^{18}F-Fluoroestradiol PET: Current Status and Potential Future Clinical Applications

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Learning Objectives: On successful completion of this activity, participants should be able to describe (1) the biology and pharmacokinetics of ^{18}F-fluoroestradiol; (2) the current experience with ^{18}F-fluoroestradiol in patient studies on breast cancer and other diseases; and (3) potential clinical applications and the possible future clinical use of ^{18}F-fluoroestradiol PET.

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Estrogen receptor (ER) expression in breast cancer is associated with a more favorable prognosis and is necessary for a response to endocrine therapies. Traditionally, ER expression is assessed by in vitro assays on biopsied tumor tissue. However, recent advances have allowed in vivo evaluation of ER expression with ^{18}F-fluoroestradiol (^{18}F-FES) PET. Clinical studies have demonstrated the use of ^{18}F-FES PET as a method for quantifying in vivo ER expression and have explored its potential as a predictive assay and method of assessing in vivo pharmacodynamic response to endocrine therapy. This review outlines the biology and pharmacokinetics of ^{18}F-FES, highlights the current experience with ^{18}F-FES in patient studies on breast cancer and other diseases, and discusses potential clinical applications and the possible future clinical use of ^{18}F-FES PET.

Key Words: estrogen receptor; positron emission tomography; breast cancer; ^{18}F-fluoroestradiol

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Breast cancer is the most common cancer in women and the second most common cause of cancer death in women in the United States, with an estimated 231,840 new diagnoses in 2015 (*1*). Approximately 75% of newly diagnosed patients have estrogen receptor (ER)–expressing breast tumors, which are associated with a more favorable prognosis (*2*). ER expression in breast cancer is traditionally assessed by in vitro assays on biopsied tissue using qualitative or semiquantitative immunohistochemical staining (*3*). A tumor's ER status predicts the likelihood of a response to ER-targeted therapy, also known as endocrine or hormone therapy (*4*). Although absence of ER by in vitro assay indicates a low likelihood of response and is associated with a worse prognosis, the presence of ER by immunohistochemistry does not necessarily guarantee a response to endocrine therapy (*5*). Nevertheless, it is important to identify ER-positive patients with recurrent and metastatic disease, who may respond to hormone therapy and potentially avoid the toxic side effects of chemotherapy (*6*).

For patients with advanced or metastatic ER-positive disease, the advent of PET and PET/CT has made it possible to evaluate ER expression in all metastatic lesions without multiple biopsies. Used with ^{18}F-FDG to detect increased glucose metabolism, PET imaging possesses widespread oncologic applications (*7*). In breast cancer, ^{18}F-FDG PET/CT is recommended primarily for locally advanced or metastatic disease when standard staging studies are equivocal or suggestive (*8*).

Other radiotracers have subsequently been developed to better characterize tumor biology, including ^{18}F-fluoroestradiol (^{18}F-FES). ^{18}F-FES targets ER, enabling in vivo imaging of ER-expressing tissues. In conjunction with ^{18}F-FDG PET or other standard imaging, ^{18}F-FES PET has the potential to assess heterogeneity in ER expression and identify sites that have lost ER expression or functionality. ^{18}F-FES PET has been evaluated in numerous breast cancer clinical studies as a promising method for quantifying in vivo ER expression, predicting response to hormone therapy, and evaluating effective ER blockade (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). This review provides a background for practitioners by highlighting the biology and pharmacology of ^{18}F-FES, reviewing current clinical experience with ^{18}F-FES, and summarizing its potential applications.

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^{18}F-FES STRUCTURE, SYNTHESIS, PHARMACOKINETICS, AND SAFETY

Early efforts to develop an ER-targeting radiotracer involved labeling steroid and nonsteroid compounds with iodine and bromine (*9*). However, the subsequent advent of PET imaging and ^{18}F—a small halogen that displayed uptake in target tissue, elimination in nontarget tissue, substitution at several positions in various estrogen analogs, and a half-life long enough to allow for multistep synthesis (*10,11*)—encouraged the development of ^{18}F-labeled compounds.

In 1984, Kiesewetter et al. found that ^{18}F-FES exhibited the highest uptake selectivity and target-to-background ratio among several ^{18}F-labeled estrogens (*10*). Newer compounds such ^{18}F-moxestrol and 4-fluoro-11β-methoxy-16α-^{18}F-FES demonstrated increased ER binding, with ^{18}F-moxestrol also displaying decreased metabolism (*12,13*). However, ^{18}F-moxestrol displays suboptimal uptake in humans, which likely arises from modest binding to sex-hormone–binding globulin (SHBG), the main plasma protein estradiol transporter, compared with ^{18}F-FES (*12*). Although adequate uptake in humans has been demonstrated by 4-fluoro-11β-methoxy-16α-^{18}F-FES, tumor uptake comparison studies and further testing are needed. To date, ^{18}F-FES remains the most widely studied ER PET imaging compound.

^{18}F-FES is highly extracted and metabolized by the liver, resulting in rapid early blood clearance and steady total blood activity by 10–15 min after injection (*11*). By 20 min after injection, only 20% of the total activity is attributable to unmetabolized ^{18}F-FES; by 120 min, only 10%. Like estradiol, unmetabolized ^{18}F-FES is heavily protein-bound in blood. Although ^{18}F-FES has much higher affinity for SHBG than for albumin, the higher concentration of albumin in blood results in an approximately 1:1 distribution of ^{18}F-FES between SHBG and albumin (*14*). Its non-SHBG–bound metabolites, comprised of glucuronide and sulfate conjugation products (*11*), are secreted in bile, resorbed via enterohepatic circulation, and renally excreted. The rate of decline in total liver activity is similar to the rate of increase in total bladder activity, suggesting that ^{18}F-FES metabolites are cleared by the kidneys at nearly the same rate as they are released into the circulation by the liver (*11*). At the highest recommended dose, 2.22×10^8 Bq, the effective dose equivalent is 0.002 mSv/MBq, with the critical organ being the liver, at 0.13 mSv/MBq (*15*). Cumulative experience in published human studies has yet to demonstrate any associated toxicities or adverse events. Collectively, these characteristics make ^{18}F-FES a favorable ER PET imaging tracer.

^{18}F-FES has been studied as an investigational diagnostic agent in Canada, Europe, and Asia. Although it is currently considered an investigational drug in the United States, several American academic centers hold Investigational New Drug approvals that support studies involving ^{18}F-FES PET and ^{18}F-FES PET/CT. The National Cancer Institute also holds an Investigational New Drug approval (79,005)—enabled by a University of Washington study (*16*)—that can support multicenter trials in National Cancer Institute–supported clinical trial networks. There has been discussion in Europe and the United States of seeking regulatory approval for ^{18}F-FES on the basis of published studies and accruing data from prospective multicenter trials.

CORRELATION OF ^{18}F-FES UPTAKE AND TUMOR ER EXPRESSION

Multiple studies have demonstrated a correlation between ^{18}F-FES uptake and tumor ER expression as measured by conventional in vitro assays (Supplemental Table 2). In 1988, Mintun et al. verified the association between ^{18}F-FES uptake and in vitro tumor ER concentration as measured by radioligand binding among patients with primary breast masses (*17*). Subsequent studies established the correlation between ^{18}F-FES uptake and immunohistochemical assay results. Peterson et al. used an SUV threshold of 1.1 to characterize tumors as ER-positive or ER-negative, reporting a correlation coefficient of 0.73 between ^{18}F-FES uptake and immunohistochemical index results (*18*) consistent with correlations from studies comparing in vitro radioligand binding assays to immunohistochemical assays (*19*).

Peterson et al. also studied the correlation between immunohistochemical assays and other ^{18}F-FES uptake quantification methods, finding that those that accounted for variable blood clearance and the presence of labeled ^{18}F-FES metabolites provided no definite advantages over simpler SUV measurements (*18*). More recently, ^{18}F-FES uptake and immunohistochemical ER expression have been demonstrated in early-stage breast cancers, though with a lower sensitivity than found in prior studies (*20*).

Other factors that can affect tumor ^{18}F-FES uptake have also been evaluated. Prior analyses posited that competition with higher circulating estrogen levels in premenopausal women may contribute to false-negative ^{18}F-FES PET results (*21*). However, Peterson et al. subsequently demonstrated no significant difference in average ^{18}F-FES uptake based on a plasma estradiol threshold of 30 pg/mL, a level typically used to indicate menopausal status (*22*). In this same study, F-FES uptake was inversely associated with plasma SHBG levels but not with testosterone levels, patient age, or disease stage at time of imaging—discrepancies suggesting that although a certain amount of binding to SHBG may be necessary to protect F-FES from metabolism, protein-bound ^{18}F-FES may be less available to tissue ER receptors and result in decreased ^{18}F-FES uptake. Thus, measurement of SHBG levels in patients could be considered, especially in clinical scenarios such as the postpartum period, when SHBG levels might be expected to be outside the typical range.

This study also revealed only a modest effect of lower injected specific activities on ^{18}F-FES uptake, suggesting that cold ^{18}F-FES would not significantly saturate tissue ERs at specific activities of greater than approximately 11.1 GBq/mol. However, since a small (~10%) negative effect on ^{18}F-FES uptake was noted for injected ^{18}F-FES masses greater than 0.2 nmol/kg, injected mass should aim to be below this value (*22*).

BASELINE ^{18}F-FES UPTAKE AS A PREDICTOR OF RESPONSE TO ENDOCRINE THERAPY

For patients with ER-positive breast cancer, endocrine therapy can potentially provide effective treatment with fewer side effects and lower morbidity than chemotherapy (*6*). However, ER positivity correctly predicts response in only 50%–60% of treatment-naïve patients (*5*) as measured by in vitro immunohistochemical assays, which require biopsies and are thus limited by sampling error and disease heterogeneity. In contrast, ^{18}F-FES PET can evaluate ER expression across all tumor sites and present a more complete picture of a patient's overall ER status.

Studies have demonstrated a correlation between response to endocrine therapy and baseline pretreatment ^{18}F-FES uptake (Supplemental Table 3). Both Dehdashti et al. and Mortimer et al. investigated baseline ^{18}F-FES uptake in ER-positive patients beginning tamoxifen

therapy (*23,24*). Using a threshold SUV of 2.0 for baseline ^{18}F-FES uptake, they reported a positive predictive value of 79%–87% and negative predictive value of 88%–100% for response.

The utility of baseline ^{18}F-FES PET imaging has also been demonstrated in patients undergoing salvage therapy with aromatase inhibitors (AIs) and fulvestrant. In a study of patients with heavily pretreated metastatic breast cancer, Linden et al. established a threshold ^{18}F-FES SUV of 1.5 for baseline ^{18}F-FES uptake, below which no patient responded (Supplemental Fig. 1) (*25*). Using a higher SUV threshold of 2.0, Dehdashti et al. demonstrated a negative predictive value of 81% for response (*26*). Both studies demonstrated a poor positive predictive value of 34%–50%, a finding consistent with known decreased objective response rates to endocrine therapy among those with recurrent and previously treated disease (*27*).

Taken together, these studies demonstrate the value of ^{18}F-FES PET in predicting endocrine responsiveness or unresponsiveness. Data from 4 studies evaluating response to tamoxifen, AIs, and fulvestrant (*23–26*) reveal that of the 159 patients who underwent pretreatment ^{18}F-FES PET imaging, only 1 with a baseline ^{18}F-FES SUV of less than 1.5 responded to endocrine therapy by demonstrating disease stabilization (Supplemental Fig. 2) (*26*).

Applying an SUV threshold of 1.5 to these data, van Kruchten et al. studied the relationship between baseline ^{18}F-FES PET and response to low-dose oral estradiol as salvage therapy (*28*). It is thought that long-term antiestrogen therapy may induce hypersensitivity to estrogens, whereby estrogen exposure activates apoptosis rather than growth pathways (*29*). In this scenario, the presence of ER, which could be measured by ^{18}F-FES PET, is necessary to induce these apoptotic pathways. The threshold SUV of 1.5 demonstrated a positive predictive value of 60% and negative predictive value of 80% for response to low-dose estradiol (*28*).

An alternative approach to predicting response uses ^{18}F-FDG PET imaging, which has been established as a predictive biomarker in cancers such as lymphoma (*30*). In breast cancer, a clinical flare can occasionally be seen with therapeutic agents possessing ER-agonist properties, where symptom exacerbation upon therapy initiation predicts subsequent response (*31*). Studies have shown that ^{18}F-FDG PET can also detect subclinical metabolic flares in patients who subsequently respond to therapy (*23,24*). ^{18}F-FDG PET can manifest transient agonist activity early after initiation of tamoxifen therapy. Comparison of ^{18}F-FDG PET findings before and 7–10 d after initiation of tamoxifen showed increased ^{18}F-FDG uptake in patients who subsequently responded but no significant change in uptake in nonresponders. Metabolic flare induced by an estradiol challenge was also predictive of response to AIs and fulvestrant as well as improved survival (*26*).

Studies supporting both pretherapy ^{18}F-FES PET and early serial ^{18}F-FDG PET to predict endocrine responsiveness have generated debate about which approach is more clinically applicable. Both radiotracers show a high negative predictive value for endocrine responsiveness, but serial ^{18}F-FDG PET possesses a higher positive predictive value for response than does pretherapy ^{18}F-FES PET (*23,24*). Some also argue that ^{18}F-FDG PET is more widely available and applied in the setting of metastatic breast cancer. However, serial ^{18}F-FDG PET requires 2 PET scans and exposure to a therapy with ER-agonist properties. In contrast, a single baseline ^{18}F-FES PET study is able to predict response for various endocrine therapies before any exposure to therapy, directing patients without ER expression away from likely unbeneficial endocrine treatments. In addition, the increasing use of therapeutic strategies combining endocrine and other targeted therapy increases the need to determine ER expression and suitability for combined treatment. One potential framework for combining both approaches would be to first use ^{18}F-FES to confirm target expression in patients whose tumors express ER and then use serial ^{18}F-FDG PET or another standard modality to predict responsiveness by assessing the pharmacodynamic response to a specific type of therapy (Supplemental Fig. 3) (*32*).

ABILITY OF ^{18}F-FES PET TO ASSESS WHOLE-BODY TUMOR BURDEN AND HETEROGENEITY OF DISEASE

One major advantage of ^{18}F-FES PET is its ability to noninvasively assess the in vivo ER status of several tumor lesions across the whole body simultaneously. Evaluating for lesions with discordant ^{18}F-FDG and ^{18}F-FES uptake can determine the heterogeneity of a patient's disease (Supplemental Fig. 4) (*16,25,33,34*).

Studies correlating ^{18}F-FES uptake with in vitro ER expression and response to hormone therapies have demonstrated the ability of ^{18}F-FES PET to image metastatic disease in vivo (Supplemental Table 4) (*17,21,33*). Among multiple metastatic sites in individual patients, ^{18}F-FES uptake was concordant with in vitro ER expression (*33*). Patients with discordant in vitro ER expression and ^{18}F-FES uptake (i.e., ER-positive but ^{18}F-FES–negative) tended to have a decreased response to hormone therapy, suggesting that ^{18}F-FES PET may identify tumor sites that are ER-positive by in vitro assay but functionally hormone therapy–resistant (*16,33,34*).

Kurland et al. specifically studied the within-patient and between-patient concordance of ^{18}F-FES uptake and a previously documented ER-positive biopsy (*35*). Although ^{18}F-FES uptake and the ratio of ^{18}F-FES to ^{18}F-FDG uptake were generally consistent across a single patient, these values varied greatly between patients despite the fact that all but one originally had ER-positive primary tumors. Thirty-four of the 91 patients, many of whom had already undergone treatment with one or more antiestrogen therapies, had an average ^{18}F-FES SUV below 1.0, suggesting that exposure to endocrine therapy may impose selective pressure for tumor phenotypes with low or nonfunctional ER expression.

There was also a small number of patients who demonstrated highly discordant ^{18}F-FES uptake across sites (i.e., ^{18}F-FES–positive and ^{18}F-FES–negative lesions), a finding that possibly reflects an emerging loss of ER expression in only some lesions. In another study evaluating within-patient concordance of ^{18}F-FES uptake, discordant ^{18}F-FES uptake was seen only in patients pretreated with endocrine therapy (*36*).

Potential discrepancies in tumor ER status and ^{18}F-FES uptake are particularly important for women with recurrent or metastatic disease. Several studies have demonstrated that although a primary tumor may have been ER-positive, its metastatic lesions may no longer express ER or may express only nonfunctional ERs (*16,33,34*). Because it is clinically infeasible to biopsy all sites of disease to determine overall ER expression, or to make a patient undergo repeated biopsies to evaluate tumor phenotype evolution, ^{18}F-FES PET imaging could represent an important adjunct for monitoring ER expression at the time of disease progression or throughout a treatment course.

UTILITY OF ^{18}F-FES PET IN ASSESSING IN VIVO PHARMACODYNAMICS

Several investigators have used ^{18}F-FES PET to study the in vivo pharmacodynamics of standard endocrine therapies (*23,24,37,38*)

and validate new investigational ER antagonists (Supplemental Table 5) (*39,40*). McGuire et al. used repeated ^{18}F-FES PET imaging to demonstrate a change in ^{18}F-FES uptake after initiation of endocrine therapy. Compared with the baseline ^{18}F-FES PET scan, decreased ^{18}F-FES uptake at known metastatic lesions 7–10 d after initiation of tamoxifen provided evidence of receptor-mediated tumor uptake of ^{18}F-FES (*41*). Mortimer et al. demonstrated similar decreases in ^{18}F-FES uptake in patients receiving tamoxifen (*24*) and showed that the mean percentage decrease in ^{18}F-FES uptake after initiation of therapy was significantly higher in responders (54.8% ± 14.2%) than in nonresponders (19.4% ± 17.3%; P = 0.0003).

Linden et al. evaluated changes in ^{18}F-FES uptake in patients receiving tamoxifen, AIs, or fulvestrant (*37*). As expected, treatment with tamoxifen, a selective ER modulator, and fulvestrant, a selective ER downregulator, was associated with a greater decrease in ^{18}F-FES uptake than treatment with AIs, which decrease the amount of circulating estrogen and do not act directly on ER. Van Kruchten et al. also used ^{18}F-FES PET to study the effects of fulvestrant on ^{18}F-FES uptake (*38*). Thirty-eight percent of patients demonstrated incomplete reduction of ^{18}F-FES uptake (defined as less than a 75% decrease in median tumor SUV), which was significantly associated with shorter progression-free survival. There was also wide variance in the median change in ^{18}F-FES SUV before and after initiation of therapy (−99% to +60%), with significantly larger decreases in patients with clinical response than in those with disease progression (median change in SUV, −88% vs. −58%). Neither clinical response nor degree of change in ^{18}F-FES uptake correlated with plasma drug levels of fulvestrant, pointing to the unique potential of ^{18}F-FES PET in evaluating the effects of fulvestrant at the receptor level.

In a related preclinical study, Heidari et al. demonstrated that increasing fulvestrant doses in murine xenografts led to parallel decreases in ^{18}F-FES uptake and ER expression by immunohistochemical assay and that these did not correlate with ^{18}F-FDG uptake (*42*). These findings suggest that changes in ER availability occur before detectable changes in tumor metabolism and growth. Since higher doses (750 mg vs. 500 mg) of fulvestrant have been studied with minimal increase in side effects (*43*), serial ^{18}F-FES PET imaging could conceivably be used to measure early blockade of ER to guide individualized ER-antagonist dosing. However, this approach would require further testing to determine its accuracy and impact.

These concepts could also be applied to new investigational endocrine therapies, both to demonstrate effective ER blockade and to identify optimal dosing for complete ER downregulation. Wang et al. described a new ERα antagonist, ARN-810, and used ^{18}F-FES PET to validate ER target engagement (*39*). Dickler et al. then evaluated ARN-810, also known as GDC-0810, in a phase I study and used ^{18}F-FES PET to assess pharmacodynamic activity and demonstrated greater than 90% suppression of estradiol binding to ER in 90% of patients (*40*).

NON–BREAST CANCER USES OF ^{18}F-FES

Uterine Endometrium and Myometrium

Tsuchida et al. first verified the correlation between ^{18}F-FES uptake and in vitro immunohistochemical measurement of ER concentration in endometrial tissue (*44*). Subsequent studies demonstrated a significant difference in both ^{18}F-FES uptake and the ratio of ^{18}F-FDG uptake to ^{18}F-FES uptake between endometrial hyperplasia and endometrial cancer, as well as between low-grade and high-grade endometrial cancer (*45,46*). Compared with endometrial hyperplasia, low-grade endometrial carcinoma displayed significantly lower ^{18}F-FES uptake and higher ^{18}F-FDG uptake, and thus higher ^{18}F-FDG–to–^{18}F-FES uptake ratios. In turn, high-grade carcinomas displayed higher ^{18}F-FDG–to–^{18}F-FES uptake ratios than did low-grade endometrial carcinomas.

^{18}F-FES PET also has potential to differentiate benign uterine leiomyomas from malignant uterine sarcomas on the basis of ^{18}F-FES uptake and ^{18}F-FDG–to–^{18}F-FES uptake ratio (*47,48*). Differentiation of sarcoma from leiomyoma can often be difficult with MRI (*49*), and ^{18}F-FDG PET findings can be equivocal (*50*). Similar to endometrial pathologies, lower ^{18}F-FES uptake and a higher ^{18}F-FDG–to–^{18}F-FES uptake ratio have been associated with malignant sarcomas (*47,48*). Given the substantial management and prognostic differences between the two entities, ^{18}F-FES PET can potentially play a role in risk stratification of indeterminate uterine masses.

Epithelial Ovarian Cancer

Up to 70% of epithelial ovarian cancers express ER at baseline (*51*), and ^{18}F-FES PET has the ability to localize primary and metastatic lesions in such cancers (*52,53*). Van Kruchten et al. studied the utility of ^{18}F-FES PET in 15 patients with suspected ovarian cancer, demonstrating a correlation between lesion ^{18}F-FES uptake and immunohistochemical ER expression, as well as 79% sensitivity and 100% specificity using an SUV threshold of 1.8 (*53*).

As in breast cancer, ^{18}F-FES PET has potential utility to evaluate and monitor heterogeneity of disease in ovarian cancer. Given results from phase II trials of endocrine therapy for epithelial ovarian cancer (*54–56*), ^{18}F-FES PET could play a role in identifying patients who would most likely benefit from endocrine therapy. Although promising, however, these results have been modest and more studies are needed to validate preliminary findings.

Other Uses

^{18}F-FES PET has demonstrated ER expression in normal brain tissues and in meningiomas (*57,58*). There is limited evidence on the relationship between tamoxifen and development of meningiomas and on the utility of tamoxifen in treating refractory meningiomas (*59,60*). Investigators have also begun studying the ligand-binding domain of human ER as a potential reporter gene and ^{18}F-FES PET as a probe for confirming successful transfection in gene and cell therapies (*61,62*). Promising results were demonstrated for various transfection techniques, suggesting additional applications for ^{18}F-FES PET in basic and translational research studies.

POTENTIAL CLINICAL USES

As described in this review, ^{18}F-FES PET has the ability to quantify regional ER expression in breast cancer and preliminarily in other cancers. As with ER assays of sampled tissue, the key value of ^{18}F-FES PET is in identifying patients whose tumors do not express ER, indicating a lack of endocrine responsiveness. Studies have also demonstrated the utility of ^{18}F-FES as a pharmacodynamic marker for endocrine therapy, especially to assess the degree of blockade by ER antagonists. Below, we review possible clinical applications in which ^{18}F-FES PET might be applicable to current and future practice.

Breast Cancer Detection and Staging

^{18}F-FES PET is unlikely to supersede ^{18}F-FDG PET as the primary PET tool for breast cancer staging given limitations such as hepatic metabolism, which precludes visualization of liver metastases, and considerable enterohepatic circulation, which complicates abdominal imaging using ^{18}F-FES PET (*11*).

Nonetheless, because it is highly specific for ER-expressing breast cancers, ^{18}F-FES could be a beneficial adjunct that expands the focus in radionuclide breast cancer imaging beyond ^{18}F-FDG for metastatic staging and possibly beyond ^{18}F-FDG and ^{99m}Tc-sestamibi for primary breast cancer diagnosis (*63,64*). ^{18}F-FES PET can clarify or detect sites poorly visualized with ^{18}F-FDG PET, such as invasive lobular carcinomas, which tend to be less ^{18}F-FDG–avid, and can help with false-positive uptake due to inflammation, healing, and other known noncancer causes of ^{18}F-FDG uptake (*7,21,34,65*). Knowledge of ^{18}F-FES uptake might also obviate invasive biopsy, particularly in the metastatic setting, potentially improving the cost-effectiveness of metastatic disease workup (*66*). Finally, our advancing knowledge about predisposing factors for specific types of breast cancer could lead to a scenario in which patients prospectively identified as being at high risk for ER-expressing cancers might benefit from adjunct screening with ^{18}F-FES PET.

Predicting Response to Endocrine Therapy

Consistent with growing emphasis on precision medicine and individualized care, as well as evidence that ^{18}F-FES PET can improve diagnostic understanding and inform therapeutic approaches (*65*), ^{18}F-FES PET could provide a tool for individualized therapy. A particular advantage of ^{18}F-FES PET is its ability to evaluate receptor status over the entire tumor volume.

In the clinic, ER PET imaging would have its greatest impact in metastatic breast cancer, for which it is not practical to biopsy all sites of disease. Such being the case, clinicians often base their choice of endocrine therapy on the ER status of the primary tumor and not of the metastatic sites. However, studies suggest that up to 30% of patients may lose ER expression at one or more sites of disease after undergoing several lines of endocrine therapy (*16,28,36,38*). In view of these considerations, the most immediately compelling clinical use of ^{18}F-FES PET appears to be as a tool for measuring regional ER expression, this being a logical extension of the current practice of assessing ER expression by tumor biopsy.

Recent trends in therapeutic strategies for ER-expressing breast cancer may increase the utility of ^{18}F-FES PET for guiding therapy selection. One such trend is to target multiple breast cancer pathways by combining agents such as everolimus or palbociclib with endocrine therapy (*8*). Additional combined therapies targeting other pathways (e.g., epidermal growth factor receptor) are likely in the future (*67*). The use of combined therapy, for which it is difficult to discern the contribution of each agent to therapeutic response, creates an increased need for biomarkers for each target of the combined therapy. An imaging-based biomarker for ER expression to predict or assess response could be especially valuable and cost-effective in the setting of patients who are being considered for combinations of endocrine therapy and other targeted agents.

Barriers to Widespread Clinical Use of ^{18}F-FES PET

Although ^{18}F-FES PET represents a promising advancement, barriers to more widespread use also exist. First, additional work is required to prospectively validate its role in different clinical contexts, similar to the process undertaken with ^{18}F-FDG PET. Moreover, its utility as one component in a multimarker approach to prognostication and management must be further understood. Finally, data from these efforts will be needed to support regulatory approvals, which could support the use of ^{18}F-FES PET in a clinical setting beyond its current investigational approvals and role. All efforts are important given that support for ^{18}F-FES PET has arisen from smaller retrospective studies or single-center prospective studies. Larger studies are needed to clarify the generalizability of the modality's reported benefits, particularly given the high associated costs and limited availability in most institutions and settings.

CONCLUSION

^{18}F-FES PET is a safe and potentially clinically valuable tool for in vivo evaluation of ER expression in breast cancer. It correlates well with traditional in vitro immunohistochemical methods and has shown potential for predicting endocrine therapy response. Limited studies have also shown the potential utility of ^{18}F-FES PET in assessing other ER-expressing tumor types, such as those of uterine and ovarian epithelial origin. The advantages of ^{18}F-FES PET over in vitro methods include its ability to assess whole-body tumor burden and heterogeneity of disease, as well as to provide serial information about the in vivo pharmacodynamics of various endocrine therapies. The studies reviewed in this paper have demonstrated promising potential clinical uses of ^{18}F-FES PET, with perhaps the most important being a tool for individualizing treatment by predicting response to endocrine therapies. Although barriers to widespread application exist, at the time of writing there are 10 open clinical trials of ^{18}F-FES PET listed on ClinicalTrial.gov, 8 of which are studying its use in breast cancer. These and future studies will shed further light on the uses of ^{18}F-FES PET in guiding drug development, assessing disease burden, and informing therapeutic decision making.

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