RESEARCH ARTICLE

The Clinical Utility of ^{18}F-Fluciclovine PET/CT in Biochemically Recurrent Prostate Cancer: an Academic Center Experience Post FDA Approval

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Abstract

Purpose: To evaluate the diagnostic performance and clinical utility of ^{18}F-fluciclovine PET/CT in patients with biochemical recurrence (BCR) of prostate cancer (PC).
Methods: ^{18}F-Fluciclovine scans of 165 consecutive men with BCR after primary definitive treatment with prostatectomy ($n = 102$) or radiotherapy ($n = 63$) were retrospectively evaluated. Seventy patients had concurrent imaging with at least one other conventional modality (CT ($n = 31$), MRI ($n = 31$), or bone scan ($n = 26$)). Findings from ^{18}F-fluciclovine PET were compared with those from conventional imaging modalities. The positivity rate and impact of ^{18}F-fluciclovine PET on patient management were recorded. In 33 patients who underwent at least one other PET imaging (^{18}F-NaF PET/CT ($n = 12$), ^{68}Ga-PSMA11 PET/CT ($n = 5$), ^{18}F-DCFPyL PET/CT ($n = 20$), and ^{68}Ga-RM2 PET/MRI ($n = 5$)), additional findings were evaluated.
Results: The overall positivity rate of ^{18}F-fluciclovine PET was 67 %, which, as expected, increased with higher prostate-specific antigen (PSA) levels (ng/ml): 15 % (PSA < 0.5), 50 % (0.5 ≤ PSA < 1), 56 % (1 ≤ PSA < 2), 68 % (2 ≤ PSA < 5), and 94 % (PSA ≥ 5), respectively. One hundred and two patients (62 %) had changes in clinical management based on ^{18}F-fluciclovine PET findings. Twelve of these patients (12 %) had lesion localization on ^{18}F-fluciclovine PET, despite negative conventional imaging. Treatment plans of 14 patients with negative ^{18}F-fluciclovine PET were changed based on additional PET imaging with a different radiopharmaceutical.
Conclusion: ^{18}F-Fluciclovine PET/CT remains a useful diagnostic tool in the workup of patients with BCR PC, changing clinical management in 62 % of participants in our cohort.

Key words: Prostate cancer, PET/CT, ^{18}F-fluciclovine, Biochemical recurrence

Introduction

Although significant advances in primary definitive treatment of prostate cancer (PC) have improved the prognosis [1], recurrence of PC is still common, occurring in 20 to

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40 % of treated patients [2, 3]. Monitoring serum PSA after treatment helps identify recurrences in otherwise asymptomatic patients. Rising PSA after initial curative intent therapy (termed biochemical recurrence, BCR) is a risk factor for development of distant metastases and prostate cancer–specific mortality [4]. Over the past decade, PET imaging of patients with BCR PC has evolved with the development of various promising radiotracers [5]. ^{18}F-Fluciclovine (^{18}F-FACBC, anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, Axumin®) was approved by the US Food and Drug Administration (FDA) in 2016 and by the European Medicines Agency (EMA) in 2017 for use in BCR PC. ^{18}F-Fluciclovine is a synthetic amino acid analog that is actively transported into cells, specifically by LAT-1 (large amino acid transporter) and ASCT2 (alanine-serine-cysteine transporter), which are both upregulated in prostate cancer [6–8]. The FDA approval was based on high diagnostic performance and histologically confirmed data in patients with BCR showing 68 % detection rate on patient basis, 62 % positive predictive value (greater than 90 % for extraprostatic disease), and 70 % specificity [9]. Prospective trials reported that 59 % of patients with BCR PC had a change in management after the ^{18}F-fluciclovine PET scan [10]. A recent update to the NCCN Guidelines® recommends that ^{18}F-fluciclovine PET be considered in the workup of patients with BCR PC [11].

Although studies prior to FDA approval have shown the usefulness and limitations of ^{18}F-fluciclovine PET/CT, it is important to evaluate its performance in real-world clinical scenarios. Here, we report our experience in an academic center of ^{18}F-fluciclovine PET/CT in patients with BCR PC, with a focus on the rate of disease localization and changes in clinical management.

Materials and Methods

Patients

We reviewed retrospective data from 297 men with histologically confirmed PC who underwent ^{18}F-fluciclovine PET/CT between September 2017 and December 2019. Inclusion criteria were patients with PC suspected of BCR after primary definitive treatment (radical prostatectomy or radiation therapy). BCR was diagnosed after prostatectomy with or without adjuvant radiotherapy at a PSA level of 0.2 ng/ml or greater, with a second confirmatory PSA level of at least 0.2 ng/ml [12]. For post radiation therapy patients, BCR was diagnosed as rise of PSA measurement of 2 or more ng/ml over the nadir [13]. The following patients were excluded: (1) received non-primary treatment such as androgen deprivation therapy (ADT) or chemotherapy ($n = 61$), (2) underwent ^{18}F-fluciclovine PET for initial staging ($n = 42$), (3) did not experience the first BCR based on the abovementioned criteria yet ($n = 23$), and (4) had no documented follow-up management plan ($n = 6$). Thus, a total of 165 patients were included in the final analysis.

Figure 1 shows a flow chart of the study population. The Institutional Review Board approved this retrospective study and waived the requirement for obtaining written informed consent.

[18]F-Fluciclovine PET/CT Protocol

We followed published ACR-ACNM practice parameters [14]. In brief, patients were advised to avoid any significant exercise 1 day prior and to not eat or drink for a minimum of 4 h prior to imaging. Approximately 3–5 min following IV administration of the radiopharmaceutical, images were acquired using the Discovery 600, 690, or MI models (GE Healthcare, Waukesha, WI, USA) from the mid-thigh to the base of the skull. A low-dose CT scan was performed for attenuation correction and anatomic correlation. The mean dosage of ^{18}F-fluciclovine administered was 389 ± 59 MBq.
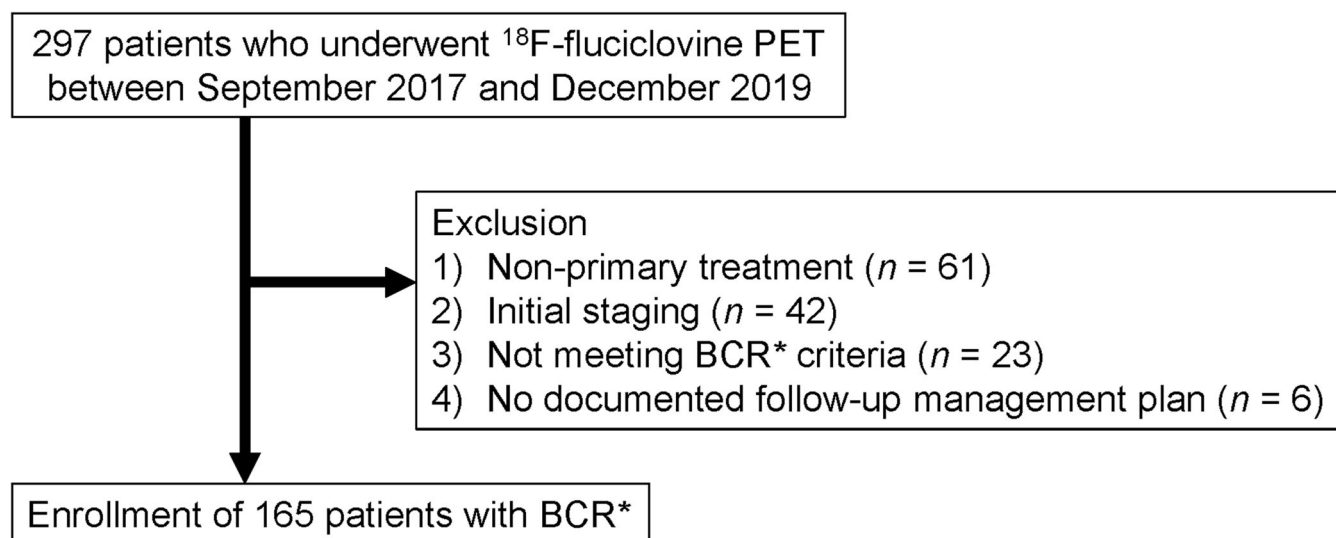
Image Analysis

[18]F-Fluciclovine PET images were visually evaluated by two board-certified nuclear medicine physicians (RN, with 11 years of experience; AI, with 15 years of experience) by consensus and according to guidelines [15], blinded to the clinical information, including other imaging. The positivity rate of ^{18}F-fluciclovine PET was correlated with PSA values, PSA doubling time, and anatomic region (prostate bed, lymph node, bone, lung, or other) on a per-patient basis. Locations of positive lesions were also divided into 2 categories: (1) prostate and (2) extraprostatic regions. In addition, positive lesions were classified into 3 categories based on their location: (1) prostate bed only, (2) pelvic-confined (pelvic-confined lymph nodes with or without prostate lesion), and (3) extra-pelvic (abdominal and retroperitoneal lymph nodes, osseous lesions, pulmonary lesions, and other visceral/soft tissue lesions with or without pelvic-confined PC). Imaging findings from abdomen and pelvis CT, pelvic MRI, and bone scan were compared to those from ^{18}F-fluciclovine PET where the field of view overlapped. Findings were considered congruent if both scans compared were negative or if the same lesions were identified on both scans.

Impact on Patient Management

The impact of ^{18}F-fluciclovine PET on patient management was evaluated by clinical chart review.

Additional PET Imaging with Other Radiopharmaceuticals

In patients who underwent other PET scans (^{18}F-NaF PET/CT, ^{68}Ga-PSMA11 PET/CT, ^{18}F-DCFPyL PET/CT, and ^{68}Ga-RM2 PET/MRI), additional findings were evaluated.

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│ 297 patients who underwent ¹⁸F-fluciclovine PET          │
│ between September 2017 and December 2019                 │
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        │         ┌──────────────────────────────────────────────────────────┐
        │────────▶│ Exclusion                                                │
        │         │ 1)  Non-primary treatment (n = 61)                       │
        │         │ 2)  Initial staging (n = 42)                             │
        │         │ 3)  Not meeting BCR* criteria (n = 23)                   │
        │         │ 4)  No documented follow-up management plan (n = 6)      │
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│ Enrollment of 165 patients with BCR*         │
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*BCR, biochemical recurrence

Fig. 1.   Flow chart of the patients enrolled.

Standard of Reference

Pathological confirmation of ^{18}F-fluciclovine PET findings was only available in a small number of cases ($n = 7$). Therefore, the diagnostic performance of clinical ^{18}F-fluciclovine PET/CT could not be evaluated.

Statistical Analysis

Continuous variables are summarized as medians and interquartile ranges (IQR) or means ± standard deviations. Values between groups were compared using the Mann-Whitney U test, Fisher's exact test, chi-squared test, or McNemar's test. Receiver operating characteristic (ROC) curves were used to calculate the area under the curves (AUCs) and to ascertain the optimal cutoff value of PSA doubling time for predicting positive ^{18}F-fluciclovine PET results, defined as the value providing the largest sum of sensitivity and specificity (Youden's index). Multivariate logistic regression analysis was also performed to identify independent predictors of positive ^{18}F-fluciclovine PET results. All statistical analyses were performed using statistical software, MedCalc version 19.2.1 (MedCalc Software, Ostend, Belgium), in which P values < 0.05 were considered statistically significant.

Results

Patients

Table 1 shows the patients' characteristics of the 165 men (50–91 years old, 71.1 ± 8.8) analyzed in this study. Primary

definitive treatment included radical prostatectomy with or without adjuvant pelvic radiation in 102 patients (62 %) and radiation therapy in 63 patients (38 %). Of the 63 patients treated with radiotherapy, only five patients received external beam radiation therapy (EBRT) within 1 year or brachytherapy within 2 years. PSA levels at the time of ^{18}F-fluciclovine PET ranged from 0.02 to 2975 ng/ml (median 3.1 ng/ml, IQR 1.0–9.6). PSA levels of 5 patients who had a previously confirmed diagnosis of BCR were below the BCR criteria at the time of the scan.

Lesions Detection

A total of 110 patients had positive ^{18}F-fluciclovine PET findings in putative sites of disease, and the remaining 55 patients had no ^{18}F-fluciclovine avid lesions. PSA in ^{18}F-fluciclovine positive cases (median 5.4 ng/ml, IQR 2.3–14.3) was significantly higher than that of negative cases (median 0.69 ng/ml, IQR 0.32–2.46) ($P < 0.05$). The overall positivity rate was 66.7 % (110/165) (95 % CI 54.8–80.4), increasing with higher PSA levels (ng/ml): 15.4 % (PSA < 0.5), 50 % (0.5 ≤ PSA < 1), 55.6 % (1 ≤ PSA < 2), 68.2 % (2 ≤ PSA < 5), and 93.7 % (PSA ≥ 5), respectively ($P < 0.0001$). The positivity rate of ^{18}F-fluciclovine PET for different PSA doubling time was 70.8 %, 69.7 %, 65.7 %, and 65.4 % for doubling time of 0–3 month, 3–6 months, 6–12 months, and greater than 12 months, respectively ($P = 0.94$). Table 2 shows the positivity rate by PSA level and doubling time. The positivity rate of patients who underwent SiPM-based PET/CT (GE Discovery MI, $n = 93$) was significantly higher than that of patients who underwent standard PET/CT (GE Discovery 690 or 600, $n = 72$)

Table 1. Patient characteristics

Number		165
Age, mean ± SD/median (range)		71.1 ± 8.8/71 (50–91)
Primary definitive treatment, no. (%)		
Radical prostatectomy		102 (61.8 %)
Radiation therapy		63 (38.2 %)
PSA (ng/ml), median (interquartile range; range)		3.1 (1.0–9.6; 0.02–2975)*
PSA doubling time (months), median (interquartile range; range)		4.6 (2.4–10.3; 0.3–59.6)
Grade group	Gleason score at initial diagnosis, no. (%)	
1	≤ 6	17 (10.3 %)
2	7 (3 + 4)	36 (21.8 %)
3	7 (4 + 3)	49 (29.7 %)
4	8	24 (14.5 %)
5	9–10	33 (20.0 %)
	Not available	6 (3.6 %)
PET/CT scanner, no. (%)		
Discovery MI		93 (55.0 %)
Discovery 690		62 (38.6 %)
Discovery 600		10 (6.4 %)

*PSA levels of 5 patients who had a previously confirmed diagnosis of BCR were below the BCR criteria at the time of the scan

(73.1 % *vs.* 58.3 %, $P = 0.046$) (Table 3), although their PSA levels were not significantly different (median 2.9 *vs.* 3.1 ng/ml, $P = 0.22$). Supplemental Table 1 shows the ^{18}F-fluciclovine PET results in 40 patients with low PSA levels (< 1 ng/ml). In these 40 patients, patients who underwent SiPM-based PET had a significantly higher positivity rate of ^{18}F-fluciclovine PET (8/19, 42.1 %) than those who underwent standard PET (3/21, 14.3 %) ($P = 0.029$). In addition, the performance of ^{18}F-fluciclovine PET was higher (sensitivity 80 %, specificity 66.7 %, AUC = 0.705) when a PSA doubling time threshold of 7 months or less was used. However, multivariate analysis revealed that the combination of a PSA doubling time threshold and SiPM-based PET did not improve lesion detection on ^{18}F-fluciclovine PET in this cohort. Forty-six (27.9 %) patients had lesions in the prostate/prostate bed. Eighty-six (52.1 %) patients had lesions in the extraprostatic region. Of these, lesions with ^{18}F-fluciclovine uptake were detected in lymph nodes in 69 (41.8 %) patients, in bone in 41 (24.8 %), and in the lung in 9 (5.5 %) patients. When 110 patients with positive ^{18}F-fluciclovine PET scan were divided into three groups according to the sites of lesions (prostate bed only, pelvic-confined, and extra-pelvic), the number of patients in each site was 28 (14.5 %), 28 (14.5 %), and 68 (37.6 %), respectively. These findings are summarized in Table 4.

Comparison with Conventional Imaging

Seventy (42.4 %) patients had at least one other concurrent conventional imaging study within 3 months before or after the ^{18}F-fluciclovine PET scan: abdomen-pelvis CT ($n = 31$), pelvic MRI ($n = 31$), and bone scan ($n = 26$). Of the three conventional scans, 55 patients had one, 12 had two, and 3 had all three scans. The lesion detection rates of CT, MR, and bone scan were 25.8 % (8/31), 64.5 % (20/31), and 26.9 % (7/26), respectively. The detection rate of ^{18}F-fluciclovine PET (54.8 %, 17/31) was significantly higher

than that of CT ($P = 0.0039$); 9/31 (29 %) patients with negative CT had positive ^{18}F-fluciclovine PET finding(s). The detection rate of ^{18}F-fluciclovine PET (83.9 %, 26/31) was significantly higher than that of MR ($P = 0.031$); 6/31 (19 %) patients with negative MRI had positive ^{18}F-fluciclovine PET finding(s). There were no patients with negative ^{18}F-fluciclovine PET who had lesions identified on CT or MRI in our cohort. Figure 2 shows an example patient who had subcentimeter local recurrence in a ^{18}F-fluciclovine avid lesion that was not detected on MRI. For dedicated bone imaging, 25/26 (96.2 %) bone scans were congruent with ^{18}F-fluciclovine PET, while 1/26 (3.8 %) patient with negative bone scan had an osseous lesion identified on ^{18}F-fluciclovine PET, as shown in Fig. 3. Table 5 summarizes these findings.

Impact on Patient Management

One hundred and two patients (61.8 %, 95 % CI 53.9–69.3) had a resulting change in clinical management due to ^{18}F-fluciclovine PET findings. These included 41 of the 102 patients (40.2 %) referred for radiation therapy with or without concurrent ADT and 51 patients (50 %) who started ADT only. Figure 4 shows the flow chart of changes in management based on ^{18}F-fluciclovine PET findings. Twelve of the 102 patients (12 %) who had a change in management had lesion localization on ^{18}F-fluciclovine PET, despite negative conventional imaging (CT, MRI, and/or bone scan).

Additional PET Imaging with Other Radiopharmaceuticals

Additional PET imaging was performed at a median of 36 days (IQR 19–69) after ^{18}F-fluciclovine PET scan. Thirty-three (20 %) patients underwent at least one other PET imaging (^{18}F-NaF PET/CT ($n = 12$), ^{68}Ga-PSMA11

Table 2. Positivity rate by PSA level (ng/ml) and doubling time (months)

PSA level	Positive scan	Negative scan	Total	Positivity rate
PSA < 0.5	4	22	26	15.4 %
0.5 ≤ PSA < 1	7	7	14	50 %
1 ≤ PSA < 2	10	8	18	55.6 %
2 ≤ PSA < 5	30	14	44	68.2 %
PSA ≥ 5	59	4	63	93.7 %
Total	110	55	165	66.7 %
PSA doubling time	**Positive scan**	**Negative scan**	**Total**	**Positivity rate**
0–3	34	14	48	70.8 %
3–6	23	10	33	69.7 %
6–12	23	12	35	65.7 %
≥ 12	17	9	26	65.4 %
Total	97	45	142*	68.3 %

*PSA doubling time of 23 patients could not be measured due to missing data

PET/CT ($n = 5$), ^{18}F-DCFPyL PET/CT ($n = 20$), and ^{68}Ga-RM2 PET/MRI ($n = 5$)). In 14 of these patients with negative ^{18}F-fluciclovine PET, additional PET imaging revealed new lesion(s). Table 6 summarizes these findings. Figure 5 shows a representative case that was negative on ^{18}F-fluciclovine PET but positive on ^{18}F-DCFPyL PET. The PSA level of the 14 patients (median 2.3 ng/ml, IQR 1.3–3.1) was significantly lower than that of patients with positive ^{18}F-fluciclovine PET scan (median 5.4 ng/ml, IQR 2.3–14.3) ($P < 0.0028$). Treatment plans of all these 14 patients were changed, and subsequent treatment resulted in decreased PSA levels.

Discussion

In our cohort, ^{18}F-fluciclovine had an overall positivity rate of 66.7 % on a per-patient basis, which was higher than that of 57 % reported in a recent prospective study of 213 patients with BCR PC [10]. One possible reason for this is that our population had a higher PSA level than the population in the recent study (median 3.1 vs. 1.0 ng/ml). Another possible reason is that SiPM-based PET/CT, which has higher spatial resolution compared with standard PET/CT [16], was used for more than half (55 %) of our patients. The SiPM-based PET/CT had a higher positivity rate than standard PET/CT in our population (73.1 % vs. 58.3 %, $P = 0.046$). Furthermore, the subanalysis highlighted the advantage of SiPM-based PET/CT over standard PET in patients with low PSA levels (< 1 ng/ml) (42.1 % vs. 14.3 %, $P = 0.029$). The scanner used for ^{18}F-fluciclovine PET/CT was

Table 3. Comparison of positivity rate between SiPM-based PET and standard PET by PSA level

	Positive scan		Negative scan		P (SiPM vs. standard)
	SiPM	Standard	SiPM	Standard	
PSA < 0.5	4	0	8	14	0.033
0.5 ≤ PSA < 1	4	3	3	4	1
1 ≤ PSA < 2	7	3	5	3	1
2 ≤ PSA < 5	18	12	6	8	0.29
PSA ≥ 5	35	24	3	1	0.54
Total	68	42	25	30	0.046

randomly assigned based on clinical workflow.

It is known that the lesion detection rate of ^{18}F-fluciclovine PET depends on PSA levels; this was confirmed by our results. According to published data, in patients with PSA values < 1 ng/ml, ^{18}F-fluciclovine PET has relatively low sensitivity for extraprostatic disease, ranging from 21 to 39 % [9, 17]. In patients with PSA values higher than 5, sensitivity is overall approximately 85 % (approximately 60 % for extraprostatic disease) [9]. Similarly to other reports [18, 19], no statistically significant higher positivity rate of ^{18}F-fluciclovine was found in patients with shorter PSA doubling time, although it is known as a prognostic factor for patients with BCR PC [20]. This may be attributed to the relatively small cohort size. The positivity rate for the prostate region was 27.9 %, which is lower than the 60.5 % (92/152) reported in the recent retrospective study by Savir-Baruch et al. [18] but comparable to 30 % (64/213) reported in the recent prospective trial by Andriole et al. [10]. In the study by Andriole et al., to minimize false-positive tracer activity due to inflammatory uptake after radiation, patients who underwent EBRT within 1 year or brachytherapy within 2 years were excluded, while patients who have recently undergone radiation therapy were included in the study by Savir-Baruch et al. The coincidence of only 5 patients in our cohort who had recently undergone radiotherapy may have been responsible for the low positivity rate in the prostate region, as well as in Andriole et al.

Our results confirm the superiority of ^{18}F-fluciclovine PET in lesion detection over CT and MR. A previous study reported that, in 53 patients with BCR PC, recurrent lesions were detected in 41 patients (77.4 %) by ^{18}F-fluciclovine PET and in 10 patients (18.9 %) by CT alone [21]. Another study reported that, in a cohort of 24 men with BCR PC, the disease detection rate was 94.7 % using ^{18}F-fluciclovine PET compared to 31.6–36.8 % for multiparametric MR [22]. The main advantage of ^{18}F-fluciclovine PET over conventional CT or MR is that ^{18}F-fluciclovine PET often detects subcentimeter lesions with increased uptake as shown in Fig. 2. For bone lesions, ^{18}F-fluciclovine PET findings were congruent with bone scan in all but one case. Although ^{18}F-fluciclovine PET typically demonstrates intense focal uptake

Table 4. Positivity rate by region in all 165 patients

Region/organ	Positive scan, n	Positivity rate, %
Prostate	46	27.9 %
Extraprostatic region	86	52.1 %
• LN	69 (pelvic, 30; extra-pelvic, 39)	41.8 %
• Bone	41	24.8 %
• Lung	9	5.5 %
Prostate bed only	24	14.5 %
Pelvic-confined*	24	14.5 %
Extra-pelvic†	62	37.6 %

*Pelvic lymph node metastasis with or without prostate lesion
†Extra-pelvic lymph node metastasis and/or distant metastasis

in lytic osseous lesions, it shows variable activity in sclerotic lesions [15]. In addition, compared with ^{18}F-FDG PET, ^{18}F-fluciclovine PET has greater heterogeneity in physiologic bone marrow uptake [15]. Accordingly, mild ^{18}F-fluciclovine uptake in dense sclerotic lesions may be masked by physiologic distribution in normal bone marrow.

^{18}F-Fluciclovine PET altered clinical management in 102 patients (62 %) including 92 patients treated with targeted radiotherapy and/or ADT (Fig. 4). Similar clinical impact of ^{18}F-fluciclovine PET was shown previously in a study where overall 126 of the 213 patients (59 %) had a change in management after ^{18}F-fluciclovine PET scan [10]. A total of 12 patients who had lesion localization only on ^{18}F-fluciclovine PET with no findings on conventional imaging had changes in clinical management. However, the extent to which patient-specific treatment decisions based on ^{18}F-fluciclovine PET have a more favorable impact on progression-free survival or overall survival than conventional imaging has not yet been reported. Therefore, additional studies are necessary to assess the impact of ^{18}F-fluciclovine PET on patient outcomes as a result of changes in patient management.

Additional PET imaging led to changes in the treatment strategy for 14 patients with negative ^{18}F-fluciclovine uptake. As previously reported, our results demonstrate that the relatively lower detection rate of ^{18}F-fluciclovine PET in patients with low PSA levels is one of its drawbacks [23]. The fact that additional PET imaging was obtained after ^{18}F-fluciclovine PET (after a median of 36 days) may have
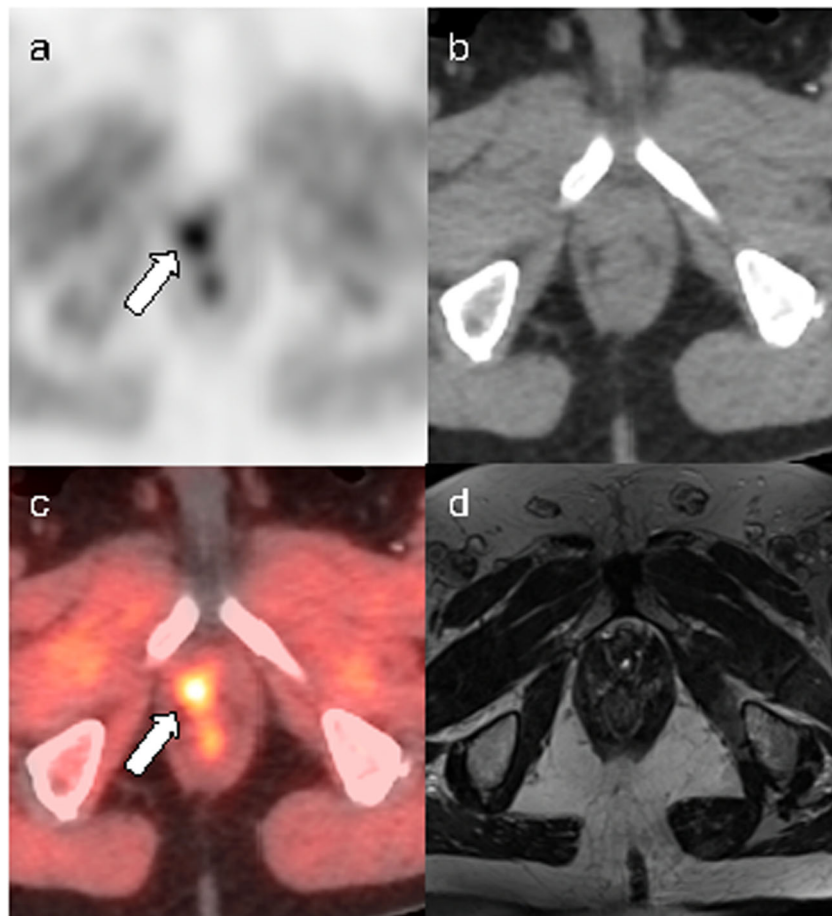

Fig. 2. A 72-year-old man with suspected BCR 3 years after radical prostatectomy underwent ^{18}F-fluciclovine PET/CT (a–c). The two most recent PSA values before the scan were 0.75 ng/ml and 1.3 ng/ml, respectively. Focal ^{18}F-fluciclovine uptake in the prostate bed was seen on axial PET and fused PET/CT (a, c, arrows). No definite lesion was found on T2-weighted MRI (d). The patients underwent salvage radiation therapy and PSA became undetectable.
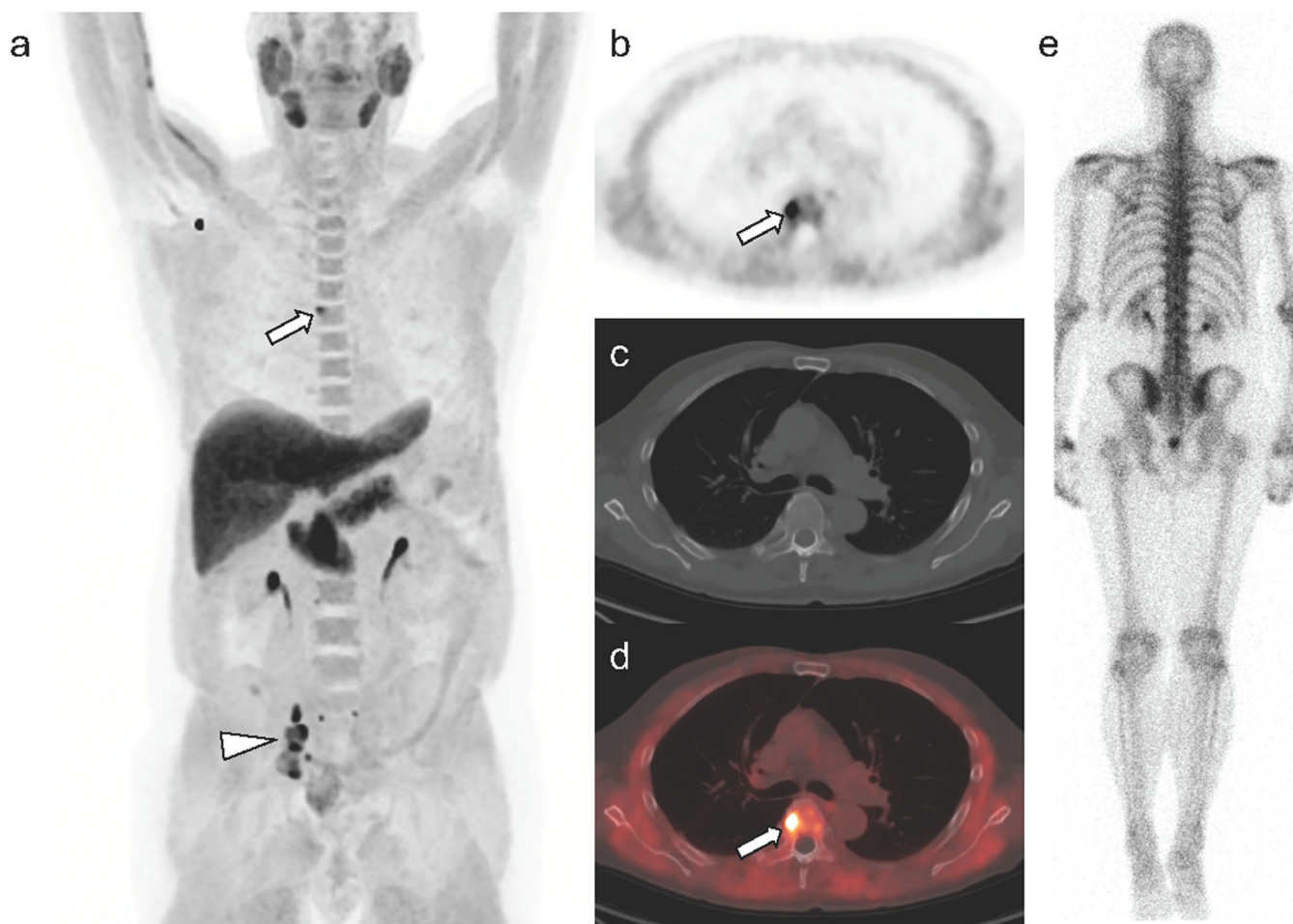
Fig. 3. A 69-year-old man with suspected BCR 10 years after radical prostatectomy underwent ^{18}F-fluciclovine PET/CT (**a–d**). The two most recent PSA values before the scan were 7.82 ng/ml and 11.12 ng/ml, respectively. ^{18}F-Fluciclovine PET/CT revealed not only right pelvic nodal metastases (**a**, arrowhead) but also small bone metastasis in T6 (**a, b, d**, arrows). Bone scan (posterior view) was negative (**e**). The patient started androgen deprivation therapy, and PSA decreased to less than 0.01 ng/ml.

favored the detection of lesions by additional PET imaging, but our results reiterated the usefulness of PSMA-based PET, which contributed to a change in treatment strategy in 11 of 14 patients. In light of the above, if ^{18}F-fluciclovine PET is negative despite clinical suspicion of BCR, further evaluation with other imaging modalities, such as PSMA-based PET/CT in research protocols until FDA approval, should be considered [15].

A growing number of studies in recent years have reported the superiority of PSMA-based PET to ^{18}F-fluciclovine PET [23–25]. The advantage of PSMA-based PET stands out in the detection of lymph node metastases in patients with low PSA concentrations (< 2.0 ng/ml) [23]. Overexpression of PSMA that is seen in not only advanced castrate–resistant PC but also early castrate–sensitive PC results in higher SUVmax and lesion-to-background ratios

Table 5. Comparison of ^{18}F-fluciclovine PET/CT findings to conventional imaging

Conventional imaging	CT ($n=31$)	MR ($n=31$)	^{99m}Tc-MDP ($n=26$)
Congruent, no. of patients (%)	20 (64.5 %)	21 (67.7 %)	25 (96.2 %)
Non-congruent, no. of patients (%)	11 (34.4 %)	10 (32.3 %)	1 (3.8 %)
➢ Positive ^{18}F-fluciclovine PET	9*	6†	1
➢ Negative ^{18}F-fluciclovine PET	0	0	0
➢ Different findings	2	4	0
Detection rate, % (no. of patients)	25.8 % (8) *vs.* 54.8 % (17)	64.5 % (20) *vs.* 83.9 % (26)	26.9 % (7) *vs.* 30.8 % (8)
(conventional *vs.* ^{18}F-fluciclovine)	($P=0.0039$)	($P=0.031$)	($P=1.0$)

*Four cases in the prostate/prostate bed, 4 cases in lymph nodes, and 1 case in bone
†Five cases in the prostate/prostate bed, 2 cases in lymph nodes (one patient had recurrent lesions in both the prostate and lymph nodes)
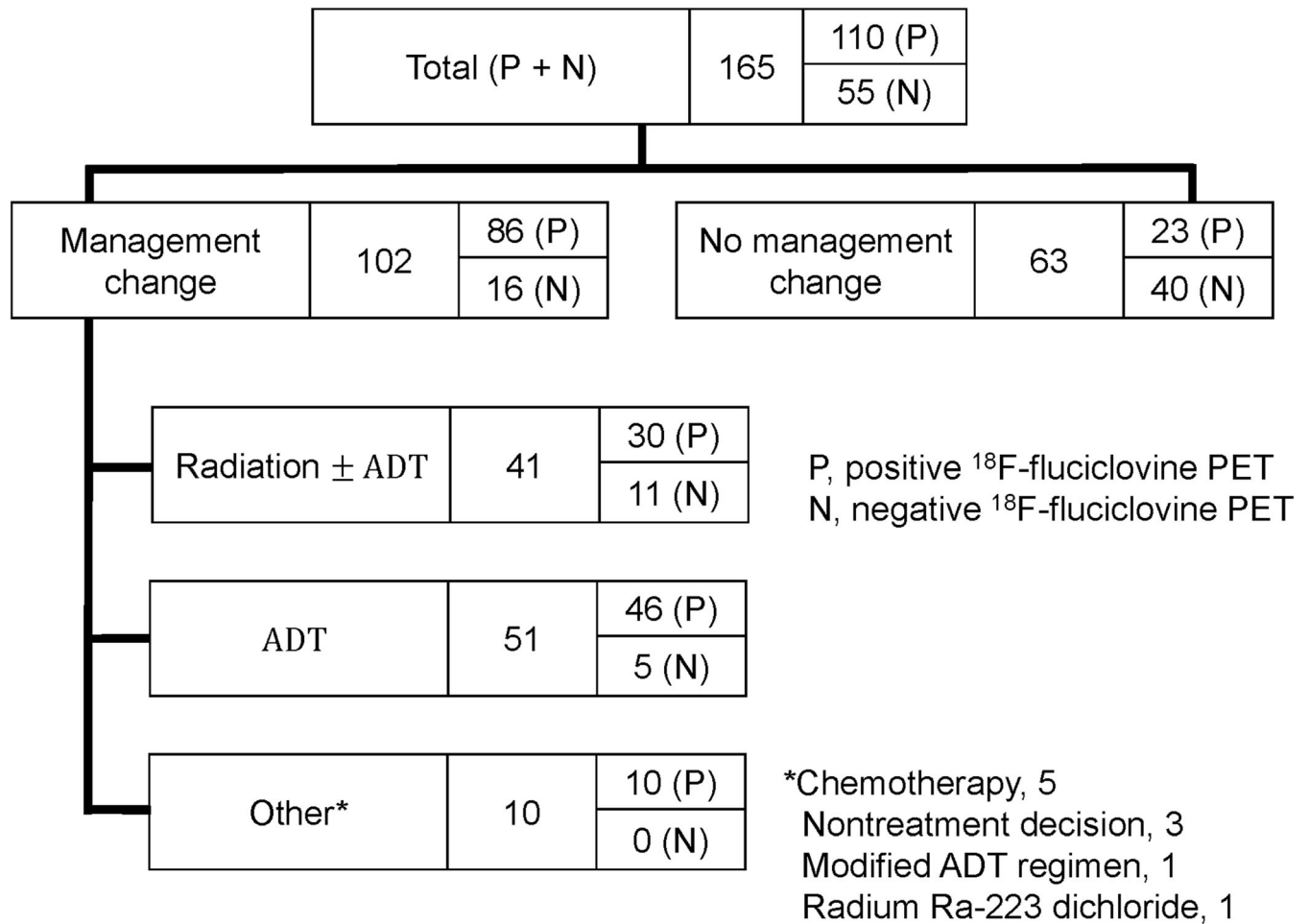
Fig. 4. Flow chart of changes in clinical management based on ^{18}F-fluciclovine PET findings. ADT, androgen deprivation therapy.

for concordantly PET positive lesions with PSMA than ^{18}F-fluciclovine [23]. On the other hand, ^{18}F-fluciclovine PET is non-inferior to PSMA PET in detecting distant metastases of patients with high PSA levels [24]. Furthermore, previous data have shown that ^{18}F-fluciclovine PET and PSMA-based PET are complementary to each other with strengths in different areas [9, 24], although, in our cohort, the small number of PSMA-based PET scans ($n = 25$) did not allow for a sufficient comparison. The advantage of ^{18}F-fluciclovine is reported to be its ability to detect curable localized disease in close anatomical relation to the urinary bladder

due to relatively slow physiological urinary excretion of ^{18}F-fluciclovine in comparison to PSMA-based PET [26], which was also shown in Fig. 5.

Our study has several limitations. Firstly, it is a retrospective single-center study. However, to reduce selection bias, all patients during the period between the initiation of the ^{18}F-fluciclovine PET at our facility and the start of the analysis were selected for inclusion in the study. Secondly, pathological confirmation of ^{18}F-fluciclovine PET findings was only available in a small number of cases ($n = 7$), because biopsy was often difficult since lesions detected on

Table 6. Fourteen patients with negative ^{18}F-fluciclovine PET/CT whose treatment plans were changed by other PET imaging

Region PET imaging	Prostate	Lymph node	Bone	Other
^{18}F-NaF PET/CT ($n = 1$)	0	0	1	0
^{68}Ga-PSMA PET/CT ($n = 2$)	1	1	1	1 (lung)
^{18}F-DCFPyL PET/CT ($n = 9$)	1	8	1	1 (chest wall*)
^{68}Ga-RM2 PET/MR ($n = 2$)	1	1	0	0

*Biopsy of ^{18}F-DCFPyL avid lesion with no significant ^{18}F-fluciclovine uptake in the right chest wall revealed metastatic prostate cancer, considered port site metastasis after laparoscopic surgery
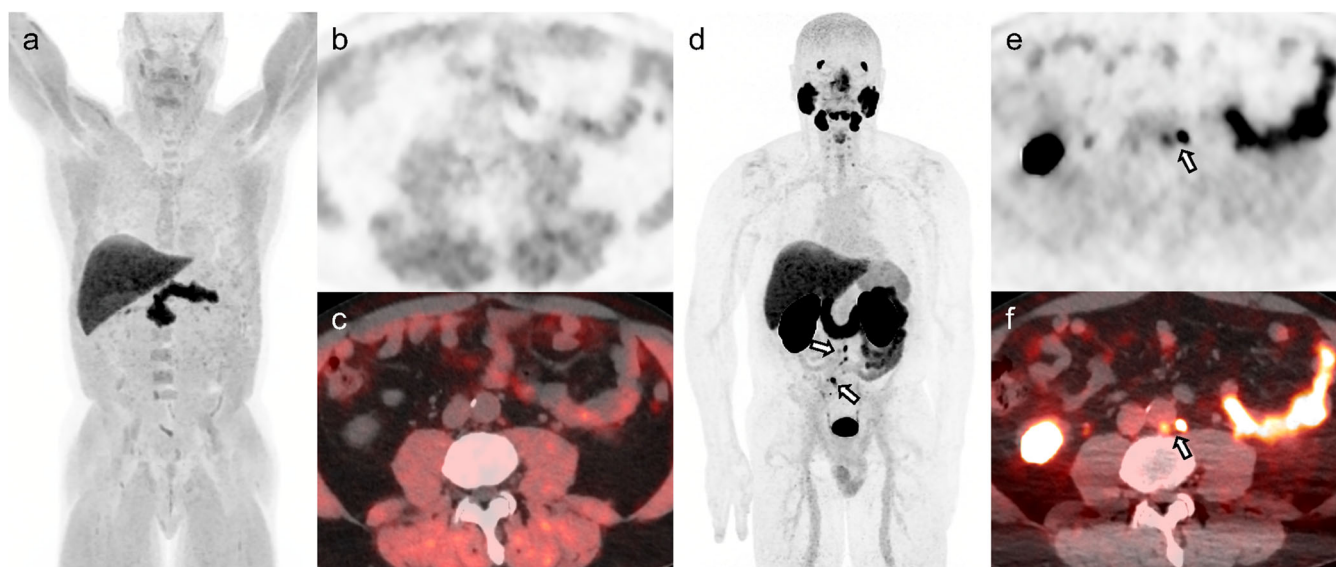
Fig. 5. A 69-year-old man with suspected BCR 6 months after radiation therapy underwent ^{18}F-fluciclovine PET/CT (**a–c**) that was negative for suspicious lesions. The PSA nadir was 1.0 ng/ml and it had risen to 8.6 ng/ml prior to the scan. ^{18}F-DCFPyL PET/CT done 1 month later showed focal ^{18}F-DCFPyL uptake in multiple small (subcentimeter) paraaortic lymph nodes, as well as along the right iliac chain (**d–f**, arrows). The patient started androgen deprivation therapy, and PSA decreased to 0.7 ng/ml.

^{18}F-fluciclovine PET were frequently subcentimeter in size. In addition, when multiple lesions are detected on ^{18}F-fluciclovine PET in putative sites of disease for PC recurrence or metastases, treating physicians often rely on post-treatment PSA changes for confirmation of positive ^{18}F-fluciclovine lesions rather than on biopsy. Therefore, we only indicated the positivity rate of ^{18}F-fluciclovine PET. Thirdly, we conducted a review of clinical charts to determine the impact of ^{18}F-fuciclovine PET on clinical management, while that several prior studies used a survey of oncologists to determine change of intended clinical management [10]. Our approach, although we assessed the impact of ^{18}F-fluciclovine PET on the clinical management based on actual changes after we confirmed in the medical records that physicians were referring to the findings of ^{18}F-fluciclovine PET, has the limitation that it is difficult to determine whether the decisions made by the treating physicians were based on imaging alone or other contributing factors such as PSA, risk and benefit of treatments, and patient preference. Further prospective studies using a questionnaire to physicians are needed to accurately assess the impact of ^{18}F-fluciclovine PET/CT.

Conclusions

^{18}F-Fluciclovine PET/CT is a useful diagnostic tool in the workup of patients with BCR PC as it changed clinical management in 64 % of participants in our cohort. In the setting of a negative ^{18}F-fluciclovine PET despite clinical suspicion of BCR, further evaluation with alternative imaging modalities including currently investigational PSMA-based PET should be considered for a more complete evaluation.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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