Multisite Experience of the Safety, Detection Rate and Diagnostic Performance of Fluciclovine (^{18}F) Positron Emission Tomography/Computerized Tomography Imaging in the Staging of Biochemically Recurrent Prostate Cancer

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Purpose: Sensitive detection of cancer foci in men experiencing biochemical recurrence following initial treatment of prostate cancer is of great clinical significance with a possible impact on subsequent treatment choice. We describe a multisite experience of the efficacy and safety of the positron emission tomography/computerized tomography agent fluciclovine (^{18}F) after biochemical recurrence.

Materials and Methods: A total of 596 patients underwent fluciclovine (^{18}F) positron emission tomography/computerized tomography at 4 clinical sites. Detection rate determinations were stratified by the baseline prostate specific antigen value. Diagnostic performance was assessed against a histological reference standard in 143 scans.

Results: The subject level fluciclovine (^{18}F) positron emission tomography/computer tomography detection rate was 67.7% (403 of 595 scans). Positive findings were detected in the prostate/bed and pelvic lymph node regions in 38.7% (232 of 599) and 32.6% of scans (194 of 596), respectively. Metastatic involvement outside the pelvis was detected in 26.2% of scans (155 of 591). The subject level detection rate in patients in the lowest quartile for baseline prostate specific antigen (0.79 ng/ml or less) was 41.4% (53 of 128). Of these patients 13 had involvement in the prostate/bed only, 16 had pelvic lymph node involvement without distant disease and 24 had distant metastases. The positive predictive value of fluciclovine (^{18}F) positron emission tomography/computerized tomography scanning for all sampled lesions was 62.2%, and it was 92.3% and 71.8% for extraprostatic and prostate/bed involvement, respectively. Fluciclovine (^{18}F) was well tolerated and the safety profile was not altered following repeat administration.

Abbreviations and Acronyms

ADT = androgen deprivation therapy
BCR = biochemical recurrence
BED-001 = Retrospective Observational Study Investigating Fluciclovine (18F) (FACBC)
CT = computerized tomography
DR = detection rate
FACBC = fluciclovine (^{18}F)
MRI = magnetic resonance imaging
PET = positron emission tomography
PPV = positive predictive value
PSA = prostate specific antigen
PSMA = prostate specific membrane antigen
SOT = standard of truth
TRUS = transrectal ultrasound

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Conclusions: Fluciclovine (^{18}F) is well tolerated and able to detect local and distant prostate cancer recurrence across a wide range of prostate specific antigen values.

Key Words: prostatic neoplasms; neoplasm recurrence, local; positron-emission tomography; flucovine F-18; tomography, emission-computed

PROSTATE cancer is the second most frequent cause of cancer related death for men in the United States.[1] Following initial diagnosis the majority of men receive treatment, usually by prostatectomy or radiation/brachytherapy.[2] Recurrence, based on rising levels of PSA, occurs in 20% to 50% of cases.[3–5] Furthermore, approximately 25% of men experiencing BCR progress to metastatic disease associated with significantly increased morbidity and mortality rates.[6,7] Consequently, BCR represents a critical juncture in disease progression and is potentially the last opportunity for curative therapy in many men.

Focal salvage therapies have demonstrated long-term biochemical control rates of 30% to 70%,[8,9] although careful selection of patients most likely to benefit is warranted due to their inherent toxicity and morbidity potential.[8–10] Patients receiving focal therapy in the presence of radiographically occult metastatic disease experience inevitable relapse and many patients elect observation until metastatic disease is confirmed or they elect treatment with ADT. The use of observation or ADT (the latter is associated with side effects, including sexual dysfunction, osteoporosis and metabolic disease[11,12]) in patients who could potentially be treated with curative intent is of equal concern as the delivery of focal therapy in patients with occult metastases.

When considering focal therapies, the accurate identification of disease stage and location is critical to ensure appropriate selection of patients without systemic involvement and guide treatment to specific involved regions. While PSA level and kinetics (PSA doubling time) provide information on risk of metastatic involvement, standard of care imaging, generally pelvic CT or MRI and bone scintigraphy, has a low diagnostic yield of only 11% of patients for visualizing sites of disease.[13] Thus, there is a clear need for better imaging approaches.

Encouraging reports of the diagnostic performance of the synthetic amino acid PET tracer FACBC, that is fluciclovine (^{18}F), in patients with BCR in 2 single center studies have been published previously.[14–16] The aim of the current study was to pool efficacy and safety data on patients with BCR who had received at least 1 injection of fluciclovine (^{18}F) to generate a multicenter data set supporting an evaluation of key determinants of diagnostic performance in relation to the incident PSA level at the time of patient scanning. Fluciclovine (^{18}F) was recently approved by the FDA (Food and Drug Administration) for use in this indication.

MATERIALS AND METHODS

Patient Selection

This study, BED-001 (ClinicalTrials.gov NCT02443571), was performed as a retrospective analysis of fluciclovine (^{18}F) in patients who had received at least 1 injection for the detection of suspected BCR after primary surgery or radiotherapy. The protocol was reviewed according to local regulations and patient informed consent obtained as required.

Patient data from November 28, 2007 to August 28, 2014 were pooled from a compassionate use program/registry in Norway and from 2 published clinical studies done at Emory University[14] and Bologna Hospital,[16] respectively. Patients in the Emory University study were enrolled on the basis of a negative bone scan.[14] The majority of patients enrolled in the Bologna study underwent no conventional imaging for suspected BCR,[16] in accordance with EAU (European Urology Association) guidelines. Patients were included in the Norwegian fluciclovine registry at the discretion of the referring physician.

A subpopulation of patients had sufficient data available to calculate diagnostic performance vs histology. They comprised the population for the primary SOT analyses.

Fluciclovine (^{18}F) Positron Emission Tomography/Computerized Tomography

Imaging Protocols. Fluciclovine (^{18}F) was manufactured by automated radio synthesis. At each clinical site the type of PET/CT scanner and specific imaging acquisition protocol were selected. The mean injected activity (or dose) was 310 MBq (median 309, range 140 to 485).

Scan Interpretation. Fluciclovine (^{18}F) PET/CT scan images were evaluated by experienced PET/CT readers prior to data collection. Specific anatomical locations (lesions) were classified as positive, negative or indeterminate for malignancy based on visual assessment of non-physiological activity against an appropriate background in a manner analogous to clinical FDG (fluorodeoxyglucose) reading.[17] The imaging positivity rate or DR, defined as the proportion of scans containing 1 or more areas considered positive for cancer, was derived at the subject and region levels. Regions of interest included the prostate/bed (residual prostate, prostate bed and

seminal vesicles), the pelvic lymph nodes, skeletal metastases, other metastatic locations (excluding pelvic lymph nodes) and extraprostatic sites (any lymph node, bone or soft tissue metastasis).

Histological Reference Standards

The reference standard for the available primary SOT cohort was histological confirmation. For the prostate/bed region standard TRUS/biopsy or MRI/TRUS fusion biopsy were used to establish truth while blinded to PET findings. When feasible, clinically relevant fluciclovine (^{18}F) positive extraprostatic areas underwent directed biopsy based on cognitive fusion of the PET/CT data with biopsy technique. Because histological sampling of fluciclovine (^{18}F) negative extraprostatic sites was not feasible, all diagnostic performance measures were not calculable for this region.

Analyses

Statistical. The safety analysis set comprised all patients with data included in the BED-001 database. The effectiveness analysis set, which comprised all patients in the database with fluciclovine (^{18}F) scan data available, was used to calculate the fluciclovine (^{18}F) DR. To assess effectiveness end points indeterminate lesions were excluded from lesion and subject level analyses. At the region level indeterminate lesions were excluded only for the region involved and, thus, denominators varied. Sensitivity analyses allocating indeterminate lesions as positive or negative were performed.

Fluciclovine (^{18}F) DR at the region and subject levels was compared to quartiles of PSA at the time of scanning for the total cohort and for each clinical site. The point estimate and the 2-sided 95% exact CI were calculated using the method of Clopper and Pearson.[18]

For the primary SOT cohort the primary effectiveness end point was the lesion level PPV of fluciclovine (^{18}F) PET/CT. The point estimate and the 2-sided 95% exact CI were calculated. The 1-sided exact binomial test was used to compare H0 (end point 0.50) vs H1 (end point 0.50 or greater). Region level sensitivity, specificity, PPV and negative predictive value were calculated, where feasible.

Safety. The occurrence of adverse events until 35 days after administration experienced by patients who received fluciclovine (^{18}F) was determined from site records.

RESULTS

Demographics

A total of 596 patients with BCR received 651 fluciclovine (^{18}F) administration. Of the 628 fluciclovine (18F) scans collected 33 revealed 1 or more lesions classified as indeterminate. A total of 143 patient scans, excluding 4 indeterminate scans, from 136 patients could be correlated with histology (table 1). [T1]

Table 2 lists demographics and select baseline characteristics for the effectiveness analysis set and primary standard of truth populations, when available. Demographics were similar between the overall and primary SOT populations except a higher proportion of patients in the primary SOT population had disease recurrence after radiotherapy. At the time of scanning 15 patients (2.5%) were receiving ADT. [T2]

Detection Rate Analysis

At the subject level the fluciclovine (18F) PET/CT DR was 67.7% (403 of 595). At the region level the DR was 38.7% (232 of 599) in the prostate/bed and 32.6% (194 of 596) in the pelvic lymph nodes. Metastatic involvement outside the pelvis was detected in 26.2% of patient scans (155 of 591), including skeletal sites in 9% (55 of 610) of cases. Findings in nonnodal soft tissue were uncommon at less than 1% of cases. On bone/CT scan 19 patients had positive findings within 3 months before and 6 months after fluciclovine scanning. Figure 1 shows representative fluciclovine (^{18}F) PET/CT positive cases. [F1]

The impact of the PSA value at the time of scanning on fluciclovine (^{18}F) PET/CT DR was investigated (fig. 2). Overall, the subject level DR was 41.4% (53 of 128 patients) in the lowest quartile of PSA (0.79 ng/ml or less). Of 53 these patients 13 had involvement in the prostate/bed only, 16 had pelvic lymph node involvement without more distant disease and 24 had distant metastases. [F2]

Figure 3 shows a case in which fluciclovine (^{18}F) PET/CT detected lymph node involvement proximal to the rectal wall, a location that renders the [F3]

Table 1. *Clinical site contribution to effectiveness analysis set and primary standard of truth populations*

Site	Pt Cohort Source	No. Subjects with Fluciclovine (^{18}F) Scan*/ No. Subject Images Analyzed	
		No. Effectiveness Analysis Set	Primary Standard of Truth
Overall	—	596/595	136/143
Emory University, Atlanta, GA	Clinical study: 18F-FACBC PET-CT for the Detection and Staging of Recurrent Prostate Carcinoma (CA129356-01)	137/127	98/105
Ospedale Sant'Orsola, Bologna, Italy	Clinical study: Anti-3-18F-FACBC vs 11C-choline PET/CT in evaluating patients with suspected prostate cancer recurrence	88/90	12/12
Oslo University Hospital, Oslo, Norway	Compassionate use experience/registry study	225/146	26/26
Aleris Helse AS, Oslo, Norway	Compassionate use experience	146/255	0/0

Excluding all intermediate results.
* Underwent fluciclovine (^{18}F) scan or scan is available.

Table 2. *BED-001 study patient demographics and select baseline characteristics*

	Recurrent Prostate Ca		Primary Standard of Truth	
No. subjects	596		140	
No. scans:				
Excluding indeterminate	595		143	
Including indeterminate	628		147	
Mean/median age (range)	67/67	(42–90)	67/68	(47–90)
No. race/nationality (%):	585	(98.2)	133	(95)
Black/African American	26	(4.4)	16	(11.4)
South Asian	1	(0.17)	1	(0.7)
White	186	(31.2)	88	(62.9)
Other	1	(0.17)	0	
Missing	11	(1.85)	7	(5)
Norwegian (predominantly white)	371	(62.3)	28	(20)
Baseline PSA:*				
No. pts (%)	537	(90.1)	132	(94.3)
Mean ng/ml/median (range)	5.43/2.0 (0.05–82.0)		6.26/3.635 (0.11–44.76)	
No. initial therapy (%):	575	(96.5)	140	(100)
Prostatectomy only	130	(21.8)	7	(5)
Prostatectomy + other (not radiotherapy)	62	(10.4)	11	(7.9)
Radiotherapy only	76	(12.8)	4	(2.9)
Radiotherapy + other (including radical prostatectomy)	266	(44.6)	92	(65.7)
Other†	41	(6.9)	26	(18.6)
Gleason score:				
No. pts (%)	355	(60)	110	(79)
Mean	7.4		6.7	
No. D'Amico class (%):	596	(100)	140	(100)
Low risk	8	(1)	5	(4)
Intermediate risk	108	(18)	45	(32)
High risk	277	(47)	43	(31)
Indeterminate	203	(34)	47	(34)

* Baseline defined as last value prior to first fluciclovine (^{18}F) administration.
† Neither radical prostatectomy nor radiotherapy.

delivery of salvage radiotherapy problematic. The patient went on to receive hormonal therapy.

Diagnostic Performance Determined vs Primary Standard of Truth

Of the 143 patients included in the primary SOT analysis 119 (83.2%) had a positive fluciclovine (^{18}F) PET/CT scan. A total of 553 lesion locations were verified histologically. Table 3 lists diagnostic performance measures.

At the region level the PPV for extraprostatic involvement was 92.3% (36 of 39 cases, 95% CI 79–98) and for prostate/bed disease it was 71.8% (74 of 103, 95% CI 62–80). Lesion level analysis involving all prostatic and extraprostatic lesions with histology resulted in a combined PPV of 62.2% (153 of 246 cases, 95% CI 55.8–68.3), which exceeded the predetermined null hypothesis. Sensitivity analysis had no statistically significant bearing on the results.

Safety Analysis

The safety analysis set comprised 596 patients who received a total of 651 fluciclovine (^{18}F) administrations. Many patients had medical conditions typical of an aging population, including cardiovascular disease and diabetes, and they were receiving concomitant medications.

Treatment emergent adverse events were experienced by 5.4% of patients (32 of 596). None were considered adverse reactions to fluciclovine (^{18}F), including 2 (hypertension and abdominal bleeding) that were considered serious. Eight reported nonserious events (1.3%) were incidental synchronous cancer findings, including 2 cases (0.3%) each of breast cancer and lung neoplasm, and 1 (0.2%) each of adenocarcinoma of the colon, gastrointestinal stromal tumor; nonHodgkin lymphoma and rectal cancer. Nine patients were noted to have extravasation of the injection with no clinical sequelae.

Laboratory reports of increased creatinine and decreased hemoglobin were considered possibly related by the investigator. However, interpretation was confounded by preexisting diabetes and hypertension, and bone metastases, respectively, suggesting no causal association. The safety profile was not noticeably altered following repeat administration.

DISCUSSION

Due to the poor performance of current imaging, several radiopharmaceuticals have been evaluated for BCR but they have proved limited in performance and/or accessibility. PSMA targeted ^{111}In capromab-pendetide demonstrates suboptimal diagnostic performance,[19] (^{18}F) FDG PET/CT provides low sensitivity,[20] (^{18}F)-fluoride PET is limited to the detection of bone metastases, country specific regulatory approval restricts ^{18}F-choline PET/CT use in Europe and the short half-life of ^{11}C-choline confines

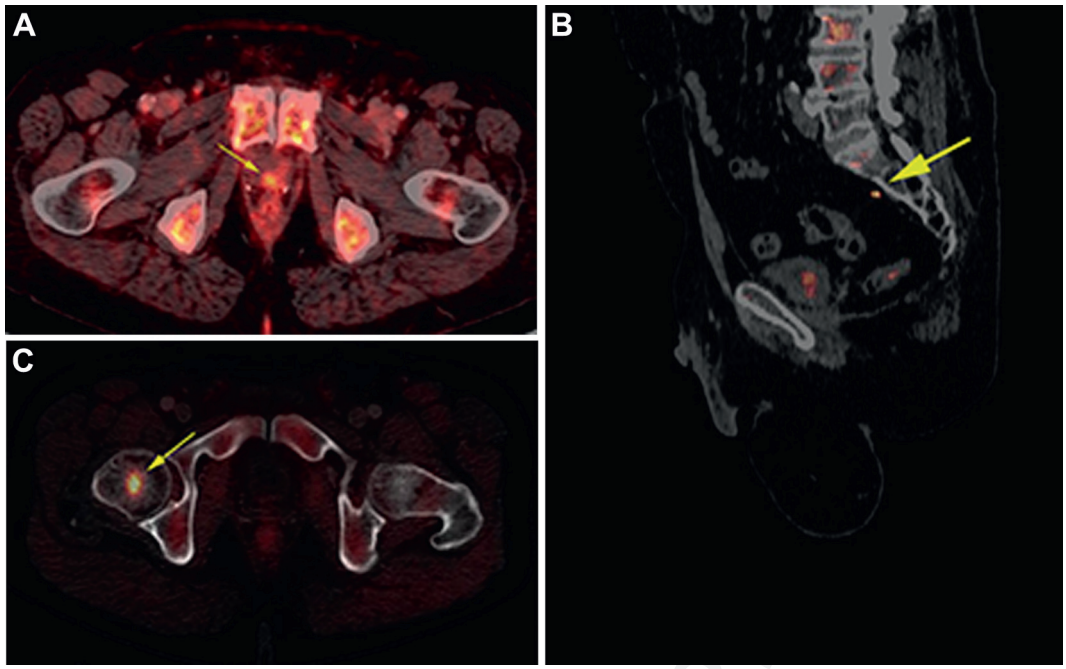

Figure 1. *A*, in 68-year-old male after radical prostatectomy with PSA rising to 0.4 ng/ml fluciclovine (^{18}F) transverse PET/CT detected recurrence (arrow) in left prostate bed. *B*, in 67-year-old male after radical prostatectomy with sipuleucel-T and bicalutamide, PSA rising to 0.91 ng/ml and negative bone scan sagittal fluciclovine (^{18}F) PET/CT detected 3 to 4 mm presacral node (arrow). *C*, in 64-year-old male after radical prostatectomy with PSA rising rapidly to 3.7 ng/ml 2 weeks before scanning transverse fluciclovine (^{18}F) PET/CT (bone window) detected solitary bone metastasis (arrow) in right proximal femur.

its use in the United States to centers with a cyclotron on site. Second generation PSMA targeting agents show promise but are still early in formal development.

In this study we explored the safety and efficacy of fluciclovine (^{18}F) in BCR. Importantly for a diagnostic product, the agent appeared well tolerated. Although any radiopharmaceutical agent exposes patients to additional radiation with the possible long-term risk of secondary cancers, the benefit-to-risk ratio appears favorable in a mainly elderly population experiencing disease recurrence.

Fluciclovine (^{18}F) PET/CT visualizes local recurrence and extraprostatic metastases with a correlation between DR and PSA levels, as observed for other agents.[21] Of particular importance is the detection of extraprostatic involvement in approximately 30% of patients in the PSA quartile 0.79 ng/ml or less, most likely representing patients with post-prostatectomy recurrence. In the cohort with histological confirmation the PPV for detecting extraprostatic disease was greater than 90%.

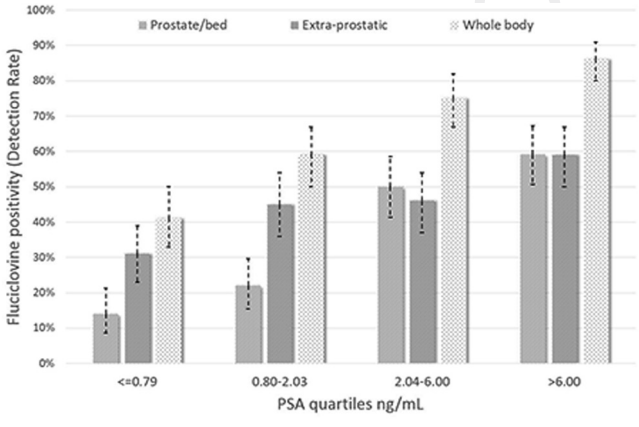

Figure 2. Impact of PSA on fluciclovine (^{18}F) PET/CT detection rate at subject and region levels in combined data set.

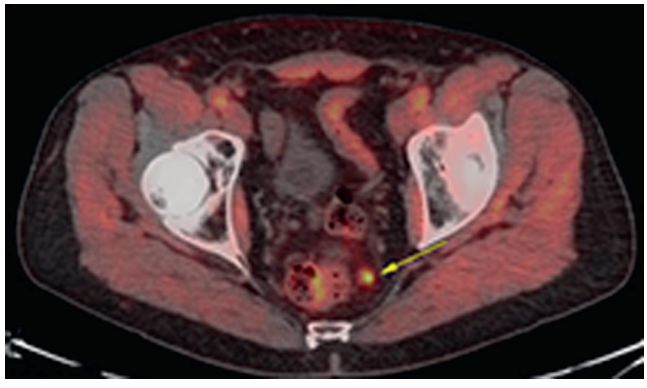

Figure 3. In 61-year-old male with PSA rising to 0.4 ng/ml after robot-assisted laparoscopic prostatectomy fluciclovine transverse PET/CT detected 8 mm mesorectal lymph node metastasis (arrow).

Table 3. *Fluciclovine (^{18}F) PET-CT outcomes vs primary standard of truth at lesion, region and subject levels in patients with recurrent prostate cancer*

	Lesion		Region: Prostate/Bed		Region: Extraprostatic		Subject	
No. pts (%):	553		127		44		143	
Pos	153	(27.7)	74	(58.3)	36	(81.8)	98	(68.5)
False-pos	93	(16.8)	20	(22.8)	3	(6.8)	21	(14.7)
Neg	216	(39.1)	14	(11.0)	1	(2.3)	14	(9.8)
False-neg	91	(16.5)	10	(7.9)	4	(9.1)	10	(7.0)
No./total No. (%)/(95% CI)								
Pos predictive value	153/246 (62.2)/(56, 68)		74/103 (71.8)/(62, 80)		36/39 (92.3)/(79, 98)		98/119 (82.4)/(74, 89)	
Neg predictive value	216/307 (70.4)/(65, 75)		14/24 (58.3)/(37, 78)		Not applicable		14/24 (58.3)/(37, 78)	
Sensitivity	153/244 (62.7)/(56, 69)		74/84 (88.1)/(79, 94)		Not applicable		98/108 (90.7)/(84, 96)	
Specificity	216/309 (69.9)/(65, 75)		14/43 (32.6)/(19, 49)		Not applicable		14/35 (40.0)/(24, 58)	

Sensitivity for detecting local recurrence approached 90%, although the 72% PPV and 33% specificity were suboptimal. This was possibly due to an overlap of malignancy with benign hyperplasia and prostatitis, as in primary disease,[22,23] and/or to the sampling error of conventional TRUS biopsy as the SOT.[24] We believe that the histological SOT used in this study represents a conservative approach to the estimation of fluciclovine (^{18}F) performance. Utilizing TRUS/PET fusion biopsy as the SOT will likely prove valuable, as will exploration of specificity optimization imaging techniques.[25]

Reports in the literature relating to the performance of choline PET agents are highly variable, mainly due to differences in the tracer and PET equipment/protocols used, and the divergent approaches to truth determination.[21] The Bologna cohort included in BED-001 contributed to a prospective intrapatient comparison of fluciclovine (^{18}F) to ^{11}C-choline demonstrating a statistically significant superior sensitivity for fluciclovine (^{18}F) at baseline PSA less than 1 ng/ml.[15]

A comparison of the performance of fluciclovine (^{18}F) and PSMA-PET agents is hindered by reports of variable performance from single center experiences. For ^{68}Ga-PSMA-HBED-CC DRs of 48% (PSA less than 0.83 ng/ml) and 58% (PSA 0.2 to less than 0.5 ng/ml) have been published.[26,27] Prospective study is needed to establish the relative performance of fluciclovine (^{18}F) compared to various PSMA agents.

Our series presents an extensive multicenter experience of fluciclovine (^{18}F) in BCR. However, it was subject to several limitations, including the lack of prospective inclusion of all patients, variable use of comparative imaging, the lack of histological verification and standardized biopsy technique, and the lack of systematic capture of information on a change in patient treatment. Notwithstanding these limitations, it is clear that fluciclovine (^{18}F) may have a significant impact on the selection of patients for focal therapy and for the guidance of such therapy to involved areas. Indeed, Scriebmann et al recently reported preliminary findings in a cohort of 41 patients scheduled for salvage radiotherapy (median PSA 0.43 ng/ml), in whom 46 fluciclovine (^{18}F) lesions (83.6%) were borderline or outside the standard planning volumes, leading to the augmentation of standard target volumes.[28]

Due to national differences in imaging guidelines, it is not feasible to give universal recommendations for fluciclovine (^{18}F) use in clinical practice in relation to other techniques. Nevertheless, it is clear that fluciclovine (^{18}F) could be considered in cases in which conventional imaging with bone scan and standard CT/MRI are negative. Furthermore, the accurate assessment of lymph node involvement by standard CT/MRI based on differential size/shape determinants is hindered by the dual problems of low sensitivity and specificity. Therefore, this presents an opportunity for replacement with fluciclovine (^{18}F) PET/CT. At this time we recommend continuing dedicated bone imaging alongside fluciclovine (^{18}F) until further evidence is generated in high risk populations.

Future study should confirm utility in terms of progression and survival measures after fluciclovine (^{18}F) guided salvage. Further understanding of fluciclovine (^{18}F) performance in populations stratified by prior treatment, PSA doubling time, Gleason score, PET equipment and acquisition variations will prove valuable and should help inform patient selection for scanning.

CONCLUSIONS

Fluciclovine (^{18}F) is well tolerated and able to detect local and distant prostate cancer recurrence across a wide range of PSA values. Work is under way to strengthen the evidence base of the demonstrable management impact on BCR and explore application in additional aspects of prostate cancer care and in other cancers.

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EDITORIAL COMMENTS

Today choline-PET/CT is the most widespread imaging technique for assessing PCa relapse. It can detect the site of recurrence with lower PSA compared to conventional imaging. Preliminary clinical reports of ^{18}F-FACBC showed an improvement in the detection rate of 20% to 40% in comparison to ^{11}C-choline.[1] Further studies comparing these 2 radiotracers demonstrated similar results (reference 15 in article). Nevertheless, ^{18}F-FACBC has some peculiar advantages, such as a shorter synthesis time as well as a longer half-life of 109 minutes. This allows for PET imaging without a cyclotron on site, thus, improving the availability of this technique.

When we look to possible salvage therapy for patients with biochemical relapse after radical treatment, both choline and ^{18}F-FACBC still have a suboptimal detection rate since it is strongly related to PSA levels. To address this void, the new PET tracer ^{68}Ga-PSMA revealed incredibly higher detection rate even with PSA less than 0.5 ng/ml compared with choline.[2] It had superior diagnostic performance in metastatic PCa assessment and some potential

therapeutic consequences. Nevertheless, nowadays some suspicions have arisen regarding a possible high rate of false-positive results of ^{68}Ga-PSMA. Thus, the competition is open and future comparative studies will show us the winner.

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The authors describe a multicenter experience of the efficacy and safety of the PET/CT agent fluciclovine (^{18}F) following BCR in 596 patients. On a patient basis the overall detection rate was 67.7% (403 of 595) whereas the detection rate in patients in the lowest quartile of baseline PSA (less than 0.79 ng/ml) was 41.4% (53 of 128). Additionally, injections were well tolerated in the entire study.

Currently, further evaluation of patients with BCR using novel PET tracers is an emerging research topic. PSMA targeting agents and ^{18}F-choline are among the most popularly studied tracers. Despite reported promising results with a number of tracers, the greatest limitation is validation with histopathology. In the current paper the authors correlated imaging findings in 136 patients, which is quite important and promising to document the impact of fluciclovine (^{18}F) in those with BCR. Further research with different tracers with histopathology validation is needed to better document tumor foci in BCR.

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