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GUIDELINES

[^{18}F]Fluciclovine PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging—version 1.0

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Abstract

The aim of this guideline is to provide standards for the recommendation, performance, interpretation, and reporting of [^{18}F]Fluciclovine PET/CT for prostate cancer imaging. These recommendations will help to improve accuracy, precision, and repeatability of [^{18}F]Fluciclovine PET/CT for prostate cancer essentially needed for implementation of this modality in science and routine clinical practice.

Keywords [^{18}F]Fluciclovine · PET · Prostate cancer · Staging · Restaging · Guideline

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Preamble

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international non-profit scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine.

The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review.

The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question. The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine includes both the art and the science of the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

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Introduction

Anti-1-amino-3-fluorocyclobutane-1-carboxylic acid labeled with [^{18}F]Fluorine previously referred to as [^{18}F]Fluciclovine has emerged as a useful molecular imaging agent in patients with prostate cancer. [^{18}F]Fluciclovine is a leucine analogue which similar to several other radiolabeled amino acids shows high uptake in cancer where increased protein turnover and nucleotide synthesis characterize the metabolic demands of the proliferating tissue. The US Food and Drug Administration (FDA) approved [^{18}F]Fluciclovine in May 2016 and the European Medicines Agency (EMA) in May 2017 for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated prostate-specific antigen (PSA) levels following prior treatment [1].

Development of [^{18}F]Fluciclovine during the late 1990s followed earlier encouraging oncologic studies on [^{11}C]-labeled unnatural amino acid 1-aminocyclobutane carboxylic acid (ACBC) [2] and resulted in the report of the first human study of [^{18}F]Fluciclovine PET in human glioma in 1999 [3]. Later, high uptake of [^{18}F]Fluciclovine in experimental and human prostate cancer and its lymph node metastases was found [4, 5], and since then, the tracer has been evaluated under different clinical scenarios in patients with local, regional, and advanced prostate cancer. Currently, in the USA, it is more widely available than [^{68}Ga]- or [^{18}F]-labeled prostate-specific membrane antigen targeting radiopharmaceuticals while the latter, in turn, is the first choice for prostate cancer imaging in corresponding situations in Europe [6]. While [^{68}Ga]- and [^{18}F]-PSMA including its different ligands and[^{18}F]Fluciclovine have completely different mechanisms of uptake, it must be recognized that preference of tracer may depend on the clinical question and disease status. It's important to point out that PSMA-targeted PET agents are currently not approved in Europe and the USA.

The uptake of [^{18}F]Fluciclovine is mediated by sodium-dependent (Na+) and independent (Na−) amino acid transport systems [7–9]. In prostate cancer, an important Na+ transporter appears to be ASCT2 (SLC1A5) (alanine-serine-cysteine transporter) [10] and that of Na−, LAT1 (SLC7A5) (large amino acid transporter), [11], although other leucine transporters may prove significant due to clonal heterogeneity and differences in androgen sensitivity [12]. ASCT2 is the principal glutamine transporter and LAT1 transports all essential neutral amino acids including other PET imaging agents such as [^{18}F]Fluoroethyltyrosine (^{18}F-FET) and [^{11}C]Methionine (^{11}C-MET) [9]. Since [^{18}F]Fluciclovine is not a substrate for intracellular metabolism, rapid efflux via the same transporters contributes to clearance of tracer where ASCT2 and LAT1 as obligate exchangers are essential to equilibrate intracellular amino acid pools [13]. Of interest is the bidirectional transport of leucine and glutamine where a reciprocal amino acid exchange in cancer cell maintains the downstream activity of the mechanistic target of rapamycin (mTOR) which regulates protein translation, growth, and apoptosis [14, 15]. In recurrent and castration-resistant prostate cancer, both Na+ and Na− transport systems continue to contribute to [^{18}F]Fluciclovine uptake while androgen receptor-mediated expression of amino acid transporters have been observed over the course of the disease [11, 16, 17]. The high impact of the Na^+system in [^{18}F]Fluciclovine imaging of prostate cancer should be noted considering the earlier tracer development focusing on the Na-transport system L in other solid tumors [9].

Goals

This guideline intends to assist physicians in recommending, performing, interpreting, and reporting the results of [^{18}F]Fluciclovine PET/CT (or PET/MRI) for prostate cancer. It covers patient selection, image acquisition, interpretation, and reporting. This document aims to provide clinicians with the best available evidence, to inform where robust evidence is lacking, and to help them to deliver the best possible diagnostic efficacy and study quality for their patients.

This guideline also presents standardized quality control/quality assurance (QC/QA) procedures and imaging procedures for static [^{18}F]Fluciclovine PET/CT. Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of [^{18}F]Fluciclovine PET/CT within multicenter trials. A standardized imaging procedure will help to promote the appropriate use of [^{18}F]Fluciclovine PET/CT and enhance subsequent research.

Quantification of [^{18}F]Fluciclovine PET/CT is defined here as measuring relative [^{18}F]Fluciclovine concentrations using a standardized uptake value (SUV) because SUV represents the most commonly used semi-quantitative parameter for analysis of tracer uptake.

Definitions

Definitions are based on the EANM procedure guidelines for tumor PET imaging, version 2.0 [18]:

PET/CT: An integrated or multimodality PET/CT system is a physical combination of PET and CT which allows sequential acquisition of PET and CT portions. The patient remains in the same position within both examinations. [^{18}F]Fluciclovine PET/CT examination may cover various coaxial imaging ranges. These are described as follows (defined in Current Procedural Terminology 2016):

Whole-body PET: From the top of the head through the feet.

Skull base to mid-thigh PET: Base of the skull to mid-thigh. Covers most of the relevant portions of the body in many oncological diseases (standard for both Europe and the USA). If indicated, cranially extended imaging may also cover the brain in the same scan (vertex to mid-thigh). In PET/CT studies, attenuation correction and scatter correction are performed using the CT data.

Computed tomography (CT): a combined X-ray source and detector rotating around the patient to acquire tomographic data. CT generates three-dimensional images of tissue density, which allows for attenuation correction of PET and tumor visualization with a high spatial resolution.

A PET/CT examination can include different types of CT scans depending on the CT characteristics, the dose, and the use (or not) of oral and/or intravenous contrast agents.

Low-dose CT scan: CT scan that is performed only for attenuation correction (CT-AC) and anatomical correlation of PET findings (with reduced voltage and/or current of the X-ray tube settings), i.e., a low-dose CT is not intended a priori for a dedicated radiological interpretation.

Diagnostic CT scan: CT scan with or without intravenous and/or oral contrast agents, commonly using higher X-ray doses than low-dose scans. Diagnostic CT scan should be performed according to applicable local or national protocols and guidelines.

[^{18}F]Fluciclovine pet diagnostic performance

Definitions

The American Urological Association (AUA), also EAU, 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 [19]. The American Society for Therapeutic Radiation and Oncology (ASTRO) + RTOG defines biochemical recurrences as three consecutive PSA values above the nadir in patients treated 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 consistent with biochemical recurrence (Phoenix definition) [20].

Indications

Restaging

[^{18}F]Fluciclovine PET sensitivity for detecting recurrent disease increases with higher Gleason scores, higher PSA levels, and possibly shorter PSA doubling times [21, 22]. Correctly characterizing recurrent prostate carcinoma requires identifying whether the disease is confined to the prostate/prostatic bed or is extraprostatic. In patients with an intact prostate, [^{18}F]Fluciclovine PET demonstrates high sensitivity and low specificity in identifying local recurrent disease with a sensitivity of 88–90% and specificity of 32–40% [23, 24]. The low specificity in patients with intact prostate is likely in part due to submaximal local therapy with residual viable prostate tissue and associated benign uptake. Thus, histological confirmation is recommended for [^{18}F]Fluciclovine uptake in the intact prostate gland.

In recurrent extraprostatic nodal disease, [^{18}F]Fluciclovine demonstrates high specificity and mid-to-high sensitivity depending on PSA level. The overall sensitivity, specificity, and accuracy of [^{18}F]Fluciclovine in the detection of recurrent extraprostatic disease are 55%, 97%, and 73%, respectively [24]. A large multisite study of 596 patients similarly found a high positive predictive value (PPV) of 92.3% in the detection of extraprostatic disease [23]. In patients with PSA values < 1 ng/mL, [^{18}F]Fluciclovine has relatively low sensitivity for extraprostatic disease ranging from 21 to 39% [23, 25]. In patients with PSA: from 0.8 to 2.03 ng/mL sensitivity is overall approximately 60% (45% for extraprostatic recurrence); from 2.04 to 6 ng/mL, it is approximately 75% (approximately 45% for extraprostatic disease); higher than 6, it is approximately 85% (approximately 60% for extraprostatic disease) [23].

If Gleason Score (GS) is analyzed, the whole body positivity doesn't change between GS lower and equal to 6, 7, and 8 and higher or equal to 9. However, for lower GS, the detection rate is higher for prostate bed relapse as compared with extraprostatic areas (approximately 60% vs approximately 25%) while this ratio is opposite for high GS (approximately 20% vs 60%).

Detection of prostate cancer bone lesions

[^{18}F]Fluciclovine has been shown to accumulate in osteolytic and osteosclerotic lesions that have a high cellular density [26]. [^{18}F]Fluciclovine typically demonstrates intense focal uptake in lytic prostate metastatic osseous lesions and variable activity in sclerotic lesions. Metastatic bone lesions may on [^{18}F]Fluciclovine PET be seen prior to changes on CT. Because there may be mild to no [^{18}F]Fluciclovine uptake in dense sclerotic lesions, supplemental skeletal-specific imaging is recommended for those patients with suspicious sclerotic lesions on CT without [^{18}F]Fluciclovine activity [27]. Unfortunately, most early clinical trials utilized a positive bone scan as exclusion criteria. Lacking evidence, [^{18}F]Fluciclovine PET is not recommended as a replacement for bone scintigraphy or ^{18}F-NaF PET/CT.

Change in radiation therapy treatment and target volume definition

Salvage radiation therapy (RT) to the prostate or prostate bed and pelvis is commonly performed in patients with biochemical failure [24, 28]. Conventional imaging such as CT and MRI is routinely used for the clinical target volume definition. Despite the consensus guidelines for the definition of target volume published by the Radiation Therapy Oncology Group (RTOG) [29], the spread of disease may be underestimated, which will result in subsequent biochemical failure. With the introduction of functional imaging such as [^{18}F]Fluciclovine PET/CT, more patients present with suspected extraprostatic disease [30]. The additional information gathered from the [^{18}F]Fluciclovine PET/CT scan may impact radiation treatment planning. A recent study reported a significant change in radiation planning in 40.5% (17/42) of patients with biochemical failure randomized to undergo [^{18}F]Fluciclovine PET/CT in addition to standard-of-care images prior to radiation therapy [21]. In 2/17 patients, radiation therapy was cancelled due to evidence of extrapelvic disease. In 15/17 patients, the pre-planning radiotherapy field was changed after [^{18}F]Fluciclovine PET/CT. The further analysis described a significant change in the target volume definition when the information from [^{18}F]Fluciclovine PET/CT was included in the treatment planning. A significant change in the radiation treatment planning was reported as well by the pivotal LOCATE trial on the impact of [^{18}F]Fluciclovine PET/CT on treatment of prostate cancer recurrence [30]. Out of 128 patients scheduled to receive radiation therapy, 65 had a major change in treatment plan involving a new treatment modality due to the results of [^{18}F]Fluciclovine PET/CT scan.

Procedure/specification of the examination

Necessary data for requesting ^{18}F-fluciclovine PET/CT

Requests for [^{18}F]Fluciclovine PET/CT should be accompanied by a concise summary of the patient's history with a focus on diagnosis, risk group, and oncological history. Aspects that should be considered in the review of the patient's files are given in the following list:

1. Indication for an imaging study
2. Prostate cancer-specific history:
   (a) Biochemical recurrence, in particular:
      i. PSA and PSA kinetics
      ii. Prior treatment and approximate dates (e.g., prostatectomy, external beam radiation therapy)
      iii. Risk group according to current EAU guidelines in prostate cancer
   (b) Current prostate cancer medications: androgen deprivation therapy (ADT) or other androgen receptor (AR)-targeted treatments. A recent history of chemotherapy, radium-223 or PSMA-targeted radioligand therapy
   (c) Relevant current symptoms (bone pain, frequent urination, nocturia, hematuria, dysuria, impotence, erectile dysfunction, or painful ejaculation)
   (d) Previous imaging findings and approximate dates
   (e) Relevant co-morbidities:
      i. Non-prostate malignancies
      ii. Allergies to [18F]Fluciclovine or any of the other ingredients of this medicine, i.e., sodium citrate, concentrated hydrochloric acid, and sodium hydroxide
      iii. Renal or hepatic impairment: to date, pharmacokinetics in these specific patients have not been characterized; careful consideration of the activity to be administered is advised.

Patient preparation

Patients should not undertake any significant exercise for at least a day before the [^{18}F]Fluciclovine PET/CT, because following strenuous exercise, there is an increase in the rate of protein synthesis and degradation and of amino acid transport which may cause an increase muscle uptake of [^{18}F]Fluciclovine.

Patients should fast for at least 4 hours prior to the scan. They may, however, drink sips of water if needed for administration of medications and to avoid dryness of the mouth. The patient should be asked not to void 30–60 min prior to injection unless it would prevent the patient from remaining still or completing the imaging.

The patient should be encouraged to be well-hydrated and urinate frequently during the first hours after the scan in order to reduce radiation exposure of the bladder.

Radiopharmaceutical

Product: [^{18}F]Fluciclovine is the international non-proprietary name (INN) for the active substance anti-1-amino-3-fluorocyclobutane-1-carboxylic acid labeled with fluorine-^{18}.

Radionuclide: fluorine-^{18}.

[^{18}F]Fluciclovine should be manufactured under good manufacturing practice (GMP) conditions and QC should follow the governing international pharmacopoeia monograph or national regulations, whichever is applicable.

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, [^{18}F]Fluciclovine is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorized in the EU [31, 32].

Recommendations for [^{18}F]Fluciclovine application and administered tracer activity

[^{18}F]Fluciclovine should be administered as a bolus intravenous injection by appropriately qualified healthcare professionals. The recommended maximum volume of injection of the undiluted product is 5 mL; however, it can be diluted with sodium chloride 9 mg/mL (0.9%) solution by a factor of 8 (dilution 1+7). The injection should be followed by an intravenous flush of sterile sodium chloride 9 mg/mL (0.9%) solution to maximize the use of dispensed activity. The recommended injected activity is 370 MBq (10 mCi). No dosage adjustment based on weight is recommended because an analysis of the potential impact of variations in body mass did not demonstrate any substantial changes in the effective radiation dose. In addition, no dosage adjustment is required for the elderly population. For the current indication of prostate cancer, there is no use of [^{18}F]Fluciclovine in children and adolescents.

Uptake time

Kinetic data in patients with prostate cancer was conducted in Phase 1 study GE148-001 [33, 34]. The results demonstrated that [^{18}F]Fluciclovine is preferentially taken up into prostate cancer cells compared with surrounding normal tissues. Tumors show rapid uptake, with the peak tumor-to-normal tissue contrast between 4- and 10-min post-injection, reaching a plateau which persists for approximately 30 minutes. Primary tumor efflux of [^{18}F]Fluciclovine begins within 15 min and a 61% reduction in mean tumor uptake is detected at 90 min. In lymph node metastases, uptake is also rapid but followed by a faster washout than in prostate tumor.

Thus, early image acquisition starting immediately following the initial injection is recommended. In particular, the goal is a 4-min interval for uptake time, with an acceptable range of 3 to 5 min (from the completion of the injection to the start of PET scanning, beginning from proximal thigh (inguinal lymph nodes included) and proceeding to the base of the skull. The interval between [^{18}F]Fluciclovine injection and imaging should be recorded.

[^{18}F]Fluciclovine PET/CT acquisition protocol and reconstruction

Imaging should start 3–5 min after the injection of [^{18}F]Fluciclovine, and a bolus injection should be performed with the patient positioned supine on the scanner table. The tracer should, when possible, be injected into the right arm with the arms down. Immediately after the injection, the arms should be raised and positioned above the head. When the patient is comfortably positioned, the CT scan should be performed, followed by the PET scan at 3–5 min post injection. An initial dynamic scan (0–5 min) of the pelvic region is optional.

The scan should be started on the pelvic region/proximal thigh including inguinal lymph nodes and prostate bed and to the base of the skull. For clinical reasons, the scan may be extended to the top of the skull. If for clinical reasons the lower extremities must be imaged, it should be performed as a separate acquisition immediately following the initial imaging, arms remaining by the sides for comfort.

If the start of the imaging for some reason is delayed for more than 20–30 min, the study is likely to have decreased lesion detection and the acquisition time per bed position should be equivalently increased. In cases of delayed scan performance, if the clinical question is not answered, a repeat scan should be considered.

While a small lesion seen on PET may be better characterized with a diagnostic-quality CT, both CT and PET acquisition parameters will be scanner- and institution dependent. Intravenous CT contrast is optional but seems to have a limited impact on image quality and interpretation and its use is of more logistic concern, though it is possible that diuresis from iodinated contrast may stimulate early radiotracer urinary excretion. Time-of-flight (TOF) PET with a reconstruction method including modeling of resolution degradation, often referred to as point spread function (PSF) reconstruction, may help with the detection of small lesions. A bone CT reconstruction algorithm in addition to the standard CT reconstruction is recommended. PET data should be fused with both standard and bone CT reconstructions.

PET/MRI may be used instead of or as a supplement to PET/CT in prostate cancer. Details about acquisition protocol and reconstruction for PET/MRI are beyond the scope of this guideline. For details, see relevant literature [33, 35, 36].

Documentation and reporting

Contents of the report

Study identification

The final report should include the full name of the patient, gender, medical record number, date of birth, and date of the examination.

Clinical information

As a minimum, a summary of relevant clinical history should include reason for referral and the specific question to be answered. The results of relevant diagnostic tests, especially PSA level and prior imaging findings, should be summarized. The type and date of comparison studies should be stated. If no comparison studies are available, a statement should be made to that effect. For further details, see paragraph above (necessary data for requesting [^{18}F]Fluciclovine PET/CT).

Technical details

Study-specific information should include the radiopharmaceutical, the amount of injected activity in megabecquerels (MBq) and/or millicuries (mCi), the route (intravenous) and anatomical site of administration, and the date and time of administration. Any dose infiltration should also be noted. The time interval between the administration of [^{18}F]Fluciclovine and the start time of the acquisition should be reported. The body parts that were covered should be described. Any non-standard position of the patient should be stated.

Camera manufacturer and PET reconstruction algorithm used should be stated. The direction and range the patient image was acquired should be stated (i.e., "images were acquired from the mid-thigh to the base of the skull"). If a non-optimized CT was performed for attenuation correction and anatomical registration of the emission images only, the description may be limited to a short statement including the mAs and kVP. If a diagnostic CT was performed, then a more detailed description of the CT protocol and anatomical findings should be provided. Dosimetry parameters should be included if required by national or local regulations. The report should state whether contrast-enhanced or non-enhanced CT was used for attenuation correction.

Description of the findings

Quality issues of the[^{18}F]Fluciclovine PET/CT, e.g., motion artifacts, halo artifacts due to high activity in the collecting urinary system, or CT attenuation artifacts (from attenuating materials), should be reported.

Interpretation

Multiplanar review and MIP of the [^{18}F]Fluciclovine PET/CT is recommended including the use of specific CT windowing optimized for soft tissue, the lung, bone, and brain when appropriate. For example, in post-prostatectomy, a review of sagittal images to detect abnormal uptake at the surgical anastomosis is especially helpful.

Review of the non-attenuation corrected images may be helpful in identifying artifacts or in cases of metallic implants (i.e., hip prostheses).

The study should be interpreted with knowledge of biodistribution of [^{18}F]Fluciclovine and use appropriate windowing. Both narrow and wide windowing should be utilized for a comprehensive review. For example, it is recommended that the study initially is viewed with the pancreas and liver as most intense organs. For liver review, a wider window setting should be used higher than SUVmax in the liver, as metastases may be obscured by high physiologic liver activity. For optimized lymph node detection, also consider narrower windows to optimize lesion detectability.

The study should also be interpreted by a physician with awareness of the pathophysiology of prostate cancer including the typical uptake patterns of prostate cancer locoregional and metastatic spread; for example, prostatectomy bed and deep pelvic lymph nodes versus peripheral inguinal or distal external iliac nodes. Interpretation is visual though SUV values may be reported for reference.

Biodistribution

Normal physiologic activity is present and most intense in the liver and pancreas (Fig. 1). Mild to moderate activity is typically seen in salivary glands, pituitary, lymphoid tissue of Waldeyer's ring, thyroid, breast parenchyma, esophagus, stomach, adrenal glands, bowel, and renal tissue. The urinary bladder wall may have physiologic mild to moderate diffuse activity as does periurethral tissue. While urinary excretion is

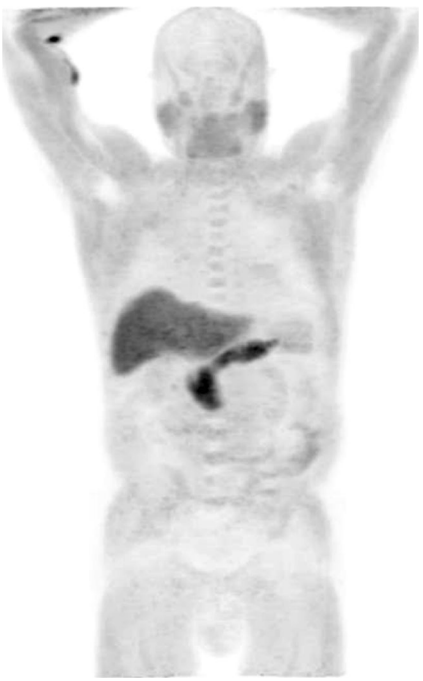

Fig. 1 Normal distribution of [^{18}F]Fluciclovine. Image was fully anonymized and the consent was waived

typically low, early urinary excretion with intense activity may be present in a subset of patients and could affect the evaluation of the prostate or prostate bed after prostatectomy, as well as the ureteral activity which should be not be confused with nodal uptake. Activity retained in the injected vessel frequently occurs and should also not be confused with pathology. The bone marrow may have heterogeneous activity more than that typically seen with FDG PET. For a more detailed discussion, the reader is directed to [37–39]. Brain parenchyma has a very low physiologic activity when the BBB is intact.

At early acquisition, the myocardium may present a mild tracer uptake, becoming more evident over time in more delayed acquisitions, in a manner similar to the muscle. Lung parenchyma has no uptake or uptake less than blood pool. Breast parenchyma has mild uptake but absent uptake or less than blood pool with increasing fatty change. Some degree of mild to moderate diffuse esophageal uptake is a variant of a normal distribution that can be found in approximately 50% of patients.

The liver and pancreas are the most intense organs on [^{18}F]Fluciclovine. Pancreatic activity is generally higher than that of the liver at early acquisition but by 15 min, it diminishes to or below that of the liver. The spleen and renal parenchyma have mild to moderate uptake and sometimes, a moderate excreted activity may be present in the proximal collecting system. The adrenals also have a mild uptake, while mild to moderate uptake can be found in the stomach, bowel, and colon.

Due to a low renal excretion of the tracer, bladder activity is typically absent or less than blood pool on early images but may increase over time in delayed acquisitions. Mild diffuse uptake in the bladder wall can also be seen on early sequences.

Usually normal prostate has mild uptake as well as at the urethral region (here, the uptake can be found in a linear configuration). No conclusive data are so far available on genital female organs due to lack of studies.

The red marrow demonstrates moderate and somewhat heterogeneous uptake, usually decreasing over time. The skeletal muscle also has mild uptake initially, with a tendency to increase over time and can be higher than the marrow at approximately 30–60 min after radiotracer injection [39].

Interpretative criteria

In general, increased uptake in soft tissue lesions is defined as uptake visually clearly above that of the bone marrow (preferred L3 vertebrae) for lesions larger than 1-cm longest dimension. Soft-tissue lesions which are smaller than 1-cm longest dimension are subject to partial volume effect, but in a typical location for metastases may still be interpreted as suspicious if uptake is visually equal to or approaches the marrow and significantly greater than blood pool. Note that criteria for scanners with PSF algorithms or Bayesian penalized likelihood reconstruction still need to be fully explored.

Specific interpretative criteria in usual sites of prostate cancer recurrence and metastases:

Bone marrow uptake (SUVmean) of vertebra L3 and abdominal aortic blood pool are recommended references.

Prostatectomy bed and seminal vesicles Sagittal and coronal images are especially useful.

- Focal uptake (SUVmax) equal to or greater than the bone marrow (SUVmean) is considered most characteristic for malignancy (or likely malignant, or suspicious for malignancy).
- If uptake is between blood pool and bone marrow, it does not meet criteria for malignancy but may still be reported as requiring close follow-up. MR correlation is especially helpful in this situation.
- If there is no increased uptake, findings should be reported as likely benign.
- In seminal vesicles, with or without a prostate, symmetric bilateral uptake similar to blood pool is likely physiologic. Asymmetric seminal vesicle uptake between blood pool and marrow may represent malignancy and MR should be considered for further evaluation.
- Uptake on anatomical correlate < 1 cm significantly greater than blood pool (i.e., close to the bone marrow) may also be considered suspicious for malignancy; MRI correlation is suggested.

Prostate (non-prostatectomy therapy such as radiotherapy, brachytherapy, cryotherapy, or HiFU (high-intensity focused ultrasound))

- Diffuse, focal, or multi-focal uptake greater than the bone marrow is considered most characteristic for malignancy (or likely malignant, or suspicious for malignancy).
- Uptake between blood pool and bone marrow does not meet criteria for malignancy but may still be reported as requiring close follow-up. MR correlation is especially helpful in this situation.
- If there is no increased focal uptake, findings should be reported as likely benign.
- If anatomical correlate for a focus of [^{18}F]Fluciclovine can be identified and the area of uptake is small (< 1 cm) and if the uptake approaches the marrow and is significantly greater than blood pool, it may also be considered suspicious for malignancy (due to partial volume effect, the threshold is lower).
- If calcification is associated with uptake, inflammation may be present. MR correlation is helpful in these situations.
- Note that anecdotally, median lobe uptake (central base invaginating into the bladder) has a higher false positivity

due to an increased presence of prostatic hypertrophy in this region.

Lymph nodes

- Uptake in lymph nodes equal to or greater than 1-cm longest diameter with a distribution typical for recurrent prostate cancer, equal to or greater than the bone marrow, is considered most characteristic for malignancy (or likely malignant, or suspicious for malignancy).
- If uptake is between blood pool and bone marrow, it does not meet criteria for malignancy but may still be reported as requiring close follow-up.
- If uptake is less than or equal to blood pool, node should be reported as likely benign.
- A small node (< 1-cm longest diameter) located in a distribution typical for recurrence and has uptake that approaches equal to or greater than the marrow (and is significantly greater than blood pool) is considered most characteristic for malignancy (or likely malignant, or suspicious for malignancy). (Due to partial volume effect, the threshold is lower.)
- If uptake is equal to or greater than blood pool but not approaching the marrow, it may be reported as not meeting criteria for malignancy but requires close follow-up.
- If uptake is less than blood pool, the node should be reported as likely benign.
- If uptake is seen in lymph nodes with an atypical location for recurrence (e.g., inguinal, distal external iliac, hilar, and axillary nodes), it may be considered suspicious for recurrence if seen in the context of other clearly malignant diseases. Otherwise, mild symmetric uptake in atypical lymph nodes may be considered physiologic.
- Distal external iliac nodes may also be suspicious for malignancy in isolation if uptake is greater than the bone marrow, and causes of false positivity are excluded such as recent procedures and/or presence of nearby vascular grafts or orthopedic hardware.
- A necrotic node may have false negative activity.
- Suspicious appearance on anatomic imaging such as round versus curvilinear nodes, grouped versus isolated nodes should be considered as factors in the interpretation of borderline lesions.

Bones

- Focal uptake clearly present on MIP or PET images is considered suspicious for malignancy.
- Lytic lesions tend to have greater uptake than sclerotic lesions.
- If a suspicious abnormality is seen on CT such as sclerosis without uptake, this could represent a false negative finding and further evaluation with alternative imaging modalities should be considered (MRI, NaF(^{18}F) PET/CT, conventional bone scan SPECT/CT, or PSMA if approved for use).
- Compared with FDG, [^{18}F]Fluciclovine has greater physiologic bone marrow heterogeneity. Careful PET windowing is helpful. Increased uptake in the bone may be present after trauma (including compression fractures).
- Areas of normal bone marrow regeneration (e.g., pelvis and proximal femurs) may also show increased physiologic uptake; consider MRI if no clear CT correlate, especially if the lesion is solitary(3).

Liver

- Focal uptake in the liver greater than that in normal liver tissue is considered suspicious for malignancy. Focal activity less than the normal liver (relatively photopenic) but higher than the bone marrow may also represent malignancy and should be further evaluated with anatomical imaging.

Incidental findings, normal variants, and important pitfalls

The reader should be well versed in the causes of false positive (FP) and negative findings of [^{18}F]Fluciclovine PET interpretation [1, 39]. In the prostate gland, potential reasons, for false positive uptake, include benign prostatic hyperplasia and post-radiation inflammation and fibrosis [40]. FP uptake in nodes may be due to acute and chronic inflammation and infection, especially if symmetric and in atypical locations for prostate cancer spread. [^{18}F]Fluciclovine uptake was also observed with inflammatory skin lesions, inguinal nodes due to ringworm infection, and musculoskeletal inflammation.

[^{18}F]Fluciclovine can be taken up by other cancer cells with upregulated amino acid transport such as breast cancer, lung cancer, colon cancer, lymphoma, hepatocellular carcinoma, multiple myeloma, squamous cell carcinoma of the scalp, and primary and metastatic tumors in the brain among others [3, 5, 39, 41–46]. Uptake in renal masses should be further investigated. As with FDG, any degree of [^{18}F]Fluciclovine uptake in a renal mass might represent malignant etiology.

Table 1 Estimated radiation-absorbed doses for adults receiving [^{18}F]Fluciclovine, following McParland et al. (34). The generic dosimetry table for ^{18}F-labelled amino acids from ICRP publication 128 (1)

Organ/tissue	Mean-absorbed dose unit administered activity (μGy/MBq)
Adrenal glands	16
Brain	9
Breast	14
Gallbladder wall	17
Lower large intestine wall	12
Small intestine wall	13
Stomach wall	14
Upper large intestine wall	13
Heart wall	52
Kidneys	14
Liver	33
Lungs	34
Muscle	11
Ovaries	13
Pancreas	102
Red bone marrow	25
Osteogenic cells	23
Skin	8
Spleen	24
Testes	17
Thymus gland	12
Thyroid	10
Urinary bladder wall	25
Uterus	45
Total body	13
Effective dose	22(μSv/MBq)

Organ/tissue		Absorbed dose per unit administered activity (μGy/MBq)			
		This work	Nye et al. [11]	Asano et al. [12]	ICRP publication 106 [27]
		Mean SD			
Adrenal glands		16.2			
Brain		8.7			
Breasts		13.7			
Gall bladder wall		16.7			
Gastrointestinal tract	Lower large intestine wall	12.5			
	Small intestine wall	13.2			
	Stomach wall	14.0			
	Upper large intestine wall	12.9			
Heart wall		51.7			
Kidneys		13.7			
Liver		33.5			
Lungs		34.5			
Muscle		10.6			
Ovaries		13.3			
Pancreas		102.2			
Red marrow		24.7			
Osteogenic cells					
Skin					
Spleen					

Table 1 (continued)

Testes			
Thymus gland			
Thyroid gland			
Urinary bladder wall			
Uterus			
Total body			
Effective dose (μSv/MBq)			
	Mean absorbed dose per unit administered activity (μGy/MBq)		
Organ/tissue	McParland [34]	ICRP128	
Adrenal glands	16 ± 0.5		19
Brain	9 ± 2		9.6
Breast	14 ± 10		9.5
Gall bladder wall	17 ± 0.2		19
Lower large intestine wall	13 ± 1		14
Small intestine wall	13 ± 1		27
Stomach wall	14 ± 1		15
Upper large intestine wall	13 ± 1		16
Heart wall	52 ± 11		22
Kidneys	14 ± 1		49
Liver	34 ± 4		35
Lungs	35 ± 5		23
Muscle	11 ± 1		10
Ovaries	13 ± 1		20
Pancreas	102 ± 31		140
Red marrow	25 ± 8		14
Osteogenic cells	13 ± 13		13
Skin	8 ± 1		8.4
Spleen	24 ± 12		25
Testes	17 ± 20		16
Thymus gland	13 ± 1		12
Thyroid gland	10 ± 1		21
Urinary bladder wall	25 ± 17		74
Uterus	45 ± 44		17
Total body	13 ± 0.2		11
Effective dose (μSv/MBq)	22 ± 2		23

Papillary renal cell carcinoma has been shown to have increased uptake, whereas clear cell carcinoma has uptake equal to renal parenchyma [45].

Benign bone lesions such as osteoid osteoma may have moderate uptake. Mild uptake may be seen in degenerative disk and facet disease, but this is less common and less intense than usually seen with ^{18}F-FDG. Intense though benign activity within a joint or at a muscular insertion has occasionally been observed. Benign meningioma may have intense uptake [47]. Pituitary and adrenal adenomas can have focal uptake greater than the surrounding tissue.

Summary and diagnosis/impression

The study should be clearly identified as normal or abnormal. Alternatively, an estimate of the likelihood of diagnosis and the differential diagnoses should be given. The reason for the study referral should be directly addressed. For prostate cancer imaging, it is recommended to structure the summary to the main tumor sites (local tumor involvement, lymph node, or bone metastases) and potential other lesions. Whenever possible, the report should provide a TNM stage including a statement whether there are categories of uncertainty. For further reading, see also the SNMMI's Procedure Standard for General Imaging and the Royal College of Radiologists' recommendations on reporting [48].

Dosimetry

The estimated absorbed radiation doses for adult patients following intravenous injection of [^{18}F]Fluciclovine are shown in Table 1. Values were calculated from human biodistribution data using OLINDA/EXM (organ level internal dose assessment/exponential modeling) software. The adult effective dose resulting from the administration of the recommended activity of 370 MBq of [^{18}F]Fluciclovine is 8 ± 1 mSv. For an administered activity of 370 MBq, the typical radiation doses to the critical organs, the

pancreas, the cardiac wall, and the uterine wall are 38 ± 11 mGy, 19 ±4 mGy, and 17 ± 16mGy, respectively [34, 49].

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Compliance with ethical standards

Conflict of interest Cristina Nanni provided consultancy for Blue Earth Diagnostics Ltd. 2018–1019. She was Principal Investigator of the project entitled *ANTI-3-18F-FACBC (anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid) in comparison to 11c-choline PET/CT in the evaluation of patients with prostate cancer radically treated and with rising PSA*, "Programma di ricerca Regione- Università 2013-Area 1 "Ricerca Innovativa", Bando "Alessandro Liberati"-Giovani Ricercatori".

Lucia Zanoni had a scientific-only relationship with the company "Blue Earth Diagnostics Ltd." as Medical Staff of the Sponsored Study BED001 (118/2014/O/Oss), (no financial relationship, no compensation received). Lucia Zanoni was Principal Investigator of the project entitled "18F-FACBC PET/CT for staging high risk prostate cancer" funded by "Programma di ricerca Regione- Università 2013-Area 1 "Ricerca Innovativa", Bando "Alessandro Liberati-Giovani Ricercatori". In the context of this project, Lucia Zanoni received a granted 1-year SSN contract as nuclear medicine project manager (both scientific and financial relationship)

Tore Bach-Gansmo is a consultant for BED, and the hospital has received research funding from BED.

Heikki Minn institution (Turku University Hospital) has a research contract with Blue Earth Diagnostics (not related to fluciclovine).

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Fenton Ingram RT(R), CNMT, PET has no financial or non-financial conflict of interest to declare.

Stefano Fanti, with respect to the mentioned paper, declares that he attended an advisory board of Blue Earth Diagnostics in 2014 and in 2015.

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Liability statement

"This guideline summarizes the views of the EANM Oncology, Bone and Joint Committee, Radiopharmacy, Neurology, Inflammation and Infection and Dosimetry Committees and SNMMI. It reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions"

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