Positron Tomographic Assessment of 16α-[^{18}F] Fluoro-17β-Estradiol Uptake in Metastatic Breast Carcinoma

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The positron-emitting estrogenic steroid 16α-[^{18}F]fluoro-17β-estradiol (FES) has been shown to exhibit selective uptake in primary breast carcinomas; the uptake of tracer by positron emission tomography (PET) is strongly correlated with the tumor estrogen-receptor concentration. We have now extended the use of this radiopharmaceutical for imaging of metastases of breast carcinoma by PET in 16 patients with clinical or radiographic evidence of metastatic disease. Increased uptake of FES was identified on PET images in 53 of 57 metastatic lesions (93%); only two apparent false-positive foci of FES uptake were seen. In seven of the patients, evaluable PET studies were obtained both before and after initiation of antiestrogen therapy. In all cases, there was a decrease in FES uptake in the tumor deposits after initiation of antiestrogen therapy, and the mean (± standard deviation) uptake decreased from 2.22 (±1.23) to 0.80 (± 0.42) × 10^{-3}% dose/ml. These results indicate that PET with FES has high sensitivity and specificity for detecting metastatic breast carcinoma and provide additional confirmatory evidence that the tumor uptake of this ligand is a receptor-mediated process.

J Nucl Med 1991; 32:1526–1531

T he estrogen-receptor content of breast carcinomas is known to be an important prognostic indicator with respect to both disease-free survival and overall mortality in this disease (*1–4*). The hormonal dependence of breast carcinomas, as indicated by the results of estrogen-receptor assays, also is predictive of the likelihood that a patient will respond to such hormonal manipulations as antiestrogen therapy (*5–9*). Currently, the estrogen-receptor status of a breast tumor can be ascertained only by an in vitro analysis of the cancer tissue. This assay suffers from intralaboratory variability and, moreover, is limited by the

intrinsic heterogeneity of receptor content within a given tumor and its metastatic lesions (*10,11*). This has stimulated research to develop a method for the in vivo assessment of estrogen-receptor content of breast cancers in order to allow for prediction of hormonal sensitivity non-invasively.

Radiolabeled steroids have been synthesized and evaluated as potential tracers for the in vivo assessment of steroid receptors by several groups of investigators (*12–15*). We have investigated several estrogen ligands as potential imaging agents and have shown in animal studies that the ligand 16α-[^{18}F]fluoro-17β-estradiol (FES) has high affinity for the estrogen receptor, giving target-to-background-tissue activity ratios exceeding 80:1 (*16*). In human studies, we have also shown uptake of FES in primary breast carcinomas and have demonstrated strong correlation between the results of in vitro estrogen-receptor assays and in vivo measurements of tumor uptake of FES by positron emission tomography (PET) (*17*). Additionally, in several patients, PET was able to demonstrate uptake of FES in surgically confirmed metastases in axillary lymph nodes.

Our previous results encouraged us to extend our work to evaluate the potential of FES as an imaging agent for detection of metastatic breast carcinoma. We also have assessed the receptor specificity of FES accumulation in breast carcinoma by quantitative PET measurements of FES uptake in metastatic tumors before and after initiation of antiestrogen therapy.

MATERIALS AND METHODS

The study population consisted of 16 non-pregnant women (mean age 58.7 yr; range 45–83 yr) with radiographic or clinical evidence of recurrent or metastatic breast carcinoma in whom treatment with antiestrogen drugs was planned. Patients with a history of recent cytotoxic chemotherapy, prior hormonal therapy, or previous radiation therapy to lesions of interest were excluded from the study. The study was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine. Participation

in the study was voluntary, and written informed consent was obtained from each subject before enrollment.

The radiopharmaceutical, FES, was synthesized by use of a robotic adaptation of a previously described method (18). This method yields a compound with high specific activity and high affinity for the estrogen receptor (19). PET imaging was performed with either SuperPETT I or SuperPETT IIB. Serial studies in any one subject were performed on the same tomograph. SuperPETT I is a whole-body positron tomograph that permits the simultaneous acquisition of time-of-flight-corrected data sufficient for reconstruction of seven contiguous transaxial slices; the performance specifications of this device have been reported previously (20,21). Data were acquired in the low-resolution mode with an effective reconstructed slice separation of 15.0 mm and an in-plane reconstructed resolution of 12 mm (full width at half maximum). SuperPETT IIB is a whole-body time-of-flight positron tomograph composed of four rings, each containing 320 barium fluoride crystals, permitting the acquisition of list-mode data sufficient to generate seven transaxial slices with a center-to-center separation of 14 mm. The tomograph has a transverse field-of-view of 50 cm and an axial field of view of 10.2 cm. When operated in its low-resolution mode, as was the case in this study, its intrinsic spatial resolution in the transaxial plane is 4–5 mm (full width at half maximum) and its axial resolution is 11.0 mm (full width at half maximum). The images were reconstructed with a Gaussian filter selected to provide transaxial resolution of approximately 10 mm (full width at half maximum).

A typical PET study commenced with the intravenous injection of 6 mCi (222 MBq) of FES. Approximately 90 min later, the patient was positioned supine in the tomograph with the lesion (or lesions) of interest, as determined by other imaging studies, in the field of view. In patients with multiple metastatic lesions (e.g., evident on bone scintigraphy), the largest was chosen for evaluation. A 20-min emission scan was obtained during the interval from 90 to 110 min after intravenous administration of the radiopharmaceutical (the time during which optimal target-to-background-tissue activity ratios were found in our earlier study) (17). This was followed by a 15-min transmission scan with a ^{68}Ge/^{68}Ga source external to the patient (a ring source in SuperPETT I and a rotating sector source in SuperPETT IIB); the transmission data were used during reconstruction to correct the emission images for attenuation. Six patients had lesions of interest in two separate areas of the body, and, therefore, two separate regions were imaged sequentially. One patient underwent emission scanning beginning immediately after injection of FES and then 90 min later to permit an assessment of the early time course of FES uptake in tumor and surrounding tissues. Patients were positioned for both pre- and post-therapy studies by the same investigator to insure similar positioning.

The images were subjectively evaluated by two experienced observers (AHM and BAS), one of whom (BAS) was blinded with respect to clinical information and the results of other imaging studies. There were no major disagreements in study interpretations between the two observers; minor disagreements were resolved by consensus. Based on their knowledge of the normal biodistribution of FES, the observers identified foci of abnormally increased FES uptake. These findings were correlated with abnormalities noted on other imaging studies, including bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and conventional radiographs.

Of the original 16 patients, 11 were placed on anti-estrogen therapy [tamoxifen in 10; toremifene in 1 (Patient 6)] after the

initial PET study and underwent PET imaging a mean of 16.6 days (range 5–68 days) after starting treatment. One patient (Patient 6) had a total of three PET studies (before antiestrogen therapy and at 5 and 68 days after initiation of treatment). In one patient, the study obtained during antiestrogen therapy was technically unsatisfactory. Of the remaining 10 patients, 7 had foci of FES uptake on pre-therapy studies that corresponded to metastatic lesions seen on other imaging studies. The PET images of these seven patients were quantitatively analyzed to determine the uptake of FES in lesions before and after antiestrogen therapy.

Small regions of interest (ROIs) (5 × 5 pixels corresponding to areas ranging from 11.6 × 11.6 mm to 19.5 × 19.5 mm, depending on the image format of a particular patient's study or studies) were placed over the areas of maximum tracer uptake in the lesions on both the pre- and post-therapy PET studies. Similar ROIs were assigned in areas of uninvolved soft tissues and bone, for estimation of nonspecific uptake of the radiopharmaceutical. The PET counts per pixel in each ROI were then corrected for the administered activity of FES, the physical decay of the radionuclide from time of injection to the midpoint of imaging, and the sensitivity of the tomograph (based on phantom studies) to yield the percentage of the injected dose per milliliter (% ID/ml). Ratios of lesion activity to that of unaffected soft tissues (L/ST) and to that of uninvolved bone (L/B) in the field of view were calculated. These semiquantitative measures of lesion FES uptake were then correlated with the response to anti-estrogen therapy (improvement was defined as symptomatic improvement and an increase in performance status, with no new lesions detected on physical examination or radiographic evaluation for at least one month) and, if known, with the results of hormone-receptor assays of the primary breast carcinomas.

The group results of the quantitative measurements of lesion uptake (% ID/ml, L/ST, and L/B) are expressed as mean ± standard deviation. Differences in group means before and after antiestrogen therapy for the % ID/ml were tested for significance by a paired Student's t-test, and those for the L/ST and L/B ratios by a Wilcoxon signed-rank test for paired data. Differences were considered significant at p values less than 0.05.

RESULTS

Metastatic lesions within the regions imaged on the PET studies were identified by other imaging studies in 14 of our 16 patients (Table 1). The pre-therapy PET images with FES demonstrated accumulation of the radiotracer in the lesion or lesions of 11 of these 14 patients (79%) and in 53 of these 57 lesions (93%). In the remaining two patients, lesions seen on CT and/or bone scintigraphy were initially suspected to represent metastases. Subsequent biopsy in one patient (Patient 4) and clinical followup in the other (Patient 13) failed to confirm that these lesions were metastases, however. The biopsy showed only changes of radiation fibrosis, although this patient developed definite evidence of metastatic tumor several months later. Clinical follow-up of the other patient indicated that the suspect lesion most likely was an insufficiency fracture. Both lesions were seen on the PET images. The FES uptake values in these lesions were 1.0×10^{-3} and 1.3×10^{-3}% ID/ml, respectively, which are within the range encountered for metastatic lesions (see below). The L/ST ratios

TABLE 1
Summary of PET Results and Receptor Assays

Patient no.	Age (yr)	Lesion location	Mean L/ST ratio	ER	PR
1	45	Axilla (micrometastases)	NDL	37 (61)	86 (403)
2	48	Lung, breast, axilla	2.9	11	<3
		Skull, brain	1.8		
3	83	Sternum	NDL	NA	NA
4	60	Chest wall*	2.8	24	<3
5	51	Pelvis	NDL	168	866
		Ribs, vertebrae	NDL		
6	68	Skull	5.2	34 (<3)	67 (<3)
		Pelvis	1.9		
7	61	Skull	2.6	176 (92)	5 (<3)
		Ribs, vertebrae	7.7		
8	64	Ribs, vertebrae	5.7	118	105
9	80	Ribs, vertebrae, sternum	3.2	83	33
		Femur	3.9		
10	65	Skull	4.0	6	NA
11	45	Liver	2.8	17 (9)	<3 (83)
12	47	Lung, lymph nodes	3.0	174	<3
13	48	Rib*	1.9	194	65
14	56	Rib	2.4	8	8
15	57	Ribs, vertebrae	5.1	274 (98)	<3 (<3)
		Skull	4.4		
16	61	Skull	2.3	275	340

ER = estrogen receptor concentration (fmol/mg protein); PR = progestin receptor concentration (fmol/mg protein). Receptor concentrations given are for the patient's primary tumor or, if in parentheses, for a second primary tumor or a metastatic lesion.

* = Benign lesion; NA = not available; NDL = definite lesion.

for these lesions were 2.8 and 1.9, and their L/B ratios were 2.5 and 1.3; these values were less than those found in the majority of the malignant lesions (see Table 1). The PET images of the single patient who was studied both immediately and 90 min after injection of FES demonstrated decreased activity at the site of a cerebellar metastasis on the early images and increased uptake of FES on the later images (Fig. 1).

The quantitative assessment of FES uptake in metastatic lesions before and after anti-estrogen therapy could be performed in fewer than half of our patients for the following reasons. Of the 16 patients who underwent baseline studies, 2 were found to have benign lesions, as noted above. One patient died soon after her original study, and another was too ill to undergo a repeat PET study. One patient was not treated with anti-estrogen drugs, and rather underwent combination chemotherapy with cytotoxic drugs. Thus, post-therapy imaging was performed in 11 patients. Unfortunately, one patient's second study was uninterpretable because of technical difficulties. Only 7 of the remaining 10 patients had definite lesions suitable for quantitative assessment on the pre-therapy images; the other 3 patients (see Table 1; Patients 1, 3, and 5) had no

definite FES uptake seen by PET at the sites of lesions shown by other imaging modalities or corresponding to microscopic metastatic disease only.

The results of the quantitative analyses before and after antiestrogen therapy in the seven evaluable patients are summarized in Table 2. The changes in lesion uptake after antiestrogen therapy are illustrated in Figures 2 and 3. The mean lesion FES uptake (± standard deviation) before anti-estrogen therapy was 2.22 (±1.23) × 10^{-3}% ID/ml. The mean uptake decreased significantly after anti-estrogen therapy (of 22 ± 19 days duration) to a value of 0.80 (±0.42) × 10^{-3}% ID/ml (p < 0.001), as did uptake in the great majority of the individual lesions (33 of 34) (Fig. 2). After anti-estrogen therapy, the FES uptake decreased by more than 50% in 80% of the 34 lesions analyzed. In the patient who underwent three PET studies (Patient 6), there was a greater reduction in FES uptake on the third study by comparison with the second (see Table 2). Both the mean L/ST ratio and the L/B ratio decreased significantly (p < 0.001) after anti-estrogen therapy. As is shown in Table 2, antiestrogen therapy resulted in clinical improvement lasting at least 3 mo in six of the seven patients. There was progression of metastatic disease within three months of initiating antiestrogen therapy in the remaining patient (despite the fact that the measured decrease in lesion FES uptake after initiation of therapy seen in this patient was of similar magnitude of that seen in the other patients). The small number of patients studied precludes an evaluation of the relationship between PET results and therapeutic outcome.

DISCUSSION

We have demonstrated that metastatic lesions from carcinoma of the breast can be detected with high sensitivity by PET as foci of increased uptake of radiolabeled FES. The findings of PET imaging correlate well with the results of other radiographic methods for defining the presence of osseous or soft-tissue metastases. PET with FES was able to demonstrate 53 of 57 individual metastatic lesions. The high sensitivity of PET with FES in this study almost certainly reflects the fact that the primary tumors of our patients were estrogen-receptor positive or borderline positive (i.e., estrogen-receptor concentration > 3 fmol/mg protein) in all of the 15 cases for which this information was available. This is higher than the overall frequency of estrogen-receptor positivity in breast carcinoma (approximately 67%) (1). Our study-entry requirement that therapy with anti-estrogen drugs was planned is the likely explanation for this high frequency of estrogen-receptor-positive tumors, since such treatment for recurrent or metastatic breast carcinoma is usually reserved for patients with estrogen-receptor-positive lesions. Of the four lesions not detected by PET, three occurred in two patients who received FES of relatively low specific activities (278 and 230 Ci/mmol, respectively); these values were more than one standard deviation below the mean specific activity
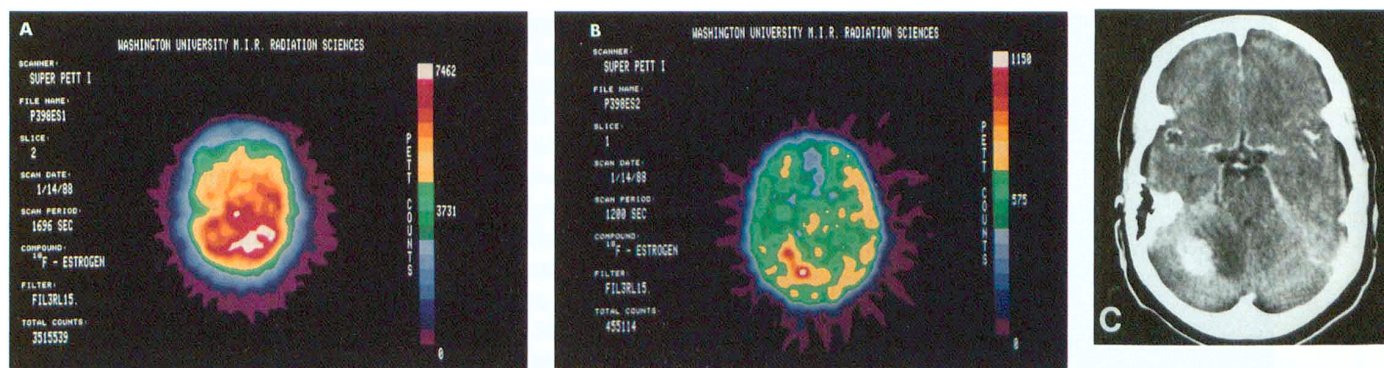
FIGURE 1. Time course of FES uptake in a cerebellar metastasis (Patient 2). (A) An early (0–20 min) PET image of the head demonstrates focally decreased activity in the left cerebellar hemisphere. (B) A later (90–110 min) PET image demonstrates increased accumulation of FES in the left cerebellar hemisphere lesion. Because the patient moved between the two image acquisitions, the early image is at a slightly lower level through the cerebellum than the later image. (C) A post-contrast CT image demonstrates an enhancing left cerebellar metastasis with adjacent edema. (All of the cross-sectional images are oriented as if viewed from above the patient.)

(1316 ± 815 Ci/mmol) of the FES preparations used in this study. The nonvisualization of these lesions may simply be a demonstration of the necessity for radioligands having high specific activity in clinical receptor imaging (22). In the third patient who had a lesion documented on other radiographic examinations that was not detected by PET, the FES preparation had specific activity within the usual range. The PET study in this patient is thus considered to represent an unexplained false-negative result.

In two of our patients, lesions initially suspected to represent metastases were not subsequently confirmed to be sites of metastatic disease. Biopsy of the presumed

metastatic lesion in one of these demonstrated only changes of radiation fibrosis, although this patient subsequently developed metastatic disease. The other patient was thought most likely to have an insufficiency fracture. These patients' lesions were visualized on PET imaging and had FES uptake values in the range of that observed with confirmed metastatic lesions. In our study, these two lesions were the only examples of false-positive results among 55 foci that showed FES accumulation on PET images. Therefore, the specificity and positive predictive value of PET with FES, although not 100%, are quite high.

TABLE 2
Effect of Antiestrogen Therapy on FES Uptake in Metastatic Lesions

Pt. No.	No. of lesions	Therapy (days)	Average % ID/ml (×10³)		Average L/ST		Average L/B		ER	PR	Response
			Pre	Post	Pre	Post	Pre	Post			
6	5	5 [68]	1.83	1.42 [0.73]	3.87	2.15 [1.67]	2.63	1.70 [1.40]	67 (34)	<3 (3)	++
7	7	21	1.31	0.36	4.06	1.53	3.15	1.31	176 (92)	5 (<3)	+
8	2	15	0.95	0.39	5.69	3.17	3.89	1.41	118	105	+
9	6	15	2.79	0.95	3.33	1.55	3.32	1.50	83	33	++
10	5	23	2.24	0.54	4.00	1.25	3.43	1.17	6	NA	—
15	4	16	4.67	1.43	4.71	1.36	4.20	1.37	274 (98)	<3 (<3)	++
16	5	16	1.89	1.20	2.31	1.20	2.27	1.62	275	340	++
mean ± s.d.		22 ± 19	2.22 ± 1.23	0.80 ± 0.42	3.80 ± 1.80	1.54 ± 0.68	3.18 ± 1.22	1.39 ± 0.44			

[ ]Results of third study.
( ) Receptor assays of second primary.
— Progression of disease in ≤3 mo on anti-estrogen therapy.
+ Improvement for ≥3 mo on anti-estrogen therapy.
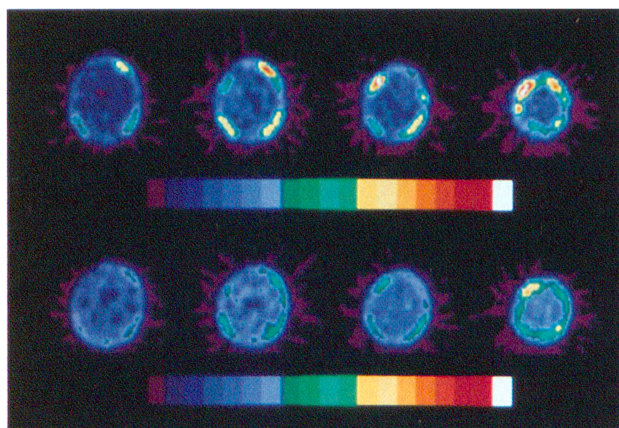++ Improvement for ≥1 yr on anti-estrogen therapy.

FIGURE 2. Multiple calvarial metastases (Patient 6). PET images obtained before antiestrogen therapy (top row) demonstrate multiple foci of radiopharmaceutical accumulation in the calvarium. The corresponding images obtained 14 days after initiation of antiestrogen therapy (bottom row) show a marked decrease in tracer uptake by these lesions.

In our previous work with this estrogen ligand and primary breast tumors (*17*), we found excellent correlation between estrogen-receptor concentrations measured in vitro and FES uptake values determined in vivo (r = 0.97). In the current study, the estrogen-receptor concentrations (which were generally measured on the patient's primary breast carcinoma) and FES uptake values in metastatic lesions did not appear to be well correlated (see Table 1). The apparent lack of correlation between estrogen-receptor concentration and FES uptake in metastatic lesions may relate to several factors. These include the well known intralaboratory variability in estrogen-receptor assays (*23*), the heterogeneity of primary breast tumors (*11*), and known differences in the estrogen-receptor content of primary and metastatic lesions in 20%–25% of patients (*24–27*). Also, there is variability in estrogen-receptor content measured in different metastatic lesions in the same patient, when visceral metastases are compared with skeletal metastases, and when assessed in lesions of patients who have undergone therapy since an initial assay (*28*).

In our prior study (*17*), the measured values of FES uptake in primary tumor were corrected for partial volume averaging by multiplying by the appropriate recovery coefficient for a lesion of known size (determined by mammography). Lesions that were evaluated in the current study were predominantly osseous metastases. The sizes of the actual tumor deposits are impossible to determine from the available correlative studies (bone scintigrams and plain radiographs), which largely reflect the reaction to the presence of tumor (but do not depict the tumor directly). Therefore, we could not correct the results for partial volume averaging, and this also may be contributing to the apparent poor correlation between the in vivo and in vitro measurements.

Our measurements of FES uptake in metastatic lesions before and after antiestrogen therapy indicated definite reduction of FES uptake in nearly all lesions (33 of 34); the mean uptake after therapy was decreased significantly by comparison with the pre-treatment result. This effect of antiestrogen therapy provides important evidence to confirm that the uptake of FES in human breast tumors is a specific interaction of the ligand with the estrogen receptor. Similar inhibition by tamoxifen of FES uptake in tissues with estrogen-receptor content has previously been demonstrated in an animal model (*29*). Although the mechanism of action of tamoxifen and other antiestrogens has not been fully elucidated, tamoxifen is known to compete with circulating estrogens for receptor binding (*30*). Thus, in the clinical setting, the use of FES uptake inhibition by antiestrogens to confirm that the uptake of this tracer is receptor-mediated may be considered essentially equivalent to the usual method involving co-administration of cold ligand.

The extent to which delivery of tracer to tumor tissue influences its uptake by the tumor is uncertain. We did not systematically evaluate tracer delivery to individual tumor deposits in this study. Our observations in a single patient (Fig. 1), who underwent both early and late PET imaging with FES, provides some insight into this problem, however. In this patient, a cerebellar metastasis exhibited relatively decreased FES uptake on images obtained from

FIGURE 3. (A) Anterior skeletal scintigram of the pelvis and femurs in Patient 9 demonstrates multiple osseous metastases. (B) Two contiguous PET images at the level of the large lesion in the right femoral diaphysis demonstrate accumulation of FES in the lesion before initiation of antiestrogen therapy (left). On the corresponding post-treatment images (right), there is marked diminution in tracer uptake by the lesion.
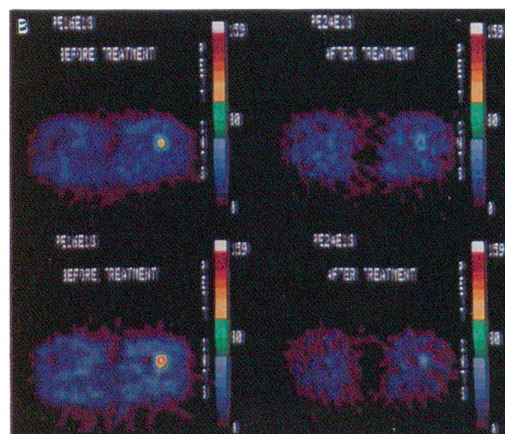
0 to 20 min after injection of tracer and increased uptake on images obtained from 90 to 120 min. Therefore, in this single case, the delivery of tracer does not appear to have been the major determinant of ligand uptake by the tumor. We have previously reported similar findings in an animal model of DMBA-induced mammary carcinoma (31).

Whether PET imaging with FES has a potential clinical role in the detection or staging of metastatic disease in patients with breast carcinoma remains to be established. Our limited experience to date suggests that this technique might have utility for detecting metastatic lesions in regions that cannot be assessed reliably by other noninvasive imaging methods (e.g., internal mammary lymph nodes). Also, PET with FES could help to determine whether metastatic disease is present when the nature of a lesion detected by conventional methods is uncertain. An example of this would be a patient in whom bone scintigraphy shows one or two focal abnormalities, either in conjunction with normal conventional radiographs or with radiographic evidence of a potentially confounding abnormality (e.g., a vertebral compression fracture). Finally, and potentially of most importance, by permitting evaluation of estrogen-receptor positivity of individual lesions noninvasively and repetitively, PET with FES may be a means for determining whether anti-estrogen therapy is appropriate and for assessing the likelihood of response to such therapy in individual patients with metastatic carcinoma of the breast.

ACKNOWLEDGMENTS

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