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ORIGINAL ARTICLE

Performance of ^{111}In-labelled PSMA ligand in patients with nodal metastatic prostate cancer: correlation between tracer uptake and histopathology from lymphadenectomy

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Abstract

Purpose Intraoperative identification of lymph node (LN) metastases (LNM) detected on preoperative PSMA PET/CT may be facilitated by PSMA radioguided surgery with the use of a gamma probe. We evaluated the uptake of ^{111}In-labelled PSMA ligand DKFZ-617 (referred to as ^{111}In-PSMA-617) in unaffected LN and LNM at the level of single LN.

Methods Six patients with prostate cancer (PCa) with suspicion of LNM on preoperative PSMA PET/CT underwent ^{111}In-PSMA-617-guided lymphadenectomy (LA; four salvage LA and two primary LA). ^{111}In-PSMA-617 (109 ± 5 MBq). was injected Intravenously 48 h prior to surgery Template LAs were performed in small subregions: common, external, obturator and internal iliac vessels, and presacral and retroperitoneal subregions (n = 4). Samples from each subregion were isolated aiming at the level of single LN. Uptake was measured ex situ using a germanium detector. Receiver operating characteristic (ROC) analysis was performed based on ^{111}In-PSMA-617 uptake expressed as standardized uptake values normalized to lean body mass (SUL).

Results Overall 310 LN (mean 52 ± 19.7) were removed from 74 subregions (mean 12 ± 3.7). Of the 310 LN, 35 turned out to be LNM on histopathology. Separation of the samples from all subregions resulted in 318 single specimens: 182 PCa-negative LN samples with 275 LN, 35 single LNM samples, 3 non-nodal PCa tissue samples and 98 fibrofatty tissue samples. The median SULs of nonaffected LN (0.16) and affected LN (13.2) were significantly different ($p < 0.0001$). Based on 38 tumour-containing and 182 tumour-free specimens, ROC analysis revealed an area under the curve of 0.976 (95% CI 0.95–1.00, $p < 0.0001$). Using a SUL cut-off value of 1.136, sensitivity, specificity, positive predictive value, negative predictive value and accuracy in discriminating affected from nonaffected LN were 92.1% (35/38), 98.9% (180/182), 94.6% (35/37), 98.4% (180/183) and 97.7% (215/220), respectively.

Conclusion Ex situ analysis at the level of single LN showed that ^{111}In-PSMA-617 had excellent ability to discriminate between affected and nonaffected LN in our patients with PCa. This tracer characteristic is a prerequisite for in vivo real-time measurements during surgery.

Keywords Radioguided surgery · ^{111}In-PSMA · Lymphadenectomy · Lymph node metastases

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer in men and can be cured by surgical removal of the prostate (radical prostatectomy) with pelvic lymphadenectomy (LA) or by radiotherapy [1–4]. As predicted by parameters such as prostate-specific antigen (PSA) level, Gleason score and TNM status, metastases may arise [3, 4]. Pelvic lymph nodes (LN) are the first site for metastases and over the course of progression, bones and soft tissue are affected [2–4]. LN metastases (LNM), if present at the time of primary therapy, should be removed during radical prostatectomy by LA in order to improve oncological outcome and to enable correct staging [2–5]. Reliable and accurate preoperative detection of LNM is indispensable for successful surgery [6, 7].

Despite primary therapy, about 15–30% of the patients will develop biochemical recurrence with elevated PSA levels and clinical recurrence possible at different sites (e.g. local relapse, LNM, bone). Positron emission tomography/computed tomography (PET/CT) targeting prostate-specific membrane antigen (PSMA) has demonstrated excellent power to detect LNM prior to surgery [6, 8–10]. Consequently PSMA PET/CT is rapidly gaining acceptance as a tool for staging and restaging of PCa [8–10]. If PSMA PET/CT indicates the presence of regional pelvic LNM as the only finding responsible for a biochemical and clinical recurrence, surgical removal (i.e. salvage LA) of the lymphatic tissue or targeted radiotherapy may be pursued in patients in good general condition [6, 11]. Active therapy approaches such as salvage LA or targeted radiotherapy are offered to eligible patients to avoid palliative systemic therapies (hormone-deprivation therapy or even chemotherapy) [3, 12, 13].

Intraoperative localization of suspected recurrent LNM may be very challenging if the metastases are small or if accessibility to the LNM is reduced, e.g. because of tissue adhesions or atypical locations of the LNM. Thus, there is the need to improve identification of LNM during surgery, regardless of whether the surgery is primary LA or salvage LA, to guide the surgeon to the region of interest [6, 14].

Recently ^{111}In-labelled PSMA ligands have been successfully introduced for SPECT/CT as well as for intraoperative use (radioguided surgery, RGS) [13–15]. After intravenous injection of ^{111}In-labelled PSMA ligand (DKFZ-617, referred to as ^{111}In-PSMA-617 [16]) prior to surgery in men with suspected LNM on PSMA PET/CT, metastases could be tracked intraoperatively by applying a gamma probe with acoustic feedback. Therefore, the surgeon would be able to measure suspected regions in situ for LNM localization and resected tissue samples ex situ for verification of successful removal.

Rauscher et al found that ^{111}In-PSMA RGS correctly classified 48 of 51 samples with histological proof of metastatic involvement from 31 patients [15]. Maurer et al. found that the sensitivity, specificity and accuracy achieved by ^{99m}Tc-RGS were 83.6%, 100% and 93.0%, respectively, in 31 patients with 58 tumour-containing samples removed during LA [13]. Currently, overall knowledge concerning RGS with ^{111}In-PSMA-617 is limited, particularly because available data on performance of the tracer are based on “mixed” resected tissue samples from one anatomical region consisting of LN, LNM and fibrofatty tissue (FFT) [13–15].

The aim of this study was to evaluate the ability of ^{111}In-PSMA-617 to discriminate between tumour tissue (mainly LNM) and nonaffected tissue (LN, FFT) in men with suspected LNM on PSMA PET/CT. Therefore extensive sample processing and measurement using a germanium detector were performed after surgery. Finally, we evaluated tracer accumulation at the level of single LN and LNM.

Table 1 Clinical characteristics and outcome of lymphadenectomy in the six patients included, four with salvage lymph node dissection (patients 1–4) and two with extended lymph node dissection during radical prostatectomy (patients 5 and 6)

Patient number	Age at surgery (years)	PSA at surgery (ng/ml)	Gleason score at primary stage	^{111}In-PSMA administered activity (MBq)	Number of anatomical subregions resected	Number of manually separated “single samples”	Number of LN removed overall	Number of LNM	Number of non-nodal PCa tissue samples removed
1	78	2.46	4 + 3	113	8	41	34	2	–
2	65	0.64	4 + 3	115	14	46	48	5	2
3	65	0.93	4 + 4	104	16	70	52	0	–
4	71	11.59	4 + 3	106	16	66	90	18	1
5	77	12.16	4 + 4	111	8	51	42	4	–
6	71	22.00	4 + 5	103	12	44	44	6	–
				Sum	74	318	310	35	3

LNM lymph node metastases, *LN* lymph node, *PSA* prostate-specific antigen, *PSMA* prostate-specific membrane antigen, *PCa* prostate cancer, *LA* lymphadenectomy

Materials and methods

Patients

From April 2016 to August 2016, six patients with suspicion of LNM exclusively (without detectable bone or visceral metastases) on PSMA PET/CT underwent LA after administration of ^{111}In-PSMA-617 prior to surgery. Two patients underwent extended LA during radical prostatectomy for primary PCa. Four patients with biochemical recurrence (PSA >0.2 ng/ml after radical prostatectomy) underwent salvage LA on a compassionate use basis. Sample processing (manual separation after surgery followed by direct measurement of the samples using the germanium detector) was planned and performed on a prospective intention basis. The local ethics committee approved this data analysis (no. 562/15). Informed consent was obtained from each subject, and all procedures were performed in accordance with the principles of the Declaration of Helsinki.

PSMA-HBED-CC PET/CT and imaging analysis

PSMA-HBED-CC (*N*,*N*′-bis-[2-hydroxy-5-(carboxyethyl) benzyl]ethylenediamine-*N*,*N*′-diacetic acid) PET/CT was performed as described by Jilg et al. [6]. Imaging was done after

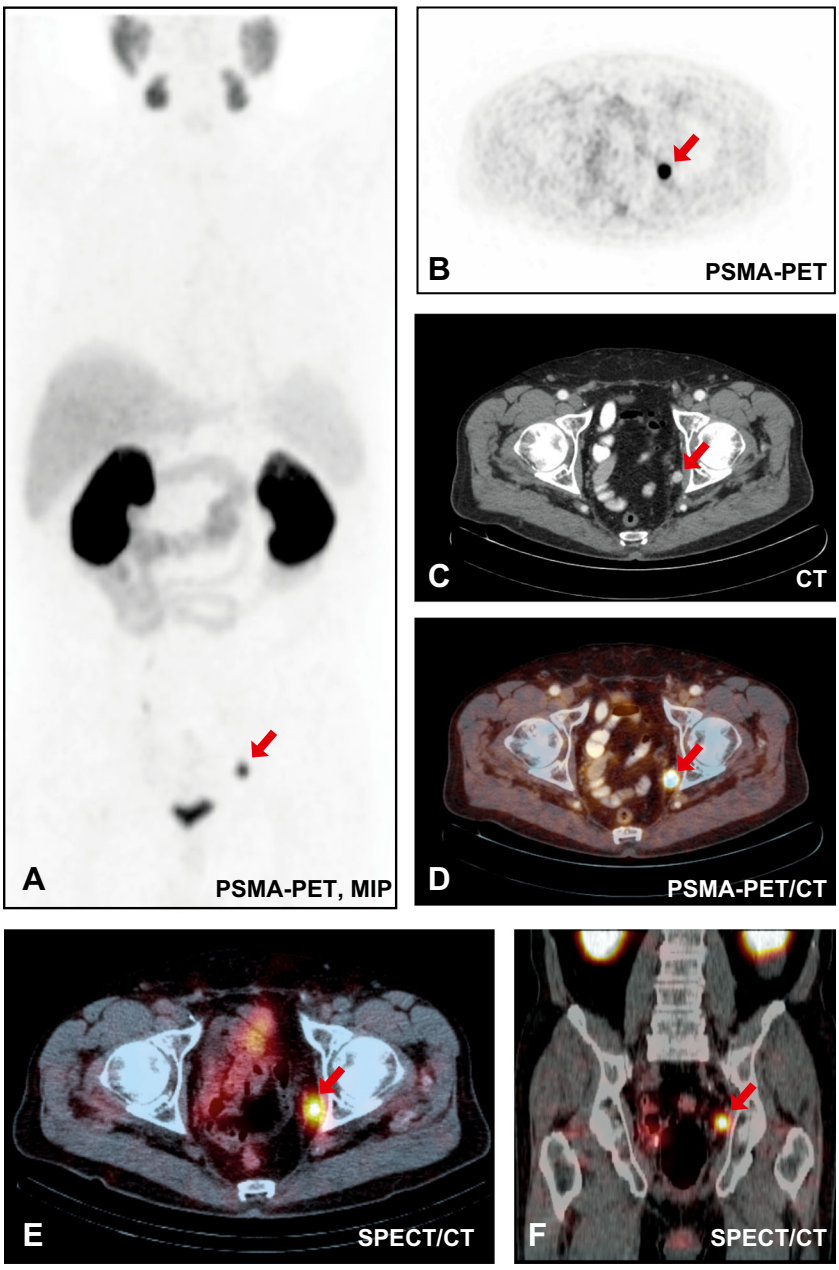

Fig. 1 Imaging in a representative patient (patient 1) with a suspected lymph node metastasis in the left iliac region. **a** Maximum intensity projection of a PSMA PET scan. **b–d** Axial PET (**b**), corresponding CT (**c**) and axial fused PET/CT (**d**) images. **c**, **d** Preoperative SPECT/CT images (**e** axial, **b** coronal). *Red arrows* suspected LNM

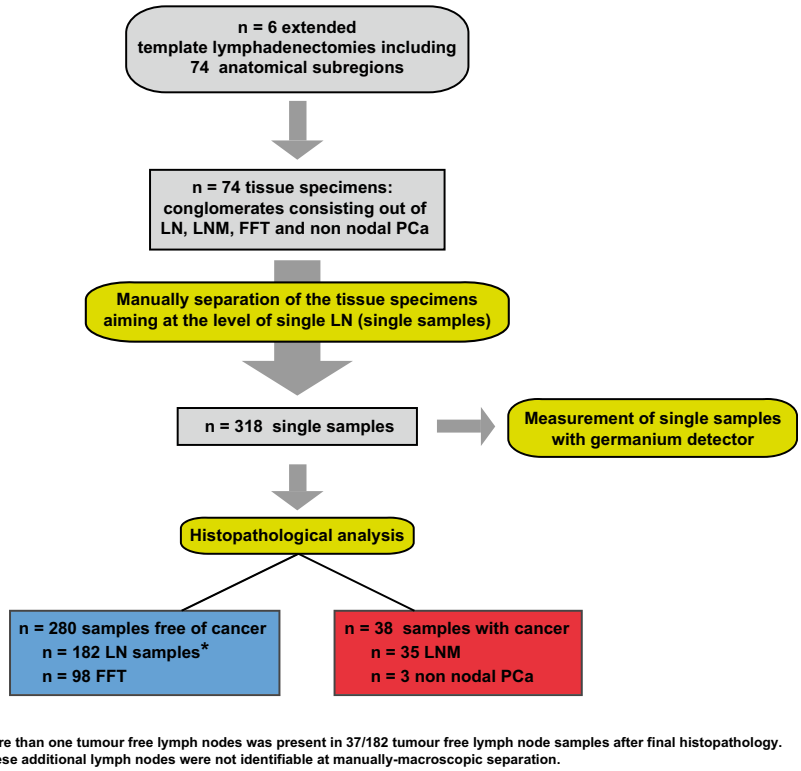

Fig. 2 Workflow and tissue sample processing from six lymphadenectomies. Resected tissue specimens from 74 subregions were manually separated to the level of 318 single samples (aiming at the level of a single LN) and measured with a germanium detector. After histopathological analysis, PCa tumour was detected in 38 of the 318 tissue samples. Of 280 samples free of cancer, 182 contained 275 tumour-free lymph nodes

injection of a mean of 213 ± 7 MBq ^{68}Ga-labelled PSMA-HBED-CC. A PSMA-positive lesion was defined as focal tracer accumulation greater than normal or physiological local background activity. Coregistered PET and CT datasets were evaluated using predefined PET window settings (inverted grey scale, SUV range 0 to 5 g/ml). All patients showed increased focal ^{68}Ga-PSMA uptake in at least one pelvic and/or retroperitoneal region.

Table 2 Origins of tissue samples from 74 subregions

Region	No. (%) of samples
Left common iliac	3 (4%)
Right common iliac	6 (8%)
Left external iliac	8 (11%)
Right external iliac	5 (7%)
Left obturator iliac	10 (14%)
Right obturator iliac	5 (7%)
Left internal iliac	7 (9%)
Right internal iliac	5 (7%)
Left presacral	7 (9%)
Right presacral	2 (3%)
Retroperitoneal	4 (5%)
Miscellaneous[a]	12 (16%)

[a] Miscellaneous regions: mesorectal, pillar of urinary bladder, near the wall of urinary bladder, lacuna vasorum, implanted metastases in the abdominal wall

^{111}In-PSMA synthesis and administration

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)-conjugated PSMA-617 was labelled with $^{111}InCl_3$ following good laboratory practice procedures within 30 min of synthesis at 95 °C in ammonium acetate buffer. PSMA-617 was obtained from ABX advanced biochemical compounds (Radeberg, Germany). The radiotracer solution was prepared by dilution with 0.9% NaCl. Binding studies have shown that ^{111}In-PSMA-617 has a high affinity for LNCaP cells [16]. The radiochemical purity of the final product was ≥97% and the decay-corrected yield was >95%. Patients were injected intravenously with ^{111}In-PSMA-617 (mean 109 ± 5 MBq) 48 h prior to surgery. SPECT/CT was performed a mean of 24.0 ± 0.8 h prior to surgery to ensure sufficient tracer accumulation in the suspected tumour lesions.

Lymphadenectomy

The regions for LA and the number of LN removed were based on the following template LAs performed as described by Jilg et al. [6]. According to the presence of PET-positive lesions (pelvic, retroperitoneal or both), a bilateral pelvic template LA (left and right common iliac vessels, external iliac vessels, obturator iliac vessels, internal iliac vessels, presacral region), a retroperitoneal template LA (aortic bifurcation, left and right paraaortic, caval, interaortocaval) or a combined pelvic and retroperitoneal

Table 3 Measurements from 318 manually separated single fibrofatty tissue (FFT) samples, tumour-free lymph node (LN) samples, and tumour tissue samples

	Weight (g)			Tracer uptake (%ID/g)			SUL[b]		
	Mean ± SD	Median (range)	*p* value (Mann-Whitney test)	Mean ± SD	Median (range)	*p* value (Mann-Whitney test)	Mean ± SD	Median (range)	*p* value (Mann-Whitney test)
FFT (n = 98)	1.069 ± 0.939	0.705 (0.03–3.81)	–	1.47E−04 ± 4.09E−04	7.0E−05 (5.5E−06 to 0.0036)	–	0.0870 ± 0.2409	0.043 (0.003–2.178)	–
LN samples (n = 182)[a]	0.806 ± 1.108	0.435 (0.01–10.0)	0.2034	4.06E−04 ± 4.61E−04	2.52E−04 (9.1E−06 to 3.45E−03)	<0.0001	0.2445 ± 0.2748	0.161 (0.005–2.077)	<0.0001
Tumour tissue samples (n = 38)	0.873 ± 1.774	0.19 (0.02–9.2)		3.21E−02 ± 3.885E−02	2.085E−02 (3.5E−03 to 2.06E−01)		19.92 ± 24.64	13.23 (0.211–132.0)	

[a] 37/182 LN samples contained more than one LN resulting in overall 275 tumour-free LN

[b] Standardized uptake value normalized to lean body mass

template LA was performed. Whenever intraoperative circumstances permitted we adhered to these templates. Nodal fibrofatty tissue from each subregion was collected separately. During LA a gamma probe was used to measure the gamma counts in situ and ex situ (when the tissue had been removed). Ex situ gamma counts allowed an assessment of whether the removed tissue specimen could be assumed to contain tumour or to be tumour-free. In cases when ex situ gamma counts were very low (indicating that the tissue resected was free of tumour) and preoperative PET/CT predicted a LNM in this anatomical region, the LA was continued to extend the search for LNM. The results of such extended searches were not evaluated in the current analysis.

Sample processing and data acquisition

Following surgery the specimens from all subregions, consisting of nodal FFT, LN and LNM, were manually separated aiming at the level of single samples (318 samples; LN and FFT) under the guidance of an experienced pathologist. The 318 single samples were weighed and tracer uptake measured. More than one tumour-free LN was present in 37 of 182 tumour-free LN samples after final histopathology. These additional LN were not identifiable on manual macroscopic separation.

Analysis of tracer uptake

The activity in each single sample was measured using a high-purity germanium detector (model GX2018-CP5+; Canberra Inc.) calibrated with a multi-isotope reference source, type VZ-2139/NG3 (Eckert & Ziegler Nuclitec, DKD-accredited measurement laboratory in Germany) and cross-calibrated for tissue sample geometry. Tracer uptake was calculated as percent injected dose per gram (%ID/g) and SUL was calculated as the standardized uptake value on PET normalized to lean body mass:

$$\mathrm{SUL} = \frac{\text{tissue sample activity}\,[\mathrm{Bq}]/\text{tissue sample weight}\,[\mathrm{g}]}{\left(\text{injected activity}\,[\mathrm{Bq}]\,2^{-\Delta t/T_{1/2}}\right)/\text{lean body mass}\,[\mathrm{g}]}$$

where Δt is the delay between patient injection and sample measurement, $T_{½}$ is the half-life of ^{111}In (2.81 days [17]). Lean body mass was calculated according to the method of Janmahasatian et al. [18].

Histopathological analysis

All resected LN (i.e. the entire LN in the case of small LN, one central slice in the case of LN >4 mm) were formalin-fixed and paraffin-embedded. The pathologist was not aware of either the PET findings or the surgeon's clinical

findings of the tissue. Histopathological evaluation of haematoxylin and eosin-stained tissue slides was performed by one pathologist. PSMA staining was performed as described by Jilg et al. [6].

Statistics

Descriptive statistics were obtained by calculating means, standard deviations (SD), medians and ranges. Continuous variables were compared using the two-sided unpaired Mann-Whitney test. Receiver operating characteristic (ROC) analysis was performed to analyse the ability of ^{111}In-PSMA-617 tracer to identify LNM using the SUL from 38 tumour-containing samples and 182 LN samples free of tumour. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were determined at the most appropriate cut-off value which was taken as the value with the highest sum of sensitivity and specificity (Youden index = 1.136). The three tumour samples with non-nodal PCa were statistically handled as LNM. Prism7 GraphPad was used for statistical analysis (https://www.graphpad.com/scientific-software/prism/).

Results

The clinical characteristics and outcomes of LA in the six patients are summarized in Table 1. All six patients had a high-risk PCa stage [19]. The time from PSMA PET/CT to LA was 2 ± 0.9 months. Figure 1 shows PSMA PET/CT and SPECT/CT imaging in a representative patient (patient 1) with a suspected LNM in the left iliac region.

Figure 2 shows the sample processing workflow. Overall, 74 subregions with 310 LN were removed (50 ± 17 per patient). The origins of the tissue samples are shown in Table 2. The nodal fibrofatty tissue from 74 small subregions was manually separated into single samples aiming at single LN (n = 318).

Histopathological analyses of the 318 single samples yielded 38 tumour samples (35 LN, 3 non-nodal tissue), 98 FFT samples and 182 tumour-free LN samples. In 37 of the 182 tumour-free LN samples more than one LN (macroscopically inseparable) was present on histopathology, resulting in 275 LN. Data on weight and tracer uptake (SUL and %ID/g) are shown in Table 3. Figure 3 shows representative nodal fibrofatty tissue from one subregion (Fig. 3a, b) and vessels containing single samples after manual separation (Fig. 3c).

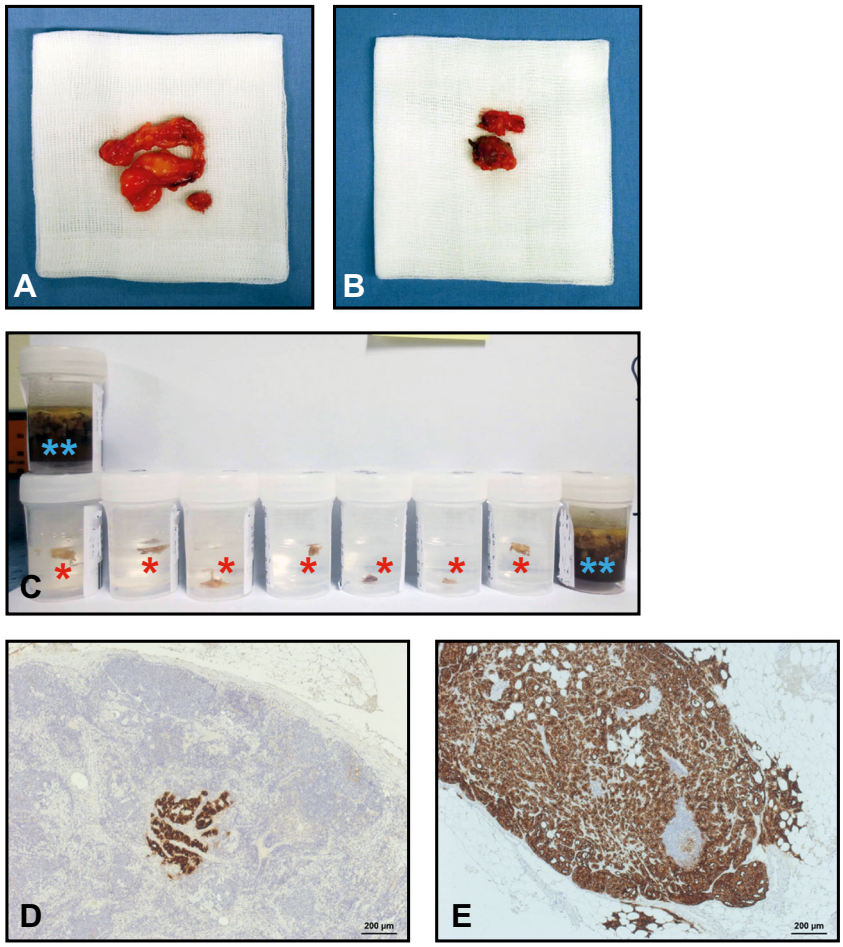

Fig. 3 Representative tissue samples. **a**, **b** Samples from a subregion before manual separation. **c** Collection of single samples after manual separation (*red stars* single lymph nodes, *blue stars* remaining fibrofatty tissue). **d**, **e** Immunohistochemistry for anti-PSMA in two representative lymph node metastases. Metastatic deposits in lymph nodes are stained brown

The numbers of FFT, tumour-free LN and LNM samples in order of increasing SUL is shown in Fig. 4. The ROC analysis showed an AUC of 0.976 (95% CI 0.95–1.00, $p < 0.0001$; Fig. 5). Based on a SUL cut-off value of 1.136, the diagnostic accuracy values of ^{111}In-PSMA-617 in discriminating between affected and non-affected nodal tissue are shown in Table 4.

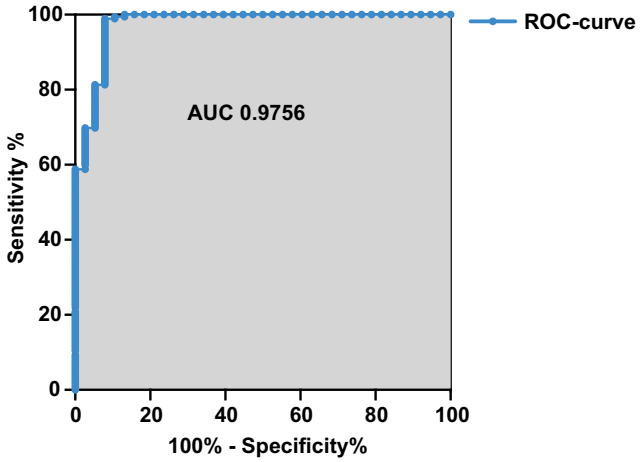

Fig. 5 Receiver operating characteristic (ROC) analysis of 38 tumour-containing und 182 tumour-free specimens shows an AUC of 0.9759 (95% CI 0.95–1.00, $p < 0.0001$)

Discussion

RGS using ^{111}In-PSMA is a novel technique described recently by Maurer et al. for detecting LNM intraoperatively in patients with the suspicion of LNM on PSMA PET/CT prior to surgery [14, 20].The aim of this study was to evaluate in detail the tracer characteristics of ^{111}In-PSMA-617 for discriminating between affected and nonaffected nodal tissue. Although we use a gamma probe during LA (RGS), the determination of gamma counts was not the focus of this analysis. Reports on the use of ^{111}In-PSMA for the detection of LNM have been based on the analysis of mixed samples from one anatomical region consisting of LN, LNM and FFT [13–15]. Consequently, tracer activity measured in such mixed samples represents the sum of the tracer distribution in different types of tissues with different uptake characteristics (LN, LNM, FFT). Accordingly, the performance of ^{111}In-PSMA and its diagnostic accuracy at the level of single LN has not yet been evaluated.

Our study is the first clinical investigation evaluating the performance of ^{111}In-PSMA-617 based on samples of single LN and LNM. This was accomplished by manual tissue separation of the specimens down to the level of single LN after surgery (whenever macroscopically possible). The relatively large number of LN removed during surgery (310 LN from six patients) indicates that larger tumour formations were not missed during surgery, suggesting that a comprehensive data record of the performance of the tracer in discriminating between LN and LNM was achieved.

SUL was significantly different between samples with PCa and nonaffected samples (Table 3, Fig. 4). The mean SUL (19.92) in tumour-containing LN was nearly 80 times higher than in tumour-free LN (SUL 0.25; Table 3). The signal-to-noise ratio for positive LN in the surgical cavity is associated with this tracer uptake ratio because the surrounding tissue in the surgical cavity typically contains tumour-free and fibrofatty tissue. This suggests that the risk of significant false-positive signals with this approach is quite small. Based on a SUL cut-off value of 1.136 only two false-positive LN samples were observed. Both samples were completely worked up by histopathology and remained tumour-free. Only three samples were designated as false-negative.

Small LNM and LNM located in anatomical regions with reduced accessibility should be identified more easily using

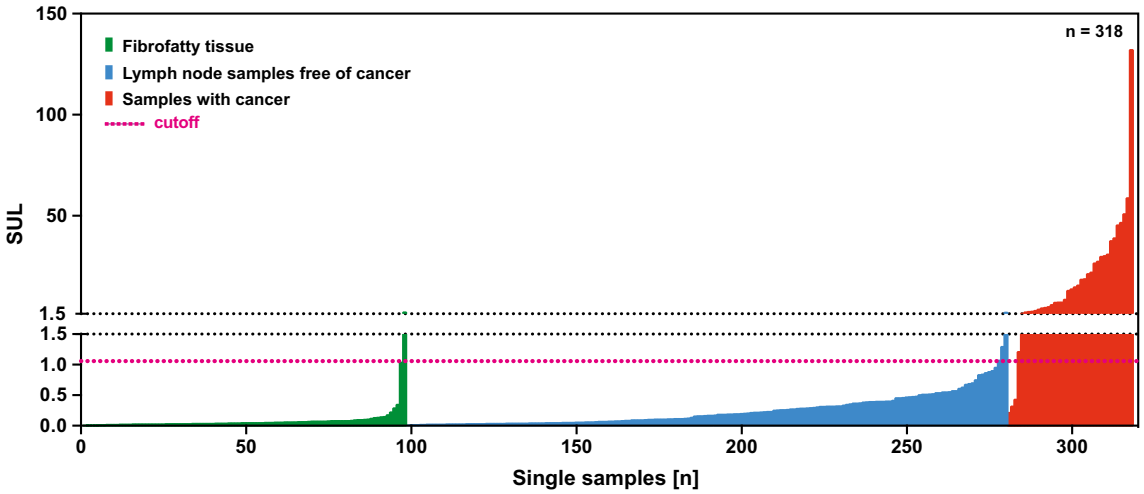

Fig. 4 Numbers of tumour-containing samples and tumour-free samples in order of increasing SUL (standardized uptake value normalized to lean body mass) showing the power of ^{111}In-PSMA-617 to discriminate between affected and non-affected samples

Table 4 Accuracy of ^{111}In-PSMA-617 in discriminating between affected and non-affected nodal tissue (220 samples from manual separation including 35 lymph node metastases, 3 non-nodal PCa tissue and 182 tumour-free lymph nodes) using a SUL cut-off value of 1.136

Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
92.1% (35/38)	98.9% (180/182)	94.6% (35/37)	98.4% (180/183)	97.7% (215/220)

the gamma probe during RGS. A reliable and helpful identification of LNM using the gamma probe during RGS is only possible if the tracer (such as ^{111}In PSMA-617) has characteristics that provide sufficient discrimination between affected and nonaffected tissue. Even though tracer uptake was measured ex situ (with a germanium detector), the discriminatory power of ^{111}In-PSMA-617 (Fig. 4) is a basic requirement for performing real-time measurements with a gamma probe. Real-time measurements could be done either in situ (e.g. pelvic regions) or at the operating table when the tissue has just been resected (ex situ) and the surgeon wants to know if the specimen is tumour-bearing or not. In cases when ex situ gamma counts were very low (indicating that the tissue was free of tumour) and a preoperative PET/CT scan predicted LNM in this anatomical region, the LA could be continued to extend the search for LNM.

Although not the focus of the present study, the performance of ^{111}In-PSMA-617 ex situ needs to be compared with the corresponding preoperative PSMA PET/CT findings. Because of the reduced lesion-to-detector distance (gamma probe to tissue) compared with PET/CT, RGS should be able to detect tumour tissue missed by PSMA PET/CT [13, 15]. As well as ^{111}In-PSMA-617, other tracers for RGS such as ^{99m}Tc-labelled PSMA are currently in development and under investigation [13, 21]. Furthermore, dual labelled nanoparticles with ^{111}In and IRDye800CW targeting PSMA-expressing tissue may enable fluorescence imaging and RGS in the near future [22].

Limitations

Although the number of samples (single LN) in our analysis seems to be considerable, the number of patients was quite low. The heterogeneity of PCa is well known, but the Gleason score did not vary dramatically among the six patients (4+3, 4+3, 4+4, 4+3, 4+4 and 4+5). All six patients were classified as having high-risk PCa and exhibited ordinary acinar adenocarcinoma. Generally, there was a selection bias because only patients with suspected LNM on PSMA PET/CT, and therefore with known PSMA-positive lesions, were included in this study.The PSA levels at the time of surgery varied in our patients (range 0.64–22.00 ng/ml). The PSA level at the most recent follow-up was available in all six patients: 0.03, 0.03, 1.00, 4.85, 18.20 and 0.03 ng/ml in patients 1–6, respectively. The mean and median follow-up was 2 years (SD 0.3 years). Presumably the PSA levels at the time of preoperative PET/CT and during RGS would have significantly affected the results, whereas the PSA response (PSA level at the most recent follow up) more or less reflects the completeness of the LA.

There are reports of the outcomes after radical salvage LA (whether radioguided or not) with numbers of patients up to 162 [11]. Most patients progress to biochemical recurrence within 2 years of surgery [3]. The ideal candidates for salvage LA have not yet been identified, and this approach should be reserved only for highly selected patients [3]. Finally, it remains to be examined whether the use of RGS for primary LA or salvage LA has a significant positive benefit for the patients with respect to biochemical recurrence-free survival or overall survival. These issues remain to be investigated in future outcome studies.

Conclusion

Uptake of ^{111}In-PSMA-617 was highly specific for PCa tissue in resected specimens (mainly LNM) in our six patients. Ex situ analysis of tracer accumulation at the level of single LN showed that the tracer has excellent performance in discriminating between affected and non-affected LN in PCa. This characteristic of the tracer is a precondition for in vivo real-time measurements during surgery.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval 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 principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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