Functional Estrogen Receptor Imaging Before Neoadjuvant Therapy for Primary Breast Cancer

Amy M. Fowler[1] and Hannah M. Linden[2]

[1]*Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; and* [2]*Department of Medicine, University of Washington, Seattle, Washington*

See the associated article on page 563.

Estrogen receptor α (ERα) is a critical prognostic and predictive biomarker in breast cancer. ERα expression is used to determine whether patients should be treated with endocrine therapy, which is designed to block ERα signaling. Endocrine therapy given for 5–10 y after surgery improves progression-free and overall survival for patients with ER-positive primary breast cancer. However, disease recurrence and development of metastatic disease can occur despite appropriate treatment with endocrine therapy. Thus, a functional test performed at the time of initial diagnosis that can identify which patients would do well with endocrine therapy alone versus those who require adjuvant chemotherapy would be impactful for improving patient outcomes.

Key Words: breast cancer; estrogen receptor; ^{18}F-fluoroestradiol; neoadjuvant therapy; molecular imaging

J Nucl Med 2017; 58:560–562
DOI: 10.2967/jnumed.116.183533

Fluoroestradiol with ^{18}F (^{18}F-FES) is a radiolabeled estrogen hormone that binds estrogen receptor α (ERα) with high affinity and has been studied extensively in metastatic breast cancer from ER-positive (ER+) tumors (*1–7*). ^{18}F-FES PET/CT imaging can evaluate ERα expression across all disease sites throughout the body including both the primary tumor and the metastases. The overall sensitivity and specificity of ^{18}F-FES PET/CT imaging for detection of ER+ breast cancer is 84% and 98%, respectively (*1–5*). In addition to defining sites of ER+ disease, ^{18}F-FES PET/CT imaging can also provide predictive information regarding the likelihood of response to endocrine therapy. Tumors with an SUV_{max} below 1.5 are unlikely to respond to endocrine therapy (*6,7*).

The study published in this issue of *The Journal of Nuclear Medicine* by Chae et al. aimed to test the ability of ^{18}F-FES PET/CT imaging to predict pathologic response to neoadjuvant therapy in patients with ER+ primary breast cancer (*8*). The patients recruited for this imaging substudy were from 1 of the 2 institutions performing a phase III randomized clinical trial of neoadjuvant chemotherapy versus endocrine therapy (*9*). The NEOCENT trial included postmenopausal patients with ER-rich (Allred score ≥ 6) primary invasive breast cancer with a 2-cm or more disease burden in the breast or axillary lymph nodes. Patients were randomized to receive either chemotherapy (6 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide at 3-wk intervals) or neoadjuvant endocrine therapy (letrozole for 18–23 wk) before surgery. ^{18}F-FES PET/CT imaging was performed before the start of therapy, with patients scanned in the prone position. The injected dose of ^{18}F-FES was 111–222 MBq, and the uptake time was 90 min. A positive ^{18}F-FES scan was defined as tracer uptake visually above background in the primary tumor or regional lymph node. A negative ^{18}F-FES definition required all lesions to have uptake equal to, or decreased, relative to background. Pathologic response was defined using the Miller–Payne grading system, with grades 1–2 designated as nonresponders and grades 3–5 as responders. Pathologic complete response (pCR) was defined as no residual invasive disease in the breast or regional lymph nodes (ypT0/Tis ypN0).

The imaging substudy consisted of 26 women, with 13 randomized to neoadjuvant chemotherapy and 13 to endocrine therapy (*8*). Twenty-four patients had positive ^{18}F-FES PET/CT imaging, and 2 had negative ^{18}F-FES scans. The 2 patients with negative ^{18}F-FES imaging were in the neoadjuvant chemotherapy group and achieved pCR. In contrast, none of the 10 patients with positive ^{18}F-FES scans assigned to the neoadjuvant chemotherapy group exhibited pCR. A baseline SUV_{max} cutoff of less than 7.3 predicted pathologic response to neoadjuvant chemotherapy but not to endocrine therapy ($P = 0.03$). For the 8 patients who received neoadjuvant chemotherapy with an ^{18}F-FES SUV_{max} less than 7.3, there was no disease recurrence after a median follow-up period of 74 mo (range, 44–85 mo). The authors' main conclusion from the study was that patients with ER-rich tumors defined by immunohistochemistry with poor ^{18}F-FES uptake may be better treated with neoadjuvant chemotherapy than endocrine therapy.

A prior study by Yang et al. also investigated the predictive value of ^{18}F-FES PET/CT imaging for response to neoadjuvant chemotherapy (*10*). Their study consisted of 18 women with stage II and III breast cancer all undergoing neoadjuvant chemotherapy with 3–6 cycles of paclitaxel and carboplatin followed by mastectomy and axillary lymph node dissection. Similar to Chae et al., they found that pretherapy ^{18}F-FES SUV_{max} was lower in pathologic responders than nonresponders. However, the ^{18}F-FES SUV_{max} values in the Yang study were all less than the cutoff SUV_{max} of 7.3 defined in the Chae study. This can partially be explained by the longer uptake time in the Chae

Received Oct. 28, 2016; revision accepted Oct. 31, 2016.
For correspondence or reprints contact: Hannah M. Linden, Medical Oncology, University of Washington, 825 Eastlake Ave. W., Seattle, WA 98109-1023.
E-mail: hmlinden@uw.edu
Published online Nov. 17, 2016.

study (90 min) than in the Yang study (60 min). It also reinforces the importance of standardization in quantitative imaging techniques used to predict or monitor response to treatment.

A strength of the Chae study is that it was performed in conjunction with a randomized clinical therapy trial. The advantage to this design is that all patients undergo ^{18}F-FES PET/CT imaging and are then randomized equally to a standardized therapeutic regimen. Thus, the predictive value of the imaging biomarker can be tested in a well-defined, relatively homogeneous patient population all receiving the same type of neoadjuvant chemotherapy or endocrine therapy. If not performed as part of a randomized clinical therapy trial, then patients will receive a variety of therapies according to the clinical care guided by their medical oncologist. This challenge was observed recently with the multiinstitutional phase II clinical trial aiming to correlate ^{18}F-fluorothymidine uptake with pathologic response to neoadjuvant chemotherapy in 51 patients with locally advanced breast cancer (American College of Radiology Imaging Network Trial 6688) (*11*). Overall, the study found that ^{18}F-fluorothymidine PET imaging after 1 cycle of chemotherapy only weakly predicted pCR. This marginal predictive performance may have been due to the heterogeneous patient population and variable chemotherapy regimens included in the protocol.

Another strength of the Chae study is the inclusion of clinical follow-up for disease recurrence, with a median follow-up of 74 mo. This is crucial information for clinical trials of neoadjuvant chemotherapy for patients with ER+ disease because pCR is not a good surrogate endpoint for patients with ER+ luminal A type breast cancer (*12*). Other important clinical outcome data that would be helpful to evaluate is whether ^{18}F-FES PET/CT imaging can result in a change in surgical management (e.g., change from lumpectomy to mastectomy), change in rates of surgical margin positivity, or surgical reexcision rates.

Results from Chae et al. add to the relatively few studies focusing on the diagnostic accuracy of ^{18}F-FES imaging of primary ER+ breast tumors, as opposed to metastatic ER+ disease. There was positive agreement between ^{18}F-FES imaging and ERα immunohistochemistry in 92% (24/26) of patients (*8*). Because of the inclusion of only strongly ER+ tumors, this value is likely higher than would be observed if patients with low ER expression were also included. Furthermore, specificity and negative predictive value cannot be determined because of the lack of ER-negative tumors. Gemignani et al. included 48 patients with ER+ and ER-negative primary breast cancer at least 1 cm in size undergoing preoperative ^{18}F-FES PET/CT imaging (*13*). Most (83%) of the study population had a median tumor size of 1.9 cm, with clinical stage I or II disease. ^{18}F-FES positivity was defined as an SUV_{max} of 1.5 or greater and was positive in 36 of 48 patients. The reference standard was ERα positivity on immunohistochemistry and was defined as 1% or greater. Forty of 48 patients had ER+ disease. Diagnostic performance data included a sensitivity of 85%, specificity of 75%, positive predictive value of 94%, negative predictive value of 50%, and accuracy of 85%.

The Chae study does have limitations. The finding that patients with ER-rich tumors and a negative ^{18}F-FES scan have an increased rate of pCR compared with those with ^{18}F-FES–positive scans is based on only 2 patients. As in other studies, patients with ER+ disease with ^{18}F-FES–negative scans comprise a small proportion of the total study population. Thus, subsequent studies with a larger number of patients are needed to confirm this finding before implementation in clinical practice. One approach for increasing the number of potential subjects with ^{18}F-FES–negative imaging and ER+ immunohistochemistry would be to include all ER+ patients (>1% tumor cells staining positive for ER or Allred score ≥ 3).

Another study drawback is the potential limited impact of their results for changing clinical management. In current U.S. practice, clinicians are not typically faced with a decision to make between neoadjuvant endocrine therapy and chemotherapy for patients with ER+ primary breast cancer (*14*). Neoadjuvant chemotherapy is not typically used because the pathologic response rate for ER+ cancers is much less than triple-negative or human epidermal growth factor receptor 2–amplified cancers and because the rates of pCR and disease-free survival do not correlate strongly for ER+ patients (*12*). Neoadjuvant endocrine therapy, on the other hand, is not typically used because of the prolonged length of time required to achieve full response, which can be from 6 to 12 mo. Thus, a neoadjuvant endocrine approach is typically used for a relatively small number of patients who are elderly or with significant comorbidities who cannot undergo upfront chemotherapy or surgery.

An interesting question based on the results of the Chae et al. study is whether their results in the neoadjuvant setting can be extrapolated to the adjuvant setting. If so, then it would follow that patients with ER+, ^{18}F-FES primary breast cancer might benefit from adjuvant chemotherapy compared with endocrine therapy alone. The question of whether the potential benefit of preventing disease recurrence by using cytotoxic chemotherapy outweighs its risk for patients with newly diagnosed ER+ breast cancer is important and affects a large proportion of patients. Although ^{18}F-FES PET/CT imaging may be one approach for guiding decisions of adjuvant chemotherapy, existing gene expression assays, such as the 21-gene recurrence score, have already been approved by the U.S. Food and Drug Administration, have been incorporated into clinical practice guidelines, are widely available for patients, and spare many of the costs and toxicity of adjuvant chemotherapy (*15*).

Thus, the ideal clinical niche for using ^{18}F-FES PET/CT imaging for patients with newly diagnosed primary ER+ breast cancer is yet to be solidified. The work published by Chae et al. herein, which presents preliminary evidence that ER+ tumors with low ^{18}F-FES uptake are unlikely to respond to endocrine therapy and may receive greater clinical benefit from chemotherapy, is intriguing. The evaluation of ^{18}F-FES as a biomarker to predict clinical benefit from endocrine therapy is currently being prospectively evaluated in the metastatic setting through an ongoing multiinstitutional phase II clinical trial (EAI142; NCT02398773).

REFERENCES

1. Dehdashti F, Mortimer JE, Siegel BA, et al. Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and in vitro receptor assays. *J Nucl Med.* 1995;36:1766–1774.
2. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. *Radiology.* 1988;169:45–48.
3. Mortimer JE, Dehdashti F, Siegel BA, Katzenellenbogen JA, Fracasso P, Welch MJ. Positron emission tomography with 2-[^{18}F]Fluoro-2-deoxy-D-glucose and 16alpha-[^{18}F]fluoro-17beta-estradiol in breast cancer: correlation

with estrogen receptor status and response to systemic therapy. *Clin Cancer Res.* 1996;2:933–939.
4. Peterson LM, Mankoff DA, Lawton T, et al. Quantitative imaging of estrogen receptor expression in breast cancer with PET and ^{18}F-fluoroestradiol. *J Nucl Med.* 2008;49:367–374.
5. van Kruchten M, de Vries EG, Brown M, et al. PET imaging of oestrogen receptors in patients with breast cancer. *Lancet Oncol.* 2013;14: e465–e475.
6. Linden HM, Stekhova SA, Link JM, et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. *J Clin Oncol.* 2006;24:2793–2799.
7. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, Welch MJ. Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. *J Clin Oncol.* 2001;19:2797–2803.
8. Chae SY, Kim S-B, Ahn SH, et al. A randomized feasibility study of ^{18}F-fluoroestradiol PET to predict pathological response to neoadjuvant systemic therapy in estrogen receptor–rich postmenopausal breast cancer. *J Nucl Med.* 2016;58:563–568.
9. Palmieri C, Cleator S, Kilburn LS, et al. NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. *Breast Cancer Res Treat.* 2014;148:581–590.
10. Yang Z, Sun Y, Xue J, et al. Can positron emission tomography/computed tomography with the dual tracers fluorine-18 fluoroestradiol and fluorodeoxyglucose predict neoadjuvant chemotherapy response of breast cancer? A pilot study. *PLoS One.* 2013;8:e78192.
11. Kostakoglu L, Duan F, Idowu MO, et al. A phase II study of 3′-deoxy-3′-^{18}F-fluorothymidine PET in the assessment of early response of breast cancer to neoadjuvant chemotherapy: results from ACRIN 6688. *J Nucl Med.* 2015;56:1681–1689.
12. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol.* 2012;30:1796–1804.
13. Gemignani ML, Patil S, Seshan VE, et al. Feasibility and predictability of perioperative PET and estrogen receptor ligand in patients with invasive breast cancer. *J Nucl Med.* 2013;54:1697–1702.
14. Schott AF, Hayes DF. Defining the benefits of neoadjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2012;30:1747–1749.
15. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016;34:1134–1150.