Biochemical Persistence of Prostate-Specific Antigen After Robot-Assisted Laparoscopic Radical Prostatectomy: Tumor Localizations Using PSMA PET/CT Imaging

Dennie Meijer[1,2], Maarten L. Donswijk[3], Yves J.L. Bodar[1,2], Pim J. van Leeuwen[4], Henk G. van der Poel[4], Wouter V. Vogel[3], Jakko A. Nieuwenhuijzen[1,4], N. Harry Hendrikse[2,5], Daniela E. Oprea-Lager[2], and André N. Vis[1,4]

[1]Department of Urology, Amsterdam University Medical Center, VU University, Prostate Cancer Network Netherlands, Amsterdam, The Netherlands; [2]Department of Radiology and Nuclear Medicine, Cancer Center Amsterdam, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands; [3]Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [4]Department of Urology, The Netherlands Cancer Institute, Prostate Cancer Network Netherlands, Amsterdam, The Netherlands; and [5]Department of Clinical Pharmacology and Pharmacy, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands

Since the introduction of radiolabeled prostate-specific membrane antigen (PSMA) PET/CT, the ability to visualize recurrent prostate cancer has improved substantially. However, diagnostic accuracy is largely lacking for radiolabeled PSMA PET/CT in patients with biochemical persistence (BCP; that is, persistently measurable prostate-specific antigen [PSA] values after robot-assisted laparoscopic radical prostatectomy [RARP]). Therefore, the aim of this study was to determine the role of PSMA (i.e., ^{18}F-DCFPyL or ^{68}Ga-PSMA-11) PET/CT imaging in patients who experience BCP after RARP and to evaluate the sites of persistent disease on PSMA PET/CT. **Methods:** In total, 150 consecutive patients with BCP after RARP who underwent radiolabeled PSMA PET/CT imaging were retrospectively evaluated. BCP was defined as any detectable first serum PSA value after RARP (≥0.1 ng/mL) at least 6 wk after surgery, in the absence of an undetectable PSA value after RARP. A multivariable logistic regression analysis was performed to identify predictors for the detection of metastases outside the prostatic fossa (≥miN1) on PSMA PET/CT. **Results:** PSMA PET/CT was performed at a median PSA value of 0.60 ng/mL (interquartile range, 0.3–2.4) after a median of 6 mo (interquartile range, 4–10) after RARP. In total, 101 of 150 patients (67%) had lesions with PSMA expression on PET/CT, and 89 of 150 (59%) had lesions with increased PSMA expression sites outside the prostatic fossa. Moreover, 39 of 150 patients (26%) had PSMA-positive lesions outside the pelvis. On multivariable analysis, higher PSA values after RARP (P = 0.004) and positive pathologic lymph node status (P = 0.006) were independent predictors for ≥miN1. **Conclusion:** In the presence of BCP, a high proportion of patients already had disease metastatic to the pelvic lymph nodes or showed evidence of distant metastases, as indicated by PSMA PET/CT. Higher PSA levels after RARP and positive pathologic lymph node status were significantly associated with metastases outside the prostatic fossa. In patients with BCP, PSMA PET/CT imaging is warranted to guide salvage treatment strategies.

Key Words: biochemical persistence; prostate cancer; PSMA PET/CT imaging

J Nucl Med 2021; 62:961–967
DOI: 10.2967/jnumed.120.252528

Received Jul. 14, 2020; revision accepted Oct. 26, 2020.
For correspondence or reprints, contact Dennie Meijer (d.meijer2@amsterdamumc.nl).
Published online Nov. 6, 2020.

In patients with localized prostate cancer (PCa), robot-assisted laparoscopic radical prostatectomy (RARP) is one of the main curative treatment options. After RARP, prostate-specific antigen (PSA) is measured to assess the oncologic outcome. If PSA becomes undetectable (i.e., <0.1 ng/mL), it is assumed that patients are free of disease. Because the half-life of PSA is 2–3 d (*1*), the serum PSA level should become undetectable within approximately 6 wk after RARP. However, a substantial percentage of patients (5%–20%) who undergo RARP retain a persistently measurable PSA (*2*,*3*). In the literature, biochemical persistence (BCP) of PSA after RARP has been associated with a poor oncologic outcome (*4*). Furthermore, BCP after RARP, defined in the European Association of Urology guidelines as any detectable PSA value (≥0.1 ng/mL) within 4–8 wk after surgery (*5*), is associated with higher tumor stages, higher Gleason scores, positive surgical margins, and impaired overall survival (*3*,*4*,*6*).

Several studies have shown that patients with BCP after RARP benefit less from local salvage therapies such as salvage radiation therapy to the prostatic fossa than do patients with rising PSA values after an initially undetectable PSA value (i.e., biochemical recurrence) (*7*,*8*). This observation may indicate that these patients might already have metastasized disease at the time of diagnosis or at the time of salvage therapy. Since the introduction of radiolabeled (either with ^{68}Ga and ^{18}F) prostate-specific membrane antigen (PSMA) PET/CT, the detection of metastases has improved substantially compared with conventional imaging techniques, such as bone scintigraphy, CT, and MRI, especially in patients with biochemical recurrence of disease (*9*). With this modern imaging technique, a more confident localization of the PCa recurrences is possible, and adjustment of management decisions appears to be more frequent (*10*). For patients who do not benefit from local salvage therapies, among those with BCP after RARP, PSMA PET/CT might be the imaging tool of choice to guide management decisions and optimize a personalized treatment approach.

Recently, Farolfi et al. (*11*) reported on a cohort of 191 patients with BCP after RARP who underwent ^{68}Ga-PSMA PET/CT with features of higher risk (median PSA level of 1.1 ng/mL; 31% were pretreated with androgen-deprivation therapy, and 58% had an

International Society of Urological Pathology [ISUP] grade group ≥ 4). The aim of the present study, however, was to determine the role of PSMA PET/CT imaging in hormone-naïve patients with early BCP after RARP. Particular attention was paid to the anatomic sites of PCa identified on PSMA PET/CT, stratified by the PSA level at scan time.

MATERIALS AND METHODS

This retrospective analysis was conducted by the Prostate Cancer Network Netherlands—that is, Amsterdam UMC, VU University Medical Center, and The Netherlands Cancer Institute—from August 2016 to June 2020. The institutional review board of both hospitals approved this study, meanwhile waiving the need to receive informed consent (VUmc2019.586 and IRBd20-016).

In the present study, we included 150 consecutive patients with BCP after RARP who underwent either 2-(3-{1-carboxy-5-[(6-^{18}F-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL) PET/CT or ^{68}Ga-PSMA-11 PET/CT. BCP was defined as any detectable first serum PSA value after RARP (≥0.1 ng/mL) at least 6 wk after surgery, in the absence of an undetectable PSA value after RARP (*5*). Patients were excluded from analysis when using androgen-deprivation therapy or antihormonal therapy before PSMA PET/CT for BCP.

Patient Data

From all included patients, demographic data, biochemical data (PSA level at BCP, PSA at the time of performing the PSMA PET/CT), radiologic data (e.g., PSMA PET/CT results before RARP and at BCP), and pathologic data (e.g., pathologic tumor stage, prostatectomy specimen ISUP grade group, surgical margin status, and pathologic lymph node status) were obtained and inserted in a comprehensive database. The time to the first PSA measurement was noted, as were the time between RARP and PSMA PET/CT and the PSA values at the first sign of BCP.

PSMA PET/CT Imaging

At VU University Medical Center, imaging was performed with an Ingenuity TF PET/CT system (Philips Healthcare), with ^{18}F-DCFPyL as the tracer. ^{18}F-DCFPyL was synthesized via direct radiofluorination at an on-site cyclotron facility compliant with good manufacturing practices (*12*,*13*). The median tracer dose was 311 MBq (interquartile range [IQR], 298–323 MBq). PET images were acquired approximately 120 min after intravenous injection.

At The Netherlands Cancer Institute, imaging was performed using a Gemini TF-II or Vereos digital PET/CT system (Philips Healthcare), with either ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL as a tracer. ^{68}Ga-PSMA-11 was radiolabeled in-house using a fully automated system (Scintomics GmbH). A fixed dose of 100 MBq or (from September 2019 onward) 150 MBq was administered to patients as an intravenous bolus. Scanning commenced approximately 45 min after injection, with 3–4.5 min per bed position for pelvis/abdomen and 2–3 min per bed position for the remainder of the scan range. ^{18}F-DCFPyL was administered as an intravenous bolus injection with a median dose of 201 MBq (IQR, 192–208 MBq). Scanning commenced after an incubation period of approximately 60 min, with 2 min per bed position over the complete scan range.

All patients were asked to drink 1 L of water 60 min before tracer injection. No diuretics were administered. Immediately before the scans, patients were required to empty their urinary bladder.

PET images were combined with either a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation) or a diagnostic CT scan (130 kV, 110 mAs) without contrast enhancement. All PET images were corrected for scatter, decay, and random coincidences; attenuation correction was performed using CT images.

Image Interpretation of PSMA PET/CT

The scans were interpreted at participating centers by experienced nuclear medicine physicians in a clinical setting. A scan was considered positive if at least one lesion was suggestive of PCa (i.e., focally higher tracer uptake than in the surrounding tissues, which was incompatible with physiologic uptake and had an anatomic substrate on CT). Following the guidelines of the European Association of Urology, and according to the PROMISE criteria (*14*), locoregional lymph node metastases were defined as lymph nodes in the true pelvis (miN1), whereas lymph nodes outside the surgical template were considered distant lymph node metastases (miM1a). Furthermore, we assessed whether lesions with increased PSMA expression were present in the bones (miM1b) and in the visceral organs (miM1c) (*5*) and whether patients with metastatic disease (i.e., ≥miN1) had unimetastatic or oligometastatic disease (2–5 metastases) (*15*,*16*) and might therefore qualify for metastasis-directed therapy.

Statistical Analysis

Numeric variables were summarized as medians and IQRs, whereas categoric variables were expressed as percentages. Univariable and multivariable logistic regression analyses were performed with predefined variables, for example, first PSA value after RARP, pathologic T-stage, ISUP grade group, surgical margin status, and pathologic lymph node status. The outcome variable was the presence of disease outside the prostatic fossa (≥miN1 disease). Moreover, a multivariable logistic regression analysis to identify predictors for lesions with PSMA expression outside the pelvis (≥miM1) was performed. Statistical analyses were performed using the Statistical Package for Social Sciences (IBM; version 25). Statistical significance was set at a P value of less than 0.05 (*17*).

RESULTS

Patient Characteristics

The present study included 150 patients with BCP after RARP. Their characteristics are presented in Table 1. Median age at PSMA PET/CT was 68 y (IQR, 62–72 y), and median PSA value after RARP was 0.3 ng/mL (IQR, 0.2–0.9 ng/mL) after a median follow-up of 99 d (IQR, 72–125 d). PSMA PET/CT was performed at a median PSA value of 0.60 ng/mL (IQR, 0.3–2.4 ng/mL) after a median of 6 mo (IQR, 4–10 mo) after RARP.

A pathologic T-stage of at least pT3 was found in 115 of 150 patients (77%), and the radical prostatectomy specimen of 114 of 150 patients (76%) was ISUP grade group 3 or higher. Moreover, 95 of 150 patients (63%) had positive surgical margins. An extended pelvic lymph node dissection was performed in 117 of 150 patients (78%), 77 of whom (66%) had evidence of malignant disease at histopathologic evaluation (pN1). The median number of removed lymph nodes was 16 (IQR, 11–22).

PSMA PET/CT Findings

In 49 of 150 patients (33%), no lesions with increased PSMA expression were detected (i.e., negative PSMA PET/CT scan) at a median PSA of 0.3 ng/mL (IQR, 0.2–0.5 ng/mL). The remaining 101 of 150 patients (67%) had a PSMA PET/CT with at least one lesion suggestive of PCa (i.e., positive) at a median PSA of 1.2 ng/mL (IQR, 0.5–4.1 ng/mL; Mann–Whitney; $P < 0.001$). PSMA PET/CT positivity stratified for the PSA value at the time of the scan is visualized in Figure 1. PSMA PET/CT positivity was observed in 24 of 57 (42%) patients with PSA values of less than 0.5 ng/mL, in 25 of 37 (68%) patients with PSA values from 0.5 to

less than 1.0 ng/mL, in 12 of 14 (86%) patients with PSA values from 1.0 to less than 2.0 ng/mL, and in 40 of 42 (95%) patients with PSA values of 2.0 ng/mL or higher (Table 2).

Anatomic Sites of Lesions with Increased PSMA Expression on PSMA PET/CT

Of 101 patients with lesions with increased PSMA expression on the PET/CT scans, 62 (61%) had detectable lesions limited to the pelvic area, 13 (13%) had lesions suggestive of PCa outside the pelvic area only, and 26 (26%) had PSMA-expressing lesions both inside and outside the pelvic area (Table 2). In total, 89 of 101 patients (88%) with tumor expressing PSMA on PET/CT had PSMA-avid sites outside the prostatic fossa (i.e., ≥miN1), whereas 39 of 101 patients (39%) had evidence of distant metastatic disease on PSMA PET/CT (≥miM1; Fig. 1). Of these 89 patients, 32 (36%) had unifocal involvement, 31 (35%) had oligometastatic disease, and 26 (29%) had polymetastatic disease.

TABLE 1
Patient Characteristics in Presence of BCP After Robot-Assisted Radical Prostatectomy

Characteristic	Data
First PSA after RARP (ng/mL)	0.3 (0.2–0.9)
Time between RARP and first PSA measurement (d)	99 (72–125)
Age at time of PSMA PET/CT (y)	68 (62–72)
Time between RARP and PSMA PET/CT (mo)	6 (4–10)
PSA at PSMA PET/CT (ng/mL)	0.60 (0.3–2.4)
PSMA PET/CT tracer	
^{68}Ga-PSMA-11	94 (63)
^{18}F-DCFPyL	56 (37)
RARP T-stage	
pT2	35 (23)
pT3a	52 (35)
pT3b	60 (40)
pT4	3 (2)
RARP grade group according to ISUP	
5 (Gleason score ≥ 9)	35 (23)
4 (Gleason score = 8)	15 (10)
3 (Gleason score 4 + 3 = 7)	64 (43)
2 (Gleason score 3 + 4 = 7)	32 (21)
1 (Gleason score 3 + 3 = 6)	4 (3)
Surgical margin status	
Negative	53 (36)
Positive	95 (63)
Missing	2 (1)
Cumulative length of surgical margin positivity (cm)	1.0 (0.3–2.0)
RARP N-stage	
pNx	33 (22)
pN0	40 (27)
pN1	77 (51)
Number of removed lymph nodes	16 (11–22)

Qualitative data are number and percentage (total $n = 150$); continuous data are median and IQR.

PSMA PET/CT Imaging Before RARP

In 56 of 150 patients (37%), PSMA PET/CT was performed before surgery. The PSMA PET/CT was suggestive of pelvic lymph node metastases in 21 of 56 patients (38%), whereas 62% (35/46 patients) had a PSMA PET/CT scan negative for metastatic disease. Of the 21 patients with PSMA-positive pelvic lymph nodes, 17 (81%) had lesions suggestive of pelvic lymph node metastases on restaging PSMA PET/CT, 12 of whom (57%) had persistent pelvic lymph nodes and 5 of whom (24%) had recurrent pelvic lymph nodes. On the other hand, only 11 of 35 (31%; χ^2; $P < 0.001$) patients with a PSMA PET/CT negative for metastases before surgery had lesions suggestive of pelvic lymph node metastases on restaging PSMA PET/CT. No differences were found in the presence of distant metastases between patients with a negative preoperative scan (9/35 patients; 26%) and those with pelvic lymph node metastases on staging PSMA PET/CT (6/21 patients; 29%; χ^2; $P = 0.82$).

Logistic Regression Analysis

On univariable logistic regression analysis, PSA value at PSMA PET/CT ($P < 0.001$), first PSA value after RARP ($P = 0.003$), ISUP grade group 4–5 compared with 1–2 in the radical prostatectomy specimen ($P = 0.02$), and pathologic lymph node status ($P = 0.001$) were predictors of having recurrent disease outside the prostatic fossa (Table 3)[ID]TBL3[/ID]. In contrast, the time between RARP and PSMA PET/CT, pathologic T-stage, and surgical margin status were found not to have a predictive role. On

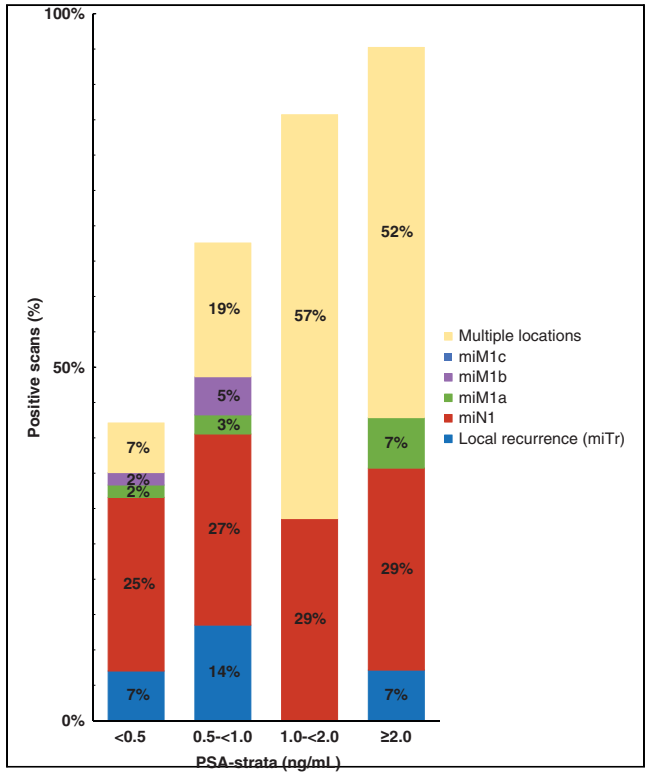

FIGURE 1. Sites of disease using PSMA PET/CT imaging, stratified per PSA level at time of PSMA PET/CT in patients with BCP after RARP.

TABLE 2
Localization of Lesions Suggestive for PCa on PSMA PET/CT Imaging, Stratified per PSA Level

	PSA			
PSMA PET/CT finding	<0.5 (n = 57)	0.5 to <1.0 (n = 37)	1.0 to <2.0 (n = 14)	≥2.0 (n = 42)
Negative for cancer	33 (57)	12 (32)	2 (14)	2 (5)
Local recurrence of disease (miTr)	4 (7)	5 (14)	0 (0)	3 (7)
Locoregional lymph node metastases (miN1)	14 (25)	10 (27)	4 (29)	12 (29)
Distant lymph node metastases (miM1a)	1 (2)	1 (3)	0 (0)	3 (7)
Bone or visceral metastases (miM1b-M1c)	1 (2)	2 (5)	0 (0)	0 (0)
Multiple locations	4 (7)	7 (19)	8 (57)	22 (52)
Stratified per location				
Negative	33 (58)	12 (32)	2 (14)	2 (5)
Inside pelvis (miTr/miN1)	19 (33)	18 (49)	6 (43)	19 (45)
Outside pelvis (≥miM1)	4 (7)	3 (8)	1 (7)	5 (12)
Inside and outside pelvis	1 (2)	4 (11)	5 (36)	16 (38)
Disease outside prostatic fossa (≥miN1)				
No	37 (65)	17 (46)	2 (14)	5 (12)
Yes	20 (35)	20 (54)	12 (86)	37 (88)
Extent of metastatic disease				
Negative/local recurrence (miTr)	37 (65)	17 (46)	2 (14)	5 (12)
Unimetastastic disease	15 (26)	10 (27)	2 (14)	5 (12)
Oligometastatic disease (2–5 metastases)	5 (9)	8 (22)	6 (43)	12 (28)
Polymetastatic disease (>5 metastases)	0 (0)	2 (5)	4 (29)	20 (48)

Data are number and percentage.

multivariable logistic regression analysis, the first PSA value after RARP (P = 0.004) and pathologic lymph node status (P = 0.006) were independent predictors for the detection of PCa deposits outside the prostatic fossa in patients with BCP after RARP (Table 3).

Second, we performed a multivariable logistic regression analysis on the detection of distant metastases (outside the pelvis) in patients with BCP after RARP. The first PSA value after RARP (P = 0.002) was an independent predictor for distant metastases on PSMA PET/CT, whereas pathologic lymph node status (P = 0.08) and surgical margin status were not (P = 0.37; Table 3).

DISCUSSION

We retrospectively assessed the value of PSMA PET/CT imaging in 150 consecutive patients with BCP after RARP. Our results showed that 101 of the 150 included patients (67%) had a positive PSMA PET/CT scan on BCP, of whom a remarkably high number, 89 (88%), showed evidence of disease outside the prostatic fossa (≥miN1). Moreover, 39 of 101 patients (39%) with a positive PSMA PET/CT scan had evidence of distant metastatic disease (≥miM1). To our knowledge, limited data are available about the sites of localized disease with PSMA expression on PET/CT in patients with BCP after RARP.

When patients with BCP were stratified for PSA value at the time of PSMA PET/CT, 42% (24/57) and 68% (25/37) of patients with a PSA value below 0.5 ng/mL and between 0.5 and 1.0 ng/mL, respectively, had a positive PSMA PET/CT scan, with lesions suggestive of PCa localizations (Table 2). These results are in line with those reported by Perera et al. in a systematic review on the oncologic outcome of patients with biochemical recurrence after radical prostatectomy, who underwent ^{68}Ga-PSMA–based imaging for staging purposes (*9*). In that study, 33%–48% and 57% of scans performed at PSA values below 0.5 ng/mL and between 0.5 and 1.0 ng/mL after RARP, respectively, were positive for cancer recurrence (*9*). Using ^{18}F-DCFPyL, Wondergem et al. reported similar percentages of positive PSMA PET/CT scans at a PSA value below 0.5 ng/mL and between 0.5 and 1.0 ng/mL: 59% (17/29 patients) and 69% (20/29 patients), respectively (*18*).

The present study, however, reported on a specific subgroup of patients with BCP after RARP, that is, those in whom the PSA level did not become undetectable after RARP. The literature described patients falling into this category as potentially having a prognostically dismal outcome compared with patients who had an undetectable PSA level postoperatively before experiencing biochemical recurrence (*3*,*4*,*6*).

Most included patients with BCP in the present cohort had locally advanced PCa, positive lymph nodes, and positive surgical margins. However, on multivariable logistic regression analysis, the first PSA value after RARP (P = 0.004) and pathologic lymph node status (P = 0.006) were statistically significantly associated with disease outside the prostatic fossa (≥miN1), whereas surgical margin status, ISUP grade group, and pathologic T-stage were not. Furthermore, in assessing distant metastatic disease, we found that the first PSA value after RARP was an independent predictor for the presence of distant metastases on PSMA PET/CT (P = 0.002). Apparently, the PSA level at BCP remains an independent predictor of

TABLE 3
Univariable and Multivariable Logistic Regression Analyses on Presence of Metastases (≥miN1 and ≥miM1) on PSMA PET/CT Imaging

	Univariable logistic regression on ≥miN1		Multivariable logistic regression on ≥miN1		Multivariable logistic regression on ≥miM1	
Parameter	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
PSA at PSMA PET/CT	2.12 (1.40–3.22)	<0.001	—	—	—	—
First PSA value after RARP	2.17 (1.30–3.62)	0.003	2.26 (1.29–3.94)	0.004	1.43 (1.14–1.80)	0.002
Time between RARP and PSMA PET/CT	1.01 (0.98–1.04)	0.69	—	—	—	—
RARP T-stage						
pT2	Reference		Reference		—	—
pT3a	1.19 (0.50–2.81)	0.69	0.49 (0.12–1.93)	0.31	—	—
pT3b	1.89 (0.81–4.43)	0.14	0.89 (0.21–3.75)	0.88	—	—
RARP grade group according to ISUP						
≥4 (Gleason score ≥ 8)	Reference		Reference		—	—
3 (Gleason score 4 + 3 = 7)	0.78 (0.36–1.71)	0.54	1.38 (0.48–3.97)	0.55	—	—
1–2 (Gleason score 3 + 3 = 6 and 3 + 4 = 7)	0.34 (0.14–0.82)	0.02	0.38 (0.10–1.45)	0.16	—	—
Surgical margin status						
Negative	Reference		Reference		Reference	
Positive	0.52 (0.26–1.07)	0.07	0.39 (0.13–1.14)	0.09	0.64 (0.25–1.68)	0.37
Cumulative length of surgical margin positivity	1.16 (0.89–1.53)	0.28	—	—	—	—
Pathologic lymph node status						
pN0	Reference		Reference		Reference	
pN1	3.75 (1.68–8.37)	0.001	4.10 (1.49–11.3)	0.006	2.64 (0.91–7.69)	0.08

≥miN1 = metastases outside prostatic fossa; ≥miM1 = metastases outside pelvis.
Data in parentheses are 95% CI.

metastasized disease even if other powerful (pathologic) predictors are assessed.

The results reported in the present study are partially comparable to a recent article evaluating ^{68}Ga-PSMA-11 PET/CT in patients with BCP (*11*), with some essential differences. Farolfi et al. (*11*) reported on a cohort in which the median PSA value at the time of PSMA PET/CT was 1.1 ng/mL, remarkably higher than the 0.6 ng/mL in the present study. Furthermore, considerably more patients had an ISUP grade group of at least 4 (58%) than in our study (33%). Interestingly, in the study performed by Farolfi et al., almost one third of cases used androgen-deprivation therapy before surgery or PSMA PET/CT, whereas we included hormone-naïve patients only. It is unknown to what extent hormonal treatment may have influenced PSMA expression, but a flare phenomenon is possible (*19*). Lastly, Farolfi et al. reported on ^{68}Ga-PSMA-11 PET/CT solely, whereas our cohort comprised also

37% who underwent ^{18}F-DCFPyL PET/CT scans. All these variables together may have resulted in a different proportion of metastases.

In studies assessing predictors of PSMA PET/CT positivity in patients with biochemical recurrence, PSA kinetics (e.g., PSA doubling time) were significantly associated with the detection rate of PSMA PET/CT (*20*). Unfortunately, because of the nature and definition of BCP, dynamic metrics are of limited value in this cohort and were therefore not calculated.

The present study is one of the few studies to report on patients with BCP after RARP in whom PSMA PET/CT was performed to locate the anatomic sites of lesions suggestive of PCa, stratified by PSA level. A significant association was found between the level of PSA at the time of PSMA PET/CT and the extent of dissemination of disease. So, at higher PSA levels, more voluminous and more distant metastatic disease was reported. This implies that radiolabeled PSMA PET/CT imaging should be performed at the earliest signs of PSA persistence, to guide potential salvage treatment (e.g., salvage radiation therapy or salvage lymph node dissection), metastasis-directed therapy in patients with oligometastatic disease, or—in patients with polymetastatic disease—early initiation of systemic treatment.

Interestingly, the surgical margin status was not a statistically significant predictor of metastatic disease on either univariable or multivariable analysis. Furthermore, no association was found between the cumulative length of surgical margin positivity and the presence of any metastases on PSMA PET/CT. Therefore, also in patients with evident positive surgical margins who experience BCP, restaging PSMA PET/CT should be performed before initiation of salvage treatment.

In the present cohort, 21 patients underwent presurgical PSMA PET/CT that showed pelvic lymph node metastatic disease (miN1). On restaging PSMA PET/CT on BCP, 17 of 21 patients (81%) had lesions suggestive of lymph node metastases in the pelvic area. When the locations of these metastases were compared between the preoperative and the postoperative PSMA PET/CT, 12 of 21 patients (57%) had persistent lymph nodes after surgery. This percentage is largely comparable to that reported by Farolfi et al. (*11*), who found persistent pelvic lymph nodes on PSMA PET/CT in 15 of 33 patients (45%).

Some limitations need to be addressed. First, no histopathologic verification of the PSMA PET/CT–detected lesions was obtained, because of comorbidity or ethical reasons. Consequently, false-positive lesions on PSMA PET/CT might have influenced our results. However, the positive predictive value of PSMA PET/CT in recurrent PCa is reported as being high (*21*). Therefore, we believe the number of false-positive lesions on PSMA PET/CT in our cohort was low. Second, we do not report on the oncologic \follow-up of patients who underwent radiolabeled PSMA PET/CT imaging on BCP. In our series, patients underwent a wide variety of treatments, such as salvage radiation therapy to the prostatic fossa, stereotactic ablative lymph node radiation therapy, salvage lymph node dissection, and different hormonal treatments. Until now, no clear recommendations on treatment preference have been made using data from well-performed randomized clinical trials. Moreover, different radiotracers and different scan protocols were used. This might have influenced the findings of the PSMA PET/CT scans. Lastly, it might well be that the results derived from the multivariable analysis on the presence of metastases reported in this study are skewed, as a substantial proportion of our patients had no evidence of disease on PSMA PET/CT. In these patients with a negative-for-cancer PSMA PET/CT result, the distribution of yet-undetected sites of PCa lesions may be different from what is reported here, possibly resulting in a different outcome.

CONCLUSION

The present study reports on the anatomic sites of PSMA PET/CT–localized disease in patients who have BCP of PSA after RARP. At BCP, a high proportion of patients already had disease metastatic to the pelvic lymph nodes or distant sites, as indicated by PSMA PET/CT. Higher PSA levels after RARP and a positive pathologic lymph node status were significantly associated with metastatic disease outside the prostatic fossa. In patients with BCP, PSMA PET/CT imaging is warranted to guide salvage treatment strategies.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the role of PSMA PET/CT imaging in patients who experienced BCP after RARP, and can we identify predictors for metastases on PSMA PET/CT?

PERTINENT FINDINGS: In this retrospective cohort study, we found that 59% of patients with BCP after RARP had metastases outside the prostatic fossa (≥miN1) on PSMA PET/CT. Higher PSA levels after RARP and a positive pathologic lymph node status were significantly associated with metastatic disease outside the prostatic fossa.

IMPLICATIONS FOR PATIENT CARE: In patients with BCP, and in those with evident positive surgical margins, PSMA PET/CT imaging is warranted to guide salvage treatment strategies.

REFERENCES

1. Lotan Y, Roehrborn CG. Clearance rates of total prostate specific antigen (PSA) after radical prostatectomy in African-Americans and Caucasians. *Prostate Cancer Prostatic Dis.* 2002;5:111–114.
2. Ploussard G, Staerman F, Pierrevelcin J, et al. Predictive factors of oncologic outcomes in patients who do not achieve undetectable prostate specific antigen after radical prostatectomy. *J Urol.* 2013;190:1750–1756.
3. Wiegel T, Bartkowiak D, Bottke D, et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. *Int J Radiat Oncol Biol Phys.* 2015;91:288–294.
4. Preisser F, Chun FKH, Pompe RS, et al. Persistent prostate-specific antigen after radical prostatectomy and its impact on oncologic outcomes. *Eur Urol.* 2019;76:106–114.
5. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer: 2020 Update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2021;79:243–262.
6. Sood A, Keeley J, Palma-Zamora I, et al. Ten-year disease progression and mortality rates in men who experience biochemical recurrence versus persistence after radical prostatectomy and undergo salvage radiation therapy: a post-hoc analysis of RTOG 9601 trial data. *Urol Oncol.* 2020;38:599.e1–599.e8.
7. Bartkowiak D, Siegmann A, Bohmer D, Budach V, Wiegel T. The impact of prostate-specific antigen persistence after radical prostatectomy on the efficacy of salvage radiotherapy in patients with primary N0 prostate cancer. *BJU Int.* 2019;124:785–791.
8. Fossati N, Karnes RJ, Colicchia M, et al. Impact of early salvage radiation therapy in patients with persistently elevated or rising prostate-specific antigen after radical prostatectomy. *Eur Urol.* 2018;73:436–444.

9. 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.* 2020;77:403–417.
10. Calais J, Fendler WP, Eiber M, et al. Impact of ^{68}Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. *J Nucl Med.* 2018;59:434–441.
11. Farolfi A, Gafita A, Calais J, et al. ^{68}Ga-PSMA-11 positron emission tomography detects residual prostate cancer after prostatectomy in a multicenter retrospective study. *J Urol.* 2019;202:1174–1181.
12. Ravert HT, Holt DP, Chen Y, et al. An improved synthesis of the radiolabeled prostate-specific membrane antigen inhibitor, [^{18}F]DCFPyL. *J Labelled Comp Radiopharm.* 2016;59:439–450.
13. Bouvet V, Wuest M, Jans HS, et al. Automated synthesis of [^{18}F]DCFPyL via direct radiofluorination and validation in preclinical prostate cancer models. *EJNMMI Res.* 2016;6:40.
14. Eiber M, Herrmann K, Calais J, et al. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med.* 2018;59:469–478.
15. Singh D, Yi WS, Brasacchio RA, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys.* 2004;58:3–10.
16. Rao A, Vapiwala N, Schaeffer EM, Ryan CJ. Oligometastatic prostate cancer: a shrinking subset or an opportunity for cure? *Am Soc Clin Oncol Educ Book.* 2019;39:309–320.
17. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol.* 2016;31:337–350.
18. Wondergem M, Jansen BHE, van der Zant FM, et al. Early lesion detection with ^{18}F-DCFPyL PET/CT in 248 patients with biochemically recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2019;46:1911–1918.
19. Aggarwal R, Wei X, Kim W, et al. Heterogeneous flare in prostate-specific membrane antigen positron emission tomography tracer uptake with initiation of androgen pathway blockade in metastatic prostate cancer. *Eur Urol Oncol.* 2018;1:78–82.
20. Pereira Mestre R, Treglia G, Ferrari M, et al. Correlation between PSA kinetics and PSMA-PET in prostate cancer restaging: a meta-analysis. *Eur J Clin Invest.* 2019;49:e13063.
21. Fendler WP, Calais J, Eiber M, et al. Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol.* 2019;5:856–863.