

Imaging of Prostate Cancer Using Fluciclovine



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KEYWORDS

• FACBC • Fluciclovine • Axumin • CT • PET • Prostate

KEY POINTS

- Functional molecular imaging with PET improves the ability to detect prostate cancer.
- Fluciclovine is beneficial for the localization of recurrent prostate disease when conventional imaging is negative.
- When interpreted with knowledge of radiotracer biodistribution and normal variants, fluciclovine PET is highly specific for extraprostatic metastasis but has lower specificity for disease within intact or treated prostate.
- Less data are available on the performance of fluciclovine in bone metastases; therefore, skeletal-specific imaging is recommended for suspected bone involvement if fluciclovine PET is unrevealing.

RADIOLABELED AMINO ACIDS AS PET RADIOTRACERS FOR PROSTATE CANCER IMAGING

Amino acids play a central role in cell metabolism and are the building blocks of proteins. Transmembrane amino acid transporters are upregulated in cancer cells to provide nutrients for tumor cell growth.^{1,2} Certain amino acids such as leucine and glutamine are key components in the mammalian target of rapamycin cancer signaling pathway.³ Because this upregulation of amino acid transport also occurs in prostate cancer cells, using an amino acid-based radiotracer can localize prostate cancer as well.⁴

Many amino acid transporter systems are overexpressed in prostate cancer, predominantly large neutral amino acid transporters (systems L: LAT1, LAT3, and LAT4) and alanine-serine-cysteine transporters (systems ASC: ASCT1, ASCT2).^{1,3,5-14} Of these transporters, LAT1 and ASCT2 are particularly associated with more aggressive tumor behavior.^{7,15-17} Both ASCT2 and LAT3 expression are stimulated by androgen signaling in androgen-dependent prostate cancer cells.¹⁸

Prostate cancer may be imaged using both radiolabeled natural and synthetic amino acids. Naturally occurring amino acids such as C-11-methionine are not optimal for imaging because

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of accumulation of metabolites in nontarget organs, whereas radiolabeled synthetic, nonmetabolized amino acid analogues are preferred due to simpler kinetics and the ability to radiolabel with longer-lived radionuclides.¹

Anti-1-amino-3-F-18-fluorocyclobutane-1-carboxylic acid (FACBC or fluciclovine) is a nonnaturally occurring amino acid analogue for which the most comprehensive clinical studies for prostate cancer have been performed to date.^{10,17,19–26} Fluciclovine is predominantly transported via ASCT2 and LAT1. Because these transporters mediate both influx and efflux of amino acids, peak uptake in tumors occurs at 5 to 20 minutes after injection with variable washout.^{17,22,27}

FLUCICLOVINE FROM DEVELOPMENT TO US FOOD AND DRUG ADMINISTRATION APPROVAL

The development of C-11 aminocyclobutane arboxylic acid (ACBC) was first described in 1978 by Washburn and colleagues.²⁸ ACBC was structurally modified from 1-aminocyclopentanecarboxylic acid. Subsequently, ACBC was radiolabeled with Carbon-11 and found to have potential for imaging soft tissue tumors in humans.²⁹ However, C-11 has a half-life of 20 minutes, which requires an on-site cyclotron for production. In 1995, Dr Mark Goodman and co-workers described the synthesis of fluorine-18 (half-life 109.8 minutes) labeled anti-1-amino-3-fluorocyclobutane-1-carboxylic acid, 3-FACBC. In 1999, they reported the evaluation of 3-FACBC in gliomas.³⁰ In 2002, the synthesis of the 3-FACBC labeling precursor and 3-FACBC were improved for routine production for clinical use.^{31,32}

Early work suggested that fluciclovine was transported into the cell most like leucine via system L, especially LAT1.^{31,33} Subsequent *in vitro* studies found that the ASC transporter system, specifically ASCT2, plays the largest role in fluciclovine transport, whereas LAT1 transport may become elevated in an acidic tumor environment or with castration-resistant cells.^{10,16–18} Thus, it is currently thought that fluciclovine transport more closely mirrors that of glutamine rather than leucine.³⁴ When compared with methionine, glutamine, choline, and acetate, uptake of fluciclovine in prostate cancer cell lines has also been noted to be higher.¹⁷ Experiments with a rat orthotopic prostate cancer model compared the uptake of fluciclovine with that of fludeoxyglucose (FDG). It was found that target-to-background ratio was higher for fluciclovine with only minimal bladder accumulation.³³

In human clinical studies, fluciclovine was initially developed for the evaluation of cerebral gliomas.³⁰ Further evaluation in human dosimetry studies demonstrated physiologic highest tracer uptake by the liver and pancreas, with less intense heterogeneous uptake within the marrow, salivary glands, lymphoid tissue, and pituitary gland, and only minimal brain and kidney uptake. Variable activity was noted in the bowel²⁷ (**Fig. 1**). When compared with FDG, fluciclovine is only minimally eliminated by the kidneys during the typical imaging time course. Hence, evaluation of fluciclovine for imaging of renal and pelvic malignancies seemed promising.

Fluciclovine was next evaluated for staging of patients with renal cancer. Although no highly promising data from renal mass evaluation were observed, an important incidental finding was reported in a patient with intense uptake within retroperitoneal lymphadenopathy and subsequent biopsy-proven metastatic prostate cancer.³⁵ Evaluation of fluciclovine for prostate cancer imaging took priority, and in 2007, Schuster and colleagues²² described the first experience with fluciclovine for the evaluation of 9 patients with primary and 6 patients with recurrent prostate cancer. Early results reported promising correlation between biopsy-proven disease and fluciclovine uptake. Further human studies with fluciclovine, which will be detailed in later discussion, demonstrated the potential to detect local and distant recurrent prostate cancer.

A New Drug Application was subsequently accepted in December 2015 by the US Food and Drug Administration (FDA) as filed by Blue Earth Diagnostics, Ltd for priority review based on data collected from 877 subjects, including 797 patients with prostate cancer in the United States and Europe, and approval was granted to fluciclovine (trade name: Axumin) on May 2016 for the clinical indication of suspected prostate cancer recurrence based on elevated prostate-specific antigen levels following prior treatment.³⁶

FLUCICLOVINE IN THE EVALUATION OF PATIENTS WITH SUSPECTED RECURRENCE OF PROSTATE CANCER

Fluciclovine has been most extensively studied in relation to recurrent prostate cancer. Fluciclovine diagnostic performance has been reported to be significantly higher than that of In-111-capromab pendetide and computed tomography (CT) in the diagnosis of patients with suspected disease relapse.^{21,24,37} A single-center study with 115

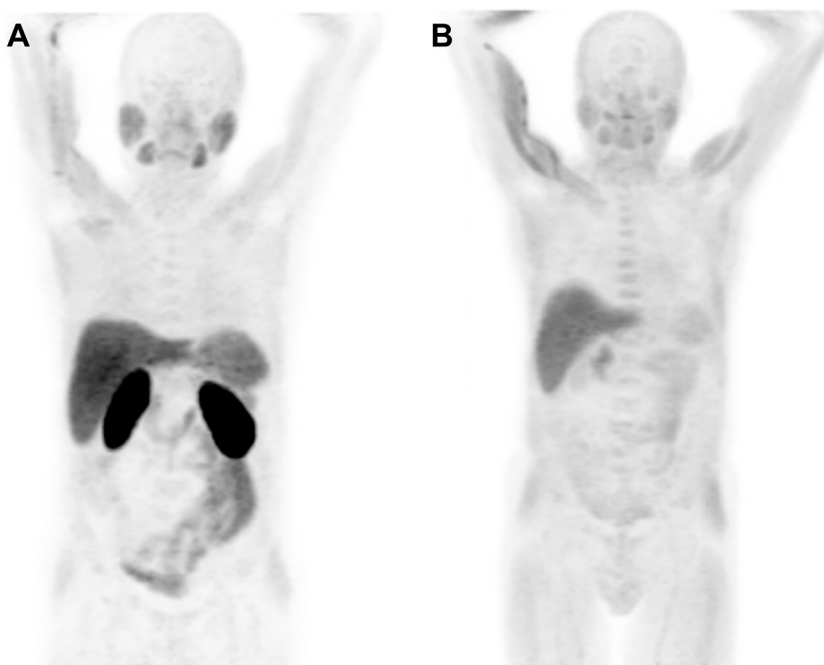


Fig. 1. Comparison of ^{11}C choline and ^{18}F fluciclovine physiologic biodistribution. ^{18}F fluciclovine (B, MIP) is physiologically found in pancreas, liver, bone marrow, and muscle, with negligible uptake in kidneys, bowel, and delayed urinary excretion, thus leading to a more favorable distribution in the abdomen and pelvis, compared with ^{11}C choline (A, MIP), for evaluating prostate cancer. (Courtesy of Dr Cristina Nanni, Programma di ricerca Regione-Università 2010-2012 Regione Emilia Romagna-Bando Giovani Ricercatori, Bologna, Italy.)

patients who underwent definitive treatment of prostate cancer and presented with biochemical failure by the American Urological Association (AUA) and American Society of Radiation Oncology (ASTRO) criteria was completed.³⁸ In a subset analysis of 93 patients with negative bone scan and In-111-capromab pendetide, single-photon emission computed tomography-computed tomography (SPECT-CT) within 90 days of the fluciclovine PET/CT, overall positive scans (positivity rate) was 82.8%. Biopsy was the primary reference standard. One hundred percent of true positive prostate/prostate bed lesions and 86.4% of true positive extraprostatic lesions were confirmed histologically. For prostate/prostate bed recurrence, fluciclovine had 90.2% sensitivity, 40.0% specificity, 73.6% accuracy, 75.3% positive predictive value (PPV), and 66.7% negative predictive value (NPV); the respective values for In-111-capromab pendetide were 67.2%, 56.7%, 63.7%, 75.9%, and 45.9%. For extraprostatic recurrence, fluciclovine had 55.0% sensitivity, 96.7% specificity, 72.9% accuracy, 95.7% PPV, and 61.7% NPV; the respective values for In-111-capromab pendetide were 10.0%, 86.7%, 42.9%, 50.0%, and 41.9%. Fluciclovine identified 14 more positive prostate/prostate

bed recurrences (55 vs 41) and 18 more patients with extraprostatic involvement (22 vs 4), and a 25.7% change in stage was reported by use of fluciclovine PET.

Similar patterns were reported when fluciclovine imaging was compared with the performance of CT (n = 53) in another subanalysis from this trial.²¹ For the prostate/prostate bed, fluciclovine had 88.6% sensitivity, 56.3% specificity, 78.4% accuracy, 81.6% PPV, and 69.2% NPV; the respective values for CT were 11.4%, 87.5%, 35.3%, 66.7%, and 31.1%. For extraprostatic regions, fluciclovine had 46.2% sensitivity, 100% specificity, 65.9% accuracy, 100% PPV, and 51.7% NPV; the respective values for CT were 11.5%, 100%, 43.9%, 100%, and 39.5%. Positivity rates with fluciclovine PET/CT varied with prostate-specific antigen (PSA) levels, PSA doubling times, and original Gleason scores, but were higher than positivity rates for CT. For PSA (ng/mL) levels of less than 1, 1 to 2, greater than 2 to 5, and greater than 5, 37.5%, 77.8%, 91.7%, and 83.3% fluciclovine scans were positive, respectively.

Although fluciclovine demonstrates high PPV for extraprostatic disease, fluciclovine utility for the evaluation of local recurrence within the prostate may be challenging with relatively higher false

positive results compared with extraprostatic locations. In particular, patients who underwent prostate-sparing initial therapies may demonstrate nonspecific uptake patterns likely confounded by prostatic hypertrophy and chronic inflammation. Savir-Baruch and colleagues³⁹ reported that the fluciclovine pattern of heterogeneous tracer distribution exhibits lower maximum standard uptake value (SUV_{max}) and lower PPV and also is associated with the presence of brachytherapy seeds when compared with focal or multifocal distribution patterns.

Evaluation of potential skeletal lesions is essential for proper staging and treatment of patients with suspected prostate cancer recurrence. Because patients with known bone metastasis were excluded from the initial studies via negative bone scan, there are less data concerning accuracy of fluciclovine for skeletal metastasis. Nevertheless, patients with fluciclovine-positive bone lesions have been reported.^{20,21,37,40} Nanni and colleagues²⁰ reported 7/89 patients in their study with bone lesions in which 5 were positive with fluciclovine (Fig. 2). Schuster and colleagues³⁷ reported 3/93 patients with uptake within skeletal lesions enrolled after negative bone scan. A phase 2a clinical trial by Inoue and colleagues⁴¹ of 10 patients reported 7 patients with abnormal increased fluciclovine uptake within metastatic bone lesions, similar to that of conventional imaging. In the authors' experience, fluciclovine demonstrates intense focal uptake in lytic prostate cancer lesions, and moderate uptake within

mixed sclerotic lesions, but there may be absent uptake in dense sclerotic lesions. Thus, it is recommended that fluciclovine should not replace the use of dedicated bone scintigraphy when clinically indicated.

FLUCICLOVINE PERFORMANCE COMPARED WITH OTHER PET RADIOTRACERS

Other reported molecular imaging PET radiotracers have demonstrated promising results in the detection of prostate cancer, including C-11 choline, F-18 choline, C-11 acetate (Fig. 3), and Ga-68 or F-18-labeled prostate-specific membrane antigen ligands (PSMA).^{40,42-49} For C-11 choline, a recent meta-analysis with 1270 patients reported a pooled sensitivity and specificity of 89% and 89%, respectively.⁴⁰ Although these results suggest that the diagnostic performance of choline is superior to that of fluciclovine, exercise must be cautioned because differences in study design, interpretative criteria, and reference standards may bias results. In fact, a single-center study by Nanni and colleagues²⁰ found fluciclovine to be slightly superior to the performance of C-11 choline for patients radically treated for prostate cancer with biochemical relapse when a single patient underwent both scans within 1 week ($n = 89$). With C-11 choline versus fluciclovine, sensitivity was 32% and 37%, specificity was 40% and 67%, PPV was 90% and 97%, NPV was 3% and 4%, and accuracy was 32% and 38%, respectively.²⁰ Overall, it was concluded that

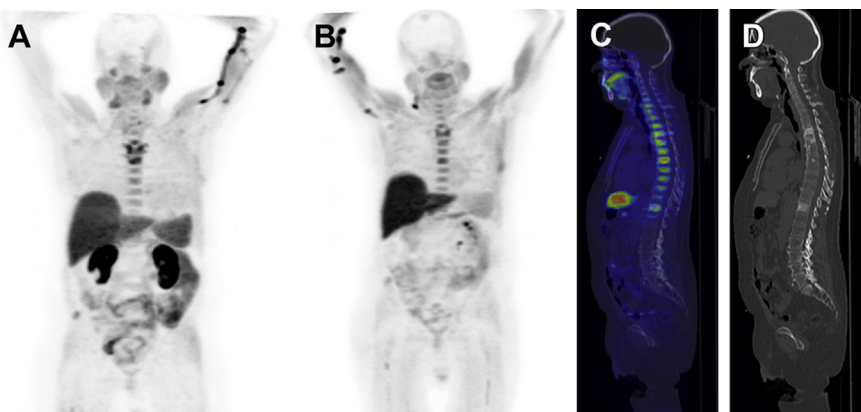


Fig. 2. 11C choline and 18F fluciclovine PET/CT detects multiple bone metastases in biochemically recurrent prostate cancer. Patient with prostate cancer treated with radical surgery and hormonal therapy, now presenting with high and rapidly increasing PSA (PSA-Trigger = 14.80 ng/mL; PSA-DT = 2.8 months; A-Vel = 33.5 ng/mL/y) underwent PET imaging. Both 11C choline (A, MIP) and 18F fluciclovine PET/CT (B, MIP; C, sagittal fused) identified multiple avid bone lesions in right femur, right iliac bone, left pubis, multiple vertebra, sternum and left scapula, corresponding to small osteosclerotic lesions on low-dose CT images (D, sagittal). Positive findings were concordant with the 2 tracers, although showing different uptake pattern. (Courtesy of Dr Cristina Nanni, Programma di ricerca Regione-Università 2010-2012 Regione Emilia Romagna-Bando Giovani Ricercatori, Bologna, Italy.)

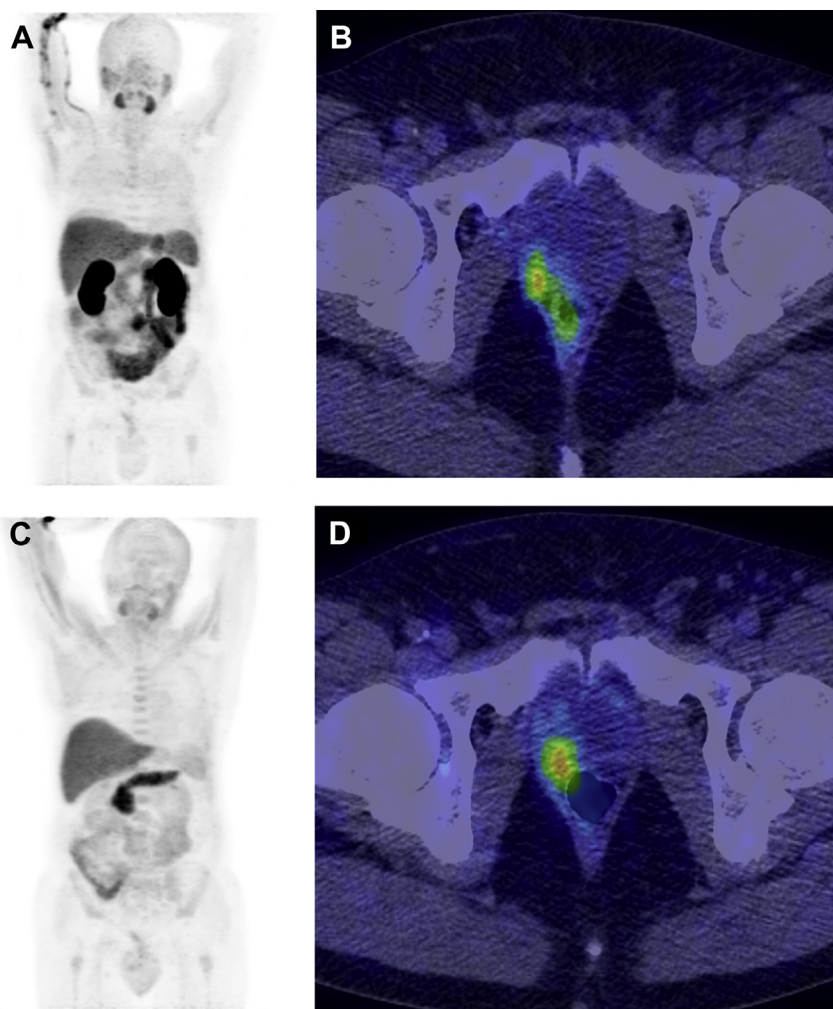


Fig. 3. ^{11}C choline and ^{18}F fluciclovine PET/CT detect local relapse in biochemically recurrent patient with prostate cancer. Patient with prostate cancer treated with radical surgery, salvage radiation, and hormonal therapy, now presenting with rapidly increasing PSA (PSA-Trigger 4.8 ng/mL, PSA-DT = 0.8 months, PSA-Vel = 24.8 ng/mL/y) and inconclusive findings at conventional ^{18}F choline PET/CT and MR imaging. ^{11}C choline PET/CT (A, B, MIP and transaxial fused) and ^{18}F fluciclovine (C, D) performed within 1 week demonstrated focal uptake in the right prostate bed, more evident with the amino-acidic compound. A subsequent transrectal ultrasound (TRUS) biopsy reported a 7- to 10-mm nodule of adenocarcinoma GS 4 + 4 thus confirming local relapse. (Courtesy of Dr Cristina Nanni, Programma di ricerca Regione-Università 2010-2012 Regione Emilia Romagna-Bando Giovani Ricercatori, Bologna, Italy.)

fluciclovine as an imaging radiotracer also demonstrates other advantages, including ease of production, longer half-life, and lower physiologic background activity.

Ga-68 PSMA as well has demonstrated promising results for the imaging of patients with suspected prostate cancer relapse.^{46–48,50} PSMA is overexpressed in prostate cancer cells. Targeting of PSMA expression was previously used in imaging with In-111-capromab pentetide directed to the intracellular epitope of the PSMA receptor, which significantly limits its diagnostic

performance. Ga-68-labeled PSMA ligands have been structured to attach to the extracellular domain, significantly increasing sensitivity.^{51,52} When Ga-68 PSMA performance was compared with F-18 choline within the same patients, Ga-68 PSMA was found to be superior to choline with significantly higher SUV_{max} . Ga-68 PSMA detected 56 lesions versus 26 with F-18 choline.⁴⁵ Similar results may well occur in comparison to PSMA-based radiotracers to fluciclovine, and direct comparison possibly will be the subject of future research.

FLUCICLOVINE EVALUATION OF PRIMARY PROSTATE CANCER

Multiparametric MR imaging (MP-MR) is considered the most useful single modality for the characterization of primary prostate cancer, although there are limitations including that of specificity.^{43,53} Turkbey and colleagues⁵⁴ investigated the use of fluciclovine PET with MP-MR imaging for 22 patients with primary prostate cancer scheduled to undergo prostatectomy and whole-mount histologic analysis. Although mean SUV_{max} of the tumor was significantly higher than that of normal prostate tissue, there was a significant overlap of fluciclovine uptake between tumor foci and benign prostate hyperplasia. Adding the information from fluciclovine PET to MP-MR increased the PPV from 50% for fluciclovine alone and 76% for MP-MR alone to 82% for a combination of all methods. The limitations of fluciclovine for primary prostate cancer had also been reported previously by Schuster and colleagues²⁵ in a 10-patient study correlating fluciclovine uptake with MR imaging and histologic sextant analysis.²⁵ Although the study reported a correlation between SUV_{max} and Gleason score and statistically significant differences in SUV_{max} between malignant and benign sextants, overlap was noted. No correlation was found between uptake (SUV_{max}) and Ki-67. Both studies concluded that fluciclovine imaging for the evaluation of primary prostate cancers was limited,

although there may be some utility as an adjunct to MP-MR and to help guide biopsy as well as possibly staging of high-risk disease. In addition, both studies suggested that delayed imaging, 15 to 20 minutes in the first study and 28 minutes in the second study, could improve diagnostic performance for the characterization of primary lesions (Figs. 4 and 5).

IMAGING PROTOCOL AND INTERPRETATIVE CRITERIA FOR SUSPECTED RECURRENT PROSTATE CANCER

Differing protocols of fluciclovine imaging have been reported.^{19,22,24,25,35,37,40,55} During early clinical investigation, triple time point imaging of the abdomen and pelvis was used, and uptake was defined as mild, moderate, or intense when activity in the region of interest was visually below that of the bone marrow (typically at L3), equal to or above that of the bone marrow, and equal to or above that in the liver, respectively. Positive lesions were defined as persistent moderate or intense uptake based on early to delayed sequences.^{24,37} Nevertheless, it was recognized that triple time point imaging is not clinically practical. A subsequent retrospective analysis compared results from early single time point imaging with multiple time point interpretation. It was concluded that early imaging with fluciclovine is feasible with modest increased sensitivity and decreased specificity.⁵⁶ Other centers have also

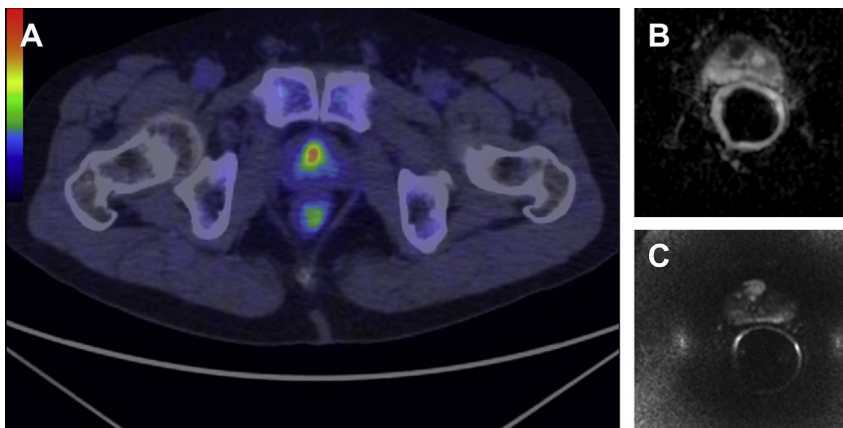


Fig. 4. Pretreatment staging 18F fluciclovine PET/CT identifies the most predominant aggressive intraprostatic lesion in primary prostate cancer (in agreement with 11C choline and MP-MR imaging). A 71-year-old patient affected by high-risk prostate cancer (PSA 8 ng/mL, GS 4 + 4, cT2) underwent MP-MR imaging (B, axT2; C, axDWI) and 11C choline PET/CT, as part of the normal staging workflow before radical surgery, and an additional 18F fluciclovine scan (A, transaxial fused), as part of an ongoing clinical trial. The procedures detected a focal right intermediate prostate lesion, corresponding to a 19-mm, GS 4 + 5 nodule of acinar adenocarcinoma. On the contrary, a smaller and less aggressive focus of GS 3 + 3 was under the limit of lesion detectability in all cases. (Courtesy of Dr Lucia Zanoni, Programma di ricerca Regione-Università Area 1-Bando Giovani ricercatori "Alessandro Liberati" 2013, Bologna, Italy.)

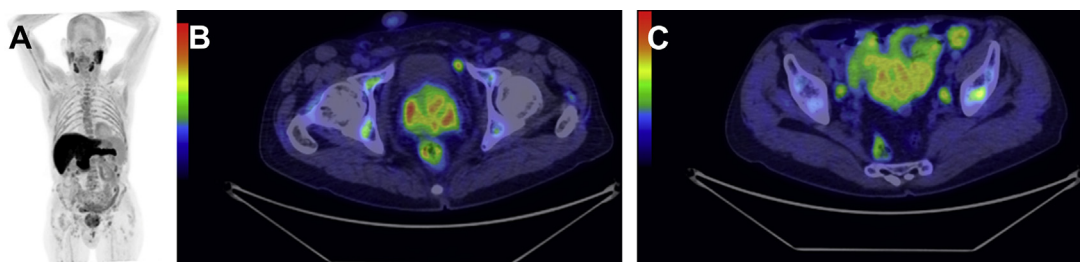


Fig. 5. Pretreatment staging ^{18}F fluciclovine PET/CT in a patient with primary prostate cancer, scheduled for radical surgery, detects multiple nodal and bone metastases leading to a change in treatment management. Patient with high-risk prostate cancer (PSA 18,65, GS 4 + 5, 50% positive core biopsy) was scheduled for radical surgery and lymphadenectomy according to pelvic MR imaging and ^{11}C choline PET/CT standard staging. The experimental tracer ^{18}F fluciclovine detected multiple avid pelvic lymphadenopathies (B and C, transaxial fused) and inhomogeneous and diffuse uptake throughout the skeleton (A, MIP). Considering the disease extent, the patient was finally excluded from surgery. (Courtesy of Dr Lucia Zanoni, Programma di ricerca Regione-Università Area 1-Bando Giovani ricercatori "Alessandro Liberati" 2013, Bologna, Italy.)

used whole-body single time point imaging with success.²⁰ With the knowledge of efflux of radiotracer with a generally downsloping time activity curve, early imaging within the first 30 minutes after injection is therefore recommended. A protocol for imaging and study interpretation as adapted from the FDA package insert and the Axumin (fluciclovine F18) Imaging and Interpretation Manual is provided in **Table 1**, and it is recommended that the full documents be reviewed by the reader.⁵⁷

As with other radiotracers, knowledge of normal physiologic distribution and variants as well as typical patterns of cancer recurrence is important for proper interpretation of fluciclovine PET. A comprehensive review paper describing radiotracer uptake patterns, incidental findings, and variants that may simulate disease is available.²³ Uptake may not only occur in prostate cancer but also in other malignancies (**Fig. 6**). Uptake may also be present in benign conditions such as inflammation and infection and other metabolically active benign lesions such as meningioma and osteoid osteoma (**Fig. 7**)

For patients who have undergone nonprostatectomy therapy, nonspecific elevation of fluciclovine uptake in remaining prostate likely due to underlying hyperplastic prostate tissue or inflammation may be present.⁵⁴ Moderate focal asymmetric uptake, visually equal to or greater than bone marrow, is considered suspicious for cancer recurrence. Ongoing studies are exploring the use of fluciclovine for biopsy planning for recurrent disease.⁵⁸ For patients with history of prostatectomy, any focal uptake within the prostate bed or seminal vesicles may be considered abnormal especially if greater than bone marrow, although small lesions (<1 cm) subject to the partial volume

effect may be suspicious if visually greater than blood pool. Review of sagittal images is especially useful for evaluation of the urethral anastomosis. Uptake within lymph nodes at sites of typical prostate cancer spread is highly specific for neoplastic involvement with a low false positives rate, and understanding the common patterns of lymph node metastasis in prostate cancer is essential to minimize false positive interpretation.^{20,24,37,55} Uptake visually equal to or above that of lumbar marrow should be considered abnormal, although with nodes less than 1 cm, uptake may be suspicious if in a typical pattern of spread and greater than blood pool. Nevertheless, for example, inguinal lymph nodes may demonstrate nonspecific moderate symmetric inflammatory uptake. For bone lesions to be considered positive, focal uptake should be clearly seen on maximum intensity projection (MIP) images. Densely sclerotic lesions may not be fluciclovine avid. In contradistinction to FDG-PET, degenerative uptake is not a common variant. Skeletal metastases resembling Schmorl nodes but with fluciclovine uptake have been described. **Table 1** provides more detailed interpretative guidelines as well as pearls, pitfalls, and variants.

GUIDELINES FOR THE USE OF FLUCICLOVINE IMAGING IN PATIENTS WITH RECURRENT PROSTATE CANCER

Fluciclovine PET is highly useful in the detection of recurrent prostate cancer even in the presence of negative or equivocal conventional imaging. The current FDA-approved indication is for men with suspected prostate cancer recurrence based on elevated blood PSA levels following

Table 1
Axumin (fluciclovine F18) imaging and interpretation manual

Fluciclovine PET/CT	Description
Imaging protocol	<p>Patient preparation:</p> <ul style="list-style-type: none"> • Avoid significant exercise for at least 1 d before PET imaging. • Nothing to eat or drink for at least 4 h (other than small amounts of water for taking medications) before radiotracer administration. • Void before starting the scanning procedure. <p>Dose and injection:</p> <ul style="list-style-type: none"> • 10 mCi/370 MBq as an intravenous bolus injection while the patient is positioned in the PET/CT scanner with arms down. • Injection into the right arm is suggested to avoid misinterpretation of stasis in left axillary vein as Virchow node. • Subsequently, administer an intravenous flush of sterile sodium chloride injection, 0.9%, to ensure full delivery of the dose. <p>Image acquisition:</p> <ul style="list-style-type: none"> • Position the patient supine with arms above the head if possible. • High-quality CT acquisition for anatomic correlation and attenuation correction. • Begin PET 3–5 min after injection (goal of 4 min). • Image from the mid thighs to base of skull. • Imaging guidelines recommend 5 min per bed position acquisition in the pelvis and 3 min per bed position in the remainder of the body, but these suggestions are scanner dependent. <p>Image reconstruction:</p> <ul style="list-style-type: none"> • The highest-quality scanner at an institution should be used. • If a scanner has time of flight, iterative reconstruction and/or a reconstruction algorithm using recovery resolution should be used. • Gaussian smoothing filter (if applicable) should not exceed 5 mm.
Diagnostic criteria	<p>Generally defined as: Localization of prostate cancer recurrence in sites typical for prostate cancer recurrence in comparison with tissue background.</p> <p>Prostate/bed</p> <p>Prostatectomy</p> <ul style="list-style-type: none"> • Focal uptake, visually equal to or greater than bone marrow, in sites typical for prostate cancer recurrence suspicious for cancer. <ul style="list-style-type: none"> ◦ However, if a focus of uptake is small (<1 cm), it may be considered suspicious if the uptake is visually greater than blood pool. <p>Nonprostatectomy</p> <ul style="list-style-type: none"> • Moderate focal asymmetric uptake, visually equal to or greater than bone marrow, is suspicious for cancer recurrence. <ul style="list-style-type: none"> ◦ However, if a focus of uptake is small (<1 cm) and in a site typical for recurrence, it may still be considered suspicious if the uptake is visually greater than blood pool. <p>Lymph nodes</p> <p>Typical sites for prostate cancer recurrence</p> <ul style="list-style-type: none"> • Uptake, visually equal to or greater than bone marrow, is considered suspicious for cancer. <ul style="list-style-type: none"> ◦ However, if a node is small (<1 cm) and in a site typical for recurrence, it may still be considered suspicious if visually greater than blood pool. <p>Atypical sites for recurrence (inguinal, distal external iliac, hilar, and axillary nodes)</p> <ul style="list-style-type: none"> • Mild, symmetric uptake is typically considered physiologic uptake, but if uptake is present within the context of other clear malignant disease, it may be considered suspicious for cancer recurrence. <p>Bone</p> <ul style="list-style-type: none"> • Focal uptake clearly visualized on MIP or PET-only images is considered suspicious for cancer. <ul style="list-style-type: none"> ◦ A bone abnormality visualized on CT (eg, dense sclerosis without uptake) does not exclude the presence of metastasis. Alternative imaging, for example, MR, NaF PET-CT, or SPECT-CT bone scan, should be considered.

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Table 1
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Fluciclovine PET/CT	Description
Differential diagnosis	<p>Prostate</p> <ul style="list-style-type: none"> • Cancer, inflammatory changes, benign prostatic hypertrophy. <p>Extraprostate</p> <ul style="list-style-type: none"> • Typical locations for nodal spread of prostate cancer: metastatic prostate cancer • Uptake may occur in other cancers • Nodal inflammation, especially if mild and symmetric and in atypical locations for prostate cancer spread such as inguinal or distal external iliac. • Uptake may also occur from benign processes such as infection, and metabolically active benign bone lesions such as osteoid osteoma.
Pearls, pitfalls, variants	<ul style="list-style-type: none"> • Performance affected by PSA levels. Less likely to be positive with PSA <1 ng/mL unless doubling time is rapid. • Read from the “inside out.” That is, be aware of typical locations for prostate cancer spread (eg, deep pelvic vs peripheral inguinal or distal external iliac nodes). <ul style="list-style-type: none"> ◦ Mild benign symmetric uptake within the inguinal lymph nodes may be seen and should not be called positive unless “disease pattern marching out of pelvis.” • Higher false positive rate within intact or treated prostate. • Abnormal activity in postprostatectomy bed is more specific. <ul style="list-style-type: none"> ◦ Sagittal images helpful with identification of disease at urethral anastomosis. • Uptake in lytic skeletal lesions is typically intense, moderate in mixed lesions, but may be absent in densely sclerotic lesions. <ul style="list-style-type: none"> ◦ If skeletal lesion is seen on CT, consider skeletal-specific imaging. • Degenerative uptake in bone is not a common variant in fluciclovine as it is with FDG and should be further evaluated for the presence of metastatic bone lesions. Skeletal metastases that resemble Schmorl nodes but with fluciclovine uptake within them have been described. • Fluciclovine may be taken up by other cancer cells with upregulated amino acid transport. Be familiar with normal physiologic patterns of activity. In these instances, further correlation with clinical presentation and/or other imaging may be helpful. • In a small percentage of patients, fluciclovine may demonstrate moderate early bladder activity, interfering with evaluation of the prostate bed.
What the referring physician needs to know	<ul style="list-style-type: none"> • Fluciclovine PET/CT demonstrates utility in the localization of recurrent prostate cancer disease (FDA-approved indication). • Fluciclovine PET can identify true positive prostate cancer foci even when conventional imaging, such as CT, MR, and bone scan, is negative. • No absolute PSA threshold is recommended. However, positivity is more likely with PSA >1 ng/mL or if PSA <1 ng/mL with rapid PSA kinetics. • Fluciclovine PET/CT scan should be considered before salvage therapy, for accurate treatment planning.

prior treatment. There is no absolute threshold for PSA level in the recommendation of when to obtain fluciclovine PET, yet clearly, diagnostic performance varies with PSA level and kinetics. Fluciclovine PET positivity rate will increase with increasing PSA and with more rapid doubling times.^{20,21,59} Based on logistic regression analysis in one study, a PSA of 1 ng/mL equated to a 71.8% probability of a positive fluciclovine scan.³⁷ One group has reported that functional imaging with choline or fluciclovine PET/CT together with MP-MR to be the most valuable imaging techniques in the detection of prostate

cancer relapse and should be highly considered before treatment planning.⁶⁰ The group acknowledged the limitation of these PET radiotracers with underlying low PSA levels of less than 1 ng/mL. They suggested that functional images may be cost-effective when PSA velocity is high and PSA doubling time is short. Therefore, until more data are available, an elevated PSA or a concerning PSA velocity or doubling time, which clinically triggers salvage therapy in patients, may be a useful reference as to when a fluciclovine PET study should be obtained in suspected recurrent prostate cancer.

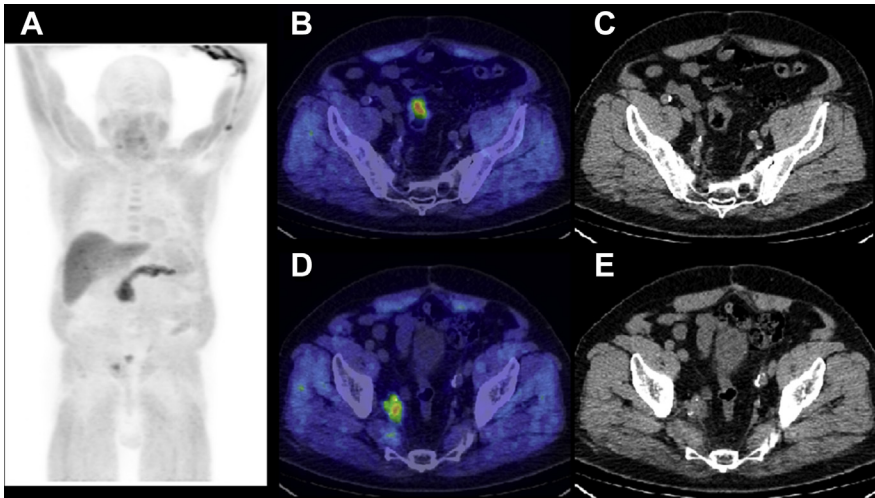


Fig. 6. ^{18}F fluciclovine PET/CT detects nodal metastasis in biochemically recurrent prostate cancer and incidental sigmoid cancer. Patient with prostate cancer treated with radical surgery, salvage radiation, and hormonal therapy, now presenting with low but rapidly increasing PSA (PSA-Trigger = 0.94 ng/mL; PSA-DT = 5.9 months; PSA-Vel = 1.1 ng/mL/y) and negative TRUS. ^{18}F fluciclovine showed 2 focal lesions in MIP images (A) corresponding with right internal iliac tissue (D, E transaxial fused and low-dose CT), causing grade II hydronephrosis, and sigmoid wall thickening (B, C). Urologic contrast-enhanced CT and bowel endoscopy confirmed the findings, in keeping with secondary nodal lesions from prostate cancer and new sigmoid cancer. The patient was treated with ureteral stenting, hormonal therapy, and bowel resection, achieving PSA response. (Courtesy of Dr Cristina Nanni, Programma di ricerca Regione-Università 2010-2012 Regione Emilia Romagna-Bando giovani Ricercatori, Bologna, Italy.)

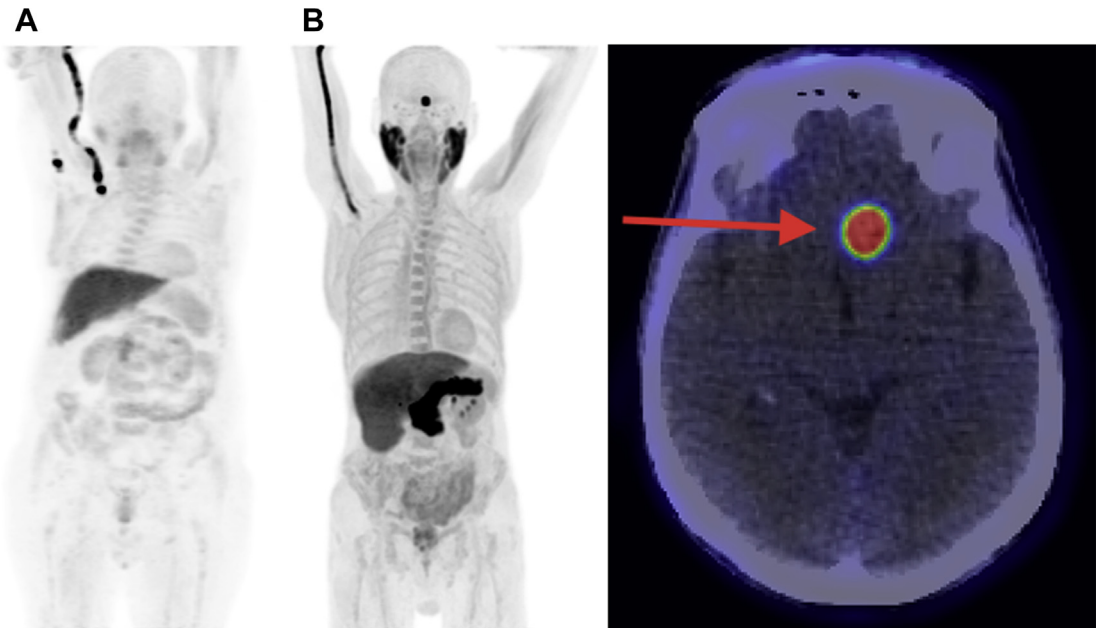


Fig. 7. Variants and pitfalls. (A) ^{18}F fluciclovine uptake along the vessel of intravenous administration. (B) ^{18}F fluciclovine avid meningioma. It is well established that physiologic tracer biodistribution in normal brain is very low or absent. In this case, PET/CT images showed intense and focal brain uptake ($\text{SUV}_{\text{max}} = 17$, MIP and transaxial fused; red arrow) in keeping with known meningioma. (Courtesy of [A] Dr Cristina Nanni, Programma di ricerca Regione-Università 2010-2012 Regione Emilia Romagna-Bando Giovani Ricercatori, Bologna, Italy; and [B] Dr Lucia Zanoni, Programma di ricerca Regione-Università Area 1-Bando Giovani ricercatori "Alessandro Librati" 2013, Bologna, Italy.)

SUMMARY

Fluciclovine is currently FDA approved for the localization of recurrent prostate cancer in a patient with elevated PSA. Based on comprehensive clinical data, fluciclovine is beneficial in the identification of disease even when other conventional imaging is negative. Knowledge of normal physiologic distribution and variants as well as typical patterns of prostate cancer spread is important for proper interpretation of fluciclovine PET.

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