The Effects of Estrogen, Progesterone, and C-erbB-2 Receptor States on ^{18}F-FDG Uptake of Primary Breast Cancer Lesions

Ayse Mavi[1], Tevfik F. Cermik[1], Muammer Urhan[1], Halis Puskulcu[2], Sandip Basu[1], Jian Q. Yu[1], Hongming Zhuang[1], Brian Czerniecki[3], and Abass Alavi[1]

[1]*Department of Radiology, Division of Nuclear Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania;* [2]*Department of Computer Engineering, Izmir Institute of Technology, Izmir, Turkey; and* [3]*Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania*

The purpose of this prospective study was to investigate whether correlations exist between ^{18}F-FDG uptake of primary breast cancer lesions and predictive and prognostic factors such as estrogen receptor (ER), progesterone receptor (PR), and C-erbB-2 receptor (C-erbB-2R) states. **Methods:** Before undergoing partial or total mastectomy, 213 patients with newly diagnosed breast cancer underwent ^{18}F-FDG PET (5.2 MBq/kg of body weight). The maximum standardized uptake value (SUV) of the primary lesion was measured in each patient. Standard immunohistochemistry was performed on a surgical specimen of the cancer lesion to characterize the receptor state of the tumor cells. Pearson χ^2 tests were performed on the cross-tables of different receptor states to test any association that may exist among ER, PR, and C-erbB-2R. Maximum SUV measurements for different receptor states were compared using factorial ANOVA in a completely random design. **Results:** After exclusion of certain lesions, 118 lesions were analyzed for this study. The mean maximum SUVs of ER-positive and ER-negative lesions were 3.03 $\pm$ 0.26 and 5.64 $\pm$ 0.75, whereas those of PR were 3.24 $\pm$ 0.29 and 4.89 $\pm$ 0.67, respectively, and those of C-erbB-2R were 4.64 $\pm$ 0.70 and 3.70 $\pm$ 0.35, respectively. χ^2 tests for ER and PR showed that if one is positive then the other tends to be positive as well ($\chi^2 = 71.054$, $P < 0.01$). For ER and C-erbB-2R states, if ER is positive, C-erbB-2R will more likely be negative ($\chi^2 = 13.026$, $P < 0.01$). No relationship was detected between PR and C-erbB-2R states ($\chi^2 = 3.695$, $P > 0.05$). ANOVAs showed that PR state alone ($F = 0.095$, $P > 0.05$) and C-erbB-2R state alone ($F = 0.097$, $P > 0.05$) had no effect on ^{18}F-FDG uptake but ER state alone had an effect ($F = 9.126$, $P < 0.01$). ER and PR being together had no additional effect on ^{18}F-FDG uptake. Our study also demonstrated that interactions exist between ER and C-erbB-2R state and between PR and C-erbB-2R state. **Conclusion:** SUV measurements may provide valuable information about the state of ER, PR, and C-erbB-2R and the associated glucose metabolism as measured by ^{18}F-FDG uptake of the primary breast cancer lesions. Such an association may be of importance to treatment planning and outcome in these patients.

Received Oct. 20, 2006; revision accepted May 15, 2007.

For correspondence or reprints contact: Abass Alavi, MD, Division of Nuclear Medicine, Hospital of the University of Pennsylvania, 3400 Spruce St., 110 Donner Bldg., Philadelphia, PA 19104.

E-mail: alavi@rad.upenn.edu

Key Words: ^{18}F-FDG PET; breast cancer; estrogen; progesterone; C-erbB-2; interactions between receptors

J Nucl Med 2007; 48:1266–1272
DOI: 10.2967/jnumed.106.037440

PET, using the radiolabeled glucose analog ^{18}F-FDG, can detect enhanced glycolysis of cancer cells and has been proven valuable in diagnosing, staging, detecting recurrences, and assessing response to therapy in a multitude of malignant disorders (*1*). ^{18}F-FDG PET is a noninvasive diagnostic modality that also provides quantitative data on the level of metabolic activity by calculating the degree of ^{18}F-FDG uptake, known as standardized uptake value (SUV). Breast cancer is the most common cancer among women, with an increasing prevalence (*2*), and is curable with early diagnosis and optimal treatment. Among various tests for predicting response to treatment, determination of estrogen receptor (ER) and progesterone receptor (PR) in tumor cells is essential for appropriate hormone therapy. The C-erbB-2 (also known as HER-2 [human epidermal growth factor receptor-2] or neu) receptor (C-erbB-2R) has recently been introduced as another predictive and prognostic marker for this malignancy. Determination of this receptor is useful for selecting patients with advanced breast cancer for treatment with therapeutic antibodies such as trastuzumab (Herceptin; Genentech) (*3*).

Breast carcinomas appear to display considerable variability with regard to ^{18}F-FDG uptake, resulting in reports of a wide range of sensitivity and specificity values that, in turn, have brought its diagnostic utility into question (*4–11*). Breast cancer lesions are noted to have characteristically lower SUVs than other malignancies. Therefore, tumor characteristics that may explain the underlying biologic properties of glucose metabolism of the lesion and, therefore, ^{18}F-FDG accumulation would require further investigation. Several studies have investigated the correlation between ^{18}F-FDG uptake and a variety of prognostic

and molecular biomarkers for predicting tumor response to therapy (*9,12–15*). Yet, based on published literature, no correlation has been reported between ^{18}F-FDG uptake and the ER, PR, and C-erbB-2R states of malignant breast cancer lesions. Thus, research studies determining factors that govern uptake of ^{18}F-FDG in proven breast lesions would be of value in defining the role of this technique in the management of patients with this cancer.

^{18}F-FDG uptake in breast cancer usually indicates the degree of tumor metabolism and hence can predict its behavior and prognosis. On the other hand, the ER, PR, and C-erbB-2R state of breast cancer is a biomarker that provides important prognostic information in addition to predicting response to therapy. The main objective of this study was to determine whether a correlation exists between ^{18}F-FDG uptake in untreated cases of breast cancer and their ER, PR, and C-erbB-2R state. In addition, we also investigated individual interactions among these receptors and how they might influence the degree of ^{18}F-FDG uptake in lesions.

MATERIALS AND METHODS

Patient Population

Two hundred thirteen consecutive patients (median age, 51 y; range, 24–80 y) with biopsy-proven primary breast cancer who were examined by film-screen mammography, ultrasound, MRI, and ^{18}F-FDG PET were enrolled in this prospective study. For the purposes of this scientific communication, we present only data that were generated with ^{18}F-FDG PET. This prospective National Institutes of Health–funded project was designed to test the role of various imaging modalities for detecting and staging primary breast cancer. This study complied with the Health Insurance Portability and Accountability Act and was approved by the Institutional Review Board. Informed consent was obtained from all patients. ^{18}F-FDG PET was performed after breast cancer had been diagnosed through biopsy. The average (and SD) time between the diagnostic biopsy and ^{18}F-FDG PET was 24 ± 13 d. None of the patients had received chemotherapy or radiation therapy before undergoing ^{18}F-FDG PET for preoperative staging. After PET, patients underwent a surgical intervention that included either partial or total mastectomy for the primary lesion. Surgical pathology results were considered to provide the definitive diagnosis against which the PET study results were compared.

Imaging Procedure and Image Analysis

PET scans were obtained on a dedicated whole-body PET scanner (Allegro; Philips Medical System). The patients fasted for at least 4 h, and serum glucose levels were less than 140 mg/dL. ^{18}F-FDG (5.2 MBq/kg of body weight) was administered intravenously through an indwelling catheter inserted into an antecubital vein. The scan was obtained 60 min after the injection. Sequential overlapping scans were obtained as a whole-body image that included the entire trunk (from neck to groin). Transmission scans using a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed using an iterative reconstruction algorithm. Both slice thickness and slice interval were 4 mm.

After image reconstruction, a region of interest was carefully drawn around the site of the breast lesion on the consequent 4–6 PET scan slices. This analysis was performed uniformly by an experienced nuclear medicine physician for the entire population examined. From these ROIs, the maximum SUV (SUVmax) was calculated by the inbuilt software of the PET scanner. The SUVmax of ^{18}F-FDG was measured from regions of interest placed at the site of the lesion as clearly visualized on the PET scan. We used only SUVmax for our analyses because the mean SUV of the lesion is operator-dependent. The interpreting physician identified the breast lesions using the traditional and widespread method of visual assessment.

Immunohistochemistry and Tissue Receptor Analysis

Immunohistochemical analyses were performed on the surgical tissue specimen of the primary breast cancer lesion. The tumor tissue was analyzed for ER, PR, and C-erbB-2R state using standardized immunohistochemical techniques and robotic autostainers (DakoCytomation, Inc.).

The ER state was evaluated using a monoclonal mouse antihuman antibody directed against ERα (clone 1D5; DakoCytomation). PR state was assayed using a monoclonal mouse antihuman antibody directed against the PR (clone PgR 636; DakoCytomation). Both procedures were performed on formalin-fixed paraffin-embedded tissue using heat-induced epitope retrieval. Binding results were visualized with the Envision+ system (DakoCytomation), which uses a horseradish peroxidase–labeled polymer that is conjugated with secondary antibodies. Diaminobenzidine was used as the chromogen (*16,17*). A visual scoring system was used for interpretation and for estimating the percentage of nuclear labels in the tumor cells. Tissues with less than 5% nuclear labeling were considered negative. The tissue analysis for C-erbB-2R state was done using the HercepTest (DakoCytomation), which uses a rabbit antihuman C-erbB-2 protein on formalin-fixed paraffin-embedded tissue using heat-induced epitope retrieval. Binding results were visualized with a dextran polymer conjugated with horseradish peroxidase and affinity-isolated goat antirabbit immunoglobulins. Diaminobenzidine was used as the chromogen. A visual scoring system was used for interpretation: 0 (no staining is observed or membrane staining is observed in less than 10% of tumor cells), 1+ (a faint, barely perceptible membrane staining is detected in more than 10% of tumor cells; cells are stained in only part of their membrane), 2+ (a weak to moderate complete membrane staining is observed in more than 10% of tumor cells), and 3+ (a strong, complete membrane staining is observed in more than 10% of tumor cells). The results were scored on a scale of 0 to 3+ using the grading system approved by the United States Food and Drug Administration. In this system (*18*) and in our study, cases scored as either 0 or 1+ were considered C-erbB-2R–negative (C-erbB-2R−) and those with either 2+ or 3+ were considered C-erbB-2R–positive (C-erbB-2R+).

Statistical Analysis

Pearson χ^2 tests were performed on the cross-tables of different receptors to test any association among ER, PR, and C-erbB-2R states. SUVmax measurements for different receptor states were compared using factorial ANOVA in completely random designs. Because of missing combinations, only 2-way ANOVA was performed on all combinations of receptors. SPSS software (SPSS Inc.) was used for all statistical analyses.

RESULTS

Among 213 patients with newly diagnosed breast cancer, 30 had undergone diagnostic excisional biopsy before

^{18}F-FDG PET, and therefore, no residual tumor was left in the surgical specimen (all tumor tissue was removed during diagnostic biopsy). Thirty-eight patients were noted to have complications due to diagnostic excisional biopsy, including seromas, hematomas, and significant inflammatory reactions. No ^{18}F-FDG uptake was detected in 31 patients, and therefore, no abnormality was visualized on PET for SUV analysis (false-negative). Among these 31 patients, 6 had tumors smaller than 5 mm. We excluded lesions smaller than 5 mm. For the remaining so-called false-negative results—25 lesions (10 noninvasive and 15 invasive)—we could not calculate SUV because the lesions had no increased ^{18}F-FDG uptake and were invisible on PET scans. Their SUVmax was as low as the background and equal to that of normal glandular tissue. Therefore, we did not include these lesions in the analyses. However, we think that their receptor states are important. Among 25 malignant lesions, all ER-positive (ER+), 18 were PR-positive (PR+) and only one was C-erbB-2R+. Thus, we excluded a total of 99 patients from consideration for this study. The remaining 114 patients with 118 malignant breast tumors (4 patients had bilateral cancer), which were clearly seen in the surgical specimen after ^{18}F-FDG PET, were considered appropriate for this analysis. We analyzed 118 (102 invasive and 16 noninvasive carcinoma in situ) malignant lesions that had undergone ^{18}F-FDG PET, and the tumor was definable on the surgical specimen. The lesion size of the 102 invasive malignant lesions ranged from 5 to 60 mm. The subtypes of invasive malignant lesions were as follows: 81 ductal, 8 lobular, 9 mixed (ductal plus lobular), 3 tubular, and 1 medullary.

We performed Pearson χ^2 tests on the cross-tables of different receptors to test for any association among ER, PR, and C-erbB-2R. Between ER and PR states, it was found that if one is positive the other tends to be positive as well ($\chi^2 = 71.054$, $P < 0.01$). If ER is positive, C-erbB2R will likely be negative in the same lesion ($\chi^2 = 13.026$, $P < 0.01$). No correlation was detected between PR and C-erbB-2R states in the tumors examined ($\chi^2 = 3.695$, $P > 0.05$).

^{18}F-FDG PET detected all 118 surgically proven malignant lesions larger than 5 mm. Among these, 82 were ER+, 36 ER-negative (ER−), 76 PR+, 42 PR-negative (PR−), 20 C-erbB-2R+, and 96 C-erbB-2R−. In 2 lesions, the C-erbB-2R state could not be determined. The mean values (and SD) of the SUVmax of ER+ and ER− lesions were 3.03 ± 0.26 and 5.64 ± 0.75, whereas those of the PR lesions were 3.24 ± 0.29 and 4.89 ± 0.67, respectively, and those of the C-erbB-2R lesions were 4.64 ± 0.71 and 3.70 ± 0.35, respectively.

ANOVA showed that the SUVmax of the ER+ lesions and the SUVmax of the ER− lesions were significantly different ($F = 9.126$, $P < 0.01$). However, no significant differences were found between the SUVs of the PR+ and PR− lesions ($F = 0.095$, $P > 0.05$) or the C-erbB-2R+ and C-erbB-2R− lesions ($F = 0.097$, $P > 0.05$). PR or C-erbB-2R states alone had no effect on ^{18}F-FDG uptake, but the ER state alone had an effect on ^{18}F-FDG uptake. ER− lesions had a significantly higher SUVmax than did ER+ lesions. In other words, statistical analysis demonstrated that ER state affects SUV irrespective of PR state, and PR state does not affect SUV irrespective of ER state. No interaction was detected between ER and PR states, indicating that the effects of ER and PR states on ^{18}F-FDG uptake were independent of each other. The effects of ER and PR on ^{18}F-FDG uptake are given in Tables 1 and 2 and Figure 1A.

TABLE 1
SUVmax Means in Different States of PR and ER

	ER					
	Negative			Positive		
PR	*n*	SUVmax	SE	*n*	SUVmax	SE
Negative	33	5.54	0.82	9	2.49	0.52
Positive	3	6.80	0.70	73	3.10	0.28

Two-way ANOVA of the ER and C-erbB-2R states showed an interaction between the effects of these receptors (Tables 3 and 4; Fig. 1B). When both these receptors are either positive or negative, the SUVmax is higher than that in lesions for which only one receptor is positive. A similar interaction exists between PR state and C-erbB-2R state (Tables 5 and 6; Fig. 1C). These interactions of C-erbB-2R with ER and PR can be interpreted as indicating that the presence or absence of C-erB-2R reverses the effects of either PR or ER on SUVmax measurements.

DISCUSSION

Breast cancer is the second leading cause of death from any malignancy among women (*2*). Although breast cancer is curable when detected early, about one third of women with breast cancer will die of the disease (*19*). Variable factors have been considered important for predicting and forecasting prognosis in these patients, including the state of ER, PR, and C-erbB-2R in the excised tumor. The results from these biologic measurements are of pivotal importance for the management of breast cancer patients. Multiple expert panels, including those of the American Society of Clinical Oncology, the National Academy of Clinical Biochemistry (United States), the National Institutes of

TABLE 2
ANOVA Table of PR and ER Effects on SUVmax

Source	Sum of squares	df	Mean square	F	*P*
ER	93.408	1	93.408	9.126	0.003
PR	7.141	1	7.141	0.698	0.405
ER × PR	0.875	1	0.875	0.085	0.771
Error	1,166.876	114	10.236		
Corrected total	1,345.293	117			

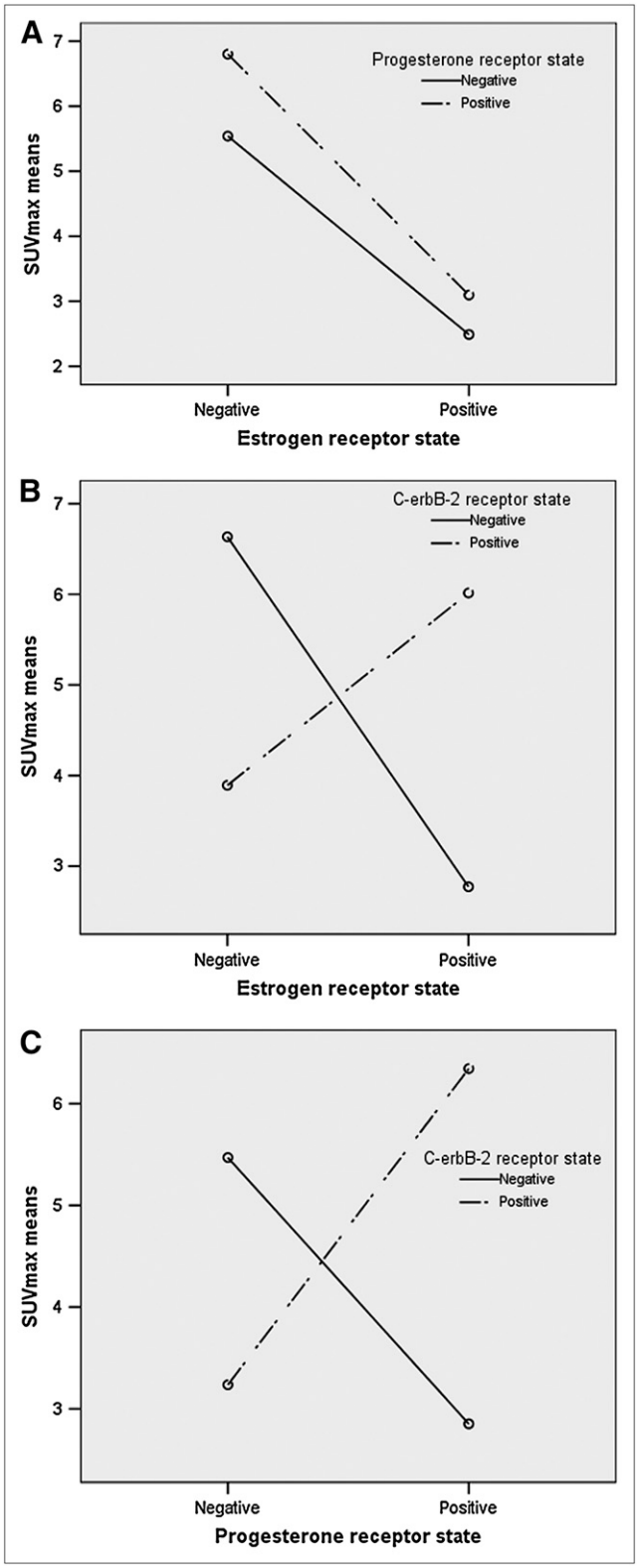

FIGURE 1. (A) Graphic presentation of SUVmax means in different combinations of ER and PR states shows no interaction between ER and PR states, indicating that effects of ER and PR states on ^{18}F-FDG uptake were independent of each other. (B) Graphic presentation of SUVmax means in different combinations of ER and C-erbB-2R states shows that for lesions in which both these receptors are either positive or negative, SUVmax is higher than for lesions in which only one is positive. (C) Graphic presentation of SUVmax means in different combinations of C-erbB-2R and PR states shows that for lesions in which both these receptors are either positive or negative, SUVmax is higher than for lesions in which only one is positive.

TABLE 3
SUVmax Means in Different States of C-erbB-2R and ER

	ER					
	Negative			Positive		
C-erbB-2R	*n*	SUVmax	SE	*n*	SUVmax	SE
Negative	23	6.63	1.10	73	2.77	0.23
Positive	13	3.90	0.62	7	6.01	1.60

Health, the European Group on Tumor Markers, and the European Society of Mastology, have recommended that ER and PR be assayed on all primary breast cancers because of the striking differences between the responses of steroid receptor–positive and –negative breast cancers to hormone therapy (*3*). Also, in advanced breast cancer the state of tumors with regard to ER and PR is of great importance before adjuvant endocrine treatment is initiated. (*20*). C-erbB-2R is a member of subclass 1 of the superfamily of receptor tyrosine kinases. Overexpression of C-erbB-2R is associated with increased mitogenesis, malignant transformation, cell motility, invasiveness, and metastasis and appears to predict a poor response to tamoxifen and other hormone therapies (*3,21,22*). However, C-erbB-2R is a recently introduced predictive marker for selecting patients with advanced breast cancer for treatment with therapeutic antibodies such as trastuzumab (*3*). In addition, C-erbB-2R+ tumors may indicate an enhanced sensitivity to high-dose anthracycline-based regimens (*3*). Overexpression of C-erbB-2R has also been suggested as an independent prognostic indicator in patients with breast cancer (*23,24*).

Although ^{18}F-FDG PET has been shown to provide useful information in most patients with breast cancer (*25*), reports describe some limitations of this methodology (*7,11,26*). Breast carcinomas vary considerably in ^{18}F-FDG uptake (*4–10*). Therefore, based on the literature reports, the appropriate role of ^{18}F-FDG PET in assessing primary lesions is unclear (*26*). The reasons for variability in sensitivity have also been investigated by several studies. Some investigated whether correlations exist between the degree of ^{18}F-FDG uptake and the receptor state of the tumor that could predict tumor response to therapy and forecast prognosis (*9,12–15*). Crowe et al. (*15*) investigated the correlation between preoperative ^{18}F-FDG uptake by a tumor and the postoperative ER and PR states of the tumor in 28 patients. Other groups have reported interesting results in 32 patients (*13*), in 86 patients (*9*), in 56 patients (*12*), and in 75 patients (*14*). However, no correlation has been reported between the degree of ^{18}F-FDG uptake and

TABLE 4
ANOVA Table of ER and C-erbB-2R Effects on SUVmax

Source	Sum of squares	df	Mean square	F	*P*
ER	10.934	1	10.934	1.175	0.281
C-erbB-2R	0.900	1	0.900	0.097	0.756
ER × C-erbB-2R	129.299	1	129.299	13.895	0.000
Error	1,042.215	112	9.305		
Corrected total	1,338.120	115			

TABLE 6
ANOVA Table of PR and C-erbB-2R Effects on SUVmax

Source	Sum of squares	df	Mean square	F	*P*
PR	0.959	1	0.959	0.095	0.759
C-erbB-2R	6.334	1	6.334	0.627	0.430
PR × C-erbB-2R	131.359	1	131.359	12.999	0.000
Error	1,131.834	112	10.106		
Corrected total	1,338.120	115			

the ER or PR content of the lesions in these studies (*26*). In our study, we were able to detect for, what is to our knowledge, the first time a correlation between ER state and ^{18}F-FDG uptake in tumors (Fig. 2). Also, instead of using the mean SUV of the lesion, which is operator-dependent, in this study we decided to use the SUVmax of ^{18}F-FDG uptake as a reliable indicator of disease activity. For the final analyses, we used only SUVmax. According to our results, ER state alone had a significant effect on ^{18}F-FDG uptake in this malignancy. ER− lesions had a significantly higher SUVmax than did ER+ lesions (5.64 ± 0.75 vs. 3.03 ± 0.26). However, neither PR state nor C-erbB-2R state alone had an effect on ^{18}F-FDG uptake. Only 1 study in the literature (*14*) has attempted to determine the relationship between C-erbB-2R state and preoperative ^{18}F-FDG uptake by breast cancer. Similar to our findings, no correlation was found between ^{18}F-FDG uptake and the C-erbB-2R state of the tumor. In this study, C-erbB-2R expression was detected in 14 patients with invasive ductal cancer, whereas no patient with lobular cancer showed immunoreactivity to C-erbB-2R. In our study, all 20 C-erbB-2R+ lesions were of the invasive ductal type. Therefore, our results were similar to those reported by this group (*14*).

According to our results, there is an association between ER and PR. The presence of one will likely accompany that of the other in these tumors. There is also a reverse association between ER and C-erbB-2R indicating that if ER is positive, C-erbB-2R will likely be negative in the malignant tissue. No association was noted between the PR and C-erbB-2R states of these tumors.

We also investigated the interactions among receptor states and the effects of such a biologic association on ^{18}F-FDG uptake in this cancer. The interactions among C-erbB-2R and ER or PR revealed that the presence or absence of C-erB-2R reverses the effects of either PR or ER on SUVmax measurements. However, such an interaction was detected between ER and PR states, indicating that the effects of these receptors on ^{18}F-FDG uptake were independent of each other. Despite the fact that many pathways and cross-talks among these receptors are still incompletely understood, we hope that the knowledge gained about their effects on ^{18}F-FDG uptake may allow for characterizing the degree of aggressiveness of the tumor. In this prospective study, we were able to show that ER− tumors have a significantly higher SUVmax than do tumors with positive receptors. This finding would suggest that in these poorly differentiated and aggressive tumors, glucose metabolism is accelerated to meet the energy demand for rapid growth. Another important finding of our study was that 25 lesions larger than 5 mm on surgical specimens and with no ^{18}F-FDG uptake were ER+ whereas 18 were PR+ and only 1 was C-erbB-2R+. We excluded these from the initial analysis, but if we were to include this population our

TABLE 5
SUVmax Means in Different States of C-erbB-2R and PR

	PR					
	Negative			Positive		
C-erbB-2R	*n*	SUVmax	SE	*n*	SUVmax	SE
Negative	31	5.47	0.87	65	2.85	0.25
Positive	11	3.23	0.52	9	6.34	1.24

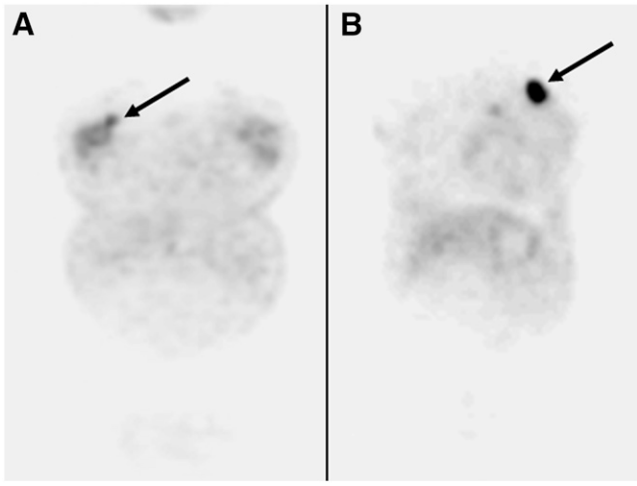

FIGURE 2. ^{18}F-FDG PET images of 2 newly diagnosed breast cancer patients who underwent preoperative PET studies. (A) Image for which measured SUVmax of right breast lesion was 2.1 (arrow). After mastectomy, surgical pathology confirmed 1.2-cm invasive ductal cancer. Tissue receptor analysis revealed that this lesion was ER+, PR+, and C-erbB-2R−. (B) Image for which measured SUVmax of left breast lesion was 9.0 (arrow). After mastectomy, surgical pathology confirmed 2-cm invasive ductal cancer that was negative for ER, PR, and C-erbB-2R. ER+ lesion showed significantly lower SUVmax than did ER− lesion.

results would be quite striking, supporting our hypothesis that poorly differentiated lesions are expected to be ^{18}F-FDG–avid in most settings. Clinical studies on gliomas and lymphomas have also demonstrated that hypermetabolic tumors are more aggressive than tumors with low metabolic rates and that ^{18}F-FDG PET can be used as a prognostic indicator in these malignancies (*27*).

It was reported that the prognosis of breast cancer may be determined on the basis of ^{18}F-FDG PET results (*28*). The state of various receptors in malignant breast tumors is a major determinant of prognosis and an important step in the initial work-up of breast carcinoma (*29–32*). Increased fluoroestradiol activity in advanced tumors predicts a favorable prognosis and a probability of response to tamoxifen (*33*). The premise of this study is to determine whether such characteristics with regard to tumor activity would allow the response to therapy to be forecast.

This study had limitations that possibly influenced the findings. First, all patients had prior diagnostic core biopsies that removed a portion of the cancer tissue. As a consequence, the overall amount of ^{18}F-FDG uptake was reduced, resulting in lowering of the overall contrast of the lesion on PET because of the partial-volume effect. On the other hand, it is possible that in some patients an inflammatory reaction after surgical intervention could have contributed to the measured uptake in the lesion site. Considering the design of the study, this type of effect was unavoidable but likely did not substantially alter the results described. In addition, we excluded patients who could have been inappropriate for this analyses because of these factors.

CONCLUSION

SUV measurements may provide valuable information about the state of ER, PR, and C- erbB-2R of primary breast cancer lesions. Based on the data described here, ER− lesions have a significantly higher SUVmax than do ER+ lesions. The results clearly demonstrated interactions that affect the degree of ^{18}F-FDG uptake (expressed as SUV) of breast cancer lesions. Also, the C-erbB-2R state interacts both with ER and with PR with regard to ^{18}F-FDG uptake. ^{18}F-FDG PET is well known as a noninvasive metabolic parameter for assessing the biologic aggressiveness of breast cancer, as our results substantiate. The implications of the interactions among receptors and between the degree of ^{18}F-FDG uptake and the receptor state need to be investigated in future studies.

ACKNOWLEDGMENT

This work was supported by Public Health Services research grant M01-RR00040 from NIH.

REFERENCES

1. Alavi A, Lakhani P, Mavi A, Kung JW, Zhuang H. PET: a revolution in medical imaging. *Radiol Clin North Am.* 2004;42:983–1001.
2. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55:10–30.
3. Duffy MJ. Predictive markers in breast and other cancers: a review. *Clin Chem.* 2005;51:494–503.
4. Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology.* 1991;179:765–770.
5. Avril N, Bense S, Ziegler SI, et al. Breast imaging with fluorine-18-FDG PET: quantitative image analysis. *J Nucl Med.* 1997;38:186–191.
6. Adler LP, Crowe JP, al-Kaisi NK, Sunshine JL. Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-D-glucose PET. *Radiology.* 1993;187:743–750.
7. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol.* 1996;14:1848–1857.
8. Scheidhauer K, Scharl A, Pietrzyk U, et al. Qualitative [^{18}F]FDG positron emission tomography in primary breast cancer: clinical relevance and practicability. *Eur J Nucl Med.* 1996;23:618–623.
9. Crippa F, Seregni E, Agresti R, et al. Association between [^{18}F]fluorodeoxyglucose uptake and postoperative histopathology, hormone receptor status, thymidine labelling 2 index and p53 in primary breast cancer: a preliminary observation. *Eur J Nucl Med.* 1998;25:1429–1434.
10. Avril N, Schelling M, Dose J, Weber WA, Schwaiger M. Utility of PET in breast cancer. *Clin Positron Imaging.* 1999;2:261–271.
11. Avril N, Rose CA, Schelling M, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. *J Clin Oncol.* 2000;18:3495–3502.
12. Avril N, Menzel M, Dose J, et al. Glucose metabolism of breast cancer assessed by ^{18}F-FDG PET: histologic and immunohistochemical tissue analysis. *J Nucl Med.* 2001;42:9–16.
13. 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.
14. Buck A, Schirrmeister H, Kuhn T, et al. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. *Eur J Nucl Med Mol Imaging.* 2002;29:1317–1323.
15. Crowe JP Jr, Adler LP, Shenk RR, Sunshine J. Positron emission tomography and breast masses: comparison with clinical, mammographic, and pathological findings. *Ann Surg Oncol.* 1994;1:132–140.
16. Mofidi R, Walsh R, Ridgway PF, et al. Objective measurement of breast cancer oestrogen receptor status through digital image analysis. *Eur J Surg Oncol.* 2003;29:20–24. 10.
17. Zekioglu O, Erhan Y, Ciris M, et al. Invasive micropapillary carcinoma of the breast: high incidence of lymph node metastasis with extranodal extension and its immunohistochemical profile compared with invasive ductal carcinoma. *Histopathology.* 2004;44:18–23.
18. Jacobs TW, Gown AM, Yaziji H, et al. Specificity of HercepTest in determining HER-2 neu status of breast cancers using the United States Food and Drug Administration-approved scoring system. *J Clin Oncol.* 1999;17:1983–1987.
19. Scheidhauer K, Walter C, Seemann MD. FDG PET and other imaging modalities in the primary diagnosis of suspicious breast lesions. *Eur J Nucl Med Mol Imaging.* 2004;31(suppl 1):S70–S79.
20. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. *J Clin Oncol.* 2003;21:1973–1979.
21. Emens LA. Trastuzumab: targeted therapy for the management of HER-2/neu-overexpressing metastatic breast cancer. *Am J Ther.* 2005;12:243–253.
22. Osborne CK, Schiff R. Estrogen-receptor biology: continuing progress and therapeutic implications. *J Clin Oncol.* 2005;23:1616–1622.
23. Pich A, Margaria E, Chiusa L. Oncogenes and male breast carcinoma: c-erbB-2 and p53 coexpression predicts a poor survival. *J Clin Oncol.* 2000;18:2948–2956.
24. Rudolph P, Alm P, Olsson H, et al. Concurrent overexpression of p53 and c-erbB-2 correlates with accelerated cycling and concomitant poor prognosis in node-negative breast cancer. *Hum Pathol.* 2001;32:311–319.
25. Yap CS, Seltzer MA, Schiepers C, et al. Impact of whole-body ^{18}F-FDG PET on staging and managing patients with breast cancer: the referring physician's perspective. *J Nucl Med.* 2001;42:1334–1337.
26. Eubank WB, Mankoff DA. Evolving role of positron emission tomography in breast cancer imaging. *Semin Nucl Med.* 2005;35:84–99.
27. Brock CS, Meikle SR, Price P. Does fluorine-18 fluorodeoxyglucose metabolic imaging of tumours benefit oncology? *Eur J Nucl Med.* 1997;24:691–705.

28. Oshida M, Uno K, Suzuki M, et al. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro[^{18}F]-D-glucose. *Cancer.* 1998;82:2227–2234.
29. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. *Breast Cancer Res.* 2007;9:R6 [Epub ahead of print].
30. Francis G, Beadle G, Thomas S, Mengersen K, Stein S. Evaluation of oestrogen and progesterone receptor status in HER-2 positive breast carcinomas and correlation with outcome. *Pathology.* 2006;38:391–398.
31. Sapino A, Marchio C, Senetta R, et al. Routine assessment of prognostic factors in breast cancer using a multicore tissue microarray procedure. *Virchows Arch.* 2006;449:288–296.
32. Allemani C, Sant M, Berrino F, et al. Prognostic value of morphology and hormone receptor status in breast cancer: a population-based study. *Br J Cancer.* 2004;91:1263–1268.
33. Mankoff DA, Peterson LM, Stekhova S, et al. Uptake of [F-18]-fluoroestradiol (FES) predicts response of recurrent or metastatic breast cancer to hormonal therapy [abstract]. *J Nucl Med.* 2003;44(suppl):126.

The Journal of NUCLEAR MEDICINE

The Effects of Estrogen, Progesterone, and C-erbB-2 Receptor States on ^{18}F-FDG Uptake of Primary Breast Cancer Lesions

Ayse Mavi, Tevfik F. Cermik, Muammer Urhan, Halis Puskulcu, Sandip Basu, Jian Q. Yu, Hongming Zhuang, Brian Czerniecki and Abass Alavi

J Nucl Med. 2007;48:1266-1272.
Published online: July 13, 2007.
Doi: 10.2967/jnumed.106.037440

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING