

Best Practices of ¹⁸F-Fluciclovine PET/CT Imaging for Recurrent Prostate Cancer: A Guide for Technologists

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Abstract

Fluciclovine is an FDA approved PET tracer indicated for patients suspected to have recurrent prostate cancer based on PSA rise after prior therapy. The performance of fluciclovine PET/CT is significantly different from that of FDG and requires special attention to patient preparation, technique of injection, and imaging time. This manuscript aims to provide nuclear medicine technologists with the best practice guidelines of fluciclovine PET/CT protocol.

Key Words: FACBC, Fluciclovine, PET/CT, Prostate cancer, Axumin

Introduction

Fluciclovine (^{18}F -fluciclovine, FACBC, Axumin $\text{\textcircled{R}}$) is an amino acid analogue PET radiotracer that was approved in 2016 by the US Food and Drugs Administration (FDA) for imaging of patients with suspected recurrent prostate cancer based on elevated prostate specific antigen (PSA) after therapy.

In prior clinical trials, fluciclovine PET/CT demonstrated higher diagnostic performance in the localization of recurrent prostate cancer along with higher specificity in small nodal disease detection when compared to conventional imaging modalities. (1-3) When compared to $^{11}\text{C}/^{18}\text{F}$ -choline, fluciclovine had similar to slightly higher diagnostic performance in recurrent prostate cancer. (4) Preliminary data of the newly investigated PSMA- ligand PET tracers showed higher diagnostic performance in recurrent prostate cancer, compared to fluciclovine. (5) More conclusive prospective clinical studies comparing PSMA to fluciclovine are soon to be published. For therapy planning in recurrent prostate cancer patients, fluciclovine PET/CT detected additional findings leading to major changes in management. (6,7)

Historically, ^{18}F - fluorodeoxyglucose (FDG) was the only FDA approved and the most clinically used PET radiotracer for cancer imaging. Although having clinical experience with FDG PET/CT might provide overall knowledge on the standard operating procedure of PET imaging, fluciclovine is a new PET radiotracer with a different imaging protocol (Table 1). Thus, it is important to provide adequate training for all the staff involved in fluciclovine image acquisition to ensure consistency and a high level of image quality.

Since the FDA approval of fluciclovine for clinical use, our institution has imaged over 240 patients, ranking us as one of the largest providers of fluciclovine PET/CT services in the Mid-Western United States. Also having board certified nuclear medicine physicians with an average of 10 years of combined expertise in research and clinical interpretation of fluciclovine PET/CT images, we would like to share our wealth of knowledge on fluciclovine PET/CT imaging with an emphasis on the factors that may affect image quality and interpretation. The purpose of this guide is to provide technologists with best practice knowledge on fluciclovine PET/CT imaging for recurrent prostate cancer.

Patient Scheduling

Currently, the only FDA approved and reimbursable indication for fluciclovine PET/CT is restaging patients with clinical suspicion of recurrent prostate cancer based on a rising PSA level after prior treatment(s). While ordering the study, both the referring physician, and the nuclear medicine physician must ensure that the fluciclovine PET/CT study is ordered for the appropriate reason to prevent challenges with insurance approval. Aside from the general indication of cancer restaging, any other clinical questions should also be noted. While scheduling the fluciclovine PET/CT scan, it is essential to remember that amino acid transporters are also upregulated in inflamed cells, although to a lesser extent than that of prostate cancer cells.(8) At this time, there is no dedicated study evaluating the influence of recent procedures on fluciclovine uptake, and no official recommendation has been made on the optimal wait time for fluciclovine imaging after an intervention. However, to keep an optimal tumor to

background ratio, it is reasonable to schedule the fluciclovine PET/CT scan at least 2 weeks after an intervention to allow time for resolution of any inflammation.

After the appropriate indication is confirmed and a date is scheduled, the fluciclovine dose needs to be pre-ordered through the national ordering department for fluciclovine. Depending on the regional demand, the order should be placed at least 48 h prior to the scheduled date. However, this can be site specific.

Patient Preparation

According to the standardized protocol, patients are recommended to need to fast for at least 4h prior to injection, including water restriction. The altered biodistribution of fluciclovine in a non-fasting population is not well investigated, compared with FDG radiotracer. Although it is recommended to reschedule the non-fasting patients, this should be discussed with the interpreting physician as exceptions may be made. In such case, a careful review of the image quality by the interpreting physician should be done. There is currently no known contraindicated medications; therefore, patients can take their prescription medications as usual with sips of water. There should be no form of exercise or physical exertion for 24 h prior to the time of imaging. Excessive exercise may potentially cause increased muscle uptake that could degrade the quality of the images. If possible, patients should be contacted and reminded of these instructions prior to the day of imaging.

On the day of imaging, the patient's compliance with the preparation instructions should be evaluated. In clinical experience, patients who voided just prior to fluciclovine

injection had higher early fluciclovine bladder excretion compared to those who did not void. Therefore, patients should be advised not to void immediately prior to injection and imaging.(9,10) For centers which perform the PET/CT scan with oral contrast, it is suggested that the patients be requested to refrain from voiding for a duration of 1 h after administration of oral contrast until the end of fluciclovine injection and imaging.(9) For patients with Foley catheter, no specific intervention is required. The ability to lie still for the duration of imaging (approximately 30 mins) is important to avoid motion artifacts. Therefore, co-morbidities that may pose challenges for imaging by preventing the patient from lying flat and any adjustments needed to accommodate for this should be communicated to the interpreting physician.

Studies have shown that parameters such as PSA and Gleason score have a positive correlation with the detection of prostate cancer recurrence, with a higher risk of having bone metastasis at $PSA > 20$ ng/ml.(11) For fluciclovine prostate imaging, PSA demonstrated a strong linear correlation with positive scans.(12) It is therefore advisable to complete a prostate cancer information questionnaire including details on Gleason score, current, and prior lowest (nadir) PSA values, use of hormonal therapy (current or past), prior therapy (prostatectomy, radiation therapy, cryotherapy, etc.), known metastatic disease, and availability of prior scans. Having such information could help guide the interpreting physician during final image interpretation, especially in equivocal cases.

Radiopharmaceutical Injection

Fluciclovine is a synthetic amino acid radiotracer with a half-life of about 110 min. This allows for same-day delivery of the tracer from a local distributor. Standard radiation safety and radiopharmaceutical administration precautions should be followed during the handling and injection of fluciclovine. According to the guidelines, the recommended injection dose per patient is 10 mCi (370 MBq) +/- 20%.

The fluciclovine is injected intravenously while the patient is in supine position within the PET/CT scanner. Although the mechanism is not well understood, the radiotracer uptake may be seen along the injected vein (Figure 1A-B). To minimize this phenomenon, it is recommended to inject the fluciclovine with arms down. Injection via the left arm may lead to left subclavian vein uptake. The uptake may appear as local focus of supraclavicular uptake and may mimic the presence of metastatic left supraclavicular lymph node, also known as Virchow's lymph node. Therefore, it is preferable that fluciclovine be injected into the right arm. The presence of supraclavicular metastatic lymph node in prostate cancer is not common, but may be seen in rare cases (Figure 1C-D) and should not be confused with vein uptake. Following the fluciclovine injection, it is recommended that an intravenous sterile 0.9% saline flush should be administered to ensure full dose delivery. After injection, the arms are positioned above the head. The remaining dose within the syringe is assayed to determine tracer residual activity. The assayed, residual and net administered dose as well as injected site should be recorded.(9) Subsequently, the net administered dose will be used for the SUV calculation.

Patient positioning

Unless otherwise required due to patient's clinical limitations, the recommended position for imaging is supine with arms up above the head (Figure 2)

Image Acquisition – CT scan

A CT scan for anatomic correlation and attenuation correction is done per site standard from mid-thigh to the skull base. The use of IV or oral contrast for the attenuation correction CT scan is per site standard. However, it is to be noted that the density of the contrast may result in an attenuation correction artifact.(13) If contrast is used, the CT images should be obtained after the PET acquisition to minimize the diuretic effect of the contrast on fluciclovine. (9) High-quality CT scan is also not mandatory but preferable for better characterization of small suspicious structures. In order to prevent respiration artifact from rapid breathing, patients should be advised to use shallow breathing patterns on both the CT and the PET imaging (Figure 3). In challenging cases, respiratory gated acquisition of PET/CT can be done. (9)

Image Acquisition – PET scan

Due to rapid fluciclovine kinetics, the highest tumor-to-normal background tissue is seen between 4-10 min after injection. Therefore, to maximize the early imaging period, it is recommended to start PET acquisition caudocranially from mid-thigh at 3-5 min (target 4 min) post injection with the bed positions set such that the prostate gland is in the middle of the first bed position. Setting the bed position as such without

excluding part of the lower pelvis can be challenging in some individuals. Hence, having the prostate gland within the middle to end of the first frame is also acceptable.

Although the company guidelines advice 5 min per bed position in the pelvis followed by 3-5 min per bed position up to the base of the skull, image acquisition is scanner- and site- dependent. At our center, using a Philips Ingenuity Time of Flight (TOF) PET/CT scanner, we use 3.5 min per bed position for the first 3 bed positions, followed by 3 min per bed position up to skull base. However, 2-5 min per bed position may be adequate using TOF and/or digital PET/CT scanners. For quality purpose, the imaging start and end times must be recorded. The entire imaging procedure is expected to take approximately 25- 30 mins per patient. In rare situations where the image acquisition is delayed such as in the case of a claustrophobic patient, scanner malfunction, etc. the sensitivity of the exam may decrease. Therefore, if the final images do not answer the clinical question, the patient will have to be rescheduled for a repeat study. Fluciclovine PET/CT can be safely repeated in 24 h after the prior injection.

Summary of patient preparation, fluciclovine injection, PET/CT acquisition, imaging pitfalls and how to avoid them, are summarized in the “outline of best practice guide for technologists performing fluciclovine PET/CT imaging”, section.

Quality Control

According to the ACR technical standards, quality control for fluciclovine PET is no different from other PET imaging such as FDG PET/CT.(9)

Normal Biodistribution of Fluciclovine

A detailed description of the normal biodistribution of fluciclovine has been published.⁽¹⁴⁾ The liver and pancreas demonstrate the most intense fluciclovine uptake, followed by moderate uptake in the marrow, pituitary, and salivary glands. Mild uptake is seen in the muscle and variable mild to moderate activity is also seen in the small bowel. The lowest fluciclovine activity is seen in the brain and lung parenchyma (Figure 4). Fluciclovine is slowly eliminated through the renal system. Therefore, over time, urine excretion of fluciclovine into the bladder is expected.

Imaging Interpretation

Fluciclovine PET/CT image interpretation was previously published. ^(3,9) Additional resources for reader training are available online through the Society for Nuclear Medicine and Molecular Imaging (SNMMI) website. Emphasis is placed on the localization of lesions with visually increased uptake (with the assistance of quantitation) to improve the specificity of disease detection. For quantitation evaluation, fluciclovine uptake is measured as maximum Standard Uptake Value (SUV_{max}) within a region of interest (ROI) drawn on the target lesion. This is compared to mean Standard Uptake Value (SUV_{mean}) of target background structures; distal abdominal aorta (preferred at the same bed position as the lesion), marrow (L3 vertebra) and Liver. Any target lesion with visualized uptake above that of marrow or liver is considered highly suspicious for malignancy. However, for lesions or lymph nodes < 1 cm on largest diameter, the SUV_{max} may be underestimated due to volume averaging. Therefore, sub-centimeter

lesions are considered suspicious for malignancy if the uptake is significantly higher than the blood pool and visually approaching that of marrow.

Due to the relatively higher physiologic uptake of fluciclovine in the liver and bone marrow, detection of metastatic liver lesions can be challenging.(15) Appropriate liver windowing is recommended to improve visualization of metastatic bone and liver disease. For lytic or CT occult bone lesions, focal intense fluciclovine uptake is considered suspicious for malignancy. On the contrary, dense sclerotic lesions may demonstrate falsely mild to no uptake.(1,2,4,16,17) With unpublished experience, we learned that focal intense fluciclovine uptake within the acetabulum and iliac bones without abnormal CT findings has a high false positive rate. Hence, in some cases, further evaluation of bone metastasis with MRI and bone SPECT or PET scans should be considered.

Fluciclovine Pitfalls

Common findings that may mimic diseases on fluciclovine PET/CT have also been published.(14) Although fluciclovine has a high detection rate for prostate cancer, non-specific uptake has been reported in inflammatory and benign processes. Most commonly seen is bilateral uptake in inguinal lymph nodes (Figure 5). Since prostate metastatic disease to inguinal lymph nodes is highly unlikely, these are mostly deemed benign. However, a unilateral inguinal lymph nodes uptake may be suspicious in the correct clinical setting. For patients who underwent radiation therapy as their initial management for prostate cancer, diffuse uptake within the treated prostate may also be nonspecific.

The secretion of fluciclovine into the ureters may mimic the presence of nodal disease. It is therefore important to identify the course of the ureter to delineate ureteric uptake from true nodal disease. Fluciclovine low bladder secretion over time makes it ideal for the evaluation of pelvic malignancy such as prostate cancer. (8,14) In clinical practice, however, a higher level of bladder uptake is being reported. (12) Higher bladder activity is noted in patients who voided just prior to fluciclovine injection compared to those who did not void (Figure 6). Hence, it is recommended to avoid voiding at least 30 min – 1 h prior to fluciclovine injection.(9,12,18,19)

Conclusion

Fluciclovine is a new FDA approved PET radiotracer for the restaging of patients with suspected recurrent prostate cancer based on a rise in PSA level after local or systemic therapy. As one of the busiest fluciclovine PET-CT imaging centers, we provide our best practice guidelines for the performance of fluciclovine PET-CT to ensure quality images for disease detection. This includes proper patient preparation, positioning, fluciclovine injection and imaging techniques to prevent artifacts and image misinterpretation.

DISCLOSURE

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The Outline of Best Practice Guide for Technologists Performing Fluciclovine PET/CT Imaging

Fluciclovine is an amino-acid based PET radiotracer that has higher diagnostic performance in prostate cancer compared to conventional imaging with especially higher specificity in the detection of nodal disease in recurrent prostate cancer.

Indications

- FDA approved for restaging of patients that are suspected to have recurrent prostate cancer based on a rise in PSA level after therapy.

Contraindications

- None

Patient preparation

- Fast for at least 4 h prior to injection of fluciclovine. Prescribed medications can be taken with sips of water only.
- Avoid exercise or physical exertion 24 h prior to the time of injection
- Advise not to void at least 1h prior to fluciclovine injection and imaging.
- Establish IV access, preferably in the right arm.

Radiopharmaceutical administration

- The recommended dose is approximately 10 mCi /370 MBq (+/- 20%) diluted with 0.9% normal saline up to 10 ml.

- Inject intravenously, preferably in the right arm while lying supine with arms down at the side. After injection, flush with 0.9% normal saline to ensure full dose delivery.
- Raise the patient's arms above the head in a ready position for imaging. If this position is challenging for the patient, an alternative and comfortable position with arms down can be used.

Image acquisition instructions

CT imaging

- After the fluciclovine injection, acquire CT scan from mid-thigh to skull base for anatomic correlation and attenuation correction.
- In cases where CT with IV contrast is required, the CT acquisition should be performed after the PET, due to the possible diuretic effect of IV contrast.

PET imaging

- Perform a scout view and set the limits of acquisition from mid-thigh to skull base.
- Set the bed positions such that the prostate is within the center of the first bed position.
- Start imaging 3-5 min (with a goal of 4 min) after fluciclovine injection to avoid abnormal biodistribution.
- Although the recommendation is to acquire images at 5 min per bed position in the pelvis followed by 3-5 min per bed position up to the base of the skull, PET/CT acquisition is site and scanner dependent. See main text for example.

- For quality and accuracy, have a pre-set fluciclovine specific imaging protocol on the PET/CT scanner.
- After image acquisition, check images for any errors or artifacts.

Pitfalls and how to avoid them

The urinary bladder excretion of fluciclovine poses a diagnostic challenge:

- Encourage patients to refrain from voiding before the injection of fluciclovine, to significantly reduce urinary bladder excretion.

For PET/CT scan with contrast, patients should be encouraged to refrain from voiding 1h prior to injection until completion of fluciclovine PET/CT scan. Fluciclovine uptake by the injected vein wall in the left arm can mimic the presence of metastatic left supraclavicular node (Virchow's node).

- Injection into the right arm is preferred.
- Inject while the patient's arms are down.
- After injection, flush with saline before lifting the arms above the head in an appropriate position for imaging.

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FIGURES AND LEGENDS

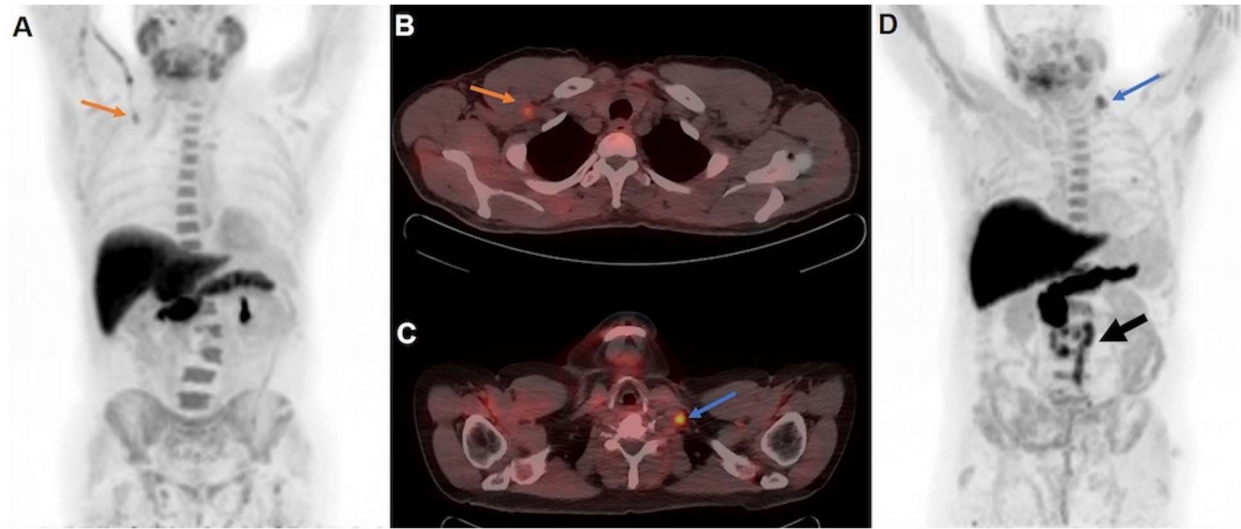


Figure 1: Fluciclovine IV injection via the right antecubital vein demonstrates increased fluciclovine uptake in the right axillary vein (A, Maximum Intensity Projection, MIP, orange arrow); A focal uptake in the subclavian space which may mimic or mask metastatic lymph node uptake (B, PET/CT transaxial image, orange arrow). Fluciclovine uptake patient who injected via the right side antecubital vein demonstrates focus of increased uptake in the left supraclavicular space correlated to an enlarge suspicious lymph node (C, PET/CT transaxial and D, MIP image, blue arrow). Additional diffuse retroperitoneal metastatic lymph nodes are noted (small black arrow).

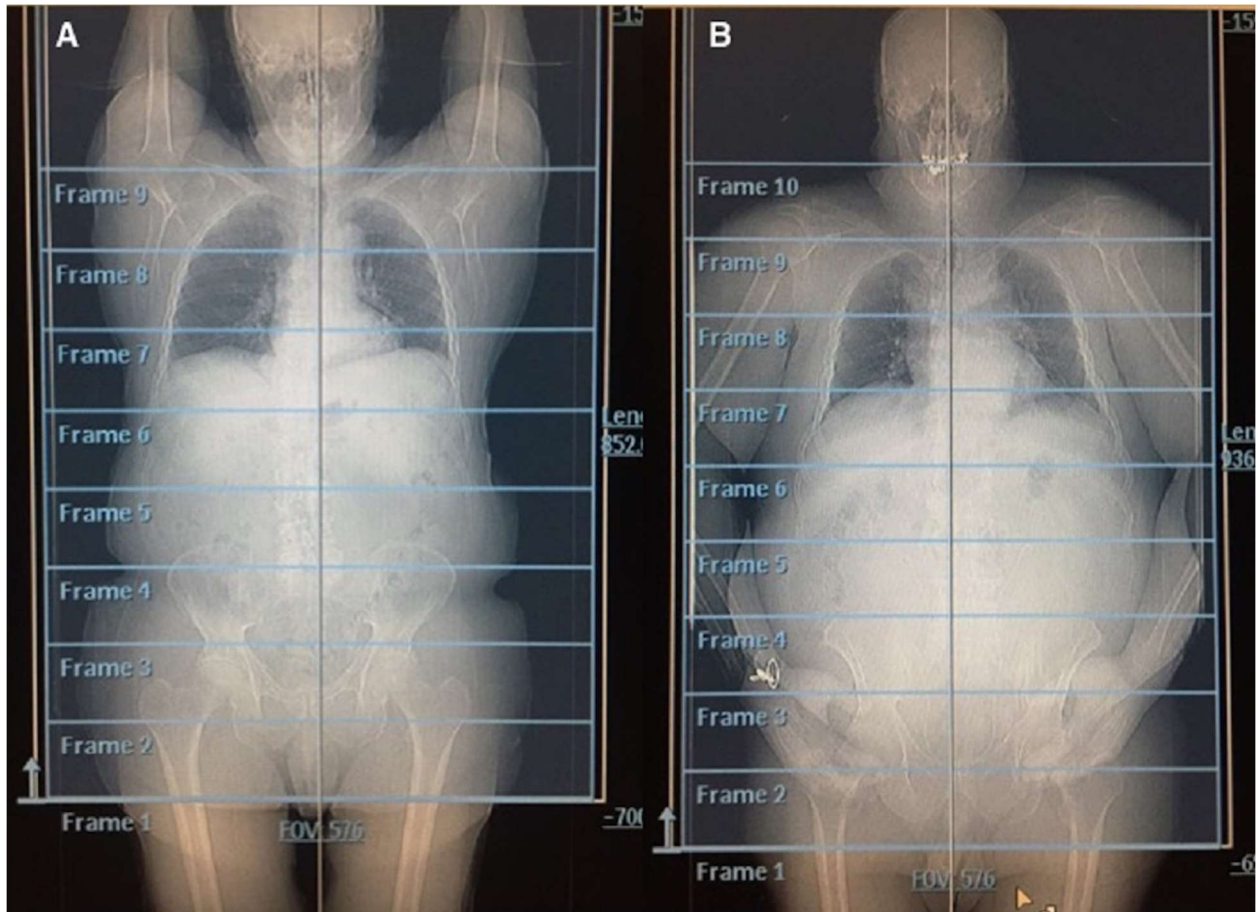


Figure 2: Scout images demonstrating the recommended positioning of a patient with arms up (CT scout image); alternative less preferred position, is with arms down (B, CT scout image).



Figure 3: PET MIP images. Respiration artifact from rapid breathing pattern on fluciclovine PET showing as artificially decreased tracer uptake by the liver dome.



Figure 4: PET MIP images. Normal biodistribution of fluciclovine with the highest uptake within liver and pancreas.

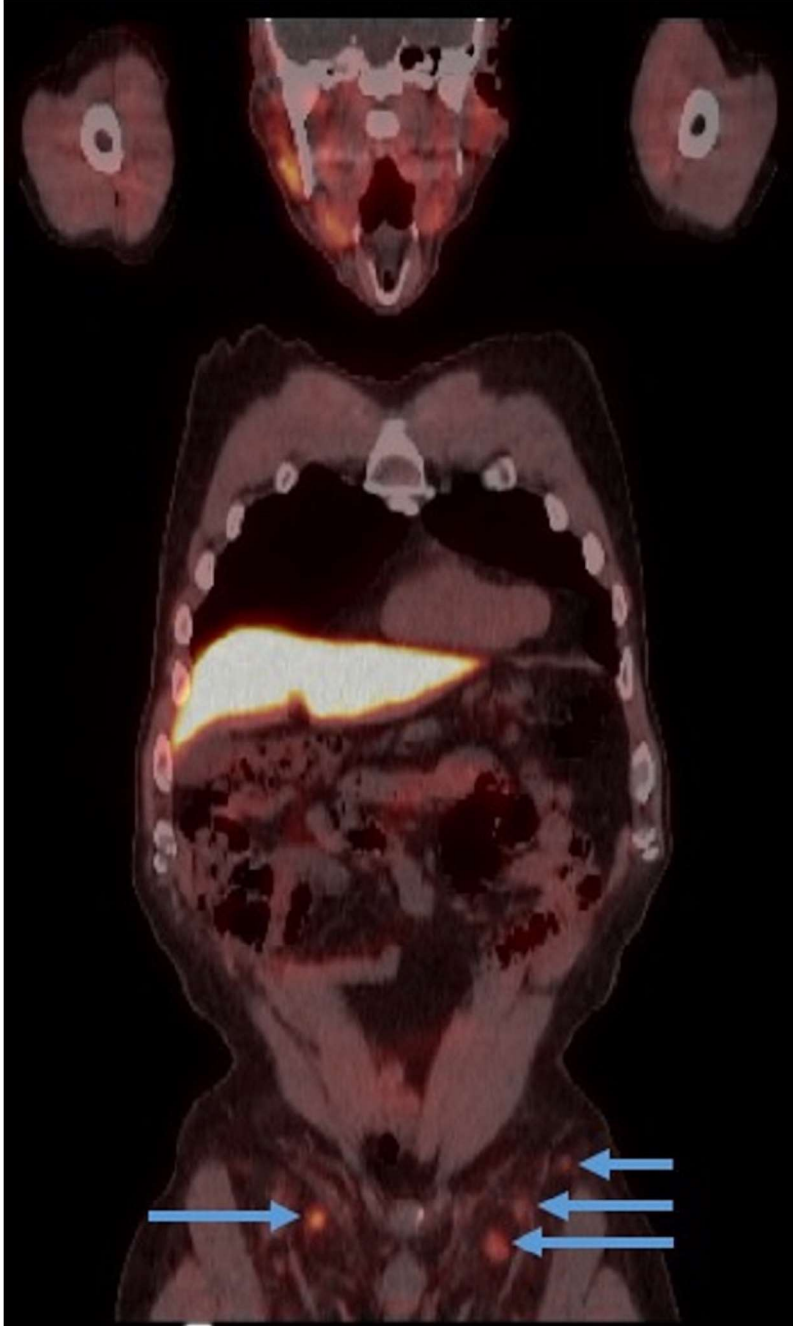


Figure 5: Fluciclovine PET/CT demonstrating moderate uptake in reactive bilateral inguinal lymph nodes (arrows).



Figure 6: Fluciclovine PET-CT coronal images demonstrating A: Mild ($SUV_{mean} > \text{blood pool}$) and B: Moderate ($SUV_{mean} > \text{Marrow} < \text{Liver}$) urine radioactivity in patients who did not void prior to the scan compared with C: Intense ($SUV_{mean} > \text{liver}$) urine radioactivity in patient who voided prior to the injection of fluciclovine.

Table 1: Differences between the imaging protocol of fluciclovine PET/CT and FDG PET/CT

	Fluciclovine PET/CT	FDG PET/CT
Patient preparation	Fast for at least 4h including water restriction	Fast for at least 4h with no water restriction
	Encourage patients not to void 1hr prior to fluciclovine injection and imaging	The patients should void immediately prior to image time.
Injection site	Right arm	Right or left arms (if applicable, contralateral arm of the cancer side)
Image acquisition	Start PET at 4 minutes post injection	Start image 30-90 minutes after injection
	Image caudocranially, from mid-thigh to skull base	Image craniocaudally (field of image is cancer specific)