Summary: Appropriate Use Criteria for Estrogen Receptor–Targeted PET Imaging with 16α-^{18}F-Fluoro-17β-Fluoroestradiol

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PET imaging with 16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES), a radiolabeled form of estradiol, allows whole-body, noninvasive evaluation of estrogen receptor (ER). ^{18}F-FES is approved by the U.S. Food and Drug Administration as a diagnostic agent "for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer." The Society of Nuclear Medicine and Molecular Imaging (SNMMI) convened an expert work group to comprehensively review the published literature for ^{18}F-FES PET in patients with ER-positive breast cancer and to establish appropriate use criteria (AUC). The findings and discussions of the SNMMI ^{18}F-FES work group, including example clinical scenarios, were published in full in 2022 and are available at https://www.snmmi.org/auc. Of the clinical scenarios evaluated, the work group concluded that the most appropriate uses of ^{18}F-FES PET are to assess ER functionality when endocrine therapy is considered either at initial diagnosis of metastatic breast cancer or after progression of disease on endocrine therapy, the ER status of lesions that are difficult or dangerous to biopsy, and the ER status of lesions when other tests are inconclusive. These AUC are intended to enable appropriate clinical use of ^{18}F-FES PET, more efficient approval of FES use by payers, and promotion of investigation into areas requiring further research. This summary includes the rationale, methodology, and main findings of the work group and refers the reader to the complete AUC document.

Key Words: 16α-^{18}F-fluoro-17β-fluoroestradiol; appropriate use criteria; estrogen receptor–targeted PET imaging

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Estrogen receptor (ER) status is currently routinely determined by immunohistochemistry of tissue samples (*1*). However, biopsy is invasive, and the lesion may be in a location that is difficult to biopsy (*2*). Because ER expression may vary spatially and temporally, the results obtained from a tissue sample may incompletely represent a patient's ER receptor distribution (*2–9*). Moreover, not all tumors that are ER-positive by immunohistochemistry respond to ER-targeted therapy (*10,11*). Alternative methods for evaluation of ER status are needed.

16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES) is a radiolabeled form of estrogen that binds to ER. PET imaging with ^{18}F-FES allows noninvasive identification of functional ER distribution (*10,11*). ^{18}F-FES uptake measured by PET correlates with ER immunohistochemistry (*7,12–17*), successfully demonstrates ER heterogeneity within individual patients (*4–6,18,19*), serves as a prognostic biomarker (*9,19–21*), provides high diagnostic accuracy for detection of ER-positive metastases (*2,7,10,15,17,22–24*), and can assess the efficacy of ER blockade (*25–28*).

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) in 2021 convened an ^{18}F-FES PET appropriate use criteria (AUC) work group made up of a multidisciplinary panel of health-care providers and researchers with substantive knowledge of breast cancer and breast cancer imaging. In addition to SNMMI members, representatives from the American College of Nuclear Medicine, the Korean Society of Nuclear Medicine, and the Lobular Breast Cancer Society were included in the work group. The purpose of these AUC is to provide expert opinion on clinical scenarios in which ^{18}F-FES PET will have an impact on management of patients with ER-positive breast cancer. The complete "Appropriate Use Criteria for Estrogen Receptor-Targeted PET Imaging with 16α-^{18}F-Fluoro-17β-Fluoroestradiol," with extensive reference documentation and other supporting material, is freely available on the SNMMI website at www.snmmi.org/auc.

METHODOLOGY

AUC Development

The work group identified 14 clinical scenarios for patients with ER-positive breast cancer for which physicians may want guidance on whether ^{18}F-FES PET would be considered appropriate.

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The work group then conducted a systematic review of evidence related to these scenarios and determined an appropriateness score for each scenario using a modified Delphi process (*29*).

The protocol for this guideline was reviewed and approved by the SNMMI guidance oversight committee and the U.S. Food and Drug Administration. The PubMed, MEDLINE, Embase, Web of Science, and Cochrane Collaboration Library electronic databases were searched for evidence that reported on outcomes of interest, with updates in the literature through June 2022.

After a complex consensus-based rating process as outlined in the complete AUC, final appropriate use scores were summarized for each clinical scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9 (Table 1). The work group emphasized that ^{18}F-FES PET is a unique imaging test that is independent from other clinically available radiotracers, such as ^{18}F-FDG PET.

Clinical Scenarios

The complete AUC document provides the evidence and data limitations for each of the 14 clinical scenarios. Summarized here is the evidence for 4 clinical scenarios for which the work group determined ^{18}F-FES PET as "appropriate" and 1 scenario deemed "may be appropriate" with substantial current investigation.

Clinical Scenario 8: Assessing ER Status in Lesions That Are Difficult to Biopsy or When Biopsy Is Nondiagnostic (Score: 8—Appropriate). The work group regarded the use of ^{18}F-FES PET as appropriate to assess ER status when the lesions are difficult to biopsy. Published examples on the use of ^{18}F-FES PET for this clinical indication are available (*2*). Lesions may be in locations that make biopsy difficult or impose substantial risk. Examples include brain lesions, spinal lesions deep to the spinal cord, or lesions adjacent to major vascular structures. In these cases, the high correlation of ^{18}F-FES PET with ER immunohistochemistry (*2,7,10,24*) may favor noninvasive imaging over the risks of biopsy.

TABLE 1
Clinical Scenarios for ER–Targeted PET with ^{18}F-FES

Scenario number	Description	Appropriateness	Score*
Diagnosis			
1	Diagnosing primary breast cancer	Rarely appropriate	2
2	Diagnosing malignancy of unknown primary when biopsy is not feasible or is nondiagnostic	May be appropriate	5
Staging			
3	Routine staging of primary tumor (T staging)	Rarely appropriate	1
4	Routine staging of axillary nodes	Rarely appropriate	3
5	Routine staging of extraaxillary nodes and distant metastases	May be appropriate	5
6	Staging ILC and low-grade IDC	May be appropriate	5
Biopsy			
7	Assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy	May be appropriate	5
8	Assessing ER status in lesions that are difficult to biopsy or when biopsy is nondiagnostic	Appropriate	8
Selection of therapy			
9	After progression of metastatic disease, for considering second line of endocrine therapy	Appropriate	8
10	At initial diagnosis of metastatic disease, for considering endocrine therapy	Appropriate	8
11	At initial diagnosis of primary breast cancer, for considering endocrine therapy	Rarely appropriate	1
Other			
12	Measuring response to therapy	Rarely appropriate	1
13	Detecting lesions in patients with suspected/known recurrent or metastatic breast cancer	May be appropriate	5
14	Detecting ER status when other imaging tests are equivocal or suggestive	Appropriate	8

*Work group scored each clinical scenario on scale from 1 to 9: scores of 7–9 indicate that procedure is appropriate for specific scenario and is generally considered acceptable; scores of 4–6 indicate that procedure may be appropriate for specific scenario and may imply that more evidence is needed to definitively classify scenario; and scores of 1–3 indicate that procedure is rarely appropriate for specific clinical scenario and is generally not considered acceptable. Division of scores into 3 general levels of appropriateness is partially arbitrary, and numeric designations should be viewed as continuum. ER = estrogen receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

Clinical Scenario 9: After Progression of Metastatic Disease, for Considering Second Line of Endocrine Therapy (Score: 8—Appropriate) and Clinical Scenario 10: At Initial Diagnosis of Metastatic Disease, for Considering Endocrine Therapy (Score: 8—Appropriate). There are several endocrine axis therapies for patients with breast cancer. These therapies act by decreasing available estrogens, degrading ER, blocking estrogen binding to ER, or decreasing downstream effects of ER signaling (*30*). The presence of ER by immunohistochemistry may not be the optimal predictive biomarker for the success of endocrine axis therapies. Patients with recurrent or metastatic ER-positive breast cancer may develop endocrine resistance despite remaining ER-positive on immunohistochemistry (*31*). Several investigators have studied ^{18}F-FES PET as a potentially superior predictive biomarker for determining whether patients with breast cancer will be successfully treated by endocrine axis therapies. To date, at least 17 prospective trials have demonstrated ^{18}F-FES PET to be successful in this role (*19–21,25,26,32–43*), as reviewed by Ulaner (*44*). These trials represent 547 subjects with ER-positive breast cancer undergoing endocrine axis therapies ranging from the earlier agents, such as tamoxifen, to the more recent introduction of aromatase inhibitors and inhibitors of cyclin-dependent kinases 4 and 6. The work group stated that this body of evidence provided strong support for the use of ^{18}F-FES PET to assist with treatment selection for patients with metastatic ER-positive breast cancer considering endocrine axis therapies. Given that more than 100,000 patients live with ER-positive metastatic breast cancer (*45*), the use of ^{18}F-FES PET for this clinical scenario has the potential to prevent large numbers of patients from receiving ineffective courses of endocrine therapies, to save time, and to reduce unnecessary side effects and the costs of ineffective treatments.

Clinical Scenario 14: Detecting ER Status When Other Imaging Tests Are Equivocal or Suggestive (Score: 8—Appropriate). It is not uncommon for imaging studies to be inconclusive or equivocal. Several studies have evaluated the ability of ^{18}F-FES PET to solve clinical dilemmas when findings on other imaging modalities were equivocal or inconclusive (*46–49*). These 4 studies include ^{18}F-FES PET scans on 181 patients with breast cancer, with more than half of ^{18}F-FES PET scans leading to alterations in patient treatment based on knowledge gained from ^{18}F-FES PET. The work group was unanimous that ^{18}F-FES was appropriate for patients with an ER-positive breast cancer and equivocal prior imaging studies, if assessment of ER status by ^{18}F-FES could change patient management.

Clinical Scenario 6: Staging Invasive Lobular Carcinoma (ILC) and Low-Grade Invasive Ductal Carcinoma (IDC) (Score: 5—May Be Appropriate). ILC is a disease distinct from the more common IDC, with unique genetic, molecular, and pathologic features (*50*). Interpretation of breast cancer imaging is influenced by tumor histology. For example, primary ILC is more difficult to detect than IDC on mammography, ultrasound, MRI, and ^{18}F-FDG PET (*51,52*). Low-grade IDC and ILC malignancies are more likely to display metastases with lower ^{18}F-FDG avidity (*52–54*). ^{18}F-FDG PET/CT has lower rates of detecting distant metastases in ILC than in IDC (*55*). Because low-grade IDC and ILC are nearly always ER-positive (*50,56*), investigators have suggested that ER-targeted imaging may be of value for patients with these malignancies, particularly when disease is not appreciable on ^{18}F-FDG PET. A head-to-head comparison of patients with metastatic ILC lesions found more than twice as many ^{18}F-FES–avid lesions as ^{18}F-FDG–avid lesions in patients who underwent both scans (*57*). The work group believes this is an area in which larger prospective trials are needed.

SUMMARY

^{18}F-FES is a radiolabeled form of estrogen that binds to ER. PET imaging with ^{18}F-FES allows noninvasive and whole-body evaluation of ER that is functional for binding. The full AUC document described in this summary represents the expert opinions of a work group convened by the SNMMI to evaluate clinical scenarios for use of ^{18}F-FES PET in patients with ER-positive breast cancer, based on a comprehensive review of the published literature. The work group concluded that the most appropriate uses of ^{18}F-FES PET are for scenarios in which clinicians are considering endocrine therapy, either after progression on a prior line of endocrine therapy or at initial diagnosis of metastatic disease; for assessing the ER status of lesions that are difficult or dangerous to biopsy; and for determining the ER status of lesions when other imaging tests have inconclusive results. The complete findings and discussions of the SNMMI ^{18}F-FES work group are available at https://www.snmmi.org/auc.

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