Clinical Potential of Estrogen and Progesterone Receptor Imaging

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KEYWORDS

- FES-PET • FFNP-PET • Estrogen receptor imaging • Progesterone receptor imaging
- Breast cancer

KEY POINTS

- 16α-[^{18}F]fluoro-17β-estradiol (FES)–PET is likely to become clinically available to predict the clinical benefit from endocrine therapy given alone or in combination with new cyclin-dependent kinase 4/6 inhibitors.
- FES-PET could help predict the therapy response at multiple points in time along the course of treatment when endocrine resistance may arise.
- FES-PET could be used for pharmacodynamic imaging to help develop new ER antagonist drug therapies.
- FES-PET can identify tumor heterogeneity and may facilitate selection of the optimal biopsy site or confirm metastatic diagnosis if biopsy is not possible.
- Progesterone receptor imaging is being investigated as a method to measure the response to therapy after endocrine therapy or early response to antiestrogen therapy.

INTRODUCTION

Most breast cancers diagnosed are estrogen receptor (ER) and progesterone receptor (PR) positive, and early outcomes are better across all stages compared with ER-, PR- disease.[1] Advances in endocrine therapy show improved outcomes for patients with ER+ tumors.[2–7] Interestingly, despite the promise of molecularly targeted therapies, ER expression is the only established biomarker of the response to cyclin-dependent kinase 4/6 inhibitors.[8] It is not uncommon for patients with ER+ tumors to have late recurrences or indolent disease several years after diagnosis or present with de novo metastatic disease.[9,10] The most common site of metastases is the bone, where biopsies may be challenging to obtain and the response is difficult to measure by current clinical imaging.[11–13]

PET with ^{18}F-radiolabeled steroid hormones can be used to image tumoral expression of ER and PR in patients with primary and metastatic breast cancer. These radiotracers include 16α-[^{18}F]fluoro-17β-estradiol (FES) for ER imaging and ^{18}F-fluoro-furanyl-norprogesterone (FFNP) for PR imaging.

Tumor uptake from FES-PET imaging has been proven to correlate with ER protein[14,15] demonstrating the functional presence of ER. Likewise, FFNP uptake as measured by tumor-to-normal breast tissue ratios has been shown to be greater in PR+ breast cancers compared with PR− cancers.[16] FES- and FFNP-PET can be used to both qualitatively and quantitatively measure uptake from all metastatic sites at the same time through whole-body scanning. These molecular imaging agents may also be used in conjunction with dedicated high-resolution PET systems for breast imaging or simultaneous breast PET/MR imaging to better depict primary ER+ tumor biology and assess changes in receptor expression through preoperative window-of-opportunity drug trials.

As new endocrine therapies and novel biologics are introduced into clinic practices, better strategies are needed to individualize therapy. In this article, the authors review the research of the most commonly used PET tracer for ER, FES, and FFNP for PR imaging and their potential use in a clinical setting. For FES, the past studies include use to predict the response to endocrine therapy as a biomarker in pharmacodynamics imaging, as means to help develop ER antagonist therapy, and to identify tumor heterogeneity. Several current and upcoming trials are discussed for their potential to contribute to the promising future of using ER and PR imaging in the clinical setting.

16α-[^{18}F]FLUORO-17β-ESTRADIOL PREDICTS RESPONSE TO ENDOCRINE THERAPY

Perhaps the most impactful use of FES-PET imaging in the clinic will be the ability to predict the effectiveness of endocrine therapy. Approximately 30% of patients with breast cancer develop tumor regression with initial endocrine therapy, and only 20% have stable disease.[17] Second- and third-line therapies are available; however, the ability to measure ER expression in all tumor sites can ultimately influence treatment decisions, especially if there is substantial heterogeneity between tumor sites. Several groups have shown that FES predicts whether patients will experience a clinical benefit with ER-directed therapies in first-line and later-line treatment.[18–21] Clinical benefit, defined as stable disease, partial response, or complete response, is clinically meaningful and a logical end point in ER+ breast cancer, whereby indolent disease does not usually show measurable tumor shrinkage. Although these data, from single centers, are convincing and clinically relevant, a multicenter trial is ongoing to confirm these single-center results.

Another study tested the ability of FES-PET to predict the response to salvage aromatase inhibitor treatment in 47 patients with heavily pretreated metastatic breast cancer with ER+ primary tumors. Treatment selection based on quantitative FES-PET and a maximum standardized uptake value (SUV$_{max}$) cutoff of 1.5 would have increased the rate of response from 23% to 34% overall and from 29% to 46% in the subset of patients with HER2− disease.[20] This study found that quantitative FES-PET provides additional information over conventional clinical criteria to predict the response to hormonal therapy in the challenging situation of patients who have received multiple prior lines of therapy.

16α-[^{18}F]FLUORO-17β-ESTRADIOL AND FLUORODEOXYGLUCOSE PET PROVIDE PROGNOSTIC INFORMATION

Like ER expression measured using immunohistochemistry, FES-PET imaging has the potential to provide prognostic information. Kurland and colleagues[7] evaluated progression-free survival (PFS) in 84 patients with ER+/HER2− breast cancer receiving endocrine therapy and lesion uptake from fluorodeoxyglucose (FDG) and FES-PET. Patients were stratified into 3 response groups: patients with low FDG uptake (suggesting indolent disease) (29%; 24 of 84), FDG-avid tumors with high FES uptake (59%; 50 of 84), and FDG-avid tumors with low FES uptake (12%; 10 of 84). The median PFS in these groups was 26.1 months (95% confidence interval [CI]: 11.2–49.7 months), 7.9 months (95% CI: 5.6–11.8), and 3.3 months (95% CI: 1.4–not evaluable), respectively. **Fig. 1** shows images of representative cases from 3 classification groups: (**Fig. 1**A) low FDG lean body mass corrected standardized uptake value (SUL) SULmax3, (**Fig. 1**B) high FDG SULmax3 and low FES SULmean3, and (**Fig. 1**C) high FDG SULmax3 and high FES SULmean3. This study suggested that FDG PET and FES-PET may help provide important prognostic information by identifying patients with indolent disease and aid in deciding when to select targeted and/or cytotoxic chemotherapy.[7]

ESTROGEN RECEPTOR AS A BIOMARKER IN PHARMACODYNAMIC IMAGING

PET imaging also has a unique role in pharmacodynamics, the study of biochemical and physiologic effects of a drug on the body. Serial imaging of ER can provide a noninvasive assessment of the effective dosing and delivery of a drug at early time points. In recent studies, FES-PET imaging has been shown to be a