Prospective Clinical Trial of ^{18}F-Fluciclovine PET/CT for Determining the Response to Neoadjuvant Therapy in Invasive Ductal and Invasive Lobular Breast Cancers

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^{18}F-labeled 1-amino-3-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine) is a leucine analog radiotracer that depicts amino acid transport into cells. ^{18}F-fluciclovine PET/CT visualizes malignancy, including prostate cancer, invasive ductal breast cancer, and invasive lobular breast cancer. Whether changes in ^{18}F-fluciclovine avidity reflect changes in tumor burden resulting from treatment has not been shown. In this prospective clinical trial (clinical trials.gov: NCT01864083), changes in ^{18}F-fluciclovine avidity after neoadjuvant therapy were compared to breast cancer therapy response, as determined by residual tumor burden on pathology, were evaluated. **Methods:** Twenty-four women with a new diagnosis of locally advanced invasive ductal breast cancer ($n = 18$) or invasive lobular breast cancer ($n = 6$) underwent ^{18}F-fluciclovine PET/CT before and after the completion of neoadjuvant systemic therapy. SUV_{max}, SUV_{mean}, metabolic tumor volume, and total lesion avidity were obtained for the primary breast tumor, axillary lymph nodes, and extraaxillary lymph nodes on each examination and corrected for background ^{18}F-fluciclovine avidity. The relationship between changes in ^{18}F-fluciclovine avidity and the percentage of reduction of tumor on pathology was assessed with the Spearman rank correlation. **Results:** The median decrease in the corrected SUV_{max} of the primary breast lesions was 99% (range, 33%–100%). The median reduction of tumor on pathology was 92% (range, 10%–100%). Changes in ^{18}F-fluciclovine avidity were strongly correlated with the percentage of reduction of tumor on pathology (Spearman ρ, 0.79; 95% CI, 0.56–0.90; $P < 0.001$). **Conclusion:** Changes in ^{18}F-fluciclovine avidity strongly correlated with the tumor response on pathology in this pilot study.

Key Words: ^{18}F-fluciclovine; PET/CT; ductal breast cancer; lobular breast cancer; response

Many tumor cells demonstrate increased amino acid transport; therefore, amino acid metabolism may be a useful target for tumor imaging (*1*). ^{18}F-labeled 1-amino-3-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine), an amino acid analog labeled with the positron emitter ^{18}F, is under investigation as an imaging agent for several types of malignancy (*2–12*). ^{18}F-fluciclovine was recently approved by the U.S. Food and Drug Administration for the detection of recurrent prostate cancer. Initial studies of ^{18}F-fluciclovine in breast cancer have provided encouraging results that warrant further investigation (*7,8*).

Although ^{18}F-fluciclovine has been shown to successfully image several types of malignancy, there is currently no evidence that changes in ^{18}F-fluciclovine avidity correlate with changes in tumor burden. Before ^{18}F-fluciclovine is used for evaluation of the tumor response, the association of ^{18}F-fluciclovine avidity and the tumor response must be demonstrated (*13*). The purpose of this trial was to assess the ability of ^{18}F-fluciclovine PET to determine the therapeutic response to neoadjuvant chemotherapy in patients with breast cancer. All patients underwent prospectively planned surgical removal of the treated primary breast malignancy, allowing for an analysis of the correlation between therapy-induced changes in ^{18}F-fluciclovine avidity and pathologic tumor burden.

MATERIALS AND METHODS

Study Design and Patients

This prospective clinical trial (clinical trials.gov: NCT01864083) was performed with institutional review board approval and written informed consent from participants. Patients who presented for evaluation at Memorial Sloan Kettering Cancer Center; who had biopsy-proven, locally advanced, nonmetastatic invasive ductal breast cancer (IDC) or invasive lobular breast cancer (ILC); and who were referred for neoadjuvant systemic therapy between August 2013 and August 2015 were invited to participate. ILC is a subtype of breast cancer that is difficult to visualize by all known imaging modalities (*14,15*), including ^{18}F-FDG PET (*16–21*). Given the continued need for better metabolic imaging agents for ILC, patients with ILC were actively sought for inclusion in the study, accounting for the higher prevalence of ILC in our cohort than in the overall breast cancer population. The planned sample size of 25 patients was chosen for financial and logistic considerations; the aims of the study were exploratory. In total, 27 patients

were invited to participate, but only 24 completed the protocol. Three patients withdrew from the protocol before the final ^{18}F-fluciclovine scan.

Exclusion criteria were an age of less than 18 y, current pregnancy or lactation, prior malignancy other than squamous or basal skin cancers, and unwillingness or inability to consent. There were no restrictions on sex or race. Clinical records were used to document patient age, sex, and race; presence of biopsy-proven known axillary or extraaxillary nodal metastases before ^{18}F-fluciclovine PET/CT; and histology, grade, and receptor status of the primary breast malignancy. Tumors were considered hormone receptor–positive if they showed greater than 1% staining for either the estrogen receptor (ER) or the progesterone receptor. Tumors were considered human epidermal growth factor 2 (HER2)–positive if they had a HER2 immunohistochemistry grade of 3+ or were amplified by fluorescence in situ hybridization at a ratio of greater than or equal to 2.0. Tumors that were negative for the ER, the progesterone receptor, and HER2 were classified as "triple negative." The initial results of pretherapy ^{18}F-fluciclovine PET/CT examinations from this trial were previously reported (7).

Verification of Malignancy

All patients had a biopsy-proven primary breast malignancy before enrollment in the clinical trial. The results of a pathologic evaluation of axillary nodes were also available for all patients. The results of a pathologic evaluation of extraaxillary nodes were available for the 3 patients with suspicious extraaxillary findings on initial ^{18}F-fluciclovine PET/CT.

^{18}F-Fluciclovine Production

^{18}F-fluciclovine was manufactured in compliance with current good-manufacturing-practice requirements at the Memorial Sloan Kettering Cancer Center Radiochemistry and Molecular Imaging Probes Core Facility. The GE FASTlab automated synthesizer, synthesizer cassettes, reagents, and materials were all supplied by GE Healthcare as previously described (22). The automated synthesis involved nucleophilic incorporation of ^{18}F-fluoride into the ^{18}F-fluciclovine precursor followed by removal of protective groups by hydrolysis and terminal sterilization with a 0.22-μm sterilizing filter. The ^{18}F-fluciclovine final drug product was formulated with a 200 mM citrate buffer solution. All manufactured ^{18}F-fluciclovine drug product batches were quality control tested to ensure conformance with the acceptance specifications for pH, appearance, radiochemical purity, radiochemical identity, radionuclidic identity, endotoxin levels, sterilizing filter integrity, and residual solvent levels before release for patient administration.

^{18}F-Fluciclovine PET/CT Imaging and Image Interpretation

Enrolled patients underwent baseline ^{18}F-fluciclovine PET/CT within 21 d of the initiation of therapy. Repeat ^{18}F-fluciclovine PET/CT was performed within 21 d of the completion of neoadjuvant therapy and before surgical management. There was no patient-specific preparation before ^{18}F-fluciclovine administration, and patients were allowed to eat and drink before the PET/CT examination. Patients were positioned on designated research PET/CT scanners, either GE Healthcare Discovery STE or GE Healthcare Discovery 710, operated in the 3-dimensional mode. ^{18}F-fluciclovine PET studies were performed as hybrid PET/CT examinations for attenuation correction, lesion localization, and availability of additional CT data. A low-milliampere (60–80 mA) CT scan of the chest was acquired first. Next, a bolus of 370 MBq (10 mCi) (±10%) of ^{18}F-fluciclovine was administered intravenously in less than 10 s. Dynamic PET imaging over the chest was performed for 30 min, with data collected for each minute and then summed into 5-min intervals. ^{18}F-fluciclovine avidity was most often greatest during the 5- to 10-min time interval; therefore, quantitative analyses of ^{18}F-fluciclovine avidity were conducted with the data collected during this time interval. ^{18}F-fluciclovine PET/CT images were reconstructed with iterative reconstruction and displayed on a PET/CT workstation (PET VCAR;

GE Healthcare) as multiplanar reconstructions. Areas of focal tracer uptake were localized with the companion CT and classified as lesions of the breast, axillary nodes, or extraaxillary nodes. Three-dimensional regions of interest were placed in areas of tracer uptake, and measures of ^{18}F-fluciclovine avidity were recorded; the measures were SUV_{max} (body weight), metabolic tumor volume (MTV; volume of tumor [cm^3] with SUV $>42\%$ of SUV_{max}), SUV_{mean} (within the MTV), and total lesion avidity (TLA; calculated as MTV $\times SUV_{mean}$). A background SUV_{max} was also measured for each examination.

Calculation of Change in ^{18}F-Fluciclovine Avidity After Therapy

On both pretreatment and posttreatment scans, the lesion SUV_{max} was corrected for background as follows: corrected SUV_{max} = lesion SUV_{max} − background SUV_{max}. When the corrected SUV_{max} was less than 0, 0 was recorded. Similar corrections were made for SUV_{mean}. When the corrected SUV_{max} and the corrected SUV_{mean} were 0 on posttreatment scans, MTV and TLA were also 0. The percentage of change in the ^{18}F-fluciclovine SUV_{max} after therapy was calculated as follows: [(pretreatment corrected SUV_{max} − posttreatment corrected SUV_{max})/pretreatment corrected SUV_{max}] × 100. Similar calculations were performed for SUV_{mean}, MTV, and TLA.

Calculation of Tumor Response in Surgical Specimens

All 24 patients proceeded to definitive surgical management of their primary breast malignancy. The entire tumor bed was marked and

TABLE 1
Patient and Tumor Characteristics

Characteristic	n	%
Sex (women)	24	100
Race		
White	18	75
Black	4	16.7
Asian	1	4.2
Hispanic	1	4.2
Histology		
IDC	18	75
ILC	6	25
Histologic grade		
Low	1	4.2
Intermediate	8	33.3
High	15	62.5
AJCC tumor stage*		
2B	13	54.2
3A	5	20.8
3B	4	16.7
3C	2	8.3
Receptor status		
(ER+ or PR+)/HER2−	11	45.8
HER2+	7	29.2
Triple negative (ER−PER−HER2−)	6	25

*Clinical classification according to seventh edition of *AJCC Cancer Staging Manual* (31).

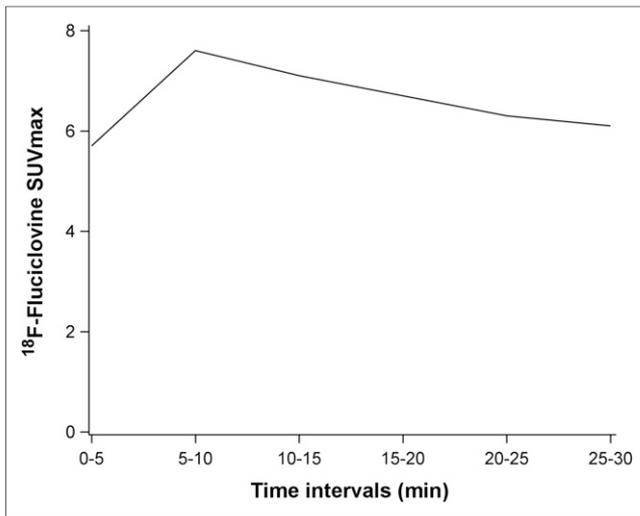AJCC = American Joint Committee on Cancer; PR = progesterone receptor.

FIGURE 1. Time–activity curve for primary breast malignancy in representative patient. ^{18}F-fluciclovine uptake was rapid, peaking at 5–10 min, and then slowly decreased until 30 min.

submitted to a pathologist who specialized in breast malignancy and had 7 y of experience with measurements for estimating the percentage of residual tumor according to published methods (*23*). In brief, the volume of the tumor bed with posttherapy changes, the volume of residual invasive or in situ tumor, and the percentage of cellularity of the tumor in the tumor bed were measured. From these measurements, the percentage of tumor volume reduction was calculated as described by Symmans et al. (*23*). A 100% pathologic tumor response, with no remaining invasive or in situ tumor, was defined as a pathologic complete response. Any reduction of less than 100% was defined as a partial response.

Statistical Analysis

Descriptive statistics were calculated for patient characteristics and measures of ^{18}F-fluciclovine avidity. The relationship between the change in ^{18}F-fluciclovine avidity after therapy and the percentage of tumor response in surgical specimens was assessed with the Spearman rank correlation, along with asymptotic 95% confidence limits, and visualized within a scatterplot with a regression line.

The proportion of patients in whom ^{18}F-fluciclovine avidity was reduced to the background level after therapy was calculated on the basis of histology (IDC vs. ILC), receptor status (ER+/HER2− vs. HER2+ vs. triple negative), and tumor grade (1 or 2 vs. 3). Because of the limited sample size and pilot nature of this prospective study, no formal hypothesis tests for group differences were conducted.

The pathologic response of the primary breast malignancy was dichotomized into a complete pathologic response (no residual invasive or in situ malignancy) and a partial pathologic response (any residual invasive or in situ malignancy).

P values of less than 0.05 were considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute Inc.).

RESULTS

Twenty-four women were prospectively enrolled to receive the institutional review board–approved protocol and underwent baseline and post–neoadjuvant therapy ^{18}F-fluciclovine PET/CT. The median age of the cohort was 53 y (range, 37–79 y). The histology of the primary breast malignancy was IDC in 18 patients (75%) and ILC in the remaining 6 patients (25%). Patient and tumor characteristics are summarized in Table 1.

Physiologic ^{18}F-fluciclovine uptake was seen in the liver, pancreas, and skeletal muscle, as previously reported (*5*). During the dynamic 30-min scan, ^{18}F-fluciclovine uptake was rapid, peaking at 5–10 min; uptake then plateaued or slowly decreased until 30 min. A time–activity curve for the primary breast malignancy of a representative patient is shown in Figure 1. Background uptake in presumably normal breast tissue was low in all patients, with SUV_{max} ranging from 0.5 to 1.5. ^{18}F-fluciclovine–avid lesions, with an avidity greater than that of the breast background, were observed in the breast (all 24 patients), axillary

TABLE 2
Numbers of Patients with ^{18}F-Fluciclovine–Avid Breast and Node Lesions and ^{18}F-Fluciclovine Avidity Measurements

Lesion	No. of patients	Parameter	Before therapy	After therapy*
Primary	24	Corrected SUV_{max}	5.5 (1.4–15.5)	0.1 (0.0–4.3)
		Corrected SUV_{max}	2.5 (1.1–6.0)	0.1 (0.0–2.2)
		MTV	15.7 (3.2–63.9)	1.3 (0.0–26.3)
		TLA	55.7 (5.0–371)	1.0 (0.0–78.4)
Axillary lymph node	19	Corrected SUV_{max}	4.9 (0.6–13.2)	0.0 (0.0–2.6)
		Corrected SUV_{max}	2.2 (0.5–6.2)	0.0 (0.0–1.3)
		MTV	4.1 (1.0–22.1)	0.0 (0.0–11.3)
		TLA	10.9 (1.0–137)	0.0 (0.0–15.0)
Extraaxillary lymph node	3	Corrected SUV_{max}	2.0 (1.4–3.2)	0.0 (0.0–0.4)
		Corrected SUV_{max}	1.2 (1.0–2.3)	0.0 (0.0–0.0)
		MTV	1.4 (1.1–1.8)	0.0 (0.0–2.5)
		TLA	3.2 (2.0–4.6)	0.0 (0.0–2.5)

*On scans after neoadjuvant therapy, breast lesions in 12 of 24 patients, axillary node lesions in 14 of 19 patients, and extraaxillary node lesions in 2 of 3 patients decreased to background levels. Lesions that decreased to background levels had corrected SUV_{max} (as well as SUV_{mean}, MTV [in cm³], and TLA) of 0.

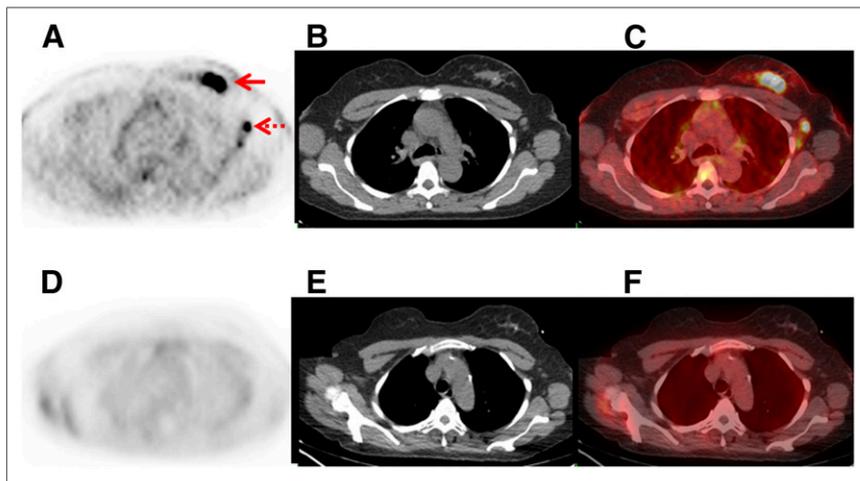Data are reported as medians, with ranges in parentheses.

FIGURE 2. Reduction in ^{18}F-fluciclovine avidity after neoadjuvant therapy in 52-y-old woman with grade 2 ER–/HER2+ IDC. (A–C) Axial ^{18}F-fluciclovine PET (A), axial CT (B), and axial fused (C) images at baseline show ^{18}F-fluciclovine–avid primary breast mass (solid arrow) and ^{18}F-fluciclovine–avid axillary node metastases (broken arrow). (D–F) Axial ^{18}F-fluciclovine PET (D), axial CT (E), and axial fused (F) images after neoadjuvant therapy show decrease in ^{18}F-fluciclovine avidity of all lesions to background levels. Pathology revealed complete pathologic response, with no residual tumor.

nodes (19/24 patients), and extraaxillary nodes (3/24 patients) on baseline ^{18}F-fluciclovine scans. On post–neoadjuvant therapy scans, breast lesions in 12 of 24 patients decreased to the background level, whereas breast lesions in the other 12 patients decreased but remained appreciably above the background level. In the 19 patients with ^{18}F-fluciclovine–avid axillary nodes at baseline, 14 lesions decreased to the background level on post–neoadjuvant therapy scans, whereas in the other 5 patients, axillary node lesions remained appreciably above the background level. In the 3 patients with ^{18}F-fluciclovine–avid extraaxillary nodes at baseline, 2 lesions decreased to the background level on post–neoadjuvant therapy scans, whereas 1 lesion remained appreciably above the background level.

The numbers of patients with ^{18}F-fluciclovine–avid breast, axillary node, and extraaxillary node lesions, as well as their median and range for measures of ^{18}F-fluciclovine avidity, are shown in Table 2. An example of a patient with primary breast cancer and axillary node metastases that all decreased to background levels after neoadjuvant therapy is shown in Figure 2.

The reduction in the corrected SUV_{max} of the 24 primary malignancies was correlated against the percentage of change in the tumor response on pathology after neoadjuvant therapy. The median decrease in the corrected SUV_{max} was 99% (range,

33%–100%). The median percentage of reduction in tumor burden on pathology was 92% (range, 10%–100%). The calculated Spearman ρ was 0.79 (95% CI, 0.56–0.90; $P < 0.001$) (Table 3). A scatterplot of the corrected SUV_{max} by the tumor response on pathology is shown in Figure 3.

The reductions in the corrected SUV_{max} of the primary malignancies after neoadjuvant therapy were further analyzed by histology, receptor status, and tumor grade (Table 4). By histology, 10 of 18 primary IDC tumors were reduced to the background level (median reduction, 100%; range, 39%–100%), whereas only 2 of 6 primary ILC tumors were reduced to the background level (median reduction, 70%; range, 33%–100%). Analogous comparisons by receptor status and tumor grade are shown in Table 4.

Only 5 patients had a complete pathologic response in their primary malignancy (no residual invasive or in situ malignancy), compared with 19 patients with a partial pathologic response (any residual invasive or in situ malignancy).

DISCUSSION

^{18}F-fluciclovine is a promising tumor marker recently approved by the U.S. Food and Drug Administration for the detection of recurrent prostate cancer. Recent studies also suggested promise for patients with breast malignancies. However, the detection of malignancy and the evaluation of a tumor response are separate tasks. Changes in ^{18}F-FDG avidity have been extensively proven to correlate with the tumor response in breast cancer and many other malignancies (24–27). This prospective clinical trial provided evidence that changes in ^{18}F-fluciclovine avidity also correlate well with the tumor response in patients with breast cancer (Spearman ρ, 0.79; $P < 0.001$).

In this prospective trial, we evaluated the treatment response in primary breast malignancies after neoadjuvant therapy. Because the entire primary breast malignancy normally undergoes surgical resection and there are established criteria for measuring the tumor response in the tumor bed from the surgical specimen (23), baseline and posttherapy/presurgery ^{18}F-fluciclovine PET/CT provides an excellent opportunity to correlate changes in ^{18}F-fluciclovine

TABLE 3
Correlation Between Percentage of Change in Corrected SUV_{max} of Primary Malignancy and Percentage of Reduction in Tumor Burden on Pathology After Neoadjuvant Therapy

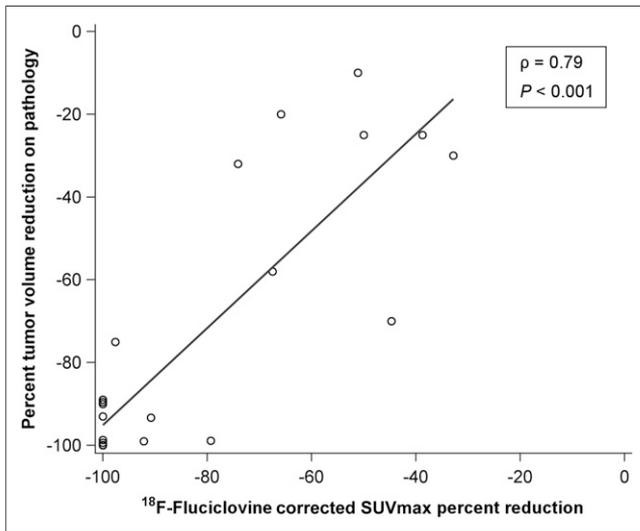| Parameter	Change/reduction		ρ	P
	SUV_{max}	Pathology		
Median	−99%	−92%	0.79	<0.001
Range	−33% to −100%	−10% to −100%		

FIGURE 3. Scatterplot of percentage of change in corrected SUV$_{max}$ vs. percentage of tumor volume reduction on pathology after neoadjuvant therapy. ρ = Spearman ρ.

avidity with the tumor response on pathology. Evaluating changes in ^{18}F-fluciclovine avidity as a measure of the tumor response may be most useful for metastatic disease; however, because metastases are not normally resected, the resected primary malignancy serves as a proxy for analysis. In this prospective trial, we evaluated ^{18}F-fluciclovine as a noninvasive biomarker of the tumor response after therapy but not as an early predictor of the tumor response.

ILC, a subtype of breast cancer that accounts for 10%–15% of primary breast malignancies (28), is difficult to visualize by all current imaging modalities (14,15), including ^{18}F-FDG PET (17,18,20,21). Therefore, the development of better metabolic imaging agents for ILC could be clinically valuable. There is preliminary evidence that ILC may be more ^{18}F-fluciclovine–avid than ^{18}F-FDG–avid (7,8). This study included 6 patients with ILC tumors, all of which were ^{18}F-fluciclovine–avid. Changes in the corrected SUV$_{max}$ appeared to correlate with the ILC tumor response, although the number of patients with

ILC was low. Only 2 of 6 primary ILC malignancies demonstrated a 100% reduction in ^{18}F-fluciclovine avidity, and both demonstrated a complete pathologic response. ILC is known to have a lower rate of a pathologic complete response after neoadjuvant therapy than IDC, although this pattern may be secondary to ILC tumors more commonly expressing ER+/HER2− receptor status, a phenotype that has a lower rate of a pathologic complete response (29,30). This pattern appeared in our small dataset.

[18]F-fluciclovine demonstrated rapid tumor uptake and a gradual decrease in avidity over time. The cause for the gradual decrease in avidity over time was not clear, but this finding may have been due to clearance of the tracer from tumor cells, as ^{18}F-fluciclovine—unlike ^{18}F-FDG—was not modified intracellularly.

No distant metastases were detected in this trial. The detection of distant metastases was limited by the restriction of imaging to include only the chest. ^{18}F-fluciclovine has prominent physiologic hepatic uptake, which may make the detection of liver metastases challenging, although lung, brain, and bone lesions may be readily visible.

The strength of this study was its design as a prospective clinical trial, which decreases study biases and allows follow-up of a well-defined cohort. However, this study was limited in sample size, which particularly limited subgroup analyses for histology, receptor status, and tumor grade.

CONCLUSION

Changes in ^{18}F-fluciclovine avidity were strongly correlated with the tumor response on pathology in this pilot study. Thus, ^{18}F-fluciclovine PET/CT shows promise for monitoring the response to therapy.

DISCLOSURE

TABLE 4
Reduction in Corrected SUV$_{max}$ of Primary Malignancy After Neoadjuvant Therapy

Tumor characteristic	No. of patients	Patients with reduction to background level		Percentage of reduction	
		n	%	Median	Range
Histology					
IDC	18	10	55.6	100.0	100.0–38.7
ILC	6	2	33.3	70.0	100.0–32.8
Receptor status					
ER+/HER2−	11	4	36.4	74.1	100.0–32.8
HER2+	7	5	71.4	100.0	100.0–44.7
Triple negative	6	3	50	98.8	100.0–67.4
Histologic grade					
1 or 2	9	3	33.3	74.1	100.0–32.8
3	15	9	60	100.0	100.0–38.7

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