

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

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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 an important therapeutic target. Approximately 70% of breast cancers will express ER at presentation, and the determination of ER expression by tissue assay, usually by immunohistochemistry, is part of the standard of care for newly diagnosed breast cancer. ER expression is important in guiding the approach to treatment, especially with the increase in relevant systemic therapies. The ER-targeting imaging agent 16 α -[¹⁸F]fluoro-17 β -estradiol ([¹⁸F]FES) is approved for clinical use by regulatory agencies in France and the United States. Multiple studies suggest the advantages of [¹⁸F]FES PET in assessing tumor ER expression, the ability of both qualitative and quantitative [¹⁸F]FES PET measures to predict response to ER-targeted therapy, and the ability of [¹⁸F]FES PET to clarify equivocal staging and restaging results in patients with ER-expressing cancers. [¹⁸F]FES PET/CT may also be helpful in staging invasive lobular breast cancer and low-grade ER-expressing invasive ductal cancers and, in some cases, may be a substitute for biopsy. The Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine in June 2023 released a procedure standard/practice guideline for [¹⁸F]FES PET ER imaging of patients with breast cancer. The goal of the standard/guideline is to assist physicians in recommending, performing, interpreting, and reporting the results of [¹⁸F]FES PET studies for patients with breast cancer and to provide clinicians with the best available evidence, inform them about areas where robust evidence is lacking, and help them deliver the best possible diagnostic efficacy and study quality for their patients. Also reviewed are standardized quality control, quality assurance, and imaging procedures for [¹⁸F]FES PET. The authors emphasize the importance of precision, accuracy, repeatability, and reproducibility for both clinical management of patients and for use of [¹⁸F]FES PET in multicenter trials. A standardized imaging procedure, in combination with already published appropriate-use criteria, will help promote the use of [¹⁸F]FES PET and enhance subsequent research. This brief summary article reviews the content of the joint standard/guideline, which is available in its entirety at <https://www.snmmi.org/ClinicalPractice/content.aspx?itemNumber=6414&navItemNumbe=10790>.

Key Words: breast cancer; estrogen receptor imaging; practice guidelines; [¹⁸F]FES PET

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Breast cancer is the most common nonskin cancer in women and remains an important cause of mortality. Systemic therapy of both early- and later-stage breast cancer is an important contributor to decreased breast cancer mortality, and advances in individualized and targeted therapy have improved outcomes and mitigated treatment toxicity. 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. Approximately 70% of breast cancers will express ER at presentation, and the determination of ER expression by tissue assay—most commonly using immunohistochemistry methods—is part of the standard of care of newly diagnosed breast cancer. 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. After a long development period and research by selective centers capable of generating novel imaging compounds, the ER-targeted PET imaging agent 16 α -[¹⁸F]fluoro-17 β -estradiol ([¹⁸F]FES) was approved for clinical use by regulatory agencies in France and the United States. Support for the use of [¹⁸F]FES PET to diagnose ER-expressing breast cancer and guide ER-targeted therapy comes from several single-center studies and some recent prospective multicenter studies. These studies demonstrated the accuracy of [¹⁸F]FES PET in assessing tumor ER expression compared with tissue assay reference standards, the ability of both qualitative and quantitative measures of [¹⁸F]FES PET to predict response to ER-targeted therapy, and the ability of [¹⁸F]FES PET to clarify equivocal staging and restaging results in patients with ER-expressing cancers. More recent data have suggested that [¹⁸F]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. More data are needed to better determine efficacy in these tasks.

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The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) in June 2023 released “SNMMI Procedure Standard/EANM Practice Guideline for Estrogen Receptor Imaging of Patients with Breast Cancer Using 16 α -[¹⁸F]Fluoro-17 β -Estradiol PET.” The goal of the guidance is to assist physicians in recommending, performing, interpreting, and reporting the results of [¹⁸F]FES PET studies for patients with breast cancer. The document aims to provide clinicians with the best available evidence, to inform them of where robust evidence is lacking, and to help them deliver the best possible diagnostic efficacy and study quality for their patients. The guideline also presents standardized quality control, quality assurance, and imaging procedures for [¹⁸F]FES PET. Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of [¹⁸F]FES PET in multicenter trials. The availability of a standardized imaging procedure will help to promote

the appropriate use of [¹⁸F]FES PET and enhance subsequent research. This brief summary reviews the content of the joint standard/guideline, which is available in its entirety, including extensive reference citations, at <https://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414&navItemNumber=10790>. The reader is referred to the complete guideline for appropriate limitations and considerations in applying these and similar practice guidelines.

DEFINITIONS AND COMMON CLINICAL INDICATIONS

The complete standard/guideline provides definitions of relevant terms, based on the EANM procedure guidelines for tumor PET imaging (version 2.0), including ranges of PET/CT anatomic focus. Common clinical indications, as previously detailed in SNMMI appropriate-use criteria (1), include assessing lesions that are difficult to biopsy or when biopsy is nondiagnostic, guiding therapy after

TABLE 1
Reporting ER Imaging of Breast Cancer Using [¹⁸F]FES PET/CT

Category	Description
Required descriptions of findings on ...	Quality of PET image, including any technical issues
	Visual analysis of clinically relevant findings, including ...
	All sites of increased nonphysiologic focal uptake greater than local background suggestive of ER-positive lesions
	Any abnormal diffuse increased uptake
	Incidental findings with focal uptake, with further investigation suggested when needed
	Lesions identified by other imaging modalities as (suspected) tumor but not showing enhanced uptake (reported as [probable] ER-negative lesions)
Synthesis of overall report impression	Quantitative analysis of sites of suspected disease, including where active disease is expected on basis of correlative imaging but visual inspection does not show uptake above background
	Detailed qualitative interpretation, specific to indication and individual clinical data, taking into consideration physiologic biodistribution of [¹⁸ F]FES
	Summary of patient history, including current and prior medications targeted to ER-expressing breast cancer
	Summary of technical components of scan, including injected activity and uptake time
	Description of areas with physiologic uptake, metabolism, and excretion of [¹⁸ F]FES
	Identification and description of sites of qualitatively abnormal uptake above background that are suspected of being ER-expressing breast cancer, including anatomic localization on CT, qualitative level of uptake, and size of lesion by CT when relevant
	Quantitative uptake for sites identified by qualitative interpretation, noting that [¹⁸ F]FES SUV _{max} > 1.5 is suggestive of ER expression
	Description of suspected false-positive or nonspecific findings
	Description of sites where uptake may be absent in lesions observed by other available imaging techniques
	Summary of heterogeneity of uptake 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
	Specific mention of qualitative and quantitative uptake by equivocal lesions, with conclusion on whether questioned lesions are ER-positive or -negative
	If [¹⁸ F]FES PET is acquired for therapy purposes, specific mention of overall qualitative and quantitative ER status of metastases, including heterogeneity of expression
For interpreting physicians, section on limitations and pitfalls of [¹⁸ F]FES PET	

This table is condensed from information in complete joint standard/guideline, available at <https://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414&navItemNumber=10790>.

progression of metastatic disease, guiding therapy at initial presentation of metastatic disease, and detecting ER-expressing breast cancer sites when other imaging tests have equivocal or suggestive results. Other emerging indications under investigation include detecting ER-expressing lesions in patients with suspected or known recurrent or metastatic breast cancer; assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy; staging invasive lobular breast cancer and low-grade ER-expressing invasive ductal cancer; and routine staging of ER-expressing extraaxillary nodes and distant metastases. Other studies suggest that [¹⁸F]FES PET can be used for detection and characterization of ER-expressing tumors other than breast cancer, such as ovarian and endometrial cancer.

The full standard/guideline details the qualifications and responsibilities of personnel performing [¹⁸F]FES PET imaging, including physicians, technologists, and medical physicists. An overview of [¹⁸F]FES properties and clinical pharmacology, as well as a review of [¹⁸F]FES biodistribution and dosimetry, is included.

PROCEDURE SPECIFICATIONS

The full standard/guideline provides comprehensive consensus specifications for practice. Detailed recommendations cover patient referral and selection through dosimetry, the imaging procedure, and both qualitative and quantitative interpretation and reporting of findings.

PATIENT SELECTION AND PREPARATION

Scheduling, including nuclear pharmacy ordering and patient preparation and precautions, is reviewed, along with a useful table of clinical information required at the time of referral. Special considerations for patients taking drugs that block the ER and reduce uptake of [¹⁸F]FES, such as tamoxifen and fulvestrant, are noted, with suggested required periods of withdrawal from these agents before [¹⁸F]FES PET is attempted.

TRACER ADMINISTRATION AND IMAGING

The full standard/guideline details the administration process for [¹⁸F]FES, the recommended administered activity (varying between 111 and 280 MBq [3–7.6 mCi]), and the mechanisms and timing of uptake for optimal imaging (usually 20–80 min after injection, with a 60-min uptake time suggested). PET/CT image acquisition considerations are reviewed, including recommended scan ranges and optional concurrent acquisition of CT images with contrast, as well as image reconstruction and processing.

IMAGE INTERPRETATION AND REPORTING

The most detailed portion of the full standard/guideline addresses the process of image interpretation and reporting of findings, with relevant recommendations specific to [¹⁸F]FES breast imaging. Initial areas covered include technical details to be noted in the report and useful background information on expected [¹⁸F]FES biodistribution and uptake in areas relevant to interpretation.

Recommended descriptions of findings and summary impressions are reviewed in the guideline and are condensed here in Table 1. Considerations of specific relevance to [¹⁸F]FES and ER binding in determining and reporting both false-negative and false-positive findings are also addressed. Of special note are recommendations on reporting and interpreting quantitative measures, including what measures to record. Although qualitative assessment is usually sufficient to discriminate a positive from a negative scan, quantitative measurements may be of additional value. In particular, when qualitative assessment is equivocal, quantitative assessment can aid in defining whether a scan should be considered positive, although careful scanner calibration is needed to interpret SUV measures.

Current findings on the potential of [¹⁸F]FES PET for quantitative prediction of treatment efficacy or failure and for serial assessment of ER-blocking drugs to assess the adequacy of receptor blockade are reviewed, as well as guidance in dosing of new drugs.

Correlative imaging, in addition to the CT component of PET/CT, is discussed as being especially important and helpful for guiding [¹⁸F]FES PET/CT interpretation and evaluation of ER heterogeneity. When [¹⁸F]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. This is one of several areas identified as needing further study. Overall, it is helpful to report [¹⁸F]FES PET/CT results in the context of contemporaneous [¹⁸F]FDG PET/CT results—both qualitatively and quantitatively—the results of other conventional imaging.

SUMMARY

The complete “SNMMI Procedure Standard/EANM Practice Guideline for Estrogen Receptor Imaging of Patients with Breast Cancer Using 16α-[¹⁸F]Fluoro-17β-Estradiol PET” provides the first comprehensive professional consensus specifications for practice, from patient referral and selection through dosimetry, the imaging procedure, and both qualitative and quantitative interpretation and reporting of findings. The availability of a standardized imaging procedure will help promote the appropriate clinical use of [¹⁸F]FES PET and enhance subsequent research.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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