International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Effect of ^{18}F-Fluciclovine Positron Emission Tomography on the Management of Patients With Recurrence of Prostate Cancer: Results From the FALCON Trial

Andrew F. Scarsbrook, FRCR,[*,†] David Bottomley, FRCR,[*] Eugene J. Teoh, DPhil,[‡] Kevin M. Bradley, FRCP,[§] Heather Payne, FRCR,[‖] Asim Afaq, FRCR,[‖] Jamshed Bomanji, FRCP,[‖] Nicholas van As, FRCR,[¶] Sue Chua, FRCR,[¶] Peter Hoskin, FRCR,[#] Anthony Chambers, FRCR,[#] Gary J. Cook, MD,[**] Victoria S. Warbey, MSc,[**] Sai Han, FRCP,[††] Hing Y. Leung, PhD,[‡‡,§§] Albert Chau, MSc,[‡] Matthew P. Miller, PhD,[‡] and Fergus V. Gleeson, FRCR,[‖‖] on behalf of the FALCON study group

Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; †University of Leeds, Leeds, United Kingdom; ‡Blue Earth Diagnostics, Oxford, United Kingdom; §PETIC, Wales Research and Diagnostic PET Imaging Centre, Cardiff, United Kingdom; ‖University College London Hospitals, NHS Foundation Trust, London, United Kingdom; ¶The Royal Marsden NHS Foundation Trust, London, United Kingdom; #Mount Vernon Cancer Centre, London, United Kingdom; **King's College London and Guy's & St Thomas' PET Centre, St Thomas' Hospital, London, United Kingdom; ††West of Scotland PET Centre, Gartnavel General Hospital, Glasgow, United Kingdom; ‡‡Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom; §§CRUK Beatson Institute, Glasgow, United Kingdom; and ‖‖Departments of Radiology and Nuclear Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Received Oct 11, 2019. Accepted for publication Jan 31, 2020.

Corresponding author: Andrew F. Scarsbrook, FRCR; E-mail: a.scarsbrook@nhs.net

This study was supported by Blue Earth Diagnostics, Oxford, UK, with a grant from Innovate UK.

Disclosure: A.F.S. reports grants from Innovate UK and salary support for research from Leeds Cares (Leeds Teaching Hospitals NHS Trust Charitable Foundation) during the conduct of the study plus nonfinancial support from Blue Earth Diagnostics, all outside the submitted work. D.B. reports travel/conference funding from Janssen, Astellas and Blue Earth Diagnostics, all outside the submitted work. A. Chau, M.P.M. and E.J.T. are employees/shareholders of Blue Earth Diagnostics Ltd. H.P. reports personal fees for advisory boards and scientific lectures from Janssen, Bayer, Astra Zeneca, Sanofi Aventis and Ferring, plus grants and personal fees from Astellas, all outside the submitted work. A.A. reports personal fees from GE, Bayer, Astellas, Janssen and Pharmatrace; nonfinancial support from Curium; personal fees and nonfinancial support from Theragnostics, all outside the submitted work. Support was also provided to A.A. by the National Institute for Health Research, the University College London Hospitals Biomedical Research Centre, and the Cancer Research UK University College London Experimental Cancer Medicine Centre. N.v.A. reports grants and personal fees from Accuray outside the submitted work. G.J.C. reports grants and personal fees from NanoMab Technology Ltd, grants from Theragnostics Ltd and nonfinancial support from Serac healthcare, all outside the submitted work. K.M.B., J.B., S.C., P.H., A. Chambers, V.S.W., S.H. and F.V.G. have nothing to disclose.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary material for this article can be found at https://doi/org/10.1016/j.ijrobp.2020.01.050.

Acknowledgments—In addition to the authors, the following individuals are members of FALCON study group: Gerard Andrade, Philip Camilieri, Katherine Hyde, Ruth Macpherson, Neel Patel, Ami Sabharwal, Manil Subesinghe, and Maria Tsakok of the Departments of Radiology and Nuclear Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Writing support was provided by Dr Catriona Turnbull and was funded by Blue Earth Diagnostics, Oxford, UK.

Int J Radiation Oncol Biol Phys, Vol. 107, No. 2, pp. 316–324, 2020
0360-3016/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.ijrobp.2020.01.050

Purpose: Early and accurate localization of lesions in patients with biochemical recurrence (BCR) of prostate cancer may guide salvage therapy decisions. The present study, ^{18}F-Fluciclovine PET/CT in biochemicAL reCurrence Of Prostate caNcer (FALCON; NCT02578940), aimed to evaluate the effect of ^{18}F-fluciclovine on management of men with BCR of prostate cancer.

Methods and Materials: Men with a first episode of BCR after curative-intent primary therapy were enrolled at 6 UK sites. Patients underwent ^{18}F-fluciclovine positron emission tomography/computed tomography (PET/CT) according to standardized procedures. Clinicians documented management plans before and after scanning, recording changes to treatment modality as major and changes within a modality as other. The primary outcome measure was record of a revised management plan postscan. Secondary endpoints were evaluation of optimal prostate specific antigen (PSA) threshold for detection, salvage treatment outcome assessment based on ^{18}F-fluciclovine-involvement, and safety.

Results: ^{18}F-Fluciclovine was well tolerated in the 104 scanned patients (median PSA = 0.79 ng/mL). Lesions were detected in 58 out of 104 (56%) patients. Detection was broadly proportional to PSA level; ≤1 ng/mL, 1 out of 3 of scans were positive, and 93% scans were positive at PSA >2.0 ng/mL. Sixty-six (64%) patients had a postscan management change (80% after a positive result). Major changes (43 out of 66; 65%) were salvage or systemic therapy to watchful waiting (16 out of 66; 24%); salvage therapy to systemic therapy (16 out of 66; 24%); and alternative changes to treatment modality (11 out of 66, 17%). The remaining 23 out of 66 (35%) management changes were modifications of the prescan plan: most (22 out of 66; 33%) were adjustments to planned brachytherapy/radiation therapy to include a ^{18}F-fluciclovine-guided boost. Where ^{18}F-fluciclovine guided salvage therapy, the PSA response rate was higher than when ^{18}F-fluciclovine was not involved (15 out of 17 [88%] vs 28 out of 39 [72%]).

Conclusions: ^{18}F-Fluciclovine PET/CT located recurrence in the majority of men with BCR, frequently resulting in major management plan changes. Incorporating ^{18}F-fluciclovine PET/CT into treatment planning may optimize targeting of recurrence sites and avoid futile salvage therapy. © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Prostate cancer is the most common cancer among males in the United Kingdom, with around 47,600 new cases diagnosed in 2016.[1] Recently reported UK prospective data from 1643 low-intermediate risk patients with prostate cancer show a low event rate after 10 years' follow-up.[2] Progression to metastatic disease was more common among patients receiving watchful waiting (5.6%) than among those receiving active treatment, although rates postprostatectomy (2.4%) and post−radiation therapy were similar (2.7%). However, as reported by current European Association of Urology (EAU) guidelines,[3] between 27% and 53% of all patients undergoing initial therapy with radical prostatectomy or radiation therapy will experience biochemical recurrence (BCR) characterized by rising prostate-specific antigen (PSA). Although this BCR may be prolonged and will not necessarily lead to clinically apparent metastatic disease, reports suggest that approximately 25% of patients with BCR progress to metastatic disease, which is associated with significantly increased morbidity and mortality.[4,5]

Early and accurate localization of lesions in patients with suspected BCR facilitates treatment when tumors are small and most amenable to localized therapy.[6] Conventional imaging, namely computed tomography (CT), magnetic resonance imaging, or bone scintigraphy, are used widely to localize recurrence and inform management after radical therapy. However, these techniques are not without limitations, particularly in patients with low PSA, meaning physicians often place emphasis on risk factors rather than negative imaging to predict probability of clinical progression.[7,8]

Use of positron-emission tomography (PET) in this setting has increased greatly in recent years. Fluorodeoxyglucose PET is widely available and may detect occult metastatic disease in certain tumors but has limited utility in prostate cancer because of its inherently low uptake and renal excretion obscuring local uptake.[9] Choline PET/CT has superior diagnostic accuracy in BCR compared with both conventional imaging and fluorodeoxyglucose.[10] However, sensitivity of choline remains suboptimal and its accuracy is poor in those with low PSA and slow PSA kinetics.[11,12] Investigational prostate-specific membrane antigen (PSMA)-based PET tracers such as ^{68}Ga-PSMA-11 show promising results in the BCR setting,[13] but are yet to be approved in Europe or the United States.

^{18}F-Fluciclovine is a synthetic amino acid radiotracer that is approved in Europe and the United States for detection of BCR of prostate cancer on account of its established diagnostic performance across a wide PSA range.[14-16] Here, we evaluate the clinical benefit of ^{18}F-fluciclovine PET/CT by

assessing the effect on management decisions for men with BCR of prostate cancer under consideration for curative-intent salvage treatment.

Methods and Materials

^{18}F-Fluciclovine PET/CT in biochemicAL reCurrence Of Prostate caNcer (FALCON; NCT02578940) was an open-label study conducted at 6 UK sites that aimed to evaluate changes to management plans after ^{18}F-fluciclovine PET/CT. Secondary endpoints comprised evaluation of the optimal PSA threshold for detecting BCR, assessment of the outcome of salvage treatment based on whether ^{18}F-fluciclovine guided the plan, and safety assessment.

Each institution obtained local review board approval. Overarching national approval and study-wide governance review was also obtained before accrual. All patients provided written consent.

Patients

Men (age $\geq$18 years, Eastern Cooperative Oncology Group 0-2) with a first diagnosis of BCR $\geq$3 months after radical treatment who were being considered for curative-intent salvage therapy because of rising PSA were eligible. BCR was diagnosed postprostatectomy as either 2 consecutive PSA rises and a final PSA >0.1 ng/mL or 3 consecutive PSA rises. Postprostatectomy patients were also required to have a PSA doubling time $\leq$15 months, or a PSA level $\geq$1.0 ng/mL at relapse. In patients who had undergone radiation therapy or brachytherapy, BCR was diagnosed as a PSA increase of $\geq$2.0 ng/mL above nadir.

Exclusion criteria included use of androgen-deprivation therapy (ADT) or undergoing choline PET/CT $\leq$3 months before screening, receiving another investigational product from 1 month before to 1 week after ^{18}F-fluciclovine, known ^{18}F-fluciclovine hypersensitivity, and bilateral hip prostheses.

Protocol

Baseline screening (blood tests, documentation of treatment/imaging history, and electrocardiogram) was conducted during the first visit. Intended management plans based on pre-existing clinical information were recorded. During visit 2, patients received routine medical screening followed by ^{18}F-fluciclovine PET/CT. Patients' vital signs and injection sites were monitored regularly for 2 hours postinjection, and patients were discharged if no adverse events (AEs) were observed.

At a follow-up appointment ($\leq$6 weeks postscan), clinicians recorded whether the prescan management plan was to remain unchanged or be altered owing to ^{18}F-fluciclovine findings. Any revisions were discussed with the patient, and the agreed approach recorded. Any postscan management change involving a new modality (eg, salvage radiation therapy to systemic therapy) was classified major, whereas changes within a modality (eg, modified radiation therapy fields) were classified other.

AEs, changes to clinical markers, vital signs, injection sites, and physical examinations were assessed throughout the study. Routine follow-up varied according to patients' management ($\leq$6 months after initiation of treatment for non-salvage therapy [eg, ADT, watchful waiting]; until the posttreatment PSA check [$\sim$8 months posttreatment completion] for salvage therapy). In men receiving salvage therapy, a treatment response was defined as a $\geq$30% decrease in PSA, stable disease as a <25% increase or <30% decrease in PSA, and disease progression as a $\geq$25% PSA increase from the most recent measurement before salvage therapy to the last reported value.

^{18}F-Fluciclovine PET/CT

^{18}F-Fluciclovine was manufactured by automated radiosynthesis. The preparation of patients and ^{18}F-fluciclovine administration adhered to standardized procedures,[17] but in brief, patients fasted for $\geq$4 hours and refrained from exercise for 24 hours prescan. ^{18}F-Fluciclovine was administered by bolus intravenous injection (370 $\pm$ 20% MBq) in the right arm 3 to 5 minutes before scanning. Patients were scanned for $\sim$25 minutess in the supine position with their arms positioned overhead, from mid-thigh to base of skull.

Scans were interpreted at site level with readers trained to interpret anatomic regions as positive or negative for ^{18}F-fluciclovine uptake according to consensus guidelines.[18] Positivity rates were determined at the patient level for the prostate/prostate bed and for extraprostatic regions (lymph nodes, bone, or soft tissue). Investigators entered scan findings and management plans in a standardized manner on a centralized electronic database.

Statistics

For the primary endpoint evaluation, a required sample size of $\geq$171 patients with complete data was estimated to allow for $\pm$6% width in a 2-sided 95% confidence interval (CI), based on the conservative assumption that 20% of patients would have a treatment change.[14] We aimed to recruit 180 patients, based on an anticipated 5% drop-out rate.

A single interim analysis of the primary endpoint was preplanned for the first 85 evaluable patients with the aim of terminating recruitment for exceeding the expected level of efficacy if the number of treatment changes was >45 (52.9%; 97.5% CI, 40.3%-62.3%), or for futility if $\leq$8 (9.4%, 97.5% CI, 3.6%-18.9%). The interim analysis reported postscan management changes for 52 out of 85 (61.2%) patients, and recruitment was stopped early owing to the predefined criteria for efficacy being met.[19]

For the primary efficacy analysis, intended and revised management plans were compared, and the number, percentage, and exact 95% CI of patients with and without postscan management changes were calculated. Data were stratified by ^{18}F-fluciclovine PET/CT result and prior treatment. For the secondary analyses, the number, percentage, and exact 95% CI of patients having a treatment response, stable disease, and disease progression were estimated overall and stratified by treatment received and whether a postscan management change occurred. The point estimate of the detection rate was estimated at regional and patient levels for a range of baseline PSA values.

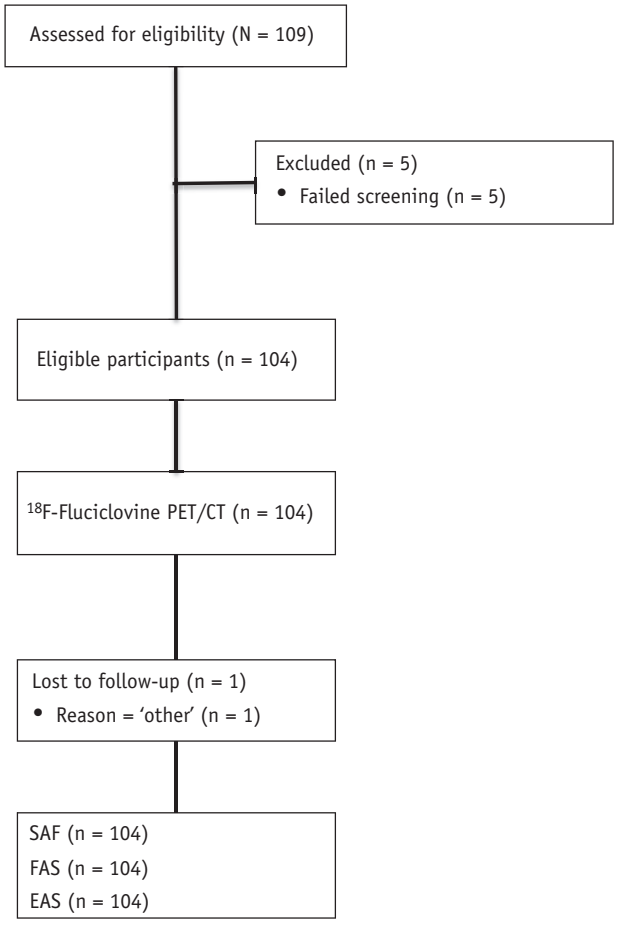

Fig. 1. Patient flow diagram. *Abbreviations*: EAS = evaluable analysis set, all patients from the FAS who have an intended treatment management plan completed and a revised management plan page completed; FAS = full analysis set, all patients enrolled who had ^{18}F-fluciclovine positron emission tomography/computed tomography (PET/CT) at baseline; SAF = safety analysis set, all subjects included in the database and who had ^{18}F-fluciclovine administered.

Table 1 Patient characteristics

Characteristics	Patients N = 104
Age, y	
Median (range)	67.0 (49-81)
Mean ± SD	67.5 ± 6.80
Race, n (%)	
Black	7 (6.7)
South Asian	1 (1.0)
White	93 (89)
Other	3 (2.9)
Time since initial diagnosis, mo	
Median (range)	57.9 (6.3-198.9)
Mean ± SD	63.1 ± 43.0
Time since adjuvant treatment, mo	
No. adjusted	43
Median (range)	66.8 (9.2-186.9)
Mean ± SD	76.2 ± 42.8
Primary therapy, n (%)	
Prostatectomy	65 (63)
With radiation therapy	5 (7.7*)
Without radiation therapy	60 (92*)
Nonprostatectomy	39 (38)
Radiation therapy alone	16 (41†)
EBRT only	1 (2.6†)
Brachytherapy only	14 (36†)
EBRT and brachytherapy	1 (2.6†)
Radiation therapy ± other treatments	22 (56†)
EBRT and ADT	17 (44†)
Brachytherapy and ADT	2 (5.1†)
EBRT, brachytherapy and ADT	3 (7.7†)
Other treatment	1 (2.6†)
PSA, ng/mL	
Whole population	
Median (range)	0.79 (0.04-28.0)
Mean ± SD	3.08 ± 4.92
Patients postprostatectomy	
Median (range)	0.32 (0.04-6.1)
Mean ± SD	0.63 ± 0.91
Patients postradiation therapy (alone)	
Median (range)	4.9 (1.74-28.0)
Mean ± SD	7.15 ± 6.07
Gleason score‡, *n* (%)	
≤6	16 (15)
7	72 (69)
≥8	16 (15)

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; SD = standard deviation.

* Denominator = number of patients with prostatectomy.

† Denominator = number of patients without prostatectomy.

‡ Data from biopsy (n = 183) and surgery (n = 150).

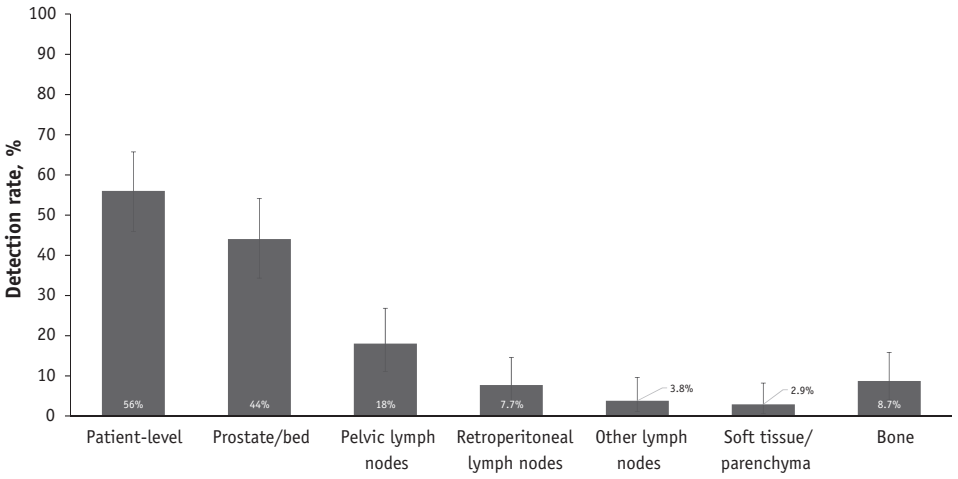

Fig. 2. Regional ^{18}F-fluciclovine detection rate. Error bars present the 95% confidence intervals. Patient-level detection comprises any patient with a positive lesion.

Results

Patients

In total, 104 evaluable patients were scanned between December 2015 and May 2017 (Fig. 1). Table 1 provides their baseline characteristics. Approximately one-quarter of patients had conventional imaging within the 90 days preceding the ^{18}F-fluciclovine PET/CT. The baseline PSA values were recorded a mean 10.8 (median, 9; range, 1-69) days before ^{18}F-fluciclovine PET/CT.

Imaging findings

^{18}F-Fluciclovine-avid lesions were detected in 58 out of 104 (56%) patients, with detection rates of 44% in the prostate/bed and 25% in extraprostatic regions (Fig. 2).

The ^{18}F-fluciclovine detection rate generally increased with increasing PSA (Fig. 3; Table E1, available online at https://doi.org/10.1016/j.ijrobp.2020.01.050). Patient-level detection was consistently high among those with baseline PSA >2.0 ng/mL, with 93% of patients showing a positive result above this threshold. Lymph node and skeletal positivity ranged from 8.9% and 3.6%, respectively, at PSA ≤1 ng/mL to 50% and 13%, respectively, at >10 ng/mL.

Therapeutic management

As presented in Figure 4 (left-hand side), the most common prescan management plan was salvage radiation therapy (n = 65, 62%; 16 of whom had adjuvant ADT). Most of the prescan plans for radiation therapy were to target the prostate bed (n = 57 [88%], 16 with adjuvant ADT), with the remainder focusing on the prostate bed and whole pelvis or with a boost determined by conventional imaging. In total, 28 (27%) patients had a prescan plan for salvage brachytherapy (3 with adjuvant ADT), 6 (6%) were

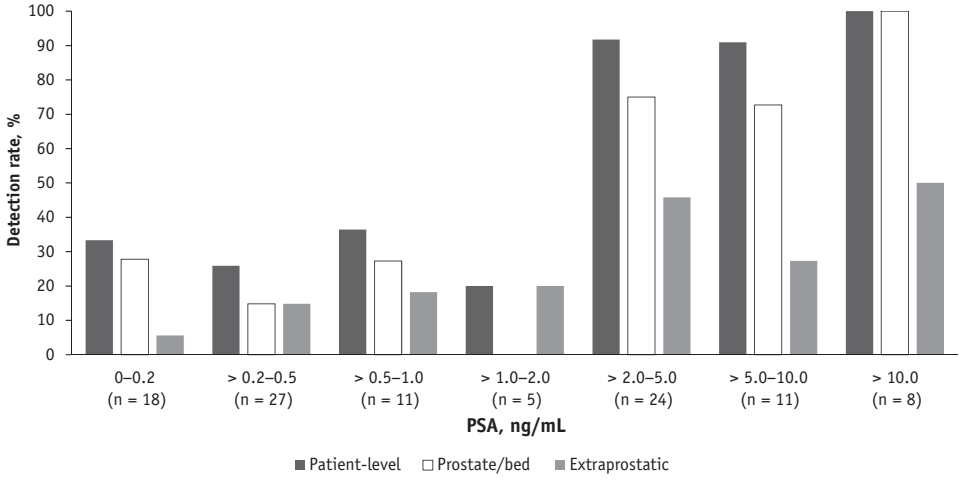

Fig. 3. ^{18}F-Fluciclovine detection stratified by prostate specific antigen (PSA) level. Patient-level detection comprises any patient with a positive lesion. The "extraprostatic" bar presents positivity in lymph nodes, soft tissues/parenchyma and bone. Patient-level n presented in parenthesis on x-axis.

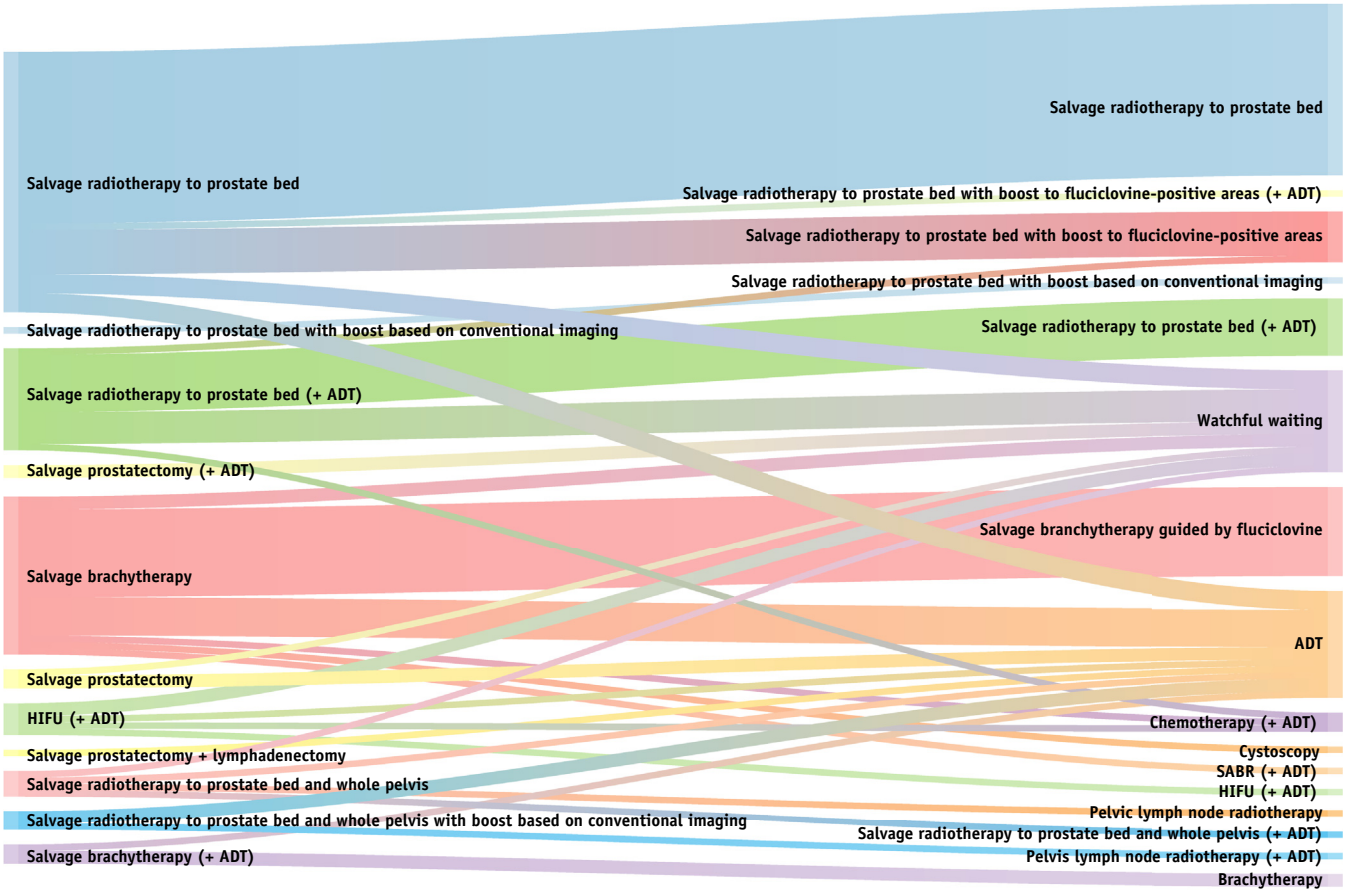

Fig. 4. Sankey diagram to show changes in management for all 104 patients from prescan plans (left) to postscan plans (right). *Abbreviation*: androgen deprivation therapy.

planning to have salvage prostatectomy (2 with adjuvant ADT), and 5 (5%) had a prescan plan for high-intensity focused ultrasound (HIFU) plus ADT.

After the ^{18}F-fluciclovine PET/CT, plans were revised for 66 out of 104 (63%) patients; 6% (4 out of 66) of these revisions occurred owing to incidental findings (eg, recurrence of melanoma, further evaluation of a lung nodule). Figure 4 depicts the changes to management plans.

Forty-three of the 66 postscan management changes (65%) were classified major. Most frequently these were from salvage therapy to systemic therapy (16 out of 66) or watchful waiting (16 out of 66), accounting for 32 out of 104 (31%) patients and 48% (32 out of 66) of all changes. Of the 16 patients who had management revised from salvage therapy to noncurative systemic therapy (7 from brachytherapy [1 with ADT], 6 from radiation therapy, 2 from prostatectomy, and 1 from HIFU with ADT), 13 (81%) had positive scans, often with distant metastases (eg, extrapelvic lymph nodes [n = 9] or skeletal metastasis [n = 4]). In total, 9 patients scheduled for salvage radiation therapy (5 with ADT), 2 for salvage brachytherapy, 3 for prostatectomy (2 with ADT), and 2 for HIFU with adjuvant ADT had their plans revised to watchful waiting; most of these patients had a negative scan result (10 out of 16, 63%). The remaining 11 out of 66 (17%) major changes (all of which were after positive scans) commonly included the introduction of chemotherapy or removal of ADT from a dual-modality approach in favor of monotherapy.

The remaining management changes were all modifications of prescan plans (23 of 66, 35%). These were revisions to plans for salvage radiation therapy to the prostate bed (n = 8) to include a boost to ^{18}F-fluciclovine-avid lesions or for salvage brachytherapy (n = 14) to be guided by ^{18}F-fluciclovine. One additional patient who had a positive scan result had planned brachytherapy modified to allow findings from cystoscopy to be considered.

Both positive and negative ^{18}F-fluciclovine results influenced plans, but the majority of patients with a revised plan had positive results (53 out of 66, 80%). In contrast, 87% (33 out of 38) of patients with no postscan revision had negative scans. Of all enrolled patients, more than half had management changes because of a positive ^{18}F-fluciclovine scan (53 out of 104, 51%). Among 58 patients with a positive scan, the most frequent major change was from salvage therapy to systemic therapy (13 out of 58, 22.4%). In this group, almost all (12 out of 13) were upstaged because ^{18}F-fluciclovine indicated metastases outside the prostate/bed.

Treatment response

Ultimately, 56 patients (54%) received salvage therapy, whether in line with proposed revised plans or not. In the 17 patients who received ^{18}F-fluciclovine-guided salvage treatment, either radiation therapy to the prostate bed with boost to areas guided by ^{18}F-fluciclovine (n = 7) or ^{18}F-fluciclovine-guided brachytherapy (n = 10), 15 out of 17 (88%) had a treatment response. Where ^{18}F-fluciclovine PET/CT did not influence delivery of salvage treatment (n = 39), 28 (72%) patients showed a response.

Safety

In total, 27 (26.0%) patients experienced a total of 38 treatment-emergent AEs. Of these, 8 (7.7%) patients had events possibly related to ^{18}F-fluciclovine. These were headache (4 patients; 1 grade 2 and 3 grade 1); 2 events each of grade 1 fatigue, dizziness, and dysgeusia; 1 grade 1 event of parosmia; 1 grade 1 tremor; 1 grade 1 increase in blood creatine phosphokinase; and 1 grade 1 erythema. One patient had a grade 1 injection site erythema that was considered definitely related to ^{18}F-fluciclovine.

Discussion

Since 2013, UK evidence-based intercollegiate guidelines have recommended PET/CT for patients suspected to have BCR where results would directly influence management,[20] but current UK National Institute for Health and Care Excellence guidelines do not discuss advanced imaging for asymptomatic patients.[21] The latest EAU guidelines, however, recommend PSMA PET/CT for patients with BCR at PSA levels as low as >0.2 ng/mL in patients who have undergone radical prostatectomy if the results will influence treatment decisions. A recommendation specifically for ^{18}F-fluciclovine is included for post−radiation therapy patients or for those post−radical prostatectomy with PSA ≥1 ng/mL where PSMA PET/CT is not available.[3] US National Comprehensive Cancer Network guidelines also recommend ^{18}F-fluciclovine in the workup of patients with recurrence of prostate cancer.[22]

Our prospective data demonstrate that ^{18}F-fluciclovine PET/CT yields detection of prostatic and extraprostatic lesions across a wide range of PSA levels; even below the EAU-advised 1 ng/mL threshold, approximately one-third of patients had positive scans. Our cohort comprised a mix of postprostatectomy and post−radiation therapy patients and had an overall median PSA of 0.79 ng/mL, or 0.32 ng/mL when only postprostatectomy patients are considered. Nevertheless, the majority of our cohort—who were still considered out of scope according to current EAU guidelines—had a management change because of ^{18}F-fluciclovine.

Previous studies have demonstrated the ability of ^{18}F-fluciclovine to influence management, including US-based ^{18}F Fluciclovine (FACBC) PET/CT in Patients with Rising PSA after Initial Prostate Cancer Treatment (LOCATE), which reported results very similar to the present study (patient-level detection of 57% with overall 59% management changes, compared with 56% and 63%, respectively).[23] The present study confirms and extends prior findings that both positive and negative results influence management. As might be expected, positive results were more likely to influence plans. The most common major change after a positive ^{18}F-fluciclovine result was from salvage therapy to systemic therapy. Nearly all (92%) of such patients showed metastases outside the prostate or prostate bed, suggesting ^{18}F-fluciclovine PET/CT may provide critical information to inform the appropriateness of salvage therapy and potentially avoid futile salvage treatment in those with extraprostatic disease.

In line with previous studies, we show ^{18}F-fluciclovine PET/CT can refine planned therapy through localization of disease.[24,25] Here, almost one-quarter of patients and 42% of those with a positive result had their prescan plan for salvage radiation therapy or brachytherapy modified. The potential success of this decision is shown by the secondary analysis of patients ultimately receiving salvage therapy. A higher rate of PSA response was observed in patients who received ^{18}F-fluciclovine-guided salvage brachytherapy or radiation therapy with boosts, compared with those who received salvage therapy without added guidance by ^{18}F-fluciclovine. It is important to note that the study was not powered to directly evaluate differences in PSA response between these groups, and the results are based on short-term PSA responses, bearing limited translational significance. Nonetheless, a trend of higher response rates in the former group hints at the potential for more sensitive imaging to direct both development and implementation of salvage approaches.

Although the majority of revised management followed positive scans, with a new imaging agent establishing confidence in negative results is paramount; we show 20% of revisions occurred despite negative results. These were predominantly changes from salvage therapy to watchful waiting, which is consistent with findings from LOCATE.[23] This confirms that negative ^{18}F-fluciclovine results were interpreted in the knowledge of ^{8}F-fluciclovine's established histologically confirmed performance[16] and suggests that patients may have avoided therapy that would otherwise be futile or significantly affect their quality of life.

Prospective studies published after the initiation of the present trial report that alternative radiotracers also affect management; both choline- and ^{68}Ga-PSMA-11 directed management changes for ~50% of patients,[26-28] similar to the results here with ^{18}F-fluciclovine. ^{18}F-Fluciclovine, however, offers numerous notable benefits over these counterparts; ^{18}F-fluciclovine yields better detection than choline and does not display the limited utility at low PSA associated with choline.[12,15,16] Two recent studies have prospectively compared the performance of

^{18}F-fluciclovine and ^{68}Ga-PSMA with interesting findings.[29,30] Although Calais et al[29] reported ^{68}Ga-PSMA-11 to achieve higher overall detection (56%) than ^{18}F-fluciclovine (26%) in a single-center, low-PSA cohort (< 2 ng/mL), Pernthaler et al[30] reported less variation between the detection rates achieved with ^{68}Ga-PSMA-11 (82.8 %) and ^{18}F-fluciclovine (79.3%). Pernthaler's cohort had a wider PSA range (median 4.1 ng/mL) than Calais'; however, when limiting to only those patients with a PSA ≤2 ng/mL, detection rates for ^{68}Ga-PSMA-11 and ^{18}F-fluciclovine were still less varied (53% vs 42%, respectively) than in the Calais study.[31] Moreover, in contrast with PSMA-based tracers, ^{18}F-fluciclovine is already approved in Europe and the United States in this indication. Data from a recent cost−consequence study also suggest that ^{18}F-fluciclovine use for patients with BCR may result in better clinical outcomes while remaining relatively cost neutral.[32] Additionally, as we show here ^{18}F-fluciclovine is well tolerated, with less than 10% of patients experiencing a related AE, the majority of which were mild.

A limitation of the present study is the lack of confirmation of imaging with histologic findings; however, the diagnostic performance of ^{18}F-fluciclovine PET/CT has been verified.[16] In addition, because improved outcomes are not guaranteed from management changes, additional longer-term follow-up is required to fully establish the benefit of ^{18}F-fluciclovine PET/CT in patients. Currently, a number of prospective phase 2/3 studies are underway that may offer valuable insights: NCT01666808, NCT03582774, NCT03762759, and NCT03525288 aim to determine the effect of ^{18}F-fluciclovine or PSMA PET/CT-guided radiation therapy plans on longer-term disease outcomes.

Another limitation is the lack of requirement for negative conventional imaging before inclusion in the study. Only around one-quarter of patients had conventional imaging within the 90 days preceding PET/CT. However, we are reassured of the positive effect of ^{18}F-fluciclovine PET/CT on management plans by the findings from the US-based study, LOCATE, which was conducted in 213 patients, all of whom had negative or equivocal conventional imaging a median of 30 days before ^{18}F-fluciclovine PET/CT.[23] The proportion of patients experiencing a change in management plan after ^{18}F-fluciclovine imaging reported by LOCATE was in line with our study.

Conclusions

The present study in which the majority of patients had their treatment plans modified after ^{18}F-fluciclovine PET/CT demonstrates the potential for ^{18}F-fluciclovine in staging patients with BCR of prostate cancer at PSA levels below thresholds where imaging is currently advocated by guidelines. Reliable localization of lesions with ^{18}F-fluciclovine PET/CT in patients with BCR of prostate cancer may help determine the most appropriate treatment approach.

References

1. Cancer Research UK. Prostate cancer statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed March 9, 2020.
2. Neal DE, Metcalfe C, Donovan JL, et al. Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the protect randomised controlled trial according to treatment received. *Eur Urol* 2020;77:320-330.
3. Mottet N, Bellmunt J, Briers E, et al. The EAU prostate cancer guidelines. Available at: http://uroweb.org/guideline/prostate-cancer/. Accessed March 9, 2020.
4. Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: The impact of time from surgery to recurrence. *Eur Urol* 2011;59:893-899.
5. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: Estimates using a dynamic progression model. *PLoS One* 2015;10:e0139440.
6. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25:2035-2041.
7. Beresford MJ, Gillatt D, Benson RJ, Ajithkumar T. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. *Clin Oncol (R Coll Radiol)* 2010;22:46-55.
8. Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of biochemical recurrence after primary curative treatment for prostate cancer: A review. *Urol Int* 2018;100:251-262.
9. Jadvar H. Imaging evaluation of prostate cancer with ^{18}F-fluorodeoxyglucose PET/CT: utility and limitations. *Eur J Nucl Med Mol Imaging* 2013;40:S5-S10.
10. Evangelista L, Cervino A, Burei M, et al. Comparative studies of radiolabeled choline positron emission tomography, histology of primary tumor and other imaging modalities in prostate cancer: A systematic review and meta-analysis. *Clin Transl Imaging* 2013;1:99-109.
11. Schiavina R, Martorana G. The promise of choline-PET/CT in the detection of recurrent prostate cancer: What are the limits of our investigation? *Eur Urol* 2013;63:797-799.
12. Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [^{11}C]choline PET/CT in patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2010;37:301-309.
13. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive ^{68}Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: A systematic review and meta-analysis. *Eur Urol* 2016;70:926-937.
14. Schuster DM, Nieh PT, Jani AB, et al. Anti-3-[^{18}F]FACBC positron emission tomography-computerized tomography and ^{111}In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: Results of a prospective clinical trial. *J Urol* 2014;191:1446-1453.
15. Nanni C, Zanoni L, Pultrone C, et al. ^{18}F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus ^{11}C-choline PET/CT in prostate cancer relapse: results of a prospective trial. *Eur J Nucl Med Mol Imaging* 2016;43:1601-1610.
16. Bach-Gansmo T, Nanni C, Nieh PT, et al. 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. *J Urol* 2017;197:676-683.
17. European Medical Association. Axumin: Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/axumin-epar-product-information_en.pdf. Accessed March 9, 2020.

18. Miller MP, Kostakoglu L, Pryma D, et al. Reader training for the restaging of biochemically recurrent prostate cancer using ^{18}F-fluciclovine PET/CT. *J Nuc Med* 2017;58:1596-1602.
19. Teoh EJ, Bottomley D, Scarsbrook A, et al. Impact of ^{18}F-fluciclovine PET/CT on clinical management of patients with recurrent prostate cancer: results from the Phase III FALCON trial. Proceedings of the American Society for Radiation Oncology, San Diego, USA. *Int J Rad Onc Biol Phys* 2017;99:1316-1317.
20. The Royal College Of Radiologists, Royal College Of Physicians Of London, Royal College Of Physicians. Surgeons Of Glasgow, Royal College Of Physicians Of Edinburgh, British Nuclear Medicine Society, et al. Evidence-based indications for the use of PET-CT in the United Kingdom. *Clin Radiol* 2016;71:e171-e188.
21. National Institute for Health and Care Excellence. Prostate cancer: Diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng131. Accessed March 9, 2020.
22. NCCN. NCCN. Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed March 9, 2020.
23. Andriole GL, Kostakoglu L, Chau A, et al. The impact of positron emission tomography with ^{18}F-fluciclovine on the management of patients with biochemical recurrence of prostate cancer: Results from the LOCATE trial. *J Urol* 2019;201:322-331.
24. Akin-Akintayo OO, Jani AB, Odewole O, et al. Change in salvage radiotherapy management based on guidance with FACBC (fluciclovine) PET/CT in postprostatectomy recurrent prostate cancer. *Clin Nuc Med* 2017;42:e22-e28.
25. Jani AB, Schreibmann E, Rossi PJ, et al. Impact of ^{18}F-fluciclovine PET on target volume definition for postprostatectomy salvage radiotherapy: Initial findings from a randomized trial. *J Nuc Med* 2017;58:412-418.
26. Hope TA, Aggarwal R, Chee B, et al. Impact of ^{68}Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nuc Med* 2017;58:1956-1961.
27. Calais J, Fendler WP, Eiber M, et al. Impact of ^{68}Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. *J Nuc Med* 2018;59:434-441.
28. Gillebert Q, Huchet V, Rousseau C, et al. ^{18}F-fluorocholine PET/CT in patients with occult biochemical recurrence of prostate cancer: Detection rate, impact on management and adequacy of impact. A prospective multicentre study. *PLoS One* 2018;13:e0191487.
29. Calais J, Ceci F, Eiber M, et al. (18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: A prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol* 2019;20:1286-1294.
30. Pernthaler B, Kulnik R, Gstettner C, et al. A prospective head-to-head comparison of 18F-fluciclovine with 68Ga-PSMA-11 in biochemical recurrence of prostate cancer in PET/CT. *Clin Nuc Med* 2019;44. e566-e557.
31. Andriole GL. What is the best PET target for early biochemical recurrence of prostate cancer? *Lancet Oncol* 2019;20:e608.
32. Jensen I, Cyr P, Gauden D. Cost-consequences of using fluciclovine (F 18) for the diagnosis and staging of recurring prostate cancer. *Value Health* 2017;20:A582.