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Impact of ^{18}F-fluciclovine PET/CT on salvage radiotherapy plans for men with recurrence of prostate cancer postradical prostatectomy

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Objectives **Imaging options to localize biochemical recurrence (BCR) of prostate cancer after radical prostatectomy (RP) are limited, especially at low prostate-specific antigen (PSA) levels. The FALCON study evaluated the impact of ^{18}F-fluciclovine PET/CT on management plans for patients with BCR. Here, we evaluate salvage radiotherapy decisions in patients post-RP.**

Methods **We conducted a subgroup analysis of post-RP patients enrolled in FALCON who had a prescan plan for salvage radiotherapy (± androgen-deprivation therapy). Patients' treatment plans post-^{18}F-fluciclovine PET/CT were compared with their prescan plans. Fisher exact test was used to determine the impact of PSA and Gleason sum on positivity and anatomical patterns of uptake.**

Results **Sixty-five (63%) FALCON patients had undergone RP. Of these, 62 (median PSA, 0.32 ng/mL) had a prescan plan for salvage radiotherapy. Twenty-one (34%) had ^{18}F-fluciclovine-avid lesions. Disease was confined to the prostate bed in 11 patients (52%) and to the pelvis in a further 5 (24%), while 5 (24%) had extrapelvic findings. Trends towards more disseminated disease with increasing PSA or Gleason sum were observed but did not reach statistical significance. Postscan, 25 (40%) patients had a management change; 17 (68%) were changed to the treatment modality (8 to systemic therapy, 8 to active surveillance, 1 other) and 8 (32%) were radiotherapy field modifications.**

Conclusions **Incorporating ^{18}F-fluciclovine PET/CT into treatment planning may help identify patients suitable for salvage radiotherapy, help augment planned radiotherapy to better target lesions and support the clinician to optimise patient management. *Nucl Med Commun* 43: 201–211 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Biochemical recurrence of prostate cancer following radical prostatectomy is primarily treated with salvage radiotherapy with or without concomitant hormone therapy. However, this is often associated with failure, with some estimates suggesting that 5 years postradiotherapy only one-third of patients have durable PSA control [1]. Failure of salvage therapy may be a consequence of the suboptimal accuracy of conventional imaging techniques such as MRI and bone scintigraphy for localising site(s) of recurrence, particularly in patients with low PSA levels, or the failure to identify very low volume nodal or metastatic disease, leading to undertreatment [2–5].

The advent of molecular imaging yields potential for more reliable localisation of local and metastatic disease to inform radiotherapy plans.^{18}F-Fluciclovine is a positron emission tomography (PET) radiotracer that is approved in the US and Europe for the detection of sites of prostate cancer recurrence [6]. ^{18}F-Fluciclovine PET/CT shows good diagnostic performance across a wide range of PSA values [6] and maybe a useful tool in identifying patients with oligometastatic disease [7]. Recent data have shown the impact that ^{18}F-fluciclovine PET/CT has on radiotherapy planning [8]. Moreover, long term outcome data from a recent prospective randomised phase 3 trial show significantly greater 4-year failure-free survival rates for postprostatectomy patients undergoing ^{18}F-fluciclovine PET/CT-guided salvage radiotherapy decisions (75.5%) compared with those whose plans were guided by conventional imaging (51.2%; $P < 0.0001$) [9].

The FALCON study (NCT02578940) evaluated the clinical benefit of ^{18}F-fluciclovine PET/CT through its impact on management plans for patients with biochemical recurrence of prostate cancer following radical prostatectomy and showed that following ^{18}F-fluciclovine PET/CT, the majority of patients experienced modifications to their management plans [10].

Given the recent reports of optimised management and improved survival with ^{18}F-fluciclovine PET/CT-guided salvage radiotherapy, we performed a secondary analysis of FALCON data to delineate the detailed management decisions made by clinicians and the anatomical sites of ^{18}F-fluciclovine-avid lesions that informed these decisions in a subset of patients who had undergone radical prostatectomy and were scheduled to have salvage radiotherapy. Prior to the advent of molecular imaging, these patients, who often present with PSA values lower than optimal for conventional imaging, would typically receive salvage radiotherapy to standard target fields [11] (i.e. prostate bed ± pelvic lymph nodes) rather following accurate identification of the sites of disease. First, we evaluate the influence of prior prostatectomy on detection rates achieved with ^{18}F-fluciclovine, and ultimately, we report the impact of ^{18}F-fluciclovine PET/CT on salvage radiotherapy plans, whether minor modifications or abortion of plans in favour of another treatment modality.

Methods

Full methods for the FALCON trial have been reported elsewhere [10], but in summary, men with a first biochemical recurrence episode following curative-intent therapy who were being considered for salvage therapy underwent ^{18}F-fluciclovine PET/CT at one of six UK sites as part of the open-label multicentre trial.

Biochemical recurrence was diagnosed postprostatectomy as either two consecutive PSA rises and a final PSA >0.1 ng/mL or three consecutive PSA rises. In addition, the patient was required to have a PSA doubling time ≤15 months if PSA level <1.0 ng/mL. For patients who had radiotherapy or brachytherapy as primary therapy, biochemical recurrence was diagnosed as a PSA increase of ≥2.0 ng/mL above the nadir. Patients who had received androgen-deprivation therapy (ADT) or had undergone choline PET/CT ≤3 months before screening were excluded as were any patients who had received another investigational product from 1 month before to 1 week after ^{18}F-fluciclovine PET/CT, any patients with known ^{18}F-fluciclovine hypersensitivity or any with bilateral hip prostheses.

^{18}F-Fluciclovine PET/CT was conducted and interpreted at each site in accordance with standard procedures [12]. Physicians documented patients' treatment plans pre- and post-^{18}F-fluciclovine PET/CT. Imaging results and management plans were stratified by prior treatment as determined from patient records.

Effect of prior prostatectomy

For the present analysis we stratified patients enrolled in FALCON according to whether or not they had undergone radical prostatectomy and evaluated the ^{18}F-fluciclovine findings by anatomic site in these two groups. The Fisher Exact Test was used to test significance between patient-level imaging findings.

Impact on radiotherapy plans

In order to explore the impact of ^{18}F-fluciclovine PET/CT on salvage radiotherapy plans, we selected all patients from the FALCON population whose primary therapy was radical prostatectomy and who had a pre-^{18}F-fluciclovine PET/CT management plan for salvage radiotherapy, with or without ADT. PET/CT findings among these patients were characterised by anatomical site and extent of disease recurrence, and were stratified by the patients' prescan PSA level and Gleason score. Significance between dichotomised groups was tested using the Fisher exact test.

^{18}F-Fluciclovine PET/CT detection rates were determined at the patient level and on a regional basis. 'Extraprostatic' detection comprised any positivity in pelvic lymph nodes (internal, external and common iliac nodes, presacral nodes, obturator nodes and perirectal nodes), retroperitoneal lymph nodes (para-aortic, retro-aortic, retrocaval, aorto-caval, para-caval and retro-crural nodes), bone or other distant metastases. Intraperitoneal and inguinal nodes were classified as 'other' lymph nodes. The patients' pre- and postscan management plans were compared in the context of the ^{18}F-fluciclovine imaging findings.

Results

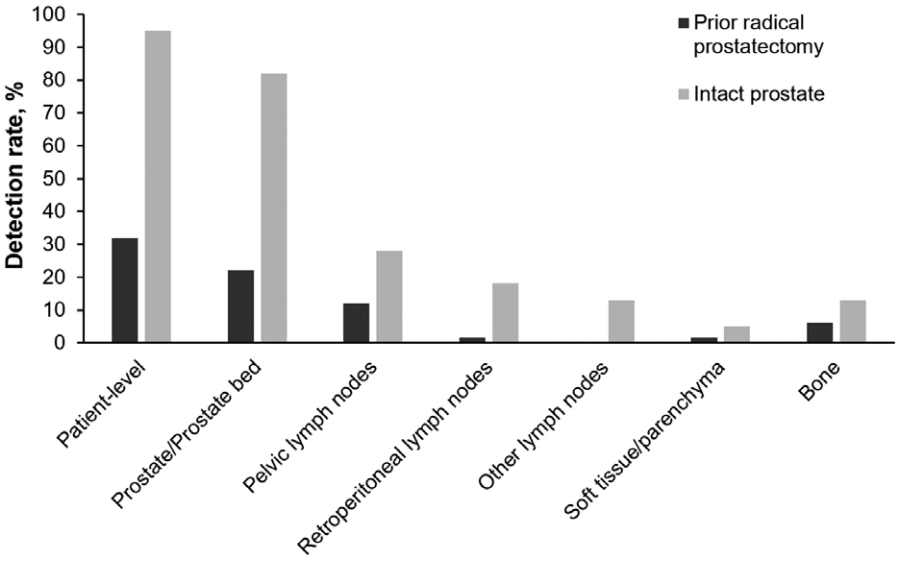
Patient cohort

In total, 104 patients (median [range] PSA = 0.79 [0.04–28.00] ng/mL), received an ^{18}F-fluciclovine PET/CT as part of the FALCON trial between December 2015 and May 2017 [10]. Of these, 65 (63%) had undergone radical prostatectomy as their initial therapy and 39 (38%) had an intact prostate. The median (range) PSA of the patients who had undergone prostatectomy was 0.32 (0.04–6.10) ng/mL and for those with an intact prostate was 4.90 (1.74–28.00) ng/mL.

Effect of prior prostatectomy

Across the whole population, ^{18}F-fluciclovine-avid lesions were found in 58 (56%) men. Patient-level detection rates were 32% (21/65) in those who had undergone prostatectomy compared with 95% (37/39) in those with an intact prostate ($P < 0.0001$). This was predominantly due to differences in detection in the prostate/prostate bed region ($P < 0.0001$; Fig. 1), over and above the differences in PSA levels between the two groups.

Fig. 1



Regional detection rates stratified by prostatectomy status in the whole FALCON study cohort ($n = 104$).

Table 1 Patient characteristics

	Patients $N = 62$
Age, years:	
Median	66
Range	49–80
Baseline PSA, ng/mL:	
Median	0.32
Range	0.04–6.1
Gleason score from surgery, n (%)	
≤6	2 (3.2%)
7	41 (66%)
≥8	11 (18%)
Missing	8 (13%)

PSA, prostate-specific antigen.

Postprostatectomy patients with a prescan plan for salvage radiotherapy

Imaging findings and impact on management among patients who had previously undergone radical prostatectomy and who had a prescan plan for salvage radiotherapy were explored. In total, 62 of the 65 postprostatectomy patients enrolled in FALCON had a prescan plan for salvage radiotherapy (16 with ADT) and are included in this analysis. Table 1 presents the baseline characteristics for these 62 patients.

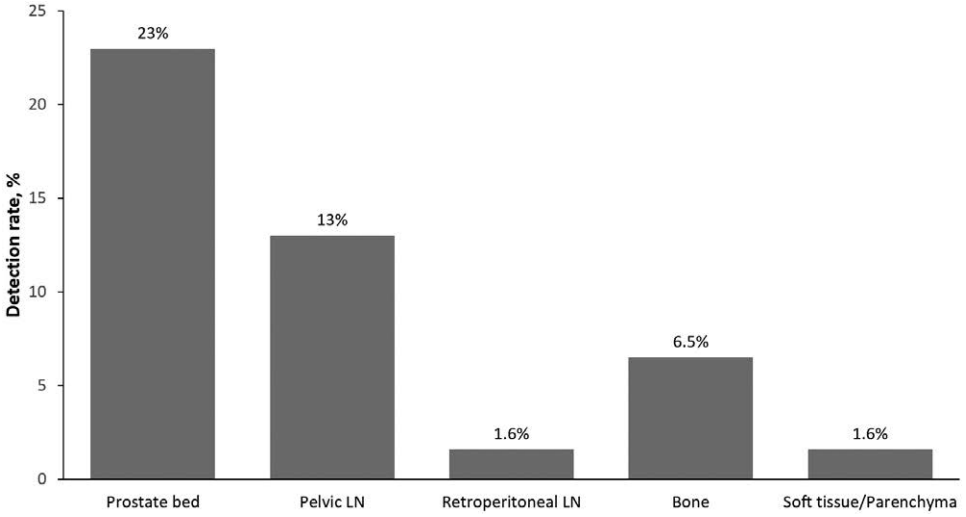
Postprostatectomy patients with a prescan plan for salvage radiotherapy – imaging results

^{18}F-Fluciclovine PET/CT detected lesions in 34% (21/62) of patients, ten of whom had evidence of extraprostatic disease. Fig. 2 presents the regional detection rates. Detection rates generally increased with increasing PSA, from 33% (6/18) at PSA levels ≤0.2 ng/mL to 50% (4/8) at PSA >1.0 ng/mL. Disease was confined to the prostate bed in 52% (11/21) of the patients with a positive scan result, and to the pelvis in a further 5 (pelvic lymph nodes; 24%), while the remaining 24% (5/21) of patients had evidence of involvement outside the pelvis.

As presented in Fig. 3, the PSA level at the time of the scan appeared to influence the extent of disease spread. While the proportion of patients with negative scans and those with disease limited to the prostate bed showed a decreasing trend with increasing PSA, the proportion of patients with metastases in any extrapelvic site increased from 0% (0/18) at PSA levels ≤0.2 ng/mL to 25% (2/8) at PSA levels >1 ng/mL. Likewise, the proportion of patients with ^{18}F-fluciclovine-avid pelvic lymph nodes increased from 6% (1/18) at PSA ≤0.2 ng/mL to 13% (1/8) at PSA levels >1 ng/mL. However, in these small groups of patients, dichotomised rates of detection (>0.5 vs. ≤0.5 ng/mL) did not reach statistical significance for extrapelvic or for pelvic lymph node only involvement ($P = 0.14$ and $P = 0.62$, respectively).

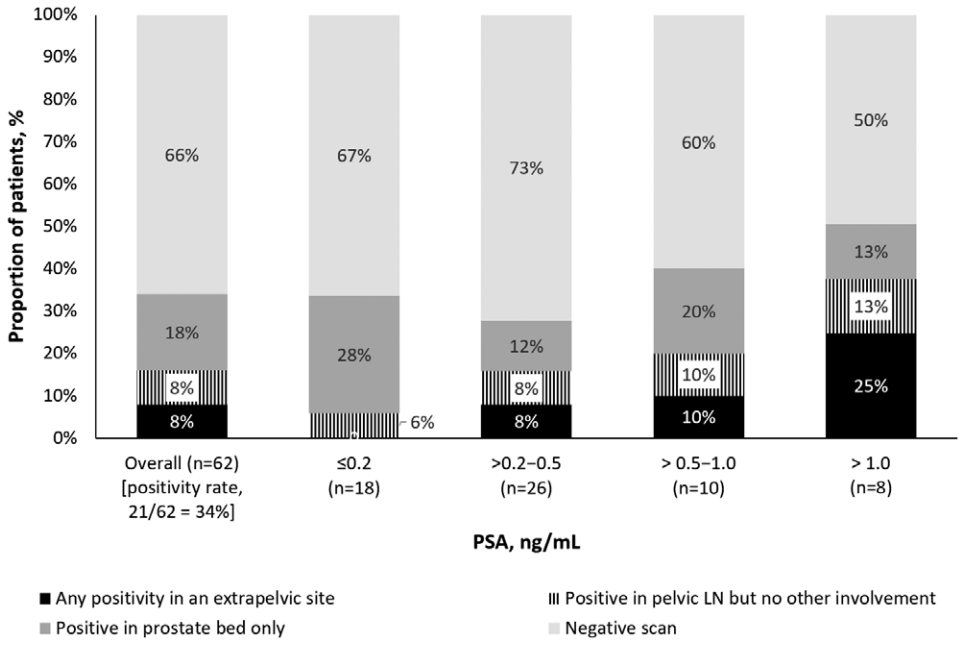
Among the 54 patients for whom baseline Gleason scores were available from the original surgery, positivity rates in patients with a Gleason sum ≤7 (21% [9/43]) were lower than in those with a sum ≥8 (55% [6/11]), approaching but not achieving statistical significance $P = 0.05$. As shown in Fig. 4, there was a trend towards more disseminated disease with increasing Gleason sum. The proportion of patients with metastases in any extrapelvic site increased from 2% (1/43) for patients with a Gleason sum ≤7 to 9% (1/11) for those with a sum

Fig. 2



Regional ^{18}F-fluciclovine PET/CT detection rates in postprostatectomy patients with a prescan plan for salvage radiotherapy ($n = 62$).

Fig. 3



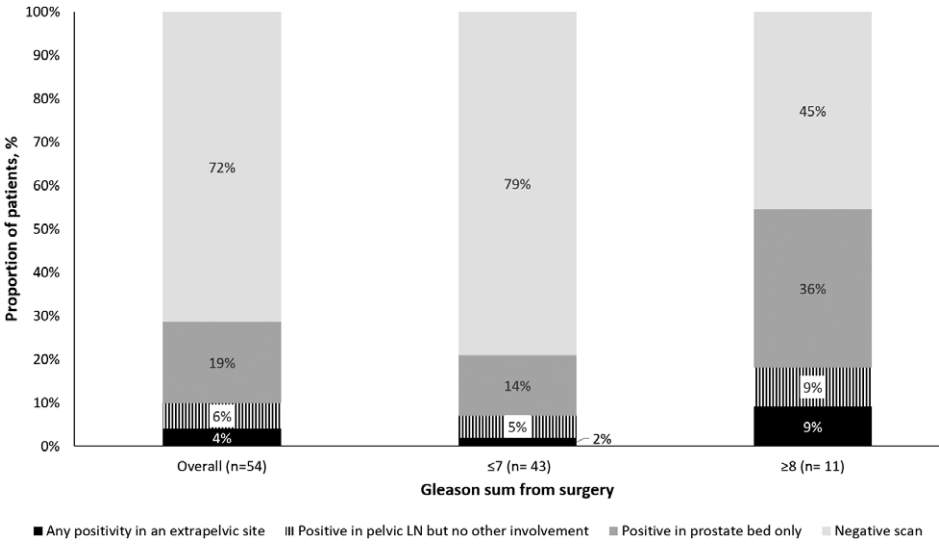
Extent of recurrence stratified by prostate-specific antigen levels in postprostatectomy patients with a prescan plan for salvage radiotherapy ($n = 62$).

≥8. The proportion of patients with ^{18}F-fluciclovine-avid pelvic lymph nodes also increased from 5% (2/43) for patients with a Gleason sum ≤7 to 9% (1/11) for those with a sum ≥8. Again, dichotomised rates of detection (sum ≤7 vs. ≥8) did not reach statistical significance for extrapelvic or for pelvic lymph node-only involvement ($P = 0.37$ and $P = 0.50$, respectively).

Postprostatectomy patients with a prescan plan for salvage radiotherapy – extent of disease dissemination and resultant changes in management

As shown in Fig. 5 (left side), the majority ($n = 55$, 89%) of the 62 patients had a prescan plan for salvage radiotherapy to the prostate bed only (16 with concomitant ADT).

Fig. 4



Extent of recurrence stratified by Gleason sum from surgery in postprostatectomy patients with a prescan plan for salvage radiotherapy ($n = 62$).

Following the [18]F-fluciclovine scan, 40% (25/62) of patients had a change to their plan (Fig. 5), 17 as the result of a positive [18]F-fluciclovine scan and 8 as the result of a negative scan. Fig. 6 presents how the extent of metastatic spread influenced the management decisions. Following a negative [18]F-fluciclovine PET/CT ($n = 41$), clinicians most commonly did not revise the prescan plan (33/41, 80%). However, 8 patients (20%) with a negative scan had a change to their planned treatment modality postscan – frequently to abort salvage radiotherapy in favour of active surveillance (6/8, 75%). Interestingly, two cases saw salvage radiotherapy aborted in favour of ADT. In both these cases, the prescan radiotherapy field derived using conventional imaging results covered the whole pelvis with one including a boost to lesion(s) identified with conventional imaging. For one of these patients, the later incidental finding of a lung nodule resulted in a change to the overall plan for prostate cancer management. The second patients' change in modality is assumed to be due to changes in patient factors.

Where [18]F-fluciclovine-avid lesions were contained within the prostate bed ($n = 11$), two patients' plans remained unchanged, one patient had salvage radiotherapy aborted in favour of ADT, another had plans for concomitant ADT to be stopped, but the most frequent management change ($n = 7$) was to modify the radiotherapy fields, most commonly to include a boost to an [18]F-fluciclovine-avid area.

Five patients had tracer-positive pelvic lymph nodes only, with 3/5 receiving a change to their treatment modality as a result (2 to ADT and 1 to active surveillance). One further patient had his radiotherapy fields reduced from the whole pelvis to focus on the [18]F-fluciclovine-avid nodes and the remaining patient experienced no change to his management plan (salvage radiotherapy to the whole pelvis).

Finally, five patients with prescan plans for salvage radiotherapy to the prostate bed (and whole pelvis in $n = 1$) had [18]F-fluciclovine-avid lesions outside the pelvis and 4/5 (80%) had a postscan change to their treatment modality as a result. These 4 patients all had metastases to bones in addition to pelvic lymph nodes ($n = 1$), prostate bed ($n = 2$) or pelvic plus retroperitoneal lymph nodes ($n = 1$) and all 4 patients had plans for salvage radiotherapy aborted in favour of either ADT ($n = 2$), ADT plus chemotherapy ($n = 1$) or active surveillance ($n = 1$). The fifth patient had [18]F-fluciclovine-avid soft tissue/parenchyma lesions and his plan remained unchanged postscan.

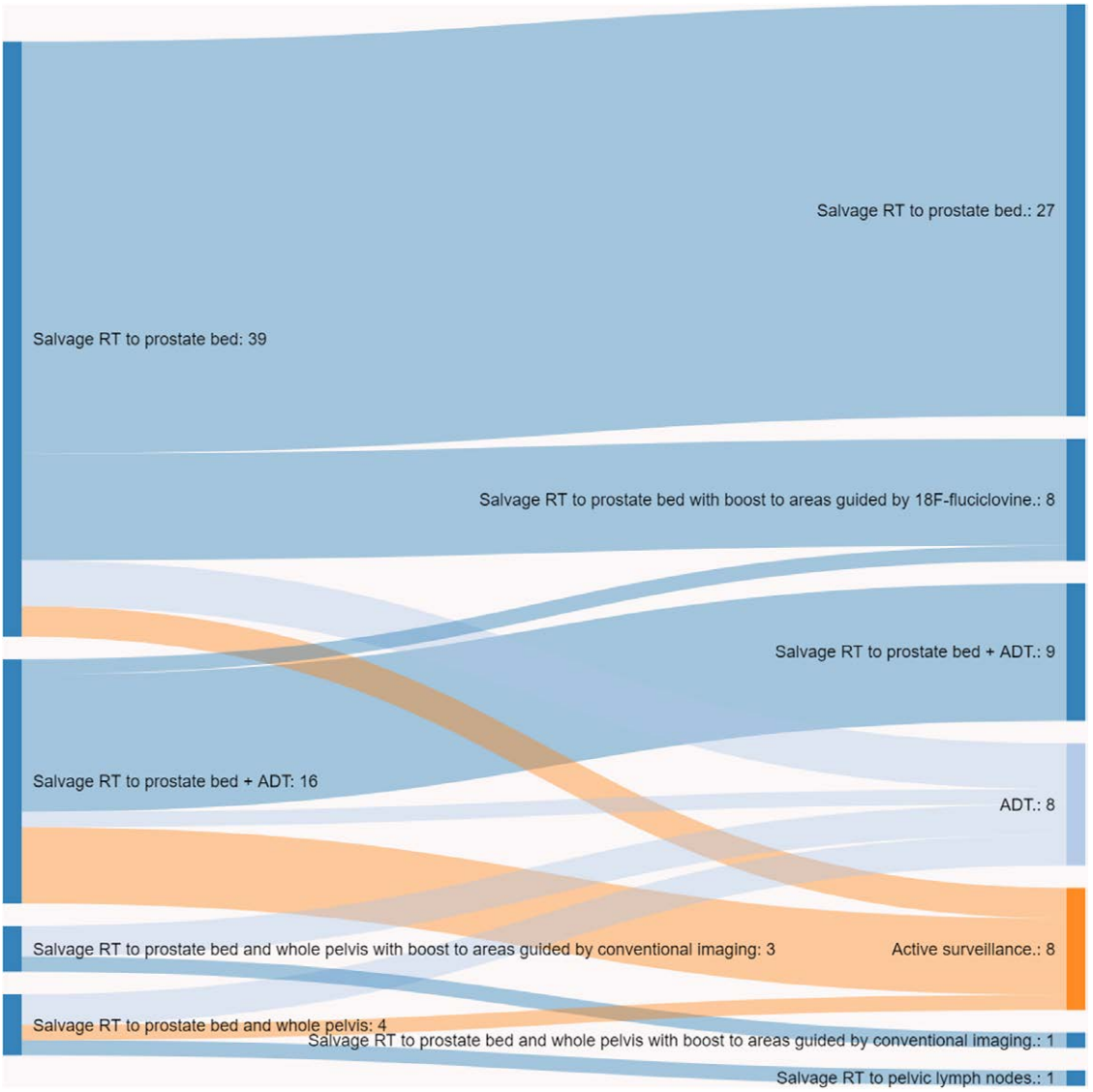
Figs. 7 and 8 present example images captured as part of the FALCON study.

Discussion

We explored detection rates and extent of disease recurrence among patients with a first recurrence of prostate cancer undergoing [18]F-fluciclovine imaging. We further explored the impact of [18]F-fluciclovine PET/CT on management plans for the patients who had undergone radical prostatectomy and who were intended for salvage radiotherapy.

Across all patients enrolled in FALCON, detection rates were found to be significantly lower in those who had undergone prostatectomy (32%) compared with those

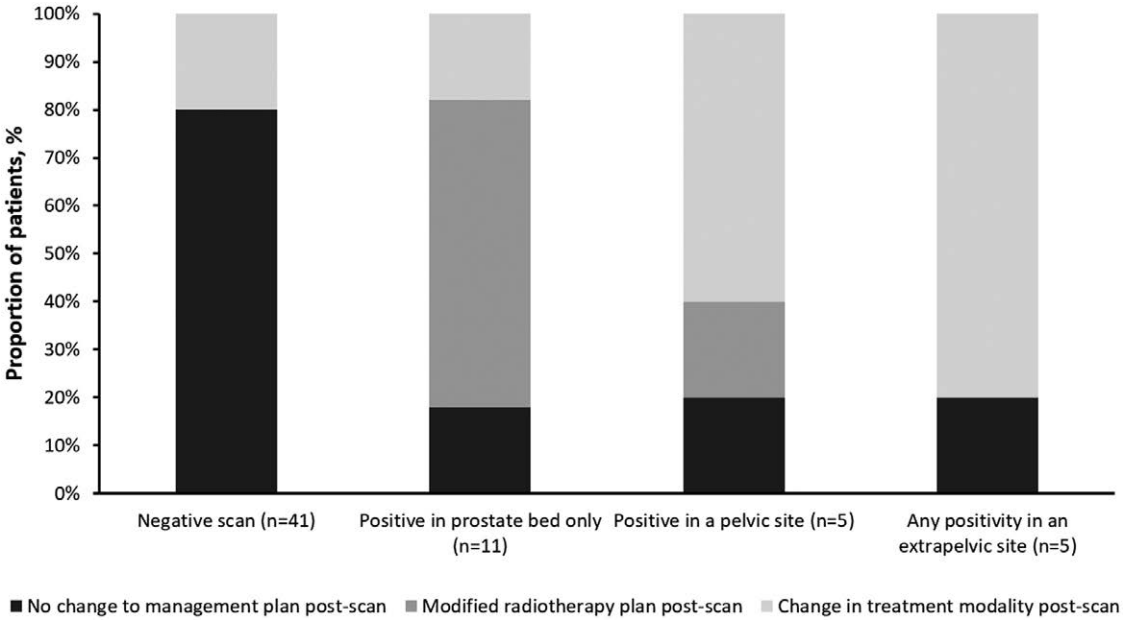
Fig. 5



Sankey diagram illustrating changes in management plans pre- and post-^{18}F-fluciclovine PET/CT for postprostatectomy patients with a prescan plan for salvage radiotherapy ($n = 62$).

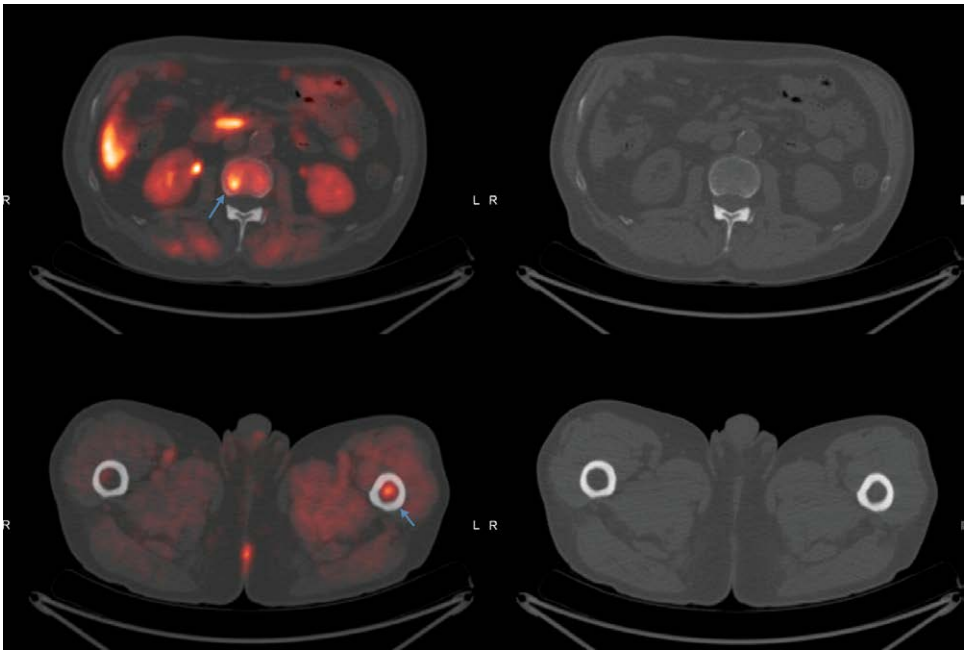
with an intact prostate (95%). These data are in line with those from a similar US-based multicentre study of ^{18}F-fluciclovine PET/CT which showed a 49% detection rate in those who had undergone prostatectomy and a rate of 84% in men with intact prostates. The authors noted the difference was attributable to prostate/bed findings (18% vs. 71%, respectively) [7] and this is supported by the present analysis. The influence of PSA on localisation of biochemical recurrence of prostate cancer with ^{18}F-fluciclovine PET/CT has been demonstrated previously [6]. While undetectable PSA levels might be expected soon after radical prostatectomy, it can take years to achieve a nadir PSA level with radiotherapy, and in some patients, PSA levels rise temporarily postradiotherapy in a phenomenon referred to as 'PSA bounce' [14,15]. Consequently, trials seeking to recruit patients with biochemical recurrence of prostate cancer typically use lower PSA thresholds to enrol patients who had previously undergone prostatectomy than for those who had radiotherapy. Accordingly, given the impact of PSA on ^{18}F-fluciclovine PET/CT detection rates, it must be considered that the lower detection rates among patients postprostatectomy compared with patients with an intact prostate that were observed in the present study and by others might be a consequence of the lower PSA thresholds used to enrol patients who had previously undergone prostatectomy compared with those who had radiotherapy [10].

Fig. 6



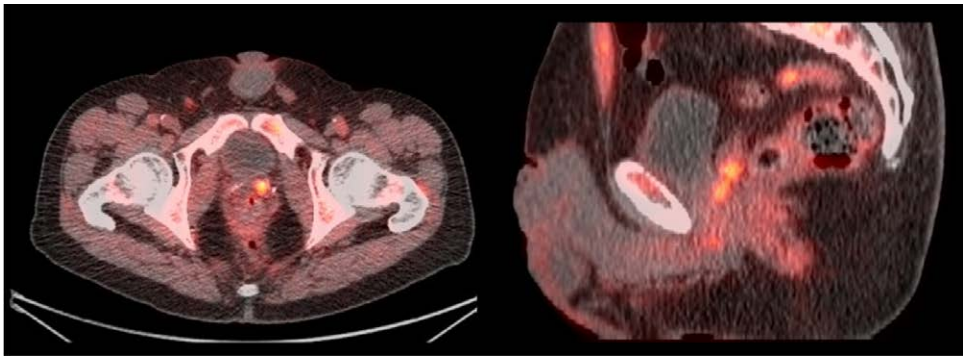
Changes to management plans stratified by extent of disease spread.

Fig 7



Axial fused PET/CT (left panel) and CT (right panel) images of a patient with a PSA level of 0.4 ng/mL 6 years after radical prostatectomy, intended for salvage radiotherapy to the prostate bed. Management was revised to ADT upon the findings of [18]F-fluciclovine avid lesions in the lumbar vertebra and left femur (blue arrows), with no corresponding abnormality on the CT component. Note is made of physiological uptake along the 3rd part of the duodenum and anal canal.

Fig. 8



Axial and sagittal fused PET/CT images of a patient with biochemical recurrence following radical prostatectomy, planned for salvage radiotherapy to the prostate bed. ^{18}F-Fluciclovine PET/CT demonstrated disease within the left seminal vesicle, leading to modification of standard radiotherapy plan to include a boost to this area. Full delineation, particularly of the caudal extent, was aided by the low level (in this case, visually absent) of radioactivity in the adjacent urinary bladder (as known for ^{18}F-fluciclovine [13]).

The main focus of the present study was on how ^{18}F-fluciclovine PET/CT influenced management decisions for the 62 patients enrolled in FALCON who were postprostatectomy and who had a prescan plan for salvage radiotherapy. Our data show that among this group of patients, there was a trend towards greater ^{18}F-fluciclovine patient-level detection rates with higher Gleason sum scores than with lower scores. Although our data from this small group of patients for whom Gleason scores were available from the original surgery do not reach statistical significance, an association between ^{18}F-fluciclovine detection rates and Gleason score has been suggested elsewhere [16,17]. We further show that despite the low median PSA level in this group of patients (0.32 ng/mL), detection rates were non-negligible at 34%. There is growing evidence for the good performance of ^{18}F-fluciclovine imaging at very low PSA levels [18] and our data that show one-third of patients with a PSA level ≤0.2 ng/mL have positive findings add further support to this trend. Moreover, the ^{18}F-fluciclovine detection rate of 33% at PSA level ≤0.2 ng/mL is marginally higher than the rates of 24–27% reported for a similar population scanned with ^{68}Ga-PSMA-11 [19].

The advent of sensitive molecular imaging techniques has seen an increasing proportion of patients being diagnosed with distant metastatic disease at restaging in comparison with conventional imaging techniques. Moreover, there is now a greater focus on patients early in the prostate cancer recurrence timeline who have limited metastatic disease burden or oligometastatic disease, which is typically characterised by up to five extraprostatic lesions (≤3 lesions in any single organ system) with a controlled primary tumour [20]. PET-guided metastases-directed radiotherapy or surgery has been shown to improve progression-free survival compared with surveillance [21] and the highest chances of salvage radiotherapy success are associated with the early identification of metastases at low PSA levels [22]. An analysis by Kim *et al.* [7] has shown that ^{18}F-fluciclovine PET/CT specifically may be a useful tool to guide targeted treatment of oligometastases. Thus, while recent data suggest that sensitive PSMA-based PET/CT may become the imaging modality of choice to direct treatment for patients with oligometastatic disease [23], emerging data on the performance of ^{18}F-fluciclovine PET/CT at low PSA levels [18] suggest it should not be overlooked. Our data show that approximately half of patients with ^{18}F-fluciclovine-avid lesions showed positivity outside the prostate bed, with the extent of spread rising with increasing PSA levels. However, similar to the findings of Solanki *et al.* [24], we were able to identify patients with prostate bed only, pelvic regional only and those with extrapelvic uptake at all PSA levels with the exception of at PSA levels ≤0.2 ng/mL where no patients had positivity in an extrapelvic site.

Here, we see that accurate delineation of disease with ^{18}F-fluciclovine PET/CT led to the treatment plans being changed for 40% of the patients, potentially minimising unnecessary or ineffective treatments. Most commonly salvage radiotherapy was changed to an alternative treatment modality (n = 17). Changes from salvage radiotherapy to ADT occurred in 8 patients (Fig. 7), frequently due to the location of ^{18}F-fluciclovine-avid lesions in pelvic lymph nodes (n = 2) or in extrapelvic regions (n = 3). Aborting salvage radiotherapy in favour of active surveillance was equally as common (n = 8), but this change was more likely the result of a negative ^{18}F-fluciclovine scan (6/8). This implies both physician and patient confidence in the absence of visible disease on ^{18}F-fluciclovine scans [25] and may be beneficial to patients in the avoidance of morbidity associated with potentially unnecessary salvage radiotherapy [26,27].

Not all changes to management plans involved a change of treatment modality. Eight patients received a modification to their existing salvage radiotherapy plan as a result of ^{18}F-fluciclovine PET/CT. In 7/8 patients, the modification was expansion of a prostate bed-only field to incorporate a boost to a lesion identified with ^{18}F-fluciclovine imaging (Fig. 8). While not verified for this small subset of patients, this approach has been recently described to optimise treatment efficacy as reflected by improved failure-free survival [9], and account for areas potentially not covered on standard contouring guidelines [28]. Conversely, we also saw a case where ^{18}F-fluciclovine PET/CT was able to guide the physician towards reducing from a whole pelvis field to focus on ^{18}F-fluciclovine-avid pelvic lymph nodes.

A number of others have reported on the impact of ^{18}F-fluciclovine PET/CT on salvage radiotherapy planning (for review see [29]). Akin–Akintayo reported that 36% of patients had a change to their radiotherapy fields as a result of ^{18}F-fluciclovine PET/CT [30]. Their group further showed that ^{18}F-fluciclovine PET led to significant increases in the defined target volume for the penile bulb compared with the prescan plan [31]. Dreyfuss et al conducted a single-centre retrospective cohort study of 336 scans from patients with biochemical recurrence of prostate cancer after primary treatment [32]. They reported that ^{18}F-fluciclovine PET/CT results changed the prescan management plans in 73% of cases and that 58% of recommendations involved a treatment modality decision. With regards to salvage radiotherapy, they report that 95% (74/78) of patients with positive scans and radiotherapy incorporated into their management plan postscan received radiotherapy directed at an ^{18}F-fluciclovine-avid lesion. While it should be considered that not all management changes will confer improved clinical outcomes, the recent work described above on validating contouring guidelines for postprostatectomy salvage radiation against ^{18}F-fluciclovine scans reports that a proportion of prostate bed and pelvic nodal recurrences are missed/incompletely covered [28]. Therefore, encompassing ^{18}F-fluciclovine PET/CT into radiotherapy planning might help target lesions that would otherwise be missed, and the results of the EMPIRE-1 trial confirm the long-term benefits of this approach [9].

The rates of ^{18}F-fluciclovine-guided management changes appear favourable compared with those observed with ^{68}Ga-PSMA. A meta-analysis of ^{68}Ga-PSMA-guided management changes reports the pooled proportion of management changes from 15 studies (1163 patients) to be 54% (95% CI, 47–60) [33]. As the authors note, there was substantial heterogeneity among the included studies, which in part is likely attributed to the differences in types of initial definitive treatment. The rate of management change (63%) reported from the whole FALCON population (104 patients) [10], is in line with that reported from the meta-analysis of ^{68}Ga-PSMA data; however, the present study focusing on a restricted cohort of only 62 patients with prior radical prostatectomy and an intended treatment plan for salvage radiotherapy reports a lower rate of change (40%).

A number of limitations to the present analysis exist. These include the lack of routine histological confirmation of the imaging results, although prior histologically confirmed data have verified the performance of ^{18}F-fluciclovine PET/CT in this setting [6]. Also, the small sample size limits the statistical certainty of some of our findings. A further limitation was that we were unable to determine the impact of PSA doubling time in this population, and although a number of recent publications have reported there to be no significant effect of PSA doubling time on diagnostic performance [16,34,35], incomplete reporting in the present study meant we were unable to explore the correlation between PSA doubling time and patterns of recurrence observed with ^{18}F-fluciclovine PET/CT.

Conclusion

Among a cohort of men planned for salvage radiotherapy for rising PSA after radical prostatectomy, ^{18}F-fluciclovine PET/CT detected sites of recurrence in approximately one-third of a predominantly low PSA cohort. The identification of ^{18}F-fluciclovine-avid lesions led to changes in the treatment modality or revisions to the radiotherapy target fields to better target the recurrent lesions in two-fifths of patients. Incorporating ^{18}F-fluciclovine PET/CT into treatment planning may help identify patients suitable for salvage radiotherapy and guide clinicians in the optimisation of management plans.

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Conflicts of interest

H.P. has attended and received honoraria for advisory boards, travel expenses to medical meetings and served as a consultant for Blue Earth Diagnostics Ltd, AstraZeneca, Astellas, Janssen, Sanofi Aventis, Ferring, Bayer and Novartis. D.B. has acted as a speaker for and received travel support from Blue Earth Diagnostics Ltd. E.J.T. is currently an employee of Blue Earth Diagnostics Ltd. J.B. and A.F.S. have no relevant conflicts to disclose. The FALCON Study was sponsored by Blue Earth Diagnostics Ltd with a grant from Innovate UK.

References

1 Geinitz H, Riegel MG, Thamm R, Astner ST, Lewerenz C, Zimmermann F, *et al*. Outcome after conformal salvage radiotherapy in patients with rising prostate-specific antigen levels after radical prostatectomy. *Int J Radiat Oncol Biol Phys* 2012; **82**:1930–1937.

2 Johnstone PA, Tarman GJ, Riffenburgh R, Rohde DC, Puckett ML, Kane CJ. Yield of imaging and scintigraphy assessing biochemical failure in prostate cancer patients. *Urol Oncol* 1997; **3**:108–112.

3 Dotan ZA, Bianco FJ Jr, Rabbani F, Eastham JA, Fearn P, Scher HI, *et al*. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. *J Clin Oncol* 2005; **23**:1962–1968.

4 Liauw SL, Pitroda SP, Eggener SE, Stadler WM, Pelizzari CA, Vannier MW, Oto A. Evaluation of the prostate bed for local recurrence after radical prostatectomy using endorectal magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2013; **85**:378–384.

5 Kelloff GJ, Choyke P, Coffey DS; Prostate Cancer Imaging Working Group. Challenges in clinical prostate cancer: role of imaging. *AJR Am J Roentgenol* 2009; **192**:1455–1470.

6 Bach-Gansmo T, Nanni C, Nieh PT, Zanoni L, Bogsrud TV, Sletten H, *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.

7 Kim EH, Siegel BA, Teoh EJ, Andriole GL; LOCATE Study Group. Prostate cancer recurrence in patients with negative or equivocal conventional imaging: a role for 18F-fluciclovine-PET/CT in delineating sites of recurrence and identifying patients with oligometastatic disease. *Urol Oncol* 2021; **39**:365.e9–365.e16.

8 Abiodun-Ojo OA, Jani AB, Akintayo AA, Akin-Akintayo OO, Odewole OA, Tade FI, *et al*. Salvage radiotherapy management decisions in postprostatectomy patients with recurrent prostate cancer based on 18f-fluciclovine PET/CT guidance. *J Nucl Med* 2021; **62**:1089–1096.

9 Jani AB, Schreibmann E, Goyal S, Halkar R, Hershatter B, Rossi PJ, *et al*. 18F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. *Lancet* 2021; **397**:1895–1904.

10 Scarsbrook AF, Bottomley D, Teoh EJ, Bradley KM, Payne H, Afaq A, *et al*.; FALCON study group. Effect of ^{18}F-fluciclovine positron emission tomography on the management of patients with recurrence of prostate cancer: results from the FALCON trial. *Int J Radiat Oncol Biol Phys* 2020; **107**:316–324.

11 Malone S, Croke J, Roustan-Delatour N, Belanger E, Avruch L, Malone C, *et al*. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. *Int J Radiat Oncol Biol Phys* 2012; **84**:725–732.

12 Miller MP, Kostakoglu L, Pryma D, Yu JQ, Chau A, Perlman E, *et al*. Reader Training for the restaging of biochemically recurrent prostate cancer using ^{18}F-fluciclovine PET/CT. *J Nucl Med* 2017; **58**:1596–1602.

13 Schuster DM, Nanni C, Fanti S, Oka S, Okudaira H, Inoue Y, *et al*. Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid: physiologic uptake patterns, incidental findings, and variants that may simulate disease. *J Nucl Med* 2014; **55**:1986–1992.

14 Freiberger C, Berneking V, Vögeli TA, Kirschner-Hermanns R, Eble MJ, Pinkawa M. Long-term prognostic significance of rising PSA levels following radiotherapy for localized prostate cancer – focus on overall survival. *Radiati Oncol* 2017; **12**:98.

15 Rosser CJ, Kuban DA, Levy LB, Chichakli R, Pollack A, Lee AK, Pisters LL. Prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002;**168**:2001–2005.

16 England JR, Paluch J, Ballas LK, Jadvar H. 18F-fluciclovine PET/CT detection of recurrent prostate carcinoma in patients with serum PSA ≤ 1 ng/mL after definitive primary treatment. *Clin Nucl Med* 2019; **44**:e128–e132.

17 Garza D, Kandathil A, Xi Y, Subramaniam RM. 18F-fluciclovine PET/CT detection of biochemical recurrent prostate cancer in patients with PSA levels <2.00 ng/mL. *Nucl Med Commun* 2021; **42**:907–913.

18 Rais-Bahrami S, Efstathiou JA, Turnbull CM, Camper SB, Kenwright A, Schuster DM, *et al*. ^{18}F-Fluciclovine PET/CT performance in biochemical recurrence of prostate cancer: a systematic review. *Pros Can Prost Dis* 2021. doi: 10.1038/s41391-021-00382-9

19 Miksch J, Bottke D, Krohn T, Thamm R, Bartkowiak D, Solbach C, *et al*. Interobserver variability, detection rate, and lesion patterns of 68Ga-PSMA-11-PET/CT in early-stage biochemical recurrence of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 2020; **47**:2339–2347.

20 Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019; **393**:2051–2058.

21 Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, *et al*. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol* 2018; **36**:446–453.

22 Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, *et al*. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007; **25**:2035–2041.

23 Savir-Baruch B, Choyke PL, Rowe SP, Schuster DM, Subramaniam RM, Jadvar H. Role of ^{18}F-fluciclovine and prostate-specific membrane antigen PET/CT in guiding management of oligometastatic prostate cancer: AJR expert panel narrative review. *AJR Am J Roentgenol* 2021; **216**:851–859.

24 Solanki AA, Savir-Baruch B, Liauw SL, Michalski J, Tward JD, Vapiwala N, Teoh EJ; LOCATE study group. ^{18}F-fluciclovine positron emission tomography in men with biochemical recurrence of prostate cancer after radical prostatectomy and planning to undergo salvage radiation therapy: results from LOCATE. *Pract Radiat Oncol* 2020; **10**:354–362.

25 Andriole GL, Kostakoglu L, Chau A, Duan F, Mahmood U, Mankoff DA, *et al*.; LOCATE Study Group. The impact of positron emission tomography with ^{18}F-fluciclovine on the treatment of biochemical recurrence of prostate cancer: results from the LOCATE trial. *J Urol* 2019; **201**:322–331.

26 van Stam MA, Aaronson NK, Pos FJ, Bosch JL, Kieffer JM, Tillier CN, van der Poel HG. The effect of salvage radiotherapy and its timing on the health-related quality of life of prostate cancer patients. *Eur Urol* 2016; **70**:751–757.

27 Spratt DE. Salvage radiotherapy after prostatectomy: two sides of the coin. *Eur Urol* 2016; **70**:758–759.

28 Harmon G, Chan D, Lee B, Miller C, Gorbonos A, Gupta G, *et al*. Validating modern NRG oncology pelvic nodal and GFRU prostate bed contouring guidelines for post-prostatectomy salvage radiation: a secondary analysis of the LOCATE trial. *Int J Radiat Oncol Biol Phys* 2021. doi: 10.1016/j.ijrobp.2021.05.009

29 Slevin F, Beasley M, Cross W, Scarsbrook A, Murray L, Henry A. Patterns of lymph node failure in patients with recurrent prostate cancer postradical prostatectomy and implications for salvage therapies. *Adv Radiat Oncol* 2020; **5**:1126–1140.

30 Akin-Akintayo OO, Jani AB, Odewole O, Tade FI, Nieh PT, Master VA, *et al*. Change in salvage radiotherapy management based on guidance with

FACBC (Fluciclovine) PET/CT in postprostatectomy recurrent prostate cancer. *Clin Nucl Med* 2017; **42**:e22–e28.
31 Jani AB, Schreibmann E, Rossi PJ, Shelton J, Godette K, Nieh P, *et al*. Impact of ^{18}F-fluciclovine PET on target volume definition for postprostatectomy salvage radiotherapy: initial findings from a randomized trial. *J Nucl Med* 2017; **58**:412–418.
32 Dreyfuss AD, Ahn GS, Barsky AR, Gillman JA, Vapiwala N, Pantel AR. ^{18}F-fluciclovine PET/CT in therapeutic decision making for prostate cancer: a large single-center practice-based analysis. *Clin Nucl Med* 2021; **46**:187–194.
33 Han S, Woo S, Kim YJ, Suh CH. Impact of 68Ga-PSMA PET on the management of patients with prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2018; **74**:179–190.
34 Savir-Baruch B, Lovrec P, Solanki AA, Adams WH, Yonover PM, Gupta G, Schuster DM. Fluorine-18-labeled fluciclovine PET/CT in clinical practice: factors affecting the rate of detection of recurrent prostate cancer. *AJR Am J Roentgenol* 2019; **213**:851–858.
35 Selnæs KM, Krüger-Stokke B, Elschot M, Johansen H, Steen PA, Langørgen S, *et al*. Detection of recurrent prostate cancer with ^{18}F-fluciclovine PET/MRI. *Front Oncol* 2020; **10**:582092.