET).**

Material and Methods: 16 patients were included in this multicenter study. Inclusion criteria were: a) PSMA-PET performed for biochemical recurrence before SLND (pre-SLND PET) and b) repeat PSMA-PET performed for persistently elevated PSA level (≥0.1 ng/mL) ≥6 weeks after SLND (post-SLND PET). Image analysis was performed by three independent nuclear medicine physicians applying the molecular imaging TNM system PROMISE. Lesions were confirmed by histopathology, presence on correlative CT/MRI/bone scan or PSA response after focal therapy.

Results: post-SLND PET identified PCa-lesions in 88% (14/16) of patients with PSA persistence after SLND. Median PSA was 1.2 ng/mL (IQR, 0.6-2.8 ng/mL). Disease was confined to the pelvis in 56% of patients (9/16) and most of these men had common iliac (6/16, 38%) and internal iliac lymph node metastases (6/16, 38%). Extrapelvic disease was detected in 31% of patients (5/16). In pre- and post-SLND PET comparison, 10/16 had at least one lesion already detected at baseline (63% PET persistence); 4/16 had new lesions only (25% PET recurrence); 2 had no disease on post-SLND PET. All validated regions (11 regions in 9 patients) were true positive. 9/14 (64%) patients underwent repeat local therapies after SLND (7/14 radiotherapy, 2/14 surgery).

Conclusions: SLND of pelvic nodal metastases was often not complete according to PSMA-PET. **About two thirds of patients had PET positive nodal disease after SLND already seen on pre-SLND PSMA-PET.** Notably, about one quarter of patients had new lesions, not detected by pre-surgical PSMA-PET.

INTRODUCTION

In cases of biochemical recurrence after radical prostatectomy (RP) it is important to determine whether the recurrence has developed at local or distant sites. Therefore, current guidelines recommend **prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET)**-imaging if the outcome will affect treatment planning (*1*). Promising efficacy of metastases-directed therapy such as salvage lymph node dissection (SLND) or salvage radiotherapy (S-RT) has been reported in several studies (*2*,*3*), but evidence on the long-term oncological impact is missing. In patients with longer PSA doubling times, lower RP specimen pathological ISUP grades and disease recurrence confined to lymph nodes, metastases-directed therapy aims at decreased risk of distant progression, later onset of ADT and potential improvement of cancer-specific survival. PSMA-PET provides localization of biochemically recurrent prostate cancer (PCa) with unprecedented accuracy even at low PSA levels (*4*–*7*). Resection of suspicious nodes is feasible, however more than half of patients demonstrate persistently elevated PSA following SLND (*8*). Accurate staging is helpful to localize the source of PSA for subsequent management decisions, including surveillance, repeat localized salvage or systemic therapy. Disease locations individually guide local re-treatment to balance efficacy and potential toxicity (*8*). **Conventional imaging does not localize relevant lesions in this clinical setting, especially at low PSA levels. PSMA-PET is a promising staging tool sensitive enough to uncover disease locations before and after salvage lymph node dissection.** We hypothesize that PSMA-PET localizes residual and new PCa lesions in patients with PSA persistence following SLND with high accuracy. **We therefore selected patients with pre/post procedure PSMA-PET to better understand disease patterns of unsuccessful salvage lymph node resection.**

MATERIAL AND METHODS

Patient Population

Between June 2013 and April 2018, datasets from 7013 patients with PSMA-PET for PCa were retrospectively reviewed at 6 high-volume nuclear medicine centers and 16 patients with PSA persistence after SLND were enrolled (**Fig. 1)**. Inclusion criteria were: a) PSMA-PET performed for biochemical recurrence of PCa before SLND (pre-SLND PET); b) repeat PSMA-PET performed for persistently elevated PSA level (≥0.1 ng/mL) ≥6 weeks after SLND (post-SLND PET). Anonymized data were centrally collected at the Department of Nuclear Medicine of the University Duisburg-Essen, Germany. This retrospective analysis was approved by the local ethics committee (reference number 18-8136-BO), which waived requirement to obtain informed consent for inclusion.

Image Acquisition

^{68}Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)]) was used as the PSMA ligand. The median injected activity was 154 MBq (IQR 100-172 MBq). The median uptake time was 64 minutes (IQR 56-77). Intravenous contrast was given before 26/32 (81%) PET/CT scans. PET imaging protocols were in accordance with the Joint SNMMI/EANM procedure guideline for PSMA-PET imaging (*9*).

Image Interpretation

Anonymized imaging datasets were evaluated independently by three experienced nuclear medicine physicians with at least two years of experience in PSMA-PET imaging following recent recommendations (*9*,*10*) and unaware of clinical history. Readers were trained based on 30 PSMA-PET cases ranging from unremarkable to extensive disease and including typical pitfalls before analyzing images (*11*). Based on the molecular imaging TNM system PROMISE, the following regions

(subregions) were systematically rated as positive versus negative for PCa (*12*,*13*): prostate bed (T), pelvic nodes (N) (internal iliac, obturator, external iliac, mesorectal, presacral, common iliac), extrapelvic nodes (M1a) (retroperitoneal, mesenteric, inguinal, above diaphragm), bone (M1b), and visceral organs (M1c). In case of discordance, consensus (PET positive versus negative) was determined by 2 versus 1 majority vote among the three readers.

Lesion Validation and Management

Local investigators reviewed patient files for correlative and follow-up information acquired during routine clinical practice. Post-SLND PET-positive findings were confirmed by histopathology, presence of lesions on correlative CT/MRI/bone scan or PSA response >50% after focal therapy acquired during clinical routine. PET-positive findings were validated as true or false-positive on a region basis.

Statistical Analysis

For continuous data median and interquartile range (IQR) were reported, while categorical variables were described using frequencies. PSMA-PET detection rate for the localization of residual PCa post-SLND was determined on a patient basis stratified by PSA at the time of PET and PSA nadir after SLND. Association between PSMA-PET results, presence of local/distant lesions and PSA at the time of PET, PSA nadir, PSA doubling time (PSA-DT) or PSA velocity (PSA-V) was evaluated with non-parametric Mann-Whitney U tests in view of their asymmetric distribution. Furthermore, individual patient data are given. Overall agreement among three readers was evaluated using Fleiss's kappa coefficient (κ). All analyses were performed using *Stata software package, version 15* (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

RESULTS

Patient characteristics are given in Table 1. The median PSA nadir after SLND was 0.4 ng/mL (IQR, 0.3-2.5 ng/mL) and the median PSA value at the time of PET post-SLND was 1.2 ng/mL (IQR, 0.6-2.8 ng/mL). Individual patient characteristics and PET findings are listed in Table 2. **Regarding PSA persistence,** disease was localized post-SLND in 14/16 patients resulting in an overall detection rate of 88%. PSA at the time of PET, PSA nadir, PSA-DT or PSA-V were not significantly associated with post-SLND PET result (positive or negative) (**Fig. 2**). In the patient-based analysis, disease confined to the pelvis was detected in 56% of patients (9/16), with predominant pelvic nodal disease (9/16, 56%) and one local recurrence (1/16, 6%). Most frequently affected pelvic nodal regions were common iliac (6/16, 38%) and internal iliac (6/16, 38%). Distant disease was detected in 31% of patients (5/16). Extra-pelvic lymph nodes were detected in 4/16 patients (25%) whereas bone lesions in 1/16 (6%). There was a statistically significant association between higher PSA (p=0.047) or shorter PSA-DT (p=0.018) at the time of PET and presence of distant lesions. Longer PSA-DT was significantly associated with presence of local lesions only (p=0.02). PET positive pelvic nodes presented with intense PSMA uptake (median SUV_{max} 15; IQR 9-21), however most were not enlarged by CT criteria (median short diameter 0.8 cm; IQR 0.5-0.9).

Pre- and Post-Surgery PET Comparison

PSMA-PET was performed before SLND with a median time of 1 months (IQR, 1–2 months). The median time between SLND and PET post-SLND was 4 months (IQR, 2-6 months). Findings on PSMA-PET before SLND are listed in Supplemental Table 1. All lesions noted on pre-SLND PET were reported for surgery planning. Median number of lymph nodes removed at SLND was 17 (IQR, 10-20). Overall, pre-SLND PET detected 24 pelvic lymph node metastases whereas SLND resulted in 88 histopathology positive nodes (226 nodes were removed in total).

After SLND, all men had PSA persistence (selection criteria for the current analysis). PET post-SLND in these 16 patients demonstrated the following: 10 (63%) had at least one lesion already detected pre-SLND (PET persistence or mixed) whereas 4 (25%) had new lesions post-SLND only (PET recurrence) (**Fig. 3**). Most frequently affected nodal regions with PET persistence were internal iliac (5/10), obturator (3/10) and external iliac (3/10 N1 regions). Lesions recurred most often in common iliac (5/10) regions. 2/16 (13%) patients had no disease on PET post-SLND.

Patient 8 presented mild focal uptake in the fifth left rib (SUV_{max} 3) before SLND. PET was read equivocal in absence of sclerosis on CT. PET post-SLND demonstrated intense focal uptake highly suggesting the presence of unifocal bone metastasis (SUV_{max} 14). Patient examples for persistent and recurrent metastases are given in **Supplemental Figs. 1** and **2**.

Inter-Reader Agreement, Lesion Validation and Management

Overall interpretation among three readers had fair agreement for the local prostate bed (Fleiss' κ 0.33) and substantial to almost-perfect agreement for pelvic nodes (κ 0.69) and distant metastases (κ 0.68).

Lesion validation was available in 9/16 patients (56%) and 11/11 validated regions were true positive: 5 with histology, 4 with imaging follow-up and 2 with PSA response >50% after S-RT (Table 3).

Management after PSMA-PET was recorded in 14/16 patients (88%). 9/14 (64%) patients had repeat local therapies: patients 1, 3, 10, 11, 13, 14 and 16 received S-RT ± ADT, patient 5 had repeat SLND. Patient 9 underwent salvage surgery confirming local PCa relapse with bladder invasion as well as a nodal metastasis. Patients 7 and 15 were started on ADT. Patient 2, 6 and 8 had surveillance.

DISCUSSION

Patients undergoing SLND often experience PSA persistence or early relapse (*8*). As management of SLND failure is beyond guideline recommendations and often individually tailored, accurate staging of persistent disease is of high importance for subsequent management decisions. Treatment options include surveillance, systemic therapy or repeat salvage attempts for localized disease.

Previously, PSMA-PET demonstrated superior accuracy for the localization of recurrent PCa at low PSA values (*4*,*14*). Furthermore, PSMA-PET localized persistent PCa after RP (*15*). **In a SLND scenario, staging patients is crucial before proceeding with surgery. However, disease location and etiology of PSA failure has not been analyzed systematically yet. PSMA-PET provides high accuracy needed to map persistent and/or new lesions after unsuccessful SLND, even for sub centimeter lymph node metastases.**

In this study, repeat PSMA-PET was assessed in 16 patients to characterize patterns of persistent versus recurrent disease locations for unsuccessful SLND defined as PSA persistence (PSA ≥ 0.1 ng/mL) after surgery.

This is the first study systematically comparing PSMA-PET before and after SLND for PSA persistence. In our highly selected cohort, repeat PSMA-PET localized disease in nearly all patients with biochemical failure after PET-informed salvage surgery. **By comparing both pre-SLND and post-SLND PET we demonstrate that lesions were already noted on PET in about two thirds of patients before salvage-surgery (persistence). PET persistence was most often noted for the internal iliac and obturator regions with more difficult surgical access.** The median size of PET-positive pelvic lymph nodes was 0.8 cm, thus, below CT/MRI size thresholds for metastatic disease (*16*,*17*). **Pre-SLND PET findings were known to the surgeon and most of the PET-**

positive regions were surgically explored during SLND indicating need for improved PET-guidance for the standard resection templates.

As demonstrated previously, PSMA-PET **outside the prostate bed** was highly reproducible and predictive for prostate cancer location (*4*,*15*). **However,** pre- and post-salvage surgery PSMA-PET underestimated the total number of diseased nodes pre-SLND (*17*). **Also, in about one-quarter of the patients, the PSMA-PET after SLND showed lesions which were not visible before SLND, rated as PET recurrence. PSA persistence indicates that lesions may have been present before surgery, but were not picked up due to sub maximal sensitivity of PSMA-PET. Deficiencies for the detection of small metastases have been characterized previously** (*17*)**.** Despite underestimation on a single lesion level, identification of diseased regions informs targeted therapy, including radiotherapy and repeat surgery, especially in a PSMA radio-guided setting (*18*). Focal therapy guided by PSMA-PET may lead to effective reduction in serum PSA levels (*4*).

In our study, about two thirds of patients underwent repeat local therapy after SLND-failure. The addition of adjuvant radiotherapy might be beneficial with regards to improved local recurrence-free survival (*19*). In this setting, patients might benefit from accurate PSMA-PET staging (*20*,*21*), however prospective randomized evidence is needed to assess oncologic outcomes.

Furthermore, patients demonstrated short PSA-DT highlighting that patient selection for salvage interventions should not only be based on imaging but also consider PSA kinetics and pathological grades.

Limitations of the present study are its retrospective design and the small cohort size of a highly selected patient group. **Bias is introduced by selection of intra-individual pre and post SLND PSMA-PET pairs, which are typically not available in the standard SLND setting. Patient characteristics and increased imaging indicate high risk, which may have led to an overestimation of detection rates. Findings may not be applicable to a general cohort of**

patients with SLND and PSA persistence. Moreover, surgical technique and eligibility criteria for SLND where not standardized among the enrolling centers. Findings might thus be not representative of the clinical salvage lymph node dissection scenario.

CONCLUSION

Comparison of pre- and post-procedure PSMA-PET revealed disease patterns in patients with biochemical persistence after salvage lymph node dissection: PSMA-PET identified locations of persistent disease in about two thirds of patients. Post-SLND PET further detect**ed** new or potentially growing metastases. About two thirds of patients underwent repeat local therapies after unsuccessful SLND, indicating potential value of accurate PSMA-PET staging for PSA persistence.

DISCLOSURE

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fees from Uromed, all outside the submitted work. No other potential conflicts of interest relevant to this article exist.

KEY POINTS

QUESTION: **Where is persistent or recurrent prostate cancer located in patients with unsuccessful salvage lymph node dissection?**

PERTINENT FINDINGS: This is a retrospective multicenter cohort study assessing **pre- and post-procedure PSMA-PET to localize** prostate cancer in patients with PSA persistence following salvage lymph node dissection. PSMA PET/CT localizes residual disease in nearly all patients**, most often in internal iliac and obturator regions. A**bout one quarter of patients had new lesions, not detected by pre-surgical PSMA-PET.

IMPLICATIONS FOR PATIENT CARE: **PSMA-PET localized** prostate cancer both before **and after unsuccessful** salvage lymph node dissection. **Lesion persistence was most often noted for regions with difficult surgical access.**

REFERENCES

1. Mottet N, van den Bergh RCN, Briers E, et al. EAU - EANM - ESTRO - ESUR - SIOG guidelines on prostate cancer. *EAU - EANM - ESTRO - ESUR - SIOG guidelines on prostate cancer*. https://uroweb.org/guideline/prostate-cancer/#11. Published 2019 (accessed July 16, 2019).
2. Ost P, Reynders D, Decaestecker K, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2018;36:446-453.
3. De Bleser E, Jereczek-Fossa BA, Pasquier D, et al. Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol*. July 2019.
4. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. *JAMA Oncol*. March 2019.
5. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med*. 2015;56:668-674.
6. Afshar-Oromieh A, Avtzi E, Giesel FL, 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;42:197-209.
7. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging*. 2017;44:1258-1268.
8. Ploussard G, Gandaglia G, Borgmann H, et al. Salvage Lymph Node Dissection for Nodal Recurrent Prostate Cancer: A Systematic Review. *Eur Urol*. 2019;76:493-504.
9. Fendler WP, Eiber M, Beheshti M, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2017;44:1014-1024.
10. Rauscher I, Maurer T, Fendler WP, Sommer WH, Schwaiger M, Eiber M. (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: How we review and report. *Cancer Imaging*. 2016;16:14.
11. Fendler WP, Calais J, Allen-Auerbach M, et al. 68Ga-PSMA-11 PET/CT Interobserver Agreement for Prostate Cancer Assessments: An International Multicenter Prospective Study. *J Nucl Med.* 2017;58:1617-1623.
12. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. *J Nucl Med*. 2018;59:469-478.
13. Taylor A, Rockall AG, Powell MEB. An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition. *Clin Oncol (R Coll Radiol)*. 2007;19:542-550.
14. Calais J, Ceci F, Eiber M, et al. 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol*. July 2019.
15. Farolfi A, Gafita A, Calais J, et al. 68Ga-PSMA-11 PET Detects Residual Prostate Cancer after Prostatectomy in a Multicenter Retrospective Study. *J Urol*. June 2019:101097JU0000000000000417.
16. Mandel P, Tilki D, Chun FK, et al. Accuracy of 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography for the Detection of Lymph Node Metastases Before Salvage Lymphadenectomy. *Eur Urol Focus*. July 2018.
17. Jilg CA, Drendel V, Rischke HC, et al. Diagnostic Accuracy of Ga-68-HBED-CC-PSMA-Ligand-PET/CT before Salvage Lymph Node Dissection for Recurrent Prostate Cancer. *Theranostics*. 2017;7:1770-1780.

18. Horn T, Krönke M, Rauscher I, et al. Single Lesion on Prostate-specific Membrane Antigen-ligand Positron Emission Tomography and Low Prostate-specific Antigen Are Prognostic Factors for a Favorable Biochemical Response to Prostate-specific Membrane Antigen-targeted Radioguided Surgery in Recurrent Prostate Cancer. *Eur Urol*. April 2019.
19. Rischke HC, Schultze-Seemann W, Wieser G, et al. Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. *Strahlenther Onkol*. 2015;191:310-320.
20. Maurer T, Robu S, Schottelius M, et al. 99mTechnetium-based Prostate-specific Membrane Antigen-radioguided Surgery in Recurrent Prostate Cancer. *Eur Urol*. April 2018.
21. Rauscher I, Düwel C, Wirtz M, et al. Value of 111 In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. *BJU Int*. 2017;120:40-47.

FIGURES

Figure 1. Consort diagram for patient selection.

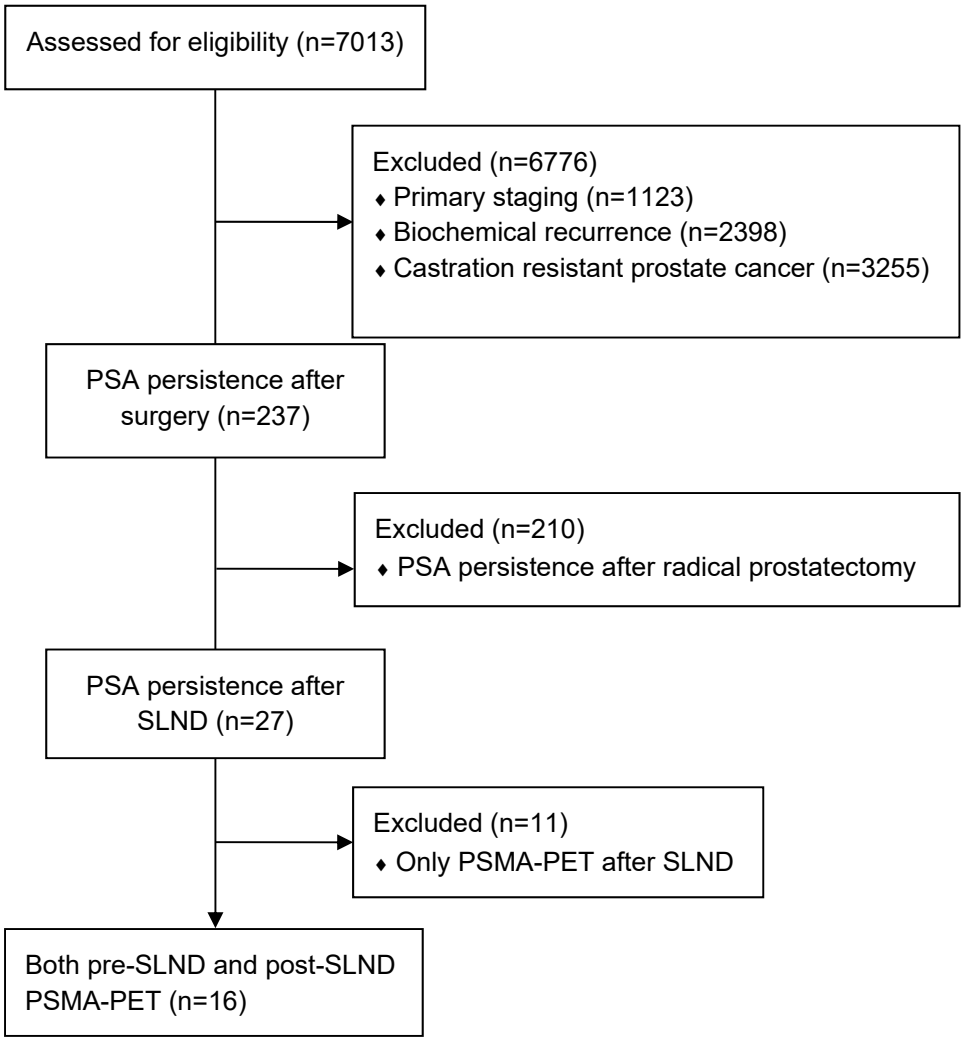


Figure 2. PSMA-PET detection Rate on a Patient Basis stratified by PSA at time of PET (A) and PSA nadir after SLND (B).

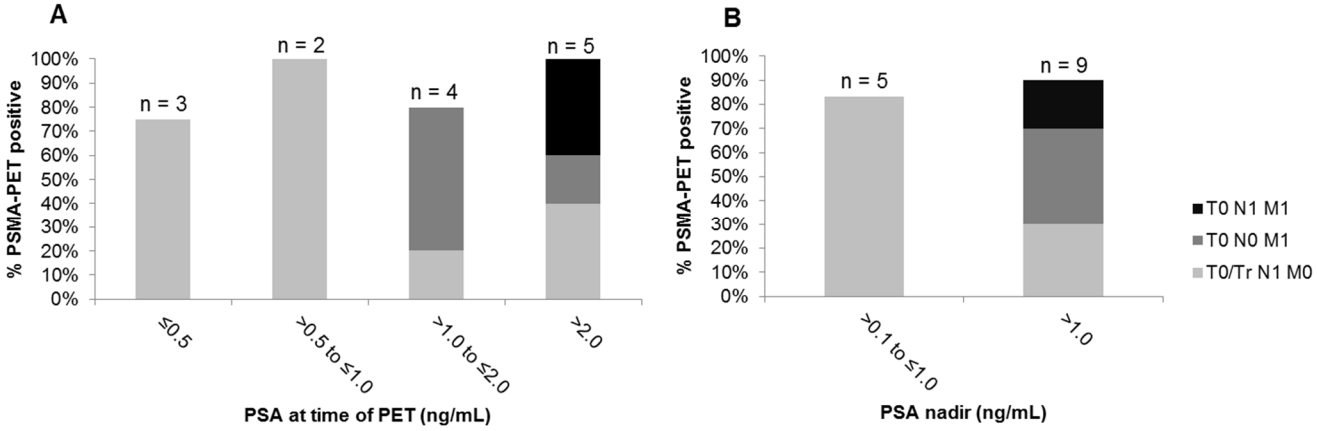


Figure 3. PSMA-PET findings in the pre- and post-SLND PET comparison (n=16 patients) shown separately for (A) pelvic lymph nodes (N1) and (B) prostate bed (Tr), distant nodes (M1a) and bone metastases (M1b).

Figure 3A

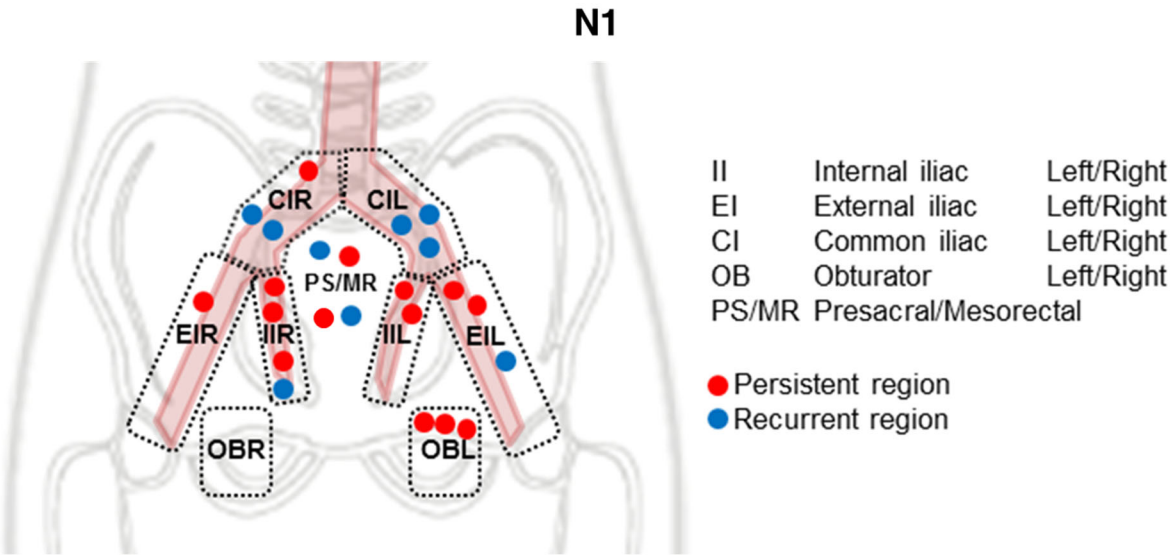
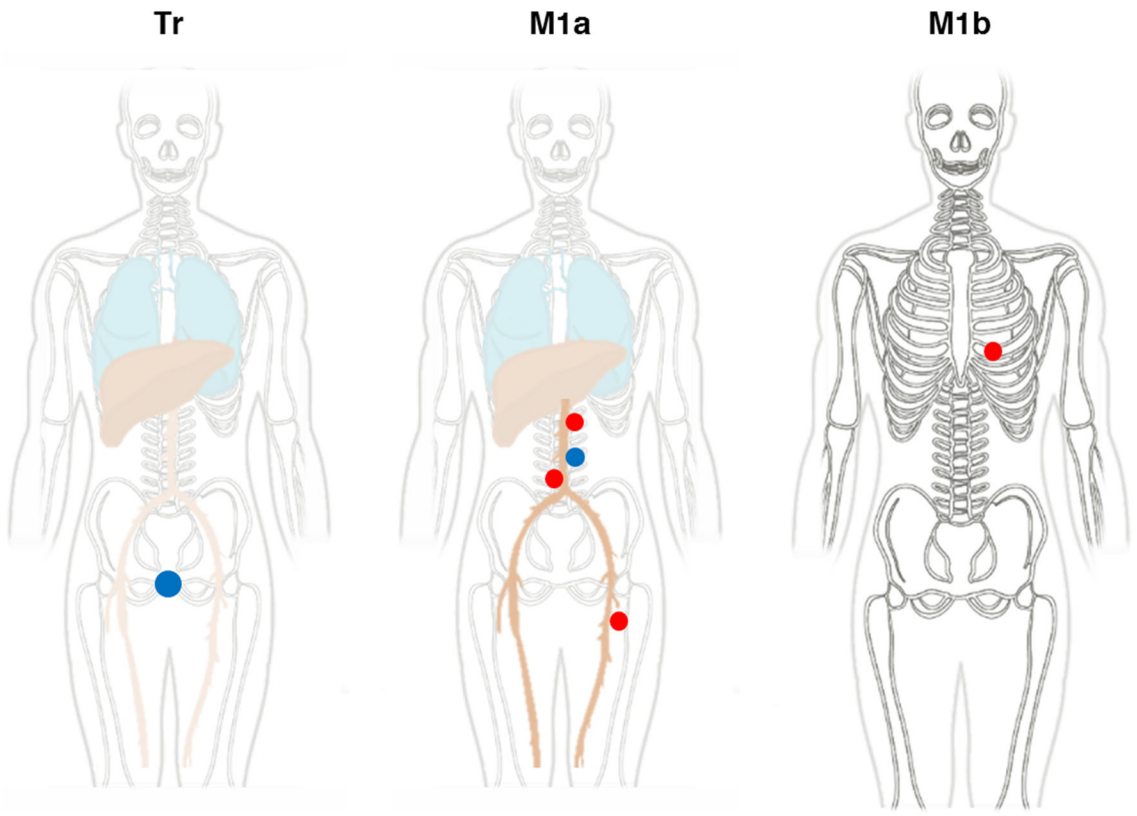


Figure 3B



TABLES

Table 1. Patient characteristics (n=16).

	Median	IQR
Age (years)	66	59–75
PSA initial (ng/mL)	6.6	5.9–88.1
PSA nadir after SLND (ng/mL)	0.4	0.3–2.5
PSA at the time of PET (ng/mL)	1.2	0.6–2.8
PSA-DT (months)	1.8	0-7.2
PSA-V (ng/mL/years)	0.7	0-2.2
∆ date pre-SLND PET - date SLND (months)	1.0	1-2
∆ date SLND - date post-SLND PET (months)	3.5	2-6
	Frequency	**%**
≥T3a	12/16	75
N1	6/13	46
ISUP Grade Group ≥4	11/16	69

Table 2. Patient details. Stage is given in accordance with PROMISE(*12*).

Patient	Age (y)	PSA at PET (ng/mL)	ISUP Grade Group	pTNM	R	Previous Treatments	Positive on Pre-SLND PET	Positive on SLND (histopathology)	Positive on Post-SLND PET	Pre- to post-PET diagnosis
1	53	0.4	4	pT3b pN1	R0	RP	T0N1(IIR)M0	IR	T0N1(IIR)M0	Persistence
2	68	0.4	2	pT2c pN0	R0	RP	T0N1(OL)M0	OL	T0N0M0	No disease
3	65	0.5	5	pT3a pN1	R0	RP	T0N1(OL,IIL)M0	PS/MR	T0N1(OL,IIL)M0	Persistence
4	63	0.8	5	pT3b	n/a	RP	T0N1(IIL)M0	IIL,CIL	T0N1(CIL,EIL)M0	New lesion**/Recurrence**
5	67	1.0	3	pT2c pN0	R0	RP	T0N1(OL,IIL)M0	IIL	T0N1(CIL,OL,IIL)M0	Persistence
6	75	1.1	2	pT2c pN0	R0	RP; S-RT	T0N1(EIL)M0	EIL	T0N0M0	No disease
7	82	1.1	4	pT3b pN0	R1	RP; S-RT	TrN1(EIR,EIL,OL)M0	negative	T0N1(CIR,EIR,EIL)M0	Persistence
8	55	1.3	5	pT3b pN1	R0	RP	T0N0M1b(uni)	negative	T0N0M1b(uni)	Persistence
9	58	1.8	5	pT3b pN1	n/a	RP	T0N0M1a(Retrop)	EIL,CIL	TrN1(CIL)M0	New lesion**/Recurrence**
10	63	2.0	5	pT3b pN1	R0	RP; ADT	T0N1(CIL,EIL,IIL)M0	CIL,EIL,IIL	T0N0M1a(Retrop)	New lesion**/Recurrence**
11	75	2.1	5	pT3b pN0	R1	RP	T0N1(EIL,OL,IIR)M1a(INR)	IIR	T0N1(EIL,OL,IIR,PS/MR) M1a(Retrop,INR)	Persistence
12	69	3.5	3	pT3a	R1	RP; S-RT	T0N0M1a(Retrop)	n/a	T0N0M1a(Retrop)	Persistence
13	83	3.6	4	pT3a pN0	n/a	RP	T0N0M0	PS/MR	T0N1(IIR)M0	New lesion**/Recurrence**
14	49	4.2	5	pT3b pN1	R1	RP, S-RT; ADT	T0N1(CIL,EIR,IIR,PS/MR)M1a(Retrop)	CIL,IIR,Retrop	T0N1(CIR,IIR,PS/MR)M1a (Retrop)	Persistence
15	74	12.0	4	pT3b	R0	RP	TrN1(CIR,EIR,PS/MR)M1a(Retrop)	EIR	T0N1(CIR,PS/MR)M0	Persistence
16	60	0.5	3	pT2a pN0	R1	RP	T0N1M0	negative	T0N1M0	Persistence

Notes: RP, radical prostatectomy; S-RT, salvage-radiotherapy; SLND, salvage-lymph node dissection; EBRT, external beam radiation therapy; ADT, androgen deprivation therapy; Retrop, retroperitoneal; n/a, not available.

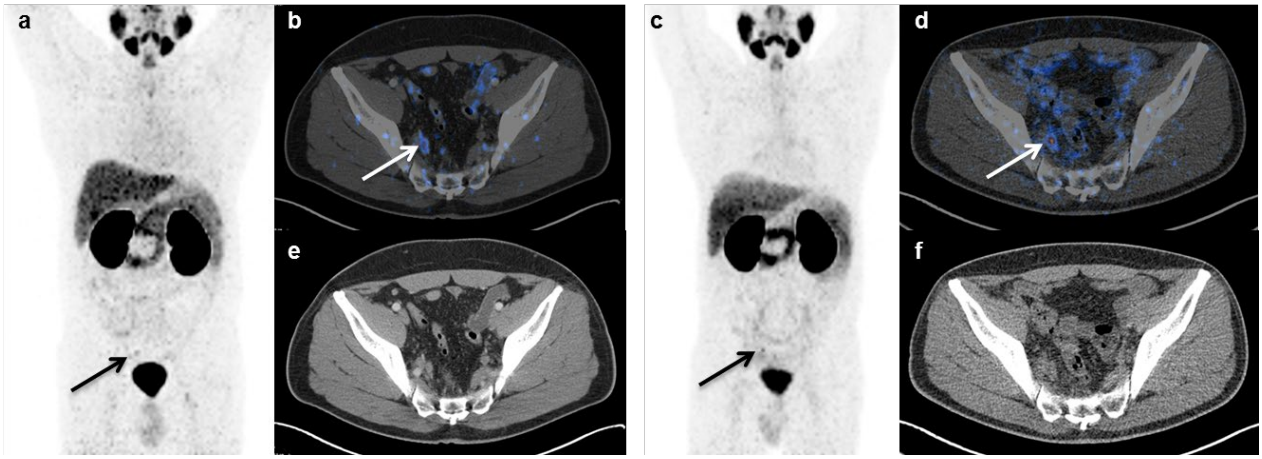
Table 3. Lesion validation.

Patient	Validated region(s)	Type of validation	Validation result
1	N1	PSA response after S-RT	True positive
5	N1	Surgery	True positive
8	M1b	Imaging follow-up	True positive
9	Tr, N1	Surgery	True positive
11	N1, M1a	Surgery, Imaging follow-up	True positive
13	N1	PSA response after S-RT	True positive
14	N1, M1a	Surgery, Imaging follow-up	True positive
15	N1	Surgery	True positive
16	N1	Imaging follow-up	True positive

Supplemental Material

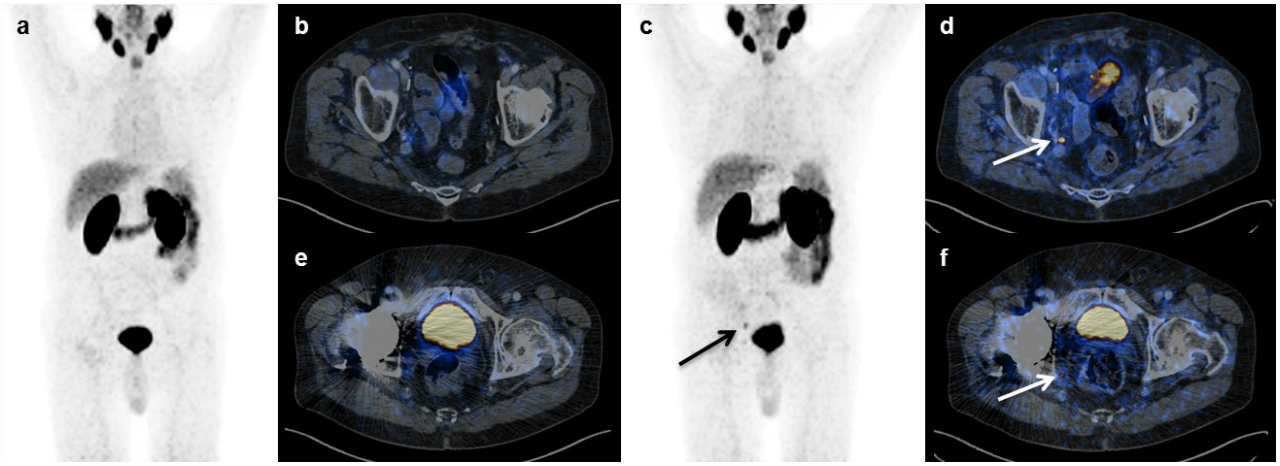
Supplemental Figure 1. Persistence of one internal iliac lymph node metastasis.

53 year-old man initially treated with radical prostatectomy and lymph node dissection for high risk PCa (ISUP grade group 4, pT3b pN1 R0) underwent ^{68}Ga-PSMA-11 PET/CT for disease restaging in October 2015 (PSA=0.36 ng/mL). Maximum-intensity-projection (a), axial PET/CT (b) and axial CT (**e**) demonstrated focal uptake in one right internal iliac node (arrows; 14x8 mm; SUV_{max}=4.5). With known PET-information, the patient was treated three weeks later with salvage lymph node dissection using a standard template (bilateral EI, II, CI resection). Histopathology confirmed adenocarcinoma in 1/12 right internal iliac nodes. Six weeks after the intervention PSA was 0.18 ng/mL and the patient underwent repeat ^{68}Ga-PSMA-11 PET/CT confirming now more intense uptake in a growing right internal iliac node positive on pre-PET (**c-d**; arrows; 20x9 mm; SUV_{max}=5.7; PET persistence).



Supplemental Figure 2. Recurrence of two obturator lymph node metastases.

83 year-old man initially treated with radical prostatectomy and lymph node dissection for high risk PCa (ISUP grade group 4, pT3a pN0 R0) underwent ^{68}Ga-PSMA-11 PET/CT for disease restaging in December 2015 with PSA=4.8 ng/mL. Maximum-intensity-projection (a) and axial PET/CT (b and **e**) demonstrate the absence of focal uptake within pelvis. With known information of PET and previous surgical fields, the patient was treated in January 2016 with more extended salvage lymph node dissection. Ten lymph nodes were removed from the following regions: right presacral, right obturatory, right iliac and paracaval; 1/10 resulted positive for PCa metastasis in the presacral region. Six weeks after the intervention PSA was 3.0 ng/mL and the patient underwent repeat ^{68}Ga-PSMA-11 PET/CT showing the appearance of two small right internal iliac nodes (8x6 mm) with PSMA uptake.



Supplemental Table 1. Pre-SLND PET findings.

Characteristic	Overall population (n=16; 100%)
ADT	
No	14 (88)
Yes	2 (12)
Positive PSMA-PET	**15 (94)**
Pelvic nodes only (N1)	9 (60)
Retroperitoneal nodes only (M1a)	2 (13)
Both (N1 M1a)	3 (20)
Other	1 (7)
N/M disease extent	
1 (unifocal)	6 (38)
2-3 (oligo)	4 (25)
≥4 (multiple/disseminated)	5 (31)