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Enhanced Clinical Decision-Making in Early Prostate Cancer Recurrence Using [18F]Fluciclovine PET/CT

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ABSTRACT

The present study assessed the role of [18F]Fluciclovine PET/CT in detecting early recurrent prostate cancer (PCa) and its influence on treatment decisions. We retrospectively reviewed 58 [18F]Fluciclovine PET/CT scans performed for suspected early recurrence. Detection rates (DR) and semiquantitative parameters were analyzed in relation to biochemical and clinical–pathological characteristics. Clinical follow-up served as the reference standard to determine sensitivity, specificity, accuracy, and predictive values (PPV and NPV). The overall DR was 66%, with lesion-specific rates of 53% in the prostate/prostate bed, 28% in lymph nodes, and 7% in bone. Higher PSA levels were associated with increased detection ($p = 0.009$), and a PSA threshold of 0.45 ng/mL was identified as optimal. Semiquantitative indices, including SUVmax and SUVmean, were useful in differentiating malignant from benign lesions. The imaging modality achieved a sensitivity of 87.1%, specificity of 80.0%, PPV of 87.1%, NPV of 80.0%, and an overall accuracy of 84.3%. Based on PET/CT findings, therapeutic management was altered in 51% of cases. These results highlight [18F]Fluciclovine PET/CT as a reliable approach for early restaging of PCa, particularly for local recurrence, and suggest that semiquantitative analysis may further improve diagnostic specificity.

Keywords: Prostate cancer, PET/CT, [18F]Fluciclovine, Biochemical recurrence

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Introduction

Although surgical and radiotherapy approaches for localized prostate cancer (PCa) have advanced significantly, a notable proportion of patients—ranging from 27% to 53%—experience rising prostate-specific antigen (PSA) levels after definitive treatment [1]. Detecting early recurrence remains difficult because conventional imaging modalities, including contrast-enhanced CT, MRI, and bone scans, often fail to identify minimal local relapse or distinguish local from systemic disease, particularly when PSA levels are low [2, 3]. Consequently, treatment decisions are frequently guided by clinical and pathological risk factors rather than imaging evidence of recurrence [1, 4].

Currently, there is no standardized imaging modality established for reliably detecting small-volume recurrence at low PSA. Molecular imaging has emerged as a promising strategy, allowing earlier detection of low-burden disease. Among PET tracers, 18F- and 11C-choline have FDA approval for restaging biochemical recurrence but demonstrate limited sensitivity for lesions in the prostate/prostatectomy bed when PSA is very low [5, 6].

Prostate-specific membrane antigen (PSMA) PET imaging, commonly labeled with 68Gallium and occasionally with 64Cu or 18F, has shown high detection rates for recurrent disease; however, its adoption is restricted by the lack of FDA approval [3].

[18F]Fluciclovine, a synthetic amino acid PET tracer, offers favorable biodistribution with minimal urinary interference. Clinical studies have reported detection rates of 56–83%, which led to FDA approval in May 2016 for PCa patients with biochemical recurrence after primary treatment [7–10]. Further research has confirmed its

utility even in patients with PSA ≤1 ng/mL, with an overall detection rate around 59% [11]. While PSA levels influence PET positivity, optimal PSA thresholds for early recurrence detection remain debated [12].

Large prospective trials, including LOCATE and FALCON, demonstrated that [18F]Fluciclovine PET/CT frequently alters clinical management, with therapeutic changes in 59–63% of cases [7, 9]. In the EMPIRE-1 trial, PET-guided salvage radiotherapy improved failure-free survival [13]. Moreover, the technique can distinguish oligometastatic from polymetastatic disease, thereby guiding individualized treatment strategies [14].

This study aimed to further evaluate the clinical utility of [18F]Fluciclovine PET/CT in early recurrent PCa by identifying biochemical and clinical–histopathological factors that affect PET detection and by assessing the impact of PET findings on therapeutic decision-making.

Materials and Methods

Patient selection

We performed a retrospective review of PCa patients undergoing [18F]Fluciclovine PET/CT for biochemical recurrence at our institution from September 2019 to September 2021.

Eligibility criteria included:

1. Histologically confirmed PCa treated with radical prostatectomy (RP), with or without adjuvant external beam radiotherapy (EBRT), or primary radiotherapy (RT);
2. Evidence of biochemical recurrence: PSA >0.2 ng/mL following RP or PSA ≥2 ng/mL above nadir after EBRT; and/or
3. Clinical suspicion of disease recurrence based on symptoms.

Based on these criteria, 58 patients were included in this single-center cohort. Clinical data were collected for each patient, including prior treatments, histopathology (initial Gleason score and stage), prior imaging studies, PSA values at the time of PET, and current or previous therapies such as androgen deprivation therapy (ADT). PSA kinetics were calculated, and patients were stratified into low- or high-risk biochemical recurrence groups according to the European Association of Urology (EAU) guidelines [15].

All participants provided written informed consent for the use of medical records for research purposes. The study protocol received approval from the local Ethics Committee (Prot. n. 0012052|08/02/2022|AOUCPG23|COMET|P). A summary of baseline demographic and clinical characteristics is presented in **Table 1**.

Table 1. Population characteristics (n = 58).

Characteristic	Value
No. patients	58
Age, y	
Mean (SD)	71 ± 7.17
Median (range)	72 (50–83)
Time from primary treatment to BRC, months	
Mean (SD)	60.24 ± 54.09
Median (range)	43 (1–219)
PSA level, ng/mL	
Mean (SD)	1.25 ± 1.18
Median (range)	0.92 (0.05–5.67)
PSA value, n (%)	
<0.5 ng/mL	20/58 (34%)
0.5–1 ng/mL	15/58 (26%)
>1 ng/mL	23/58 (40%)
PSA Doubling Time, months	
Mean	52
Median (range)	9 (4.20–2241.10)
PSA Doubling Time, n (%)	

<12 months	31/58 (53%)
≥12 months	27/58 (47%)
Gleason Score, n (%)	
<8	38/58 (66%)
≥8	20/58 (34%)
EAU BCR Risk Group, n (%)	
Low-Risk	17/58 (29%)
High-Risk	41/58 ((71%)
Primary treatment, n (%)	
RP	27/58 (47%)
RT	6/58 (10%)
RP + RT	25/58 (43%)
Ongoing hormonal therapy, n (%)	
Yes	13/58 (22%)
No	45/58 (78%)

Abbreviations: PSA: Prostate Specific Antigen; EAU: European Association of Urology; BCR: Biochemical recurrence; RP: radical prostatectomy; RT: radiotherapy.

Imaging protocol and evaluation

All [18F]Fluciclovine PET/CT scans were conducted following established clinical protocols. Patients were instructed to avoid strenuous physical activity the day before imaging, to fast for at least four hours prior to the scan, and to refrain from urinating for 30–60 minutes before tracer injection [15]. Imaging was performed using a hybrid PET/CT system (Discovery 710, GE, Milwaukee, WI, USA). Following intravenous administration of 370 MBq [18F]Fluciclovine, a low-dose CT scan was first acquired for attenuation correction and anatomical reference, immediately followed by a PET scan 3–5 minutes post-injection. PET acquisitions spanned from the mid-thigh to the base of the skull, typically covering 5–6 bed positions; in selected cases, imaging extended to the vertex. PET data were collected in three-dimensional mode with 2.5 minutes per bed position. CT acquisition parameters included pitch 0.98, gantry rotation speed of 0.5 s, 120 kVp, and a tube current of 140 mA, modulated automatically.

Image interpretation was performed on a dedicated workstation (AW Server 4.7, GE, Milwaukee, WI, USA). All scans were reviewed visually using Maximum Intensity Projection (MIP), axial, sagittal, and coronal reconstructions, with final reads made in consensus by two experienced nuclear medicine physicians (C.F. and V.L.) with at least three years of experience in [18F]Fluciclovine PET/CT interpretation and full access to relevant clinical information. Lesions were considered positive if tracer uptake exceeded surrounding background activity and was not attributable to physiological distribution. For lesions larger than 1 cm, vertebral body L3 uptake served as a reference; for lesions under 1 cm, the abdominal aorta blood pool was used [16]. Discrepancies were resolved by a third nuclear medicine physician (A.G.N.) through consensus discussion.

Data analysis

Detection rate

PET/CT-positive lesions were reported as the "detection rate" (DR), as histological confirmation was not consistently available. DR was assessed both per patient and per lesion (prostate/prostatectomy bed, lymph nodes, and bone). Analyses were stratified by biochemical and clinical–histopathological parameters, including PSA levels (<0.5, 0.5–1, >1 ng/mL), PSA doubling time (<12 vs. ≥12 months), Gleason score (<8 vs. ≥8), EAU BCR risk group (low vs. high), interval from primary treatment to recurrence (TTR), primary therapy type (RP, RT, or combination), and current androgen deprivation therapy (yes vs. no). Optimal PSA and TTR thresholds predicting positive PET scans were also evaluated.

Follow-up and reference standard

Clinical follow-up of at least three months post-PET was collected, including PSA measurements, additional diagnostic procedures, and initiation or modification of therapy. Follow-up served as the reference standard to determine PET accuracy, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. PET results were categorized as:

- True positive (TP): PET-positive lesions confirmed by subsequent anatomical imaging or biopsy, or corroborated by a biochemical response (PSA decline) or stable PSA following therapy.
- True negative (TN): PET-negative patients with no evidence of recurrence on follow-up imaging or declining PSA without therapy.
- False positive (FP): PET-positive findings not confirmed on follow-up imaging, with PSA declining without intervention.
- False negative (FN): PET-negative scans where follow-up imaging revealed recurrence, or PSA decreased only after therapy.

The impact of PET results on subsequent therapeutic management was also assessed.

Semiquantitative PET analysis

For all PET-positive lesions, semiquantitative parameters were calculated, including maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), metabolic tumor volume (MTV), total lesion activity (TLA = SUVmean × MTV), and tumor-to-background ratio (T/Bratio), defined as the ratio of lesion SUVmax to SUVmean of the abdominal aorta or bone marrow.

The lesion with the highest tracer uptake was defined as the reference lesion for per-patient analysis. Per-lesion analysis considered the lesion with the highest uptake in each anatomical compartment (prostate/prostatectomy bed, lymph nodes, and bone). The distribution of semiquantitative PET metrics was then examined according to biochemical factors (PSA, PSA doubling time) and clinical–histological characteristics (Gleason score, EAU BCR risk group, TTR, primary treatment, and ongoing therapies).

Subgroup analyses

We further categorized patients according to the extent of disease on PET/CT, differentiating between lesions confined to the prostate/prostatectomy bed and those with spread beyond the prostate, including lymph nodes or bone. Oligometastatic disease was defined as the presence of one to three lesions, regardless of location, whereas polymetastatic disease included four or more lesions [17]. Within these subgroups, we examined the distribution of biochemical markers (PSA levels and PSA doubling time) and clinical-pathological characteristics (Gleason score, EAU BCR risk category, time from initial treatment to recurrence, primary treatment modality, and ongoing therapy) alongside PET-based semiquantitative parameters.

Statistical methods

Continuous data were summarized as mean ± standard deviation (SD) or median with range, while categorical variables were expressed as counts and percentages. Associations for categorical variables—such as PSA categories (<0.5, 0.5–1, >1 ng/mL), PSA doubling time (<12 vs. ≥12 months), Gleason score (<8 vs. ≥8), BCR risk (low vs. high), primary therapy (RP, RT, RP + RT), and use of hormonal therapy (yes/no)—were evaluated using Chi-square or Fisher's exact tests. For continuous non-normally distributed data, comparisons were made using the Mann–Whitney U test or Pearson correlation as appropriate.

ROC curve analysis was employed to evaluate the diagnostic performance of [18F]Fluciclovine PET/CT relative to continuous variables. Optimal cut-off values to distinguish positive from negative scans and malignant from benign lesions were determined using Youden's index. Statistical significance was defined as $p < 0.05$. Analyses were conducted with SPSS version 28 (IBM Corp., Armonk, NY, USA).

Results and Discussion

Detection rates of [18F]fluciclovine PET/CT

In our cohort, [18F]Fluciclovine PET/CT scans were positive in 38 of 58 patients, corresponding to an overall detection rate of 66%. When assessed by lesion location, uptake was observed in the prostate/prostatectomy bed in 31 patients (53%), in lymph nodes in 16 patients (28%), and in bone in 4 patients (7%) **(Figure 1)**.

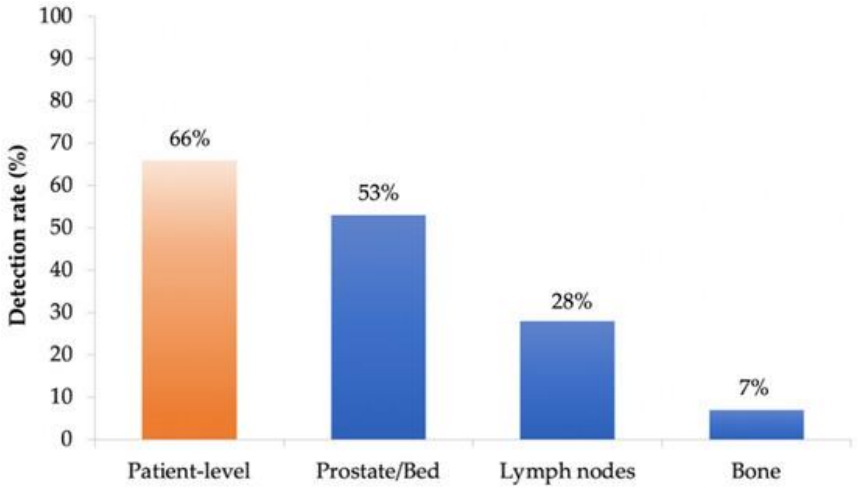
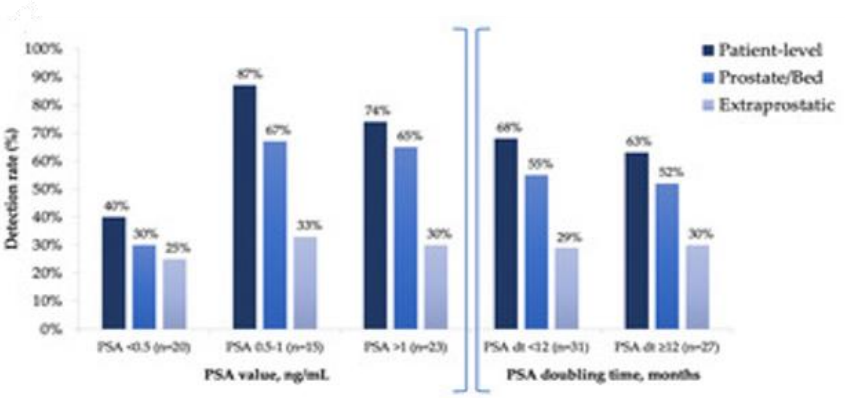
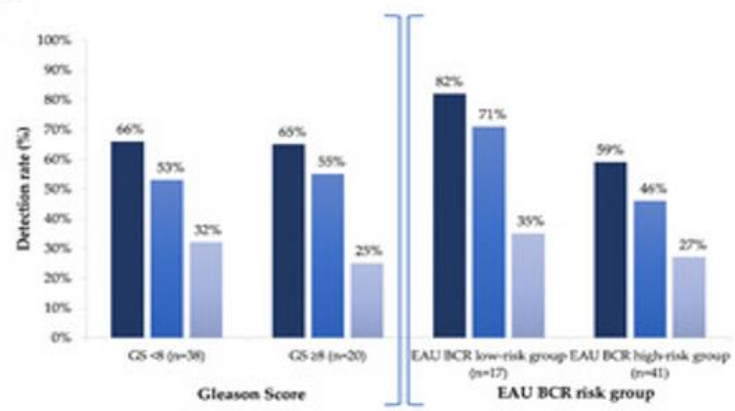


Figure 1. Per-patient and per-lesion detection rate of [^{18}F]Fluciclovine PET/CT.

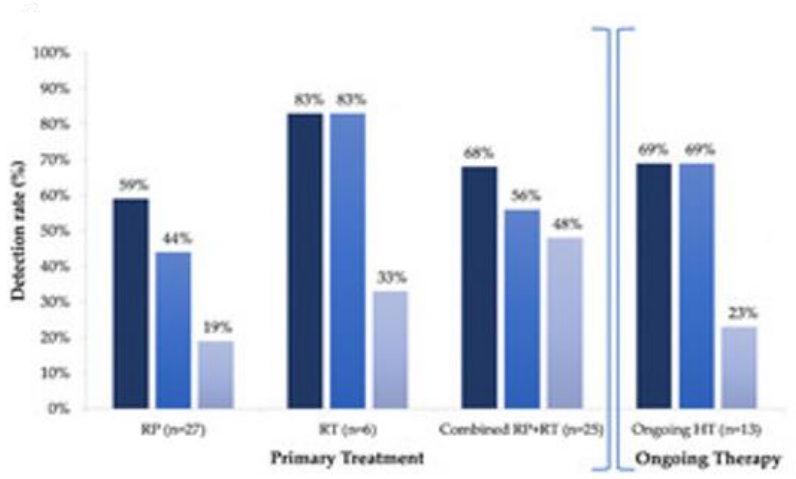
The cohort had a mean PSA of 1.25 ng/mL at the time of imaging (median: 0.92 ng/mL; range: 0.05–5.67). Patients with positive [18F]Fluciclovine PET/CT scans exhibited significantly higher PSA levels compared to those with negative scans (p = 0.009). Detection rates varied according to PSA, with 40% (8/20) in patients with PSA < 0.5 ng/mL, increasing to 87% (13/15) in the 0.5–1.0 ng/mL group and 74% (17/23) in patients with PSA > 1.0 ng/mL. A similar trend was observed for lesions located in the prostate or prostatectomy bed, where detection rates rose from 30% (6/20) in the lowest PSA group to 67% (10/15) and 65% (15/23) in the 0.5–1.0 ng/mL and >1.0 ng/mL groups, respectively (p = 0.034) **(Figure 2a)**. Other factors analyzed, including PSA doubling time, Gleason score, EAU BCR risk classification, and current hormonal therapy, did not significantly predict scan positivity (p > 0.05) **(Figures 2a–2c)**.



a)



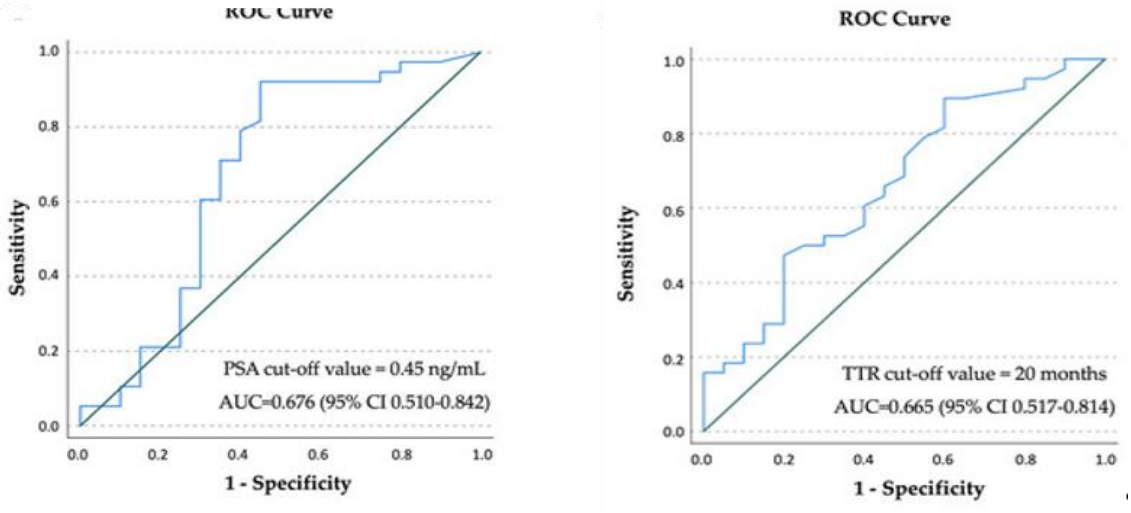
b)



c)

Figure 2. Illustrates the detection rates of [18F]Fluciclovine PET/CT on both a per-patient and per-lesion basis, stratified by (a) PSA levels and PSA doubling time, (b) Gleason Score (GS) and EAU-defined biochemical recurrence (BCR) risk categories, and (c) type of primary treatment—radical prostatectomy (RP), radiotherapy (RT), or a combination of RP + RT—as well as ongoing hormonal therapy (HT).

Receiver operating characteristic (ROC) analysis identified a PSA threshold of 0.45 ng/mL as the most effective cut-off for predicting a positive [18F]Fluciclovine PET/CT result, achieving 92% sensitivity and 55% specificity, with an area under the curve (AUC) of 0.676 (95% CI: 0.510–0.842) **(Figure 3a).**



a) b)

Figure 3. ROC analysis: (a) the PSA optimal cut-off value was 0.45 ng/mL with an AUC of 0.676 and (b) time from primary treatment to PSA relapse (TTR) optimal cut-off value was 20 months with an AUC of 0.665.

Figure 3 illustrates the results of ROC curve analyses, identifying a PSA threshold of 0.45 ng/mL as optimal for predicting positive [18F]Fluciclovine PET/CT scans, yielding an AUC of 0.676 **(Figure 3a)**. Similarly, the interval from initial treatment to biochemical recurrence (TTR) of 20 months was found to best distinguish patients with positive scans, with an AUC of 0.665 **(Figure 3b)**.

A shorter TTR was significantly associated with positive PET/CT results both when analyzed per patient ($p = 0.040$) and per lesion within the prostate/prostatectomy bed ($p = 0.030$). Using the 20-month cut-off, sensitivity reached 90%, while specificity was 40%, confirming that earlier recurrences were more likely to be detected by the scan.

Clinical follow-up

Follow-up information was available for 51 patients (88% of the cohort). Among these, 27 patients (53%) were confirmed as true positives, 16 patients (31%) as true negatives, 4 patients (8%) as false positives, and 4 patients (8%) as false negatives. These findings were used to evaluate the diagnostic accuracy of [18F]Fluciclovine PET/CT, as summarized in **Table 2**.

Table 2. Diagnostic performance of [^{18}F]Fluciclovine PET/CT.

[^{18}F]Fluciclovine PET/CT Diagnostic Performance		
	Value	95% CI
Sensitivity	87.10%	70.17% to 96.37%
Specificity	80.00%	56.34% to 94.27%
PPV	87.10%	73.55% to 94.25%
NPV	80.00%	60.96% to 91.11%
Accuracy	84.31%	71.41% to 92.98%

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value.

Analysis of clinical follow-up revealed that [18F]Fluciclovine PET/CT results led to modifications in the treatment plan for 51% of patients (26 out of 51), with the vast majority of these changes occurring after a positive scan (96%, 25/26) **(Figure 4)**. Prior to imaging, most patients were under active clinical surveillance. The treatment adjustments most commonly involved initiation of systemic hormonal therapy (38%, 10/26) or the delivery of radiotherapy (31%, 8/26) **(Figure 5)**. In contrast, no changes to the therapeutic approach were made for 49% of patients (25/51), predominantly following negative PET findings (76%, 19/25).

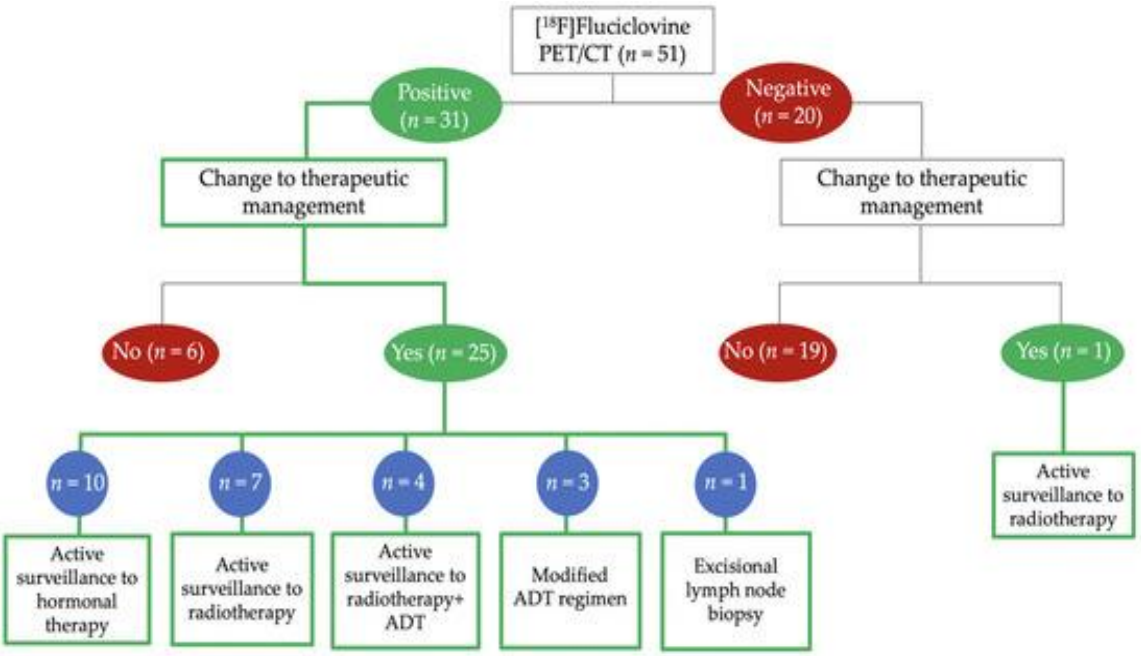
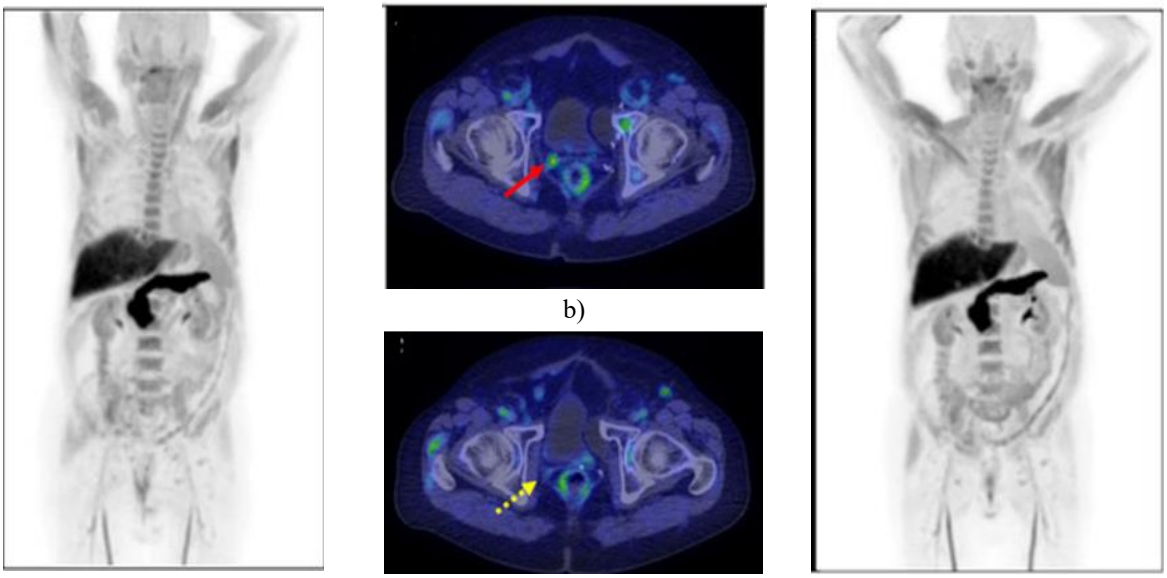


Figure 4. Impact of [^{18}F]Fluciclovine PET/CT scan on clinical management of the PCa patients. ADT, androgen deprivation therapy



a) b) b) d)

Figure 5. Representative pre- and post-treatment [18F]Fluciclovine PET/CT scans of a 72-year-old male with PSA recurrence after radical prostatectomy in 2015. The patient's initial tumor stage was pT2cN0 with a Gleason Score of 7 (4 + 3), classified as high-risk per EAU BCR criteria. At the time of imaging, PSA had risen to 0.26 ng/mL, with a doubling time of 5.13 months. Pre-therapy PET/CT images ((a) MIP; (b) axial fused PET/CT) revealed increased tracer uptake in the right prostatectomy bed (red arrow). Based on these findings, the treatment plan was adjusted to radiotherapy. Follow-up PET/CT after 4 months ((c) axial fused PET/CT; (d) MIP) demonstrated metabolic regression of the lesion (yellow dotted arrow), consistent with a subsequent PSA decrease to 0.05 ng/mL.

Semiquantitative PET/CT findings

Among patients with positive PET scans (66%, 38/58), the lesion with highest uptake (reference lesion, RL) was most commonly located in the prostate/prostatectomy bed (71%, 27/38), followed by lymph nodes (21%, 8/38) and bone (8%, 3/38). Mean values of semiquantitative parameters were: SUVmaxRL 4.40, SUVmeanRL 2.72, T/BratioRL 1.59, MTVRL 5.09, and TLARL 14,986.82.

On a per-patient basis, semiquantitative measures did not show statistically significant differences across biochemical or clinical–histological subgroups ($p > 0.05$). Nonetheless, there was a noticeable trend for higher SUVmaxRL and SUVmeanRL with elevated PSA levels, particularly when PSA exceeded 1.0 ng/mL **(Table 3)**. Pearson correlation confirmed a significant positive linear association between PSA and SUVmaxRL ($p = 0.006$) and PSA and SUVmeanRL ($p = 0.003$).

Table 3. Per-patient semiquantitative analysis in relation to biochemical and clinical–histological variables.

[^{18}F]Fluciclovine PET Parameters	**Mean SUVmax$_{RL}$ (Range)**	**p**	**Mean T/Bratio$_{RL}$ (Range)**	**p**	**Mean MTV$_{RL}$ (Range)**	**p**	**Mean TLA$_{RL}$ (Range)**	**p**	**Mean SUVmean$_{RL}$ (Range)**	**p**
PSA Value, ng/mL										
<0.5	3.85		1.74		6.44		16,683.44		2.35	
	(2.90–5.24)		(0.70–2.60)		(2.03–15.43)		(3392.10–44,146.60)		(1.63–3.34)	
0.5–1	3.93	0.149	1.2	0.106	5.3	0.416	16,111.94	0.618	2.51	0.195
	(1.6–9.00)		(0.70–2.20)		(0.66–16.87)		(1089.20–81,840.10)		(0.93–5.90)	
>1	5.03		1.82		4.32		13,529.53		3.05	
	(2.20–12.20)		(0.60–5.23)		(1.75–11.99)		(3708.10–34,779.60)		(1.29–7.90)	
PSA doubling time, months										

<12	5.00 (1.90–12.20)	0.45	1.77 (0.70–5.23)	0.128	4.58 (0.66–15.43)	0.601	15,519.87 (1089.20–81,840.10)	0.954	2.88 (1.16–7.90)	0.504
≥12	3.96 (1.60–7.90)		1.3 (0.60–2.60)		5.51 (1.10–16.87)		13,479.49 (1952.90–38,385.20)		2.46 (0.93–4.81)	
Gleason Score										
<8	4.49 (2.00–12.20)	0.952	1.61 (0.60–5.23)	0.627	4.82 (0.66–16.87)	0.259	14,511.89 (1089.20–81,840.10)	0.3	2.81 (1.20–7.90)	0.927
≥8	4.14 (1.60–7.50)		1.54 (0.90–2.90)		5.72 (2.24–15.43)		16,239 (2079.90–44,146.60)		2.51 (0.93–4.30)	
EAU BCR Risk Group										
Low-Risk	4.15 (2.10–7.90)	0.917	1.22 (0.60–1.80)	0.058	5.1 (1.10–16.87)	0.846	12,605.06 (1952.90–38,385.20)	0.846	2.5 (1.29–4.81)	0.964
High-Risk	4.58 (1.60–12.20)		1.8 (0.70–5.23)		5.22 (0.66–15.43)		16,861.75 (1089.20–81,840.10)		2.82 (0.93–7.90)	
TTR, months										
≤20	5.65 (3.1–12.20)	0.982	1.97 (0.80–3.80)	0.505	6.49 (2.37–15.43)	0.63	22,583.48 (4384.30–44,146.60)	0.505	3.65 (1.90–7.90)	0.697
>20	4.25 (1.60–9.00)		1.55 (0.60–5.23)		4.92 (0.66–16.87)		14,093.1 (1089.20–81,840.10)		2.62 (0.93–5.90)	
Primary treatment										
RP	4.16 (1.60–7.90)	0.835	1.29 (0.60–2.20)	0.141	4.1 (0.66–16.87)	0.237	10,219.34 (1089.20–38,385.20)	0.197	2.53 (0.93–4.81)	0.913
RT	3.82 (2.10–5.00)		1.25 (0.70–1.79)		8.45 (1.10–15.43)		22,677.74 (1952.90–44,146.60)		2.59 (1.80–3.40)	
RP + RT	4.69 (2.40–12.20)		1.99 (0.70–5.23)		4.81 (1.75–13.98)		16,444.07 (3392.10–81,840.10)		2.88 (1.63–7.90)	
Ongoing hormonal therapy										
Yes	4.73 (1.90–9.00)	0.521	1.85 (0.70–5.23)	0.1	6.81 (1.75–15.43)	0.325	22,207.29 (4531.70–81,840.10)	0.124	2.88 (1.16–5.90)	0.436
No	4.28 (1.60–12.20)		1.44 (0.60–3.80)		3.98 (0.66–16.87)		10,744.88 (1089.20–38,385.20)		2.67 (0.93–7.90)	

Abbreviations: PET: Positron Emission Tomography; SUVmax: maximum Standardized Uptake Value; T/Bratio: Tumor-to-Background ratio; MTV: Metabolic Tumor Volume; TLA: Total Lesion Activity; SUVmean: mean Standardized Uptake Value; PSA: Prostate Specific Antigen; EAU: European Association of Urology; BCR: biochemical recurrence; TTR: time from primary treatment to PSA relapse; RP: radical prostatectomy; RT: radiotherapy.

Using clinical follow-up as the reference standard, ROC curve analysis determined optimal thresholds for distinguishing malignant from benign lesions, with SUVmaxRL at 2.05 (AUC = 0.618, 95% CI 0.353–0.883) and SUVmeanRL at 1.75 (AUC = 0.624, 95% CI 0.389–0.860).

Analysis by subpopulations

Among patients with positive PET scans, 55% (21/38) exhibited disease confined to the prostate or prostatectomy bed, whereas 45% (17/38) showed extraprostatic involvement, with or without concurrent prostate bed lesions.

Within the extraprostatic group, PET imaging revealed lymph node involvement in 76% (13/17) and bone metastases in 24% (4/17) of cases.

Oligometastatic disease, defined as one to three lesions regardless of location, was present in 95% (36/38) of positive scans, while polymetastatic disease (four or more lesions) accounted for the remaining 5% (2/38).

A significant association was observed between the type of primary treatment and disease spread: patients who received both radical prostatectomy and radiotherapy were more likely to develop extraprostatic disease on PET/CT ($p = 0.005$) compared with those with localized recurrence. No statistically significant differences were noted between subpopulations regarding other biochemical or clinical–histological parameters included in the analysis **(Table 4)**.

Table 4. Subpopulations analysis in relation to biochemical and clinical–histological variables.

Characteristic	Overall Positivity (n = 38)	Prostate/Bed Disease (n = 21)	Extraprostatic Disease (n = 17)	p Value	Oligometastatic Disease (n = 36)	Polymetastatic Disease (n = 2)	p Value
PSA Value, ng/mL							
Mean (SD)	1.38 ± 1.20	1.35 ± 1.20	1.35 ± 1.23	0.706	1.43 ± 1.21	0.61 ± 0.21	0.182
Median (range)	1 (0.05–5.67)	0.96 (0.26–5.67)	1.00 (0.05–5.23)		1.00 (0.05–5.67)	0.61 (0.46–0.76)	
PSA Value, ng/mL							
<0.5	8/38 (21%)	3/21 (14%)	5/17 (29%)	0.518	7/38 (18%)	1/2 (50%)	0.379
0.5–1	13/38 (34%)	8/21 (38%)	5/17 (29%)		12/36 (33%)	1/2 (50%)	
>1	17/38 (45%)	10/21 (48%)	7/17 (41%)		17/36 (47%)	0/2 (0%)	
PSA doubling time, months							
<12	21/38 (55%)	12/21 (57%)	9/17 (53%)	0.527	19/36 (53%)	2/2 (100%)	0.299
≥12	17/38 (45%)	9/21 (43%)	8/17 (47%)		17/36 (47%)	0/2 (0%)	
Gleason Score							
<8	25/38 (66%)	13/21 (62%)	12/17 (71%)	0.416	24/36 (67%)	1/2 (50%)	0.573
≥8	13/38 (34%)	8/21 (38%)	5/17 (29%)		12/36 (33%)	1/2 (50%)	
EAU BCR Risk Group							
Low-Risk	14/38 (37%)	8/21 (38%)	6/17 (35%)	0.565	14/36 (39%)	0/2 (0%)	0.393
High-Risk	24/38 (63%)	13/21 (62%)	11/17 (65%)		22/36 (61%)	2/2 (100%)	
TTR, months							
Mean (SD)	69.18 ± 56.63	74.76 ± 62.52	62.29 ± 49.40	0.642	71.92 ± 56.86	20 ± 19.80	0.205
Median (range)	53.5 (5–219)	58 (5–219)	38 (6–178)		56.5 (5–219)	20 (6–34)	
RP Alone, n (%)							
Yes	16/38 (42%)	11/21 (52%)	5/17 (29%)	0.137	16/36 (44%)	0/2 (0%)	0.329
No	22/38 (58%)	10/21 (48%)	12/17 (71%)		20/36 (56%)	2/2 (100%)	
RT Alone, n (%)							
Yes	20/38 (53%)	5/21 (24%)	0/17 (0%)	0.051	5/36 (14%)	0/2 (0%)	0.751
No	18/38 (47%)	16/21 (76%)	17/17 (100%)		31/36 (86%)	2/2 (100%)	
Combined RP + RT, n (%)							
Yes	17/38 (45%)	5/21 (24%)	12/17 (71%)	**0.005**	15/36 (42%)	2/2 (100%)	0.193
No	21/38 (55%)	16/21 (76%)	5/17 (29%)		21/36 (58%)	0/2 (0%)	
Ongoing HT, n (%)							
Yes	9/38 (24%)	6/21 (29%)	3/17 (18%)	0.346	9/36 (25%)	0/2 (0%)	0.578
No	29/38 (76%)	15/21 (71%)	14/17 (82%)		27/36 (75%)	2/2 (100%)	

Abbreviations: PSA: Prostate-Specific Antigen; EAU: European Association of Urology; BCR: Biochemical Recurrence; TTR: time from primary treatment to PSA relapse; RP: radical prostatectomy; RT: radiotherapy; HT: hormonal therapy. Bold indicates statistically significant results.

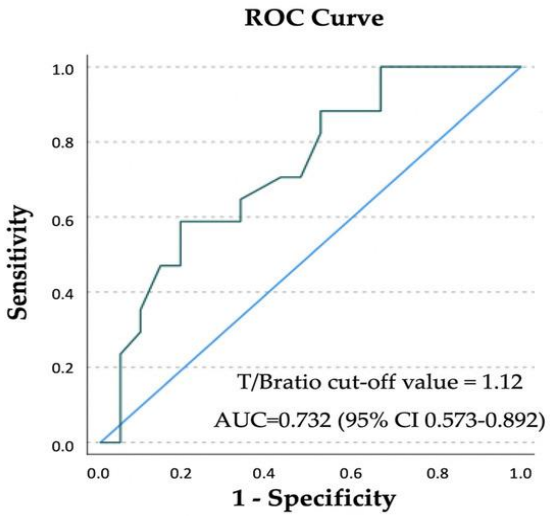


Figure 6. [^{18}F]Fluciclovine PET/CT performance in relation to T/Bratio. ROC analysis identified the optimal cut-off value of 1.12 with an AUC of 0.732.

Regarding the semiquantitative analysis, the extraprostatic disease subgroup exhibited a significantly higher T/BratioRL compared with localized disease (p = 0.014) **(Table 5)**. ROC curve analysis determined an optimal T/BratioRL threshold of 1.12, yielding 88% sensitivity and 43% specificity, with an AUC of 0.732 (95% CI 0.573–0.892), which was associated with an increased likelihood of extraprostatic involvement **(Figure 6)**.

Table 5. Correlation between semiquantitative parameters and subpopulation analysis.

[^{18}F]Fluciclovine PET Parameters	Overall Positivity (n = 38)	Prostate/Bed Disease (n = 21)	Extraprostatic Disease (n = 17)	p Value	Oligometastatic Disease (n = 36)	Polymetastatic Disease (n = 2)	p Value
$SUVmax_{RL}$							
Mean (SD)	4.37 ± 2.18	4.24 ± 1.80	4.205 ± 2.74		4.31 ± 2.04	6.10 ± 4.10	
Median	4	4.1	3.16	0.862	4.1	6.1	0.597
Range	1.60–12.2	1.9–7.9	1.60–12.20		1.60–12.20	3.20–9.00	
$T/Bratio_{RL}$							
Mean (SD)	1.59 ± 0.91	1.39 ± 0.97	1.785 ± 0.82		1.57 ± 0.92	2.00 ± 0.28	
Median	1.3	1.2	1.75	**0.014**	1.3	2	0.159
Range	0.60–5.23	0.6–5.23	0.70–3.80		0.60–5.23	1.80–2.20	
MTV_{RL}							
Mean (SD)	5.15 ± 4.04	4.9 ± 3.67	4.375 ± 4.54		4.91 ± 3.79	8.18 ± 8.21	
Median	3.88	3.88	2.58	1	3.85	8.18	0.774
Range	0.66–16.87	1.1–15.43	0.658–16.87		0.66–16.87	2.37–13.98	
TLA_{RL}							
Mean (SD)	15,118.79 ± 15,635.73	12,804.89 ± 10,867.18	14,943.725 ± 21,128.58		13,424.30 ± 10,896.86	43,112.20 ± 54,769.52	
Median	10,024.8	8312.7	5647.6	0.622	10,064.45	43,112.2	0.774
Range	1089.20–81,840.10	1952.90–44,146.60	1089.20–81,840.10		1089.20–44,146.60	4384.30–81,840.10	
$SUVmean_{RL}$							
Mean (SD)	2.76 ± 1.35	2.62 ± 1.04	2.625 ± 1.79		2.66 ± 1.26	3.90 ± 2.83	
Median	2.4	2.6	1.97	0.977	2.5	3.9	0.597
Range	0.93–7.90	1.16–4.81	0.93–7.90		0.93–7.90	1.90–5.90	

Abbreviations: PET: Positron Emission Tomography; SUVmax: maximum Standardized Uptake Value; T/Bratio: Tumor-to-Background ratio; MTV: Metabolic Tumor Volume; TLA: Total Lesion Activity; SUVmean: mean Standardized Uptake Value; SD: standard deviation. Bold: the only statistically significant result.

In **Figure 7 a** representative clinical case of our sample is reported.

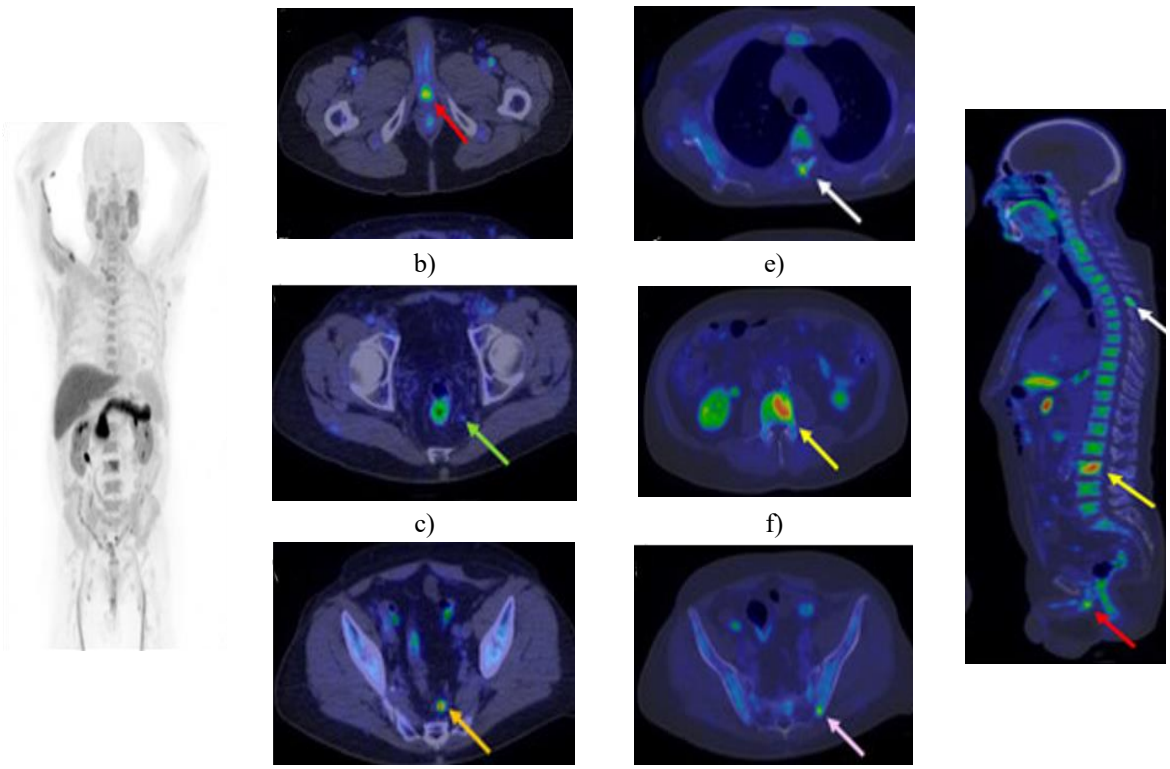


Figure 7. [18F]Fluciclovine PET/CT in a 68-year-old patient experiencing PSA relapse after prostatectomy (2011). The initial staging was pT2aN0R0 with a Gleason Score of 7 (3 + 4), categorized as high EAU BCR risk. At the time of imaging, PSA had risen to 0.76 ng/mL, with a PSA doubling time of 3.4 months. Images ((a) Maximum Intensity Projection; (b–g) axial fused PET/CT; (h) sagittal fused PET/CT) revealed elevated [18F]Fluciclovine uptake in the prostatectomy bed (SUVmax 6.4, T/Bratio 1.6, red arrow), left pararectal lymph node (SUVmax 1.9, T/Bratio 0.95, green arrow), left presacral lymph node (SUVmax 8.0, T/Bratio 2.0, orange arrow), D4 vertebra spinous process (SUVmax 6.3, T/Bratio 1.5, white arrow), L3 vertebra (SUVmax 9.0, T/Bratio 2.2, yellow arrow), and left iliac bone (SUVmax 6.0, T/Bratio 3.0, pink arrow).

Discussion

Molecular imaging has become increasingly incorporated into the diagnostic evaluation of PCa patients with rising PSA, demonstrating superior performance over conventional imaging in localizing recurrent disease early [18]. Despite this, the optimal imaging modality for detecting recurrence at low PSA levels remains debated.

EAU guidelines suggest PSMA-labeled PET/CT for patients with biochemical recurrence when PSA exceeds 0.2 ng/mL and when imaging results are expected to guide treatment decisions. In cases where PSMA PET/CT is unavailable, [18F]Fluciclovine or Choline PET/CT is recommended for PSA >1 ng/mL [1]. The NCCN guidelines, however, do not specify a PSA threshold, instead recommending [18F]Fluciclovine PET/CT after conventional imaging for ambiguous findings [19].

Selecting the most appropriate radiotracer according to patient characteristics and clinical availability enables a personalized imaging approach to guide therapeutic decisions. Accordingly, we examined biochemical and clinical–histological factors influencing [18F]Fluciclovine PET/CT positivity in patients with low PSA, aiming to optimize diagnostic yield and patient selection.

Previous studies have established that pre-scan PSA strongly affects [18F]Fluciclovine PET/CT detection rate. A multicenter cohort of 600 patients reported an overall positivity of 67.7%, including 38.7% in the prostate/prostatectomy bed, 32.6% in lymph nodes, and 26.2% in extrapelvic sites, with 41.4% detection in patients with PSA <0.79 ng/mL [20]. Scarsbrook *et al*. prospectively reported a 56% overall DR, including 33% for PSA <0.2 ng/mL, indicating efficacy at very low PSA [7]. Similarly, Dreyfuss *et al*. observed a 65% DR overall and 58% among patients with PSA <0.2 ng/mL [21]. Consistently, our cohort showed a 66% overall DR, with detection increasing for PSA >0.5 ng/mL (40% for PSA <0.5 ng/mL; 87% for PSA 0.5–1 ng/mL; 74% for PSA >1 ng/mL), predominantly in the prostate bed.

However, there is no consensus regarding the optimal PSA threshold for recurrence detection, with suggested values ranging from 0.3 to 1 ng/mL [22, 23]. In our study, 0.45 ng/mL emerged as the optimal cutoff for patient selection. Most positive lesions were located in the prostate/prostatectomy bed (53%), benefiting from minimal urinary interference, compared to lymph node (28%) and bone involvement (7%). In contrast, Bulbul *et al*. reported nearly equal detection in prostate and extraprostatic sites (35% vs. 37%) for PSA <1 ng/mL [11].

Disease aggressiveness also influenced detection rates. Higher DR was observed in aggressive tumors (GS ≥8, T3–T4 stages, castration-resistant) [24–26]. Notably, our study is the first to evaluate the impact of TTR on [18F]Fluciclovine PET/CT detection, showing a significant inverse relationship, with an optimal cutoff at 20 months, whereas the EAU BCR risk groups did not reach significance, consistent with Selnæs *et al*.'s findings [27].

Primary treatment type influenced recurrence localization. Data from the FALCON trial indicated lower DR in post-prostatectomy patients (32%) versus intact prostate (95%), mainly due to prostate/bed lesions [18]. Our cohort showed patients who received combined surgery and radiotherapy were more likely to develop extraprostatic disease ($p = 0.005$), suggesting combined therapy provides better local control but may not prevent distant recurrence. ADT did not negatively affect PET positivity, in line with preclinical studies [28].

Current EANM guidelines recommend visual interpretation of [18F]Fluciclovine PET scans [16]. While standardized criteria are lacking, semi-quantitative parameters can aid interpretation in equivocal cases. Consistent with Zanoni *et al*., SUVmax serves as a predictive imaging biomarker correlating with tumor aggressiveness [29]. In our analysis, PSA levels were significantly correlated with SUVmaxRL ($p = 0.006$) and SUVmeanRL ($p = 0.003$), confirming this relationship.

The role of SUVmax in distinguishing malignant from benign lesions remains debated, which can limit the specificity of [18F]Fluciclovine PET/CT [29]. In the same study, the use of T/Bratio measurements, specifically T/Bratio-AORTA and T/Bratio-L3, improved both sensitivity and specificity, with optimal cut-offs ranging from 2.7–3.75 and 1.35–1.55, respectively [29]. In our cohort, SUVmax and SUVmean proved useful for differentiating malignant from benign findings, with optimal cut-offs of 2.05 and 1.75. Additionally, higher T/Bratio values were associated with extraprostatic, more advanced disease. Further studies are required to validate these semi-quantitative measures and establish standardized cut-off values for PET image interpretation.

In line with findings from the LOCATE [9] and FALCON [7] trials, we observed that [18F]Fluciclovine PET/CT prompted a change in clinical management in 51% of patients. In these trials, pre-scan management often involved salvage radiotherapy. LOCATE reported treatment changes from salvage radiotherapy or systemic therapy to watchful waiting in 25% of PET-negative patients, and from ADT to radiotherapy in 24% of PET-positive patients [9]. FALCON similarly documented treatment adjustments to systemic therapy or watchful waiting based on scan results [7]. In our series, the most common modifications following a positive PET scan involved switching from clinical surveillance to either systemic hormone therapy (38%) or radiotherapy (31%), thereby reducing the risk of undertreatment.

Accurate delineation of disease extent is critical for guiding management, particularly when distinguishing oligometastatic from polymetastatic disease. Although PSMA-based PET tracers show high sensitivity, the increasing evidence supporting [18F]Fluciclovine's performance at low PSA levels underscores the value of amino acid tracers in imaging oligometastatic disease [14, 17]. In our cohort, 95% of PET-positive patients were classified as oligometastatic, influencing treatment decisions.

Literature on [18F]Fluciclovine PET/CT performance in recurrent PCa remains heterogeneous [30]. A recent meta-analysis reported pooled sensitivity and specificity of 86.3% and 75.9%, respectively [25], while Schuster *et al*. found lower specificity (40%) but higher sensitivity (90.2%) [31]. A larger cohort of 596 patients showed similar performance (sensitivity 88.1%, specificity 32.6%) [20]. In our study, [18F]Fluciclovine PET/CT maintained high sensitivity (87%) and higher specificity (80%), although the lack of histological confirmation may have influenced these results.

When considering the relative strengths of available PET tracers, [18F]Fluciclovine has demonstrated superior detection rates compared to 18F/11C-Choline, especially at low PSA levels [6, 32, 33]. However, comparisons with 68Ga-PSMA PET/CT are mixed [34]. Some studies, such as Pernthaler *et al*., report improved detection of local recurrence with [18F]Fluciclovine compared to PSMA (37.9% vs. 27.6%), particularly near the bladder [10]. Conversely, Calais *et al*. suggested PSMA PET is preferable after radical prostatectomy, showing overall higher detection (56% vs. 26%) [35]. Limited availability of PSMA tracers restricts their clinical use, whereas [18F]Fluciclovine is more widely accessible in the US and Europe [6]. These considerations highlight the ongoing

challenge in selecting the most appropriate PET tracer, which should be tailored to patient characteristics to optimize clinical management.
This study has several limitations, including its retrospective single-center design and relatively small sample size, the absence of tissue confirmation as a reference standard, and the need for longer follow-up to evaluate outcomes after PET-guided changes in therapy.

Conclusion

[18F]Fluciclovine PET/CT is an effective imaging tool for early restaging in patients with recurrent PCa. A PSA threshold of 0.45 ng/mL may serve as an appropriate cut-off for patient selection. The technique demonstrated a high detection rate (66%) of recurrent lesions, particularly in the prostate bed (53%), likely due to minimal urinary excretion of the tracer, and influenced clinical management in 51% of patients. Semi-quantitative parameters, especially SUVmax and SUVmean, may further improve specificity, aiding differentiation between malignant and benign lesions and optimizing therapeutic decision-making.

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Conflict of Interest: None

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Ethics Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Azienda Ospedaliera Universitaria Policlinico, Bari; Italy; protocol code: 0012052|08/02/2022|AOUCPG23|COMET|P; date of approval: 8 February 2022.
Informed consent was obtained from all subjects involved in the study.

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