SNMMI Procedure Standard/EANM Practice Guideline for Estrogen Receptor Imaging of Patients with Breast Cancer Using 16α-[^{18}F]Fluoro-17β-Estradiol PET

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PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. Its 15,000 members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science 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. Currently, the EANM represents more than 9,000 specialists from 41 different countries within Europe and serves the interests of a community far beyond these numbers and any geographic boundaries.

The SNMMI/EANM will periodically define new standards/guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients. Existing standards/guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated. Starting in February 2014, the SNMMI guidelines have been referred to as procedure standards. Any practice guideline or procedure guideline published before that date is now considered an SNMMI procedure standard.

Each standard/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/EANM recognizes that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document.

The EANM and SNMMI have written and approved these standards/guidelines to promote the use of nuclear medicine procedures with high quality. These standards/guidelines are intended to assist practitioners in providing appropriate nuclear medicine 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, the SNMMI/EANM cautions against the use of these standards/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 medical professionals, taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the standards/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 standards/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 standards/guidelines.

The practice of medicine involves not only the science but also the art of dealing with 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 standards/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 standards/guidelines is to assist practitioners in achieving this objective.

1. INTRODUCTION

Breast cancer is the most common non-skin cancer in women and remains an important cause of mortality (*1*). Systemic therapy of both early and later stage breast cancer is an important contributor to decreased breast cancer mortality (*2,3*), and advances in individualized and targeted therapy have improved outcomes and mitigated treatment toxicity (*4*). The estrogen receptor (ER), a steroid hormone receptor important in female physiology, is a significant contributor to breast carcinogenesis and progression and, as such, is a useful therapeutic target (*5*). Approximately 70% of breast cancers will express ER at presentation, and the determination of ER expression by tissue assay—most commonly by using immunohistochemistry methods—is part of the standard of care of newly diagnosed breast cancer (*6*). ER expression carries both prognostic and predictive information and is important in guiding the approach to treatment, especially the use of ER-targeted systemic therapy (*3*). After a long development period and research by selective centers capable of generating novel imaging compounds (*7*), the ER-targeted positron emission tomography (PET) imaging agent, 16α-[^{18}F]fluoro-17β-estradiol ([^{18}F]FES), was approved for clinical use by regulatory agencies in France and the United States. As highlighted in recent reviews (*8*), support for the use of [^{18}F]FES PET to diagnose ER-expressing breast cancer and guide ER-targeted therapy came from a number of single-center studies and some recent prospective multicenter studies. These studies demonstrated (1) the accuracy of [^{18}F]FES PET in assessing tumor ER expression compared with tissue assay

reference standards (*9,10*), (2) the ability of both qualitative and quantitative measures of [^{18}F]FES PET to predict response to ER-targeted therapy (*11-13*), and (3) the ability of [^{18}F]FES PET to clarify equivocal staging/restaging results in patients with ER-expressing cancers (*10,14*). More recent data have suggested that [^{18}F]FES PET/CT may be helpful in the staging of invasive lobular breast cancer and low-grade ER-expressing invasive ductal cancers and may be a substitute for biopsy in some cases (*15,16*). More data are needed to better determine efficacy in these tasks.

2. GOALS

The goal of providing guidelines is to assist physicians in recommending, performing, interpreting, and reporting the results of [^{18}F]FES PET studies for patients with breast cancer. This document aims to provide clinicians with the best available evidence, to inform them 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 procedures and imaging procedures for [^{18}F]FES PET. Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of [^{18}F]FES PET in multicenter trials. A standardized imaging procedure will help to promote the appropriate use of [^{18}F]FES PET and enhance subsequent research.

3. DEFINITIONS

The following definitions are based on the EANM procedure guidelines for tumor PET imaging, version 2.0 (*17*).

PET/computed tomography (CT): An integrated or multimodality PET/CT system is a physical combination of PET and CT that allows sequential acquisition of PET and CT portions. The patient remains in the same position in both examinations. [^{18}F]FES PET/CT examination may cover various axial imaging ranges, described as follows:

- Whole-body PET: From the top of the head through the feet.
- Torso 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 United States). If indicated, cranially extended imaging may also cover the brain in the same scan (vertex to mid-thigh). In PET/CT studies, attenuation correction (AC) and scatter correction are performed by using the CT data.
- Vertex-to-thigh: A variant of torso PET that starts at the top of the head (vertex) instead of the skull base.

For [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET/CT, the most commonly used range for breast cancer is skull-base to thigh (torso) (*17*). However, unlike [^{18}F]FDG, [^{18}F]FES has low background uptake for normal brain, facilitating the detection of ER-expressing brain and skull lesions, 2 sites where breast cancer metastases can frequently occur. The consensus of the expert writing group, therefore, is that standard [^{18}F]FES PET/CT should be taken from vertex to mid-thigh. However, since [^{18}F]FES PET may provide advantages for detecting and/or characterizing bone lesions beyond this range, some studies may use whole-body imaging, especially in patients with known or suspected extremity lesions beyond mid-thigh.

Computed tomography: CT is a combined X-ray source and detector rotating around the patient to acquire tomographic data. CT generates 3-dimensional images of tissue density, which allows for AC of PET and tumor visualization with high spatial resolution.

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

- Low-dose CT scan: CT scan that is performed for AC (CT-AC) and anatomical correlation of PET findings (with reduced voltage and/or current of the X-ray tube settings); that is, low-dose CT is not intended a priori for a dedicated radiological interpretation.
- Diagnostic CT scan: CT scan with or without IV and/or oral contrast agents, using higher X-ray doses than those used in low-dose scans. Diagnostic CT scans should be performed according to applicable local or national protocols and guidelines.

PET/magnetic resonance imaging (MRI): An integrated or multimodality PET/MRI system is a physical combination of PET and MRI devices that allows simultaneous or sequential acquisition of PET and MRI images. Though used less commonly in current clinical practice than PET/CT, PET/MRI may have advantages for anatomical definition in certain parts of the body, including the brain, neck, liver, and pelvis, as noted in some studies of PET/MRI for breast cancer (*18*). As with diagnostic CT, MRI acquisition protocols should be performed in accordance with local or national protocols and guidelines.

4. COMMON CLINICAL INDICATIONS

In general, [^{18}F]FES PET has been targeted to patients, both female and male, with breast cancers that expressed ER at the time of diagnosis (*8*). Most studies have shown [^{18}F]FES PET to be most helpful and likely to be clinically impactful in patients with more advanced breast cancer such as known or suspected metastatic disease (Stage IV), locally advanced breast cancer (Stage

III), or possibly locoregional breast cancer with more advanced axillary disease (Stage IIB), in analogy to the impact of [^{18}F]FDG PET/CT (*19*).

Clinical indications for the use of [^{18}F]FES PET have been previously discussed in the appropriate use criteria (AUC) for [^{18}F]FES PET and scored as appropriate (*20*), which assume known or highly suspected ER-expressing breast cancer. These indications are as follows:

(1) Assess lesions that are difficult to biopsy or where biopsy is nondiagnostic.

(2) Guide therapy after progression of metastatic disease.

(3) Guide therapy at the initial presentation of metastatic disease.

(4) Detect ER-expressing breast cancer sites when other imaging tests are equivocal or suspicious.

Other emerging indications were also described, noting that more data are needed to better support these indications (*20*):

(5) Detect ER-expressing lesions in patients with suspected/known recurrent or metastatic breast cancer.

(6) Assess ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy.

(7) Stage invasive lobular breast cancer and low-grade ER-expressing invasive ductal cancer.

(8) Routinely stage ER-expressing extra-axillary nodes and distant metastases.

Although beyond the scope of this breast cancer-focused guideline, prior studies have shown that [^{18}F]FES PET can be used for the detection and characterization of ER-expressing tumors other than breast cancer, such as ovarian cancer and endometrial cancer (*21*).

5. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

5. 1. Physician

[^{18}F]FES PET examinations should be performed by, or under the supervision of, a physician specialized in nuclear medicine and certified by accrediting boards. Physicians who interpret [^{18}F]FES PET results should also complete appropriate training. This training should include gaining experience in reading [^{18}F]FES PET results under the guidance of an experienced reader, attending training sessions offered at scientific and professional meetings, and/or studying online material that provides background and case examples for [^{18}F]FES PET that include history and follow-up. Resources to support training are under development by the SNNMI, EANM, and commercial entities at the time of this guideline writing.

5.2. Technologist

[^{18}F]FES PET examinations should be performed by qualified registered or certified nuclear medicine technologists. See *Nuclear Medicine Technologist Scope of Practice and Performance Standards* for further details (*22*). According to location of practice, additional qualifications may be requested for technologists to use the CT and MRI component of the scanner.

5.3. Medical Physicist

PET systems and protocols should comply with the international standard of quality. Procedures should pay attention to dosimetry and radiation protection to limit the radiation exposure of patients and health care personnel. A medical physicist should optimize protocols, ensuring that the established standards are met. A medical physicist can assist physicians in adhering to and

maintaining good practice by monitoring and optimizing the radiation dose and by developing algorithms to reduce the radiation exposure of the CT component.

6. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

6.1. Introduction to Procedure-Specific Guidelines

6.1.1. Overview of [^{18}F]FES Properties and Clinical Pharmacology

Although other tracers for ER imaging have been studied, thus far only [^{18}F]FES has received approval for clinical use, and [^{18}F]FES has by far the most published data for use as a probe for detecting ER-expressing breast cancer (*7,8*). [^{18}F]FES is a close analog of estradiol and, similar to estradiol, has high binding affinity for the ER (*23*) and the steroid transport protein, sex hormone-binding globulin (SHBG) (*23,24*). Like estradiol, [^{18}F]FES is a lipophilic compound, and SHBG binding is an important determinant of [^{18}F]FES biodistribution (*25*). Local saturation of SHBG at the [^{18}F]FES injection site is a factor in its uptake along the injecting vein (*24*), leading some investigators to suggest using a slower infusion rather than a bolus injection. After injection, [^{18}F]FES promptly accumulates in ER-expressing tissue in the first 20–30 minutes after injection, with a plateau in uptake at approximately 60 minutes after injection (*26*). Akin to other steroids, [^{18}F]FES is also rapidly taken up and metabolized by the liver, largely into sulfate and glucuronide conjugates of [^{18}F]FES that are excreted in bile and enter into enterohepatic circulation in the small and proximal large intestines, leading to the presence of low levels of labeled metabolites in the blood and excretion into the urine (*26-28*). High uptake of [^{18}F]FES and its metabolites in the liver obscures uptake in breast cancer liver metastasis, limiting accuracy and utility in that site of disease (*27*). Normal biodistribution is discussed later in this document in Section 6.4 (Image Interpretation and Reporting). Studies have shown that

circulating estrogens in premenopausal nonpregnant patients and postmenopausal patients do not significantly affect FES uptake (*29*); however, pharmacological doses of estradiol analogs and/or agents that occupy the ER binding site, such as tamoxifen and fulvestrant, can interfere with [^{18}F]FES uptake into ER-expressing cancer sites (*12,30-32*). For this reason, ER-blocking medications must be considered in patient selection and preparation for [^{18}F]FES PET, as discussed in Sections 6.2 (Patient Selection and Preparation) and 6.2.3 (Required Clinical Information).

6.1.2. [^{18}F]FES Dosimetry

[^{18}F]FES biodistribution and dosimetry have been studied in patients. The estimated effective dose equivalent of [^{18}F]FES was 0.022 mSv/MBq (80 mrem/mCi) (*27*) (See Table 1). The organ that received the highest dose was the liver (0.13 mGy/MBq [470 mrad/mCi]), followed by the gallbladder (0.10 mGy/MBq [380 mrad/mCi]) and the urinary bladder (0.05 mGy/MBq [190 mrad/mCi]) (*27*). These estimates were obtained for an almost entirely female population, but are expected to be similar in males, given the similar biodistribution observed in limited studies of male patients.

In 2007, in its publication 103, the International Commission on Radiological Protection (ICRP) revised the tissue weighting factor (W_T), leading to a value for the effective dose, which is different from the effective dose equivalent. Thus, Talbot et al. (*33*) intended to apply the W_T of ICRP publication 103 to the data of the aforementioned study (*27*), with the drawback that the absorbed dose by some organs included in the calculation of the effective dose was missing in this study. However, since none of those organs (esophagus, salivary glands, mucosa of the mouth, lymphatic nodes) have a specific uptake of [^{18}F]FES in normal women or men, Talbot et

al. (*33*) assumed that their absorbed dose would be similar to that of the 10 organs constituting the remaining tissues and obtained a value of 0.025 mSv/MBq for the effective dose.

6.2. Patient Selection and Preparation

6.2.1. Requests for [^{18}F]FES PET

The nuclear medicine imaging facility should check with its local nuclear pharmacy provider as to the availability of the radiotracer before scheduling the examination. Advanced notice may be required for radiotracer delivery. The study requisition should include clinical information about the patient to justify the study and to allow coding of the examination or study, information about the ability of the patient to cooperate with the test, confirmation that the patient is not pregnant, notification if the patient is breastfeeding, and information about current medications in case mild sedation is necessary. It is also helpful to know if the patient needs to be accompanied by a guardian. Some centers provide warnings on their request forms to avoid patients who are currently taking interfering medications such as tamoxifen and fulvestrant (see Section 6.2.3 [Required Clinical Information]).

6.2.2. Patient Preparation and Precautions

Patient selection for [^{18}F]FES PET should be guided by the clinical indications described in the SNMMI-EANM AUC guidelines (*20*) and summarized earlier. There are important considerations for patient selection that require the review of relevant clinical history data for each patient, including current and prior ER-blocking medications and prior biopsy documentation of tumor ER expression, further described in Section 6.2.3.

Unlike [^{18}F]FDG uptake, [^{18}F]FES uptake does not appear to be significantly affected by dietary state or exercise, and therefore fasting and avoidance of strenuous exercise are not required. As with any radiopharmaceutical injection, fertility and possible pregnancy should be reviewed and pregnancy testing ordered if there is uncertainty about pregnancy status. Depending on institutional guidelines, serum or point-of-care urine pregnancy testing the day of the exam is acceptable. Instruct the patient to arrive early for their appointment to allow for the additional time required to collect the sample, perform the pregnancy test, and obtain results well in advance of the planned time of injection. Patients should also be queried regarding breastfeeding, with its suggested avoidance for at least 4–12 hours, noting that specific guidance for ^{18}F compounds has thus far been issued only for [^{18}F]FDG (4 hours) and that the same guidelines suggest 4 half-lives for other commonly used isotopes for diagnostic imaging, such as technetium-99m (*34*).

6.2.3. Required Clinical Information

As a minimum, a summary of relevant clinical history should include the reason for referral and the specific clinical question to be answered (see **Table 2**). Earlier conventional imaging results should be available for review. Information on menopausal status; previous treatment, particularly any previous treatment with a selective estrogen receptor modulator (SERM) and/or selective estrogen receptor degrader (SERD); and, if recently treated, the date of the last treatment dose should be provided. Information about the phase of the menstrual cycle could be added, but this is not required. It has been reported (*35*) that fluctuation in endogenous estrogen levels during the menstrual cycle can have some effect on [^{18}F]FES uptake in the endometrium, but these effects are relatively small and do not appear to affect breast cancer lesional uptake of

[^{18}F]FES (*29*). Oral contraceptives induce plasma estradiol (equivalent) levels in the same range as natural estradiol levels during the menstrual cycle (*36*). Therefore, it seems unlikely that fluctuations in endogenous estrogen levels or oral contraceptives will affect the interpretation of [^{18}F]FES PET results outside of the uterus. This information should be carefully noted.

Special attention needs to be paid to drugs that block the ER and reduce the uptake of [^{18}F]FES, such as tamoxifen and fulvestrant. To avoid this drug interaction, several teams have recommended the discontinuation of ER antagonists for at least 6 weeks. Although some authors have suggested that previous use of ER antagonists may still result in somewhat lower tracer uptake and more [^{18}F]FES-negative lesions (*37*), others have demonstrated no significant effect on FES uptake for patients with tamoxifen withdrawal over 2 months (*38*). Aromatase inhibitors do not interfere with tracer binding and therefore are allowed (*10,29,39*). It should also be noted that other drugs given in conjunction with ER-targeted agents that target closely related tumor growth pathways, such as CDK4/6 and mTOR inhibitors, do not appear to interfere with the binding of [^{18}F]FES to ER+ tumor sites (*40*).

Some additional discussion is warranted for patients receiving a class of drugs known as SERDs. The most used SERD in current practice, fulvestrant, is given as a depot injection, typically monthly, and has a relatively long clearance time. Fulvestrant has a half-life of 40 days, and in current US Food and Drug Administration (FDA) guidelines, a washout time of 28 weeks prior to [^{18}F]FES is recommended. Novel oral SERDs, such as elacestrant, which is newly approved by the FDA, have a half-life of only 27–47 hours (*41*). The withdrawal period needed, therefore, will differ between various ER-targeting drugs and should be a subject of further research. For the oral SERD rintodestrant, for example, it was recently shown that tumor FES uptake was already restored ≥ 5 days after treatment withdrawal (*42*). Even for fulvestrant, a

withdrawal period of 6 weeks may be sufficient for visualization of ER-positive tumors given that a substantial number of patients receiving treatment do not have complete blockage of tumor [^{18}F]FES uptake (*30,37,43*). For accurate quantitative measures, especially in a research setting, longer withdrawal may be needed; however, appropriate clinical care should not be delayed in order to perform [^{18}F]FES PET.

6.3. Tracer Administration and Imaging

6.3.1. Radiopharmaceuticals

The properties and clinical pharmacology of [^{18}F]FES were described earlier. As [^{18}F]FES is an agent designed to image a receptor that is active in the presence of estrogenic ligand concentrations in the nanomolar range, consideration of the injected mass of FES, in addition to the quantity of radioactivity, is important. Early studies suggested that [^{18}F]FES uptake in ER-expressing tissues might be sensitive to the tracer's molar activity, which has been an important consideration in early studies characterizing [^{18}F]FES PET pharmacology (*28*). More data based on a larger experience suggest that for human imaging, injected doses of up to 5 micromoles do not significantly affect the uptake of the tracer in ER-expressing tumors and normal tissues (*29*). Nevertheless, injected tracer mass dose—and therefore the molar activity of the tracer—is an important component of [^{18}F]FES quality control and is a consideration that has been recognized by commercial producers.

6.3.2. Administered Activity

[^{18}F]FES is administered intravenously through an established IV catheter, preferably placed on the opposite side of the known breast cancer. As the radiotracer [^{18}F]FES is sticky, a larger size IV needle is recommended, for example, 20 gauge or larger. Injecting through an implantable port

is discouraged, again related to the lipophilicity of [^{18}F]FES. The recommended activity varies between 111 and 280 MBq (3–7.6 mCi) (*44,45*). The recommended activity may vary by regulatory authority and supplier and may also depend on patient characteristics and PET scanner performance characteristics, the general guidance being to use the lowest activity that provides clinically acceptable images.

[^{18}F]FES is generally administered as a single IV injection of 10 mL or less. Slow administration over 1–2 minutes may be helpful to reduce retention of tracer in veins near the administration site (*45*), as this may decrease the likelihood of saturating SHBG and lessen tracer deposition along the peripheral vein of injection (*24*). Taking into consideration radiation exposure of the technologist performing the injection, it may be helpful to use a syringe pump to infuse the activity or other automated injection method, although this is not required and not commonly done in most centers. In addition, adequate flushing of the injection line is important. The final [^{18}F]FES formulation contains a small amount of ethanol, which tends to sting during injection. Diluting the product with normal saline reduces the likelihood of this occurring.

6.3.3. Uptake Time

After the patient is injected, there are no restricted activities. The patient may read, listen to music, or relax comfortably.

The uptake time usually ranges between 20 and 80 minutes after administration of [^{18}F]FES, the ultimate goal being to produce the best quality images (*45*). Earlier scan times have been suggested, on the basis of prior studies of biodistribution, to avoid interference with tracer excreted into the intestines (*27,28*), as well as to facilitate interpretation of abdominal and pelvic images; however, further study of this important consideration is needed. Overall, the majority of

recent studies, including the 2 major studies that prospectively validated the accuracy of [^{18}F]FES PET assessment of lesional ER status compared with biopsy (*9,46*), used a 60-minute uptake time. From these studies, for ease of clinic scheduling templates already in use for [^{18}F]FDG PET, a 60-minute uptake time is suggested.

6.3.4. Image Acquisition

Instruct the patient to void prior to placing them on the imaging table. Patients are typically imaged supine and with arms overhead; however, practice may vary depending on institutional preferences and approaches established for [^{18}F]FDG PET. As discussed earlier, some centers have used the skull base to mid-thigh torso survey used for [^{18}F]FDG PET; however, a scan range from skull vertex to knees or to toes is suggested if extending the range coverage would be advantageous in further assessing sites such as bone and brain, noting that unlike [^{18}F]FDG, [^{18}F]FES has low uptake in the normal brain. This consideration emphasizes the importance of obtaining the patient's complete clinical history when scheduling the exam and suggests a need for further study.

CT and PET acquisition parameters for the scan will depend on the PET/CT system used to collect the images and the injected activity. State-of-the-art time-of-flight scanners with multiple detector arrays and advanced computing power may allow for shorter scan times without sacrificing lesion detection and image quality. Per the prescribing information, total scan time will range from approximately 20 to 30 minutes for a step and shoot or continuous bed motion acquisition. Although there is some consideration for acquiring the scan in the caudocranial direction, where imaging the bladder early on when it is at its most empty may be helpful, there is no evidence to support this approach vis-à-vis the craniocaudal direction that is most commonly used for FDG PET. If performing a diagnostic CT in the same imaging session, do the PET/CT

scan first, acquiring the lower dose CT-AC images for the PET. On completion, perform the diagnostic CT scan with IV contrast, if warranted. If a long-field-of-view PET/CT system is used, much shorter acquisition times can be applied (3 minutes or less).

6.3.5. Image Reconstruction and Processing

Image reconstruction parameters will vary by the PET/CT system and institutional standards. New iterative reconstruction algorithms on modern scanners such as point-spread-function modeling or Bayesian penalized likelihood algorithm improve the detection of small lesions. Use of reconstruction characteristics similar to standard [^{18}F]FDG imaging protocols is suggested, as is recording of reconstructions in the transversal, coronal, and sagittal planes and of fused images in addition to axial PET and CT images. Including a maximum intensity projection volume-rendered PET image in the imaging data set is also helpful.

6.4. Image Interpretation and Reporting

6.4.1. Technical Details

Study-specific information should include the radiopharmaceutical, amount of injected activity, radiopharmaceutical batch, route (IV) and anatomical site of administration, date and time of administration, and body weight and height, preferably measured on the day of the scan. If extravasation is seen, it should also be noted. The interval between the administration of the radiopharmaceutical and the start of the acquisition should be reported. The acquisition protocol (e.g., acquisition time/bed position), scanner and reconstruction protocol, and body parts covered by imaging should be described. Any nonstandard position of the patient and any other deviation from the standard protocol (e.g., movement of the patient, premature termination of the scan)

should be stated. If a low-dose CT was performed for AC and anatomical registration of the emission images only, the description may be limited to a short statement that includes the milliampere seconds (mAs) and peak kilovoltage (kVp). If such details are already specified in the acquisition protocol, only deviations from the protocol need to be reported. Dosimetry parameters of the CT portion of the PET/CT should be included only if required by national or local regulations.

6.4.2. Background Information: Expected [^{18}F]FES Biodistribution Relevant to Interpretation

At 1 hour after injection, the biodistribution in a patient with no ER-positive disease shows the liver as part of the primary metabolic pathway; there is biliary excretion, and activity is seen transiting the small bowel (**Figure 1**). [^{18}F]FES and its metabolites have an entero-hepatic loop and therefore limited activity reaches the colon. A small amount of renal and bladder activity is also seen, demonstrating a renal excretory pathway related to the excretion of conjugates of [^{18}F]FES (*26,47*). Retained [^{18}F]FES is commonly seen in the veins of the injected extremity. Prominent uptake in the uterus is typically seen. Mild physiological uptake can be seen in the pituitary gland (*48*) and ovaries, although these are more variably seen than the uterus.

Uptake of [^{18}F]FES depends on ER density in tumors and physiological tissue. Uptake in bone is slightly higher than in lung, fat, and muscle for unknown reasons (*27*), but likely having to do with a combination of increased flow and lipophilicity of bone marrow, as well as the physiological interaction of estrogens with bone. These factors may also explain the observed gradient in bone uptake from cervical to lumbar spine. Bone uptake in the lumbar spine may be higher than a maximum standardized uptake value (SUV_{max}) of 1.5, which is often used as a threshold for ER-positive lesions (*37*). Brain [^{18}F]FES uptake is low, despite ER expression

(mainly the ER-β subtype) in brain tissue. However, [^{18}F]FES can readily penetrate the blood-brain barrier and ER-expressing brain metastases can be clearly detected with [^{18}F]FES PET. Detection of ER-positive tumors should be based on comparison with tissue background outside of organs with high physiological uptake and regions with high activity due to hepatobiliary and urinary excretion.

6.4.3. Required Descriptions of Findings

At a high level, the following items should be described in the report of the clinical interpretation of the [^{18}F]FES PET/CT study:

- The quality of the PET image, including any technical issues (e.g., motion artifacts, halo artifacts due to high activity in the collecting urinary system, or attenuation artifacts from attenuating materials).
- Visual analysis of clinically relevant findings, including the following:
    - All sites of increased nonphysiological focal uptake greater than local background suspicious for ER-positive lesions (see Figure 2, for example).
    - Any abnormal diffuse increased uptake (that may be due to, e.g., post-therapy inflammation or other changes).
    - Incidental findings with focal [^{18}F]FES uptake with further investigation suggested when needed.
    - Lesions identified by other imaging modalities as (suspected) tumor, but not showing any enhanced [^{18}F]FES uptake should be reported as (probable) ER-negative lesions, noting that treated bone metastases may appear as sclerotic lesions on CT, but do not represent active disease.

    - Lesions found on CT, not suspected to be tumor and with no [^{18}F]FES uptake, should also be noted.

- Quantitative analysis of sites of suspected disease, including those sites where active disease is expected on the basis of correlative imaging such as CT or [^{18}F]FDG PET but visual inspection does not show [^{18}F]FES uptake above background. Most studies thus far have used measures such as SUV_{max}. Alternative measures such as peak or mean values, as well as SUV lean (SUL) instead of SUV, have been studied (*29*) but are not routinely used. This is described in more detail in Section 6.4.6 (Correlation of [^{18}F]FES PET with Other Imaging Modalities).

Review of the [^{18}F]FES PET/CT should include a detailed qualitative interpretation. The text that follows highlights considerations for defining scan findings as positive and negative for ER-expressing breast cancer. In all cases, the [^{18}F]FES PET images must be interpreted according to the indication and the individual clinical data, taking into consideration the physiological biodistribution of [^{18}F]FES, particularly the high physiological background in the liver. In general, all extrahepatic lesions with greater uptake than the local tissue and/or vascular background are considered positive, that is, testifying to the presence of ER. A slight increase in tracer uptake may be observed in ER-negative tumors in case of increased perfusion, likely related to nonspecific binding, especially in more lipophilic tissues. When uptake in all lesions is equal to or lower than background, a scan can be considered negative, suggesting absence of ER expression in all tumor lesions. In the case of equivocal lesions, that is, lesions with uptake around or minimally above physiological background, quantitative analysis should be performed as described later in this section.

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Image windowing that is optimal for interpreting [^{18}F]FES PET/CT is not the same as for [^{18}F]FDG PET/CT. Visualizing lesions with SUV as low as 1–1.5 is important for identifying ER-expressing cancer sites, but is typically below the level of uptake for [^{18}F]FDG-positive cancer sites. High uptake in the liver may lead to automatic windowing that is too high for scan interpretation and may need manual adjustment of predefined windows for [^{18}F]FES PET/CT versus the defaults often used to review [^{18}F]FDG PET/CT studies.

In general, whole-body [^{18}F]FES PET can be considered positive when at least one lesion is clearly above physiological background (*46*); however, substantial heterogeneity due to the presence of both ER-positive and ER-negative lesions can exist and is important to report. See Section 6.4.6 (Correlation of [^{18}F]FES PET with Other Imaging Modalities).

6.4.4. False-Negative and False-Positive Findings on Visual Analysis

Interpretation requires knowledge of potential (false) negative findings, which include active ER-expressing cancer sites that are masked by nearby organs with high background, or true negative findings due to active cancer sites without ER expression. Some specific considerations include the following:

- The absence of [^{18}F]FES uptake does not necessarily imply absence of tumor. [^{18}F]FES detects ER that is functional and available for ligand binding (*7,49*). Malignancies that do not express ER, such as ER-negative breast cancers and most malignancies that arise from other body sites, are unlikely to be detected on [^{18}F]FES PET (*49*).
- Physiological [^{18}F]FES uptake by the liver makes PET evaluation of this organ more difficult (*50*), but still possible in some cases (*51*). In the case of visual assessment of liver metastases, hot spots with higher uptake than physiological uptake in the liver can

be considered to express ER. However, cold spots with lower uptake than the liver can either be ER-positive or ER-negative lesions. The biliary excretion of [^{18}F]FES into the small intestine may mask small lesions of peritoneal carcinomatosis. Fatty food may slightly increase the biliary excretion of [^{18}F]FES, but this effect is likely too small to have diagnostic consequences (*52*).

- There is insufficient evidence to support the use of [^{18}F]FES PET to evaluate ER expression in pleural effusion and ascites: likely the tumor cell density is insufficient, and there is limited tracer availability in effusions to accurately determine ER expression.
- Lesions that are small compared with the resolution of the PET scanner may remain undetected as a result of partial volume effects. Skin lesions may not show up on the [^{18}F]FES PET for this reason, for example. Whether a small lesion can be detected not only depends on the size of the lesion and the resolution of the scanner, but also on the ER expression level within the tumor and the local background signal.
- Pharmacological treatment with drugs that bind to the ER (e.g., tamoxifen and fulvestrant) should be taken into consideration, as previously mentioned. These drugs will compete with [^{18}F]FES for the binding site on the ER and therefore cause false-negative findings.

The following sources of *false-positive results* should also be considered and noted (see Figure 3, for example):

- Physiological ER is usually visualized in uterine endometrium and myometrium, and it may be variably visualized in the pituitary and ovary (*35*).

- Lung alveoli have been noted to have a modest level of [^{18}F]FES retention (*27*). For this reason, dependent lung areas with atelectasis (and thus increased density) may have uptake above background levels. Areas of lung that underwent radiation may demonstrate (usually diffuse) [^{18}F]FES avidity, which may be associated with pulmonary fibrosis (*53-55*).
- False-positive results of enhanced [^{18}F]FES uptake have been reported in cases of fibrous dysplasia (*56*) or insufficiency fracture (*31*).
- Diffuse [^{18}F]FES uptake in the absence of a morphological abnormality on CT may be observed in the spine, with predominance in the lumbar vertebrae (*37*). However, high levels of diffuse uptake in marrow-producing areas have been reported that may also indicate diffuse marrow-based spread (*15,16,57*).
- Benign neoplasms that express ER and may be [^{18}F]FES avid include meningiomas and uterine leiomyomas (*58,59*).
- Malignancies other than breast cancer that may be [^{18}F]FES avid include endometrial cancer, ovarian cancer, and leiomyosarcoma (*21,60-62*).
- The expression of estrogen receptor beta (ERß) by diffuse large B-cell lymphoma (DLBCL) has recently been proposed as a potential therapeutic target (*63*). However, data confirming [^{18}F]FES uptake by DLBCL are not available, and the binding of [^{18}F]FES to ERß has been reported to be considerably lower than to ER-alpha, the ER variant associated with breast cancer (*7*).

6.4.5. Reporting and Interpreting Quantitative Measures

The following considerations are important for reporting and interpreting quantitative measures, including what measures to record. [^{18}F]FES PET as a diagnostic tool has good sensitivity and specificity for ER-expressing lesions. Although qualitative assessment is usually sufficient to discriminate a positive from a negative scan, in some instances, quantitative measurements can be of additional value. For example, when [^{18}F]FES uptake in a lesion is around or only slight above physiological background, this gives rise to doubt as to whether a scan should be considered positive. Various studies have evaluated quantitative measurements of [^{18}F]FES uptake in the tumor in relation to immunohistochemistry results. The most commonly used threshold to discriminate ER-positive from ER-negative disease is a $SUV_{max} \geq 1.5$, which has been shown to be a robust threshold in prospective studies (*47,64*); it should be noted, however, that these studies did not examine lesions smaller than 1 cm, where partial-volume effects may lead to a lower measured uptake and could lead to false-negative findings when using the SUV_{max} 1.5 threshold. In a recent meta-analysis, quantitative analysis of [^{18}F]FES PET results rendered 86% sensitivity and 85% specificity for ER-expressing lesions (*65*). The accuracy appears to be higher in bone metastases than in lymph node metastases. A recent report noted that lymph nodes with an SUV_{max} in the range of 1.5–2.5 have a relatively high degree of false positives (*47*). Moreover, in some bone regions, such as the lumbar vertebrae, background uptake is already higher than the SUV_{max} threshold of 1.5 (*37*). In these regions, tumor uptake should at least be higher than background uptake to be considered a positive finding and have quantitative measures recorded. Altogether, these findings show that when qualitative assessment of [^{18}F]FES PET is equivocal, quantitative assessment can aid in defining whether a scan should be considered positive, but careful scanner calibration is needed to interpret the SUV uptake measures.

In addition to its diagnostic value, [^{18}F]FES PET can also be used quantitatively to predict treatment efficacy/failure, which is particularly useful when evaluating disease with heterogeneous uptake. [^{18}F]FES PET has a high negative predictive value; namely, lesions without FES uptake (SUV_{max} <1.5) lack response to hormone treatment (*11,12,66,67*). This is consistent with the findings that a lack of ER expression by assay of tumor biopsy material predicts a lack of response (*68*) and, in conjunction with tissue assay, can be helpful for guiding clinical treatment decisions.

Although not part of currently recommended practice, studies have shown that quantitative assessment of serial [^{18}F]FES PET before and after ER-blocking drugs (SERMs and SERDS) can assess the adequacy of receptor blockade (*30-32*), may provide value for predicting response (*32*), and can be used to guide the dosing of new drugs (*38*). Although not part of the current recommended use for [^{18}F]FES PET, these applications have been studied in the research setting.

6.4.6. Correlation of [^{18}F]FES PET with Other Imaging Modalities

Correlative imaging, in addition to the CT component of PET/CT, is important and helpful for guiding [^{18}F]FES PET/CT interpretation and evaluation of ER heterogeneity. In patients with breast cancer, lesion identification can be driven by conventional imaging such as CT, MRI, [^{18}F]FDG PET/CT, and bone scintigraphy. [^{18}F]FES PET and conventional imaging, including [^{18}F]FDG PET examinations, may provide complementary diagnostic information in staging or restaging patients with breast cancer. The additional information on disease localization can be helpful in interpreting [^{18}F]FES PET/CT, especially for lesions not expressing ER (and thus negative on [^{18}F]FES PET). Conversely, [^{18}F]FES can be useful when conventional imaging is inconclusive, such as when [^{18}F]FDG uptake of a lesion is equivocal or when [^{18}F]FDG does not detect a suspected recurrence due, for example, to high background uptake or low glucose

metabolism. Several studies have found that [^{18}F]FES PET could detect lesions that were not detected by [^{18}F]FDG PET or other conventional imaging modalities (*15,16*). The detection rate of [^{18}F]FES PET is low for liver metastases, and photopenic areas in the liver that are of tissue density on CT should be considered suspicious for metastases (*10,38,69-71*).

When [^{18}F]FES PET is used in combination with correlative imaging that identifies sites of active disease, the combination can qualitatively assess the expression of ER in individual lesions and can therefore assess the heterogeneity of disease (*50*). Various studies have shown that ERs can be heterogeneously expressed among metastases within the same individual, with up to 30%–40% of patients with ER-positive disease having both [^{18}F]FES-positive and [^{18}F]FES-negative metastases (*37*). A few small studies have shown that heterogeneous [^{18}F]FES uptake, compared with homogeneous [^{18}F]FES uptake in all metastases, is associated with poor survival and shorter duration of response to treatment (*40,72*). This supports the need for further study and consideration of reporting the fraction of known lesions that are positive by [^{18}F]FES PET, a measure that has been noted to be predictive in these studies. Some studies have examined [^{18}F]FDG PET to help describe tumor clinical phenotype on the basis of glucose metabolism (*73,74*). The combination of [^{18}F]FDG PET and [^{18}F]FES PET may allow differentiation between indolent and more aggressive tumors. For the subset of patients with higher tumor [^{18}F]FDG uptake ($SUL_{max} < 3$), [^{18}F]FES can help differentiate between those who preserve endocrine sensitivity and those who do not. These phenotypic considerations can potentially help guide treatment decision making (*74,75*). Overall, it is helpful to report [^{18}F]FES PET/CT results in the context of contemporaneous [^{18}F]FDG PET/CT results—both qualitatively and quantitatively—and/or the results of other conventional imaging.

6.4.7. Synthesizing an Overall Report Impression

In the final [^{18}F]FES PET report, the following items should be mentioned:

- Summary of patient history, including current and prior medications targeted to ER-expressing breast cancer.
- Summary of the technical components of the scan, including injected activity and uptake time.
- Description of the areas with physiological uptake, metabolism, and excretion of [^{18}F]FES.
- Identification and description of sites of qualitatively abnormal uptake above background that are suspicious for a site of ER-expressing breast cancer, including the details of anatomical localization on CT and a relevant description of the qualitative level of [^{18}F]FES uptake and items such as the size of the lesion by CT when relevant.
- Recording quantitative uptake for sites identified by qualitative interpretation can be helpful, noting that an SUV_{max} of [^{18}F]FES > 1.5 is suggestive of ER expression. This should be done in accordance with institutional practice for other PET studies, where SUV is provided for the most prominent or most clinically impactful lesions.
- Description of suspected false-positive or nonspecific findings (*53*).
- Description of sites where [^{18}F]FES uptake may be absent in lesions observed by other available imaging techniques (CT, MRI, [^{18}F]FDG PET, bone scan).
- A summary of heterogeneity of [^{18}F]FES across sites of known disease with reference to other correlative imaging and specific discussion of concordance with contemporaneous [^{18}F]FDG PET/CT findings when available.

- If the [^{18}F]FES PET was performed to solve a diagnostic dilemma, specific mention of the [^{18}F]FES qualitative and quantitative uptake by the equivocal lesion(s) should be reported with a conclusion on whether the lesions posing diagnostic challenges are ER positive or ER negative by [^{18}F]FES PET.
- If the [^{18}F]FES PET was performed for therapy rationale, specific mention of the overall qualitative and quantitative ER status of the metastases by [^{18}F]FES PET should be described, including consideration of heterogeneity of expression.

Interpreting physicians should consider including a section on the limitations and pitfalls of [^{18}F]FES PET. These include concerns of limited accuracy for liver and small intestinal lesions and that [^{18}F]FES PET is not indicated in the case of liver-only disease. In addition, there is insufficient evidence to support the use of [^{18}F]FES PET to evaluate ER expression in pleural effusion and ascites.

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Liability Statement

This guideline summarizes the views of the joint SNMMI-EANM [^{18}F]FES Guidelines Committee. It reflects recommendations for which neither the SNNMI nor EANM can 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.

Table 1: Dosimetry for [^{18}F]FES

Radiation Absorbed Dose to Organs

Organ	Mean* (mGy/MBq)	SD (mGy/MBq)	25%† (mGy/MBq)	75%† (mGy/MBq)
Adrenals	0.023 (85)	0.003	0.021	0.025
Brain	0.010 (36)	0.001	0.009	0.010
Breasts	0.009 (32)	0.002	0.008	0.010
GB wall	0.102 (379)	0.041	0.075	0.134
LLI	0.012 (45)	0.001	0.011	0.013
Small intestine	0.027 (99)	0.015	0.017	0.038
Stomach	0.014 (50)	0.001	0.013	0.014
ULI	0.030 (110)	0.016	0.019	0.042
Heart wall	0.026 (96)	0.004	0.024	0.029
Kidney	0.035 (128)	0.004	0.032	0.038
Liver	0.126 (466)	0.030	0.105	0.149
Lungs	0.017 (61)	0.002	0.015	0.018
Muscle	0.021 (79)	0.001	0.021	0.022
Ovaries	0.018 (66)	0.002	0.016	0.019
Pancreas	0.023 (84)	0.002	0.021	0.024
Red marrow	0.013 (48)	0.002	0.012	0.014
Bone surface	0.014 (53)	0.001	0.014	0.015
Skin	0.005 (18)	0.000	0.005	0.005
Spleen	0.015 (54)	0.003	0.012	0.017
Testes	0.012 (44)	0.001	0.011	0.012
Thymus	0.014 (50)	0.001	0.013	0.014
Thyroid	0.012 (45)	0.001	0.012	0.013
UB wall	0.050 (186)	0.020	0.036	0.066
Uterus	0.039 (145)	0.013	0.031	0.049
Lens	0.009 (33)	0.000	0.009	0.009

*Values in parentheses are mrad/mCi.
†Determined assuming normal curve with given mean and SD.
GB = gallbladder; LLI = lower large intestine; ULI = upper large intestine; UB = urinary bladder.
Effective dose equivalent = 0.022 mSv/MBq (0.004 SD).

Table 2: Clinical information needed at the time of referral for [^{18}F]FES PET

• Patient demographics, including age, height, and weight, with recommended weight measurement at the time of the scan.
• Breast cancer stage and subtype, including ER expression at diagnosis, as well as any recent biopsy.
• Pregnancy and breastfeeding status, including recent pregnancies.
• Menopausal status and date of last menstrual period of premenopausal women
• Prior and current treatment, including any ER-targeted therapy, with special attention to the timing of ER-blocking drugs such as SERMs (e.g., tamoxifen) and SERDs (e.g., fulvestrant). Recent site-specific radiotherapy should also be noted.
• Recent breast cancer staging studies, including and especially [^{18}F]FDG PET, to be used for comparison to [^{18}F]FES PET.

[^{18}F]FES = α-[^{18}F]fluoro-17β-estradiol positron emission tomography; PET = positron emission tomography; ER = estrogen receptor; SERMs = selective estrogen receptor modulators; SERDs = selective estrogen receptor degraders; [^{18}F]FDG = [^{18}F]fluorodeoxyglucose.

Figure 1: Normal biodistribution of [^{18}F]FES, demonstrating expected pattern of normal organ uptake and tracer excretion, along with expected retention in the peripheral vein(s) used for injection. Image courtesy of Courtney Lawhn-Heath, MD.

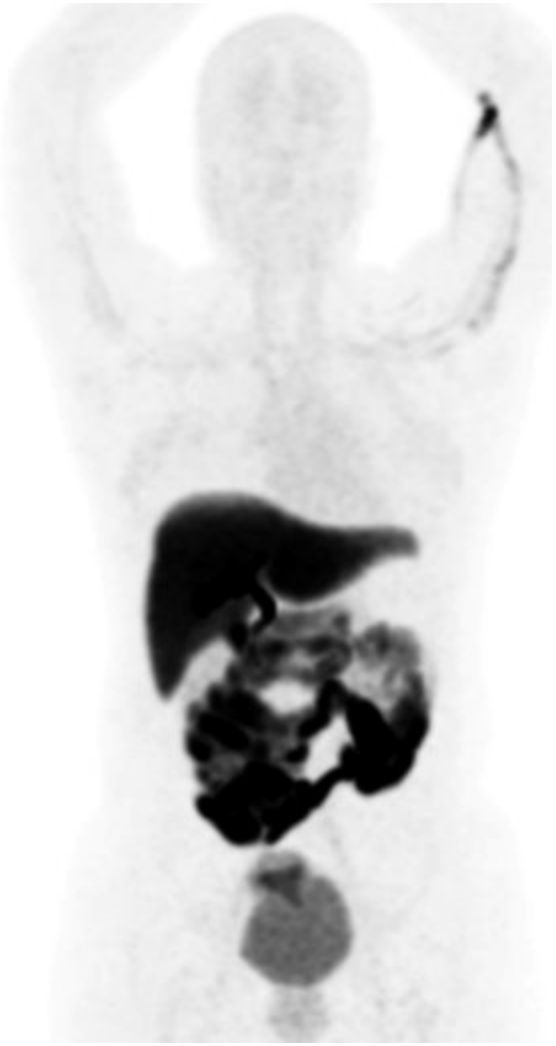


Figure 2: True-positive [^{18}F]FES PET example in patient with widespread innumerable ER-expressing bone metastases with uptake clearly higher than normal background bone/bone marrow uptake.

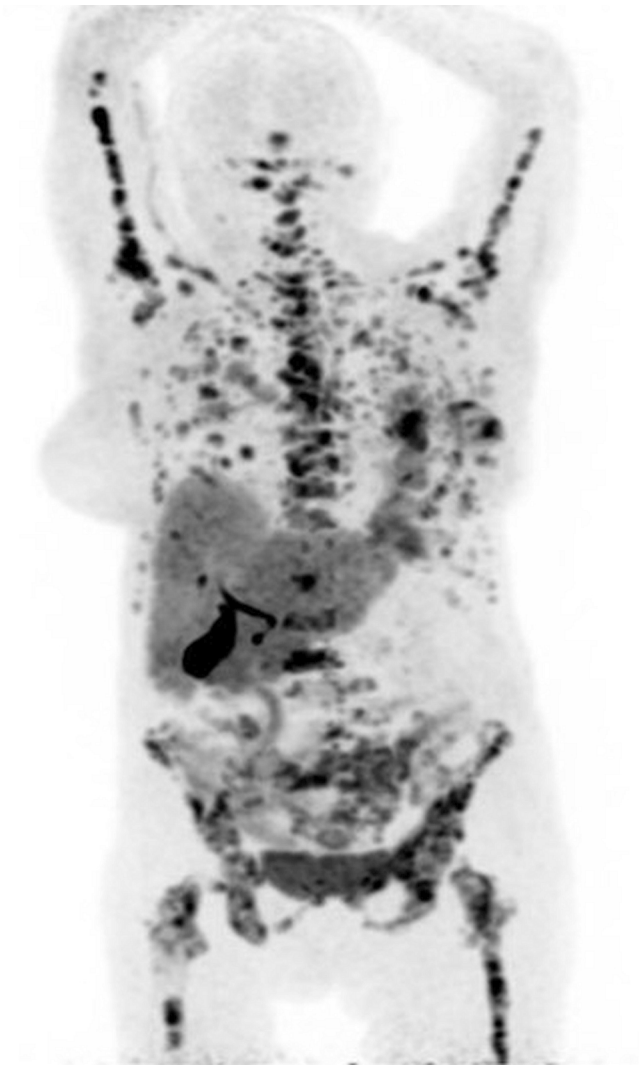
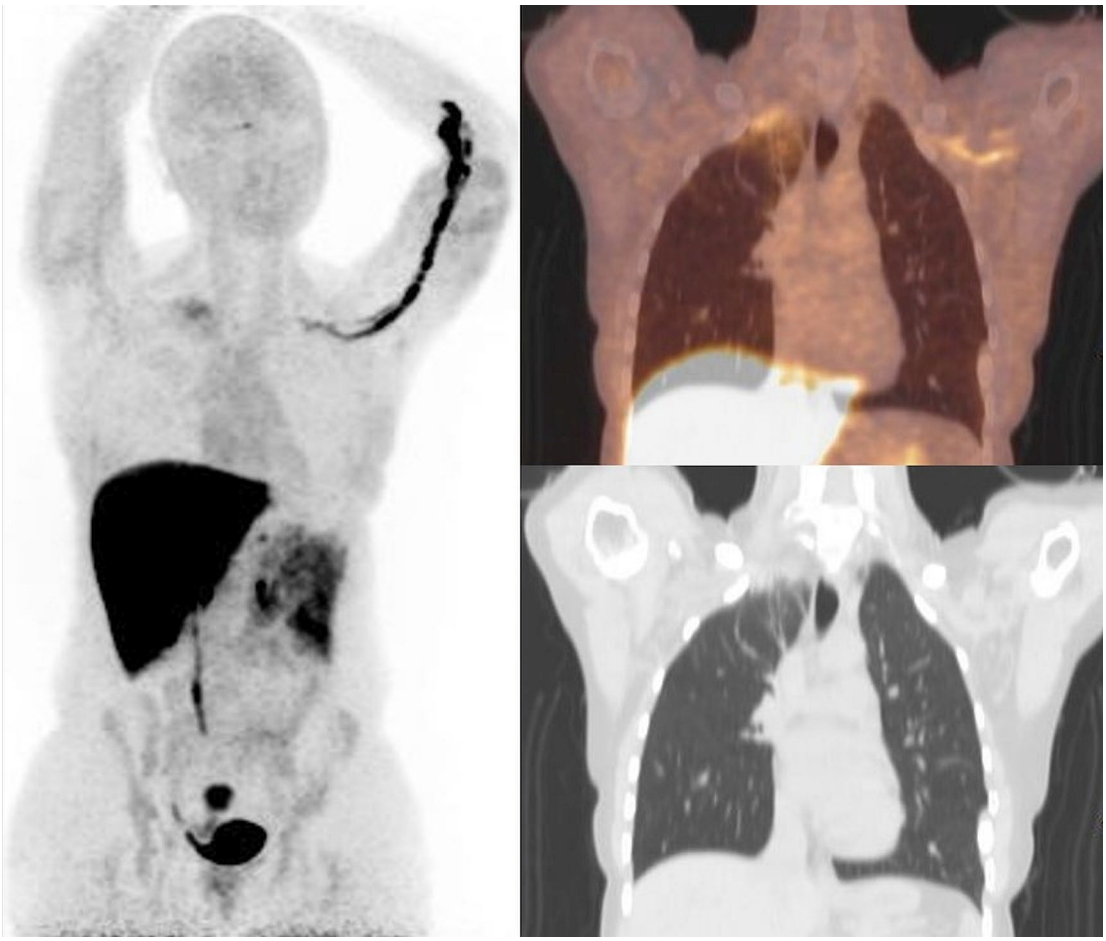


Figure 3: False-positive [^{18}F]FES PET example. Imaging of a patient with a history of an ER-expressing breast cancer and prior right breast radiotherapy shows false-positive [^{18}F]FES uptake in the right lung apex related to the impact of radiotherapy on adjacent lung. Residual tracer uptake in the infusion path from the left arm to the central circulation is seen, as is normal expected uptake in the uterus.



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