

Distribution of prostate cancer recurrences on gallium-68 prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron-emission/computed tomography after radical prostatectomy with pathological node-positive extended lymph node dissection

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Objectives

To examine the anatomical distribution of prostate cancer (PCa) recurrence on gallium-68 prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron-emission tomography (PET)/computed tomography (CT) in patients with biochemical recurrence (BCR) after undergoing radical prostatectomy (RP) with pathological lymph node metastasis (pN1) in their extended pelvic lymph node dissection (ePLND), and to compare the location of PCa recurrence with the location of the initial lymph node metastasis at ePLND.

Materials and Methods

We retrospectively reviewed 100 patients with BCR (PSA 0.05–5.00 ng/mL) after RP with pN1 ePLND who underwent ⁶⁸Ga-PSMA PET/CT to guide salvage therapy. Clinical and pathological features and anatomical locations of PCa recurrence on ⁶⁸Ga-PSMA PET/CT were obtained, and management impact was recorded.

Results

In all, 68 patients (68%) had a positive and 32 patients (32%) had a negative ⁶⁸Ga-PSMA PET/CT result. Of the 68 patients

with a positive ⁶⁸Ga-PSMA PET/CT, 44 (65%) showed abnormal uptake only in the pelvic area, seven (10%) only outside the pelvic area, and 17 (25%) both within and outside the pelvic area. ⁶⁸Ga-PSMA PET/CT-positive pelvic lymph nodes were often (84%) detected on the same side as the lymph node metastasis diagnosed at ePLND. Based on the outcomes of the ⁶⁸Ga-PSMA PET/CT, change of management was noted in 68% of the patients.

Conclusion

Recurrence of PCa on ⁶⁸Ga-PSMA PET/CT was limited to the pelvis in the majority of patients with BCR after RP with pN1 ePLND. Moreover, recurrence was often detected on the same side as the lymph node metastasis at ePLND. The results confirm the diagnostic value of ⁶⁸Ga-PSMA PET/CT in patients with BCR after RP with pN1 ePLND. Prospective studies are needed to support the long-term benefit of ⁶⁸Ga-PSMA PET/CT-dictated management changes.

Keywords

⁶⁸Ga-PSMA PET/CT, radical prostatectomy, lymph node-positive, biochemical recurrence, lymph node metastasis, anatomical distribution, #ProstateCancer, #PCSM

Introduction

In patients with biochemical recurrence (BCR) after radical prostatectomy (RP) without evidence of lymph node metastases, salvage radiotherapy to the prostatic fossa is the most effective treatment option with curative intent [1-4]. However, for patients with BCR after a pathological node-positive (pN1) extended pelvic lymph node dissection (ePLND) at the time of RP, salvage radiotherapy to the prostatic fossa is not the standard of care because of a lack of consistent evidence [5,6]. According to the guidelines of the European Association of Urology, three management options have to be discussed with patients with pN1 ePLND at RP: either to start androgen deprivation therapy (ADT), adjuvant ADT combined with radiotherapy, or observation [7]. Improved survival is seen in retrospective analyses of patients receiving ADT and adjuvant radiotherapy in comparison to patients receiving ADT or observation only [8]. Although not mentioned in the guidelines, clinicians frequently recommend observation with possible salvage radiotherapy to the prostatic fossa and pelvic lymph nodes in case of BCR in patients with pN1 at ePLND. This strategy aims to reduce overtreatment with adjuvant therapies and might avoid unsuccessful radiotherapy if early prostate cancer (PCa) recurrence is detected outside the pelvis (M1).

Gallium-68 prostate-specific membrane antigen (^{68}Ga -PSMA) positron-emission tomography (PET)/CT has been shown to improve the detection of metastatic disease in PCa, particularly in the setting of disease recurrence [9,10]. The objective of this study is to determine the anatomical distribution of PCa recurrence and to compare this location with that of the initial lymph node metastasis on ePLND. Furthermore, we evaluated ^{68}Ga -PSMA PET/CT-induced management changes in patients considered for salvage radiotherapy to the prostatic fossa and pelvic lymph nodes.

Materials and Methods

General

This retrospective analysis was conducted after obtaining the approval of the Netherlands Cancer Institute (RBd19081). At the Erasmus Medical Centre, all patients have given consent to be included in the imPRINT prospective database (NL7165 [NTR7389]). At St Vincent's Hospital, Sydney, all patients have given consent to be included in the Prostate Cancer Imaging Database (ProCan-I). The ProCan-I was approved by the Institutional Human Research and Ethics Committee of St Vincent's Hospital, Sydney.

Patient Population

Between February 2015 and January 2019, ^{68}Ga -PSMA PET/CT was undertaken in 100 patients with BCR (defined as

PSA ≥ 0.05 ng/mL) after RP with one or more lymph node metastases on ePLND. Patients treated with radiotherapy or any systematic treatment after RP or who had a PSA level ≥ 5.0 ng/mL at the time of ^{68}Ga -PSMA PET/CT were excluded. Data on the clinical and pathological features and anatomical locations of PCa recurrence on ^{68}Ga -PSMA PET/CT were retrospectively collected from the electronic patient files. The data were gathered from patients treated in the Netherlands Cancer Institute (Amsterdam, $n = 55$), the Erasmus Medical Centre (Rotterdam, $n = 28$), and St Vincent's Prostate Cancer Centre (Sydney, $n = 17$).

Imaging Protocol

^{68}Ga -PSMA-11 was used as the tracer and produced on-site according to the Good Manufacturing Practices regulations. The tracer was administered to the patients as an i.v. bolus injection (2.0 MBq/kg, St Vincent's; 100 MBq fixed-dose, Netherlands Cancer Institute; 1.5 MBq/kg, Erasmus Medical Centre). Imaging commenced at 60 min (St Vincents and Erasmus Medical Centre) or 45 min (Netherlands Cancer Institute) after injection. The scanning parameters at St Vincents were: Philips[®] Ingenuity TOF-PET/64-slice CT, i.v. contrast-enhanced, dose-modulated CT scan with diagnostic CT of abdomen/pelvis region and low dose CT for the remaining whole body; whole-body PET acquisition 3 min/bed position, with correction for randoms, scatter and decay using the Philips[®] Body-dynamic.xml and Body.xml reconstruction protocol. The scanning parameters at the Netherlands Cancer Institute were: Philips Gemini TF-II PET/16-slice CT, dose-modulated low-dose CT scan (40 mAs, 2 mm reconstruction) from the proximal femora to skull base, used for attenuation correction and anatomical correlation, followed by PET imaging of the same region, 3 min per bed position for pelvis/abdomen and 2 min per bed position for the remainder. The scanning parameters at the Erasmus Medical Centre were: Siemens Biograph mCT, dose-modulated low-dose CT scan (30 ref mAs, 3-mm reconstruction) from proximal femora to skull base used for attenuation correction and anatomical correlation, followed by PET imaging of the same region with 3 min per bed position for patients ≤ 70 kg and 4 min for patients > 70 kg.

Imaging Analysis

All ^{68}Ga -PSMA PET/CT scans were interpreted by experienced nuclear medicine physicians. Positive sides were divided into two main groups: inside the pelvic area (below L4) or outside the pelvic area (above L5). Inside the pelvic area was divided into the prostatic fossa, the pelvic lymph nodes, or both. Outside the pelvic area was divided into nodes, bones, or nodes and bones. If PCa recurrence was detected both inside and outside the pelvic area, patients were categorized as having recurrence outside the pelvic area. In

addition, for all patients with a pelvic lymph node recurrence at ^{68}Ga -PSMA PET/CT, the anatomical region(s) of recurrence (right or left external iliac, obturator fossa, internal iliac or presacral space) was correlated to the anatomical region(s) of the pathological positive node(s) in the ePLND at time of RP.

Management Impact

Two experienced oncological urologists and two experienced radiation oncologists determined proper standard therapies based on patients' characteristics and the ^{68}Ga -PSMA PET/CT results. 'Minor management impact' was defined as detection of PCa recurrence in the standard radiation field, allowing for administration of extra high dosed radiotherapy on visual lesions. 'Major management impact' was defined as detection of PCa recurrence outside the standard radiation field, therefore averting any salvage radiotherapy to the pelvis.

Statistical Analysis

Means, median and frequencies were used as descriptive statistics. We used descriptive statistics to report patient population characteristics and detection rates of ^{68}Ga -PSMA PET/CT according to subsequent PSA group. A logistic regression analysis was used to identify predictors for

pathological uptake outside the pelvic area, considering pT stage, lymph node ratio, surgical margin status, grade group, the time interval between RP and BCR, PSA persistence or BCR after RP, and PSA level at the time of ^{68}Ga -PSMA PET/CT. PSA persistence after RP was defined as PSA >0.1 ng/mL within 4 months after surgery. Subsequently, the probability of finding distant metastases at PSMA PET/CT was statistically analysed using univariate logistic regression, to assess the correlation with the previously mentioned variables. In addition, multivariable logistic regression analyses were used. *P* values <0.05 were considered significant. Statistical analysis was performed with SPSS v. 22 (IBM, Armonk, NY, USA).

Results

^{68}Ga -PSMA PET/CT Results

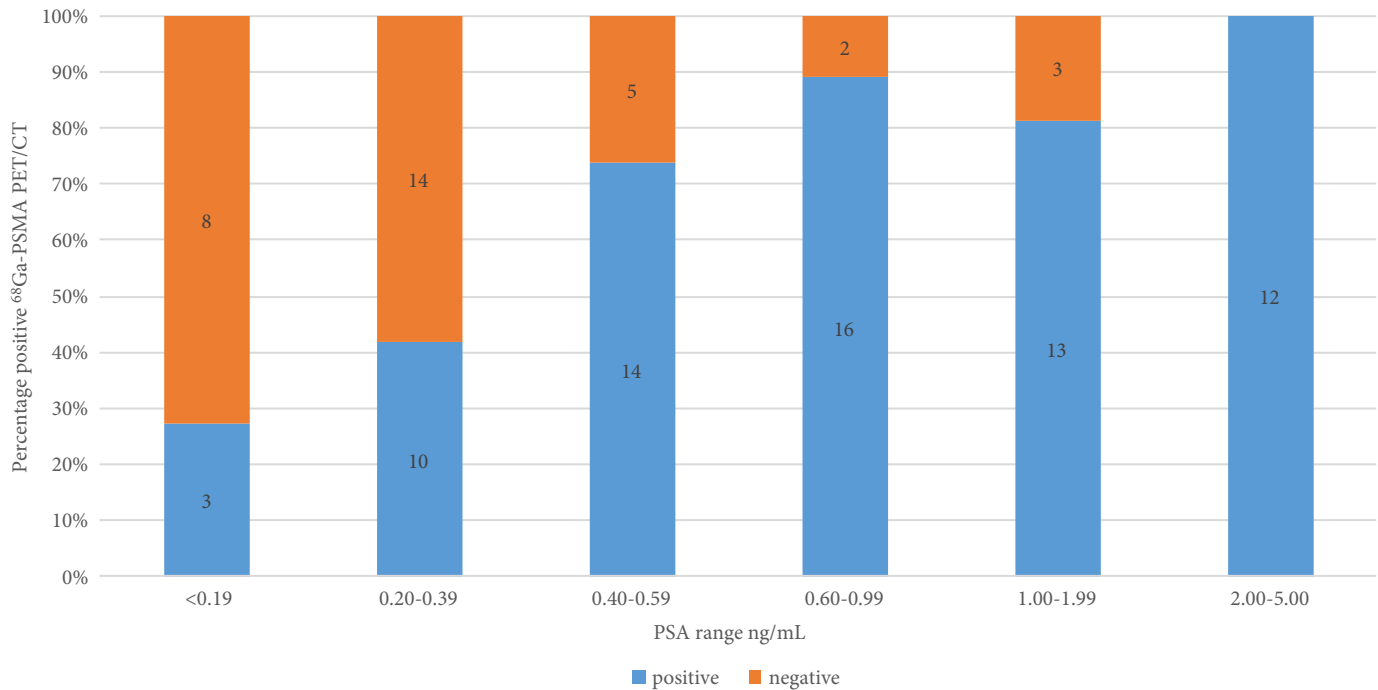
A total of 100 patients were included in this retrospective analysis. Patient characteristics are presented in Table 1. Of the 100 patients included, 68 (68%) had a tumour-positive ^{68}Ga -PSMA PET/CT at a median (interquartile range) PSA of 0.69 (0.42–1.26) ng/mL, 32 patients (32%) had a negative ^{68}Ga -PSMA PET/CT scan at a median (interquartile range) PSA of 0.26 (0.20–0.38) ng/mL (*P* < 0.05). The corresponding percentages of positive ^{68}Ga -PSMA PET/CT scans, stratified by PSA level, are shown in Fig. 1.

Table 1 Patient characteristics.

	All patients (<i>n</i> = 100)	Patients with positive ^{68}Ga -PSMA PET/CT (<i>n</i> = 68)	Patients with negative ^{68}Ga -PSMA PET/CT (<i>n</i> = 32)
Age during ^{68}Ga -PSMA PET/CT, years			
Mean (\pm SD)	67 (\pm 6.6)	67 (\pm 6.6)	66 (6.5)
Age at RP			
Mean (\pm SD)	65 (\pm 6.9)	65 (\pm 6.4)	64 (\pm 7.9)
PSA during ^{68}Ga -PSMA PET/CT, ng/mL			
Median (IQR)	0.49 (0.29–1.09)	0.69 (0.42–1.26)	0.26 (0.20–0.38)
Time interval RP – ^{68}Ga -PSMA PET/CT			
Months, median (IQR)	10 (4.9–28)	10 (5.1–33)	9.6 (4.5–19)
Tumour stage RALP, <i>n</i> (%)			
\leq pT2c	13 (13)	10 (15)	3 (9)
pT3a	27 (27)	20 (29)	7 (22)
pT3b	59 (59)	37 (55)	22 (69)
pT4	1 (1)	1 (1)	0 (0)
Positive margins, <i>n</i> (%)	29 (29)	20 (29)	9 (28)
ISUP grade, <i>n</i> (%)			
2	21 (21)	9 (13)	12 (38)
3	27 (27)	15 (22)	12 (38)
4	18 (18)	16 (24)	2 (6)
5	28 (28)	22 (32)	6 (18)
Missing	6 (6)	6 (9)	0 (0)
Number of LNs removed at ePLND, median (IQR)	16 (12–22)	17 (13–19)	15 (12–19)
Number of positive LNs at ePLND, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
PSA nadir (RP)			
<0.1 ng/mL	38 (38)	25 (37)	13 (41)
\geq 0.1 ng/mL	47 (47)	32 (48)	15 (47)
Missing	15 (15)	11 (16)	4 (13)

^{68}Ga -PSMA, gallium-68-prostate-specific membrane antigen; ePLND, extended pelvic lymph node dissection; IQR, interquartile range; ISUP, International Society of Urological Pathology; LN, lymph node; PET, positron-emission tomography; RALP, robot-assisted laparoscopic prostatectomy; RP, radical prostatectomy.

Fig. 1 Percentage positive gallium-68 prostate-specific membrane antigen (^{68}Ga -PSMA) positron-emission tomography (PET)/CT scans, stratified by PSA level.



Anatomical Distribution of Pathological Lesions

Of the 68 patients with a positive ^{68}Ga -PSMA PET/CT, 44 (65%) showed abnormal uptake only in the pelvic area, seven (10%) only outside the pelvic area, and 17 (25%) both within and outside the pelvic area (Fig. 2). Of the 44 patients with ^{68}Ga -PSMA PET/CT uptake in the pelvic area, eight (18%), 29 (66%) and seven (16%) showed uptake in the fossa only, in the pelvic lymph nodes only and in both the prostatic fossa and the pelvic lymph nodes, respectively. Of the 24 patients with pathological uptake outside the pelvic area, 13 (54%), eight (33%) and three (13%) showed uptake in the distant lymph nodes only, bones only and in both the lymph nodes and bones, respectively (Fig. 3). In 36 patients, ^{68}Ga -PSMA PET/CT showed PCa recurrence in the pelvic lymph nodes without evidence of distant metastases. In 31 of these patients (86%), the exact anatomical location of the lymph node metastasis at ePLND was known. In these patients, the median number of removed lymph nodes during ePLND at time of RP was 17. ^{68}Ga -PSMA PET/CT detected lymph node metastasis in the same anatomical location as the initial lymph node metastasis in 10 patients (32%; eight out of 10 in the obturator fossa). In 16 patients (52%), the lymph node metastasis was detected in an adjacent anatomical region on the same side of the pelvis (eight out of 16 in the presacral space). In five patients (16%), the lymph node metastasis was detected in an anatomical region on the contralateral side to the initial lymph node metastasis.

Analysis of Risk Factors for Distant Metastases

Only PSA at the time of ^{68}Ga -PSMA PET/CT was significantly associated with the detection of PCa recurrence outside the pelvic area (odds ratio 1.9, 95% CI 1.0–3.4; $P = 0.039$ [Table 2]). The corresponding percentages of PCa recurrences outside the pelvic area was 24% for PSA 0.0–0.49 ng/mL, 28% for PSA 0.5–0.99 ng/mL, 43% for PSA 1.00–2.49 ng/mL, and 56% for PSA 2.5–5.0 ng/mL.

Management Impact

In 24 patients (24%), ^{68}Ga -PSMA PET/CT detected PCa recurrence outside the pelvic area, thus having a major management impact. The detection of recurrence in the pelvic lymph nodes or prostatic fossa in 44 patients (44%) resulted in an adjusted radiotherapy plan with a boost to the visible lesion (minor management impact).

Discussion

Today, there are conflicting opinions on the optimal treatment strategy for patients with pathologically proven lymph node metastases in their ePLND template at RP. Our results show that two-thirds of these patients have their first detectable early recurrence on ^{68}Ga -PSMA PET/CT in the prostatic fossa and/or pelvic lymph nodes. Pelvic lymph node metastases identified by ^{68}Ga -PSMA PET/CT were most often

Fig. 2 Overview of the anatomical distribution of recurrent prostate cancer in patients experiencing a biochemical recurrence after radical prostatectomy with pathological node-positive extended lymph node dissection on gallium-68 prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron-emission tomography (PET)/CT.

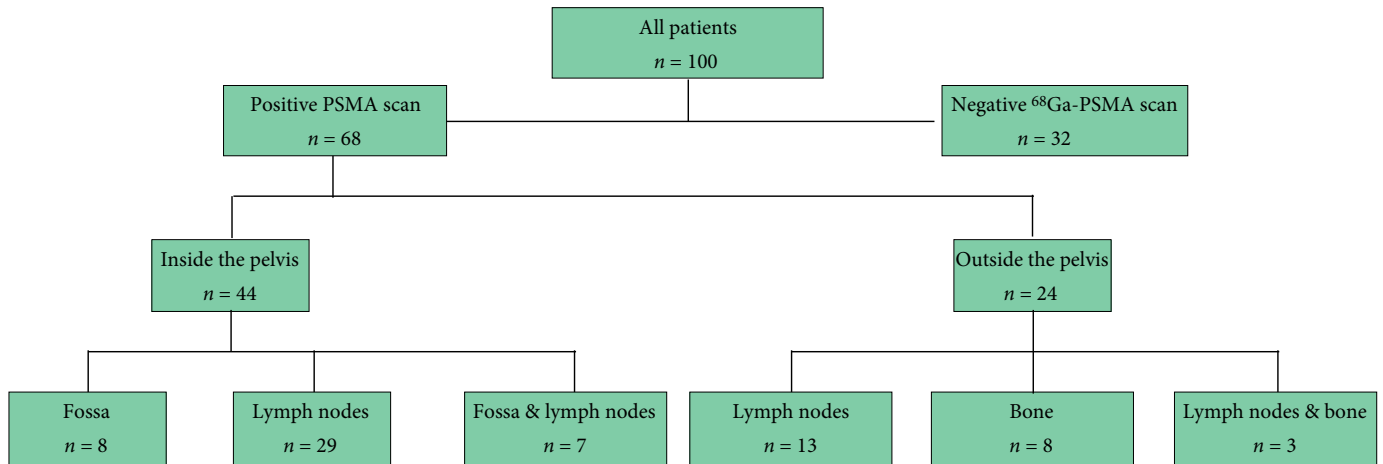
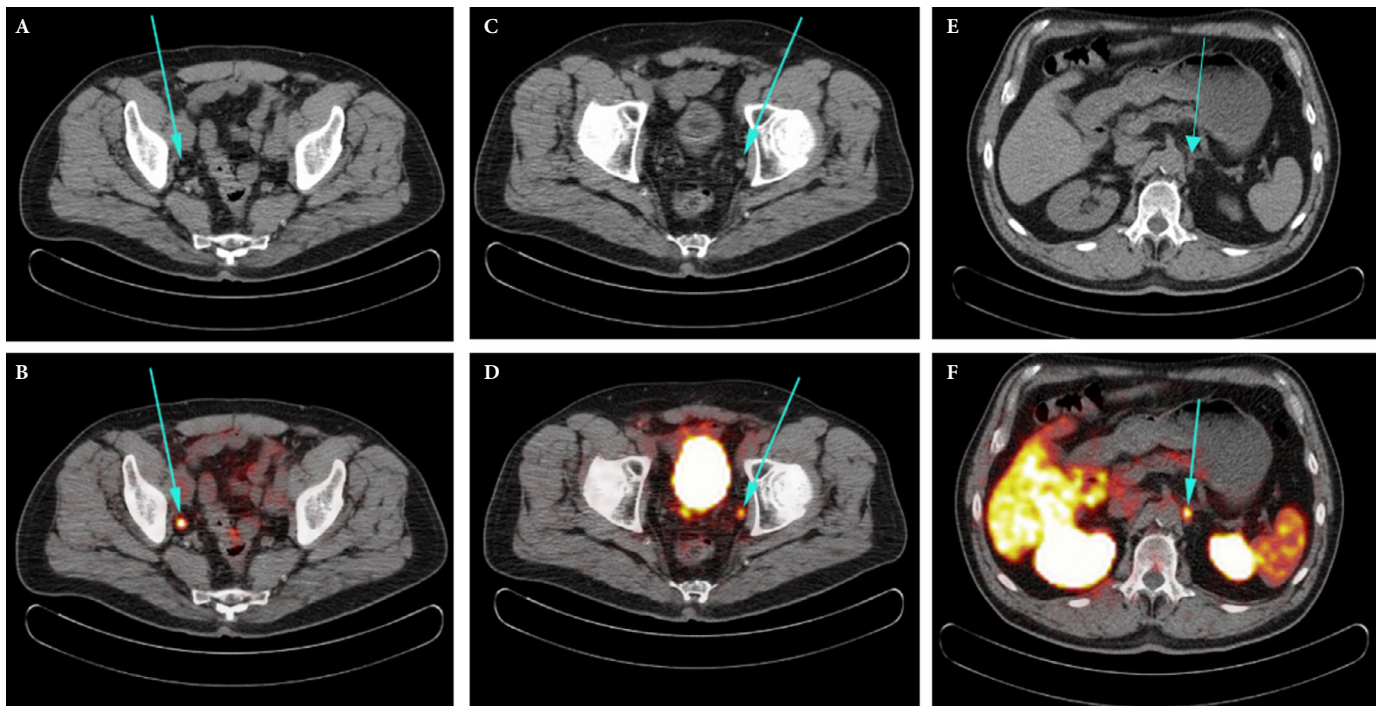


Fig. 3 Example showing a patient with PSA 1.46 ng/mL and positive lesions in and outside the pelvis area. Non-contrast-enhanced CT images (**A, C** and **E**) with corresponding fused gallium-68 prostate-specific membrane antigen (⁶⁸Ga-PSMA) positron-emission tomography/CT images (**B, D** and **F**).



detected on the same side of the lymph node metastasis at ePLND. On the one hand, by detecting PCa recurrence outside the standard radiotherapy field, ⁶⁸Ga-PSMA might have avoided unsuccessful salvage therapy in one-third of the patients considered for adjuvant or early salvage radiotherapy to the pelvis. On the other hand, since most of the first detectable PCa recurrences were located inside the pelvis,

adjuvant or early salvage radiotherapy might be the advocated treatment strategy in these patients with high-risk PCa.

This is the first analysis to show the anatomical distribution of PCa recurrence on ⁶⁸Ga-PSMA PET/CT in patients with BCR after RP with pN1 in the ePLND. The results show that ⁶⁸Ga-PSMA PET/CT enables the identification of disease

Table 2 Regression analysis of the probability of finding distant metastases.

Clinical variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
ISUP grading				
GG2	Reference	-	-	-
GG3	1.0 (0.3–3.5)	0.9	1.0 (0.2–5.2)	0.8
GG4	0.6 (0.1–2.9)	0.5	0.4 (0.05–3.7)	0.6
GG5	0.8 (0.2–2.8)	0.7	0.3 (0.03–1.9)	0.3
LNR	5.6 (0.02–1522.8)	0.5	0.2 (0.0–365.0)	0.6
Surgical margin RP				
No	Reference	-	-	-
Yes	0.9 (0.4–2.4)	0.9	2.0 (0.5–7.8)	0.3
PSA at ⁶⁸ Ga-PSMA PET/CT	1.6 (1.0–2.3)	0.034	1.9 (1.0–3.4)	0.039
Time RP and ⁶⁸ Ga-PSMA	1.0 (1.0–1.0)	0.8	0.9 (0.8–1.0)	0.081
T-stage				
pT2	Reference	-	-	-
pT3a	0.6 (0.1–2.9)	0.6	1.0 (0.1–7.5)	0.9
pT3b	0.5 (0.1–1.8)	0.3	1.0 (0.2–6.6)	0.9
BCR persistence				
BCR	Reference	-	-	-
Persistence	1.5 (0.5–4.4)	0.4	0.5 (0.1–2.6)	0.4

⁶⁸Ga-PSMA, gallium-68-prostate-specific membrane antigen; BCR, biochemical recurrence; GG, grade group; ISUP, International Society of Urological Pathology; LNR, lymph node ratio; OR, odds ratio; RP, radical prostatectomy.

recurrence in most of these patients. However, there remains a lack of evidence from prospective studies to support the long-term benefit of ⁶⁸Ga-PSMA PET/CT-dictated management changes. A previous study showed a 0% detection rate for lymph node metastases <2 mm using ⁶⁸Ga-PSMA PET/CT, a 60% detection rate for lesions 2.0–4.9 mm and an 86% detection rate for lymph node metastases ≥5.0 mm [11]. Thus, currently ⁶⁸Ga-PSMA PET/CT underestimates the extent of the disease, and patients with lymph node-positive PCa often harbour microscopic metastatic PCa. Our detection rates, stratified by the different PSA values, are in accordance with earlier publications [12]. In our analysis, we did not focus on other predictors of positive ⁶⁸Ga-PSMA PET/CT, such as grade group, and the study only included patients with high-risk PCa, and the correlation between predictors and the chance of having a positive PSMA PET/CT has already been described and externally validated [12].

In their retrospective analysis of 209 patients with pN1 ePLND at RP, Mandel et al. [13] showed that, of the patients with a limited nodal disease (one to two positive lymph nodes), 37% remained metastasis-free at a median follow-up of 60.2 months without the need for salvage treatment. Seiler et al. [14] showed that a subset (8%) of the 88 patients who had undergone RP and had tumour-positive ePLND without adjuvant treatment had not experienced BCR at a median follow-up of 15 years. In a systematic review of oncological outcomes after salvage lymph node dissection, Ploussard et al. [15] reported 2- and 5-

year BCR-free survival of 23–64% and 6–31%, respectively, in patients with a tumour-positive salvage ePLND. These results support early localization of loco-regional disease recurrence in order to benefit from salvage therapies.

Pelvic lymph node metastases identified by ⁶⁸Ga-PSMA PET/CT were detected on the same side as the node metastasis at ePLND in 84% of the cases, and in the same anatomical region as the initially diagnosed lymph node metastasis in 32% of the cases. This suggests an incomplete ePLND. Briganti et al. [16] have shown that the estimated number of lymph nodes necessary for optimal staging accuracy ranges between 20 and 28. Abdollah et al. [17] reported that the removal of 20 nodes resulted in accurate staging in 90% of their patients. Of the 31 patients with PCa recurrence detected on ⁶⁸Ga-PSMA PET/CT in the pelvic lymph nodes only, ≥20 lymph nodes were removed during ePLND in only 11 patients (35%), suggesting a suboptimal ePLND in most of the patients. This may explain the high probability of pelvic lymph node recurrence on the same side as the initial lymph node metastasis, and suggests a role for adjuvant therapy (e.g. radiotherapy) at least in lymph node-positive patients at RP with a limited number of nodes removed at ePLND.

Abdollah et al. [18] showed that, in patients with PCa with lymph node metastases, the removal of a higher number of lymph nodes during RP was associated with improvement in the cancer-specific survival rate. Also, they identified the optimal candidates for adjuvant radiotherapy among patients with lymph node-positive PCa at RP, i.e. those with one to two positive nodes, pathological Gleason score 7–10 and pT3b/4 disease, and those with three to four positive nodes, regardless of local characteristics [19]. In the present study, two-thirds of the patients had their first detectable recurrence at ⁶⁸Ga-PSMA PET/CT in the prostatic fossa and/or pelvic nodes. In other words, a subset of these patients might have been ideal candidates for adjuvant radiotherapy, with potentially improved outcomes. This finding suggests adjuvant radiotherapy of the pelvis in a selection of patients with lymph node positive PCa at RP should at least be considered.

Only PSA level at time of the scan was a significant predictor for the detection of metastatic disease outside the pelvic area on ⁶⁸Ga-PSMA PET/CT. Patients with biochemical persistence after RP have worse prognosis and higher risk of a positive ⁶⁸Ga-PSMA PET/CT than patients with an undetectable PSA after RP, regardless of the pN1 status [20]. In the present univariable and multivariable analyses, a higher rate of detection of metastatic disease outside the pelvic area was not observed in patients with biochemical persistence compared to patients with BCR; therefore, patients with PSA persistence should not automatically be excluded from salvage radiotherapy to the prostatic fossa and pelvic lymph nodes. However, our multivariable analysis was limited in its

statistical power, and larger cohorts of patients are required in order to evaluate the true correlation.

Based on current guidelines, the available management recommendations are limited by the level of evidence for the treatment of men with tumour-positive ePLND at time of the RP. Treatment options are to start either ADT, adjuvant ADT combined with radiotherapy, or observation. Observation with possible (early) salvage radiotherapy combined with ADT in case of BCR is not listed in these guidelines. ^{68}Ga -PSMA PET/CT has been reported to have a management impact in roughly two out of three individuals with BCR after RP [21]. In our selection of pN1 patients, in one-third of these patients the primary location of disease recurrence on ^{68}Ga -PSMA PET/CT was outside the pelvic area; therefore, adjuvant radiotherapy to the prostatic fossa and pelvis would likely result in missing the correct location of the recurrence and subsequent treatment failure in these patients. As a consequence, the results suggest a role for ^{68}Ga -PSMA PET/CT-guided salvage therapy in patients with pN1 ePLND, enabling better patient selection. Also, ^{68}Ga -PSMA PET/CT might be used for detection and treatment planning by fusing the ^{68}Ga -PSMA with the planned CT to allow 'dose sculpting', that is, delivering a high dose to macroscopic disease while better sparing the surrounding normal tissue. In our cohort, ^{68}Ga -PSMA PET/CT would have allowed dose sculpting in 44 of the 100 patients. This results in a more personalized approach, which may also decrease radiotherapy-related toxicity.

The present study has several limitations. First, it was a retrospective analysis of a relatively small sample size and therefore has relatively low statistical power. Nevertheless, the aim of the study was to generate a hypothesis, rather than define recommendations in this patient population. Second, ^{68}Ga -PSMA PET/CT was not performed at a predefined serum PSA level and the different institutions had different imaging protocols; therefore, some patients did not have multiple PSA values available before ^{68}Ga -PSMA PET/CT and calculation of PSA doubling time was not possible. Third, all patients underwent MRI/CT and bone scintigraphy for primary staging. ^{68}Ga -PSMA PET/CT is often used for preoperative staging. This might influence location of recurrence in these patients. Fourth, different imaging analysis methods were used among the different centres; however, all nuclear physicians were experienced in reporting ^{68}Ga -PSMA PET/CT. These results, therefore, might not be directly applicable to clinical practice. Lastly, no follow-up data are yet available and consequently, it is unknown to what extent ^{68}Ga -PSMA PET/CT has missed disease recurrences outside the pelvis. Nevertheless, to date, this is the first and largest study on this subject in a population that underwent RP with a pN1 ePLND. Future studies should focus on the efficacy of ^{68}Ga -PSMA-guided salvage therapies.

In conclusion, patients with BCR after RP with pN1 ePLND are a heterogeneous population; therefore, having a clear vision of disease spread in such patients is essential. In this study, most of the first ^{68}Ga -PSMA PET/CT-detectable disease recurrence was located inside the pelvis, with positive pelvic lymph nodes often detected on the same side as the lymph node metastasis at ePLND. This study confirms the value of ^{68}Ga -PSMA PET/CT for the detection of PCa recurrence at low PSA values in men with BCR after RP, and highlights the importance of high-quality ePLND. Finally, prospective studies are needed to support the long-term benefit of ^{68}Ga -PSMA PET/CT-dictated management changes.

Conflicts of Interest

None declared.

References

- Gandaglia G, Briganti A, Clarke N *et al.* Adjuvant and salvage radiotherapy after radical prostatectomy in prostate cancer patients. *Eur Urol* 2017; 72: 689–709
- Briganti A, Karnes RJ, Joniau S *et al.* Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol* 2014; 66: 479–86
- Suardi N, Gandaglia G, Gallina A *et al.* Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. *Eur Urol* 2015; 67: 299–309
- Tilki D, Mandel P, Seeliger F *et al.* Salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy. *J Urol* 2015; 193: 484–90
- Kaplan JR, Kowalczyk KJ, Borza T *et al.* Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy. *BJU Int* 2013; 111: 1208–14
- Briganti A, Karnes RJ, Da Pozzo LF *et al.* Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol* 2011; 59: 832–40
- EAU Guidelines. Edn. Presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2.
- Touijer KA, Karnes RJ, Passoni N *et al.* Survival outcomes of men with lymph node-positive prostate cancer after radical prostatectomy: a comparative analysis of different postoperative management strategies. *Eur Urol* 2018; 73: 890–6
- Perera M, Papa N, Roberts M *et al.* Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol* 2019; 77: 403–17
- Afshar-Oromieh A, Avtzi E, Giesel FL *et al.* The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2015; 42: 197–209
- van Leeuwen PJ, Emmett L, Ho B *et al.* Prospective evaluation of ^{68}Ga -prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int* 2017; 119: 209–15
- Kraft P, Maurer T, Gafita A *et al.* Pre-test (68)Ga-PSMA-ligand PET/CT positivity in early biochemical recurrent prostate cancer after radical prostatectomy—validation of a prediction model. *EJNMMI Res* 2020; 10: 6

- 13 Mandel P, Rosenbaum C, Pompe RS et al. Long-term oncological outcomes in patients with limited nodal disease undergoing radical prostatectomy and pelvic lymph node dissection without adjuvant treatment. *World J Urol* 2017; 35: 1833–9
- 14 Seiler R, Studer UE, Tschan K, Bader P, Burkhard FC. Removal of limited nodal disease in patients undergoing radical prostatectomy: long-term results confirm a chance for cure. *J Urol* 2014; 191: 1280–5
- 15 Ploussard G, Gandaglia G, Borgmann H et al. Salvage lymph node dissection for nodal recurrent prostate cancer: a systematic review. *Eur Urol* 2019; 76: 493–504
- 16 Briganti A, Chun FK, Salonia A et al. Critical assessment of ideal nodal yield at pelvic lymphadenectomy to accurately diagnose prostate cancer nodal metastasis in patients undergoing radical retropubic prostatectomy. *Urology* 2007; 69: 147–51
- 17 Abdollah F, Sun M, Thuret R et al. Lymph node count threshold for optimal pelvic lymph node staging in prostate cancer. *Int J Urol* 2012; 19: 645–51
- 18 Abdollah F, Gandaglia G, Suardi N et al. More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. *Eur Urol* 2015; 67: 212–9
- 19 Abdollah F, Dalela D, Sood A et al. Impact of adjuvant radiotherapy in node-positive prostate cancer patients: the importance of patient selection. *Eur Urol* 2018; 74: 253–6
- 20 Ceci F, Bianchi L, Borghesi M et al. Prediction nomogram for (68)Ga-PSMA-11 PET/CT in different clinical settings of PSA failure after radical treatment for prostate cancer. *Eur J Nucl Med Mol Imaging* 2020; 47: 136–46
- 21 Bianchi L, Schiavina R, Borghesi M et al. How does (68) Ga-prostate-specific membrane antigen positron emission tomography/computed tomography impact the management of patients with prostate cancer recurrence after surgery? *Int J Urol* 2019; 26: 804–11

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Abbreviations: 68Ga-PSMA, gallium-68-prostate-specific membrane antigen; ADT, androgen deprivation therapy; BCR, biochemical recurrence; ePLND, extended pelvic lymph node dissection; PCa, prostate cancer; PET, positron-emission tomography; RP, radical prostatectomy.