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Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer

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Objectives

To assess the accuracy of 68Gallium-prostate-specific membrane antigen (68Ga-PSMA) positron emission tomography/computed tomography (PET/CT) for lymph node (LN) staging in intermediate- and high-risk prostate cancer (PCa).

Materials and Methods

From April to October 2015, 30 patients with intermediate- (n = 3) or high-risk (n = 27) PCa were prospectively enrolled. Patients underwent preoperative 68Ga-PSMA PET/CT. Both visual and semi-quantitative analyses were undertaken. Subsequently, all patients underwent radical prostatectomy (RP) with an extended pelvic lymph node dissection. The sensitivity, specificity, and positive (PPV) and negative predictive value (NPV) for LN status of 68Ga-PSMA were calculated using histopathology as reference.

Results

Eleven patients (37%) had lymph node metastases (LNMs); 26 LNMs were identified in the 11 patients. Patient analysis showed that 68Ga-PSMA PET/CT had a sensitivity of 64% for the detection of LNMs, its specificity was 95%, the PPV was 88%, and the NPV was 82%. In total, 180 LN fields were analysed. In the LN-region-based analysis, the sensitivity of 68Ga-PSMA PET/CT for detection of LNMs was 56%, the specificity was 98%, the PPV was 90% and the NPV was 94%. The mean size of missed LNMs was 2.7 mm. Receiver-operating characteristic curve analysis showed a high accuracy of maximum standardized uptake value (SUV_{max}) for the detection of LNMs, with an area under the curve of 0.915 (95% confidence interval 0.847–0.983); the optimum SUV_{max} was 2.0.

Conclusions

In patients with intermediate- to high-risk PCa, 68Ga-PSMA PET/CT had a high specificity and a moderate sensitivity for LNM detection. 68Ga-PSMA PET/CT had the potential to replace current imaging for LN staging of patients with PCa scheduled for RP.

Keywords

68Ga-PSMA, PET/CT, radical prostatectomy, pelvic lymph node dissection, #ProstateCancer, #PCSM

Introduction

Radical prostatectomy (RP) is the most widely used treatment for patients with localized prostate cancer (PCa) [1]. In patients with an intermediate- to high-risk PCa, a bilateral extended pelvic lymph node dissection (ePLND) is recommended at the time of the RP if the estimated risk for positive lymph nodes (LNs) exceeds 5% [2,3]. It is generally accepted that an ePLND provides important information for prognosis, which cannot be matched by other current imaging or procedures. In addition to staging, ePLND may also be curative, or at least beneficial, in a subset of patients with limited LN metastases [4,5].

Conventional imaging techniques are inadequate for LN staging in PCa. MRI, CT, positron emission tomography (PET)/CT and fluorescence sentinel lymph node detection are neither sensitive nor specific enough to reliably detect LN

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metastases before RP [6–9]. Recent data on the novel PET tracer agent Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] (PSMA) has shown promising sensitivity (33–85%) and specificity (82–100%) for both the detection of PCa recurrence and LN metastases [10–16]. This new PET tracer relies on the hyper-expression of prostate-specific membrane antigen (PSMA), a trans-membrane folate hydrolase, on the surface of PCa cells. This overexpression has been observed both locally, regional and in metastatic lymph nodes and in soft tissue and bone [13,14,17,18].

The objective of the present study was to assess prospectively the accuracy of 68Ga-PSMA PET/CT for preoperative LN staging in intermediate- to high-risk PCa, using histopathology as the 'gold standard'.

Materials and Methods

Patient Population

Between April and October 2015, patients aged <80 years with biopsy-proven intermediate- to high-risk PCa suitable for RP with ePLND were prospectively evaluated at St Vincent's Hospital, Sydney. All the patients had a >5% risk of LNMs, based on the updated Briganti nomogram [19], and had received no previous therapy and had no previous/other malignancy. Clinical T stage was assessed with DRE. All patients with a positive bone scan, with suspected extra-nodal disease on contrast-enhanced CT, or on hormonal therapy at the time of PET/CT investigation or before surgery, were excluded. Written informed consent was obtained from all patients as part of the Prostate Cancer Imaging Database (ProCan-I). The trial was approved by the Institutional Human Research and Ethics Committee (SVH 14/242).

Imaging Protocol

The PSMA (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC) was produced on-site with a Good Laboratory Practice-compliant procedure using a TRASIS® automated radio-pharmacy cassette with radio-pharmacy quality control undertaken using a high-pressure liquid chromatography method. All PET/CT imaging was undertaken using a Phillips® Ingenuity TOF–PET/64-slice CT scanner. For the PSMA PET/CT, a non-contrast-enhanced CT scan was performed 60 min after tracer injection using the following CT variables: slice thickness of 2 mm, with 2 mm slices, soft tissue reconstruction kernel, 120 keV and 50 mAs, pitch of 0.828, 600-mm field of view and a 512 matrix. Immediately after CT scanning, a whole-body PET scan (vertex to knees) was acquired for 2 min per bed position. The emission data were corrected for randoms, scatter and decay using Phillips® Body-dynamic.xml and Body.xml reconstruction protocol. All images were viewed and reported using Phillips® Fusion Viewer. A PSMA PET/CT was performed <4 weeks before surgery in all patients, and repeated in all patients with a false-positive scan result <3 months after surgery.

Image Analysis

The 68Ga-PSMA PET/CT images were interpreted by two experienced nuclear medicine physicians (L.E. and B.H.). Data for all 68Ga-PSMA scans were analysed visually and quantitatively. Visual analysis included a four-point certainty scoring scale (definitely negative, equivocal probably negative, equivocal probably positive, definitely positive), as well as the anatomical site and size of lesions. The PSMA uptake in the lymph nodes was semi-quantitatively analysed using the maximum standardized uptake value (SUV_{max}), which was calculated based on the measured activity, decay-corrected administrated dose, and patient weight. All LNs were assigned to their respective anatomical location, measured in the short axis, and an SUV_{max} was assigned to each individual LN.

Surgical Technique

One accredited highly experienced robotic urological surgeon performed all the RPs with ePLND using a transperitoneal robotic approach at St Vincent's Hospital, Sydney. Before surgery, the surgeon reviewed the results of the 68Ga-PSMA PET/CT scan. An ePLND was performed up to and including the bifurcation of the common iliac artery, along the external iliac (the distal limit being the deep circumflex vein and femoral canal), the internal iliac vessels and the obturator fossa. The lateral limit was the external iliac vein and the medial limit was the perivesical fat. All specimens were prospectively mapped according to their anatomical location, i.e. left/right external iliac, left/right internal iliac and left/right obturator.

Histological Examination

After dissection, specimens from all enrolled patients were sent for histopathological examination according to International Society of Urological Pathology (ISUP) protocols by one uropathologist who was blinded to the results of the PSMA PET/CT. RP specimens were processed according to the protocol described previously [20]. LN tissue was examined by palpation, visual inspection and sectioning. The transversely sliced (± 1-mm sections) LNs were processed and paraffin-embedded. These paraffin blocks were serially sectioned. Disease positivity was defined as the presence of any metastatic deposits of PCa in the LNs examined. For each metastatic LN the largest diameter (expressed in mm) of the metastatic deposits was recorded.

Image Reconstruction

All equivocal probably and definitely positive LNs on 68-GaPSMA PET/CT were assigned to their anatomical location: left/right external iliac; left/right internal iliac; and

left/right obturator. Positive matching was defined as the correlation between test positivity and histological positivity. Histopathological analysis of the LNs was used as the reference standard. 68Ga-PSMA PET/CT was repeated in all patients with a false-positive scan result (i.e. a positive LN on 68Ga-PSMA PET/CT but no positive LN found in histopathology). In these patients, the initial scan was used for all analyses.

Statistical Analysis

Means, median and frequencies were used as descriptive statistics. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 68Ga-PSMA PET/CT were calculated for a per-patient analysis, bilateral side analysis, a LN-region-based analysis, and a LN-specific analysis. For the bilateral side, LN-region-based and LN-specific, a logistic generalized estimating equation model was used to take into account the correlation between the different regions within one patient. Binary logistic regression and area under the curve (AUC) analyses were performed to explore the relationship between SUV scores (continuous) and the detection of PCa (binary) within the prostate and in LNs, using a generalized estimating equation model to adjust for the correlation between different regions within one patient. *P* values <0.05 were taken to indicate statistical significance. Statistical analysis was carried out with SPSS v. 21 (SPSS INC., Chicago, IL, USA).

Table 1 Patient characteristics.

Age, years	
Mean (± SD)	65 (± 8.5)
Median (IQR)	65 (60–71)
PSA (ng/ml)	
Mean (± SD)	8.2 (± 4.5)
Median (range)	8.1 (5.2–10.1)
Clinical stage, *n* (%)	
T1c	6 (20)
T2	18 (60)
T3	6 (20)
Gleason score biopsy, *n* (%)	
4 + 3 = 7	5 (17)
4 + 4 = 8	5 (17)
4 + 5 = 9	19 (66)
5 + 4 = 9	1 (3)
Pathological stage, *n* (%)	
T2	9 (30)
T3a	13 (43)
T3b	8 (27)
Gleason score RP, *n* (%)	
4 + 3 = 7	7 (23)
4 + 4 = 8	5 (17)
4 + 5 = 9	16 (54)
5 + 4 = 9	2 (6)
Total number of LNs removed	536
No. LNs removed per patient	
Mean (± SD)	17.8 (± 7.0)
Median (IQR)	16 (12-20)
Number of N1 patients (%)	11 (37)
Total number of positive LNs	26

IQR, interquartile range; LN, lymph node; RP, radical prostatectomy.

Results

Patients

A total of 30 men met the inclusion criteria. Three had intermediate-risk PCa (10%) and 27 had high-risk PCa (90%). Baseline patient characteristics are shown in Table 1. Eleven of 30 patients (36.6%) had histologically proven LNMs. Table 2 details the characteristics of those with LNMs. Overall, 536 LNs were resected, with 26 harbouring metastases (4.9%). Statistically significant correlation was found between LN-positive patients and the outcomes of the Briganti nomogram, as well as with the number of positive LNs per patient ($P < 0.05$). Positive LNs were located in the internal iliac region ($n = 5$), the external iliac ($n = 10$) and the obturator fossa ($n = 11$). One patient had a positive LN finding on PET/CT outside the standard ePLND region. This LN was located in the left meso-rectum, immediately posterior to rectum and 1 cm anterior to the inferior margin of S2, technically not resectable at surgery. This LN could therefore not be included in further analysis. This patient received adjuvant radiotherapy with good biochemical response up to 3 months after treatment.

Performance of 68Ga-PSMA PET/CT

Table 3 shows the detection rate of 68Ga-PSMA PET/CT for LNMs as a function of the diameter of the metastatic deposit based on histopathology. The mean diameter of the metastatic deposits of true-positive LNs was significantly larger (4.73 ± 1.45) than the metastatic deposit of false-negative LNs (2.73 ± 1.29; $P = 0.001$). Figure 1 shows the only false-positive LN detected by 68Ga-PSMA PET/CT in the present study preoperatively and 2 months after RP. This node was located close to the iliac bifurcation and was directly related to the ureter. At re-imaging 2 months after surgery this LN was undetectable, but ureteric activity persisted. PSA was undetectable at 6 weeks and 3 months after surgey; no adjuvant treatment was given.

Overall, the specificity of 68Ga-PSMA PET/CT for the preoperative detection of LNMs was very high, but the sensitivity was moderate. In a per-patient analysis, the sensitivity, specificity, PPV and NPV were 64, 95, 88 and 82%, respectively. On LN-region-based analysis, the sensitivity, specificity, PPV and NPV were 54, 99, 92 and 94%, respectively. Detailed results are shown in Table 4.

Performance of 68Ga-PSMA PET/CT SUV for Detecting LNMs

The performance characteristics of SUV for detecting PCa are shown in Fig. 2. For detecting LNMs, the ROC curve for SUV_{max} in detecting LNMs was AUC 0.915 (95% CI 0.847–0.983). This means that a threshold of $SUV_{max} = 2.0$ would

Table 2 Characteristics of the patients with lymph node metastases in 11 patients.

Patient	Age, years	PSA, ng/mL	cT	Clinical Gleason scor	pT	Pathological Gleason score	No of LNM	Size of LN, mm	PSMA (SUV)	Positive LN site
1	64	8.2	T3a	4 + 5	T3a	4 + 5	8	4 + 3 + 4 + 4 + 4 + 4 + 3 + 0.2	2.0 + 2.0 + 2.0 + 2.0 + 2.0 + 2.0 + 2.5 + neg	l int iliac, l ext iliac, l obt, l obt, l obt, l obt, r int iliac, r ext iliac
2	65	1.9	T3a	5 + 4	T3b	5 + 4	3	5 + 4 + 4	2.9 + neg + neg	r obt, r int iliac, l obt
3	59	10.0	T2b	4 + 5	T3b	4 + 5	3	9 + 5 + 3	3.9 + neg + neg	l int iliac, l ext iliac, r int iliac
4	61	5.8	T2a	4 + 5	T3b	4 + 5	3	8 + 4 + 2.5	6.3 + 3.6 + neg	r obt, r ext iliac, r ext iliac
5	67	4.5	T2c	4 + 5	T3b	4 + 5	2	5 + 0.8	2.5 + neg	l obt, r ext iliac
6	73	9.0	T2b	4 + 5	T3a	4 + 5	2	5 + 4	2.6 + 2.8	r ext iliac, l obt
7	71	18.0	T2a	4 + 5	T3b	4 + 5	1	5	2.6	r ext iliac
8	76	15.1	T3a	4 + 5	T3b	4 + 5	1	1.8	neg	l ext iliac
9	74	4.1	T3a	4 + 5	T3a	4 + 5	1	1.5	neg	l ext iliac
10	59	6.5	T3a	4 + 5	T3a	4 + 5	1	2.5	neg	l obt
11	71	10.5	T1c	4 + 5	T3b	4 + 5	1	2.2	neg	l obt

ext, external; int, internal; LN, lymph node; LNM, lymph node metastases; obt, obturator; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value.

Table 3 Detection rate 68-Ga PSMA positron emission tomography/CT according to the diameter of the lymph node metastases.

Diameter of LNM, mm	Detection rate PSMA PET/CT, *n* (%)
0.1–1.9 (n = 4)	0 (0)
2.0–4.9 (n = 15)	9 (60)
≥ 5.0 (n = 7)	6 (86)

PET, positron emission tomography.

have a 4% false-positive rate (1−specificity) and would detect 92% of LNMs (sensitivity). To improve cancer detection, theoretically the threshold could be lowered to SUV_{max} = 1.5; this would still detect 92% of cancer cases, but would increase the false-positive rate to 31% of patients. In this ROC analysis, the optimum SUV_{max} for detection of LNM was 2.0 (sensitivity 0.870 and specificity 0.950; Fig. 2).

Discussion

In the present study we showed that 68Ga-PSMA PET/CT had a high specificity (99%) and moderate sensitivity (54%) for the detection of LNMs in men with intermediate- and high-risk PCa based on a region-based analysis. These results are consistent with the limited retrospective results reported for 68Ga-PSMA PET/CT in the preoperative LN staging of patients with PCa, which showed a 33–73% sensitivity [13,15], and confirms an important future role of 68Ga-PSMA PET/CT.

We found a moderate sensitivity for nodal staging, with almost all undetected LNMs (91%) measuring < 5 mm, based on histopathology. This was not surprising. With current state-of-the-art 'time of flight' PET CT technology, the spatial resolution of PET cameras is between 4.9 and 5.1 mm [21]. To detect lesions below this size requires intense PSMA signal activity in order to overcome the limitations of 'partial volume effect' on current PET technology. While this intense PSMA activity was present in 60% of LN deposits of 2.0–4.9 mm (histopathology) in the present study, a significant portion of involved nodes with deposits of <5 mm (and all <2 mm) were not visible to the imaging specialist. This is a reflection of the known varying intensity of PSMA receptor activity in PCa. PCa with a higher density of PSMA receptors on the cell membrane will be detected at low volume, while PCa with a relative paucity of receptor expression may only be more readily identified at larger volumes. Meanwhile, 68Ga-PSMA PET/CT remains highly specific for the detection of LNMs, with excellent diagnostic characteristics for SUV (AUC 0.915; 95% CI 0.847–0.983). In the present study, an SUV ≥ 2.0 corresponded with a 96% specificity for LNMs. Nevertheless, the sensitivity remains moderate, which implies that PSMA PET/CT underestimates the extent of the disease and thus cannot replace ePLND in patients who undergo RP for intermediate- to high-risk PCa.

While the sensitivity and specificity of PSMA PET/CT in the present study were similar to some of those previously shown

Fig. 1 Example of a 68Ga-PSMA positron emission tomography/CT scan in a patient before (left) and after (right) radical prostatectomy with pelvic lymph node dissection. Patient was diagnosed with a false-positive lymph node (standardized uptake value = 2.7), next to the right common iliac in direct relationship with the ureter. This lymph node was not seen on the postoperative scan (only the surgical clips). Histology was negative, and thus considered as false-positive in the present study.

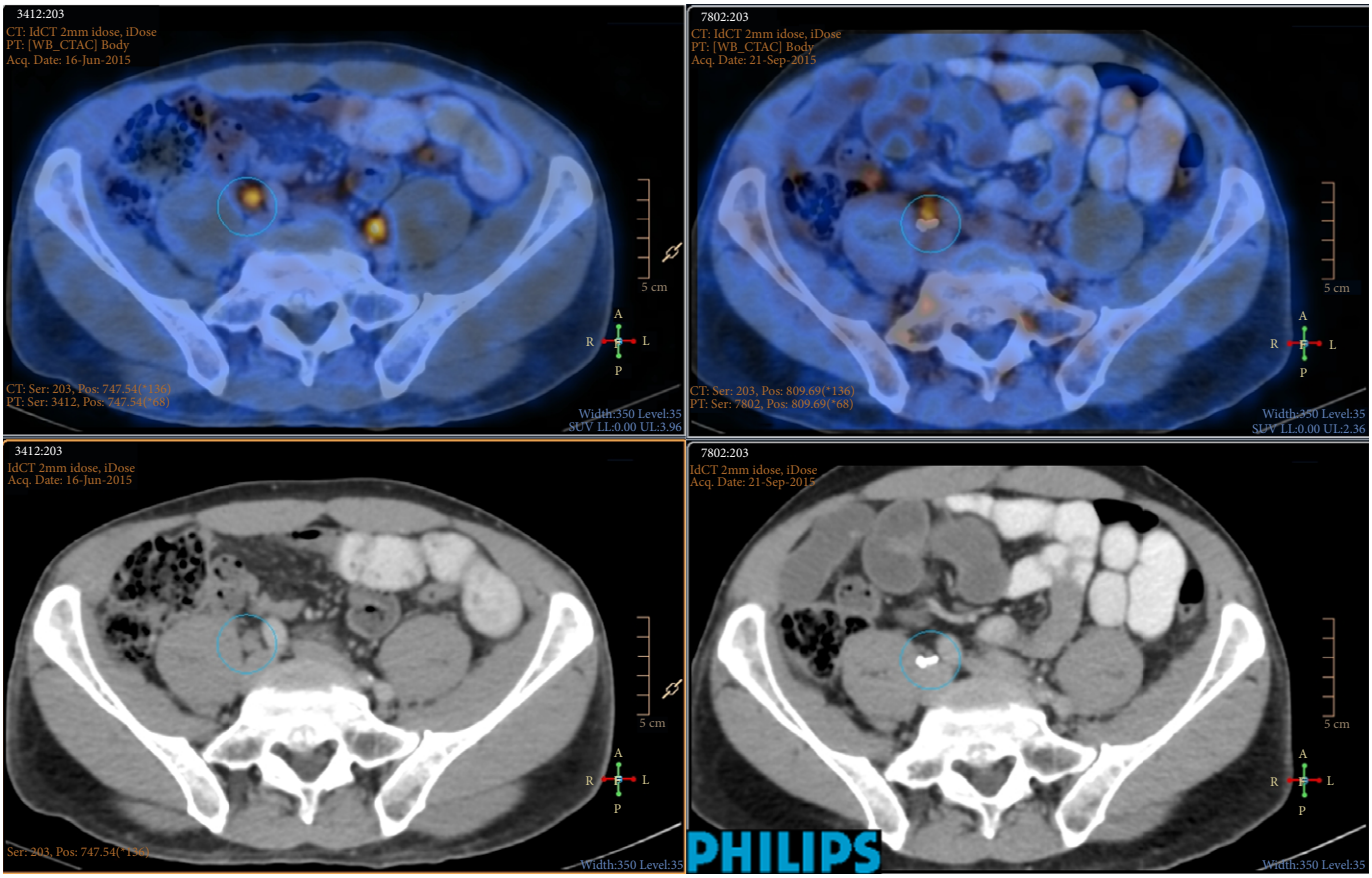


Table 4 Sensitivity, specificity, PPV and NPV of 68-GaPSMA in the detection of LNMs.

	Specificity, %	Sensitivity, %	PPV, %	NPV, %
Patient analysis	95	64	88	82
Side analysis	98	56	90	86
Region analysis	99	54	92	94
Node analysis	100	58	94	98

PPV, positive predictive value; NPV, negative predictive value.

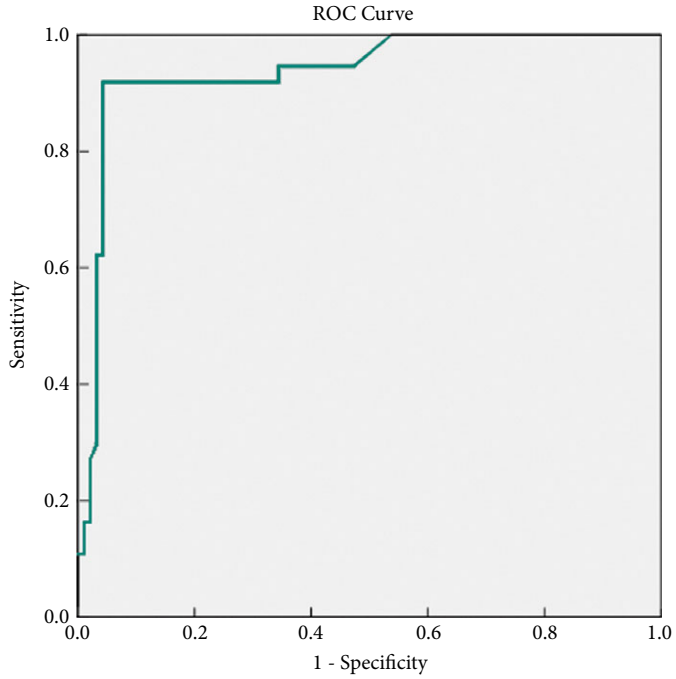
with 11C-choline PET in the preoperative LN staging of patients with PCa [22], there are a number of important differences. Sensitivity has been reported at similar levels; however, the size of the false-negative lesions in this study were significantly smaller than the size previously reported with 11C-choline PET [22]. In the present study, the mean size of true-positive LNMs was 4.7 (±1.4) mm vs a false-negative LNM size of 2.7 (±1.3) mm. In a large study on 11C-choline preoperatively, the median size of positive LNMs was 9.2 mm, vs 4.2mm for the false-negative LNMs [23].

Budiharto et al. [24] reported a 15% true-positive rate for the detection of LNMs >2 mm with 11C-choline compared with the 64% true-positive rate for LNMs >2 mm in the present study. Finally, it is obvious that there are significant differences in histopathology assessment and extent of LN dissection among studies, with significant influence on the sensitivity reported.

It has been shown that PSMA is expressed in benign and malignant prostatic epithelium, in primary cancer and in LNMs, with the greatest expression of PSMA in the primary cancer [25]. In the present study, 68Ga-PSMA PET/CT was clearly positive in all primary tumours, but further studies are needed to investigate the possible contribution of 68Ga-PSMA PET/CT to multiparametric MRI for the primary detection of PCa. Currently, multiparametric MRI is the best imaging method for the detection of significant PCa.

The present study has some limitations. First, the selection of patients with high probability of having LNMs might have overestimated the diagnostic performances of 68Ga-PSMA

Fig. 2 Receiver-operating characteristics (ROC) curve for standardized uptake value in 68Ga-PSMA positron emission tomography/CT for detecting lymph node metastases (area under the curve 0.937; 95% CI 0.88–0.985).



Diagonal segments are produced by ties.

PET/CT. Secondly, pre-sacral LNs were not removed, which might have influenced the sensitivity results [26]. Third, because all PET/CT scans were reported by experienced nuclear medicine physicians, the present results may not be directly adaptable to clinical practice. Obviously, validation of our results in a general clinic with less experienced physicians is indicated. Finally, the study has a small sample size. Nevertheless, we are certain that prospective studies relying on histological validation represent the most comprehensive approach for evidence acquisition. This is the first prospective evaluation of a method, frequently used in clinical practice, to determine the sensitivity and specificity for the detection of LNMs in patients with PCa.

In conclusion, we established the value of 68Ga-PSMA PET/CT for the detection of LNMs in patients with intermediate- and high-risk PCa. 68Ga-PSMA PET/CT had a high specificity and moderate sensitivity for the detection of LNMs. ePLND remains the gold standard staging method for patients with intermediate- and high-risk PCa undergoing RP. Nevertheless, 68Ga-PSMA PET/CT has the potential to become a promising method for identification of LNMs preoperatively and in patients with recurrent PCa.

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Conflict of Interest

No conflict of interest.

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Abbreviations: 68Ga-PSMA, 68Gallium-prostate-specific membrane antigen; PET, positron emission tomography; LN, lymph node; PCa, prostate cancer; RP, radical prostatectomy; ePLND, extended pelvic lymph node dissection; PPV, positive predictive value; NPV, negative predictive value; LNM, lymph node metastases; ROC, receiver-operating characteristic; SUV_{max}, maximum standardized uptake value; AUC, area under the curve.