Positron Emission Tomography with 2-[\textsuperscript{18}F]Fluoro-2-deoxy-D-glucose and 16\alpha-\textsuperscript{18}F]Fluoro-17\beta-estradiol in Breast Cancer: Correlation with Estrogen Receptor Status and Response to Systemic Therapy\textsuperscript{1}

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ABSTRACT

We assessed the value of positron emission tomography (PET) with 2-[\textsuperscript{18}F]fluoro-2-deoxy-D-glucose (FDG) and 16\alpha-[\textsuperscript{18}F]fluoro-17\beta-estradiol (FES) in women with breast cancer for predicting response to systemic therapy. Results of FES-PET were correlated with estrogen receptor (ER) status.

Forty-three women with locally advanced or metastatic breast cancer underwent FDG-PET and FES-PET prior to institution of systemic therapy. All patients had measurable disease and had tumors submitted for ER determination. Cancers were considered functionally hormone sensitive if the standardized uptake value of the lesion on FES-PET was \(\geq 1.0\) (FES+) and hormone resistant if the standardized uptake value was <1.0 (FES−). Information obtained by FES-PET was compared with the results of ER assays. The tumor response to chemotherapy and hormonal therapy was correlated with intensity of uptake by both FDG-PET and FES-PET.

The ER status of the breast cancers was negative (ER−) in 20 patients, positive (ER+) in 21 patients, and unknown in 2 patients. All 20 of the ER− tumors were also FES−. However, of the 21 ER+ tumors, 16 were FES+ and 5 were FES−. Thirty patients were treated initially with chemotherapy, and 21 (70%) demonstrated objective responses. We were unable to correlate the response to chemotherapy with information obtained by FDG-PET or FES-PET. Thirteen patients were treated with hormone therapy, and 8 (61%) responded to that therapy. Only 1 of the 5 patients whose tumors were ER+ but FES− received hormone therapy, and this treatment resulted in disease stabilization only. Multiple sites of disease were assessed by FES-PET in 17 patients with metastatic breast cancer. Functional hormone sensitivity, defined by FES-PET, was concordant with multiple lesions in 13 (76%). Ten patients with locally advanced breast cancer developed recurrent disease. The initial site of recurrence was the breast in 5 patients. Of the 5 patients with systemic recurrence, 4 had disease detected at the site of recurrence on the pretreatment FDG-PET study but not detected on pretreatment computed tomography.

In our experience, FDG-PET imaging is more sensitive than conventional imaging methods, including computed tomography, in staging women with breast cancer. When compared with the in vitro assay of ER status, FES-PET has an apparent sensitivity of 76% and specificity of 100%. Our finding of a subset of patients who have tumors that are ER+ and FES− suggests that the functional assessment of hormone sensitivity by PET imaging can identify patients with ER+ disease whose tumors are likely to be hormone refractory.

INTRODUCTION

By using a variety of radiopharmaceuticals labeled with positron-emitting radionuclides (\textsuperscript{11}C, \textsuperscript{13}N, \textsuperscript{18}F, and \textsuperscript{15}O), PET\textsuperscript{3} can yield cross-sectional images that reflect tissue biochemistry. Two radiopharmaceuticals in particular hold promise for the diagnosis and management of breast cancer. The most extensively studied is FDG. A glucose analogue, FDG is taken up by cancer cells (1, 2). Thus, FDG-PET imaging can identify patients with ER+ disease whose tumors are likely to be hormone refractory.
tive staging of lung cancer than conventional imaging methods (5). In patients with primary brain tumors treated with surgery and radiation therapy, FDG-PET can distinguish recurrent cancer from radiation necrosis (6). Similarly, FDG-PET has proven to be a reliable means for differentiating recurrent colorectal cancer from posttreatment scarring in the pelvis (7). In the evaluation of breast cancers, FDG-PET similarly can distinguish benign from malignant breast masses, detect axillary nodal metastases, and detect both osseous and soft tissue distant metastases (8, 9). The efficacy of treatment has also been monitored by FDG-PET. In women with locally advanced breast cancer treated with chemohormonal therapy, Wahl et al. (10) reported that a decrease in tumor FDG uptake shortly after initiation of effective therapy was seen before a clinical response could be documented (10).

Another radiopharmaceutical of potential benefit in the diagnosis and management of breast cancer is FES. Estrogen and progesterone dependency are characteristics of breast cancer that predict the natural history of the disease, in part, and are used to direct systemic therapy. Currently, the in vitro measurement of ERs and PRs in tumor tissue provides an estimation of that hormone dependency. However, the quantitative and qualitative methods for assessing ERs in tissue have several limitations. These assays provide only limited information about the functional status of the ER, and none of them is highly specific in identifying patients whose tumors will regress with hormone therapy. FES-PET has the potential to provide functional information about ER activity in individual tumor sites. The majority of breast cancers are ER+, a status that is associated with a longer disease-free interval after initial therapy and a longer survival even after the development of metastases. In treating advanced ER+ breast cancer, hormonal therapies produce objective response rates of 30–40%, whereas cytotoxic chemotherapy regimens produce objective response rates of 70% (11, 12). A functional assessment of ER positivity is critically needed to identify which patients will benefit from the less-toxic hormonal therapies.

Our initial experience suggests that FES-PET provides information about the estrogen dependency of breast cancer similar to that provided by the ER assays. We previously reported a direct quantitative relationship between the uptake of FES in primary breast carcinomas measured in vivo by PET and the ER concentrations measured in vitro (13). FES-PET is highly sensitive for detecting metastatic lesions of ER+ cancers. Additionally, we have demonstrated a decrease in tumor FES uptake in patients with metastatic breast cancer treated with tamoxifen (14).

To evaluate the potential role of FES-PET and FDG-PET in predicting the efficacy of systemic therapy, women with locally advanced or widely metastatic breast cancer underwent PET imaging prior to institution of systemic therapy. We have correlated the results of PET imaging with in vitro assays of hormone receptor status, response to systemic therapy, and disease outcome.

**Materials and Methods**

**Patients.** All women with locally advanced or metastatic breast cancer were considered eligible for the study. Biopsies of the primary tumors or metastatic lesions were obtained for diagnosis and ER determination in all patients. When an excisional biopsy was performed, fresh or fresh-frozen tumor was submitted for quantitative measurement of hormone receptor concentrations, determined by the immunoperoxidase technique (15). Tumor ER levels >3 fmol/mg protein were considered ER+, and those ≤3 fmol/mg protein were considered ER−. When tissue confirmation of cancer was obtained by needle biopsy or fine-needle aspiration, additional specimens were submitted for hormone receptor determination by an immunohistochemical technique. The avidin-biotin-peroxidase complex techniques for the ER and PR were used to determine receptor status on these specimens (16). All patients had cancer lesions assessable for response and underwent chemotherapy or hormone therapy.

Staging evaluation included physical examination, complete blood count, liver function studies, and chest radiography. Patients with locally advanced breast cancers routinely underwent CT of the chest before initiation of therapy. If the alkaline phosphatase was elevated or the patient complained of bone pain, bone scintigraphy was performed. Likewise, CT of the abdomen was performed if liver function abnormalities were identified. Additional imaging studies (CT or bone scintigraphy) were also performed if an unexplained abnormality was seen on FDG-PET.

All patients were interviewed by a single nuclear medicine physician (F.D.), who reviewed the study objectives and patient risks. Treatment of the cancer was initiated only after completion of PET imaging, definitive biopsy, and staging workup. The research protocol was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine. Each patient gave her written informed consent.

**Treatment.** Systemic therapy was initiated after completion of the PET imaging and was not specified in the initial design of this study. Treatment was left to the discretion of the treating medical oncologist, and clinical follow-up was provided by that physician.

**Radiopharmaceutical Synthesis.** FES was synthesized by a robotic adaptation of a previously described method (17). FES prepared by this method has a high specific activity and a high affinity for ERs (18). FDG was prepared by a robotic adaptation of standard methods, as described previously (19).

**PET Imaging.** The first 10 patients were imaged with SuperPETT-IIB. The subsequent 33 were imaged with a Siemens ECAT EXACT scanner. The performance characteristics of these scanners have been described previously (13, 20). The paired studies of any one patient were always performed on the same scanner.

FES-PET and FDG-PET studies were performed on 2 separate days (34% had the FES study first and 66% had the FDG study first). In 81% of cases, the two studies were done within 3 days of each other, and 58% were performed on consecutive days. The maximum interval between the two studies was 9 days. For the FES-PET study, 6 mCi (222 MBq) FES were administered i.v. Approximately 90 min later, the patient was positioned supine in the PET scanner so that the field of view included the lesion(s) of interest (as determined by physical examination or from correlative imaging studies). A 30-min emission scan and a 10–15-min transmission scan were per-
formed at each bed position. Prior to the FDG-PET study, patients fasted for at least 4 h. Ten mCi (370 MBq) FDG were administered i.v., and imaging was begun approximately 30 min later. Similar bed positions and durations of both emission and transmission images were used for the FES and FDG studies.

Image Analysis. All PET images were prospectively evaluated qualitatively by at least two experienced nuclear medicine physicians. Based on the knowledge of normal biodistribution of the radiopharmaceuticals, foci of abnormal radiotracer accumulation were identified and recorded. Regions where abnormalities existed on clinical examination or radiographs were also specifically evaluated. On FDG-PET, all lesions were then graded definitely or probably abnormal (categorized as representing a tumor), equivocal, or normal (in the case of an abnormality identified on radiography or clinical examination for which no corresponding abnormality was present on PET). On FES-PET, images were reviewed for the presence (categorized as FES+) or absence (categorized as FES−) of focally increased uptake. In a given patient, FES and FDG images were reviewed independently. At least one of the observers was blinded to all clinical and correlative radiographic findings. For final interpretation, the PET images were then correlated with the clinical, radiographic, and surgical findings and with the results of the clinical follow-up. There was 100% agreement between blinded and unblinded observers in PET image interpretation.

In addition to the above subjective analysis, regions of interest were drawn around areas of increased tracer accumulation to determine the local tissue accumulation of radiopharmaceuticals. A SUV was then calculated for these areas (21). The SUV is a decay-corrected measurement of activity per unit volume of tissue (nCi/ml) adjusted for administered activity per unit of body weight (nCi/kg). The SUVs for both FDG and FES were multiplied by appropriate recovery coefficients for lesions smaller than 2.5 cm. The sizes of the lesions were determined by physical examination or correlative radiographic studies. In patients with multiple lesions, only the lesion(s) of primary clinical interest and/or those with histopathological verification were chosen for semiquantitative analysis. On FES-PET, presumptively hormone-sensitive disease (FES+) was defined as a tumor SUV of ≥1.0, and presumptively hormone-resistant disease (FES−) was defined as a tumor SUV of <1.0.

Response Criteria. The objective response was defined by standard response criteria: (a) complete response, complete disappearance of all clinically detectable disease for at least 4 weeks; (b) partial response, 50% or greater decrease (sum of the products of two longest perpendicular diameters) of all measurable lesions lasting at least 4 weeks, without an increase in size of any area of known malignant disease or appearance of any new area of malignant disease; (c) minor response, decreases of all measurable lesions by less than 50%; (d) stable disease, measurable lesions unchanged in size or less than 25% increases in the sizes of measurable lesions being followed and no new lesions; and (e) progression, a greater than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of any new lesions.

Survival. The survival distributions were estimated using the Kaplan-Meier method (22).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient profile</th>
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<tbody>
<tr>
<td>No of Patients</td>
<td>43</td>
</tr>
<tr>
<td>Median age (yr)</td>
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</tr>
<tr>
<td>(Range, 33–76)</td>
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<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>14</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>25</td>
</tr>
<tr>
<td>Perimenopausal</td>
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</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Disease status</td>
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<tr>
<td>Locally advanced/inflammatory</td>
<td>25</td>
</tr>
<tr>
<td>Recurrent/metastatic disease</td>
<td>18</td>
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RESULTS

We studied a total of 43 patients; the patient characteristics are summarized in Table 1. Their median age was 56 (range, 33–76) years. At study entry, 25 were postmenopausal, 14 were premenopausal, 3 were perimenopausal, and 1 was of unknown menopausal status. Twenty-five patients presented with locally advanced or inflammatory breast cancer, 15 had widespread metastatic disease, and 3 had recurrent disease of the chest wall.

Hormone receptors were assessed by quantitative measurement in 20 patients and by immunohistochemical assay in 25 patients (in 2 patients, both measurements were performed). The tumors were ER+ in 21 patients and ER− in 20 patients. ER status could not be determined in 2 patients because of inadequate tissue or because of technical difficulties in performing the assay.

Correlation of ER Assays with Results of FES-PET and Response to Therapy. Table 2 summarizes the correlation of pathologically determined ER status with presumptive hormone sensitivity defined by FES-PET. Of the 21 ER+ tumors, 16 were FES+, and 5 were FES−. The mean SUV for FES uptake was 2.6 ± 1.6 in 16 ER+/FES+ patients and 0.62 ± 0.18 in the FES+/ER− patients. Thus, the apparent sensitivity of FES-PET was 76%. Ten patients were treated with chemotherapy, and 11 received hormonal therapy. Of those receiving hormonal therapy, 7 experienced complete or partial responses. Three additional patients demonstrated tumor regression, although not of a sufficient magnitude to meet the partial response criteria. All 10 of these patients with ER+ tumors showing at least minimal tumor regression were also presumptively estrogen sensitive by FES-PET. Six of 10 patients responded to chemotherapy. In the remaining patient, the tumor was ER+ but FES−, and she experienced only disease stabilization after 18 months of receiving tamoxifen.

All 20 ER− tumors were also FES−. The mean SUV for FES uptake was 0.51 ± 0.23 in this group. Fifteen of the 18 patients treated with chemotherapy responded to that treatment. Only 2 patients whose tumors were ER− and FES− were treated with hormonal therapy, and 1 responded to that treatment.

The tumor ER status was unknown in the remaining two patients; one whose tumor was FES+ (SUV, 1.2) responded to chemotherapy, and the other patient’s tumor was FES− (SUV, 0.5) and failed to respond to chemotherapy.

FDG-PET uptake did not correlate with the FES status, nor were we able to correlate FDG-PET uptake with ER or menopausal status.
**Table 2** Response to therapy by ER and FES status

<table>
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<tr>
<th>ER status</th>
<th>FES status</th>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>NR</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>NR</th>
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<td>ER+</td>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
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<td>FES−</td>
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<td>2</td>
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<td>9</td>
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*CR, complete remission; PR, partial remission; MR, minor response; SD, stable disease; NR, no response.*

**Fig. 1** Systemic metastatic lesion detected by pretreatment PET in a 70-year-old woman with inflammatory breast cancer. A, transaxial FDG-PET image of the chest demonstrates increased accumulation of FDG in the left breast tumor (long arrow) and an axillary nodal metastatic lesion (short arrow). B, FES-PET image at the same level in the chest shows no abnormal uptake of FES in either the primary tumor or axillary lymph nodes, consistent with the negative ER status of the patient’s tumor. C, FDG-PET image of the upper abdomen demonstrates a metastatic lesion in the liver (arrow); abdominal CT (not shown) at the same time as the PET studies was normal. The patient was treated with systemic chemotherapy, surgery, and radiation therapy. Six months after completion of therapy, she first developed recurrent breast cancer in the liver.

**ER Concordance.** Fifty different metastatic foci were imaged by FDG-PET and FES-PET in 17 patients with metastatic disease (2–5 lesions per patient). The results of FES-PET were concordant in 46 (92%) of the lesions. Four patients each had a single discordant site, with 5 different foci imaged in 1 patient, 4 foci in 1, 3 foci in 1, and 2 foci in 1. Thus, 13 (76%) of 17 patients had concordant hormone sensitivity of all lesions as defined by the results of FES-PET.

**Sites of Disease Recurrence.** Based on their initial examination and staging evaluation, 25 women were classified as having locally advanced breast cancer. Ten have developed recurrent disease on follow-up ranging from 12 to 58 months. The initial site of relapse was confined to the breast in 5 patients; 2 patients developed vertebral metastases; and 1 each developed recurrence in the pericardium, peritoneum, or liver.

Although the pretreatment conventional imaging studies in these 10 patients were normal, FDG-PET identified abnormalities in the pericardium, spine (2), or liver in the 4 patients whose disease first recurred at these sites. Fig. 1 demonstrates pretreatment FDG-PET of a patient who presented with inflammatory breast cancer and had a metastasis in the liver demonstrated as well. The liver metastasis was the first site of disease recurrence in this instance.

**Survival and FES-PET Results.** With a median follow-up interval of 23 months, 17 patients have died. The median survival of the 26 FES− patients was 21.6 months; 13 of these patients (50%) have died, including 2 of the 5 patients (40%) whose tumors were ER+ but FES−. Despite a median follow-up of 22 months in the 17 FES+ patients, the median survival has not been reached, because only 4 patients (24%)...
Fig. 2 Survival by FES-PET status. —, FES−; ——, FES+.

have died (Fig. 2). The mean SUV for FDG uptake in ER+ patients was 4.0 ± 2.1, and in ER− patients it was 4.4 ± 3.0. No correlation could be found between FDG uptake and overall survival.

DISCUSSION

The pathological methods used to assay for the ER have distinct limitations. The conventional methods, including dextran-coated charcoal and sucrose gradient techniques, require a fresh or fresh-frozen tumor specimen. These techniques cannot be used to measure receptor status on bodily fluids, such as bone marrow aspirates or effusions, or on bone specimens. Because the conventional methods rely on the measurement of the binding by the receptor of a labeled estradiol, false-negative results can be obtained in patients who are taking replacement estrogen or are receiving hormonal therapy. The immunohistochemical techniques can identify the ER in bone and liquid specimens and can identify the receptor independent of exogenous hormone use by the patient. The utility of this method, however, may be limited, because the receptor antigen may be present even if the ER is nonfunctioning (23).

FES-PET has the potential to provide functional information about the hormone responsiveness of breast cancer, distinct from that provided by in vitro assays of the ER, because the method directly evaluates the accumulation of the hormone at individual tumor sites in vivo. When we performed serial FES-PET imaging in women with metastatic breast cancer treated with tamoxifen, a decrease in FES-PET uptake was seen after institution of the hormonal therapy (14). Presumably, this decrease correlates with binding of the drug to the tumor ER, thereby blocking the in vivo uptake of the radiopharmaceutical. Whether FES-PET can identify patients with hormone-responsive disease more accurately than ER assays remains to be determined. In the current study, we noted that 70% of FES+ patients treated with hormones demonstrated objective responses. Compared with the ER assay, we found the sensitivity of FES-PET to be 76% and the predictive accuracy of FES negativity to be 80%. We hypothesize that those patients whose tumors are ER+ but FES− are functionally hormone resistant. These patients may constitute the 40–45% of individuals with ER+ breast cancer who fail to benefit from hormonal therapy. We are seeking to evaluate this hypothesis further in our future trials.

The information obtained from FES-PET imaging often overlaps that provided by the pathological assay of the ER. The survival of women with ER+ breast cancer is superior to that of patients with ER− disease, independent of the stage of disease. The median survival of patients with FES− disease in this series (including those patients whose tumors were ER+) was 21.6 months, whereas the median survival has not yet been attained in the FES+ patients, despite a median follow-up interval of 22 months. When multiple tumor sites from a single patient are submitted for in vitro ER determination, concordant positive or negative results are obtained in 75–85% of patients (24, 25). In the present series, concordance among multiple lesions within a patient by FES-PET was observed in 76% of the patients. The intensity of FES uptake varies among individual patients, just as the quantitative value of the ER varies. We previously reported a linear relationship between the FES uptake measured in vivo
by PET and the ER concentrations of the tumor measured in vitro (13).

The PR is a product resulting from estrogen binding to the ER. In some studies, the PR appears to be a better predictor of hormone responsiveness than the ER. The strongest predictor of hormone responsiveness is the presence of both the ER and PR, for which responses are seen in 67% of such patients. However, as an independent variable, the PR is more predictive of hormone responsiveness than the ER (26). Yet to be answered is whether FES uptake predicts hormone responsiveness more accurately than does the PR. Because only five patients were ER+ and FES−, and only one underwent hormonal therapy, this question could not be answered in the present trial.

As has been reported with other cancers (3), we found FDG-PET imaging in breast cancer to have a high degree of sensitivity and specificity. Of the 25 women with locally advanced breast cancers, 4 of the 5 patients who developed distant metastases did so at sites that were identified by the pretreatment FDG-PET study but not detected by conventional imaging studies. This experience indicates the high sensitivity of FDG-PET relative to these conventional imaging methods (chest radiography, CT, and bone scintigraphy). To date, we have encountered no false-positive results with FDG-PET in patients with advanced breast cancer.

We were not able to demonstrate a correlation between tumor FDG uptake and either the ER or response to chemotherapy. The technique for quantifying FDG uptake used in this study has since been refined. With improved methods for quantifying FDG uptake, a more accurate assessment of tumor glucose metabolism may be possible. Not surprisingly, we were also unable to demonstrate a correlation between FES uptake and chemotherapy responsiveness. The response to chemotherapy has, in general, not been closely correlated with the hormone receptor status (27, 28).

In this study, FDG-PET provided additional information about staging women with locally advanced breast cancer. The specificity of FDG-PET imaging was high. Likewise, the sensitivity of FES-PET was high in ER+ disease, and the specificity was high in ER− patients. Although the number of patients studied is small, our data suggest that FES positivity may predict hormone responsiveness more accurately than do the results of in vitro ER assays. Systemic therapy was not dictated in the design of this study. Most ER+/FES− patients received chemotherapy. We are now engaged in a rigorous trial in which women with advanced disease are given systemic therapy according to their ER status, with all ER+ patients receiving hormone therapy. We envision that, in the future, PET imaging with FDG and FES will be of importance in the diagnosis, staging, and treatment of breast cancer.

REFERENCES


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