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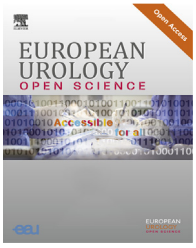

European Association of Urology

Brief Correspondence

Intraoperative Molecular Positron Emission Tomography Imaging for Intraoperative Assessment of Radical Prostatectomy Specimens

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Article info

Article history:
Accepted May 25, 2023

Associate Editor:
Guillaume Ploussard

Keywords:
SpecimenPET/CT
Prostate cancer
Prostate-specific membrane antigen positron emission tomography/computed tomography
Radical prostatectomy

Abstract

In this prospective two-center feasibility study, we evaluate the diagnostic value of intraoperative ex vivo specimenPET/CT imaging of radical prostatectomy (RP) and lymphadenectomy specimens. Ten patients with high-risk prostate cancer underwent clinical prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) preoperatively on the day of surgery. Six patients received ^{68}Ga-PSMA-11 and four ^{18}F-PSMA-1007. Radioactivity of the resected specimen was measured again using a novel specimenPET/CT device (AURA10; XEOS Medical, Gent, Belgium) developed for intraoperative margin assessment. All index lesions of staging multiparametric magnetic resonance imaging could be visualized. Overall, specimenPET/CT correlated well with conventional PET/CT regarding detection of suspicious tracer foci (Pearson coefficient 0.935). In addition, specimenPET/CT demonstrated all lymph node metastases detected on conventional PET/CT (n = 3), as well as three previously undetected lymph node metastases. Importantly, all positive or close (<1 mm) surgical margins could be visualized in agreement with histopathology. In conclusion, specimenPET/CT enables detection of PSMA-avid lesions and warrants further investigation to tailor RP, based on a good correlation with final pathology. Future trials will prospectively compare ex vivo specimenPET/CT with a frozen section analysis for the detection of positive surgical margins and assessment of biochemical recurrence–free survival.

Patient summary: In this report, we examined prostatectomy and lymphadenectomy specimens for suspicious positron emission tomography (PET) signals after preoperative tracer injection. It was found that in all cases, a good signal could be visualized, with a promising correlation of surface assessment compared with histopathology. We conclude that specimenPET imaging is feasible and may help improve oncological outcomes in the future.

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https://doi.org/10.1016/j.euros.2023.05.017

Avoidance of positive surgical margins (PSMs) during radical prostatectomy (RP) is of particular interest, as unfavorable PSMs (>3 mm and/or multifocal) confer a higher oncological risk of developing metastases and might necessitate additional postoperative radiotherapy [1]. Besides a negative impact on oncological outcome, additional therapy might also negatively influence continence and potency—key components of quality of life in patients undergoing RP. Thus, precise localization of prostate cancer (PC) is crucial for diagnosis and therapy. Schlomm et al [2] described that intraoperative frozen sectioning (IFS) has the potential to significantly increase nerve sparing during RP while reducing PSMs [2]. Additionally, preoperative imaging such as multiparametric magnetic resonance imaging (mpMRI) may guide IFS to significantly reduce PSMs [3]. On the contrary, novel PC-directed molecular imaging with positron emission tomography (PET) targeting prostate-specific membrane antigen (PSMA) with ^{68}Ga- and ^{18}F-labelled PET agents is usually used to improve staging [4].

The main objective of our feasibility study was to evaluate whether PSMA-directed PET radiopharmaceuticals in combination with a novel specimenPET/CT scanner can be used to detect a sufficient signal of PC lesions within dissected prostate and lymph node specimens, and whether imaging findings may also be used for intraoperative margin assessment. For this, patients with histologically proven high-risk PC underwent PSMA PET/CT immediately followed by RP and consecutive ex vivo specimenPET/CT imaging (AURA10; XEOS Medical, Gent, Belgium) of retrieved specimens, with a median time of 36.5 min post injection (p.i.; interquartile range [IQR]: 31; 60.8 min) to conventional PET, 204 min p.i. (IQR: 177.3, 220.3) to the start of RP, and 331 min p.i. (IQR: 308.8, 380.5) to specimenPET/CT (Fig. 1 and the Supplementary material). A pilot analysis with two PC patients recently showed promising results in terms of spatial resolution and assessment of PC localization, although the design with an intraoperative injection differs from the approach presented here [5].

In our series, ten consecutive patients with locally advanced PC received PSMA PET/CT followed by RP and extended pelvic lymphadenectomy on the same day. In six men, ^{68}Ga-PSMA-11 was given, while four received ^{18}F-PSMA-1007. Written informed consent for study participation was obtained (local ethics committee approval: 19-8749-BO). In case of metastatic PC, surgery would have been cancelled. RP was performed robotically by two experienced surgeons (B.A.H., >500 cases, and T.M., >500 cases). After removal, tumor specimens were transferred into trays and examined immediately by specimenPET/CT. The total acquisition time was 12 min (2 min CT and 10 min PET).

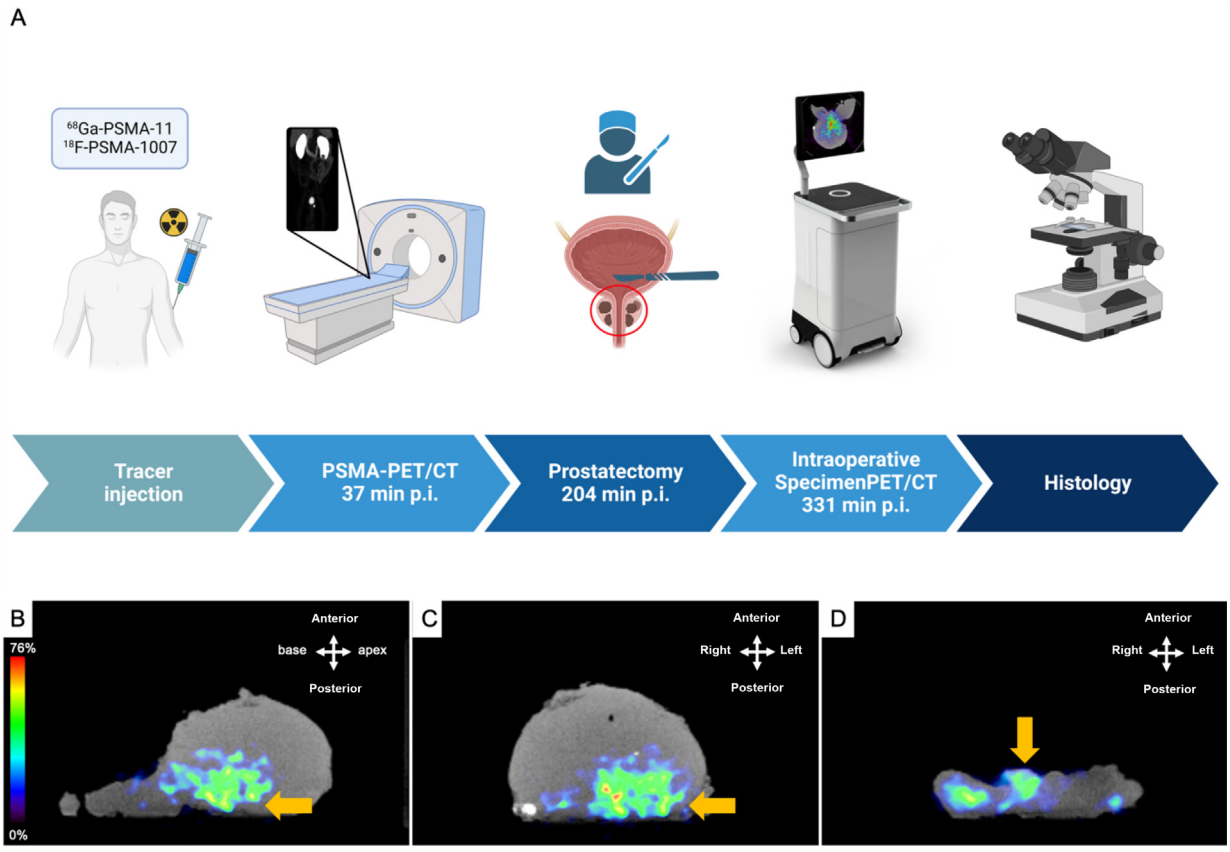

Fig. 1 – (A) Outline of the study schedule as a "one-stop shop protocol". Examination of prostate specimen in patients undergoing radical prostatectomy after preoperative PSMA PET/CT. After removal of the prostate, the specimen was immediately examined by specimenPET/CT. The corresponding time data after injection are given below as median. (B) The specimenPET/CT images of a representative prostate specimen in the sagittal plane, the transverse plane (C) of the prostate as well as (D) of the attached seminal vesicles and vas deferens after preoperative ^{68}Ga-PSMA-11 administration. The orange arrow suggests margin involvement, with histopathological close surgical margin of the left dorsal lobe and positive surgical margins of the right seminal vesical and vas deferens. PET/CT = positron emission tomography/computed tomography; p.i. = post injection; PSMA = prostate-specific membrane antigen.

The spatial resolution PET of about 1 mm, combined with high-resolution CT with a resolution of about 0.2 mm, enables direct assessment of findings in the operating room. To provide anatomic references for areas of increased radiotracer uptake, PET data are coregistered to CT reconstructed images, resulting in high detail cross-sectional imaging in three dimensions. In the current feasibility study, surgery was not influenced by PET imaging. Pathological workup, referred to as the gold standard, was performed according to current clinical standards by two dedicated pathologists with more than 10 yr of experience in genitourinary pathology. For the current analysis, quadrants were digitally reconstructed to whole mounts.

Patient demographic, histopathological, and imaging data are shown in Table 1. In all ten patients, index lesions of mpMRI (n = 11) were visualized correctly on conventional PSMA PET/CT. Fourteen out of 15 lesions (93%) of conventional PSMA PET/CT were also PSMA-positive intraoperatively by specimenPET/CT, resulting in a significant correlation with the Pearson coefficient of 0.935 (p = 0.001). No additional lesions were detected. The one additional faint lesion in conventional PET/CT, which could not be visualized in specimenPET/CT, was located basally immediately in the urethral region, so that an artifact due to urine is also possible. Histopathologically, there was no evidence of tumor. Histopathology proved negative surgical margins in six patients. PSMs were found in four men with pT3 disease. These matched with suspicious tracer signal displayed in the ex vivo specimenPET/CT. Of note, one patient had two PSMs at the right seminal vesicle and isolated tumor cells in the right vas deferens. Both findings could be imaged on specimenPET/CT. In addition, there was a suspicion of a PSM dorsally on the left in the prostate. Histopathology also confirmed this finding with a very close surgical margin (<1 mm) and revealed pT3b, pN1, and R1 (bifocal) with Gleason grade group of 5. In this patient, the estimated activity at the time of intraoperative specimenPET/CT was only 1.3 kBq/ml with ^{68}Ga-PSMA-11 (Fig. 1 and Supplementary Fig. 1). Overall, there were nine areas close to the surgical margin in addition to the PSM, all of which could be confirmed histopathologically. This very promising result is in contrast with other molecular imaging techniques such as Cerenkov luminescence imaging, where, on the one hand, artificial signals complicate

Table 1 – Patient and imaging characteristics

Patient characteristics (n = 10)		
Age (yr), median (IQR)	65.6 (60.8; 70.5)	
BMI (kg/m^2), median (IQR)	27.4 (24.7; 28.8)	
Initial PSA (ng/ml), median (IQR)	8.15 (5.7; 12.9)	
T stage at biopsy, n (%)		
T1c	5 (50)	
cT2a	1 (10)	
cT2b	2 (20)	
cT3a	1 (10)	
cT3b	1 (10)	
ISUP-GGG at biopsy, n (%)		
ISUP 3	2 (20)	
ISUP 4	2 (20)	
ISUP 5	6 (60)	
T stage at prostatectomy, n (%)		
pT2c	2 (20)	
pT3a	4 (40)	
pT3b	4 (40)	
ISUP-GGG at prostatectomy, n (%)		
ISUP 2	1 (10)	
ISUP 3	2 (20)	
ISUP 4	1 (10)	
ISUP 5	6 (60)	
Pathological lymph node status		
pN0	7 (70)	
pN1	3 (30)	
Resection status		
R1-resection	4 (40)	
R0-resection	6 (60)	
NCCN risk score at prostatectomy		
High risk, n (%)	10 (100)	
Imaging characteristics	^{68}Ga-PSMA-11 (n = 6)	^{18}F-PSMA-1007 (n = 4)
Activity injected (MBq), median (IQR)	172 (138.8; 180.8)	223.5 (211.3; 273.3)
Tracer activity at PET/CT (kBq/ml), median (IQR)	18.6 (13.2; 26.6)	40.2 (22.9; 71.7)
Activity at specimenPET/CT (kBq/ml), median (IQR)	1.0 (0.5; 1.4)	7.7 (3.4; 8.7)
Time from injection to specimenPET/CT (min), median (IQR)	310 (264; 358.5)	392.5 (323.5; 433.8)
Preoperative SUVmax, median (IQR)	12.9 (10.6; 17.3)	26 (12.4; 40)

BMI = body mass index; GGG = Gleason grade group; IQR = interquartile range; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; SUVmax = maximum standardized uptake value. Values are given as median and interquartile range or absolute numbers and percent.

the assessment and, on the other hand, the minimum activity was missed in our one stop protocol [6,7]. There was increased activity at the time of intraoperative imaging with ^{18}F-PSMA-1007 (p = 0.01; Supplementary material, and Supplementary Fig. 2 and 3); ^{18}F has a longer half-life and provides a higher resolution due to lower positron energy, when comparing with ^{68}Ga (0.65 vs 1.9 MeV). The spatial resolution achieved in preclinical scanners is about 1.1 mm for ^{18}F and 2.1 mm for ^{68}Ga [8,9]. A segmentation algorithm was used to improve PET display in correlation with histopathology. By adjusting the fade level, the operator has some control over the contrast level in the final image. An analysis for radiotracer foci segmentation showed an optimal threshold of 11–30% of the maximal signal for assessing surgical margins. However, this calculation is based on a small number of cases, so further validation in a larger cohort is needed. Interestingly, this small collective did not show a typical background signal, as is the case with conventional PET/CT. Preoperative PSMA PET/CT demonstrated a suspicious lymph node status in one of ten patients. In this patient, all dissected PSMA PET/CT–positive lymph nodes were also confirmed by specimenPET/CT after dissection and histopathology, while no additional lymph node metastases were identified by final histopathology (Supplementary material, and Supplementary Fig. 4). Importantly, specimenPET/CT detected three more lymph node metastases in two additional patients, 6 mm and twice 5 mm in long axis diameter, all confirmed by histopathology. Owing to the size of the lymph node metastasis, a lack of visualization on conventional PET/CT may be due to spatial resolution [10].

We acknowledge limitations of this feasibility study. Statistical analysis is limited due to the inclusion of a small sample size. Patients were selected based on a high likelihood of PSMs and are therefore not representative of the general population that will undergo RP. Nevertheless, the included patients are those who could benefit most from an intraoperative margin assessment. The time dependency between injection and RP requires a good cooperation between urology and nuclear medicine, and is currently a limitation for part of the urological centers. As outlined by Muraglia et al [5], intraoperative injection without conventional PET/CT would facilitate procedures. The optimal injection volume and the time interval between injection and separation of the prostate from the blood supply should be investigated in further studies. However, intraoperative specimenPET/CT employs nuclear medicine methods to inform urological surgery for improved local treatment of PC. This new imaging modality brings the urology and nuclear medicine communities more closely together to make progress in PC [11].

This study demonstrates that PSMA-based specimenPET/CT as part of a one-stop shop protocol is feasible and a promising technique for intraoperative margin assessment in PC. The diagnostic accuracy of specimenPET/CT will now be evaluated in a larger population to validate the quantitative threshold between 11% and 30% of maximal signal, to distinguish PSMs from negative surgical margins, in addition to visual inspection alone. In the future, this might improve surgery, and reduce the necessity of adjuvant radiotherapy and the risk of local recurrence after RP.

***Author contributions*:** Christopher Darr had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Darr, Fragoso Costa, Maurer, Herrmann, Hadaschik.
Acquisition of data: Kahl, Darr, Moraitis, Engel, Al-Nader, Falkenbach, Köhler, Klutmann.
Analysis and interpretation of data: Darr, Fragoso Costa, Köhler, Klutmann, Falkenbach, Kleesiek, Reis, Köllermann.
Drafting of the manuscript: Darr, Fragoso Costa, Kahl.
Critical revision of the manuscript for important intellectual content: Kesch, Krafft, Fendler.
Statistical analysis: Darr, Fragoso Costa, Engel, Kleesiek, Köhler, Fendler, Klutmann.
Obtaining funding: None.
Administrative, technical, or material support: Moraitis, Fragoso Costa, Kahl, Engel, Kesch, Krafft.
Supervision: Maurer, Fendler, Herrmann, Hadaschik, Kleesiek.
Other: None.

Financial disclosures: Christopher Darr certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Christopher Darr reports personal fees from Janssen-Cilag, and travel fees from Janssen-Cilag and Ipsen. Wolfgang P. Fendler reports fees from SOFIE Bioscience (research funding), Janssen (consultant, speaker), Calyx (consultant, image review), Bayer (consultant, speaker, research funding), Novartis (speaker), and Telix (speaker) outside of the submitted work. Tobias Maurer reports personal fees from Bayer, Sanofi-Aventis, Astellas, and Phillips Advanced Accelerator (speakers' bureau), and consultant fees from Applications International S.A., Novartis, Telix, ROTOP Pharma, GEMoAb, Astellas, Axiom, Blue Earth Diagnostics, and ABX. Claudia Kesch has received consulting fees from Apogepha, research funding from Advanced Accelerator Applications (Novartis) and Curie Therapeutics, and compensation for travel from Janssen Pharmaceuticals. Boris A. Hadaschik reports personal fees from ABX, Bayer, LightPoint Medical Inc., Janssen R&D, Bristol-Myers-Squibb, and Astellas; research funding from Profound Medical, German Cancer Aid, German Research Foundation, Janssen R&D, Bristol-Myers-Squibb, MSD, Pfizer, and Astellas; and travel fees from AstraZeneca, Janssen R&D, and Astellas. Ken Herrmann reports personal fees from Bayer, Sofie Biosciences, SIRTEX, Adacap, Curium, Endocyte, and BTG. The other authors declare that no relevant conflicts of interest that may directly or indirectly influence the content of the manuscript submitted exist.

***Funding/Support and role of the sponsor*:** This work was funded by the "Deutsche Forschungsgemeinschaft - DFG" (project number: HA 5160/5-1). The funding organization did not influence the study design or the analysis in any way.

***Acknowledgments*:** We thank the study participants for their motivation to participate and support our project. Also, special thanks to XEOS Medical for providing the AURA10 imager and support during this time. Furthermore, we would like to thank Viopsy for supporting us in the processing of the acquired data, especially the reconstruction of the whole mounts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.05.017.

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