Diagnostic Efficacy of ^{68}Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer

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Abbreviations and Acronyms

CT = computerized tomography

GEE = generalized estimating equation

LN = lymph node

MR = magnetic resonance tomography

PCa = prostate cancer

PET = positron emission tomography

PLND = pelvic LN dissection

PPV = positive predictive value

PSMA = prostate specific membrane antigen

RPX = radical prostatectomy

Purpose: Current standard imaging techniques are insufficient to reliably detect lymph node metastases in prostate cancer. Recently ligands of PSMA (prostate specific membrane antigen) were introduced in PET (positron emission tomography) of prostate cancer. Thus the aims of this retrospective analysis were to 1) investigate the diagnostic efficacy of ^{68}Ga-PSMA-PET imaging for lymph node staging in patients with prostate cancer scheduled for radical prostatectomy and 2) compare it to morphological imaging (computerized tomography and magnetic resonance tomography) with histopathological evaluation as the standard of reference.

Materials and Methods: A total of 130 patients with intermediate to high risk prostate cancer were staged with ^{68}Ga-PSMA-PET/magnetic resonance tomography or PET/computerized tomography from December 2012 to November 2014 before radical prostatectomy and template pelvic lymph node dissection. Histopathological findings of resected tissue were statistically correlated with the results of ^{68}Ga-PSMA-PET and morphological imaging in a patient and template based manner.

Results: Lymph node metastases were found in 41 of 130 patients (31.5%). On patient based analysis the sensitivity, specificity and accuracy of ^{68}Ga-PSMA-PET were 65.9%, 98.9% and 88.5%, and those of morphological imaging were 43.9%, 85.4% and 72.3%, respectively. Of 734 dissected lymph node templates 117 (15.9%) showed metastases. On template based analysis the sensitivity, specificity and accuracy of ^{68}Ga-PSMA-PET were 68.3%, 99.1% and 95.2%, and

Accepted for publication December 3, 2015.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by the European Union Seventh Framework Program (FP7) under Grant Agreement 294582 ERC Grant "MUMI" and Grant Agreement 256984 EndoTOFPET, and the Deutsche Forschungsgemeinschaft (DFG) under Grant Agreement SFB 824.

* No direct or indirect commercial incentive associated with publishing this article.

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‡ Financial interest and/or other relationship with Scintomics.

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0022-5347/16/1955-1436/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.12.025
Vol. 195, 1436-1443, May 2016
Printed in U.S.A.

those of morphological imaging were 27.3%, 97.1% and 87.6%, respectively. On ROC analysis ^{68}Ga-PSMA-PET performed significantly better than morphological imaging alone on patient and template based analyses ($p = 0.002$ and <0.001, respectively).

Conclusions: In patients with intermediate to high risk prostate cancer preoperative lymph node staging with ^{68}Ga-PSMA-PET proved to be superior to standard routine imaging. Thus it has the potential to replace current standard imaging for this indication if confirmed by prospective studies.

Key Words: prostatic neoplasms; glutamate carboxypeptidase II, human; positron-emission tomography; lymph nodes; neoplasm staging

In newly diagnosed, intermediate to high risk PCa cases current guidelines recommend CT or MR to evaluate metastatic spread to LNs.[1] However these staging modalities depend only on morphological information and LN involvement is mainly assessed by size. Pelvic LNs larger than 8 to 10 mm are usually considered suspicious.[2] However about 80% of metastatic LNs in PCa are smaller than 8 mm.[3] Thus the sensitivity of morphological cross-sectional imaging remains low with no significant difference in performance between CT and MR.[2]

In the last 2 decades PET has evolved as a new imaging modality based on molecular information. By the combination with standard cross-sectional imaging such as CT or MR the information obtained by PET can be co-registered to anatomical structures, thus potentially increasing sensitivity and specificity.[4,5] In PCa the most intensively studied radiotracers include ^{18}F-fluorocholine and ^{11}C-choline.[6] However, their routine use for LN staging in primary PCa cases is discouraged in current guidelines due to lack of sensitivity.[7]

Recently ligands of PSMA were introduced in PET of PCa, which target an extracellular domain of this transmembranous cell surface protein.[8–10] PSMA is almost exclusively expressed in prostate tissue and it is often substantially over expressed on PCa cells.[11] Due to this direct molecular targeting and its favorable lesion-to-background ratio PSMA ligands might improve the detection of metastatic LNs in primary PCa. Initial studies in recurrent PCa described the first promising results, although microscopical tumor metastases might still be missed.[12,13] Therefore the purpose of our retrospective analysis was to evaluate the diagnostic value of ^{68}Ga-PSMA-PET in comparison to morphological imaging for LN staging in patients with intermediate to high risk PCa undergoing RPX with PLND.

MATERIALS AND METHODS

Patients

From December 2012 to November 2014 all consecutive patients with intermediate to high risk PCa according to D'Amico et al[14] without concomitant cancer who underwent ^{68}Ga-PSMA-PET and subsequent RPX at our institution were included in analysis. All patients gave written informed consent for the anonymized evaluation and publication of their data. The retrospective analysis was approved by the Technische Universität München ethics committee (permit 5665/13).

A total of 130 consecutive patients underwent RPX and standardized template PLND, which were done a median of 21.0 days (IQR 11–39) after ^{68}Ga-PSMA-PET/MR in 95 and after ^{68}Ga-PSMA-PET/CT in 35 (table 1). Template PLND was performed as previously described.[15,16] Template based analysis of resected LNs was chosen since exact LN tracking is impossible, especially in the cases of normal-sized LNs due to disorientation during resection and histological evaluation. Therefore tissue from each anatomical template was sent separately for histological evaluation, allowing for correlation to preoperatively performed ^{68}Ga-PSMA-PET. Uropathologists were blinded to the results of ^{68}Ga-PSMA-PET/CT and PET/MR. Histopathological findings of resected LNs were correlated with the results of morphological imaging (MR or CT) alone and with those of ^{68}Ga-PSMA-PET in a patient and template based manner.

^{68}Ga-HBED-PSMA Synthesis

Images were obtained using ^{68}Ga-labeled HBED-CC,[17] which was synthesized as described previously.[18] The ligand was labelled with $^{68}Ga^{3+}$ (half-life 67.6 minutes) using a ^{68}Ge/^{68}Ga radionuclide generator (iThemba Labs, Cape Town, South Africa) by means of a fully automated module (Scintomics, Fürstenfeldbruck, Germany), and a

Table 1. *Patient characteristics*

No. pts	130	(100)
Median at imaging (IQR/range):		
Age	66.5	(61.0–72.0/45–84)
PSA (ng/ml)	11.55	(6.85–24.50/0.57–244.0)
Median Gleason score	7	(7–8/6–10)
No. D'Amico risk (%):		
Intermediate	42	(32.3)
High	88	(67.7)
No. pathological stage (%):		
pT2c or less	56	(43.1)
pT3a	30	(23.1)
pT3b or greater	44	(33.8)
pN0	89	(68.5)
pN1	41	(31.5)
Median No. LNs (IQR/range):		
Removed	21	(12–30/2–115)
Metastatic	0	(0–1/0–39)