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ORIGINAL ARTICLE

Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with ^{68}Ga-PSMA-HBED-CC than with ^{18}F-Fluoroethylcholine PET/CT

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Abstract
Aim [^{68}Ga]PSMA-HBED-CC (^{68}Ga-PSMA) is a novel and promising tracer for highly sensitive combined integrated positron emission tomography and X-ray computed tomography (PET/CT) diagnosis of recurrent prostate cancer (PCA). Our aim was to assess the sensitivity, specificity, positive and negative predictive value (PPV/NPV), and accuracy per lesion, as well as the positive predictive value per patient of ^{68}Ga-PSMA PET/CT using post-lymphadenectomy histology as a standard, and to compare these values to those obtained in a patient collective scanned using ^{18}F-Fluoroethylcholine (^{18}FEC) PET/CT.
Methods Thirty eight patients had ^{18}FEC and 28 patients had ^{68}Ga-PSMA. We performed a pelvic and/or retroperitoneal lymphadenectomy, if necessary supplemented by resection of locally recurrent lesions in accordance with imaging results.
Results In 30/38 ^{18}FEC and 23/28 ^{68}Ga-PSMA patients ≥1 focus of PCA was identified in postsurgical histology, leading to a per-patient PPV of 78.9 % for ^{18}FEC and 82.1 % for ^{68}Ga-PSMA. In ^{18}FEC and ^{68}Ga-PSMA patients, a total of 378 and 308 lymph nodes and local lesions were removed, respectively. For ^{18}FEC and ^{68}for Ga-PSMA, the respective sensitivity (95 % confidence interval) was 71.2 % (64.5–79.6 %) and 86.9 % (75.8–94.2 %), specificity was 86.9 % (82.3–90.6 %) and 93.1 % (89.2–95.9 %), PPV was 67.3 % (57.7–75.9 %) and 75.7 % (64.0–98.5 %), NPV was 88.8 % (84.4–92.3 %) and 96.6 % (93.5–98.5 %), and accuracy was 82.5 % (78.3–86.8 %) and 91.9 % (88.7 %–95.1 %).
Conclusion In the present series Ga-PSMA PET/CT shows a better performance than FEC PET/CT with a significantly higher NPV and accuracy for the detection of locoregional recurrent and/or metastatic lesions prior to salvage lymphadenectomy.

Keywords Ga-68-PSMA PET/CT · F-18-Fluoroethycholine PET/CT · Prostate cancer · Salvage lymphadenectomy · Histology

Introduction

In patients with a prostate cancer (PCA), recurrence either locally or in the pelvic or paraaortal lymph nodes, a salvage lymphadenectomy (sLAD) can be discussed as a palliative therapy in order to slow disease progression and postpone systemic treatment [1, 2]. In order to properly select patients for such a procedure, the identification of target lesions as well as the exclusion of systemic disease is important. Combined integrated positron emission tomography and X-ray computed tomography (PET/CT) with radioactively labeled choline or derivatives thereof is currently recommended as a more sensitive imaging modality than exclusively morphologic imaging methods, but results of radiocholine PET/CT still leave

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room for improvement, especially at low serum levels of prostate specific antigen (PSA) [1, 3–5].

Recently, a novel radiotracer targeted at the prostate specific membrane antigen (PSMA) was introduced [6, 7]. Though not without pitfalls [8], [^{68}Ga]PSMA-HBED-CC (^{68}Ga-PSMA) in initial studies has shown a promising performance [6, 7, 9, 10]. Especially at very low PSA levels, ^{68}Ga-PSMA seems to perform markedly better than ^{18}F-Fluoromethylcholine [11]. A positive ^{68}Ga-PSMA PET/CT signal was described in lymph node metastases as small as 2.4 mm [12], thus potentially significantly outperforming any form of dedicated morphologic imaging [13].

To the best of our knowledge no direct comparison of the diagnostic value of radiocholine and ^{68}Ga-PSMA for the prediction of surgical findings has yet been reported. In our center we have a long tradition of image guided salvage lymphadenectomy in patients with recurrent PCA, first based on ^{18}FEC and more recently also based on ^{68}Ga-PSMA PET/CT. The aim of the present study was to compare the results of histological analysis of surgically removed tissues with the results of PET/CT scans performed with ^{68}Ga-PSMA and compare the diagnostic performance of ^{68}Ga-PSMA with the one determined in a prior patient collective scanned with radioactively labelled choline.

Materials and methods

Patients

In the present retrospective study we included 66 patients who underwent sLAD after PET/CT (38 patients after ^{18}FEC PET/CT, 28 after ^{68}Ga-PSMA PET/CT) between February 1, 2009 and August 31, 2015. Details on the patient characteristics, divided by PET/CT tracer, are given in Table 1.

PET/CT

Patient selection for either of the different tracers was purely periodical: up to October 2013, patients were scanned with ^{18}FEC, whereas from October 2013 onwards patients were scanned using ^{68}Ga-PSMA. In our department ^{18}FEC and ^{68}Ga-PSMA PET/CTs were acquired as follows:

^{18}FEC tracer application

[^{18}F]Fluoroethylcholine (^{18}FEC) was purchased commercially (Eckert&Ziegler, Berlin, Germany). All patients fasted for at least 4 hours before the examination. Patients received an intravenous injection of 3 MBq/kg body weight ^{18}FEC 60 minutes before start of the PET/CT scan.

^{68}Ga-PSMA tracer application

The tracer for ^{68}Ga-PSMA PET/CT was produced in our in-house radiopharmacy. Briefly, [^{68}Ga]PSMA-HBED-CC, the ^{68}Ga-labelled HBED-CC conjugate of the PSMA-specific pharmacophore Glu-NH-CO-NH-Lys, was synthesized by adaption of a previously reported method [14]. ^{68}Ga generator eluate (0.05 M HCl, 1.2 mL, generator: ITG, Garching, Germany) reacted with a 430 μL aqueous solution containing 26.4 μM precursor (ABX GmbH, Dresden, Germany) and 0.28 M NH_4OAc for 1 min at 30 °C. The labelled n.c.a. tracer was purified via a RP cartridge (Sep-Pak C18 Plus Light Cartridge, 130 mg Sorbent, Waters) and formulated in 10 mL PBS containing 5 vol-% EtOH.

Patients then received an intravenous injection of 2 MBq/kg body weight ^{68}Ga-PSMA 45 minutes before the start of the PET/CT scan.

PET/CT scanning

PET/CT scanning in our department was performed using a Philips Gemini TF 16 (Philips Medical Systems, Best, The Netherlands). This machine consists of a time-of-flight capable, fully three-dimensional (3D) Positron-Emission-Tomograph combined with 16-slice CT. The patient bore has a diameter of 71.7 cm with active transverse and axial field of views (FOVs) of 57.6 and 18 cm.

Patients were measured in cranio-caudal (^{18}FEC) or caudo-cranial (^{68}Ga-PSMA) orientation with their arms raised to decrease beam-hardening artefacts. First, a mid-inspiratory low dose whole body neCT from the base of the skull to the upper thigh was performed for attenuation correction purposes (imaging parameters: collimation 16 × 1.5 mm; pitch 0.812; rotation time 0.4 second; effective tube current–time product of 30 mAs; tube voltage of 120 kVp). Afterwards, a diagnostic CT in maximum inspiration was acquired in the venous phase after intravenous application of X-ray contrast medium application (Ultravist 300; Bayer Pharma AG, Berlin, Germany). This CT too was acquired from the base of the skull to the upper thigh (imaging parameters: collimation 16 × 0.75 mm; pitch 0.813; rotation time 0.75 second; effective tube current–time product of 200 mAs; tube voltage of 120 kVp).

For subsequent CT reconstruction, we used a medium-smooth soft-tissue kernel (window centre 60; window width 450) at a slice thickness of 5 mm with an overlapping increment of 3.5 mm.

Following the CT, a PET of the same body volume was performed. Data were collected in list mode for all coincident events along with their time stamps over multiple time points with an acquisition time of 1.5 minutes per bed position. Slices of 4 mm thickness (pixel size = 4x4 mm2) were reconstructed using the iterative proprietary BLOB-OS-TF algorithm (number of iterations = 3, number of subsets = 33),

Table 1 Characteristics of the patient groups scanned with ^{18}F-Fluoroethylcholine (^{18}F-FEC) and ^{68}Ga-labelled Prostate Specific Membrane Antigen-HBED-CC (^{68}Ga-PSMA) PET/CT, as well as p-values for tests for differences between the groups

	^{18}F-FEC	^{68}Ga-PSMA	p-value
No. of patients	38	28	
Median age at surgery, years	65 (55–75)	67 (46–79)	0.82 (MW)
Gleason score at diagnosis	18 (47 %)	16 (57 %)	0.88 (Chi)
≤7	11 (29 %)	9 (32 %)	
>7	9 (24 %)	3 (11 %)	
Unknown			
Median PSA, ng/ml	2.7 (0.3–8.4)	2.35 (0.04–8)	0.25 (MW)
Primary therapy:	33 (87 %)	23 (82 %)	0.21 (Chi)
Prostatectomy	5 (13 %)	3 (11 %)	
Radiation therapy	0 (0 %)	2 (7 %)	
HIFU			
Time since primary therapy at surgery, months	53 (4–163)	74 (4–197)	0.12 (MW)
Hormone therapy at PET/CT	9 (24 %)	12 (43 %)	0.10 (Chi)
Yes	29 (76 %)	16 (57 %)	
No			
Prior salvage/adjuvant radiation therapy	24 (63 %)	16 (57 %)	0.62 (Chi)
Yes	14 (37 %)	12 (43 %)	
No			
Median duration of surgery, minutes	135 (60–163)	136 (75–250)	0.58 (MW)

Values are given as no. of patients (% of the total number of patients in the respective group) or as median (range)
HIFU high frequency ultrasound, *MW* Mann–Whitney Test, *Chi* Chi-squared test

which was provided by the manufacturer. Datasets were fully corrected for random coincidences, scatter radiation, and attenuation. Low dose neCT and venous phase ceCT data sets were used for attenuation correction resulting in two PET image data sets based on the same set of raw emission data (Figs. 1 and 2).

Clinical PET/CT assessment

The Hermes Hybrid Viewer version 2.0C (Hermes Medical Solutions, Stockholm, Sweden) was used for image assessment. After acquisition, all images were assessed clinically by one of four board-certified nuclear medicine physicians in our department of nuclear medicine.

Surgery

Based on imaging results, a surgical resection of lesions reported in the former prostate bed, the seminal vesicles, and the pelvic or retroperitoneal lymph nodes were performed. In each procedure we attempted to perform a systematic dissection of the complete anatomic region shown to be affected with at least one lesion on PET/CT. All material removed from each of these regions was separately sent in for pathological analysis. In case of an isolated lesion in the pelvis on PET/CT, an extended pelvic lymph node dissection was performed including the fossa obturatoria, internal and external iliac artery, and common iliac artery up to the ureteral crossing [15, 16]. In case of a maximum of two scan positive foci in the

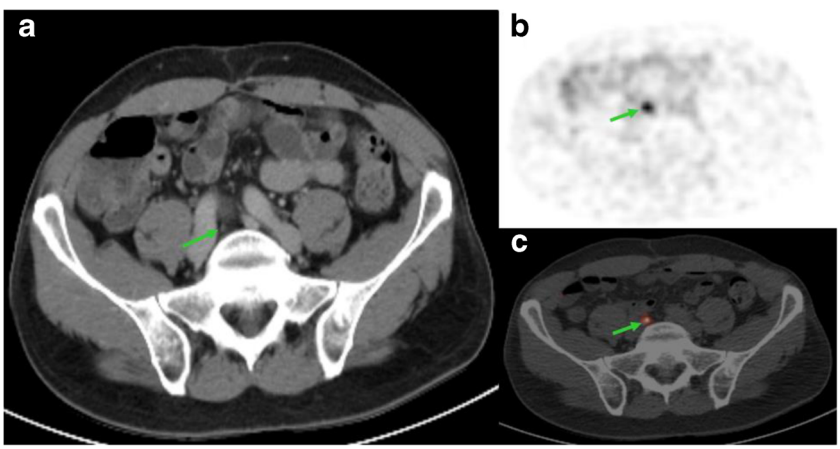

Fig. 1 (**a**) Contrast enhanced CT, (**b**) PET and (**c**) PET/low-dose CT fusion of a ^{68}Ga-PSMA PET/CT in a patient with a PSA of 2,1 ng/ml. In all three images the green arrow points towards a single positive lymph node with a short-axis diameter of 3 mm along the right common illiac artery. Subsequent extensive pelvic lymph node dissection revealed one lymph node metastasis in the lymph node indicated by the PET/CT and 22 non-cancerous lymph nodes

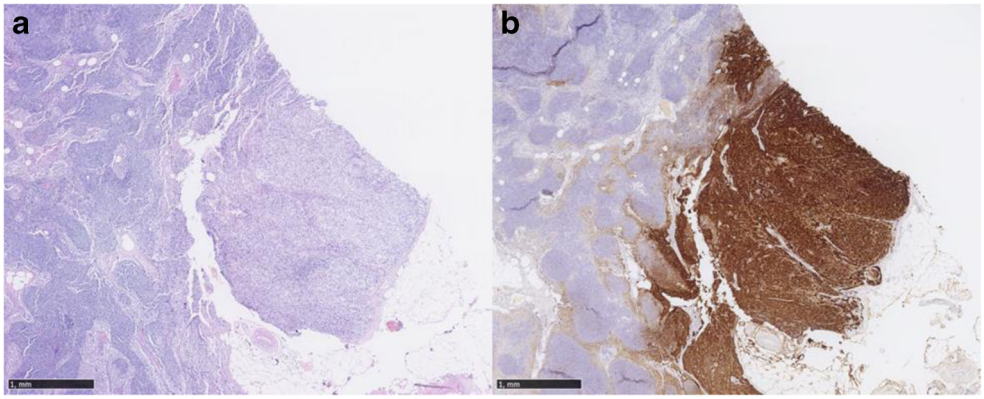

Fig. 2 Histological analysis of the PSMA positive lesion seen in ^{68}Ga-PSMA PET/CT in Fig. 1: (**a**) HE staining and (**b**) Immunohistochemical staining for prostate specific membrane antigen (PSMA)

retroperitoneum, a retroperitoneal lymph node dissection was added. Retroperitoneal lymph node dissection was performed within the boundaries known by post chemotherapy retroperitoneal lymph node dissections in testicular cancer. The lateral, cranial, and caudal boundaries are both ureters, renal vessels, and the ureteral crossing of the iliac artery [15, 16].

Pathological analysis

All samples were assessed macro- and microscopically by an experienced board-certified uro-pathologist (RK). The surgically removed material was dissected and each lymph node was embedded in paraffin blocks. Subsequently, 4–6 μm slices were cut from each lymph node. In addition to standard Hematoxylin-Eosin staining, immunohistochemical analyses were performed as needed to secure a diagnosis. For the present study, the written pathology report as produced after surgery was used.

Assessment

The number of PET/CT positive foci for each of the surgically relevant compartments (former prostate bed, left or right sided pelvic regions subdivided in fossa internal/external, and common iliac artery, or paraaortal and interaortocaval, as well as paracaval lymph nodes) was assessed independently by two board certified nuclear medicine physicians who had extensive experience with ^{18}FEC and ^{68}Ga-PSMA PET/CT (FFB/FAV). Both physicians were blinded to patients' history and clinical results. In cases of differing scan interpretations, the images were discussed and a consensus was reached.

In a second session, the results of the pathological analysis of the surgical specimens and the re-analysis of the PET/CT scans were discussed between a urological surgeon who has participated in the operations (DP) and the nuclear medicine physicians in order to match the PET/CT findings with the histological specimen based on the report of the surgical procedure.

A lesion was considered false positive on PET/CT, if histological analysis of that region revealed no prostate cancer lesions. If a lower number of lesions was found on histological analysis than on PET/CT, the numerical difference between the two analyses was considered false positive.

A lesion was considered false negative on PET/CT, if histological analysis of that region revealed prostate cancer lesions. If a higher number of lesions was found on histological analysis than on PET/CT, the numerical difference between the two analyses was considered false positive.

A lesion was considered true positive on PET/CT, if histological analysis of that region revealed the same number of prostate cancer lesions as reported on PET/CT. A lesion was considered true negative, if histological analysis revealed no prostate cancer lesion in a region where PET/CT showed no lesions, or if there was no difference in the number of positive lesions in a particular region between PET/CT and histological analysis if in the same region negative specimen were also present.

Based on the results of this comparison, the sensitivity, specificity, positive (PPV), negative predictive value (NPV), and accuracy of ^{18}FEC and ^{68}Ga-PSMA PET/CT was calculated as well as the 95 % confidence interval (CI) for each of these values.

Statistical analysis

Statistical analyses were performed using SPSS 23 (IBM corp., Armonk, NY, USA). Differences between values for sensitivity, specificity, PPV, NPV, and accuracy were considered significant if the 95 % CI showed no overlap between ^{18}FEC and ^{68}Ga-PSMA PET/CT. In other statistical tests $p < 0.05$ was considered to indicate significance. For comparisons between groups, we used the Mann–Whitney and Chi-squared tests.

Results

Results per patient

In Table 1 the baseline characteristics of each of the two groups are given. It can be seen that no significant differences in baseline characteristics existed between the ^{18}FEC and ^{68}Ga-PSMA, therefore the groups are comparable for the purpose of this study.

All patients included in the study had at least one positive focus on PET/CT. In 30/38 ^{18}FEC and 22/28 ^{68}Ga-PSMA patients, at least one focus of PCA was identified in postsurgical histological analysis, leading to a per-patient PPV of 78.9 % for ^{18}FEC and 82.1 % for ^{68}Ga-PSMA. Since no histological information is available on patients with a negative scan, we cannot calculate the 95 % CI or per patient sensitivity, specificity or NPV.

Results per lesion

In Table 2 the results of the per lesion comparison between PET/CT and histology and the calculated values of sensitivity, specificity, PPV, NPV, and accuracy as well their 95 %-CI are given for both the ^{18}FEC and the ^{68}Ga-PSMA PET/CT groups.

Although the sensitivity, specificity, and PPV of ^{68}Ga-PSMA PET/CT all appear higher than for ^{18}FEC PET/CT, the 95 %-CIs for these values still overlap. However, the NPV and accuracy of ^{68}Ga-PSMA PET/CT both are significantly higher than the one for ^{18}FEC PET/CT.

Discussion

To the best of our knowledge, the study presented here is the first one which directly compares the diagnostic performance of ^{18}FEC and ^{68}Ga-PSMA PET/CT using the results of pathological analysis of surgical specimens removed in image guided surgery as a standard of reference. The results show that ^{68}Ga-PSMA PET/CT is significantly more accurate than ^{18}FEC PET/CT.

Even though ^{18}FEC in the present study was inferior to ^{68}Ga-PSMA, the detection rates for both tracers in the present study were dramatically better than reported in some former series in pre-prostatectomy patients [17, 18]. Another recent study in contrast reported comparable accuracy and a somewhat lower sensitivity in the same setting [19]. However, the pre-prostatectomy setting may not be comparable to the salvage lymphadenectomy setting reported here.

Tilki et al. [20] in a collective of 56 patients with suspected recurrence after prostatectomy found a sensitivity, specificity, PPV, and NPV for ^{18}FEC of 39.7 %, 95.8 %, 75.7 %, and 83.0 %, respectively. Whereas the present study largely agrees with the value for specificity, PPV, and NPV, we in contrast found a much better per-lesion sensitivity (71.2 %) in a collective in the same setting.

Rinnab et al. reported a per-patient PPV of 53 % for ^{11}C-labelled choline PET/CT [21], where histological analysis of tissues removed at salvage lymphadenectomy only identified PCA lesions in 8/15 patients with a positive PET/CT. A small series of ten patients scanned with ^{11}C-labelled choline PET/CT reported by Schilling et al. [22] reported a per-patient PPV of 70 %. With 82.1 %, the PPV found in the present study was considerably higher than the former and still somewhat better than the latter.

Table 2 Results of the per lesion comparison between PET/CT and histology for the patient groups scanned with ^{18}F-Fluoroethylcholine (^{18}F-FEC) and ^{68}Ga-labelled Prostate Specific Membrane Antigen-HBED-CC (^{68}Ga-PSMA) PET/CT, as well as the values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95 % confidence intervals for these values between brackets

^{18}FEC	Histology positive	Histology negative	
PET/CT positive	74	36	*PPV:* 67.3 % (57.7–75.9 %)
PET/CT negative	30	238	*NPV:* 88.8 % (84.4–92.3 %)
	sensitivity: 71.2 % (64.5–79.6 %)	*specificity:* 86.9 % (82.3–90.6 %)	*accuracy:* 82.5 % (78.3–86.8 %)
^{68}Ga-PSMA	Histology positive	Histology negative	
PET/CT positive	53	17	*PPV:* 75.7 % (64.0–98.5 %)
PET/CT negative	8	230	*NPV:* 96.6 % (93.5–98.5 %)
	sensitivity: 86.9 % (75.8–94.2 %)	*specificity:* 93.1 % (89.2–95.9 %)	*accuracy:* 91.9 % (88.7–95.1 %)

Very few studies have yet reported any correlation with histology for ^{68}Ga-PSMA PET/CT. Afshar-Oromieh et al. [6] reported a lesion-based sensitivity, specificity, NPV, and PPV of 76.6 %, 100 %, 91.4 % and 100 %, respectively, based on histological analysis of biopsy or surgery samples of 42 patients with suspected recurrent PCA. Thus, our reported sensitivity is higher but considering the 95 % confidence interval, not significantly so.

A recent study by Hijazi et al. [23] also examined the diagnostic performance of ^{68}Ga-PSMA PET/CT in recurrent prostate cancer based on lymphadenectomy specimens. Based on 213 removed lymph nodes, they found a sensitivity of 94 %, a specificity of 99 %, a PPV of 89 %, and an NPV of 99.5 %. Although these values are slightly to somewhat better than those reported for ^{68}Ga-PSMA PET/CT in the present study, the difference is not of a magnitude that the current results for ^{68}Ga-PSMA PET/CT cannot be considered to roughly be in agreement.

However, importantly for clinical practice, the increased sensitivity in our study appears to go hand in hand with a, not statistically significant, decrease in PPV - meaning that some lesions in fact showed a positive signal on ^{68}Ga-PSMA PET/CT, which were subsequently proven free of PCA.

The results of the present study are hampered by its retrospective nature. Patient selection was performed based on scan results rather than on an a priori study plan. Hence, it is not possible to estimate sensitivity, specificity, NPV, or accuracy on a per-patient basis as those patients with a negative scan were not referred for surgery. However, we assume that this has not affected the per-lesion sensitivity as we dissected entire anatomical compartments, including those lymph nodes which were negative on PET/CT, and not just removed those lesions which appeared positive on PET/CT; thus the present study should provide a fair estimate of the false negative rate for both tracers. Furthermore, patients generally did not return to our centre for follow-up scanning but were instead taken care of by their attending urologist. As a consequence, we were unable to ascertain whether a seemingly false-positive PET/CT scan was indeed false positive rather than that the positive lesion was missed during surgery and artificially lowering the accuracy rate in the present study. Again, we assume that this matter would have a similar impact on the results for both tracer groups, thus not markedly influencing the comparison.

Also inherent to the retrospective nature of the present study is the lack of data on patients who were not operated upon due to a negative PET/CT result. This is especially of concern in the ^{68}Ga-PSMA PET/CT group, as it has been described that up to 10–15 % of prostate cancers can show a lack of PSMA expression either primarily or develop so in the course of disease [24, 25]. It is, therefore, possible that the estimates for ^{68}Ga-PSMA PET/CT in the present study are somewhat inflated - due to the retrospective nature of the study it is however impossible to ascertain whether this is in fact the case and, if so, to what extent. Especially the NPV for the presence of lymph node metastases has to be interpreted with the limitation that it is only valid for PSMA-positive PCA - for the entire, unselected population of PCA patients the NPV in ^{68}Ga-PSMA PET/CT is likely lower. Notwithstanding such concerns, the current data remain valid at least for the group of ^{68}Ga-PSMA PET/CT positive patients. This means that in patients with ^{68}Ga-PSMA PET/CT positive lesions, it can be safely assumed that those nodes not positive on the scan will in fact turn out to be negative on histological analysis.

Furthermore, the use of ^{18}FEC might not represent the optimal tracer for PET/CT using radiolabelled choline as a tracer in patients with recurrent prostate cancer. A recent review of the literature [26] indicated for instance that the upper limit of reported detection rates of lymph node metastases for ^{18}FEC was 39 %, whereas the upper limit reported for ^{18}F-fluoromethylcholine was 50 %. Similarly the sensitivity for ^{18}FEC had an upper reported limit of 85.7 versus 96 % for ^{18}F-fluoromethylcholine. However, considering that the lower reported limit for ^{18}FEC was 62 % versus 42.9 % for ^{18}F-fluoromethylcholine, the difference between the tracers appears neither to be statistically significant. Furthermore, the sensitivity reported in the present study even exceeds the upper limit of the bandwidth reported thus far, showing that perhaps the optimum for ^{18}FEC has not yet been reported.

The present study does not compare the two tracers within the same patient, but rather compares two different patient groups. This can potentially influence the results as prostate cancer, like most cancers, is a heterogeneous disease, and the comparison of different patient groups may be influenced by this heterogeneity. However, as far as we were able to ascertain based on the known important variation factors such as the Gleason score, prior therapies or medication, which may influence the scan results such as androgen deprivation therapy [4], we believe that the results of this comparison are valid for clinical practice as there were no significant differences between the baseline characteristics of the two different patient groups. Furthermore, all patients underwent surgery with the same urological team applying the same imaging-oriented surgical strategy on all patients regardless of the tracer used. Thus, for both groups comparable histological verification was achieved. Also, the present results are in good agreement with studies comparing the ^{18}FEC and ^{68}Ga-PSMA within patients, where it was shown that ^{68}Ga-PSMA PET/CT or PET/MRI resulted in a higher lesion detection rate than ^{18}FEC.

The PPV is an important component for guiding extended lymphadenectomy, especially when extending surgery beyond the standard pelvic sites into the retroperitoneal space. The PPV of ^{68}Ga-PSMA PET/CT in the present study is

tendentially higher than the PPV of ^{18}FEC. It is, therefore, desirable to confirm these values in a greater patient series in order to allow smaller effects to show with statistical significance. Furthermore, further research is required to investigate the limiting factors which contribute to the limitation of the PPV for both ^{18}FEC and ^{68}Ga-PSMA PET/CT, as the PPV is the worst performing parameter for both tracers.

Although more research is necessary to confirm the high NPV found here for ^{68}Ga-PSMA PET/CT, it is conceivable that in the future this may lead to a change of the surgical strategy for salvage lymphadenectomy. In PSMA positive PCA this might allow a more selective lymph node removal on the assumption that lymph nodes which are negative on PET/CT are truly unaffected by PCA metastases. To further improve the diagnostic outcome and lower the probability of missing positive lesions, the recently introduced intraoperative gamma probe guided surgery using an ^{111}In labelled PSMA ligand might be an option [27]. Therefore, a more selective surgical strategy, possibly aided by prior radioactive labelling of affected lymph nodes, may be instrumental in reducing surgical morbidity without sacrificing therapeutic efficacy.

The clinical consequences of the present results are considerable. As the present study unequivocally shows that ^{68}Ga-PSMA PET/CT is more accurate, has a higher NPV, and shows clear tendencies towards higher sensitivity, higher specificity, and a higher PPV than ^{18}FEC PET/CT, ^{68}Ga-PSMA PET/CT is to be preferred over ^{18}FEC for PET/CT based identification of recurrent and/or metastatic PCA lesions in patients with rising/persistent levels of prostate specific antigen after primary therapy.

Conclusion

^{68}Ga-PSMA PET/CT is more accurate and has a higher negative predictive value than ^{18}FEC PET/CT for the identification of locally recurrent lesions and pelvic or abdominal lymph node metastases of prostate cancer prior to salvage lymphadenectomy. Therefore, ^{68}Ga-PSMA PET/CT should be preferred for preoperative imaging, and the results may be used to guide a more selective surgical approach.

Compliance of ethical standards

Disclosure of potential conflicts of interest David Pfister has received consultancy fees and payment for speaker bureaus from Astellas, Ipsen, Sanofi, and Janssen. Axel Heidenreich has received consultancy fees and payment for speaker bureaus from Amgen, Janssen, Ipsen, Sanofi, and Takeda (for whom he is also a board member); research and travel support from Astellas; and a research grant from Sanofi. Florian F. Behrendt has received research support and speaker fees from Bayer. Frederik A. Verburg is a consultant to Bayer and Genzyme. Daniel Porres, Isabell Heidegger, Ruth Knuechel, and Florian Steib have nothing to declare.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study is a retrospective one; for this type of study formal consent is not required.

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