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Platinum Priority – Brief Correspondence

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Initial Experience of ^{68}Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy

Lars Budäus[a,†,*], *Sami-Ramzi Leyh-Bannurah*[a,b,†], *Georg Salomon*[a], *Uwe Michl*[a], *Hans Heinzer*[a], *Hartwig Huland*[a], *Markus Graefen*[a], *Thomas Steuber*[a], *Clemens Rosenbaum*[a,b]

[a] *Martini-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;*
[b] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany*

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Abstract

Prostate-specific membrane antigen (PSMA) overexpression theoretically enables targeting of prostate cancer (PCa) metastases using gallium Ga 68 (^{68}Ga)–labeled PSMA ligands for positron emission tomography/computed tomography (PET/CT) imaging. Promising detection rates have been reported when using this approach for functional imaging of recurrent PCa; however, until now, the diagnostic accuracy of ^{68}Ga-PSMA PET/CT for preoperatively identifying lymph node metastases (LNMs) had not been assessed. We retrospectively compared preoperative ^{68}Ga-PSMA PET/CT lymph node (LN) findings with histologic work-up after radical prostatectomy (RP). Overall, 608 LNs containing 53 LNMs were detected during RP. LNMs were present in 12 of 30 patients (40%). The ^{68}Ga-PSMA PET/CT scans identified 4 patients (33.3%) as LN true positive and 8 patients (66.7%) as false negative. Median size of ^{68}Ga-PSMA-PET/CT–detected versus undetected LNMs was 13.6 versus 4.3 mm ($p < 0.05$). Overall sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA PET/CT for LNM detection were 33.3%, 100%, 100%, and 69.2%, respectively. Per-side analyses revealed corresponding values of 27.3%, 100%, 100%, and 52.9%. Conversely, ^{68}Ga-PSMA PET/CT enabled tumor visualization in the prostate. In 92.9% of patients, the intraprostatic tumor foci were correctly predicted. Overall, ^{68}Ga-PSMA PET/CT is a promising tool for functional imaging; however, our initial experience revealed substantial influence of LNM size on the diagnostic accuracy of ^{68}Ga-PSMA PET/CT.

Patient summary: We assessed the diagnostic accuracy of ^{68}Ga-PSMA PET/CT in high-risk prostate cancer patients prior to radical prostatectomy. We found that lymph node metastasis detection rates were substantially influenced by lymph node metastasis size.

† Both authors contributed equally.
* Corresponding author. Martini-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Tel. +49 40 7410 51300; Fax: +49 40 7410 51323.
E-mail address: budaeus@martini-klinik.de (L. Budäus).

Recent series suggest that prostate cancer (PCa) patients with minimal lymph node (LN) involvement can be cured by extended pelvic lymph node dissection (ePLND) when radical prostatectomy (RP) is performed as initial therapy [1]. In addition, despite sparse data on oncologic outcomes, surgical treatment of recurrent PCa is increasingly discussed. These developments underscore the need for a reliable staging modality. Traditionally, conventional imaging criteria of LN

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metastases (LNMs) are based on nodal size and irregular shape; however, this approach resulted in low sensitivity for smaller LNMs. To overcome these limitations, computed tomography (CT) and magnetic resonance imaging (MRI) were combined with functional imaging by using choline-based imaging (positron emission tomography [PET]).

Recently, gallium Ga 68 (^{68}Ga)–labeled prostate-specific membrane antigen (PSMA) PET/CT, which uses the affinity of the ^{68}Ga-labeled PSMA ligand to PSMA expressing PCa cells, emerged as a new, promising tracer [2]. Especially in patients suffering biochemical recurrence (BCR) after primary therapy, promising results were reported for ^{68}Ga-PSMA PET/CT compared with F 18 fluoromethylcholine [2]. These results were attributed to PSMA overexpression in higher grade, metastasized, or castration-resistant PCa cells and its transmembrane location [3]. Consequently, a dramatic increase of ^{68}Ga-PSMA PET/CT use for LN staging was seen in Europe.

It is uncertain that these promising results can also be applied to LN staging because the majority of reports on ^{68}Ga-PSMA PET/CT stem from BCR cohorts and/or provide only limited histopathologic confirmation of LNM status. We decided to analyze the ability of ^{68}Ga-PSMA PET/CT to detect LNMs in patients referred for RP to the Martini Clinic, a large tertiary referral center in Germany. Between June 2014 and March 2015, 58 patients with pretreatment ^{68}Ga-PSMA PET/CT were available for analysis. All ^{68}Ga-PSMA PET/CT scans were initiated according to the referring urologist's discretion for staging. To minimize the influence of heterogeneous patient characteristics on the diagnostic performance of ^{68}Ga-PSMA PET/CT, our analyses were restricted to a homogenous cohort of 30 patients (Table 1). All patients harbored a nomogram-calculated risk of LNMs >20% [4]. Based on the supposed oncologic benefit of RP, the cohort also comprised selected patients for whom surgery was performed as part of a multimodal treatment, even when LNMs were detected by imaging. All patients underwent an interdisciplinary institutional tumor board and received an informed consent among patient, urologist, and radio-oncologist. Moreover, written consent for retrospective data analyses was given by all patients. All ^{68}Ga-PSMA PET/CT scans were performed nationwide in five imaging centers performing 200–1500 ^{68}Ga-PSMA PET/CT scans per year. The ePLND included a standardized template of fossa obturatoria and arteria iliaca externa, interna, and communis. RP specimens were processed by dedicated uropathologists, and immunhistochemistry was used for assessment of LN status.

Overall, 608 LNs were resected, with 53 harboring metastases (8.7%) in 12 of 30 patients (40.0%) (Table 2). The mean and median LN yields per patient were 20.3 and 18.5 (interquartile range: 13.5–27.5), respectively. The ^{68}Ga-PSMA PET/CT scans identified 4 of 12 patients (33.3%) as LN positive (true positive). No suspicious extrapelvic LNMs or visceral lesions were detected. In eight patients with histologically confirmed LNMs, ^{68}Ga-PSMA PET/CT was negative (false negative; 66.7%). Comparison of intranodal tumor deposit revealed that median size of ^{68}Ga-PSMA PET/CT–detected versus undetected LNMs was 13.6 mm (range: 4.0–20.0 mm) versus 4.3 mm (range: 1.0–10.8 mm)

Table 1 – Patient characteristics (n = 30) stratified by nodal status

	Total patients (n = 30)	No LN metastases (n = 18)	LN metastases (n = 12)	p
Age, yr, mean, median (range)	62.3, 63.0 (44.0–75.0)	62.1, 62.5 (44.0–74.0)	62.7, 64.0 (47.0–75.0)	0.755
PSA, ng/ml, mean, median (range)	38.9, 8.8 (1.4–376.0)	11.9, 8.0 (4.2–36.6)	79.5, 24.1 (1.4–376.0)	0.021
Gleason score at RP (%)				0.015
3 + 4	9 (30.0)	8 (44.4)	1 (8.3)	
4 + 3	10 (33.3)	7 (38.9)	3 (25.0)	
≥4 + 4	11 (36.7)	3 (16.7)	8 (66.7)	
pT stage at RP, no. (%)				<0.001
pT2	11 (36.7)	11 (61.1)	0 (0.0)	
pT3a	4 (13.3)	4 (22.2)	0 (0.0)	
pT3b	12 (40.0)	3 (16.7)	9 (75.0)	
pT4	3 (10.0)	0 (0.0)	3 (25.0)	
Intraprostatic PCa size, mm, mean, median (range)	33.3, 32.5 (8.0–63.0)	27.6, 28.4 (8.0–39.0)	41.8, 40.5 (28.0–63.0)	0.003
Intraprostatic PCa volume, ml, mean, median (range)	11.7, 5.4 (0.3–68.1)	4.1, 4.3 (0.3–8.0)	23.0, 16.0 (3.4–68.1)	<0.001
LNs removed, no. (%)	608 (100)	393 (64.6)	215 (35.4)	0.346
LNMs removed, no. (%)	53 (100)	–	53 (100)	
Intranodal LNM size, mm *, mean, median (range)	7.3, 4.7 (1.0–20.0)	–	7.3, 4.7 (1.0–20.0)	
Overall LNM size, mm *, mean, median (range)	23.5, 23.0 (4.0–64.0)	–	23.5, 23.0 (4.0–64.0)	
PSMA, MBq, mean, median (range)	169.4, 165.0 (106.0–269.0)	150.5, 158.5 (106.0–170.0)	207.3, 200.0 (153.0–269.0)	0.167
SUV, maximal LN, mean, median (range)	5.3, 5.3 (5.1–5.5)	–	5.3, 5.3 (5.1–5.5)	
SUV, maximum PCa, mean, median (range)	8.3, 6.2 (1.3–22.3)	8.1, 5.6 (2.1–20.5)	8.6, 6.9 (1.3–22.3)	0.849

LN = lymph node; LNM = lymph node metastasis; PCa = prostate cancer; PSA = prostate specific antigene; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; SUV = standardized uptake value

* Largest/index lymph node per patient is presented.

Table 2 – Histopathologic lymph node characteristics of the total patient population ($n = 30$) stratified by ^{68}Ga-PSMA PET/CT detection of lymph node metastases

	No LN metastases ($n = 18$)			LN metastases ($n = 12$)		
	PSMA negative ($n = 18$)	PSMA positive ($n = 0$)	p	PSMA negative ($n = 8$)	PSMA positive ($n = 4$)	p
LNs removed, no. (%)	393 (64.6)	–	NA	141 (23.2)	74 (12.2)	0.833
LNMs removed, no. (%)	0 (0)	–	NA	19 (35.8)	34 (64.2)	0.808
Intranodal LNM size, mm *, mean, median (range)	–	–	NA	4.5, 4.3 (1.0–10.8)	12.8, 13.6 (4.0–20.0)	0.048
Overall LNM size, mm *, mean, median (range)	–	–	NA	19.4, 20.5 (4.0–40.0)	31.8, 25.5 (12.0–64.0)	0.368

LN = lymph node; LNM = lymph node metastasis; NA = not applicable; PSMA = prostate-specific membrane antigen.
* Largest/index lymph node per patient is presented.

($p < 0.05$). Sensitivity analyses of ^{68}Ga-PSMA PET/CT false-negative results for further work-up revealed positive immunohistochemical PSMA staining in LNMs. In addition, an internal positive control was given by the intraprostatic main tumor. Such a ^{68}Ga-PSMA–related signal was detected in all patients except one with a previous history of transurethral resection of the prostate. The calculated per-patient sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 33.3%, 100%, 100%, 69.2%, and 73.3%, respectively, for initial PCa nodal staging by ^{68}Ga-PSMA PET/CT (Table 3).

Similar corresponding values were reported for choline-based PET imaging [5,6]. Moreover, our results suggest that ^{68}Ga-PSMA PET/CT is similarly susceptible to the major weakness of micrometastastic size of tumor deposits [7]. In contrast, a sensitivity of 88.1% for LNM detection by ^{68}Ga-PSMA PET/CT was achieved in other series [8]. However, within this series, the majority of lesions were not verified by histopathology. Moreover, only the minority of patients with histologic verification received systematic surgery, thus precluding regions without a positive PET signal. Consequently, a certain degree of misclassification may be assumed. Another difference hinges on the presence of the untreated prostate as the primary and largest focus of PCa when ^{68}Ga-PSMA PET/CT is used for staging prior to RP. Therefore, it may be hypothesized that a marked PSMA uptake by the prostate may lead to shortage or depletion of ^{68}Ga-PSMA PET/CT ligands within the blood pool, subsequently leading to an insufficient signal of LNMs as a pharmacokinetic confounder. This may explain PET findings in our cohort in initial PCa staging compared with other reports assessing patients undergoing restaging [9]. Other potential explanations for different detection rates may be restricted perfusion in LNMs due to a critical size or vascularization threshold, limiting the exposure and binding of the gallium-labeled PSMA ligand. This hypothesis is supported by a semiquantitative observation that immunohistochemical PSMA staining was most intense in primary PCa and lowest in LNMs [3]. Moreover, ^{68}Ga-PSMA PET/CT was performed nationwide, so different expertise among centers may not be ruled out despite high-volume imaging. Based on missing information for each individual reader, we were not able to account for interobserver variation; however, previous series on nodal PCa staging by choline-based PET/CT revealed good to excellent interobserver reproducibility [10]. In addition, sensitivity analyses in our study did not reveal interinstitutional differences of detection rates, and results from multiple institutions allow assessment of a new imaging modality in daily clinical practice. Finally, results may be influenced by the sample size. Our cohort, however, represents the largest homogeneous existing series in which the Ga-PSMA PET-CT findings were validated by systematic histopathology, indicated by current PLND templates.

Table 3 – Results of ^{68}Ga-PSMA PET/CT lymph node metastases verified by histopathology after radical prostatectomy and extended pelvic lymph node dissection

	No LN metastases ($n = 18$)	LN metastases ($n = 12$)	
PSMA positive ($n = 4$), n (%)	0 (0)	4 (33.3)	PPV 100%
PSMA negative ($n = 26$), n (%)	18 (100)	8 (66.7)	NPV 69.2%
	Specificity 100%	Sensitivity 33.3%	Accuracy 73.3%

LN = lymph node; NPV = negative predictive value; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.

Our initial experience revealed that, similar to other staging modalities, ^{68}Ga-PSMA PET/CT is also limited in detecting all LNMs prior to RP when using histology as the reference standard. Therefore, in daily clinical practice, ePLND during RP remains standard of care. Another PET/CT ligand, ^{68}Ga-BAY86-7548, a synthetic bombesin receptor antagonist, and combined ultrasmall superparamagnetic particles of iron oxide (USPIO) and diffusion-weighted MRI are potential alternatives to ^{68}Ga-PSMA, achieving sensitivities of 67% and 65–75%, respectively [11,12]. Nonetheless, PSMA PET can still be considered one of the most promising approaches for PCa imaging based on its unique and stable expression in PCa cells. Technical advances in, for example, spatial resolution potentially combined with multiparametric MRI and/or USPIO or emerging PET ligands like ^{68}Ga-BAY86-7548 or ^{89}Zr-Df-IAB2 M are recent approaches for further fine-tuning PET imaging [11–13]. These

developments may overcome the limitations of ^{68}Ga-PSMA in our study and improve diagnostic performance of PET LN staging in the foreseeable future.

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Study concept and design: Budäus, Leyh-Bannurah, Rosenbaum, Graefen, Huland, Steuber.
Acquisition of data: Budäus, Leyh-Bannurah, Rosenbaum, Michl, Steuber, Salomon.
Analysis and interpretation of data: Budäus, Leyh-Bannurah, Rosenbaum, Salomon, Michl, Heinzer, Huland, Graefen, Steuber.
Drafting of the manuscript: Budäus, Leyh-Bannurah, Rosenbaum, Huland, Steuber.
Critical revision of the manuscript for important intellectual content: Salomon, Michl, Heinzer, Huland, Graefen, Steuber.
Statistical analysis: Budäus, Leyh-Bannurah, Rosenbaum.
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