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Original Article

Results from a prospective registry of ^{18}F-Fluciclovine PET/CT use in prostate cancer management: a cautionary lesson for implementation of PSMA PET

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Abstract: Background: ^{18}F-Fluciclovine positron emission tomography (PET) was FDA-approved in the U.S. in 2016 and was the most sensitive imaging modality for prostate cancer (PC) until the approval of prostate-specific membrane antigen (PSMA) PET in 2020. However, providers' reasons for ordering ^{18}F-Fluciclovine PET/CT (FluPET) in practice and impact on patient care remain poorly defined. This prospective registry at a tertiary academic center describes patterns of FluPET use and outcomes prior to the FDA approval of PSMA PET in December 2020. Methods: Providers ordering FluPET for patients with PC were surveyed before, ≤2 weeks after, and ≥1 year after imaging to assess reasons for obtaining FluPET, projected treatment plan, changes in plan due to FluPET findings, and toxicity attributable to the change in treatment plan. Baseline patient characteristics, FluPET results, and longitudinal outcomes were collected. Results: Between 12/2018-09/2021, 62 patients with localized PC (8.1%), biochemical recurrence (BCR; 80.6%), non-metastatic castration-resistant PC (CRPC) (3.2%), metastatic castration-sensitive PC (3.2%), or metastatic CRPC (4.8%) were enrolled and underwent FluPET. Most scans (90.3%) were performed prior to the FDA approval of PSMA PET 12/2020. FluPET was most often obtained to guide local salvage or metastasis-directed therapies (90.3%); other reasons (non-exclusive) were initial staging (9.6%) or clarifying equivocal lesions from other imaging (9.6%). FluPET detected ≥1 PC lesion in 74.2% of patients. After FluPET, 48.4% of providers reported changing treatment plans, which was more likely when FluPET was positive (60.9% vs 12.5%, P<0.001), and often involved initiation of systemic therapy (19.4%). Treatment changes were reported in 57% of patients with BCR1 and 48.2% of patients with BCR2. In contrast, only 20% of patients with distant metastatic disease had a change in treatment. Among patients in the BCR1 and BCR2 cohort, treatment plan changes were associated with a median time to next treatment that was not reached after a median follow-up of 67.6 months. There was no statistically significant difference in overall survival between patients with biochemical recurrence (BCR) who did and did not have a treatment plan change. A year after FluPET, reported potential toxicities from treatment plan changes were minimal. Conclusion: FluPET was utilized across the disease spectrum of PC, primarily to guide local salvage or metastasis-directed therapies, given its improved sensitivity for detecting prostate bed recurrence due to the slow physiologic excretion of ^{18}F-fluciclovine. Notably, a positive FluPET frequently prompted initiation of systemic therapy; however, the clinical benefit of such management remains uncertain. Moreover, providers often selected multiple, sometimes conflicting, treatment plans following FluPET, reflecting uncertainty in translating imaging findings into definitive management decisions. A larger, prospective registry using PSMA PET with a requirement for providers to select a single post-scan treatment strategy is warranted to better assess whether imaging-guided treatment changes improve clinical outcomes.

Keywords: Imaging, radiotracers, nuclear medicine, PSMA PET/CT, ^{18}F-Fluciclovine PET/CT, clinical decision-making

Introduction

^{18}F-Fluciclovine positron emission tomography (PET) is a next-generation imaging modality that was approved by the U.S. FDA in May 2016 for "suspected prostate cancer recurrence based on elevated prostate-specific antigen (PSA) levels following prior treatment", based on two unpublished studies conducted in men with rising PSA levels following radical prostatectomy and/or radiation [1, 2]. Prior to the U.S. FDA approval of prostate-specific membrane antigen (PSMA) PET in December 2020 for similar indications, ^{18}F-Fluciclovine PET was the most sensitive imaging modality for prostate cancer (PC) that was widely available in the U.S., and it was first incorporated in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of PC in February 2018 [3, 4]. The NCCN guidelines suggested consideration of ^{18}F-Fluciclovine PET for work-up of progression in a range of disease states, from initial definitive therapy for localized disease to progression of metastatic castration-resistant prostate cancer (mCRPC) [5]. Notably, ^{18}F-Fluciclovine PET/CT (FluPET) differs from PSMA PET due to physiologic

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Table 1. Baseline characteristics

Characteristic	N[a] (%)
Median Age, Yrs (IQR)	68.0 (62.8-72.0)
Race	
White	47 (90.4)
Black	3 (5.8)
Other	2 (3.8)
Median Yrs Since Diagnosis (IQR)	6.0 (2.0-10.0)
Prior Local Therapy	
None	6 (9.7)
Radical Prostatectomy	17 (27.4)
Radiation	17 (27.4)
Both Radical Prostatectomy and Radiation	22 (35.5)
Prior Systemic Therapy	
Androgen Deprivation Therapy	35 (56.5)
Novel Hormonal Agent	5 (8.1)
Taxane Chemotherapy	3 (4.8)
Prostate Cancer Disease State	
Localized	5 (8.1)
1st Biochemical Recurrence	21 (33.9)
2nd Biochemical Recurrence	29 (46.8)
Non-Metastatic Castration-Resistant	2 (3.2)
Metastatic Castration-Sensitive	2 (3.2)
Metastatic Castration-Resistant	3 (4.8)
Median PSA Prior to FluPET, ng/mL (IQR)	2.8 (0.7-6.4)

[a]Some variables have data for fewer than 62 patients due to missing values. Abbreviations: Yrs, Years; IQR, Interquartile Range; PSA, Prostate-Specific Antigen; FluPET, ^{18}F-Fluciclovine PET/CT.

delay of ^{18}F-Fluciclovine passage into the bladder, making it ideal for identifying local recurrence in the prostate bed post-radical prostatectomy.

Prior clinical trials investigated the use of FluPET in patients with biochemical recurrence (BCR) after curative intent treatment for localized PC, who were being considered for salvage therapy and showed that FluPET findings frequently resulted in a change in the management plan. Overall, the frequency of reported treatment changes ranged from 35-63% in these studies [6-8]. However, prospective data on FluPET use for PC in practice outside of a clinical trial and its effect on provider management, including for disease states other than BCR after curative intent therapy, have not previously been described. Here, we report results of FluPET use and clinical outcomes from a prospective registry at a tertiary academic center. We hypothesized that FluPET will facilitate early identification of local recurrence and metastatic PC, amenable to both local definitive and systemic therapy, offering potential to improve long-term outcomes in the future.

Patients and methods

From December 2018 to September 2021, we prospectively enrolled patients with histologically or cytologically confirmed prostate adenocarcinoma who had plans to undergo FluPET imaging at our tertiary academic center. Patients were provided with an informed consent form and given opportunity to ask questions about the study. Informed consent forms were obtained per institutional review board, ethics committee and institutional requirements. Patients were excluded if they had a previous diagnosis of a second, non-prostate malignancy requiring systemic therapy. Providers ordering FluPET were surveyed before, ≤2 weeks after, and ≥1 year after imaging to document their initial reasons for obtaining FluPET, the therapeutic options they were considering prior to FluPET, changes to their treatment plan due to FluPET findings, and toxicity potentially attributable to these changes in treatment plan (Appendices 1, 2, 3). Baseline patient characteristics, FluPET results, and longitudinal outcomes were collected prospectively. FluPET scans were read by different radiologists, thus FluPET was deemed positive or indeterminate as per the clinical significance indicated in the provider's notes.

Statistical analysis was performed using SPSS Version 29 (IBM, Armonk, NY) and PRISM software. Treatment changes following FluPET were determined using χ^2. Student's t-test was used to determine difference in treatment plan changes in terms of highest maximum SUV or number of positive lesions/nodal groups. Fisher's exact test was used to determine difference in positive FluPET by PSA range. Binary logistic regression was used to determine if a higher pre-scan PSA level was associated with greater likelihood of having a positive FluPET. PSA levels in patients with BCR were compared using the Mann-Whitney U test. Survival analyses and hazard ratios were analyzed in PRISM using the log-rank test. This study was approved by our institutional review board.

Results

Of 69 patients enrolled between December 2018 and September 2021, 62 patients ultimately underwent FluPET imaging with baseline characteristics as described in **Table 1**. Most patients (90.3%) were consented for this study prior to the FDA approval of PSMA PET. The vast majority of providers that ordered FluPET were from medical oncology (81.8%). The majority of providers ordered FluPET to guide local salvage or oligometastasis-directed therapies (90.3%). Other reasons providers indicated (non-exclusive) were for initial staging purposes (9.6%) or for clarifying equivocal lesions found on conventional imaging tests (9.6%). Prior to obtaining FluPET, providers reported considering options (non-exclusive) described in **Table 2** for therapeutic management, including observation (69.4%), local therapies such as surgery, radiation, or cryotherapy (25.8%), and systemic therapy involving androgen deprivation therapy, with or without docetaxel chemotherapy or novel hormonal agents such as abiraterone acetate and enzalutamide (51.6%). Many providers selected more than one option (43.5%), even though the questionnaire requested the selection of only

Table 2. Treatment plans before and after ^{18}F-Fluciclovine PET/CT

Disease State	Treatment Considered Before FluPET (N, %)[a]			Treatment Changes Reported After FluPET[b] (N, %)				
	Obs	Local	Systemic	Any Change	Obs	Local	Systemic	Local & Systemic
All	43 (69.4)	16 (25.8)	32 (51.6)	30 (48.4)	3 (4.8)	10 (16.1)	12 (19.4)	5 (8.1)
Localized	0 (0.0)	3 (60.0)	4 (80.0)	2 (40.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)
1st BCR	14 (66.7)	9 (42.9)	11 (52.4)	12 (57.1)	0 (0.0)	4 (19.0)	5 (23.8)	3 (14.3)
2nd BCR	26 (89.7)	2 (6.9)	12 (41.4)	14 (48.3)	3 (10.4)	5 (17.2)	5 (17.2)	1 (3.4)
M0 CRPC	1 (50.0)	0 (0.0)	2 (100.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
mCSPC	1 (50.0)	1 (50.0)	2 (100.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
mCRPC	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Treatments considered are non-exclusive; providers could selection more than one option so sum may not equal 100%. Abbreviations: FluPET-^{18}F, Fluciclovine PET/CT; Obs, Observation; BCR, Biochemical Recurrence; M0 CRPC, Non-Metastatic Castration-Resistant Prostate Cancer; mCSPC, Metastatic Castration-Sensitive Prostate Cancer; mCRPC, Metastatic Castration-Resistant Prostate Cancer. [b]Represents the final changed plan and the percentages are out of a total of 62 patient. 30 patients had a change in plan (48.4% of total patients in this study).

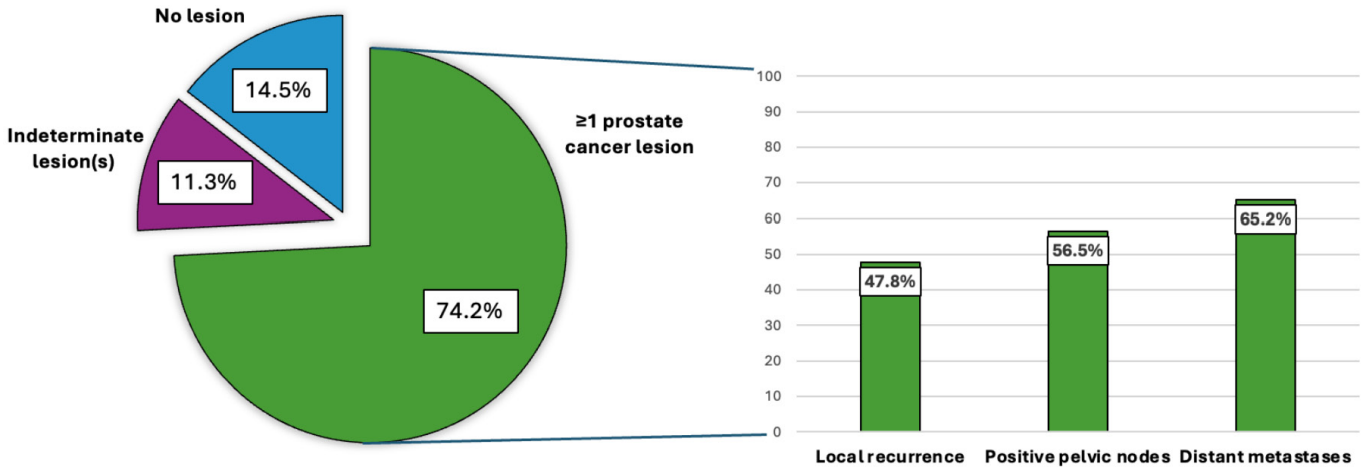

Figure 1. ^{18}F-Fluciclovine PET/CT results and detection of prostate cancer lesions. Pie chart demonstrating the proportion of 18F-Fluciclovine PET/CT scans which detected at least one prostate cancer lesion, only indeterminate lesion(s), or no lesions. Bar graph detailing the location of prostate cancer lesions that were detected on positive scan.

one treatment option. Interestingly, 32.3% of providers selected observation as well as local or systemic therapy, suggesting they would proceed with surveillance if imaging were negative for metastatic disease and systemic therapy if imaging showed metastatic disease.

FluPET was read as positive for one or more PC lesions in 74.2% of patients, as having indeterminate lesions in 11.3% of patients, and as having no evidence of PC lesions in 14.5% of patients. Providers indicated ordering FluPET for equivocal lesions on conventional imaging for six patients, four of whom had a positive FluPET. of the 46 FluPET scans read as positive for one or more PC lesions, local recurrence was detected in 22 patients (47.8%), positive pelvic nodes in 26 patients (56.5%), and distant metastases in 39 patients (65.2%; **Figure 1**). The mean number of positive lesions or nodal groups detected on these scans was 3.9 (SD 3.6), and the mean highest maximum standardized uptake values (SUV) of positive lesions was 7.7 (SD 5.6). Of the 62 patients who had FluPET imaging, positive findings were observed in 40% of patients who had a baseline PSA<0.5 (5 patients), 57% who had PSA 0.5-2 (21 patients), 83% who had PSA 2-5 (18 patients), and 94% who had PSA>5 (18 patients, P=0.0098). Having a higher pre-scan PSA level was associated with greater likelihood of having a positive FluPET scan (OR 1.4 per 1.0 ng/mL increase in PSA; 95% CI 1.0-1.8, P=0.04).

After FluPET, 48.4% of providers reported that imaging findings changed their treatment plan: 4.8% of treatment plans were changed to observation, 16.1% to local therapies, 19.4% to systemic therapy, and 8.1% to a combination of local and systemic therapies (**Table 2**). For patients who were started on systemic therapy following FluPET, 29.4% received ADT alone and 70.6% received ADT plus abiraterone acetate. Treatment changes were reported in 57% of patients with BCR1, 48.2% of patients with BCR2, and only 20% of patients with distant metastatic disease. 6 of 9 patients who had a positive FluPET post-radical prostatectomy at BCR1 had a treatment change. 66.7% of patients in this group had a PSA<1. 12 of 15 patients with positive FluPET post-radical prostatectomy at BCR2 had a treatment change. 50% of patients in this group had a PSA<1. Treatment changes were more likely to be reported when FluPET was read as positive for PC

(60.9% vs. 12.5%, P<0.001). Amongst patients with positive FluPET, there was no significant difference between patients who did and did not have treatment plan changes in terms of the highest maximum SUV or number of positive lesions/nodal groups.

The largest cohort of patients in this study were in BCR1 and BCR2 (50 patients). This included 25 patients in the treatment plan change group vs 24 patients in the no treatment plan change cohort. 92% of patients in the treatment plan change group had a positive FluPET and underwent local and/or systemic therapy. In contrast, 54.2% of patients had a positive FluPET and an equivalent number of patients underwent initial observation in the no treatment plan change group. PSA at the time of FluPET was 2.66 ng/ml in the treatment plan change group vs 2.80 ng/ml in the no treatment change group (P=0.5753, Mann-Whitney U test). A post-hoc analysis of overall survival (OS) was not reached in either group with a median follow up time of 65.3 months in the treatment plan change group and 67.6 months in the no treatment plan change group (HR 0.502; 95% CI 0.1012 to 2.488, P=0.41). Median time to next treatment (TTNT) was not reached in the treatment plan change group vs 67.6 months in the no treatment plan change group (HR 0.6051; 95% CI 0.2449 to 1.495, P=0.25).

At least a year after FluPET was performed, with 85.5% of patients still in follow-up, providers reported potential toxicity in only one patient where FluPET-guided a treatment plan change. The provider cited possible increased side effects from being on continuous rather than intermittent androgen deprivation therapy and patient anxiety resulting from the knowledge of having positive lesions on FluPET.

Discussion

PSMA PET was rapidly adopted in clinical practice following its approval in late 2020 due to higher overall sensitivity and specificity of lesion detection. In contrast to ^{18}F-Fluciclovine, ^{68}Ga-PSMA-11 is rapidly secreted in the urine. Thus, FluPET retains an advantage over PSMA PET in detection of local recurrence following prostatectomy. A prospective clinical trial by Fendler et al., showed local recurrence in the prostate bed is detected in less than 25% of patients with a positive PSMA PET [11]. Moreover, they found a high rate of false positive and false negative lesions in the prostate bed (11 of 17 and 5 of 8 respectively). Indeed, a prospective head-to-head comparison of FluPET and PSMA PET in BCR showed a significantly higher detection rate (37.9% vs 27.6%) for local recurrence [12]. A second prospective study comparing these two imaging platforms showed a slightly increased but not significant detection rate in the prostate bed using FluPET, whereas all other regions were detected at a higher rate using PSMA PET [13]. Importantly, in our study positive FluPET findings at BCR1 and BCR2 post-prostatectomy with PSA<1 resulted in treatment changes in >50% patients. This is higher than retrospective PSMA PET studies showing management changes in 33.8% of patients following prostatectomy [14]. Similarly, Calais et al., conducted a post hoc analysis showing a major impact on radiation therapy in 39% patients with BCR and a positive PSMA PET CT following RP [15]. In our study, 47.8% of patients (22 of 46) with a positive FluPET had recurrence in the prostate bed. This is similar to observations from the EMPIRE-1 trial where 40.5% of patients had ^{18}F-Fluciclovine uptake in the prostate bed only following prostatectomy [10]. Overall, detection of recurrence in the prostate bed in our study and EMPIRE-1 is increased compared to similar studies investigating BCR using PSMA PET. In sum, slow urinary excretion of ^{18}F-Flucicovine permits improved detection of local prostate recurrence following prostatectomy and subsequently impacts treatment decisions by providers.

As expected, most FluPET scans described in our study were ordered for patients with BCR (80.6%), with most providers intending to use FluPET results to pursue options for local salvage or oligometastatis-directed therapy. However, close to 20% of scans were ordered for other prostate cancer disease states, ranging from localized PC (prior to curative intent therapies) to mCRPC. This suggests those providers felt that next-generation imaging modalities such as FluPET had potential utility across the disease spectrum. This is reflected in the current use of PSMA PET imaging. NCCN guidelines suggest using PSMA PET in a range of disease states, including initial staging for unfavorable intermediate and high risk localized disease, biochemically recurrent PC, work-up of progression in later disease states and use in mCRPC to determine eligibility for Lu-177-PSMA-617 therapy [9].

In the context of prospective FluPET studies following BCR, one study assessed FluPET to guide salvage radiation following first BCR after radical prostatectomy (N=79) with previously negative conventional imaging (CT or MRI of abdomen/pelvic and bone scan). This group reported a 35.4% rate of decision changes due to FluPET results, including four patients aborting plans for radiation; however, no further detail was provided on what the other decision changes entailed [6, 10]. The FALCON trial (N=104) also focused on patients with BCR with FluPET-avid lesions detected in 56% of patients (44% prostate/bed, 18% pelvic lymph nodes, 7.7% retroperitoneal lymph nodes, 3.8% other lymph nodes, 2.9% soft tissue, 8.7% bone; **Table 3**) [7]. The most common pre-FluPET plan was for radiation (60%). Plans were revised for 63% of patients, with a 41% rate of major changes to a different or multiple modalities (e.g. excluding changes within a single modality, such as modifying radiation fields). The most common changes were from local salvage to systemic therapy (15%), or de-escalation to observation (15%). Most patients with a revised treatment plan had positive FluPET (80%), whereas most patients who were de-escalated to observation had negative FluPET (63%).

Table 3. Comparison of prospective studies using ^{18}F-Fluciclovine PET/CT

Characteristic	Prospective Study		
	UW-FACBC	FALCON	LOCATE
Clinical Trial	No	Yes	Yes
Number of Patients	62	104	213
Negative Imaging Prior to FluPET Mandatory	No	Yes	Yes
FluPET Obtained Only for BCR	No	Yes	Yes
FluPET Positive%	74%	56%	57%
Multiple Treatment Options Considered	Yes	No	No
Treatment Plan Change%	49%	63%	59%
Treatment Plan Change to Systemic Therapy%	27%	15%	5%
Treatment Plan Change to Observation%	5%	15%	15%

Abbreviations: FluPET, ^{18}F-Fluciclovine PET/CT; BCR, Biochemical Recurrence.

The LOCATE trial (N=213) studied patients with BCR after radical prostatectomy and/or radiation but otherwise was designed similarly to the FALCON trial [8]. That study required that patients have negative or equivocal conventional imaging findings in the preceding 60 days. FluPET-avid lesions were detected in 57% of patients (30% in the prostate/prostate bed, 38% outside the prostate including 29% in lymph nodes, 2.3% in soft tissue, and 11% in bone; **Table 3**). The most common pre-FluPET plan was for radiation (62%). Plan management was revised in 59% of patients, and revisions were more likely if FluPET was positive (70%). Similar to the FALCON trial, patients whom providers planned to de-escalate to observation were more likely to have negative FluPET (66%). Major plan revisions occurred in 46% of patients; the most frequent plan modifications were de-escalation to observation (15%), change from systemic therapy to curative-intent salvage therapy (14%), or change from salvage therapy to systemic therapy alone (5%).

In contrast to the FALCON and LOCATE trials, for patients who had BCR in our study, the most frequently considered pre-FluPET plan was observation rather than local therapies such as radiation (**Tables 2** and **3**). Our study had a higher rate of positive FluPET findings than the FALCON and LOCATE trials, including a higher rate of positive findings outside of the prostate/prostate bed. This is not surprising given our patient population was not limited to BCR. Moreover, our registry did not have eligibility criteria, such as previously negative conventional imaging, limits on PSA doubling time, and exclusions based on receipt of prior therapy, making it closer to "real world" scenarios. We also reported on the average number of positive lesions or nodal groups detected and average maximum SUV of positive lesions, which the other studies did not. The rate of major changes to management plans were 41% and 46% in the FALCON and LOCATE trials, respectively, which was similar to the major change rate of 48.4% in our study (**Table 2**). Like the FALCON and LOCATE trials, management changes in our study were more common with positive FluPET findings. However, only 4.8% of providers in our study reported de-escalating patients to observation (compared to 15% in FALCON and LOCATE; **Table 3**). This may be because observation was considered more strongly pre-FluPET and because of higher rate of positive FluPET findings in our study. In line with this, escalation involving systemic therapy (either systemic therapy alone, or in combination with local therapies) was more common in our study (27.5%). Importantly, unlike the FALCON and LOCATE trials, our provider questionnaire allowed providers to select more than one potential management plan, inadvertently revealing the uncertainty providers felt in managing these patients. Further, our study was unique in that it collected longitudinal provider feedback a year or more after FluPET on whether treatments resulting from FluPET findings may have resulted in additional harm or toxicity to the patient, which in general, it did not.

To our knowledge, this is the only study that reports prospective data on FluPET use and effect on provider management outside of clinical trial settings. Prior clinical trials that examined use of FluPET for clinical management focused on biochemically recurrent PC, whereas our descriptive findings show that providers used FluPET to guide management of patients with treatment-naïve localized disease or with metastatic disease [6-8]. Our registry is also the only one to collect provider input on why they chose to order FluPET imaging for their patient and long-term toxicity data based on treatment selections resulting from FluPET findings.

When providers were asked to select their potential treatment plans prior to FluPET results, they were requested to select only one option. Yet, they often selected more than one option, some in direct conflict with one another (e.g. observation vs. local or systemic therapies). A major lesson learned from this prospective study was that management uncertainty among treating providers before imaging often translated into ambiguity in determining subsequent therapy. This finding underscores the importance of deliberate pre-scan planning whenever novel imaging modalities are used. Treatment strategies should be outlined in detail prior to imaging to ensure that the study meaningfully informs management decisions, rather than being performed simply to gather additional information.

The rate of treatment changes providers reported based on FluPET findings was fairly high, consistent with prior literature [6-8]. Only 10% of treatment changes made involved de-escalation to observation, while 50% of plan changes incorporated local therapy and 57% incorporated systemic therapy (40% involved systemic therapy alone, without a plan for any local therapy). This is consistent with our finding that treatment plan changes were significantly more likely to occur if FluPET detected one or more lesions consistent with PC. Most FluPET scans were ordered in the hopes of opening possibilities for local sal-

vage or oligometastasis-directed therapies, however, patients often experienced escalation to systemic therapy instead. This is likely due to stage migration, and it is unclear if resultant treatment changes and/or intensification improved clinically meaningful endpoints such as OS.

An important unanswered question is whether treatment plan changes, most often treatment intensification in our study, translate into improved clinical outcomes. A preliminary post-hoc analysis of the largest cohort in our study (50 patients across BCR1 and BCR2) suggests that providers made appropriate clinical judgments when incorporating FluPET findings into their decisions. Patients whose management did not change had a median time TTNT exceeding 3 years. In contrast, patients whose treatment plan was modified (predominantly intensified) demonstrated a prolonged TTNT, with the median not reached after a median follow-up of 67.6 months (HR 0.61; 95% CI 0.24-1.50; P=0.25). Although not statistically significant, there was also a trend toward improved OS in patients who underwent a treatment plan change (HR 0.50; 95% CI 0.10-2.49; P=0.41).

Despite the small sample size, these findings suggest that treatment modification following FluPET may have been beneficial, particularly considering that this group likely had more advanced disease at the time of imaging (92% FluPET positive in the treatment plan change group vs. 54.2% in the no treatment plan change group). Yet their outcomes were not clearly worse. Larger, prospective registry studies incorporating PSMA PET will be essential to more definitively determine whether treatment plan changes lead to improved clinical outcomes.

Several limitations should be considered when interpreting the results of this study. First, this was a registry study designed with the intent of understanding use of FluPET outside of clinical trial settings. Therefore, eligibility criteria for enrollment in the study were very permissive, and the study did not provide any guidance to providers on how to interpret or utilize FluPET results. Although this may be viewed as a potential limitation, it also increases the generalizability of these results. Similarly, we did not have central reads of FluPET scans. Radiology reads were provided as standard of care by our expert nuclear medicine physicians per their usual practice and clinical significance was determined by the treating physicians. This study was also limited by its descriptive nature, relatively short follow up (one year) in a patient subset, small sample size in a single academic center and was prone to selection and confounding biases. The registry closed earlier than planned due to the FDA approval of PSMA PET in 2020 and changing clinical practice patterns, wherein most of our providers stopped ordering FluPET in favor of PSMA PET. Nevertheless, we expect that many of the questions that we explored in this registry and the concepts behind our hypothesis-generating findings are more broadly relevant to understanding the use of PSMA PET in clinical practice. We believe a similar study of provider use of PSMA PET in prostate cancer would yield valuable insights into how the field is using this powerful new tool.

Conclusion

In this prospective registry, FluPET was utilized across the PC disease spectrum, most commonly to guide local salvage or oligometastasis-directed therapies, given the higher detection rate of ^{18}F-fluciclovine in the prostate bed. However, provider uncertainty in interpreting FluPET findings was evident in the frequent selection of multiple, and sometimes contradictory, treatment plans. Although a positive FluPET often prompted treatment intensification, the clinical benefit of such management remains unproven. Lessons learned from this study, particularly the need for providers to commit to a single, clearly defined post-scan treatment strategy, should inform the design of future prospective registry studies using PSMA PET. Such refinements would enable a more rigorous evaluation of whether PET-guided treatment decisions, especially in the BCR setting, translate into meaningful clinical benefit.

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Disclosure of conflict of interest

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Abbreviations

BCR, Biochemical Recurrence; FluPET, ^{18}F-Fluciclovine PET/CT; mCRPC, Metastatic Castration-Resistant Prostate Cancer; NCCN, National Comprehensive Cancer Network;

PC, Prostate Cancer; PET, Positron Emission Tomography; PSA, Prostate-Specific Antigen; PSMA, Prostate-Specific Membrane Antigen; SUV, Standardized Uptake Values.

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Appendix 1. Baseline physician questionnaire

Fluciclovine (FACBC) PET/CT registry of prostate cancer patient characteristics, interventions and outcomes: physician questionnaire

Physician Name: _____Date Form Completed: _____

Patient Name: _____Patient MRN: _____

1. Please indicate the reason(s) for ordering fluciclovine PET/CT imaging (check all that apply).

☐ Initial staging prior to consideration of definitive local therapy

☐ For BCR after 1 prior local therapy, to help guide salvage treatment

☐ For BCR after≥2 prior local therapies, to help guide additional salvage treatment

☐ To clarify suspicious or equivocal findings seen on another imaging modality

☐ For treatment response monitoring

☐ Other. Please specify: _____

2. Has this patient ever had fluciclovine PET/CT imaging before?

☐ Yes

☐ No

Date of prior fluciclovine PET/CT: _____

Are you ordering the current fluciclovine PET/CT for direct comparison to the prior fluciclovine PET/CT?☐ Yes ☐ No

3. Imagine that fluciclovine PET/CT or other next-generation imaging modalities were not available to you. What would be your recommended treatment plan for this patient if you had to make a decision without having the results of fluciclovine PET/CT available? Please select only one option below.

☐ Observation

☐ Local procedure to the prostate/prostate bed only

Please specify: ☐ Surgery ☐ Radiation ☐ Cryotherapy ☐ Other: _____

☐ Local procedure to metastatic lesion(s) only (includes pelvic lymph nodes)

Type(s) of metastatic lesion(s): ☐ Lymph node ☐ Bone ☐ Visceral mets

Treatment modality: ☐ Surgery ☐ Radiation ☐ Other: _____

☐ Local procedure(s) to both prostate/prostate bed AND metastatic lesion(s) (includes pelvic lymph nodes)

Type(s) of metastatic lesion(s): ☐ Lymph node ☐ Bone ☐ Visceral mets

Please specify: ☐ Surgery ☐ Radiation ☐ Cryotherapy ☐ Other: _____

☐ ADT alone (+/-bicalutamide lead-in)

☐ ADT+treatment intensification (e.g. docetaxel, novel anti-androgens)

☐ Other. Please specify: _____

Additional Comments? _____

Appendix 2. Post-fluciclovine PET/CT physician questionnaire

Fluciclovine (FACBC) PET/CT registry of prostate cancer patient characteristics, interventions and outcomes: physician questionnaire

Physician Name: _____Date Form Completed: _____

Patient Name: _____Patient MRN: _____

1. Do you consider the fluciclovine PET/CT results to be positive (e.g. demonstrating at least 1 region of prostate cancer?)

☐ Yes

In your best estimation, how many regions (i.e. radiation fields) are positive?

☐ 1-3 regions ☐ 4-5 regions ☐ ≥6 regions

Where are the positive regions located? Select all that apply.

☐ Prostate/prostate bed ☐ Lymph nodes ☐ Bone ☐ Visceral mets

☐ Not sure; sites seem indeterminate or equivocal for prostate cancer.

☐ No

In the previous questionnaire, we asked you to select what your best recommended treatment plan for the patient would be if fluciclovine PET/CT or other next-generation imaging modalities were not available to you.

2. Do the results of the fluciclovine PET/CT change your previously selected plan?

☐ Yes

☐ No

3. If you selected "Yes" above, what is the new treatment plan now? Please select one.

☐ Observation

☐ Local procedure to the prostate/prostate bed only

Please specify: ☐ Surgery ☐ Radiation ☐ Cryotherapy ☐ Other: _____

☐ Local procedure to metastatic lesion(s) only (includes pelvic lymph nodes)

Type(s) of metastatic lesion(s): ☐ Lymph node ☐ Bone ☐ Visceral mets

Treatment modality: ☐ Surgery ☐ Radiation ☐ Other: _____

☐ Local procedure(s) to both prostate/prostate bed and metastatic lesion(s) (includes pelvic lymph nodes)

Type(s) of metastatic lesion(s): ☐ Lymph node ☐ Bone ☐ Visceral mets

Please specify: ☐ Surgery ☐ Radiation ☐ Cryotherapy ☐ Other: _____

☐ ADT alone (+/-bicalutamide lead-in)

☐ ADT+treatment intensification (e.g. docetaxel, novel anti-androgens)

☐ Other. Please specify: _____

Additional Comments? _____

Appendix 3. One-year visit physician questionnaire

Fluciclovine (FACBC) PET/CT registry of prostate cancer patient characteristics, interventions and outcomes: physician questionnaire

Physician Name: _____Date Form Completed: _____

Patient Name: _____Patient MRN: _____

In retrospect, do you believe that fluciclovine PET/CT imaging might have led to a therapy that may have added some additional toxicity for this patient?

☐ No

☐ Yes. Please specify: _____

Additional Comments? _____