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ORIGINAL ARTICLE

^{68}Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy

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Abstract

Objectives The primary objective was the evaluation of Gallium 68 (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography/computed tomography (PET/CT) detection rate, for identifying the site of prostate cancer (PCa) relapse (local vs systemic), stratifying the population according to different clinical stages of biochemical recurrence (BCR). Secondary aims were: 1) to evaluate the association of clinical/pathologic features and ^{68}Ga-PSMA-11 PET/CT detection rate, 2) to compare ^{68}Ga-PSMA-11 PET/CT with other imaging procedures, and 3) to evaluate the positive predictive value (PPV) in a per-patient analysis.

Material and methods This population was enrolled through a prospective, open label, single-center trial performed at the Nuclear Medicine of the University Hospital of Bologna (Eudract: 2015-004589-27 OsSC). The inclusion criteria were: (1) proven PCa, (2) surgery or radiotherapy as definitive therapy, (3) proven BCR, (4) prostate-specific antigen (PSA) 0.2–2 ng/ml, (5) age ≥ 35 years, and 6() willing to sign an informed consent. Three-hundred and thirty-two (332) patients were enrolled between March 2016 and June 2017; mean/median PSA was 0.84/0.61 ng/ml, 97.9% (325/332) of patients received radical prostatectomy and 2.1% (7/332) radiotherapy. Different patterns of BCR were identified by referent physicians as follows: (a) persisting detectable PSA after radical prostatectomy in 13.5% (45/332) of patients (subgroup 1), (b) first-time PSA failure after radical therapy in 44.9% (149/332) (subgroup 2), and (c) PSA increase after salvage or hormonal therapy in 41.6% (138/332) (subgroup 3).

Results Primary objective: ^{68}Ga-PSMA-11 PET/CT detection rate was 53.6% (CI 95% 48.1%–59.1%). In a patient-based analysis, disease confined to pelvis (prostate bed and/or lymph-nodes) was detected in 24.7% of cases (82/332). The presence of at least one distant lesion was observed in 28.9% of cases (96/332). The detection rate in different subgroups was: subgroup 1 = 64.5%, subgroup 2 = 45.6%, and subgroup-3 = 58.7%. Secondary objectives: 1) PSA ($p = 0.041$) and PSAdt ($p = 0.001$) showed association with ^{68}Ga-PSMA-11 PET/CT detection rate, and 2) correlative imaging was available in 73.2% of patients (243/332). When ^{68}Ga-PSMA-11 PET/CT was positive, correlative imaging resulted negative in 83% of cases (108/130). 3) The calculated PPV was 96.2%.

Conclusion Our data confirmed the efficacy of ^{68}Ga-PSMA-11 PET/CT for detecting local vs systemic disease in PCa patients presenting PSA failure after radical therapy. Furthermore, ^{68}Ga-PSMA-11 PET/CT detection rate is different depending on the clinical stage of BCR, and this information should be taken into consideration by referring physicians.

Keywords PSMA PET/CT · Biochemical recurrence · Prostate cancer · PSMA prostate · PSMA prospective · First biochemical recurrence

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Introduction

Biochemical recurrence (BCR) after primary therapy for localized or locally advanced prostate cancer (PCa) is a frequent event [1]. Within 10 years, 20–40% of patients undergoing radical prostatectomy (RP) and 30–50% of patients undergoing radiotherapy (RT) will experience BCR [2]. Because BCR after RP or RT occurs before clinical and radiographic evidence of cancer, the diagnostic yield of conventional imaging techniques is poor in asymptomatic patients [1–3]. Several clinical parameters such as serum prostate specific antigen (PSA) levels, PSA doubling time (PSAdt), PSA velocity (PSAvel), pathologic Gleason score (ISUP Grade Group), pathologic stage, and nodal invasion are used to stratify patients into various risk groups for local vs systemic recurrence [4]. Although these models (nomograms) are characterized by a good accuracy in predicting local versus distant relapse, they cannot reliably predict recurrence sites and the extent of metastatic disease [5].

Salvage RT (SRT) after RP is usually decided on the basis of BCR, without imaging [6]. Since patients in the early stages of BCR are still potentially curable, the ability to precisely localize recurrence site(s) is critically important to stratify patients to best therapeutic approach [i.e., salvage radiation therapy, metastases-directed therapy, hormonal therapy —androgen deprivation therapy (ADT) — or combination therapies] [7].

As precision medicine evolves, the contribution of molecular imaging to the management of PCa patients, especially for positron emission tomography (PET), is gaining importance [8, 9]. Highly successful approaches to measure the expression of the prostate specific membrane antigen (PSMA) have been introduced recently [10–12]. PSMA is a reliable tissue marker for PCa and an ideal target for PET imaging [10–12]. The agent mostly used in clinical studies (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)]) is labeled with ^{68}Ga (^{68}Ga-PSMA-11) and is currently undergoing extensive clinical evaluation [13–15]. At present, the accuracy of ^{68}Ga-PSMA-11 PET/CT in the recurrent setting has been calculated considering BCR as a single and homogenous category.

However, the definition of BCR represents itself an inhomogeneous category, since it can include patients presenting first-time PSA relapse, patients already treated with salvage radiotherapy (S-RT), hormone-naïve patients or receiving ADT, and patients who already failed several lines of therapy, including the new generation of antiandrogens (abiraterone, enzalutamide) or chemotherapy. Thus, different clinical stages of disease are included in the same definition. Low PSA values do not necessarily reflect early recurrence, while high PSA values are not necessarily related to advanced disease. As a consequence, the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT may vary considering these different stages in patients with PSA failure. Nevertheless, initial results already attested a high accuracy for ^{68}Ga-PSMA-11 PET/CT to detect disease in patients with BCR and low PSA levels [13–16].

For these reasons, we designed our study to evaluate the performance of ^{68}Ga-PSMA-11 PET/CT in the recurrent setting, stratifying our population according to different clinical stages of disease.

Materials and methods

Objectives

The primary objective was the evaluation of ^{68}Ga-PSMA-11 PET/CT detection rate for identifying the site(s) of relapse (disease confined to pelvis vs distant relapse) in a population with low PSA values (0.2–2 ng/m), and assessing ^{68}Ga-PSMA-11 PET/CT performance at different clinical stages of BCR.

Secondary objectives were:

2.1. The association of clinical/pathologic features (PSA, PSAdt, PSAvel, ISUP Grade Group, TNM, concomitant therapies, time to biochemical relapse) and ^{68}Ga-PSMA-11 PET/CT detection rate.
2.2. The comparison of ^{68}Ga-PSMA-11 PET/CT performance with other imaging procedures performed during BCR in the course of routine work-up evaluation.
2.3. The evaluation of positive predictive value (PPV) in a per-patient analysis.

Study design and inclusion/exclusion criteria

The cohort of patients included in this analysis was enrolled through an open-label, single-center, prospective registry study performed at the Nuclear Medicine of the S.Orsola-Malpighi University Hospital of Bologna, Italy and approved by Local Ethics Committee (Prot. PSMA-PROSTATA; Eudract: 2015-004589-27 OsSC). From March 2016 to June 2017 all patients matching the following inclusion criteria were prospectively enrolled: 1) histologically proven PCa, 2) RP or RT as definitive therapy, 3) proven BCR, 4) PSA levels between 0.2 and 2.0 ng/ml, 5) age ≥ 35 years, and 6) willing to sign an informed consent. Exclusion criteria were: 1) Unable to lie flat, still, or tolerate a PET scan, 2) history of treatment for another cancer within 12 months prior to ^{68}Ga-PSMA-11 PET/CT scan. The administration of concomitant therapies, including ADT, were allowed.

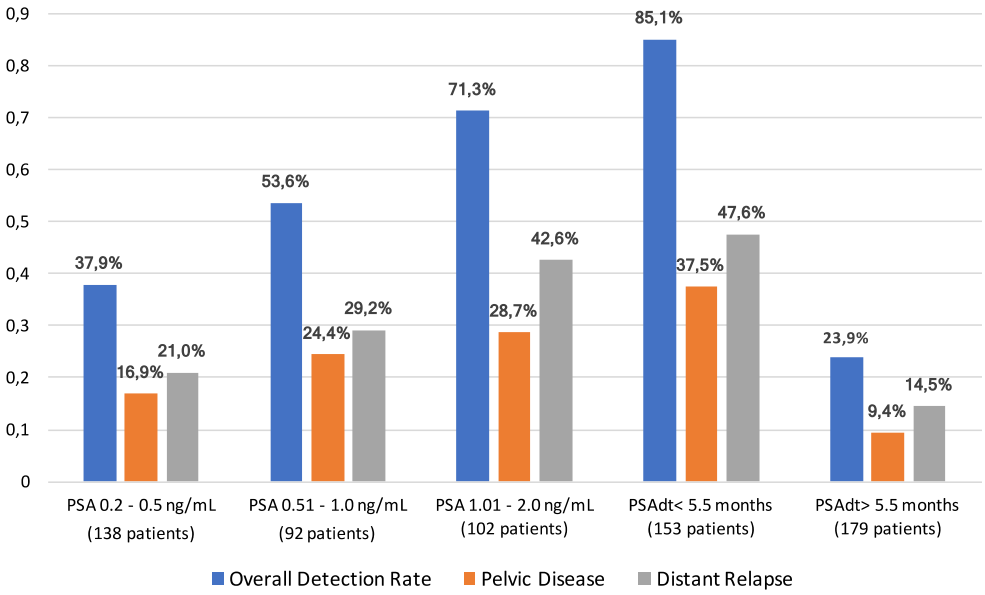

Fig. 1 ^{68}Ga-PSMA-11 PET/CT detection rate stratified by PSA levels (0.2–0.5; 0.51–1.0; 1.01–2 ng/ml) and PSAdt (higher or lower than 5.5 months)

Population characteristics

Four hundred and thirty-four (434) PCa patients were investigated from March 2016 to June 2017 at our institution. Three hundred and thirty-two (332) consecutive patients met inclusion/exclusion criteria and were included in this analysis. Mean PSA was 0.84 ng/ml (range 0.2–2 ng/ml), mean PSAdt was 7.4 months (range 0.8–54.3 months), mean PSAvel was 0.98 ng/ml/year (range 0.1–19.3 ng/ml/year). RP was the primary therapy in 97.9% (325/332) of patients, while radiotherapy was the primary therapy in 2.1% (7/332) of cases. Seventy-five of 332 patients (22.5%) underwent salvage therapies during BCR. Population characteristics are reported in detail in Table 1.

Different clinical stages of BCR were identified by referring physicians (urologist and/or radiation oncologist) in a tumor board, and our cohort was grouped into three different categories, namely: a) persisting detectable PSA after radical prostatectomy in 13.5% (45/332) (subgroup 1), b) first-time PSA failure after radical therapy in 44.9% (149/332) (subgroup 2), and c) PSA increase after salvage or hormonal therapy in 41.6% (138/332) (subgroup 3).

Radiopharmaceuticals

^{68}Ga-PSMA was synthesized at the radio-pharmacy of the Service of Nuclear Medicine of the S.Orsola Malpighi University Hospital of Bologna. ^{68}Ga-PSMA-HBED-CC(Glu-NH-CO-NH-Lys-(Ahx)-[[^{68}Ga]Ga(N,N′-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N′-diacetic-acid]) (^{68}Ga-PSMA-11) was prepared in a similar procedure as described by Eder et al. [17, 18].

Imaging procedure

^{68}Ga-PSMA-11 PET/CT was performed with a standard technique. All studies were performed using a dedicated 3D PET/

Table 1 Population characteristics

Population characteristics: $n = 332$ patients		
Characteristics	Mean/median ± SD	Range
Age years)	68.2/69 ± 7.1	54–83
PSA initial (ng/ml)	11.9/8.9 ± 12.9	3–125
PSA (ng/ml)	0.84/0.61 ± 0.62	0.2–2.00
PSAdt (months)	7.4/5.8 ± 7.3	0.8–54.3
PSAVel (ng/ml/yr)	0.98/0.6 ± 2.1	0.1–19.3
Time to BCR* (months)	36.2/25.0 ± 34.5	1–209
	Frequency	%
* < T3a	123/332	37.0%
* ≥ T3a	209/332	62.9%
* N1	52/332	15.7%
* R1	124/332	37.3%
* ISUP Grade Group < 4	202/332	60.8%
* ISUP Grade Group ≥ 4	130/332	39.2%
Primary therapies	Frequency	%
* RP	74/332	22.2%
* RP + LND	251/332	75.6%
* Primary radiotherapy	7/332	2.2%
Therapies during BCR	Frequency	%
* Salvage radiotherapy	63/332	18.9%
* Salvage LND	12/332	3.6%
* ADT	94/332	28.3%
* ADT at the time of the scan	34/332	10.2%

Time to BCR time from primary therapy to first biochemical recurrence, *RP* radical prostatectomy, *LND* lymph node dissection, *ADT* androgen deprivation therapy

CT state-of the art system with time of flight (TOF) technology (Discovery 690; GE Healthcare, Milwaukee, WI, US). The tomograph results were validated for a proper quantification and quality of the images recorded. Patients did not need any preparation before the procedure. A mean dose of 2 MBq/Kg body weight of ^{68}Ga-PSMA was administered intravenously. An attenuation-corrected whole-body scan (skull base to mid thighs) in three-dimensional mode (emission time: 3 min per bed position with an axial field-of-view of 15.6 cm per bed position) starting 60 min after tracer injection was acquired. A low-dose CT scan was performed for attenuation correction of the PET emission data. Emission data could be also corrected for the scatter and the random coincidence events by dedicated software.

Analysis of images

All ^{68}Ga-PSMA-11 PET/CT images were analysed with dedicated software (eNTEGRA; GE Healthcare) which allows for the review of PET, CT, and the fusion of imaging data. PET images were independently interpreted by two nuclear medicine physicians with more than 5 years of experience. In cases of disagreements between readers, the final diagnosis was reached by the opinion of a third reader. Visual interpretation was the main criterion for the final diagnosis. Each suspicious lesion was assigned to a certain category: positive vs negative. The main criteria of positivity was: any area of focal uptake of the radiotracer (single or multiple), higher than the surrounding background, that did not correlate with physiologic tracer uptake, regardless of the presence of lesions in the low-dose CT. Semi-quantitative analysis of all suspected lesions was performed by calculating the maximum standardized uptake value (SUVmax). The dimension of pathologic findings was assessed by the low-dose CT.

PET-positive lesions were classified as suspected "locally confined relapse" [prostate/prostate bed relapse and/or iliac lymph nodes (LNs)] or suspected "distant relapse" (retroperitoneal LNs and/or above iliac bifurcation LNs and/or bone lesions and/or other visceral lesions).

Validation of positive findings

^{68}Ga-PSMA-11 PET/CT-positive findings were validated by one of the following procedures: 1) histological confirmation when feasible by: TRUS-guided biopsy in patients with suspicious lesions located at the level of prostatic bed; LNs dissection in patients with suspicious lesions located at the level of pelvic and/or retroperitoneal nodes; a biopsy of the suspicious lesion in patients with metastases in other sites; or 2) lesion-targeted imaging or clinical follow-up (increase/decrease of PSA levels following treatment). Negative ^{68}Ga-PSMA-11 PET/CT scans were considered false negative by definition.

Statistical analysis

All data reported were expressed as mean, standard deviation (SD), range and median for each value. PSA kinetics was calculated according to Khan et al. [19]. The demographic and clinical variables were assessed by a descriptive analysis. Continuous variables were compared between the two groups using the non-parametric Mann–Whitney test in view of the asymmetric distribution of the variables. The chi-square test was used for categorical variables. The association between clinical and pathologic features and ^{68}Ga-PSMA-PET/CT pathological findings was assessed using univariate and multivariate Cox regression analysis. The effective PSA levels at the time of the scan, PSAdt, and PSAvel were coded as continuous variables. Gleason score (ISUP grading < 4 vs ≥ 4), tumour stage ($<$ T3 vs $\geq$ T3), ongoing ADT (yes vs no), age (< 65 vs ≥ 65), time from primary therapy to BCR (TTR) ($<$ 12 months vs $\geq$ 12 months) were coded as categorical variables. The odds ratio (OR) computed by the logistic regression, together with their 95% CI, were reported. The regression coefficients of each variable were calculated. The Hosmer–Lemeshow test was used to assess the goodness of fit in the multivariate analysis. All tests were 2-sided. Sensitivity and PPV (with 95% CI) of ^{68}Ga-PSMA-11 PET/CT were evaluated. Statistical significance was taken at a p value of less than 0.05. All data were analysed using the SPSS statistical software package (version 21; SPSS Inc.).

Results

Primary objective

^{68}Ga-PSMA-11 PET/CT resulted positive in 178 patients out of 332, resulting in an overall detection rate of 53.6% (CI 95% 48.1%–59.1%). In the patient-based analysis, disease confined to pelvis (prostate/prostate bed and/or lymph nodes) was detected in 24.7% of cases (82/332). The presence of at least one distant lesion (extra-pelvic nodes and/or bone and/or visceral) was detected in 28.9% of cases (96/332). ^{68}Ga-PSMA-11 PET/CT detection rate stratified by PSA levels and PSAdt is reported in Fig. 1.

^{68}Ga-PSMA-11 PET/CT detection rate in different stages of BCR was: subgroup 1 = 64.5%, subgroup 2 = 45.6%, subgroup 3 = 58.7%. These results, together with the incidence of confined to pelvis vs distant disease, are reported in Table 2.

Overall, 344 lesions expressing PSMA were evaluated. The results of the per-lesion analysis are displayed in Table 3; 45.4% of patients (151/332) had one to three PSMA positive lesions (oligometastatic disease), while 8.2% (27/332) had more than three PSMA-positive lesions (multimetastatic disease). Two examples of different locations are reported in Figs. 2 and 3.

Table 2 ^{68}Ga-PSMA-11 PET/CT detection rate stratified in accordance with clinical indication

Different stages of PSA failure	No. of patients	Mean PSA (ng/ml)	PSMA PET/CT detection rate	Locally confined relapse[a]	Distant relapse[b]	Oligometastatic disease (one to three lesions)
Group 1: persisting high PSA after RP	45	0.56	64.5%	40%	24.4%	51.1%
Group 2: fFirst-time BCR (no salvage therapies)	149	0.73	45.6%	24.8%	20.8%	42.9%
Group 3: BCR after salvage therapies	138	0.95	58.7%	19.5%	37.6%	48.5%
Overall population	332	0.84	53.6%	24.7%	28.9%	45.7%

RP radical prostatectomy, *BCR* biochemical recurrence, *mCRPC* metastatic castration-resistant prostate cancer

[a] Prostate bed and/or pelvic lymph-node

[b] At least one distant lesion (extra-pelvic nodes and/or bone and/or other visceral metastasis)

Secondary objectives

Objective 2.1 In the univariate Cox regression analysis (Supplemental data 1) PSA, PSAdt, and PSAvel showed significant association with ^{68}Ga-PSMA-11 PET/CT detection rate. PET-positive patients had higher PSA values (PET-positive = 0.97 ng/ml vs PET-negative = 0.68 ng/ml; $p = 0.009$), faster PSAdt (PET-positive = 4.6 months vs PET-negative = 10.9 months; $p = 0.001$) and faster PSAvel (PET-positive = 1.29 ng/ml/year vs PET-negative = 0.44 ng/ml/year; $p = 0.009$). These data are reported in detail in Table 4. The univariate analysis demonstrated no shifting with regard to the effect of the single variables. In the multivariate Cox regression analysis, only PSA (OR = 3.304; CI 95% = 1.052–10.372; $p = 0.041$) and PSAdt (OR = 0.807; CI 95% = 0.720–0.907; $p = 0.001$) maintained significant association with ^{68}Ga-PSMA-11 PET/CT detection rate (Supplemental data 1). None of the other parameters evaluated (age, ISUP grade group, TNM, surgical margins, TTR, on-going ADT) reached statistical significance in the regression analysis. In the multivariate analysis, the Hosmer–Lemeshow test demonstrated no lack of fitness within the model.

Objective 2.2 Correlative imaging (choline PET, MRI, CT, bone scintigraphy) performed during BCR in the course of routine work-up evaluation was available in 73.2% of patients (243/332). The mean time between ^{68}Ga-PSMA-11 PET/CT and correlative imaging was 3.7 months (range 0.7–6 months). Choline PET/CT was available in 137 patients, pelvic mp-MRI in 78 patients, and bone scintigraphy in 45 patients. The comparative analysis between these imaging procedures and ^{68}Ga-PSMA-11 PET/CT is reported in detail in Table 5. With regard to the 178 ^{68}Ga-PSMA-11 PET/CT-positive patients, correlative imaging was available in 130/178 and resulted negative in 83% of cases (108/130).

Objective 2.3 The mean follow-up in this patient-series follow-up was 15.3 months (range 9.8–25.3). PET negative scans (154) were considered false negative by definition, since all patients documented proven BCR. PET findings validation was available in the 59% of patients presenting PSMA-positive lesions (105/178). In ten cases, PSMA-positive lesions were validated by biopsy/histology, and in 95 cases by clinical/diagnostic follow-up. One patient with high PSMA expression in the prostate bed resulted inconclusive at TRUS-guided biopsy (lack of patient compliance).

Table 3 Lesion-based analysis

Lesion-based analysis

Type of lesion	No. of patients	No. of lesions	Mean SUVmax	Median SUVmax	SUVmax range	Mean/range size (mm)
Prostate	4	4	11.2	9.1	6.7–16.2	/
Prostate bed	24	24	11.9	9.9	3.7–28.4	10 (9–11)
LNs	88	202	9.8	6.5	2.7–45.1	8.4 (4–35)
Bone	62	110	10.7	6.1	2.5–52.7	9.5 (4–25)
Lung[a]	3	3	6.4	3.2	1.4–8.3	9 (8–14)
Epididymis[a]	1	1	25.5	25.5	/	25

[a] Histologically proven prostate cancer metastases

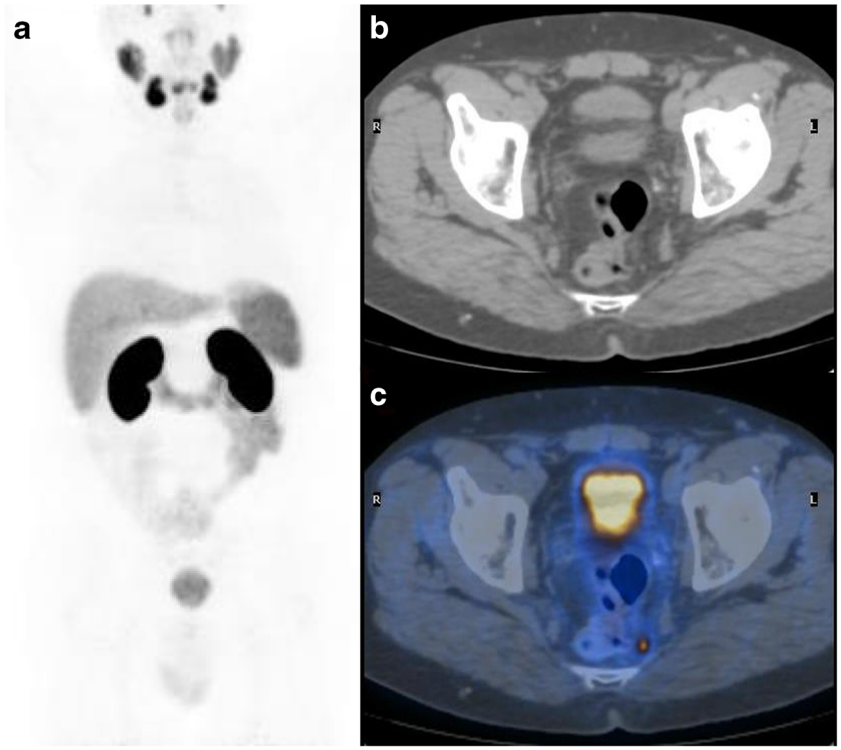

Fig. 2 A 60-year-old patient, T3a N1 (2/18) Mx, ISUP Group 4. Treated with RP as primary treatment, TTR 12 months, PSA 0.34 ng/ml, PSADT 5 months. 68Ga-PSMA PET-CT shows an intense focal uptake (SUVmax 4.7) in a 5-mm pararectal LN. **a** MIP projection. **b** CT images. **c** Fused PET & CT images

Subsequently mp-MRI resulted positive. This patient was considered true positive. Two patients underwent salvage pelvic lymph node dissection due to the presence of one small pre-sacral PSMA-positive lymph node. The histological analysis resulted negative. Nevertheless, PSA levels increased after surgery in both cases. Both patients were further investigated with ^{68}Ga-PSMA-11 PET/CT showing the persistence of PMSA positive lymph nodes, increased in dimensions and uptake. These two patients were considered true positive. Four patients have been validated as false positive: one patient with PSMA uptake in the urethrovesical anastomosis (negative at TRUS-guided biopsy), one patient with two mesorectal and one presacral nodes (histological analysis after pelvic surgery resulted negative), one patient with PSMA uptake in the right humerus (degenerative disease), and one patient with mediastinal nodule with PSMA uptake (basaloid thymic carcinoma

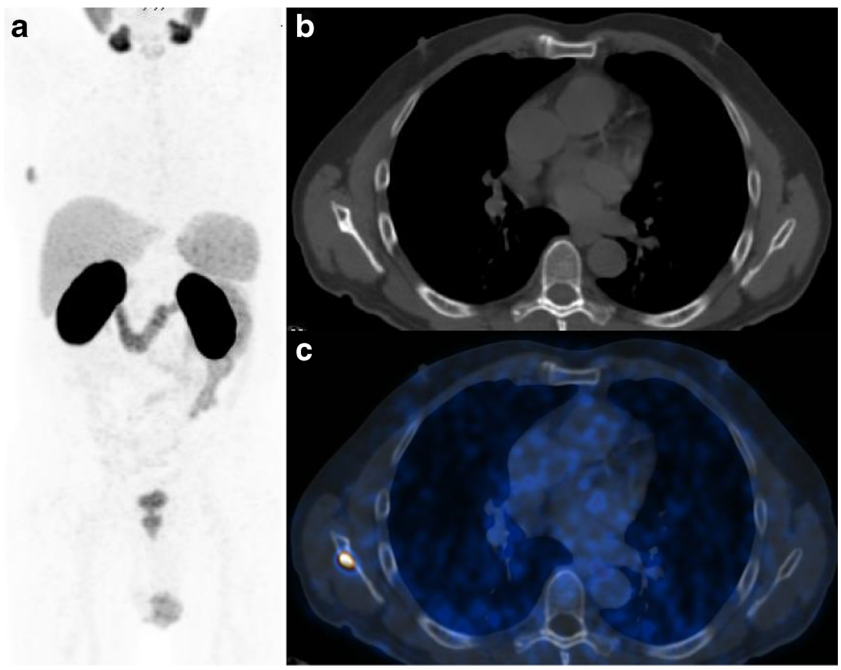

Fig. 3 A 68-year-old patient, T3b N0 Mx, ISUP Group 5. Treated with RP as primary treatment followed by adjuvant RT TTR 24 months, PSA 2.1 ng/ml, PSADT 4 months At the time of PSMA, PET/CT patient was receiving bicalutamide 150 mg/die. 68Ga-PSMA PET-CT shows an intense focal uptake (SUVmax 13.1) in the right scapula in a small osteoblastic lesion. **a** MIP projection. **b** CT images. **c** Fused PET & CT images

Table 4 Comparison of PSA, PSAdt, and PSAvel in PET-positive and PET-negative patients

		No. of patients	Mean	SD	95% confidence interval for mean		*P* value
					Lower bound	Upper bound	
PSA (ng/ml)	Negative	154	0.68	0.56	0.43	0.81	0.009
	Positive	178	0.97	0.56	0.79	1.11	
	Total	332	0.89	0.58	0.68	0.93	
PSAdt (months)	Negative	154	10.93	7.82	8.28	13.57	0.001
	Positive	178	4.62	4.52	3.29	5.94	
	Total	332	7.35	6.89	5.85	8.86	
PSAVel (ng/ml/year)	Negative	154	0.44	0.42	0.29	0.58	0.011
	Positive	178	1.29	1.93	0.72	1.86	
	Total	332	0.92	1.54	0.58	1.26	

SD standard deviation

after thoracic surgery). Overall, 154 patients were considered false negative, four false positive and 101 true positive. Accordingly, the per-patient PPV was 96.2%, (CI 95%: 95.60–96.70%).

Discussion

In this study, we investigated a cohort of consecutive PCa patients prospectively enrolled, who experienced PSA failure after radical therapy and PSA < 2 ng/ml. We recorded a detection rate of 53.6%, with an incidence of distant lesions in 28.9% of cases. These results confirm the importance of PSMA-based PET imaging to identify PCa relapse, especially for detecting lesions outside of the pelvis, as recently reported [13–15, 20–27]. Mean PSA was 0.84 ng/ml in our population and the 58.4% of patients (162/332) were referred to ^{68}Ga-PSMA-11 PET/CT when PSA became significant after radical therapy for the first time (subgroup 1 and subgroup 2). The enrollment of patients in early stages of BCR can explain the slight lower overall detection rate reported in our study, compared with ^{68}Ga-PSMA-11 PET/CT performance reported in literature. In a recent meta-analysis [26] considering 16 studies and 1309 patients, the calculated pooled detection rate was 58% for PSA range of 0.2–1.0 ng/ml, which increased to 76% for the 1.01–2.0 ng/ml subgroup. In our patient series, the calculated detection rate was 44.2% for patients with PSA 0.2–1.0 ng/ml, which increased to 71.3% for the 1.01–2.0 ng/ml subgroup.

Although PSA is a valid parameter to stratify the likelihood of positive PET scan, it does not offer precise information regarding the real stage of disease. Patients presenting first-time BCR generally have low PSA values at time of imaging. In these cases, low PSA levels generally reflect lower burden of the disease. However, low PSA values can be observed, for instance, in patients presenting PSA recurrence after salvage radiotherapy, or in hormone-sensitive patients previously treated with ADT or castration-resistant patients undergoing systemic treatment. Thus, patients with the same PSA value may present a different likelihood of positive PET scan. For this reason, we decided to assess the diagnostic accuracy of ^{68}Ga-PSMA-11 PET/CT at different clinical stages of the BCR, regardless of the PSA absolute value. Our population was stratified into three different categories, as identified by referring physicians. In patients with persisting high PSA level after RP or in patients with first-time BCR (subgroup 1 and subgroup 2), ^{68}Ga-PSMA-11 PET/CT detected PCa locations in 64.5 and 45.6% respectively. In this sub-group, approximately 90% of patients had only 1–3 lesions (oligo-metastatic disease). This population represents exactly the ideal candidates for salvage therapy, either radiation or surgery. The efficacy of ^{68}Ga-PSMA-11 PET/CT should be tested in selected cohorts and stratified in accordance with the real stage of the disease (early BCR vs advanced disease). In our study, we observed different performance of ^{68}Ga-PSMA-11 PET/CT in different stages of BCR. (See Table 2). In later stages (subgroup 3), detection rate was higher compared to first-time BCR (subgroup 2), with higher incidence of distant lesions

Table 5 Comparison of ^{68}Ga-PSMA-11 PET/CT results with choline PET/CT, pelvic mp-MRI, and bone scintigraphy

	Choline PET/CT (137)		Pelvic mp-MRI (78)		Bone scintigraphy (45)	
	Choline +	Choline −	mp-MRI +	mp-MRI −	Bone scan +	Bone scan −
PSMA +	11	73	6	32	5	20
PSMA −	2	51	3	37	0	20

and multi-metastatic disease. It is interesting to note the high detection rate (64.5%, with distant lesions detected in 24.4% of cases) in subgroup 1, despite the lowest PSA values (mean PSA 0.56 ng/ml) among the three categories. This data may suggest the presence of extended disease not detected by imaging prior to radical prostatectomy. In a pre-surgery setting, ^{68}Ga-PSMA-11 PET/CT might improve the success rate of RP by identifying patients with occult metastases and thus reducing the incidence of patients with persisting high PSA level after surgery. It should be noted that at present, the European Association of Urology (EAU) guidelines does not suggest the use of any PET imaging procedures (including PSMA PET) prior to radical therapy [1].

Results in literature suggest a superior detection rate of ^{68}Ga-PSMA-11 PET/CT over other techniques, including choline-based and fluciclovine-based PET/CT imaging [23, 28]. Our study confirms these results: in our patient series, when ^{68}Ga-PSMA-11 PET/CT was positive, correlative imaging resulted negative in 83% of cases. In a few cases only, choline PET/CT or mp-MRI resulted positive while ^{68}Ga-PSMA-11 PET/CT resulted negative (1.5 and 3.8% of cases respectively).

In this patient series, we observed that PSA and PSAdt were associated with ^{68}Ga-PSMA-11 PET/CT detection rate. Compared to another recently published study [29], we did not observe significant association between ADT and ^{68}Ga-PSMA-11 PET/CT. However, in our cohort only a few patients had concurrent ADT at the time of imaging. Our results on predictive factors might facilitate patient selection for PSMA-ligand PET, especially for patients with first-time BCR (subgroup 2), who had the lowest detection rate in our series.

Finally, we were able to calculate the PPV in a large cohort of consecutive patients prospectively enrolled. Despite PSMA not being a PCa-specific biomarker, the recorded PPV (calculated in 105 positive patients) of 96.2% is very promising, attesting the low incidence of false-positive findings for PSMA-ligand PET.

Limitation

A limitation of this study is the limited number of patients validated by histology ($n = 10$). However, histopathological correlation in systemic or distant tumor recurrence is often not feasible due to ethical and practical reasons. Notably, follow-up imaging was available in approximately 60% of cases. However, the availability of correlative imaging in all patients, prior to PET scan or immediately after, would be preferable.

Only 105 out of 178 positive scans have been validated by histology or clinical/diagnostic follow-up, while all negative scans (142) were considered false negative by definition. Accordingly, the calculation of the sensitivity in our series might have been affected by the lack of positive scan validation. For this reason, we decided to do not provide data about sensitivity in this patient series.

Finally, in this analysis we did not report about the impact of ^{68}Ga-PSMA-11 PET/CT on treatment strategies, as this was not among the original aims of this study. However, our group recently published the data about the intention to treat analysis performed in a smaller subpopulation of this prospective cohort [18].

Conclusion

Our results confirmed the efficacy of ^{68}Ga-PSMA-11 PET/CT for detecting local vs distant disease relapse in PCa patients presenting BCR and low PSA levels after radical therapy. We recorded an overall detection rate of 53.6%, with a detection of distant lesions in 28.9% of cases. Furthermore, ^{68}Ga-PSMA-11 PET/CT detection rate can differ depending on the clinical stage of biochemical recurrence and this information should be taken into consideration by referring physicians.

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Compliance with ethical standards

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.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest Authors declare no conflict of interest.

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