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# Role of $^{18}$F-FCH PET/CT in Detecting Recurrences of Prostate Cancer After Curative Treatments

## *Küratif Tedavilerden Sonra Prostat Kanseri Nükslerinin Tespitinde $^{18}$F-FCH PET/BT'nin Rolü*

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### Abstract

**Objectives:** To evaluate the role of $^{18}$F-fluorocholine ($^{18}$F-FCH) positron emission tomography/computed tomography (PET/CT) in prostate cancer (PC) patients with biochemical recurrence who were submitted to different curative treatments.

**Methods:** Seventy-five patients with PC who underwent $^{18}$F-FCH PET/CT for biochemical recurrence were retrospectively analyzed to distinguish patients who were submitted only to prostatectomy (PR group), only to radiotherapy (RT) on prostate with curative intent (RT group), and to both (PR + RT group). Correlations between $^{18}$F-FCH PET/CT and outcome and between prostate-specific antigen (PSA) values and sites and the number of metastases were analyzed. The performance of $^{18}$F-FCH PET/CT in relation to the PSA value and of maximum standardized uptake value ($SUV_{max}$) value in relation to patient outcome were assessed by receiver operating characteristic (ROC) curves.

**Results:** $^{18}$F-FCH PET/CT relapses mostly involved lymph nodes, bones, and prostate bed. K-cohen test showed moderate agreement with the outcome in the whole population and in the PR group, whereas in the RT group it was perfect and in PR + RT fair. A statistically significant difference in PSA values was observed in the presence of lymph node metastases and with multiple metastases. ROC curves showed PSA cut-off values of 1.96 ng/dL, 1.95, 1.81, and 2.96, respectively, in the whole population, PR, RT and PR + RT group. $SUV_{max}$ cut-off values of 3.75, 3.45, and 4.7 were described in the whole population, PR group, and PR + RT group.

**Conclusion:** The study confirms that $^{18}$F-FCH PET/CT is still valid in PC patients with suspected biochemical recurrence. Therefore, we can affirm that it still makes sense to perform it both with high PSA values and with lower values when prostate-specific membrane antigen tracers are not available.

**Keywords:** $^{18}$F-FCH PET/CT, prostate cancer, biochemical recurrences, radical prostatectomy, curative radiotherapy

### Öz

**Amaç:** Farklı küratif tedavilere yönlendirilmiş olan biyokimyasal nükslü prostat kanseri (PK) olan hastalarda $^{18}$F-florkolin ($^{18}$F-FCH) pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) rolünü değerlendirmektir.

**Yöntem:** Biyokimyasal nüks için $^{18}$F-FCH PET/BT uygulanan 75 PK'li hasta, yalnızca prostatektomi (PR grubu) uygulanan, yalnızca küratif amaçlı prostat radyoterapisi (RT) uygulanan (RT grubu) ve her ikisi birden uygulanan hastalar (PR + RT grubu) olmak üzere üç gruba ayrılarak retrospektif

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olarak analiz edildi. $^{18}$F-FCH PET/BT ile sonlanım arasındaki korelasyon ve prostat spesifik antijen (PSA) değerleri ile metastaz bölgeleri ve sayısı arasındaki korelasyon analiz edildi. $^{18}$F-FCH PET/BT'nin PSA değerine göre performansı ve $SUV_{maks}$ değerinin hasta sonlanımına göre performansı alıcı işletim karakteristik (ROC) eğrileri ile değerlendirildi.

**Bulgular:** $^{18}$F-FCH PET/BT relapsları çoğunlukla lenf nodlarını, kemikleri ve prostat yatağını tutuyordu. K-cohen testi tüm popülasyonda ve PR grubunda sonlanımla orta derecede uyum gösterirken, RT grubunda mükemmel ve PR + RT grubunda iyi uyum gösterdi. Lenf nodu metastazı varlığında ve çoklu metastaz varlığında PSA değerlerinde istatistiksel olarak anlamlı farklılık gözlendi. ROC eğrileri tüm popülasyonda, PR, RT ve PR + RT gruplarında sırasıyla 1,96 ng/dL, 1,95, 1,81 ve 2,96 PSA kesme değerlerini gösterdi. Tüm popülasyonda, PR grubunda ve PR + RT grubunda $SUV_{maks}$ kesme değerleri 3,75, 3,45 ve 4,7 olarak gösterildi.

**Sonuç:** Çalışma, biyokimyasal nüks şüphesi olan PK'li hastalarda $^{18}$F-FCH PET/BT'nin hala geçerli olduğunu doğrulamaktadır. $^{18}$F-FCH PET/BT'nin kullanımının hem yüksek PSA değerlerinin varlığında hem de prostat spesifik membran antijeni izleyicileri mevcut olmadığında daha düşük PSA değerlerinin varlığında hala anlamlı olduğu doğrulanmıştır.

**Anahtar kelimeler:** $^{18}$F-FCH PET/BT, prostat kanseri, biyokimyasal nüksler, radikal prostatektomi, küratif radyoterapi

## Introduction

Prostate cancer (PC) is the most frequent cancer in men and the third leading cause of death in developed countries. Multiple treatment options are available depending on several factors, both patient- and disease-related. Curative treatment options include surgery and radiation therapy. In addition, in the modalities of surgical and radiation therapy, the technique options vary. Because of the various aspects that can influence the therapeutic choice, an unequivocal estimate of the possibility of recurrence cannot be performed (1).

In patients with PC, recurrences after radical treatment can occur in 20-50% of patients after radical prostatectomy (PR) and in 30-40% of patients after radiotherapy (RT) (2).

Detection and localization of all recurrences is important for selecting the appropriate treatment. After curative treatments, the state of the disease is monitored by prostate-specific antigen (PSA) setting. When PSA levels increase, there is a need to confirm the suspicion of recurrence and to assess whether the disease is localized or metastatic (1).

Imaging methods are needed to detect and localize recurrences, and to conventional methods, nuclear medicine offers numerous possibilities for restaging PC patients. Today, with technological progress, numerous radiopharmaceuticals have demonstrated high diagnostic performance in PC patient management. However, their distribution is not feasible in all nuclear medicine operative units in western countries and even less in the remaining ones.

Among all positron emission tomography/computed tomography (PET/CT) whole body techniques, the use of $^{18}$F-fluorocholine ($^{18}$F-FCH) until the last decade was celebrated as the most important and most innovative radiopharmaceutical for the evaluation of PC patients (3).

$^{18}$F-FCH is a substrate for phosphatidylcholine synthesis, a cell membrane component with increased biosynthesis in tumor tissues; the upregulation of choline kinase activity induced by cancer results in higher choline uptake by neoplastic cells. Several studies have investigated the role of $^{18}$F-FCH PET/CT in the management of PC, and the evaluation of recurrence after radical treatment has emerged as the main clinical application (1,2).

Currently, $^{18}$F-FCH PET/CT is in the background compared to the new radiopharmaceutical, but all advantages such as easier production, long half-life, and easy supply are still valid (1,3).

On the basis of these statements, the aim of this study was to analyze the state of the art in our territorial reality with the aim of evaluating the role of $^{18}$F-FCH PET/CT in the detection of relapses in patients with localized PC treated with PR and/or RT.

## Materials and Methods

Seventy-five patients with a diagnosis of PC (adenocarcinoma) who underwent $^{18}$F-FCH PET/CT for the biological suspicion of PC relapse from October 2020 to November 2021 were included in the study. A retrospective observational analysis was performed, and the institutional review board did not require ethical committee approval for the review of patient files. All patients provided written informed consent to the use of their data for clinical research in an anonymous form.

Fourty-one/75 patients were previously submitted only to PR (PR group), 13/75 were submitted only to RT on the prostate with curative intent (RT group), and 21/75 patients were submitted to both procedures with curative intent (PR + RT group).

The inclusion criteria consisted of: histologically proven PC, treatment with curative intent (PR and/or RT), and

biochemical recurrence as defined by the guidelines of the European Association of Urology (4).

Patients with distant metastases at diagnosis or with non-diagnostic scans were excluded. The mean age of the patients was 71 years (range 42-87 years old) and the mean Gleason score at diagnosis was 7 (range 5-9). The mean time between treatment and $^{18}$F-FCH PET/CT was 6 years (range 1-16 years), and the mean PSA level at the time of $^{18}$F-FCH PET/CT was 5.85 ng/mL (range 0.02-79 ng/mL, median 1.97 ng/mL).

### $^{18}$F-FCH PET/CT

$^{18}$F-FCH PET/CT preparations consisted of a 6-h fast. A dose of approximately 3-4 MBq/kg body weight (range 240-390 MBq/kg) of $^{18}$F-FCH PET/CT was intravenously administered. All scans were obtained using a hybrid PET/CT scanner (Discovery 710, GE, General Electrics, Milwaukee, WI, USA). After 5 min post-injection, early $^{18}$F-FCH PET/CT images of the pelvis were acquired targeting the prostate area, followed by a whole-body image acquisition after 60 min, from the skull base to the proximal third of the femurs (5-6 bed positions). A 3D acquisition mode PET scan was performed for the same longitudinal coverage (2.5 min per bed position). The PET data were reconstructed over a 128 matrix with a pixel size of 4.75 mm and a slice thickness of 2 mm. The following co-registered CT parameters were used: pitch 0.98, gantry rotation speed of 0.5 s/rot, 120 kV, and modulated tube current of 140 mA. CT images were used for image fusion and anatomical localization and for attenuation correction of emission data.

### Image Analysis

Image analysis was performed using a dedicated workstation (AW Server 4.7, General Electrics, Milwaukee, WI, USA). $^{18}$F-FCH PET/CT scans were independently evaluated by two nuclear medicine physicians with at least 5 years of experience in image reading and who were aware of clinical data. In the event of disagreement, a third nuclear medicine physician's opinion was reached.

Maximum intensity projection, PET, CT, and PET/CT fused images in different planes (axial, sagittal, and coronal) were visualized simultaneously to correctly interpret the scans. Examinations were considered positive in the presence of focal areas of detectable increased tracer uptake, visually more intense than the background, not correlating with physiological tracer uptake and inflammatory articular processes, with or without any underlying lesion identified on the co-registered CT (5). The semiquantitative parameter maximum standardized uptake value ($SUV_{max}$) was collected in all visualized lesions.

### Validation of Results and Outcomes

All patients were followed for at least 1 year after $^{18}$F-FCH PET/CT, and data on outcome were collected. The final response regarding the presence of relapses was obtained from the results of surgical procedures performed and/or clinical instrumental follow-up.

### Statistical Analysis

Analyses were performed in the entire population and in the 3 subgroups (PR, RT and PR + RT). Quantitative variables are expressed as mean standard deviation (SD). Categorical variables are presented with absolute and relative frequencies.

Chi-square and Kruskal-Wallis tests were applied to establish if the groups were comparable. The K-cohen test was applied for correlation between $^{18}$F-FCH PET/CT results and outcome. The Mann-Whitney U test was used to compare the differences between continuous non-normally distributed variables such as PSA values and sites and the number of metastases detected at $^{18}$F-FCH PET/CT and patient outcome. The performance of $^{18}$F-FCH PET/CT in relation to the PSA value was assessed using the receiving operating characteristic (ROC) curve generated by plotting sensitivity versus specificity. The performance of the $SUV_{max}$ value in relation to the patient outcome was also assessed using the ROC curve; a cut-off value was also identified. Statistical significance was assumed for p-values 0.05. All statistical analyses were performed using SPSS statistical software, version 25 (IBM Corporation, Armonk, NY, USA).

## Results

The comparison performed for the main clinical variables among the total population and the groups showed that there were no statistically significant differences; therefore, the groups were comparable even if numerically different (Table 1).

### Lesions Distribution

$^{18}$F-FCH PET/CT was positive in 46/75 (61.3%) patients and negative in 29/75 (38.7%) patients. On the 46 positive $^{18}$F-FCH PET/CT, 6/46 (13%) showed only local recurrences, 24/46 (52.2%) showed lymph node involvement, 7/46 (15.2%) showed bone metastases, 1/46 (2.2%) showed both local and lymphatic involvement, 5/46 (10.9%) showed lymphatic and bone involvement, and 3/46 (6.5%) patients showed both bones and other distant metastases in the lung.

Considering the 41 patients in the PR group, $^{18}$F-FCH PET/CT was positive in 24/41 (58.5%) patients, whereas it was negative in 17/41 (41.5%) patients. On the 24

| Table 1. Characteristics of the whole population | | | | | |
|---|---|---|---|---|---|
| | **Total (n=75)** | **PR (n=41)** | **RT (n=13)** | **PR + RT (n=21)** | **p-value** |
| **Age** | | | | | |
| Mean ± SD<br>Median (range) | 71±7.20<br>70 (42-87) | 71±7.78<br>71 (42-87) | 71±7.10<br>70 (62-83) | 70±6.28<br>70 (47-79) | 0.600* |
| **Gleason score, n (%)** | | | | | |
| <8<br>≥8 | 47 (63%)<br>28 (37%) | 28 (68%)<br>13 (32%) | 9 (69%)<br>4 (31%) | 10 (48%)<br>11 (52%) | 0.243** |
| **PSA, ng/mL** | | | | | |
| Mean ± SD<br>Median (range) | 5.74±12.71<br>1.94 (0.02-79) | 4.84±12.93<br>1.43 (0.02-79) | 4.25±3.66<br>2.56 (0.20-10.70) | 8.41±15.66<br>2.50 (0.20-54.20) | 0.132* |

*Kruskal-Wallis test; **Chi-square test, SD: Standard deviation, PR: Prostatectomy, RT: Radiotherapy, PSA: Prostate-specific antigen

positive $^{18}$F-FCH PET/CT, 5/24 (20.8%) showed only local recurrences, 11/24 (45.7%) showed only nodal lymph node involvement, 1/24 (4.2%) showed only bone metastases; 2/24 (8.4%) showed both local and lymphatic involvement, 4/24 (16.7%) showed lymphatic and bone involvement, and 1/24 (4.2%) patient showed local, node, and bone metastases (Figure 1).

Considering the 13 patients in the RT group, $^{18}$F-FCH PET/CT was positive in 10/13 (77%) patients, while it was negative in 3/13 (23%) patients. On the 10 positive $^{18}$F-FCH PET/CT images, 3/10 (30%) showed nodal lymph node involvement, 5/10 (50%) bone metastases (Figure 2), 1/10 (10%) showed both local and bone involvement, and 1/10 (10%) showed both bones and lung metastases.

Considering the 21 patients in the PR + RT group, $^{18}$F-FCH PET/CT was positive in 12/21 (57.2%) patients, whereas it was negative in 9/21 (42.8%) patients. On the 12 positive $^{18}$F-FCH PET/CT images, 1/12 (8.3%) showed only local recurrences, 9/12 (75.1%) showed nodal lymph node involvement, 1/12 (8.3%) bone metastases, and 1/12 (8.3%) patient showed both bones and distant metastases in the lung.

The distribution of relapses in $^{18}$F-FCH PET/CT in all patients and as a function of the treatment performed is shown in Figure 3.

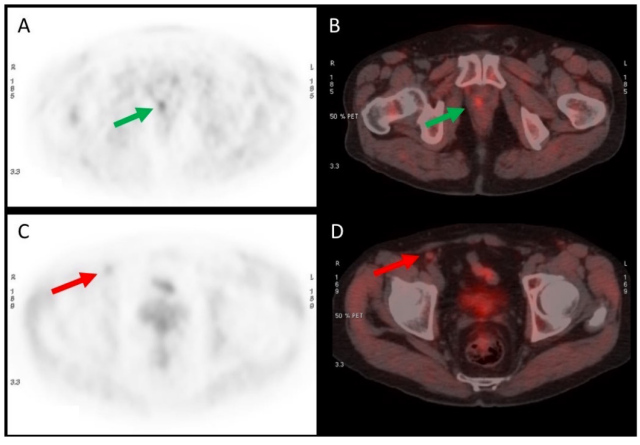


**Figure 1.** Seventy-eight years old man submitted 13 years before to PR for PC Gleason 7. He performed $^{18}$F-FCH PET/CT because of PSA levels of 6.03 ng/dL. Axial PET (A) and fused images (B) showed local relapse (green arrows, $SUV_{max}$: 3.2) and (C, D) involvement of the right iliac lymphnode ($SUV_{max}$: 2.0, red arrows)
PR: Prostatectomy, PC: Prostate cancer, PET/CT: Positron emission tomography/computed tomography, PSA: Prostate-specific antigen, $SUV_{max}$: Maximum standardized uptake value, $^{18}$F-FCH: $^{18}$F-fluorocholine

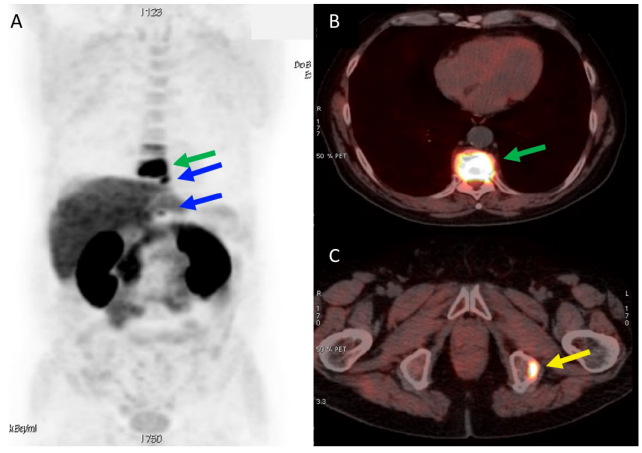


**Figure 2.** Sixty-four years old man submitted 6 years before to RT for PC Gleason 7. He performed $^{18}$F-FCH PET/CT because of PSA levels of 2.56 ng/dL. MIP (A) and fused images (B, C) showed multiple bone lesions such as in D10 vertebra ($SUV_{max}$: 23.5, green arrow), D9 and D12 vertebrae (blue arrows) and left ischium ($SUV_{max}$: 20.1, yellow arrow)
RT: Radiotherapy, PC: Prostate cancer, PET/CT: Positron emission tomography/computed tomography, PSA: Prostate-specific antigen, MIP: Maximum intensity projection, $SUV_{max}$: Maximum standardized uptake value, $^{18}$F-FCH: $^{18}$F-fluorocholine

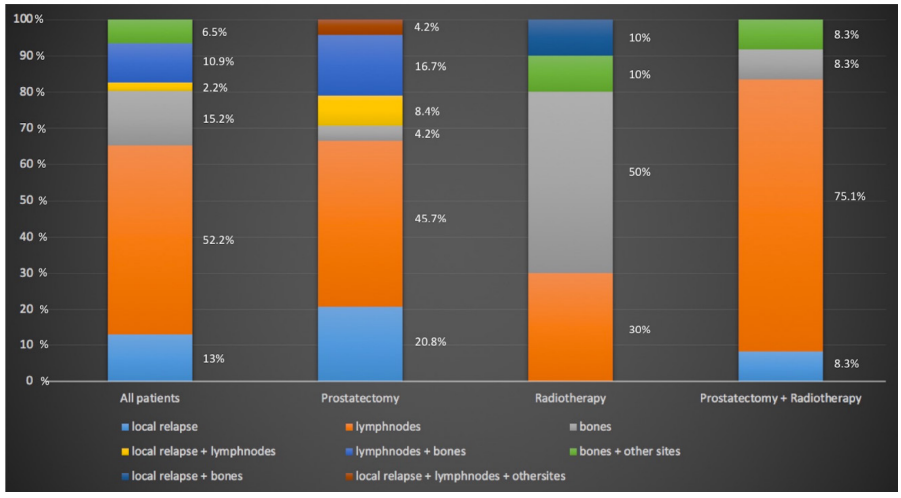


**Figure 3.** Distribution of relapses in [18]F-FCH PET/CT in all patients and as a function of the treatment performed
PET/CT: Positron emission tomography/computed tomography, [18]F-FCH: [18]F-fluorocholine

## Outcome

At the follow-up, 50/75 (66.7%) patients were involved by relapses and/or metastases of PC; in the PR group, 25/41 (61%) patients, in the RT group, 10/13 (77%) patients and in PR + RT group 15/21 (71.4%) patients. Results concerning the agreement between [18]F-FCH PET/CT and the outcome are reported in Table 2.

## PSA Level Evaluation

Considering the total population, mean PSA values were 9.34 ng/mL (range 0.36-79) in patients with positive concordance, 1.60 ng/dL (range 0.17-5.35) in patients with [18]F-FCH PET/CT positivity not confirmed at the follow-up, 1.20 (range 0.02-3.20) in patients concordant in excluding the disease, and 1.63 (range 0.92-2.50) in patients for whom relapses were not detected at [18]F-FCH PET/CT. The Mann-Whitney U test showed PSA levels higher in patients with positive [18]F-FCH PET/CT with difference statistical significant (p<0.0001) also in lymph nodes (p=0.002) and bone evaluation (p=0.007) and in patients with equal or more than 3 lesions (p<0.0001) regardless of the site.

In the PR group, mean PSA values were 8.50 ng/mL (range 0.36-79.00) in patients with positive concordance, 1.65 ng/mL (range 0.17-5.35) in patients with [18]F-FCH PET/CT positivity not confirmed at follow-up, 1.09 ng/mL (range 0.02-3.20) in patients concordant in excluding the disease, and 1.70 ng/mL (range 0.92-2.40) in patients for whom relapses were not detected at [18]F-FCH PET/CT. The Mann-Whitney U test showed PSA levels higher in patients with positive [18]F-FCH PET/CT with difference statistically significant (p=0.03) also in lymph nodes (p=0.021) and bone evaluation (p=0.038) and in patients with equal or more than 3 lesions (p=0.040) regardless of the site.

**Table 2. [18]F-FCH PET/CT and outcome agreement**

| | Positive concordant | Negative concordant | Discordant ([18]F-FCH PET/CT positivity not confirmed) | Discordant (relapses not detected at [18]F-FCH PET/CT) | |
|---|---|---|---|---|---|
| Total (n=75) | 40 (53.4%) | 19 (25.3%) | 6 (8%) | 10 (13.3%) | K=0.538 (95% CI: 0.341-0.736) Moderate |
| PR (n=41) | 20 (48.8%) | 12 (29.3%) | 4 (9.7%) | 5 (12.2%) | K=0.544 (95% CI: 0.282-0.806) Moderate |
| RT (n=13) | 10 (77%) | 3 (23%) | - | - | Perfect |
| PR + RT (n=21) | 10 (47.7%) | 4 (19%) | 2 (9.5%) | 5 (23.8%) | K=0.290 (95% CI: -0.111-0.690) Fair |

PR: Prostatectomy, RT: Radiotherapy, PET/CT: Positron emission tomography/computed tomography, [18]F-FCH: [18]F-fluorocholine, CI: Confidence interval

In the RT group, mean PSA values were 5.26 ng/mL (range 0.84-10.70) in patients with positive concordance and 0.89 ng/mL (range 0.2-1.33) in patients with concordance after excluding the disease. The Mann-Whitney U test showed that PSA levels were higher in patients with positive [18]F-FCH PET/CT with difference statistical significant (p=0.028) regardless of the sites and number of lesions.

In the PR + RT group, mean PSA values were 15.74 ng/mL (range 1.18-54.20) in patients with positive concordance, 1.47 ng/mL (range 0.90-2.04) in patients with [18]F-FCH PET/CT positivity not confirmed at follow- up, 1.96 ng/mL (range 0.20-2.92) in patients with concordance in excluding the disease, and 1.54 ng/mL (range 1.04-2.50) in patients for whom relapses were not detected at [18]F-FCH PET/CT. The Mann-Whitney U test showed PSA levels higher in patients with positive [18]F-FCH PET/CT with difference statistically significant (p=0.028) also in lymph nodes (p=0.016) and in patients with equal or more than 3 lesions (p=0.020) regardless of the site.

ROC curves elaborated to identify the optimal cut-off for predicting [18]F-FCH PET/CT positivity in all the groups analyzed are reported in Figure 4, while their results are reported in Table 3.

### $SUV_{max}$ Analysis

The mean $SUV_{max}$ values in the [18]F-FCH PET/CT-positive patients were as follows: in the whole population, 7.8 (range 1.6-27.1); in the PR group, 6.8 (range 3.2-16.4); in the RT group, 9.2 (range 5.2-13.2); and in the PR + RT group, 6.0 (range 2.0-9.7).

ROC curves elaborated to identify the optimal cut-off of $SUV_{max}$ in predicting the presence of the disease at the outcome are reported in Figure 5, while their results are reported in Table 4.

## Discussion

Considerable progress has been made in the field of radical treatments for locally advanced PC, and currently, there are numerous choices that allow customizing the therapy on the basis of the characteristics of the disease and the patient's needs.

Radical surgical procedures have diversified, such as RT, for which technological advances have made it possible to create increasingly sophisticated protocols. Advances in external beam RT delivery techniques, such as intensity modulated RT and volumetric arc RT, allow delivery of the maximum dose to the target volume while sparing surrounding healthy tissue, optimizing response to treatment, and reducing genitourinary and intestinal

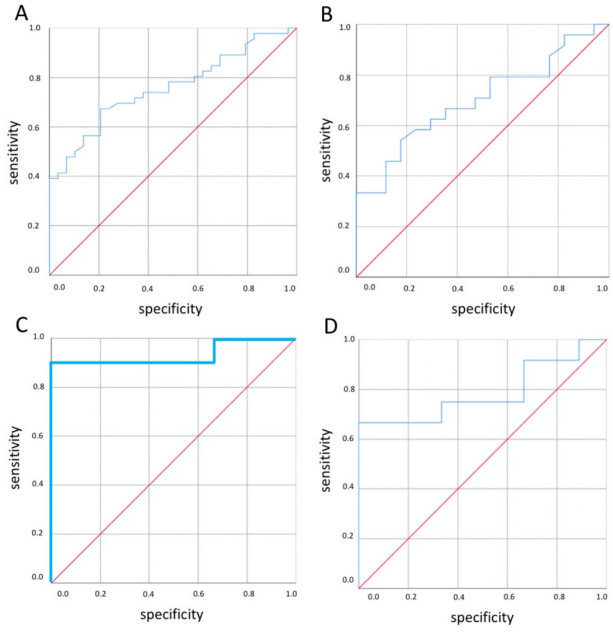


**Figure 4.** ROC analysis of PSA values optimal cut-off of for predicting [18]F-FCH PET/CT positivity; A: total population; B: patients submitted only to PR; C: patients submitted only to RT; D: patients submitted to PR + RT ROC: Receiver operating characteristic, PET/CT: Positron emission tomography/computed tomography, PSA: Prostate-specific antigen, PR: Prostatectomy, RT: Radiotherapy, [18]F-FCH: [18]F-fluorocholine

**Table 3. Results about PSA levels in predicting [18]F-FCH PET/CT positivity**

| | Cut-off | Sensitivity | Specificity | |
|---|---|---|---|---|
| Total (n=75) | 1,965 ng/mL | 67.4% | 79.3% | AUC =0.757<br>95% CI 0.651-0.864 |
| PR (n=41) | 1.95 ng/mL | 54.2% | 82.4% | AUC =0.701<br>95% CI 0.542-0.860 |
| RT (n=13) | 1.81 ng/mL | 90% | 100% | AUC =0.933<br>95% CI 0.789- 1.000 |
| PR + RT (n=21) | 2.96 ng/mL | 66.7% | 100% | AUC =0.787<br>95% CI 0.585- 0.990 |

PR: Prostatectomy, RT: Radiotherapy, PSA: Prostate-specific antigen, PET/CT: Positron emission tomography/computed tomography, AUC: Area under the curve, CI: Confidence interval, [18]F-FCH: [18]F-fluorocholine

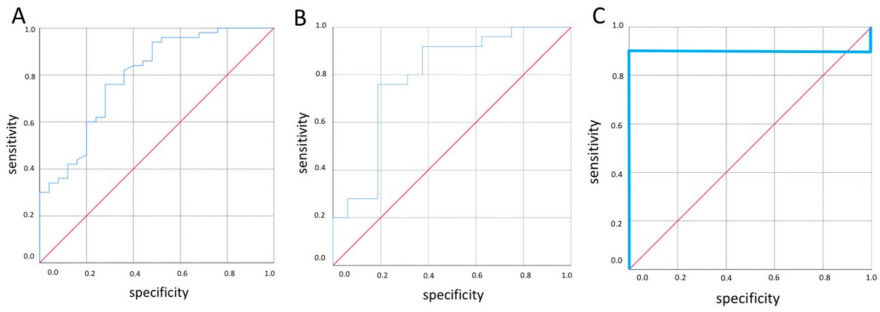


**Figure 5.** ROC analysis of the $SUV_{max}$ optimal cut-off in predicting the presence of the disease at the outcome; A: total population; B: patients submitted only to PR; C: patients submitted to PR + RT
ROC: Receiver operating curve, $SUV_{max}$: Maximum standardized uptake value, PR: Prostatectomy, RT: Radiotherapy

| **Table 4. Results about $SUV_{max}$ in predicting the presence of the disease at the outcome** | | | | |
|---|---|---|---|---|
| | **Cut-off** | **Sensitivity** | **Specificity** | |
| Total (n=75) | 3.75 | 87.5% | 83.3% | AUC =0.908 (95% CI 0.802-1.000) |
| PR (n=41) | 3.45 | 90% | 75% | AUC =0.850 (95% CI 0.629-1.000) |
| PR + RT (n=21) | 4.7 | 90% | 100% | AUC =0.900 (95% CI 0.714-1.000) |
| PR: Prostatectomy, RT: Radiotherapy, AUC: Area under the curve, CI: Confidence interval, $SUV_{max}$: Maximum standardized uptake value | | | | |

inflammation. In recent years, RT with curative intent has expanded the fields of application, and approximately 41% of PC patients are treated by it alone (1,6).

Recurrence after curative treatment varies according to the procedure applied although the level of risk retains the most important role. Disease recurrence occurs in approximately 30% of patients who were treated for PC. Agarwal et al. (7) analyzed the United States database of "The Cancer of the Prostate Strategic Urological Research Endeavour" and reported 23% rate of recurrences in patients submitted to PR and 63% in the RT group. They also reported that their results are in line with the literature for the PR group (range 15-33%) and higher in the RT group (range 37-48%) (7). This therefore makes ever present the necessity of diagnosing the presence of relapses. Our results showed relapses in 61% of patients in the PR group and 77% in the RT group, while it was 66.7% in the entire population analyzed. However, these higher results are certainly influenced by the selection of patients who were submitted to [18]F-FCH PET/CT for biochemical recurrence.

It is well known that metabolic/functional changes commonly precede anatomical changes; thus, PET/CT is being increasingly used in clinical oncological settings (8). In this regard, [18]F-FCH PET/CT has emerged as a method for disease localization in PC patients with biochemical relapse after primary treatment. The greatest advantage of PET/CT is that it is a whole-body, non-invasive imaging capable of assessing disease recurrence in multiple anatomical sites. Currently, even though prostate-specific membrane antigen (PSMA) tracers are downsizing the importance of the clinical use [18]F-FCH PET/CT, the literature available for it is much more abundant than for recent PSMA tracers; thus, it is much more supported for clinical routine execution. The more recent guidelines still propose [18]F-FCH PET/CT in patients with PC after PR and/or RT with increasing PSA levels (9,10).

In early studies from 1998, [18]F-FCH PET/CT showed several positive detection rates (30-80% of patients) because of the heterogeneity of the sample population recruited. In 2003, there was a boom in clinical studies in patients with biochemical recurrences after PR and less frequently after RT, but these studies were abandoned in the next decade (11). The aim of this study was to evaluate the role of [18]F-FCH PET/CT in PC patients with suspected recurrences by distinguishing them by type of treatment performed. Our results confirm better results in the positive detection rate of metastases in all groups analyzed, showing results from 47.7% in patients of the PR + RT group to 77% in patients of the RT group.

The prostate bed, lymph nodes (mostly pelvic ones), and the skeleton are the most frequently affected sites of relapses, relating to 34%, 66%, and 29% of PC patients, respectively.

Local recurrences occur in 30-50% of patients after PR, but the $^{18}$F-FCH PET/CT evaluation of the postsurgical prostatic bed may be limited by the small size of recurrent lesions and the presence of radioactive urine; even after RT, the inflammatory uptake at the prostatic site can be limited. In the case of recurrence in the prostatic bed, $^{18}$F-FCH PET/CT reached a pooled sensitivity of 75.4% (66.9-82.6%) and a pooled specificity of 82.0% (68.6-91.4%) (12,13,14,15).

Evangelista et al. (13), in their meta-analysis of literature from 2000 to 2013, concluded that $^{18}$F-FCH PET/CT was highly sensitive and specific, especially for lymph node evaluation in PC patients with biochemical recurrence. In lymph node metastases, $^{18}$F-FCH PET/CT showed a pooled sensitivity of 100% (90.5-100%) and a pooled specificity of 81.8% (48.2-97.7%); despite these data, false positives may be possible because of inflammatory changes or artifacts of small bowel activity (13,16,17).

Skeletal metastases are more frequent in the spine and pelvis, and $^{18}$F-FCH PET/CT showed elevated specificity (11).

The pattern of relapse sites of $^{18}$F-FCH PET/CT observed in this analysis was consistent with the natural spread of the disease involving predominantly lymph nodes followed by bones and the prostate bed, both in the whole population and in the groups analyzed. It should be noted that there were no discrepancies in the identification and interpretation of bone lesions in this analysis.

In this study, only 6/75 patients resulted in false positives, 4 of them were in the PR group and 2 in the PR + RT group; in all of these patients, single lymph nodes in the iliac or inguinal region were indicated as sites of disease, but they were reactive on biopsies results.

Ten/75 patients were false negative, 5 of them were in the PR group and 5 in the PR + RT group; the patients of the PR group had PSA values between 0.92 and 2.40 ng/dL when they underwent $^{18}$F-FCH PET/CT, and the subsequent follow-up showed the presence of local recurrence, whereas in the 5 patients of the PR + RT group (PSA between 1.04 and 2.00 ng/dL), subsequent investigations showed the presence of disease in the iliac lymph nodes.

The most effective factor that linearly influences the sensitivity of $^{18}$F-FCH PET/CT is the PSA level.

Conventionally, increasing PSA levels are considered the most sensitive tool for detecting PC recurrence, even if it cannot distinguish between local and distant recurrences (13). The definition of biochemical recurrence differs according to the primary treatment: in patients treated with PR, PSA levels greater than 0.2 ng/mL and rising on at least two consecutive measurements performed 3 months apart signify biochemical failure; in patients treated with RT, PSA value 2 ng/mL higher than the lowest (nadir) post-therapeutic represents biochemical failure (18,19). For this reason, in the population analyzed, the PSA levels reported have wide variability.

Numerous articles have shown a significant relationship between $^{18}$F-FCH PET/CT positive detection rate and PSA value with a trend toward a more "systemic" disease with increasing PSA; however, there is not a cut-off value that can distinguish local or distant metastases (1,13). Chondrogiannis et al. (1) reported an elevated positive detection rate for PSA levels higher than 6 ng/mL (100%). Giovacchini et al. (12) showed that the detection rate reached a plateau for higher PSA values (84% for PSA >10 ng/mL), but Graziani et al. (20) in their most numerous study showed a fair positive detection rate of about 55% with a mean PSA of 4.9 ng/mL (1).

$^{18}$F-FCH PET/CT positive detection rate worsens for PSA values within 1 and 2 ng/mL (about 45.9% and 54%) or mean values around 2.0 ng/mL (67%) after PR. A low detection rate is observed for PSA values less than 1.0 ng/mL (7%) (12,21).

Studies that performed ROC curves revealed similar results for PSA values distinguishing positive $^{18}$F-FCH PET/CT from negative independently by the curative treatment performed: Giovacchini et al. (12) showed a best value of 1.37 ng/mL in patients submitted to PR and Graziani et al. (20) showed a value of 1.16 ng/mL in PR + RT patients. Summarizing all these results, it can be deduced that $^{18}$F-FCH PET/CT should not be restricted to patients with PSA >5 ng/mL; performing $^{18}$F-FCH PET/CT with PSA levels between 1 and 2 ng/mL may imply the possibility of false negatives; instead, for patients with PSA lower than 1 ng/mL, the indication for $^{18}$F-FCH PET/CT should be critically discussed in the context of multidisciplinary tumor boards. In any case, the minimum cut-off value that makes $^{18}$F-FCH PET/CT invalid in restaging PC patients is not established (1,12,13,22,23).

In our analysis, a mean PSA value of 9.34 ng/dL was observed in true positive patients even if the range was between 0.36 and 79; this value was 8.5 ng/dL in the patients of the PR group with the same range, whereas in the patients of the RT group, the PSA mean value was 5.26 ng/dL and in the PR + RT group it was 15.74 ng/dL.

According to literature results in this study's whole population, a statistically significant difference in PSA values emerged in the case of the presence of multiple metastatic lesions and lymph node metastases, which were in any case the most frequently described sites in our population.

Despite the high mean PSA values described, the ROC curves in our groups of patients showed cut-off values of

1.96 ng/dL, 1.95, 1.81, and 2.96, respectively, confirming that this interval is critical for the validity of $^{18}$F-FCH PET/CT, regardless of population size and selection criteria.

The analysis of semi-quantitative parameters has been addressed in numerous studies, but to date there is no unanimous consensus except in considering $SUV_{max}$ as the most reproducible parameter.

However, considering only the literature concerning recurrences and metastases after curative therapies, only a few studies have collected and analyzed data concerning $SUV_{max}$.

Siminiak et al. (24) considered a population selected similarly in our study, but they described $SUV_{max}$ results distinguishing patients by the sites of relapses: they reported a mean $SUV_{max}$ of 3.0 (2.3-4-0) in 27 patients with only local relapses and of 4.9 (3.8-8.0) in 35 patients involved by distant metastases. Wetter et al. (25) reported a mean $SUV_{max}$ in bone lesions of 5.5 (SD =3.1) independently by staging or restaging of PC. The analysis we report confirms that the mean $SUV_{max}$ values are widely variable regardless of the type of treatment received; furthermore, the ROC curve identified values and cut-offs quite similar to those reported in the literature and very similar in the 3 groups analyzed (3.75 vs. 3.45 vs. 4.7).

### Study Limitations

This study remains limited by its retrospective design and small sample size; nevertheless, to the best of our knowledge, it represents the most updated cohort of patients selected with regard to curative treatment. Furthermore, the limit concerning the different number of patients in groups was excluded by the application of statistical tests.

## Conclusion

Currently not all radiopharmaceuticals for PC are available in all territorial PET/CT reference operative units; therefore, we consider it suitable to provide updated data on the results of $^{18}$F-FCH PET/CT, which is currently more widely diffused.

Our study confirms that $^{18}$F-FCH PET/CT is valid in the evaluation of PC patients with suspected biochemical recurrence, regardless of the treatment performed and the PSA values, which are higher in case of multiple lesions, independent of the sites of metastases.

Therefore, we can affirm that it still makes sense to perform $^{18}$F-FCH PET/CT in patients with biochemical recurrence both in the presence of high PSA values and lower values.

### Ethics

**Ethics Committee Approval:** A retrospective observational analysis was performed, and the institutional review board did not require ethical committee approval for the review of patient files.

**Informed Consent:** All patients provided written informed consent to the use of their data for clinical research in an anonymous form.

### Authorship Contributions

Surgical and Medical Practices: F.T., A.S., A.C., Concept: C.A., A.N.A., A.R.P., Design: C.A., A.R.P., Data Collection or Processing: F.T., A.S., C.F., Analysis or Interpretation: A.N.A., C.F., Literature Search: A.C., D.R., Writing: C.A., D.R.

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