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Evaluating appropriateness of 18F-fluciclovine PET/CT relative to standard of care imaging guidelines and the impact of ADT on positivity: a prospective study in 62 Veterans Administration patients at a single institution

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Background **According to the National Comprehensive Cancer Network Guidelines, 18F-fluciclovine PET/CT is considered appropriate after negative standard of care (SOC) imaging.**

Objective **To prospectively compare 18F-fluciclovine to SOC imaging, investigate whether it should be done when SOC imaging is (+), and evaluate its detection rate in patients receiving androgen deprivation therapy.**

Methods **We recruited 57 prostate cancer patients with biochemical recurrence with 18F-fluciclovine PET/CT and SOC imaging within 30 days. Prostate-specific antigen (PSA) level, Gleason score (GS), history of radical prostatectomy (RP), radiation therapy (RT) or hormone therapy (HT) were reviewed.**

Results **The 57 patients had a median PSA of 2.6 and average GS of 7.4; 27 (47.4%) had RP, 28 (49.1%) had RT, 1 (1.75%) had HT and 1 (1.75%) observation only. 18F-fluciclovine identified disease recurrence in 45/57 patients (78.9%), including oligometastasis in 18/45 (40%). SOC imaging identified recurrent disease in 12/57 patients (21.1%) while 18F-fluciclvoine identified additional sites of disease in 11/12 (91.7%). The (+) 18F-fluciclovine studies had a median PSA 2.6 ng/ml compared to 6.0 ng/ml in the (+) SOC studies.**

Conclusion **18F-fluciclovine was superior to SOC imaging for lesion detection, identification of oligometastasis and identification of additional sites of disease.** ***Nucl Med Commun*** **XXX: XXXX–XXXX**

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Keywords: androgen deprivation therapy, fluciclovine, PET/CT, prostate cancer

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Introduction

Prostate cancer is the second most frequent malignancy in men worldwide [1] and, in the United States, prostate cancer is the second leading cause of cancer related death [2]. The 10-year relative survival for localized stage prostate cancer was 100% from 2001 to 2016 per the Centers for Disease Control [2]. However, the survival outcome is significantly lower with distant metastasis. The 5-year survival rate for local or regional disease is 100% and for distant metastasis 31% [3]. Furthermore, prostate cancer biochemical recurrence (BCR) after curative intent treatment affects 30–50% of patients in the first 10 years after initial therapy [4,5].

Diagnostic imaging is an important part of initial cancer staging and identifying sites of disease in BCR. Standard of care (SOC) imaging has been either MRI of the prostate or contrast computed tomography (cCT) in addition to bone scan. MRI or cCT has limitations for nodal assessment, including lower sensitivity for detection of small subcentimeter and or morphologically normal shaped lymph nodes. Nodal disease outside of the field of view of pelvic MRI and cCT abdomen and pelvis will also be missed. Bone scan has low sensitivity for small lesions and lytic lesions. Missed disease sites from SOC may have led to a change in management, which potentially increased survival.

In recent years, new imaging modalities have emerged for the assessment of disease in prostate cancer. 18F-Fluciclovine (Axumin), a synthetic amino acid analogue PET radiotracer, was approved by the U.S. Food and Drug Administration (FDA) in May 2016 for PET/CT imaging in men with suspected BCR, based on elevated prostate specific antigen (PSA), following prior treatment. 18F-Fluciclovine was able to identify extraprostatic disease and nodal disease which appear benign on anatomical imaging [6,7]. However, it was not without limitations. Potential false positives include benign prostatic hypertrophy, acute and chronic inflammation (i.e. prostatitis, reactive lymph nodes, and postradiation inflammation). False positives can also be due to benign

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tumors such as pituitary adenoma, meningioma, osteoid osteoma, and adrenal gland adenomas. False negatives can result due to small lesion size and dense sclerotic lesions (due to low cellularity).

The FDA has since approved prostate specific membrane antigen (PSMA) agents, gallium 68 PSMA-11 in December 2020, 18F-piflufolastat in May 2021, and 18F-flotufolastat in May 2023 for use in cases of newly diagnosed high-risk disease and BCR. Multiple studies have shown PSMA agents to be superior to fluciclovine for detection of BCR [8]. 18F-Fluciclovine, however, may have an advantage over PSMA agents in the detection of recurrent disease in the prostate bed after prostatectomy and the detection of lymph nodes located near the bladder due to decreased bladder activity which can decrease sensitivity for the detection of nearby lesions.

Under the National Comprehensive Cancer (NCCN) guidelines, 18F-fluciclovine PET/CT is considered appropriate only after negative SOC imaging. The purpose of this study is to prospectively compare performance of 18F-fluciclovine to SOC imaging, investigate whether it should be done even when SOC imaging is positive (+), and evaluate the impact of androgen deprivation therapy (ADT) on scan positivity.

Materials and methods

Patient selection and informed consent

Veterans Administration Hospital Institutional Review Board (IRB) approval and informed consent was obtained, and we recruited 62 BCR prostate cancer patients from 18 Dec 2018 to 24 Jun 2021 undergoing 18F-fluciclovine PET/CT and SOC (bone scan and cCT) imaging within a 30-day period at a single Veterans Administration site as part of a prospective study comparing the detection of recurrent prostate cancer.

Inclusion and exclusion criteria

Inclusion criteria were history of localized prostate cancer with subsequent definitive treatment and BCR as evidenced by rising PSA. Patients were excluded if there was no concurrent cCT and bone scan within 30 days of 18F-fluciclovine PET/CT. Patients were excluded for not having a documented Gleason score.

18F-Fluciclovine PET/CT imaging protocol

An intravenous injection of 370 Mbq/kg (10 mCi/kg) 18F-fluciclovine was administered to patients. Image acquisition started within 3–5 min of radiotracer injection, beginning with the pelvis. All scans were acquired using a Siemens Biograph cCT Flow 64 PET/CT scanner (Siemens Healthineers, Erlangen, Germany). Scan speed was 0.4 mm/s phase one and 0.7 mm/s phase two. The PET component is composed of lutetium oxyorthosilicate-based crystals. The CT component of the PET/CT scanner consisted of a 64-slice multidetector helical CT. The CT imaging data was used for anatomic localization. The field of view was from the top of head to the upper thighs. The reconstruction process in the scanner was based on the Siemens 3D ordered subset expectation maximization [9].

Diagnostic CT with contrast

cCT of the abdomen and pelvis was performed on a 16-slice Siemens SOMATOM Definition Flash 128 whole body CT scanner and Siemens SOMATOM Definition Edge 128 whole body CT scanner with multiple contiguous 0.6 mm acquired axial images from the diaphragm to the upper thigh with 90–120 kVp (based on the patient's body habitus) and autoadjusted tube current (mA) with administration of intravenous contrast agent. Image slice reconstruction was performed using 5 mm slice thickness and sent to picture archiving and communication system.

Whole body bone scan

The patient was administered 740–110 MBq (20–30 mCi) Tc-99 m methylene diphosphonate intravenous. Approximately 2 h later, delayed anterior and posterior whole-body scans and static spot images of the skull and pelvis were obtained. If there was significant bladder activity or a lesion of interest in the pelvis, additional lateral and oblique views were also obtained. Our institution uses a dual-head gamma camera with parallel hole, low energy, high resolution collimators (Siemens Symbia EVO, Siemens Symbia INTEVO 16, and Siemens Symbia Bold INTEVO Scintillation Cameras). Scanning speed was 20 cm/min. Computer acquisition, processing, and display of images were performed using Siemens Syngo MI applications.

Image interpretation

The 18F-fluciclovine PET/CT and SOC reports were reviewed at initial assessment to determine whether the scan showed lesions and were therefore (+). These images were then reviewed by a board-certified nuclear medicine physician with over 25 years of experience to confirm the presence of lesions. The (+) 18F-fluciclovine PET/CT and (+) SOC scans were then assessed for the location of lesions and to categorize lesions as local, regional, or distant metastasis. Local disease was defined as disease recurrence in the prostate for patients with intact prostate gland or disease recurrence in the prostate bed for patients with prostatectomy. Regional disease was defined as nodal disease involving the periprostatic region, internal iliac lymph node, or external iliac lymph node. Distant metastasis was defined as common iliac lymph nodes, retroperitoneal lymph nodes, inguinal lymph nodes, and nodal disease above the diaphragm. Distant metastasis also included visceral organs and osseous metastasis [10]. The (+) 18F-fluciclovine PET/CT and (+) SOC scans were also assessed for oligometastasis defined as five or fewer metastatic lesions. The

(+) 18F-fluciclovine and SOC scans were compared to see if additional sites of disease were identified by either modality compared to the other.

Chart review

The patient's 18F-fluciclovine and SOC reports along with the electronic medical records were reviewed to determine the patient's age at the time of the scan, PSA, and Gleason score. These same reports and clinic notes from the treating physicians were reviewed to determine whether the patients had prostatectomy, radiation therapy, or hormone replacement.

Statistical analysis

The median PSA, average Gleason score, average age, and respective ranges of the cohort were calculated. The percentage of the cohort with radical prostatectomy and radiation therapy was calculated. The percentage of patients with (+) 18F-fluciclovine PET/CT and SOC scans was calculated. The percentage of 18F-fluciclovine (+) and SOC patients with oligometastasis was determined. The percentage of (+) scans with additional sites of disease compared to the other imaging modality was also assessed. Subset analysis of the median PSA, average Gleason score, and range of the 18F-fluciclovine (+) and 18F-fluciclovine (-) patients was performed. Subset analysis of the 18F-fluciclovine (+) and 18F-fluciclovine (-) patients with history of radical prostatectomy, radiation therapy, hormone therapy, and observation was done. Hormone therapy status of each patient was analyzed in terms of whether the patient had been on ADT for a short time (2 months or less) or long time period (6 months or longer) prior to the 18fluciclovine PET/CT scan. ADT prior to the 18F-fluciclovine PET/CT scan was also categorized as current (patient being on ADT) or remote (last ADT was at least 1 year prior to PET/CT). The Mann–Whitney test was utilized in subset analysis to determine whether there were differences in the median PSA between 18F-fluciclovine (+) versus 18F-fluciclovine (-) studies and between 18F-fluciclovine (+) versus SOC (+) studies. An independent-samples *t*-test was utilized to determine whether there were differences in the average Gleason score between 18F-fluciclovine (+) versus 18F-fluciclovine (-) studies and between 18F-fluciclovine (+) versus SOC (+) studies. Analyses were completed in IBM SPSS Statistics version 27 (IBM, Armonk, New York, USA).

Results

Patient characteristics

In this prospective, Health Insurance Portability and Accountability Act compliant and IRB approved study, we recruited 62 BCR prostate cancer patients from 18 Dec 2018 to 24 Jun 2021 who were to undergo 18F-fluciclovine PET/CT and SOC (bone scan and cCT) imaging within a 30-day period at our institution. A total of 5 patients were excluded: 2 with no concurrent CT scan and 3 for not having a documented Gleason score. Therefore, 57 patients were included in the data analysis. The 57 BCR prostate cancer patients meeting the study criteria had an average age of 70.6 years (range 49–94 years), median PSA of 2.6 (range 0.001–110 ng/ml), and average Gleason score of 7.4 (range 6–9). Of the 57 cases, 27 (47.4%) had radical prostatectomy, 28 (49.1%) had radiation therapy, 1/45 (1.75%) hormone therapy only, and 1/45 (1.75%) underwent observation only. Table 1 summarizes the patient characteristics.

18F-Fluciclovine PET/CT identified sites of disease recurrence in 45 of 57 patients (78.9%). The (+) 18F-fluciclovine studies had a median PSA of 2.6 ng/ml (range 0.15–110 ng/ml) and average Gleason score of 7.4 (range 6–9). There were 12 out of 57 18F-fluciclovine (-) studies (21.1%) with median PSA 2.0 ng/ml (range 0.001–5.5 ng/ml) and average Gleason score of 7.5 (range 6–9). There was no significant difference between the 18F-fluciclovine (+) studies versus 18F-fluciclovine (-) studies for mean PSA (*P*-value 0.06) or average Gleason score (*P*-value 0.39). Of the 45 18F-fluciclovine (+) studies, 18 (40.0%) had radical prostatectomy, 25 (55.6%) had radiation therapy, 1 (2.2%) had hormone therapy only, and 1 (2.2%) underwent observation only. Of the 12 (-) 18F-fluciclovine studies, 9 (75%) had radical prostatectomy and 3 (25%) had radiation therapy. The results are shown in Table 2.

The hormone therapy status of the 18F-fluciclovine (+) versus 18F-fluciclovine (-) studies was analyzed to see whether long-term hormone therapy affected 18F-fluciclovine scan positivity. The data showed that of the 14 patients who were on current long-term ADT, 13 (92.9%) had (+) scans. Of the 9 patients with remote history of long-term ADT, 7 (77.8%) had (+) scans. Also, there were 12 patients who had a short remote course of ADT of which 10 (83.3%) had (+) scans. This data is summarized in Table 3.

The SOC imaging identified recurrent disease in only 12 out of 57 patients (21.1%). The SOC (+) 18F-fluciclovine studies had a median PSA 6.0 ng/ml (0.15–110 ng/ml) and average Gleason score 7.8 (range 6–9). The SOC (-) studies had a median PSA 2.0 ng/ml (range 0.001–23 ng/ml) and average Gleason score 7.3 (range 6–9). Of the 12

Table 1 Patient characteristics

Number of patients	57
Age (average)	70.6 yr (range 46–94 yr of age)
PSA (median)	2.6 ng/ml (range 0.001–110 ng/ml)
Gleason score (average)	7.4 (range 6–9)
Radical prostatectomy	27 (47.4%)
Radiation therapy	28 (49.1%)
Hormone therapy only	1 (1.75%)
Observation only	1 (1.75%)

PSA, prostate specific antigen.

Table 2 Characteristics of 18F-fluciclovine (+) versus 18F-fluciclovine (-) cases

	18F-Fluciclovine (+)	18F-Fluciclovine (-)	*P*-value
No. of cases (out of 57 total cases)	45 (78.9%)	12 (21.1%)	
PSA (median)	2.6 ng/ml (range 0.15–110)	2.0 ng/ml (range 0.001–5.5)	0.06
Gleason score (average)	7.4 (range 6–9)	7.5 (range 6–9)	0.39
Radical prostatectomy	18 (40.0%)	9 (75%)	
Radiation therapy	25 (55.6%)	3 (25%)	
Hormone therapy only	1 (2.2%)	N/A	
Observation only	1 (2.2%)	N/A	

PSA, prostate specific antigen.

Table 3 ADT status and 18F-fluciclovine positivity

	Total no. of cases	No. of cases with 18F-fluciclovine (+) scan
No ADT	22	15 (68.2%)
ADT short (remote)	12	10 (83.3%)
ADT long (current)	14	13 (92.9%)
ADT long (remote)	9	7 (77.8%)

Current, on ADT at time of 18F-fluciclovine PET/CT; long, ADT for 6 months or longer; remote: off ADT at least 1 year prior to 18F-fluciclovine PET/CT; short, ADT for 2 months or less.
ADT, androgen deprivation therapy.

Table 4 Characteristics of 18F-fluciclovine (+) versus SOC (+) cases

	18F-Fluciclovine (+)	SOC (+)	*P*-value
No. of cases (out of 57 total cases)	45 (78.9%)	12 (21.1%)	
PSA (median)	2.6 ng/ml (range 0.15–110)	6.0 (range 0.15–110)	0.10
Gleason score (average)	7.4 (range 6–9)	7.8 (range 6–9)	0.18

PSA, prostate specific antigen; SOC, standard of care.

(+) SOC studies, 5 (41.7%) had radical prostatectomy, 6 (50%) radiation therapy, and one patient was under observation only (8.3%).

Table 4 shows a comparison of the PSA and Gleason score of 18F-fluciclovine (+) and SOC (+) studies. The 18F-fluciclovine (+) studies had a lower PSA compared to SOC (+) studies although the result was not statistically significant (median PSA 2.6 versus median PSA 6.0, respectively with *P*-value 0.10). There was no significant difference in Gleason score between the 18F-fluciclovine (+) versus SOC (+) studies (average Gleason score 7.4 versus 7.8, respectively with *P*-value 0.18).

Compared to SOC, 18F-fluciclovine identified significantly more sites of disease. Figure 1 shows an example of a case where SOC imaging was negative and 18F-fluciclovine PET/CT identified a subcentimeter left common iliac lymph node. Also, of the 12 SOC (+) cases, 18F-fluciclovine identified additional sites of disease in 11/12 (91.7%). Figures 2 and 3 show examples of cases where 18F-fluciclovine PET/CT showed additional sites of disease compared to SOC imaging. Furthermore, 18F-fluciclovine identified oligometastasis in 18 out of 45 (+) studies (40%). There were no SOC (+) cases with oligometastasis. Of the cohort of 57 patients with BCR, there were 12 patients (21.1%) for which neither 18F-fluciclovine or SOC identified a site of disease recurrence.

Discussion

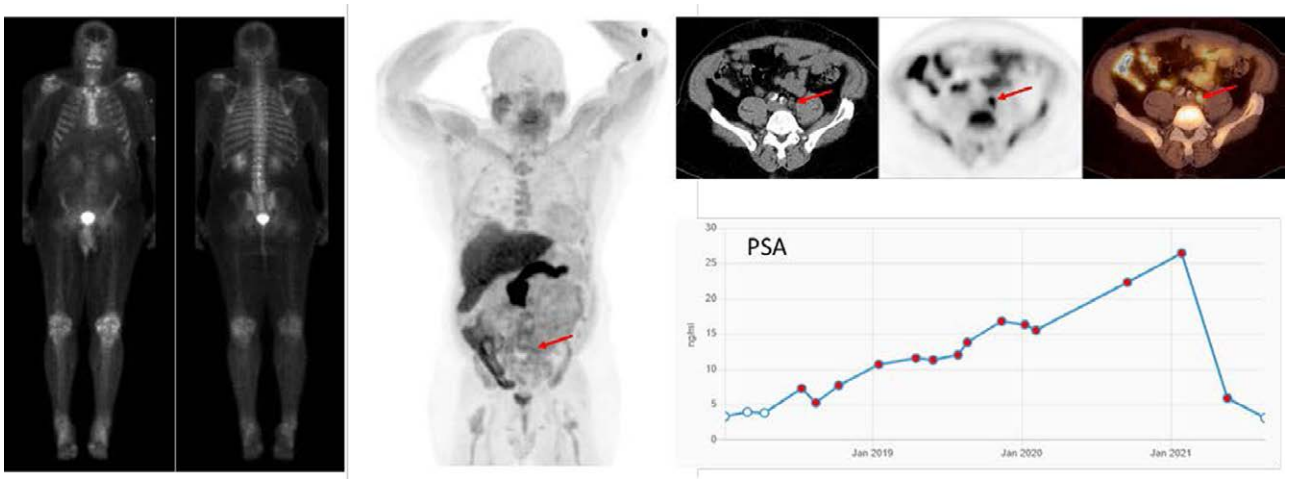
We carried out a prospective analysis comparing the performance of 18F-fluciclovine to SOC imaging for the identification of sites of disease in BCR prostate cancer patients. Our study showed that 18F-fluciclovine was superior to SOC imaging for the detection of sites of disease. Furthermore, 18F-fluciclovine identified oligometastasis (an important management consideration) and identified additional sites of disease compared to SOC. Also, the data showed 18F-fluciclovine PET/CT was able to detect lesions in patients on long-term ADT. These findings challenge the current practice of doing PET/CT imaging in BCR prostate cancer only when SOC imaging is negative.

Since the FDA approved 18F-fluciclovine in May 2016 for PET/CT imaging in men with suspected BCR based on elevated PSA following prior treatment, various cancer and imaging consensus groups have endorsed its use. The NCCN supports adding PET/CT imaging with either 18F-fluciclovine or a PSMA agent for equivocal results on initial bone imaging for patients with radical prostatectomy PSA persistence or BCR. In addition, for initial risk stratification and staging for clinically localized disease, the NCCN also supports adding PET/CT imaging with either 18F-fluciclovine or a PSMA agent for equivocal results on initial bone imaging [11].

A large multicenter study of 596 prostate cancer BCR patients assessing the diagnostic performance and safety of 18F-fluciclovine PET/CT showed an overall detection rate of 67.7% [12]. Our study showed that 18F-fluciclovine PET/CT identified sites of disease recurrence in 45 of 57 patients (78.9%). The higher positivity rate for 18F-fluciclovine PET/CT in our study may be due to the improved expertise of nuclear medicine physicians and radiologists over time in reading 18F-fluciclovine PET/CT studies.

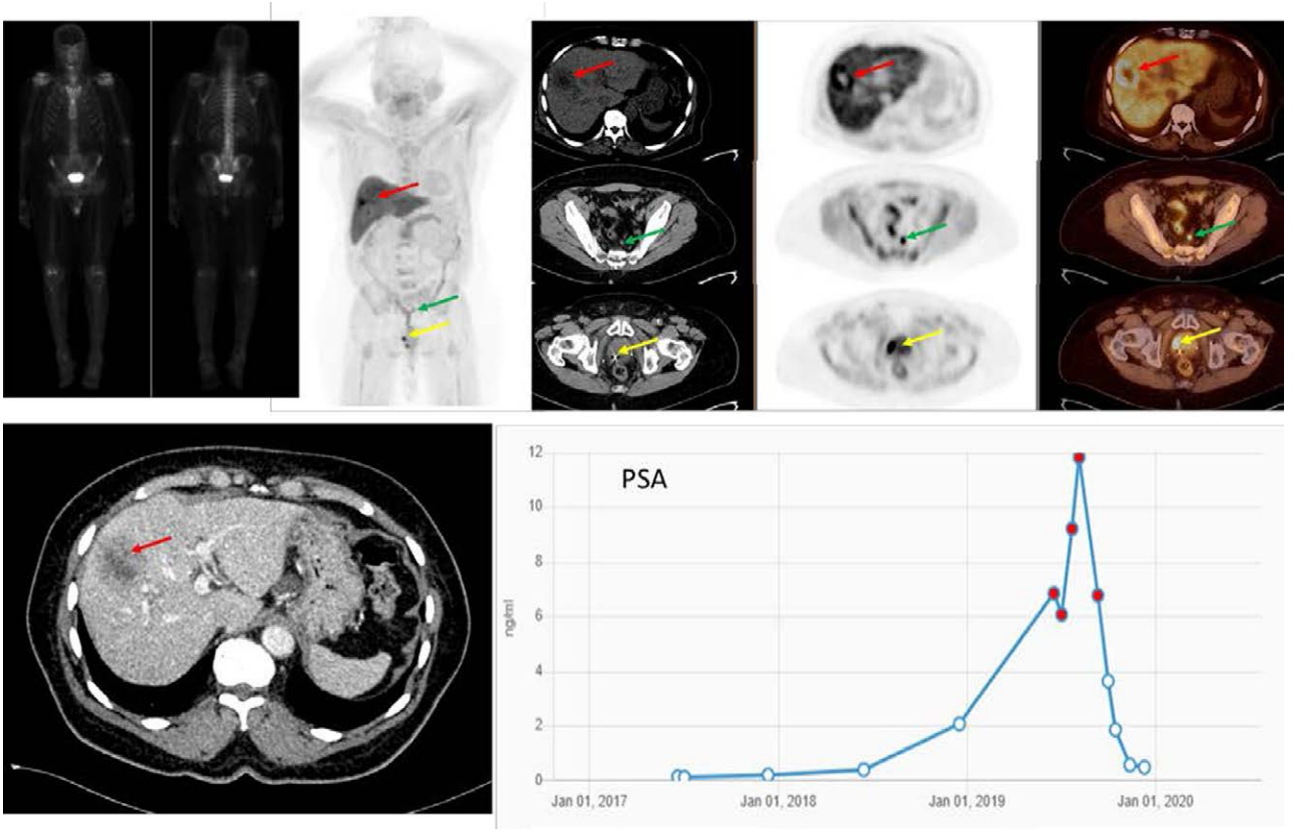
This can be especially true in assessing nodal disease in the pelvis when those lymph nodes are subcentimeter in size. Lymph nodes 1 cm are considered (+) when radiotracer uptake is greater than blood pool and approaching bone marrow. Such small lymph nodes which appear anatomically normal would be considered benign on CT. Figure 1 gives an example of a small subcentimeter lymph node showing 18F-fluciclovine avidity on PET which is not detected on SOC imaging. Another imaging concern

Fig. 1



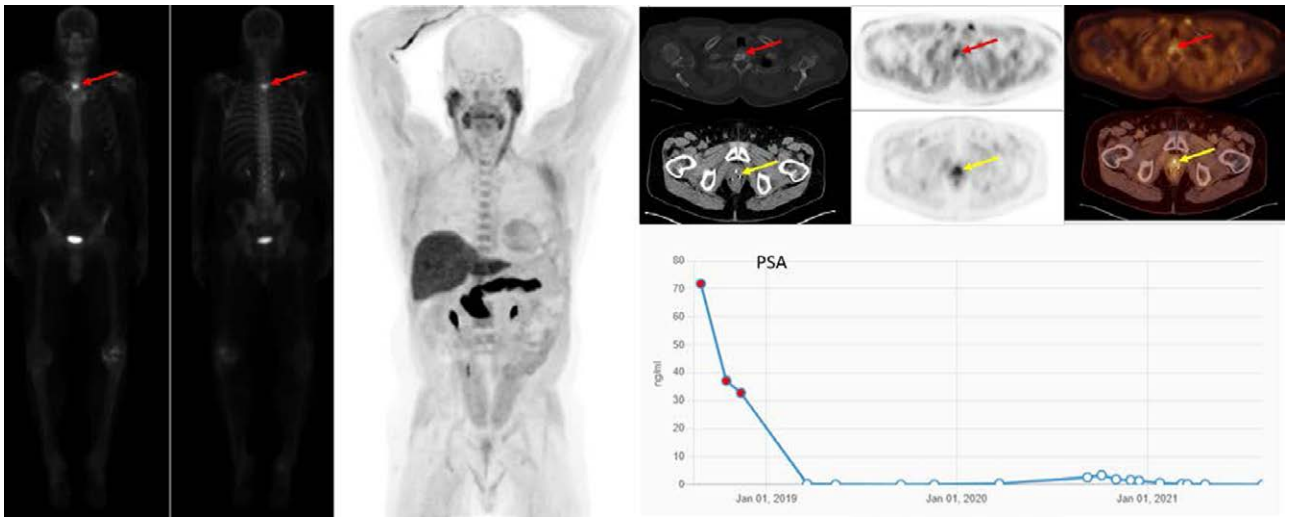
65-Year-old male with prostate cancer (Gleason score 4 + 3 = 7), BCR, and status-post radical prostatectomy. PSA 22.3 ng/ml. Bone scan (left) and cCT abdomen/pelvis (not shown) were negative. 18F-Fluciclovine PET/CT images (center and top right) showed a subcentimeter 18F-fluciclovine avid left common iliac lymph node (red arrows). On the bottom right there is a graph of PSA versus time showing decreased PSA after hormone therapy. BCR, biochemical recurrence; cCT, contrast CT; PSA, prostate specific antigen.

Fig. 2



86-Year-old male with prostate cancer (Gleason score 4 + 3 = 7), BCR, and status-post radiation therapy. PSA 6.0 ng/ml. Bone scan (top left) was negative. cCT abdomen/pelvis showed necrotic right hepatic lobe lesion (red arrow, bottom left). 18F-Fluciclovine PET/CT images (top center and top right) showed a 18F-fluciclovine avid necrotic appearing right hepatic lobe lesion (red arrows) and additional sites of disease in a left presacral lymph node (green arrows), and right prostate lobe lesion located laterally (yellow arrows). There is a graph of PSA versus time (bottom center) showing decreased PSA after hormone therapy. BCR, biochemical recurrence; cCT, contrast CT; PSA, prostate specific antigen.

Fig. 3



68-Year-old male with prostate cancer (Gleason score 4 (G4 (G8), BCR, and status-post radiation therapy. PSA 2.6 ng/ml. Bone scan (left) showed activity in T1 vertebral body (red arrow) and cCT chest/abdomen/pelvis showed sclerotic T1 vertebral body lesion (not shown). 18F-Fluciclovine PET/CT images (center and top right) showed 18F-fluciclovine avid sclerotic lesion at T1 on the right side (red arrows) and additional site of disease in the prostate bed (yellow arrows). There is a graph of PSA versus time (bottom right) showing decreased PSA after external beam radiation therapy to T1 and hormone therapy. BCR, biochemical recurrence; cCT, contrast CT; PSA, prostate specific antigen.

regarding pelvic nodal disease, besides the detection of small subcentimeter lymph nodes, is the detection of nodal disease near the bladder or localized near the ureters. This is where 18F-fluciclovine PET/CT may have an advantage over PSMA PET/CT labeled with 18Fluorine or 68Gallium. In a prospective head-to-head trial of 18F-fluciclovine PET/CT versus 68Gallium-PSMA PET/CT, of 58 patients with BCR prostate cancer, 18F-fluciclovine PET/CT detected more curable localized disease in close anatomical relation to the bladder compared to 68Gallium-PSMA [13]. 18F-Fluciclovine PET/CT typically does not show significant bladder activity as the pelvis is imaged first 3–5 min after radiopharmaceutical administration because of the rapid kinetics of 18F-fluciclovine. The result is a high target to background ratio of (+) pelvic nodes localized near the bladder or ureter. With PSMA (18F or 68Ga labeled) PET/CT, the uptake time for the radiotracer is longer and there is usually significant intense bladder activity and sometimes intense activity in the ureters which can make assessment of pelvic nodal disease challenging.

Prostate cancer with oligometastasis represents an intermediate state between a localized tumor and widespread metastatic disease [14]. Prostate cancer tumors that give rise to the oligometastatic state may be biologically and genetically different from those that give rise to widespread metastatic lesions. There is accumulating clinical evidence which indicates that patients with oligometastatic disease have improved clinical responses from metastasis-directed therapy [15,16]. Therefore, the identification of oligometastatic prostate cancer can affect management. 18F-Fluciclovine identified oligometastasis in 18 out of 45 (+) studies (40%). There were no SOC (+) cases with oligometastasis. The identification of oligometastasis can highlight the need for more aggressive management.

18F-Fluciclovine PET/CT identified additional sites of disease compared to SOC imaging. This can also affect management. Figure 3 demonstrates an example where SOC imaging identified a sclerotic lesion on the right side of T1. 18F-Fluciclovine PET/CT identified additional sites of disease in the prostate bed. The identification of disease in the prostate bed will likely lead to radiation therapy to the prostate bed in addition to therapies aimed at the T1 lesion. This study also showed that 18F-fluciclovine was able to detect lesions at a lower PSA compared to SOC (see Table 4) although this result was not statistically significant. The (+) 18F-fluciclovine studies had a median PSA of 2.6 ng/ml (range 0.15–110 ng/ml) and average Gleason score of 7.4 (range 6–9). The SOC (+) studies had a median PSA 6.0 ng/ml (0.15–110 ng/ml) and average Gleason score 7.8 (range 6–9). Patients with lower PSA would be better served with higher quality diagnostic imaging than SOC imaging. Under current guidelines, the patient in Fig. 3 would not have received further evaluation with PET/CT with either 18F-fluciclovine or PSMA. SOC imaging identified an osseous lesion as the cause for BCR prostate cancer, even though there was disease recurrence in the prostate bed which was not detected by SOC imaging.

In the past few years, the FDA has approved PSMA-targeted PET radiotracers for prostate cancer imaging which have become preferentially used over 18F-fluciclovine. Furthermore, PSMA will likely continue to be the first line PET imaging agent given the approval of Pluvicto (177Lu-PSMA-617) in March 2022 for prostate cancer therapy in adults with PSMA (+) metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. These medical advances in the imaging and therapy of prostate cancer represent a breakthrough in the care of prostate cancer. Improved molecular imaging, however, is revealing new considerations in the imaging of prostate cancer that make it clear that there is still a role for 18F-fluciclovine in the imaging of prostate cancer.

18F-Fluciclovine could be considered for prostate cancer imaging in patients who have low PSMA avidity. Studies have shown that about 20% of prostate cancer patients do not express PSMA [17,18]. In a prospective study by Hope *et al*. assessing the impact of 68Ga-PSMA 11 PET/CT on the management of patients with BCR prostate cancer, there were 103 patients (82%) with disease detected on 68Ga-PSMA-11 PET [17]. In a retrospective study by Pomykayla *et al*. looking at the relationship of serum PSA and the incidence of osseous metastases detected by 68Ga-PSMA-11, it was reported that 321 of 388 patients (83%) had a (+) 68Gallium-PSMA-11 study [18]. Similar results have been found with 18F-PSMA radiotracers in the imaging of prostate cancer [19–21]. In a study using 18F-PSMA-1007 to detect lesions in BCR prostate cancer patients after radical prostatectomy in 251 patients, 81.3% had evidence of recurrence on 18F-PSMA-1007 PET/CT [19]. Bidakhvidi *et al*. also found positivity rate of 80% using 18F-PSMA-1007 in the detection of lesions in patients with BCR prostate cancer [20]. In addition, the literature from 177Lu-PSMA therapy studies has shown that 20–25% of metastatic castrate resistant prostate cancer (mCRPC) patients are excluded from clinical trials of 177Lu-PSMA therapy due to imaging demonstrating uniformly low PSMA uptake of lesions or discordant lesions showing low PSMA and high 18F-fluorodeoxyglucose (FDG) uptake [22–24]. For these patients, other PET imaging agents should be considered such as 18F-fluiclvovine, 18F-FDG, or Sarcophagine-Bombesin imaging agents.

The reason why prostate cancer cells become PSMA (-) is likely multifactorial. Some reasons may be mutations in the promoter or enhancer region controlling gene expression, development of small cell neuroendocrine type prostate cancer, ADT, and the development of mCRPC. The PSMA promoter and enhancer that controls transcription of the gene for PSMA are located within the third intron of FOLH1. Certain mutations in these regulatory elements of gene expression can result in decreased levels of PSMA [25]. There are cases of prostate cancer patients developing small cell neuroendocrine carcinoma during therapy and showing PSMA (-) lesions [26,27]. There is research that shows that approximately 1 out of 6 patients with progressive hormone-resistant prostate cancer has neuroendocrine prostate cancer [28]. Treatment emergent neuroendocrine prostate cancer is a very aggressive malignancy and typically disseminates to visceral organs such as lung and liver. Most cases of treatment emergent prostate cancer occurs in patients with mCRPC that have been treated with ADT and or taxane based chemotherapy [29]. As therapy targeting the androgen receptor pathway is utilized more frequently and earlier during prostate cancer therapy the number of treatment emergent neuroendocrine prostate cancer is likely to rise.

18F-Fluciclovine PET/CT may be a better option for imaging patients with treatment emergent small cell/neuroendocrine prostate cancer and mCRPC. 18F-Fluciclovine uptake is dependent on sodium-dependent amino acid transporters (ASCT) such as ASCT1 and ASCT2. Sodium-independent LAT1, LAT2, and SNAT2 transporters provide a smaller contribution to 18F-fluciclovine cellular uptake [30–33]. Chu *et al*. studied the genome-wide expression profiles of five mCRPC cohorts to characterize relative expression of fluciclovine transporter (LAT1-4, ASC1-2) and PSMA (FOLH1) genes [34]. Five hundred and eighteen mCRPC specimens were included and three of the five cohorts were enriched with treatment emergent small cell/neuroendocrine tumors. 18F-PSMA expression was downregulated in mCRPC when compared to primary localized tumors. Treatment emergent small cell/neuroendocrine tumors showed even greater reduction in PSMA expression compared to mCRPC. LAT1 and LAT4, however, were overexpressed in mCRPC when compared to primary tumors and LAT1 showed even greater expression in treatment emergent small cell/neuroendocrine tumors. ASCT2 was less expressed in mCRPC. To date there are case reports of 18F-fluciclovine PET positivity in neuroendocrine tumors, both dedifferentiated prostate cancer and secondary malignancies [35–37]. Small cell/neuroendocrine prostate cancer, however, can lose 18F-fluciclovine positivity likely due to becoming more poorly differentiated [38]. There is a need for clinical studies evaluating the utility of 18F-fluciclovine PET/CT in the evaluation of treatment emergent small cell/neuroendocrine tumors.

There may be a role for 18F-fluciclovine PET/CT in the evaluation of prostate cancer patients treated with long-term ADT. Most of the literature suggest that long-term ADT decreases PSMA-ligand uptake [39–42]. The range of long-term ADT varied in these studies from 3 to 7 months. The minimum time interval for long-term ADT on lowering PSMA-ligand uptake is not well defined and

one must consider that short-term ADT increases PSMA ligand uptake [43,44]. Also, another factor that influences whether long-term ADT will result in decreased PSMA-ligand uptake is whether the patient has metastatic castrate sensitive prostate cancer. In the retrospective analysis by Afshar-Oromieh *et al*., of 306 patients with castration sensitive prostate cancer, they found that continuous long-term ADT significantly reduced the visibility of lesions on PSMA PET/CT. Whereas in a study by Bach-Gansmo *et al*. in which patients received ADT for a median of 2 years (range 3 months to >10 years), pre-scan long-term ADT showed that time of ADT did not influence detection on 18F-fluciclovine PET/CT [45]. More research needs to be done in this area, but the thought is that long-term ADT causes tumor lesions to get smaller and partial volume effects become more relevant, which results in decreased PSMA-ligand uptake as demonstrated on PSMA PET/CT. This would be avoided with 18F-fluciclovine PET/CT. The data from our study shows that long-term ADT did not lower 18F-fluciclovine positivity. The data showed that of the 14 patients who were on current long-term ADT, 13 (92.9%) had (+) scans (see Table 3).

The main strength of this study is that it is a prospective study and had fewer potential sources of bias and confounding. By having a prospective study, we did not have the selection bias of only being able to assess BCR prostate cancer patients who had equivocal SOC imaging. We were able to assess patients with (+) SOC imaging with 18F-fluciclovine PET/CT and see whether there were differences. Also, studies from other institutions have not had the advantage of being able to assess intermediate risk patients. This has immediate implications for our practice setting as within the Veterans Administration patients who are intermediate risk can potentially get PET/CT imaging instead of SOC imaging at the request of the treating physician. Another advantage of a prospective study is that there was no selection bias regarding Gleason score or PSA. Also, because our study was a prospective one, we could control the confounding variable of the time between the 18F-fluciclovine PET/CT and SOC imaging compared to a retrospective study. The prospective design of our study also allowed us to control for the confounding variable regarding the type of SOC imaging. SOC imaging can involve pelvic MRI instead of cCT abdomen and pelvis. We selected SOC imaging involving cCT abdomen and pelvis instead of pelvic MRI so that comparisons could more easily be made with the low dose CT portion of the PET/CT study. Also, SOC imaging with cCT can have the confounding variable of being either cCT abdomen and pelvis or cCT of the pelvis based upon what the treating physician ordered. Our prospective study had the advantage of picking the SOC imaging with broader cCT field of view (abdomen and pelvis) compared to pelvis only imaging.

A limitation of this study is that there was no confirmation of true positivity with histopathology of the identified lesions. Review of the medical records showed that treating physicians typically did not biopsy lesions. In most cases, however, the patients underwent treatment, and we were able to see that there was a decrease in PSA. Another limitation is the small sample size. Although the sample size is small, it is larger than other recently published studies [46–48].

In conclusion, compared with SOC imaging 18F-fluciclovine PET/CT was superior for the detection of sites of disease as demonstrated by a higher positivity of scans, identification of oligometastasis, and the identification of additional sites of disease compared to SOC imaging. This suggests that (-) SOC imaging should not be a prerequisite for 18F-fluciclovine PET/CT, nor should (+) SOC imaging eliminate the need for 18F-fluciclovine PET/CT. Also, as PSMA agents are superior to fluciclovine for detection of BCR, these agents should also be considered before SOC imaging. The data showed 18F-fluciclovine PET/CT was able to detect lesions in patients on long-term ADT which suggests that 18F-fluciclovine should be considered when PSMA agents fail to identify sites of disease those patients. As nuclear medicine's role in prostate cancer has moved into theranostics, it is clear that PSMA agents have the advantage over 18F-fluciclovine. Ongoing trials using a high affinity radiohybrid PSMA-targeted PET imaging agent such as LIGHTHOUSE (newly diagnosed prostate cancer) and SPOTLIGHT (patients with BCR prostate cancer who had undergone primary treatment with radiation therapy only) using 18F-rhPSMA-7.3 have shown high detection rates including the identification of distant extrapelvic disease which can change management [49,50]. The use of radiohybrid PSMA-targeted PET imaging agents presents the possibility of also treating these patients with Lu-177 or Ac-225. Furthermore, this agent may have low bladder activity which would address the difficulty in identifying localized disease in close anatomical relation to the bladder for which we suggested consideration of 18F-fluciclovine PET/CT as a better alternative. These radiohybrid PSMA compounds are investigational and have not received FDA approval therefore 18F-Fluciclovine PET/CT may still play a role in prostate cancer imaging.

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Conflicts of interest

There are no conflicts of interest.

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