

The Impact of 18F-DCFPyL PSMA PET-CT in the Management of Prostate Cancer Biochemical Recurrence

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Abstract

Purpose: We evaluated the findings from 18F-DCFPyL PSMA PET-CTs performed on patients presenting biochemical recurrence (BCR) of prostate cancer (PCa) and assessed its impact on staging. **Methods and materials:** This was a multicenter retrospective analysis of patients with PCa and BCR who underwent 18F-DCFPyL PSMA PET-CT in 2020. The patients were stratified into two groups: BCR after prostatectomy (PSA \geq 0.2 ng/mL) or BCR after radiotherapy (PSA \geq 2 ng/mL + nadir). We analyzed the lesions according to number and location. The Shapiro-Wilk test was used to estimate the distribution of the variables. We calculated representative statistics for the quantitative variables including the mean, standard deviation, median, and interquartile range. The association between qualitative variables was examined using Chi-squared tests. **Results:** 40 patients with BCR were analyzed; 67.5% presented disease progression, predominantly distant recurrence (42.5%), which was found exclusively in bone; 55% presented \leq 5 lesions and of these, 68.2% only presented 1 lesion. There was a change in staging in 66.7% of the cases; 17.7% received ablative treatment with stereotactic radiotherapy (SABR). **Conclusions:** 18F-DCFPyL PSMA PET-CT represents a new way to manage patients with BCR that, in this study, resulted in a change in staging in 66.7% of cases and early identification of oligometastatic progressions in the subgroup of patients with PSA < 0.5 ng/mL.

Keywords

Prostate Specific Membrane Antigen, Prostate Cancer, PET-CT PSMA 18F-DCFPyL, Biochemical Recurrence

1. Introduction

According to figures from the Spanish National Institute of Statistics (INE), prostate cancer (PCa) is the most prevalent neoplasm and is the third leading cause of mortality (after lung and colorectal cancer) in the male population in Spain [1] [2] [3]. Of the patients with localized or locally advanced PCa treated with radical prostatectomy or radiotherapy, between 27% - 53% will experience a local or distant recurrence in the 10 years following treatment [4] [5]. Biochemical recurrence (BCR) is determined based on the level of prostate-specific antigen (PSA) present in the blood, according to the Phoenix criteria [6]. The challenge so far has been to find an imaging test that complements this analytical parameter which can provide more information about the location of the recurrence, especially when PSA values are low. The sensitivity and specificity of conventional imaging techniques (CITs) in patients with BCR and low PSA levels are limited, especially when PSA < 1 ng/mL [7]. 11C-choline or 18F-choline PET-CT is currently the main test used in prostatectomized patients with PSA levels > 1 ng/mL [8]. Until now, the problem facing physicians has been the underdiagnosis of patients with BCR values < 1 ng/mL by CITs. However, the relative efficiency of 68Ga-PSMA-11 PET-CT for the determination of locoregional and distant recurrences in these patients has been reported [9]. Furthermore, the 18F radiotracer has recently been shown to offer crucial advantages over 68Ga, including [1] greater availability; [2] increased detectability because of its lower photon energy (0.6 MeV for 18F vs. 2.3 MeV for 68Ga) which improves image resolution and photonic richness (96.6% vs. 89.1%, respectively); and [3] its longer half-life (1.83 h vs. 1.13 h, respectively), which allows late studies and facilitates discrimination [10] [11] [12]. This current study aimed to describe the outcomes after performing 18F-DCFPyL PSMA PET-CT in patients with BCR, and to analyze whether the use of this technique resulted in a change in the staging and management of these patients.

2. Materials and Methods

Patient population: This was a descriptive study carried out in 40 patients with PCa and BCR from one of two centers who underwent 18F-DCFPyL PSMA PET-CT. The patients were stratified into the following groups: BCR after radical prostatectomy with PSA \geq 0.2 ng/mL or BCR after external radiotherapy with PSA \geq 2 ng/mL + nadir [13]. Of all these patients, 75% had previously undergone CITs and some of them had not presented conclusive or suspicious signs of malignancy. The median follow-up period of the patients was 12 months.

Image acquisition and analysis: The 18F-DCFPyL radiopharmaceutical was synthesized in a cyclotron, according to good manufacturing practice conditions. The GE Discovery IQ 5r PET-CT equipment (GE Healthcare) underwent routine quality controls by the European Association of Nuclear Medicine Research Ltd., according to the recommendations of the European Association of Nuclear Medicine (EARL), which promotes scientific and inter-center initiatives

[14]. The patients did not require prior fasting or withdrawal or modification of their medications, nor were they administered a diuretic. A peripheral venous line was placed and they were injected with ^{18}F -DCFPyL at a dose of 333 MBq (9 mCi). The rest period ranged from 80 to 120 minutes. Next, a CT (120 Kv, 25 - 120 mA) was performed to obtain the correction map, and then a whole-body PET acquisition was carried out. The images were corrected for decay, scatter, randomness and coincidences, and photon attenuation and were reconstructed, applying an iterative Bayesian penalty algorithm (Q.Clear) with a β of 350 q, to improve the convergence of the lesion, guaranteeing a sufficient signal-to-noise ratio. The imaging test results were evaluated with the AW 3.2 expansion 3.0 processing server and Volume Viewer software (GE Healthcare) by two senior specialists in nuclear medicine, according to PSMA RADS 1.0 criteria [15] [16], by collecting the peak standardized uptake value (SUV) normalized by lean body mass (SUL) value of each of the lesions [17] [18]. The number of lesions as well as their location were analyzed and coded.

Statistical analysis: As the study sample comprised fewer than 50 patients we used the Shapiro–Wilk test to assess the distribution of the variables; $p \leq 0.05$ for those with a non-normal distribution which were presented as medians and interquartile ranges (P25 - P75); while $p > 0.05$ for those with a normal distribution which were represented as means and standard deviations. The association between qualitative variables was studied using Chi-squared tests, using Fisher exact tests when the frequency was less than 5.

3. Results

Patient characteristics: 40 patients with a median age at diagnosis of 66.5 years (range 48 - 78) were included in this study. The primary tumor was treated by radical prostatectomy in 75% of cases, while the remaining patients received radiotherapy. Of the latter, one patient received a brachytherapy boost after external radiation therapy. The group characteristics are shown in **Table 1**.

Characteristics of the primary tumor: in the overall sample, the median PSA at the time of diagnosis of the primary tumor was 7.08 ng/mL (range 5 - 13.6); 46.2% of the patients were stage II and III, respectively. According to the International Society of Urological Pathology (ISUP) prognostic group classification guidelines, the most frequent classification was ISUP3 (in 30% of the cases). Of the 75% of patients who underwent radical prostatectomy, half had positive margins. In addition, 80% of the patients who received irradiation were also treated with hormonal therapy (for 24 months in 87.5% of the cases).

Evaluation of the recurrence sites and number of lesions: ^{18}F -DCFPyL PSMA PET-CT provided conclusive evidence of local, lymph node, or distant progression in 27 patients. Lymph node recurrences (26.7%) included both regional (pelvic, hypogastric, obturator, internal or external iliac, and sacral) and extra-pelvic lymphadenopathies. Distant recurrence was observed in 42.5% of these patients, in bone in every case (**Figure 1**). The number of lesions observed

Table 1. Patient characteristics.

Variables	Global <i>n</i> = 40	BCR ¹ after pros- tatectomy <i>n</i> = 30	BCR ¹ after radiotherapy <i>n</i> = 10
Age (years)	66.5 (48 - 78)	65.50 (48 - 72)	71 (58 - 78)
PSA ² at diagnosis (ng/mL)	7.08 (5 - 13.6)	6.89 (4.14 - 45.83)	10.07 (4.62 - 55.65)
Stage			
II	46.2%	55.2%	20%
III	46.2%	34.5%	80%
IVa	7.7%	10.3%	
ISUP³			
1	22.5%	16.7%	40%
2	25%	26.7%	-
3	30%	40%	20%
4	7.5%	6.7%	10%
5	15%	10%	30%
D'Amico risk			
Intermediate risk	17.5%	20%	10%
High risk	82.5%	80%	90%
1st treatment			
Surgery	75%	100%	-
EBRT ⁴	EBRT ⁴ 22.5% EBRT ⁴ + BT ⁵ 2.5%		EBRT ⁴ 90% EBRT ⁴ + BT ⁵ 10%
Hormonal therapy			
Yes	20%	-	80%
No	80%	-	20%
Time HT⁶ (months)			
12 months	-	-	12.5%
24 months	-	-	87.5%
Surgical margins			
Positive	37.5%	15 (50%)	-
Negative	37.5%	15 (50%)	-
BCR ¹ -free interval (months)	20.5 (1 - 162)	17 (1 - 118)	85.5 (12 - 162)
PSA ² doubling time (months)	9.78 (1.31 - 75.45)	7.61 (1.51 - 33.25)	12 (0.9 - 60.85)
Comorbidities			
Diabetes mellitus	17.5%	20%	10%
Arterial hypertension	62.5%	60%	70%
Dyslipidemia	50%	60%	20%
Cardiological	20%	20%	20%

BCR¹ = biochemical recurrence; PSA² = prostate specific antigen; ISUP³ = International Society of Urological Pathology; EBRT⁴ = external beam radiotherapy; BT⁵ = brachytherapy; HT⁶ = hormonal therapy.

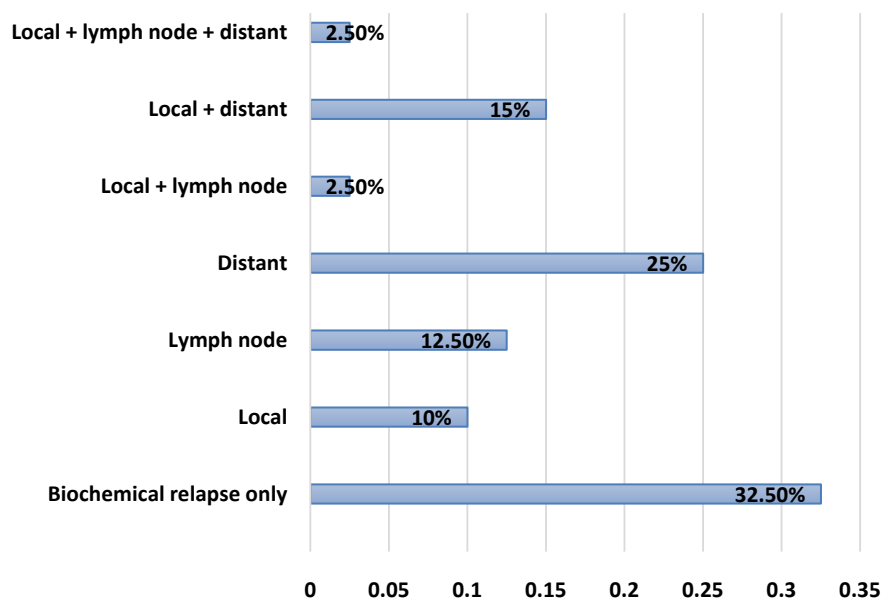


Figure 1. Recurrence site.

upon progression (1, 2, 3, 4, 5, 6 - 10, or >10) were quantified and used to recode the patients into three groups: local, lymph nodes and distant recurrence. Of the patients with local, lymph nodes, or distant relapses, 55% had ≤ 5 lesions (**Figure 2**) and within this group, only 1 lesion was observed in 68.2% of cases. Of note, 66.7% of patients with a lesion belonged to the prostatectomized subgroup. Eight of the patients had PSA levels of 0.2 - 0.5 ng/mL and presented ≤ 5 lesions, with a significance level of $p = 0.001$ (**Figure 3**). Of all the patients, 75% had previously undergone CITs (CT, bone scintigraphy, or MRI) or 18F-choline PET-CT imaging. Although the latter was considered a new generation imaging test, it is indicated in prostatectomized patients with PSA > 1 ng/mL and so we considered it a routine test for this patient profile. After comparing these prior results with those from the 18F-DCFPyL PSMA PET-CT, the latter imaging resulted in a change in staging in 66.7% of cases (**Table 2**), hence indicating that conventional CITs currently lead to underdiagnosis, especially in the surgical subgroup (65% vs. 35%, $p = 0.064$). The detection of distant disease was 65% (vs. 25% regional vs. 10% local), of which 23.1% had metastatic involvement with low PSA levels (<0.5 ng/mL). This modification in the initial staging allowed 9 patients (45%) to be treated with ablative intent using SBRT techniques (**Table 3**). Finally, in the subgroup of patients undergoing radiotherapy in which both CITs and 18F-DCFPyL PSMA PET-CT were performed, the change of staging after PET PSMA was statistically significant ($p = 0.038$; **Table 2**). The use of 18F-DCFPyL PSMA PET-CT as an initial diagnostic test detects disease in 70% of cases, showing a trend between its use and the detection of disease ($p = 0.29$).

4. Discussion

The purpose of this study was to evaluate the impact of 18F-DCFPyL PSMA

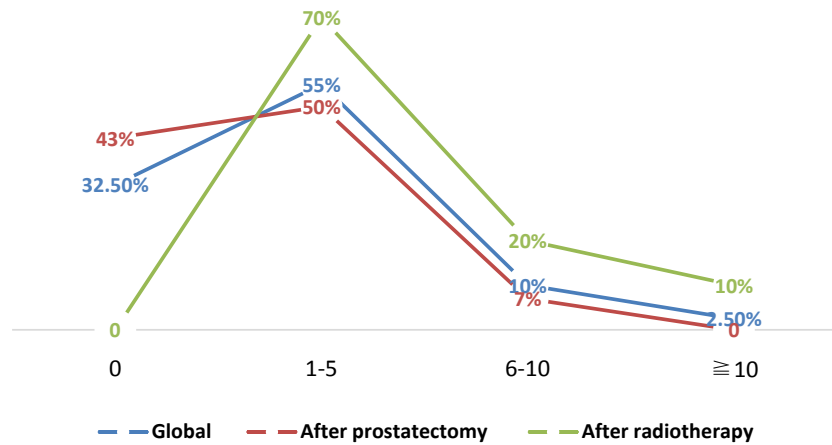


Figure 2. Number of lesions according to the primary treatment ($p = 0.008$).

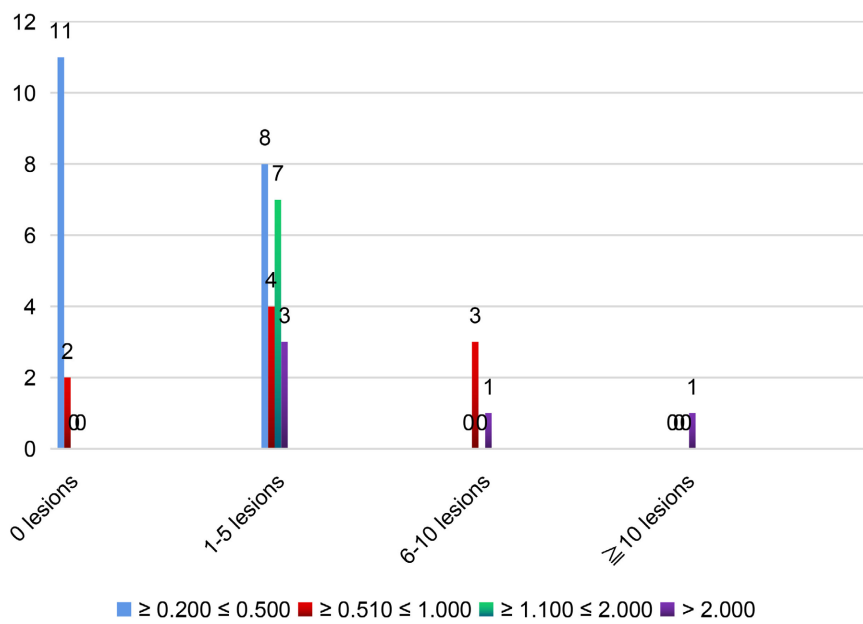


Figure 3. Number of lesions as a function of prostate specific antigen levels (ng/dL) during biochemical recurrence ($p = 0.001$).

Table 2. Staging change based on primary treatment with previous conventional tests ($p = 0.038$).

		1st tumor treatment			
		Prostatectomy	Radiotherapy	Global	
Staging change after 18F-DCFPyL PSMA PET-CT	YES	n	13	7	20
		%	43.30%	23.30%	66.70%
	NO	n	10	0	10
		%	33.30%	0.00%	33.30%
Total		n	23	7	30
		%	76.70%	23.30%	100.00%

n: number of patients, % percentage.

Table 3. Therapeutic attitude in comparable patients who have modified their staging.

	Global <i>n</i> = 20	BCR ¹ after prostatectomy <i>n</i> = 13	BCR ¹ after radiotherapy <i>n</i> = 7
RT ²	5%	7.7%	-
HT ³	30%	15.4%	57.1%
RT + HT	10%	15.4%	-
SBRT ⁴ + HT	25%	23.1%	28.6%
RT + SBRT + HT	20%	30.8%	-
Enzalutamide + HT	10%	7.7%	14.3%

BCR¹ = biochemical relapse; RT² = external radiotherapy; HT³ = hormonal therapy; SBRT⁴ = stereotactic body radiotherapy.

PET-CT on the diagnosis and therapeutic management of patients with PCa BCR after local treatment. Patients with BCR after prostatectomy and with PSA levels > 1 ng/mL usually undergo a 18F-choline PET-CT [5]. Moreover, prostatectomized patients with PSA < 0.5 ng/mL are usually administered salvage radiotherapy, without first performing complementary imaging tests. This indication assumes that most recurrences are local and mainly occur near the anastomosis. In addition, no imaging tests with sufficient sensitivity or specificity to better study these recurrences are currently available [5]. However, despite this salvage treatment, some of these patients subsequently present both regional and distant recurrences, which has led to the need for complementary studies to help determine the location of these recurrences with greater precision and thus, individualize patient treatments.

There is now sufficient bibliographic evidence demonstrating the diagnostic benefit of 68Ga-PSMA-11 PET-CT in patients with PCa BCR, to support its use in the detection of disease in these patients when PSA < 1 ng/mL, thereby making it the imaging technique of choice for this patient subgroup [19] [20]. The 18F radiotracer is even more valued than 68Ga because of its advantageous characteristics over the latter, as discussed above [21] [22]. Both 68Ga and 18F have shown acceptable sensitivity and specificity when it comes to detecting progression, even with low PSA levels [10] [23].

In Spain, 68Ga-PSMA-11 is performed in two situations: after treatment of the primary tumor in patients with BCR and PSA < 2 ng/mL, or in those with any PSA level and a recent (in the last 6 months) 18F-choline PET-CT figure negative for malignancy. Despite the proven benefits of the use of 68Ga-PSMA-11, the 18F-DCFPyL PSMA radiopharmaceutical has not yet been authorized for use in clinical practice. However, while a multicenter phase III European clinical trial (PYTHON) analyzing 18F-DCFPyL PSMA PET-CT in patients with PCa and BCR is underway [24], the Spanish Ministry of Health does allow its compassionate use when requested with a supporting report. The limited experience of Spanish centers in the management and evaluation of images using 18F-DCFPyL

PSMA PET-CT, means that it would be helpful to collect and analyze the data arising from the collective experience of our centers.

Many authors have written about recurrence sites in oligometastatic PCa patients [25] [26], although controversy remains when determining the number of lesions that should classify different patient sub-groups, the best treatment type, and therapy administration sequence. For example, a maximum of 3 or 5 lesions currently defines the intermediate stages of disease, but insufficient biological evidence is available to establish a definitive figure. In this sense, Lievens *et al.* pointed out that no validated biomarkers that differentiate the intermediate stage of oligometastatic disease are currently available. Ideal candidates to identify these patients would be microRNAs, free circulating DNA, or intratumoral heterogeneity, and would not focus exclusively on the number of lesions present [26]. In our work, we classified the number of lymphadenopathies by considering affected lymph nodes as independent lesions and not as a group when they occurred within the same lymph node region. It is possible that although only one affected region may be present in a patient with a PCa recurrence, this region may contain a conglomerate tumor, thereby increasing the overall tumor burden. By stratifying our patients according to individual lesions, we tried to extrapolate the theoretical tumor volume more accurately. Recent clinical trials have demonstrated the clinical benefit of treating patients with this oligometastatic profile in terms of increased BCR-free survival and metastatic progression-free survival [27] [28].

Although the study by Rousseau *et al.* [21] had a larger sample size, the characteristics of the patients they included were like those included in this present study, especially in terms of the lesion distribution in patients with ≤ 5 lesions. In addition, Giesel *et al.* [22] presented similar levels of bone recurrence after ^{18}F -DCFPyL PSMA PET-CT as we report here. When we analyzed our subgroups in greater detail, the patients that had undergone irradiation presented more progressions, which ties in with the fact that the characteristics of these patients (e.g., ISUP 4 - 5, higher mean age) tended to be associated with a poorer prognosis. The patients in our sample were hormone-sensitive, except for one who was castration-resistant. Many studies published in the academic literature have examined these two profiles [21], but in this current work, we wanted to focus on a single, more homogeneous group.

Our objective was to diagnose a subgroup of patients who presented a low disease burden that could be treated with ablative intention rather than exclusively with hormonal therapy. Thus, by using ^{18}F -DCFPyL PSMA we obtained a more precise diagnosis in 66.7% of our cohort, leading to a change in treatment in oligometastatic patients and reaffirming the data already described in the literature [21] [29]. This greater specificity in categorising patients allows us to intensify our therapeutic efforts and thus theoretically prolong progression-free survival and delay the initiation of systemic treatment. We identified a subgroup of patients with PSA < 0.5 ng/mL who presented lymph node or distant progression that would have been understaged and therefore undertreated had we not

performed an 18F-DCFPyL PSMA PET-CT. Indeed, there was a tendency towards significance ($p = 0.29$) among the patients who only underwent 18F-DCFPyL PSMA PET-CT imaging. The TITAN study [30] suggests that this diagnostic test will allow the early detection of patients with hormone-sensitive metastatic PCa, allowing them to start timely treatment with second-generation hormone therapy, thereby directly impacting their overall survival.

Regarding the limitations of our study, first, this was a retrospective, descriptive, observational study with a small sample size. The fact that most, but not all, of the patients we included had previously undergone CITs (75%) reduced the value of our data analysis because there were no results to compare our data to in 25% of the cases. As an initial diagnostic test, 18F-DCFPyL PSMA PET-CT may involve a bias, however, this test may be useful when faced with a clinical picture in which there is BCR in the absence of correlation with conventional CITs along with the clinical deterioration of the patient, which therefore corresponds to a decline in quality of life. Confirmation of the diagnostic benefit of this imaging test in patients with BCR will require the development of randomized studies to compare this procedure with CITs and to quantify the real impact of changing patient staging based on 18F-DCFPyL PSMA PET-CT imaging in terms of BCR-free survival and overall survival. This work, and other similar studies are currently being planned in the hospital centers involved in this work.

5. Conclusion

18F-DCFPyL PSMA PET-CT could lead to a change in the management of patients with BCR. This test promotes the early diagnosis of oligometastatic relapses, especially in patients with PSA levels < 0.5 ng/mL, allowing physicians to make better therapeutic decisions for these patients.

Compliance with Ethical Standards

The research ethics committee approved the study at both hospitals.

Research with Human and/or Animal Participants

The authors declare that no animal research was carried out.

Conflicts of Interest

All the listed authors gave their approval for the submission of the article; none of them have any potential conflicts of interest associated with this research.

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