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Update on 18F-fluciclovine PET for prostate cancer imaging

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ABSTRACT

Positron emission tomography (PET) is a functional imaging method that can exploit various aspects of tumor biology to enable greater detection of prostate cancer than can be provided by morphologic imaging alone. Anti-1-amino-3-[^{18}F]-flurocyclobutane-1-carboxylic acid (18F-fluciclovine) is a non-naturally occurring amino acid PET radiotracer that is recently United States Food and Drug Administration approved for detection of suspected recurrent prostate cancer. The tumor imaging features of this radiotracer mirror the upregulation of transmembrane amino acid transport that occurs in prostate cancer due to increased amino acid metabolism for energy and protein synthesis. This continuing medical education article provides an overview on 18F-fluciclovine PET diagnostic capabilities for primary and metastatic disease, including reviews of published comparisons to conventional imaging and other molecular imaging agents. Additionally, imaging procedure and interpretation is detailed including physiologic and pathologic uptake patterns and pitfalls.

INTRODUCTION

Prostate cancer is the most common cause of cancer in men and is the third most common cause of cancer-related death in men (*1*). In the initial phase, prostate cancer spreads almost exclusively through lymphatic channels and bones, with pelvic nodes being the primary and most frequent site of nodal dissemination. However, in 10-15% of cases, presacral, para-aortic, and paracaval nodes can be the primary site of nodal disease. Prostate-specific antigen (PSA) doubling time, time to PSA relapse, Gleason score, and pathological stage are the principal clinical parameters used to determine likelihood of local or distant recurrent disease.

Current guidelines recommend the use of ^{99m}Tc- methylene diphosphonate bone scan as well as computed tomography (CT) or magnetic resonance imaging (MRI) to determine the extent of disease in men with high risk primary, recurrent, or metastatic prostate cancer. These

conventional imaging modalities are limited in terms of their sensitivity for detecting small volume sites of prostate cancer and may underestimate the burden of disease.

2-deoxy-2-[18F]fluoro-glucose (FDG) has been extensively studied but has a limited role in the detection of metastatic prostate cancer, as the low glycemic activity of hormone naïve prostate cancer cells limits FDG uptake (*2*). Phospholipid precursors such as ^{11}C-choline have been widely used in detecting localized prostate cancer as well as metastases. ^{11}C-choline was approved by the U.S. Food and Drug Administration (FDA) for use in men with biochemically recurrent prostate cancer (*3*). However, the utility of radiolabeled choline positron emission tomography (PET) is limited due in patients with low PSA values (< 1.0 ng/mL) and increased uptake in areas of inflammation may affect specificity. Prostate-specific membrane antigen (PSMA) is a transmembrane type II glycoprotein that is expressed by prostate cancer cells with a number of PSMA specific radiotracers developed for use to detect prostate metastasis.

Amino acids are essential to cell metabolism and growth and cancerous cells have a much higher nutrient demand compared to normal tissues (*4*). Several amino acid transporter systems are over expressed in prostate cancer; specifically large neutral amino acid transporters (system L: LAT1, LAT3, and LAT4) and alanine-serine-cysteine transporters (system ASC: ASCT1 and ASCT2) (*5,6*). Of these, LAT3, ASCT1, and ASCT2 are upregulated with androgen simulation and LAT1 and ASCT2 are associated with a more aggressive tumor phenotype (*7*). Anti-1-amino-3-[^{18}F]-flurocyclobutane-1-carboxylic acid (18F-fluciclovine) is a non-naturally occurring amino acid first synthesized by Dr. Mark Goodman, and initially developed for the evaluation of cerebral gliomas (*8*). 18F-fluciclovine transport is primarily mediated by sodium-dependent amino acid transporters, specifically system ASC (ASCT2), with contribution by sodium-independent system L (LAT1) (*5*). Because these amino acid transporters most involved in 18F-fluciclovine transport mediate influx and efflux of amino acids, washout of radiotracer occurs over time. Thus, early imaging is recommended to maximize

lesion conspicuity (*9*). In addition, though amino acid PET imaging is less prone to inflammatory uptake than is FDG, it may still occur, potentially confounding interpretation.

Early 18F-fluciclovine biodistribution studies demonstrated relatively low urinary excretion, with urinary bladder organ doses ranging from 12 – 25 μGy/MBq (*10*) compared to 73 ± 42 μGy/MBq for FDG (*11*) and 60 μGy/MBq for to *O*-(2-18F-fluoroethyl)-L-tyrosine (*12*). For this reason, in combination with early imaging times, attention was turned from brain glioma imaging to renal and pelvic malignancies. One of these studies involved a patient with renal cell carcinoma who incidentally was found to have intense 18F-fluciclovine uptake in retroperitoneal lymph nodes, which were biopsy proven to be metastatic prostate cancer (*9*). Subsequent studies with 18F-fluciclovine demonstrated uptake in both primary and metastatic prostate carcinoma as well as increased uptake in recurrent prostate carcinoma within the prostatectomy bed, lymph nodes, and bone (*13*).

A new drug application was accepted in December 2015 by the FDA for priority review based on data collected from 877 subjects, including 797 patients with prostate cancer in the United States and Europe. Approval was granted to 18F-fluciclovine (trade name: Axumin) in May 2016 for the clinical indication of suspected prostate cancer recurrence based on elevated PSA levels following prior treatment and has Medicare pass through reimbursement effective January 2017. It should be noted that 18F-fluciclovine has been studied to image other malignancies such as breast (*14*) and glioma (*15*) but discussion of these applications is beyond the scope of this article.

18F-fluciclovine PET Diagnostic Performance

Primary Disease and Staging

Several studies have evaluated 18F-fluciclovine PET in the setting of primary prostate cancer with the conclusion that 18F-fluciclovine PET should not be used by itself to completely

characterize primary lesions. Additionally, it should be noted that primary tumor characterization is not an FDA approved indication. A multicenter trial involving 68 patients with primary prostate cancer and who were scheduled for either radical prostatectomy or hormone therapy, underwent 18F-fluciclovine PET-CT imaging and found a high sensitivity and specificity of 92.5% and 90.1% for the focus of primary disease (*16*). Yet, additional studies reported lower specificity in the prostate. In a study with 10 patients with prostate cancer scheduled to undergo radical prostatectomy that underwent dynamic pelvic imaging (*17*), the highest combined sensitivity and specificity was 81.3% and 50.0% respectively. While sextants with prostate cancer had the highest maximum standardized uptake value (SUV_{max}) there was overlap between prostate cancer and areas of benign tissue. In a more comprehensive study involving 22 patients with primary prostate cancer, 18F-fluciclovine PET was compared to multiparametric MRI. In these patients, the mean SUV_{max} of the tumor was significantly higher than in the normal prostate, but there was again overlap between the 18F-fluciclovine mean SUV_{max} in prostate cancer and benign prostate hyperplasia (BPH), 4.5 ± 0.5 vs 4.3 ± 0.6 respectively. Interestingly, combining the information of 18F-fluciclovine PET with MRI in this study increased the PPV from 50% for 18F-fluciclovine PET and 76% for MRI, to 82% for the combined data (*18*). Similar findings were reported in a recent study of 26 men with primary prostate cancer who underwent 18F-fluciclovine PET-CT followed by PET-MRI (*19*) which found a high sensitivity and low specificity in primary tumor identification, but 18F-fluciclovine PET did not outperform MRI alone in prostate lesion detection. It should be noted that Elschot and coworkers have explored the value of delayed time point imaging (18-23 min and 33-38 min) for differentiating between prostate cancer and benign tissue and reported improved performance (*20*).

Limited data has been reported for staging in the setting of primary prostate cancer. A study involving 68 patients with primary prostate cancer compared 18F-fluciclovine PET-CT to

whole body contrast enhanced CT, and found a sensitivity, specificity and accuracy of 64.5%, 99.6%, and 95.5% for extraprostatic nodal disease with 18F-fluciclovine PET-CT vs 71%, 100%, and 96.6% for contrast enhanced CT for nodal disease > 1 cm in the short axis (*16*). Though unable to be confirmed with the reference standard, 18F-fluciclovine PET detected subcentimeter (5-9 mm) lymph nodes in 13 patients not considered positive by CT. A recent study of 28 patients with high risk prostate cancer underwent simultaneous 18F-fluciclovine PET-MRI prior to surgery and found a high specificity (100%) but low sensitivity (30%) for detection of regional lymph node metastases (*21*). Therefore, in the setting of primary prostate cancer, 18F-flucicloivne PET does not replace lymph node dissection and histopathological confirmation but can be useful to guide biopsy.

Recurrent Disease

The American Urological Association defines biochemical recurrence after radical prostatectomy as having a PSA level ≥ 0.2 ng/mL, followed by a subsequent confirmatory PSA ≥ 0.2 ng/mL (*22*). Following radiation therapy, the American Society for Therapeutic Radiation and Oncology defines three successive PSA rises above the nadir as consistent with biochemical evidence of recurrence; however, this only applies to patients with external beam radiotherapy. A Consensus Committee concluded any rise in PSA levels of 2 ng/mL or more above the nadir, despite the form of radiation therapy, is biochemical evidence of prostate cancer recurrence (Phoenix Definition) (*23*).

The defining factor in therapy planning for recurrent prostate carcinoma is determining whether disease is confined to the prostate/prostatic bed or is extraprostatic. Identification of pelvic metastatic disease will result in modification of the radiation field to cover pelvic lymph nodes, and the presence of extrapelvic disease will change the therapeutic approach from potential curative salvage therapy to systemic hormonal treatment. On a per-patient basis, 18F-fluciclovine PET sensitivity for detecting recurrent disease varies with PSA values, with reported

detection rates in the post-prostatectomy biochemical failure setting of 72.0%, 83.3%, and 100% at PSA levels < 1, 1–2, and ≥2 ng/ml respectively (*24*). A mixed post-prostatectomy and non-prostatectomy cohort demonstrated a 18F-fluciclovine detection rate of 37.5% at PSA < 1, 77.8% at PSA 1-2, and 91.7% at PSA > 2, and 83.3% at PSA > 5 ng/ml (*25*). Additional studies have found 18F-fluciclovine detection rates ranging from 21%-38.7% at PSA values of <1 ng/mL (*26,27*). It is believed that differences in detection rate at low PSA levels between studies is likely related to PSA kinetics. For example, higher original Gleason scores and a shorter PSA doubling time are correlated with positive findings on 18F-fluciclovine PET-CT; an evaluation of patients with positive findings were found to have an average PSA doubling time of 3.25 ± 2.09 months vs 31.2 ± 22.02 months in patients with negative findings (*28*).

In identifying recurrent disease in the treated prostate/prostatectomy bed, 18F-fluciclovine PET-CT demonstrates high sensitivity, low specificity, and moderate PPV (Fig. 1). An analysis of 93 patients demonstrated an overall sensitivity, specificity, positive predictive value (PPV) and accuracy of 90.2%, 40.0%, 75.3%, 73.6% respectively (*29*). This series consisted of a relatively high proportion of patients who had undergone cryotherapy and brachytherapy, potentially leaving residual viable prostate tissue which may be more prone to confounding uptake due to inflammation or prostatic hypertrophy. Further analysis on post-prostatectomy cohorts are ongoing. Similar diagnostic performance of local recurrence was demonstrated in a large multisite study of 596 patients, having a sensitivity of 88.1%, specificity of 32.6%, and PPV of 71.8% (*27*). Therefore, as with primary disease, histological confirmation of findings in the prostate or prostate bed is recommended.

[Fig. 1]

Not accounting for PSA levels or doubling times, the sensitivity, specificity, PPV, and accuracy of 18F-fluciclovine in detection of recurrent extraprostatic disease has been reported to be 55.0%, 96.7%, 95.7%, and 72.9% respectively (*29*). The multisite study of 596 patients

mirrored the high PPV of 92.3% in detection of extraprostatic disease (*27*). In a study of 53 patients comparing 18F-fluciclovine to standard CT criteria for pathologically enlarged lymph nodes, the presence of extraprostatic true-positive lesions was noted in 29% patients with 18F-fluciclovine, whereas CT was true-positive in 7% patients. The smallest short-axis diameters reported positive on 18F-fluciclovine PET-CT and CT were 0.4 cm and 0.9 cm, respectively (*25*). Thus, 18F-fluciclovine PET-CT demonstrates clear superiority to CT for the detection of both local and distant disease in the clinical scenario of biochemical failure (Fig. 2). Test-retest reproducibility in target tissues and untreated malignant lesions in patients with a follow-up 18F-fluciclovine PET-CT found a SUV_{mean} difference of less than 20%. 18F-Fuciclovine uptake in malignant lesions without interim therapy increased or remained stable over time (*30*).

[Fig. 2]

Osseous Disease

18F-fluciclovine has been shown to accumulate in osteolytic and osteoblastic lesions, including early-stage osteoblastic bone metastatic lesions that have abundant cellular components (*31*). Additionally, 18F-fluciclovine has been shown to have uptake in osseous lesion prior to morphological changes detected by CT. 18F-fluciclovine typically demonstrates intense focal uptake in lytic prostate metastatic osseous lesions, moderate uptake in mixed sclerotic lesions, and mild to no uptake in dense sclerotic lesions (Fig. 3). Because there may be little to no 18F-fluciclovine activity in dense sclerotic lesions, skeletal specific imaging is recommended to supplement 18F-fluciclovine PET-CT in these cases.

[Fig. 3]

When compared to standard osseous scintigraphy, 18F-fluciclovine demonstrates equivalent or better results in limited studies. A phase 2a clinical trial of 10 patients with untreated prostate cancer found 7 patients had increased 18F-fluciclovine uptake in osseous

metastatic lesions which was comparable to findings with conventional imaging (*32*). In a study involving 68 patients, 18F-fluciclovine PET-CT was found to have a moderate concordance rate of osseous metastatic disease when compared to combined bone scintigraphy and contrast enhanced CT; however, 7 patients did have positive 18F-fluciclovine findings which were negative on combined conventional bone scan and contrast enhanced CT imaging (*16*). While it may be concluded that a dedicated bone scan may not be necessary if a patient has definitively positive osseous disease with 18F-fluciclovine PET, most early clinical trials utilized a positive bone scan as an exclusion criteria. Thus, it is not recommended at this time that 18F-fluciclovine PET replace dedicated bone scintigraphy.

Comparison to other Molecular Imaging Agents

Several studies have compared 18F-fluciclovine to other molecular imaging probes. PSMA is a transmembrane protein that is highly overexpressed in the majority of prostate cancers, with only 5-10% of primary prostate cancer lesions shown to be PSMA negative (*33*). Currently, the only FDA approved PSMA-agent is a radiolabeled anti-PSMA antibody (ProstaScint, capromab pendetide; EUSA Pharma, Langhorne, PA). Capromab pendetide, however, targets an intracellular epitope of PSMA which cannot be accessed in viable tumor cells and therefore limits diagnostic performance. Direct comparisons between 18F-fluciclovine PET-CT with ^{111}In-capromab pendetide demonstrates superior diagnostic performance for 18F-fluciclovine PET-CT in detecting both prostate/prostatectomy bed recurrence and extra-prostatic disease (*29*).

Direct comparison between 18F-fluciclovine and 11C-choline PET-CT have demonstrated overall superior imaging performance for 18F-fluciclovine in biochemical recurrent prostate cancer. A comparison study of 89 patients with biochemical relapse after radical prostatectomy found 18F-fluciclovine had a sensitivity, specificity, and accuracy of 37%, 67%, and 38% respectively for nodal disease vs 32%, 40%, and 32% for 11C-choline. 18F-

fluciclovine demonstrated positive osseous uptake in 5/89 patients including 5 false negative whereas 11C-choline had positive osseous disease in 6/89 patients with one false positive and 5 false negative as determined by clinical and imaging follow-up (*26,34,35*). Overall, in side by side comparison, 18F-fluciclovine detected more disease on a per patient and lesion basis with higher PPV than choline. While no direct comparison has been performed between 11C-choline and 18F-fluciclovine in the setting of primary prostate cancer, 11C-choline has been reported to also have relatively limited accuracy for localization of tumors within the prostate (*36,37*).

Several small molecule PSMA agents have been explored that bind to the active site in the extracellular domain of PSMA. A comparison of 10 patients with prostate cancer recurrence underwent sequential Ga-68 PSMA-11 and 18F-fluciclovine PET-CT imaging (*38*). The authors reported superior detection rate with Ga-68 PSMA-11 compared to 18F-fluciclovine which is in keeping with other published literature which reports high conspicuity of PSMA targeted lesions compared with other imaging agents such as 11C-choline (*39*). An individual comparison case of a man with prostate cancer recurrence imaged with both 18F-fluciclovine and the PSMA radiotracer ^{18}F-DCFPyL has been reported (*40*). The authors similarly describe superior lesion conspicuity with ^{18}F-DCFPyL compared to 18F-fluciclovine; however, ^{18}F-DCFPyL demonstrated significant activity in the ureters and bladder which the authors noted could obscure disease in the pelvis. Though both papers conclude that more data is needed to compare the merits and drawbacks of each modality, it seems likely that the newer PSMA radiotracers will have superior detection especially at lower PSA values.

Therapy Management

A wide range of factors including PSA, PSA doubling time, and Gleason score, as well as imaging results are considered prior to deciding to offer salvage radiotherapy (*41*). Poor patient selection is believed to be a contributor to the high biochemical failure rates seen after salvage radiotherapy, with accurate imaging essential for correct planning. Current treatment

planning mostly relies on conventional imaging, which may be unrevealing in the initial stages of prostate cancer recurrence. In a study involving 42 post prostatectomy patients randomized to undergo 18F-fluciclovine PET-CT after conventional radiotherapy planning, radiotherapy decisions were changed in 40.5% of patients after 18F-fluciclovine PET (*24*). However, the authors noted there was no statistically significant impact in this study on whether to actually offer radiotherapy, as only 2 of 42 patients had radiotherapy cancelled due to evidence of extrapelvic disease. In another analysis from this trial, use of 18F-fluciclovine PET changed the planning volumes for 83% of lesions without a change in toxicity (*42,43*). These results compare to studies involving other PET agents such as ^{11}C-choline resulting in salvage radiotherapy adjustments in 13% - 33% of patients (*44,45*).

Patient Preparation and Imaging Protocol

Patient preparation includes fasting the patient for 4 hours before the study to equalize plasma amino acid levels, except for small amounts of water to ingest medications. Note that the effects of suboptimal fasting on 18F-fluciclovine biodistribution have not been evaluated in humans. Patients are encouraged to avoid heavy exercise as this has been observed to increase muscle uptake.

Gastrointestinal contrast media may be administered to improve visualization. It is best to have the patient void before oral contrast administration approximately 30 minutes before scanning. Due to potential early bladder activity, the patient should be encouraged to withhold from voiding immediately before being placed in the PET-CT scanner, since a relatively distended bladder may mitigate occasional early 18F-fluciclovine excretion.

Several different protocols for imaging recurrent prostate cancer with 18F-fluciclovine PET have been reported incorporating early and delayed sequences (*29,46*). Comparable results have been obtained when using a more practical early single time point (3-5 min) protocol which

is the current recommendation (*26*). Though scanner dependent (*47*), a successful protocol employed at our facility on a time-of-flight PET scanner involves first obtaining a CT from skull base to thigh in the craniocaudal direction with arms raised (Fig. 4). The patient is then brought out of the scanner without shifting position and an arm is lowered for injection. Unlike, FDG and other radiotracers, no prolonged uptake phase is required and the patient is injected with a 10 mCi (370 MBq) intravenous bolus injection while on the table. The injected arm is then raised, followed by PET imaging commencing at 3-5 minutes (target 4 minutes) post 18F-fluciclovine injection in a caudocranial direction at 3.5 min per table position (Fig. 4) which results in adequate coverage to the skull base by 25 min post-injection. Starting acquisition caudally for the indication of suspected recurrent prostate cancer is especially critical with 18F-fluciclovine due to relatively rapid kinetics resulting in average highest tumor to background activity up to 20-30 minutes after injection, though individual lesions may have prolonged retention. If the scan is started too early (<3 min) biodistribution may be altered with increased blood pool.

Image Interpretation

18F-fluciclovine PET-CT should be interpreted with knowledge of physiologic biodistribution and typical patterns of prostate cancer recurrence (e.g., prostatectomy bed and deep pelvic lymph nodes versus peripheral inguinal or distal external iliac nodes) though distant disease may also be present (Fig 5).

Typically, the liver and pancreas demonstrate most intense physiologic uptake. The pituitary gland, salivary glands and lymphoid tissue of Waldeyer's ring, thyroid gland, breast parenchyma, esophagus, stomach and bowel, and renal parenchyma may have mild to moderate 18F-fluciclovine uptake. Note that uptake in a renal mass should be considered suspicious for malignancy. Papillary renal cell carcinoma has been shown to have increased uptake whereas clear cell carcinoma has reported uptake equal to renal parenchyma (*9*). The

urinary bladder wall typically has physiologic diffuse mild to moderate activity. Periurethral tissue may have mild to moderate parallel activity and therefore, sagittal images can help differentiate physiologic uptake in the urethra from disease in the prostatectomy bed (Fig. 1). Early bladder activity in a small percentage of patients may interfere with evaluation of the prostatectomy bed, prostate and seminal vesicles. Attention should be paid to the ureters in these cases so as to avoid confusion with nodal uptake. Adrenal glands have mild to moderate, physiologic, unilateral or bilateral uptake. Activity in the arm or subclavian vein on the side of injection may retain radiotracer and can be differentiated from abnormal nodal uptake by careful correlation on PET-CT.

Several benign conditions can demonstrate increase 18F-fluciclovine uptake leading to false-positive findings (*48*). Benign prostatic hypertrophy, acute and chronic inflammation (including post radiation) and infection all demonstrate varying levels of 18F-fluciclovine uptake. Reactive lymph nodes with uptake have been described adjacent to vascular grafts. Cutaneous and musculoskeletal inflammation has variable activity.

General criteria for positivity is uptake clearly above that of the bone marrow (preferred L3 vertebrae) for lesions >1 cm. Soft tissue lesions and lymph nodes smaller than 1 cm, subject to partial volume effect, may still be considered suspicious if uptake is visually equal to or approaches marrow and significantly greater than blood pool as observed in the abdominal aorta.

For patients post-prostatectomy, uptake in the prostatectomy bed and seminal vesicles greater than bone marrow is considered suspicious for recurrence. In patients with an intact prostate (e.g. post radiation therapy, high intensity focal ultrasound, cryotherapy) focal asymmetric uptake equal to or greater than bone marrow should be considered suspicious for

cancer recurrence. Diffuse and symmetric homogenous uptake should be significantly greater than marrow to be considered suspicious. Heterogeneous uptake should be treated as multifocal. It has also been anecdotally noted that median lobe uptake may have greater false positivity.

Uptake greater than bone marrow in lymph nodes with a distribution typical for recurrent prostate cancer is suspicious for malignancy. Uptake in lymph nodes with an atypical location for recurrence (e.g. inguinal, distal external iliac) should only be considered suspicious if uptake is asymmetric, intense, and/or in the context of other clearly malignant disease. Otherwise, mild symmetric uptake in these nodal groups is considered physiologic.

Bone marrow may have heterogeneous activity, more so than is typically seen with ^{18}F-FDG PET. Focal uptake clearly visualized on MIP images in osseous tissue is considered suspicious for cancer. 18F-fluciclovine uptake in lytic metastatic lesions is typically intense and there is moderate intensity in mixed sclerotic lesions. Indolent sclerotic lesions may not demonstrate 18F-fluciclovine uptake. A suspicious bone abnormality visualized on CT only (i.e. dense sclerosis without uptake) is considered non-specific and does not exclude the presence of metastasis. Suspicious CT findings without 18F-fluciclovine uptake may be evaluated with alternative imaging modalities for further characterization (e.g., MRI, ^{18}F-NaF PET-CT, ^{99m}Tc methylene diphosphonate SPECT/CT). Degenerative disk and facet uptake is less commonly seen with 18F-fluciclovine than with FDG. Malignant uptake in what initially appeared to be a Schmorl's node with irregular borders has been described. Benign and malignant bone lesions (e.g. osteoid osteoma and multiple myeloma) have reported uptake (*48*). Finally, single pelvic, non-focal, or non-mass-like 18F-fluciclovine activity not associated with a CT abnormality in our experience has been uncommonly seen with benign follow-up and should therefore be considered equivocal, warranting further evaluation with MR or biopsy (Fig. 6).

[Fig. 5]

[Fig. 6]

CONCLUSION

18F-fluciclovine is FDA approved for the localization of recurrent prostate cancer in patients with elevated PSA. Comprehensive clinical data demonstrates that 18F-fluciclovine is beneficial in the identification of the site or sites of suspected recurrent disease. 18F-fluciclovine demonstrates improved accuracy when compared to conventional imaging modalities for whole body staging. Knowledge of normal physiologic distribution and variants as well as typical patterns of prostate cancer spread is important for proper interpretation of 18F-fluciclovine PET. Further studies will be needed to evaluate 18F-fluciclovine in comparison to PSMA radiotracers and to more completely characterize patterns of bone and other malignant uptake.

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Figure Legends

Figure 1

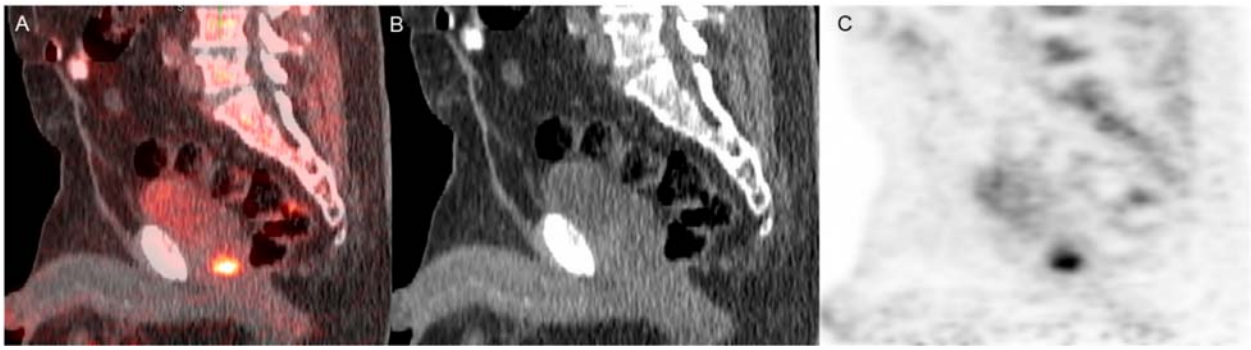

Figure 1. 66 year old male with biochemical recurrence of prostate cancer (PSA of 29.3 ng/mL). 18F-fluciclovine PET-CT found a single suspicious focus of uptake in the prostate resection bed. Sagittal (A) fused PET-CT, (B) CT, (C) PET. Patient underwent external beam radiation of lesion with corresponding PSA nadir (0.27 ng/mL)

Figure 2

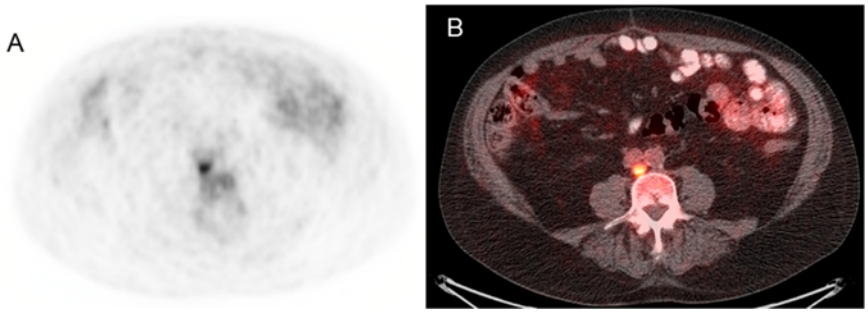

Figure 2. 73 year old male with biochemical recurrence of prostate cancer after prostatectomy and lymphadenectomy (PSA of 1.02 ng/mL; doubling time of 4.5 months). 18F-fluciclovine PET-CT found a single 0.9 cm retrocaval lymph node with SUV > bone marrow. Transaxial (A) PET, (B) fused PET-CT. Surgical excision was positive for metastasis and subsequent PSA nadir (0.08 ng/mL)

Figure 3

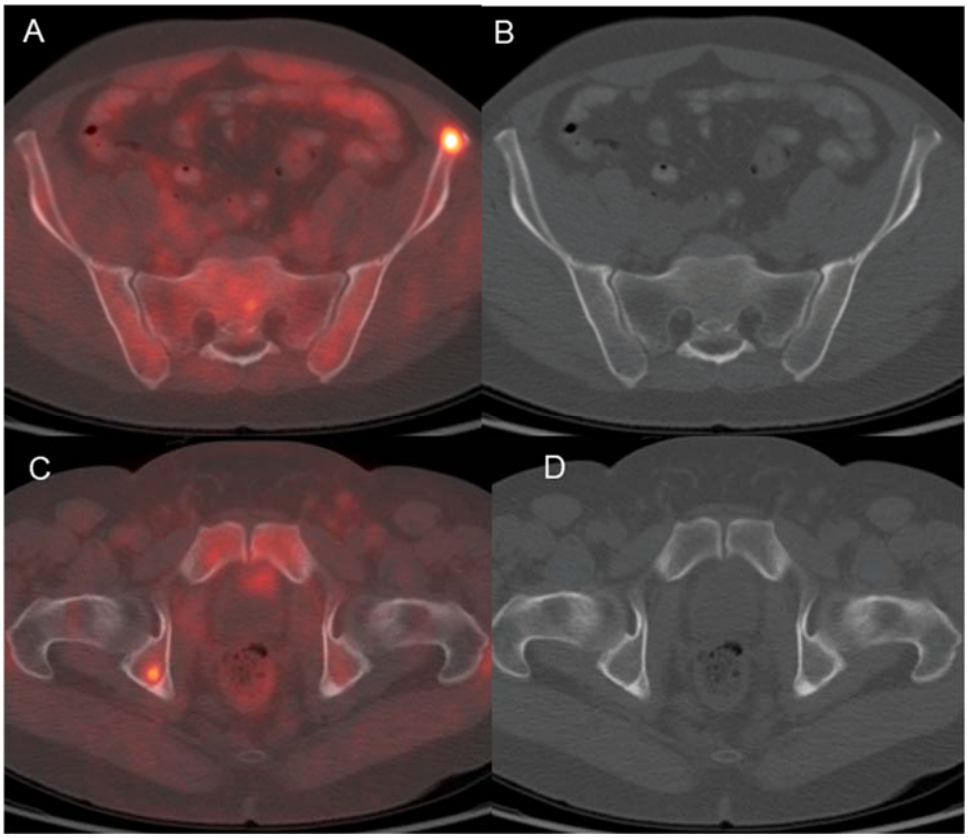

Figure 3. 50 year old male with biochemical recurrence of prostate cancer after prostatectomy (PSA of 3.2 ng/mL; doubling time of 1.4 months). MRI of abdomen initially read as negative and subsequent 18F-fluciclovine PET-CT found multiple osseous metastases. Transaxial fluciclovine PET-CT through subtle left iliac bone lytic lesion (A) fused, (B) CT. Transaxial fluciclovine PET-CT through silent right acetabular lesion(C) fused, (D) CT

Figure 4

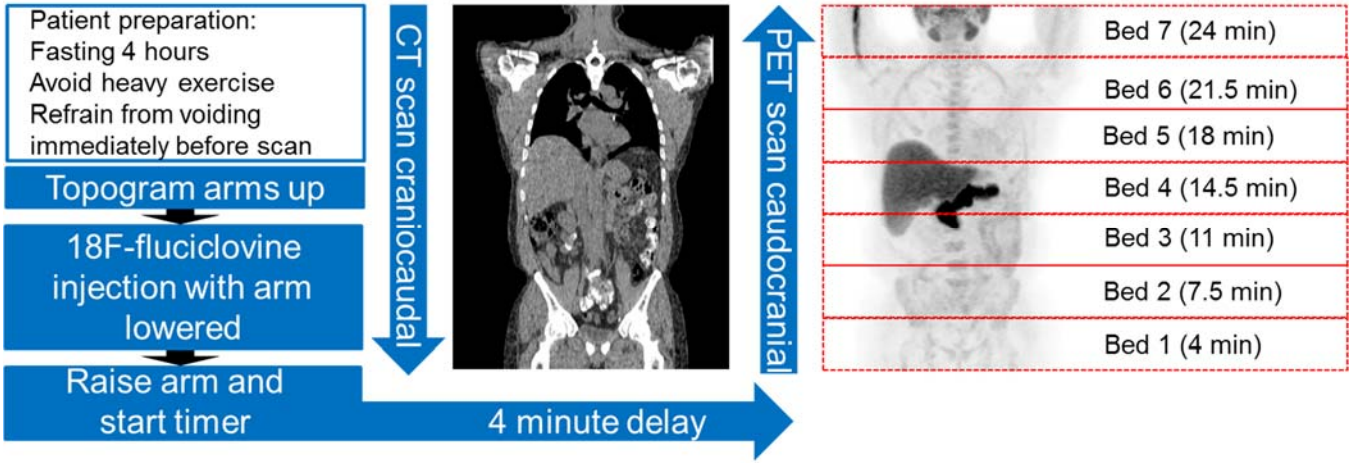

Figure 4. Schema of 18F-fluciclovine PET-CT acquisition adapted from the Emory clinical protocol (see text). Maximum intensity projection (MIP) of 18F-fluciclovine demonstrating normal biodistribution. Note relatively increased pancreas uptake compared to liver consistent with ideal time of image acquisition after injection. PET bed times are post injection.

Figure 5

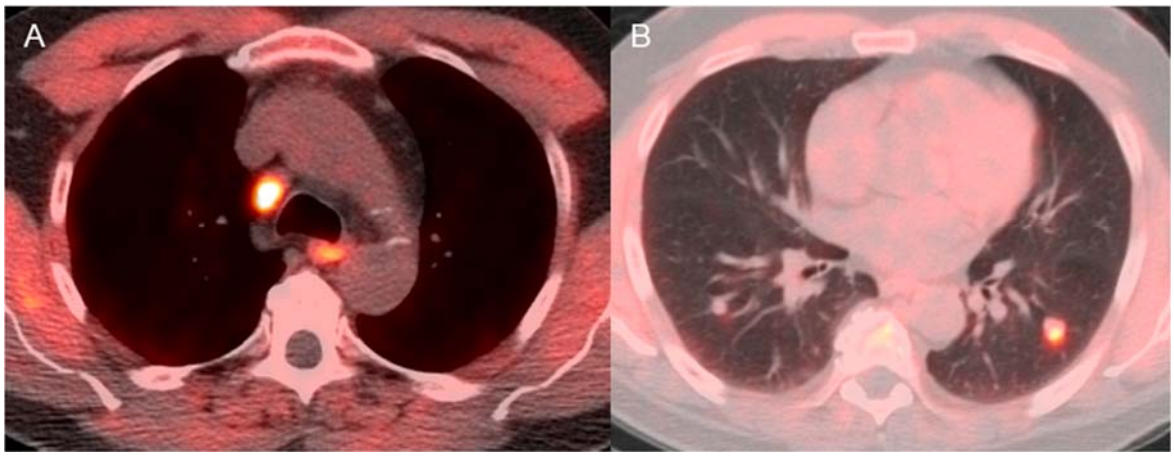

Figure 5: 60 year old male with biochemical recurrence of prostate cancer after prostatectomy (PSA of 16.4 ng/mL; doubling time of 6.4 months). 18F-fluciclovine PET-CT found metastatic mediastinal nodes and pulmonary nodules. Transaxial fused 18F-fluciclovine PET-CT (A) mediastinal nodes, and (B) pulmonary nodules. Patient started on hormonal therapy with subsequent resolution of lymphadenopathy and pulmonary nodules and undetectable PSA.

Figure 6

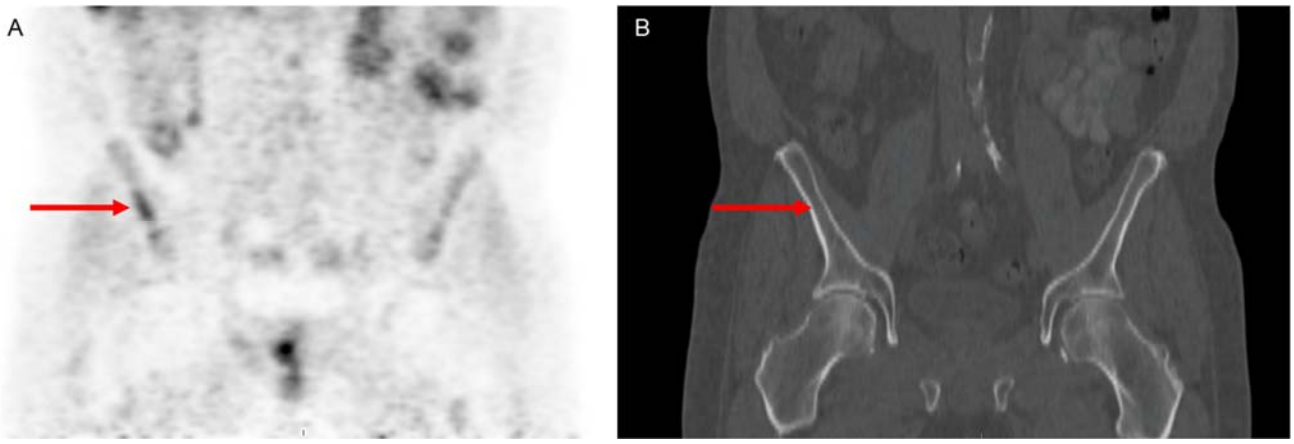

Figure 6:

60 year old male with biochemical recurrence of prostate cancer (PSA of 6.2 ng/mL). 18F-fluciclovine PET-CT demonstrated uptake in the right iliac bone without CT correlate and prostate bed (not shown). Coronal images of right iliac bone lesion (arrows): PET (A), CT (B). Biopsy of right iliac bone found benign sclerosis. Note that 18F-fluciclovine PET uptake was linear and ill-defined, atypical for prostate metastases.