Journal of Nuclear Medicine, published on November 17, 2016 as doi:10.2967/jnumed.116.183335

A prospective clinical trial of ^{18}F-Fluciclovine PET/CT neoadjuvant therapy response in invasive ductal and invasive lobular breast cancers

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Word count: 4,275 (5,000 word limit)

Financial Support: Susan G. Komen for the Cure Research Grant KG110441 (GAU), MSKCC Biostatistics Core and Radiochemistry & Molecular Imaging Probe Cores (P30 CA008748), MSKCC Breast Cancer Research Fund, and GE Healthcare.

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Running title: ^{18}F-Fluciclovine therapy response

ABSTRACT

Fluorine-18-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 (IDC) and invasive lobular breast cancers (ILC). It has not been shown whether changes in ^{18}F-Fluciclovine avidity reflect changes in tumor burden resulting from treatment. This prospective clinical trial (clinical trials.gov NCT01864083) evaluates changes in ^{18}F-Fluciclovine-avidity compared to breast cancer therapy response, as determined by residual tumor burden on pathology.

Methods: Twenty-four women with a new diagnosis of locally advanced IDC (n = 18) or ILC (n = 6) underwent ^{18}F-Fluciclovine PET/CT before and after the completion of neoadjuvant systemic therapy. Standardized uptake value (SUV)max, SUVmean, metabolic tumor volume (MTV), and total lesion avidity (TLA) were obtained for the primary breast tumor, axillary lymph nodes, and extra-axillary lymph nodes on each exam, and corrected for background ^{18}F-Fluciclovine avidity. The relationship between changes in ^{18}F-Fluciclovine-avidity and percent reduction of tumor on pathology was assessed using Spearman's Rank correlation.

Results: The median decrease in ^{18}F-Fluciclovine $SUV_{max\ corrected}$ of the primary breast lesions was 99% (range 33-100%). The median reduction in tumor on pathology was 92% (range 10-100%). Changes in ^{18}F-Fluciclovine-avidity were strongly correlated with percent reduction of tumor on pathology (Spearman's rho 0.79, 95% CI: 0.56-0.90, $p<0.001$).

Conclusion: Changes in ^{18}F-Fluciclovine-avidity strongly correlate with tumor response on pathology in this pilot study.

Keywords: ^{18}F-Fluciclovine, ^{18}F-FACBC, PET/CT, ductal, lobular, breast cancer, response

INTRODUCTION

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

While ^{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 being used for the evaluation of tumor response, the association of ^{18}F-Fluciclovine avidity and tumor response must be demonstrated (*13*). The purpose of this trial was to assess the ability of FACBC PET to determine therapeutic response to neoadjuvant chemotherapy in patients with breast cancer. All patients underwent prospectively planned surgical removal of the treated primary breast malignancy, which allowed 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 IRB approval and written informed consent from participants. Patients presenting for evaluation at Memorial Sloan Kettering Cancer Center with biopsy-proven locally advanced, non-metastatic IDC or ILC, who were referred for neoadjuvant systemic therapy between August 2013 and August 2015, were invited to participate. ILC is a subtype of breast cancer which 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, these patients were actively sought for inclusion into the study, which accounts 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 logistical considerations; the aims of this study were exploratory. In total, 27 patients were accrued, but only 24 completed the protocol. Three patients withdrew from the protocol before the final ^{18}F-Fluciclovine scan.

Exclusion criteria were age less than 18 years, current pregnancy or lactation, prior malignancy other than squamous or basal skin cancers, and patients unwilling or unable to consent. There were no restrictions on gender or race. Clinical records were used to document patient age, gender, race, and presence of biopsy-proven known axillary or extra-axillary nodal metastases prior to ^{18}F-Fluciclovine PET/CT, as well as histology, grade and receptor status of the primary breast malignancy. Tumors were hormone receptor-positive if they stained as estrogen receptor (ER) > 1% and/or Progesterone receptor (PR) > 1%. Tumors were human epidermal growth factor 2 (HER2)-positive if they were HER2 immunohistochemistry 3+ and/or fluorescent in situ hybridization amplified with ratio of >/= 2.0. Tumors that were negative for ER, PR, and

HER2 were classified as “triple negative”. Initial results from pre-therapy ^{18}F-Fluciclovine PET/CT exams from this trial were previously reported (*7*).

Verification of Malignancy

All patients had biopsy-proven primary breast malignancy prior to enrollment in the clinical trial. Pathology for axillary nodes was also available for all patients. Pathologic evaluation of extra-axillary nodes was available for the 3 patients with suspicious extra-axillary findings on the 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 MSKCC Radiochemistry and Molecular Imaging Probes Core Facility. The GE FASTlab automated synthesizer, synthesizer cassettes, reagents, and materials were all supplied by GE Healthcare (Oslo, Norway) 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 using a 0.22μm sterilizing filter. The ^{18}F-Fluciclovine final drug product was formulated with 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 prior to release for patient administration.

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

Enrolled patients underwent baseline ^{18}F-Fluciclovine PET/CT within 21 days of initiating therapy. Repeat ^{18}F-Fluciclovine PET/CT was performed within 21 days of completing post-neoadjuvant therapy and before proceeding to surgical management. There was no patient-specific preparation prior to ^{18}F-Fluciclovine administration and patients were allowed to eat and drink prior to the PET/CT examination. Patients were positioned on designated research PET/CT scanners, either a GE Discovery STE or GE Discovery 710, operated in 3D mode. The ^{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 CT (60-80 mA) of the chest was acquired first. Then a bolus of 370MBq (10 mCi) +/- 10% of ^{18}F-Fluciclovine was administered intravenously in under 10 seconds. Dynamic PET imaging over the chest was acquired for 30 minutes, with data collected for each minute, then summed into 5 minute intervals. ^{18}F-Fluciclovine avidity was most often greatest during the 5 to 10-minute time interval, and therefore quantitative analyses of ^{18}F-Fluciclovine avidity were conducted using the data collected during this time interval. The ^{18}F-Fluciclovine PET/CT images were reconstructed using iterative reconstruction, and displayed on a PET/CT workstation (PET VCAR, GE Healthcare, Milwaukee, WI) in multiplanar reconstructions. Areas of focal tracer uptake were localized using the companion CT and classified as lesions of the breast, axillary nodes, or extra-axillary lesions. Three-dimensional regions of interest were placed in areas of tracer uptake and measures of ^{18}F-Fluciclovine avidity were recorded, including SUV_{max} (body weight), Metabolic tumor

volume (MTV, cubic centimeter volume of tumor with SUV greater than 42% of SUV_{max}), SUV_{mean} (within the MTV), and total lesion avidity (TLA = MTV x SUV_{mean}). A background SUVmax was also measured for each exam.

Calculation of change in ^{18}F-Fluciclovine-avidity following therapy

On both the pre-treatment and post-treatment scans, lesional SUVmax was corrected for background as follows, $SUV_{max\ corrected} = SUV_{max\ lesion} - SUV_{max\ background}$. When $SUV_{max\ corrected}$ was less than zero, zero was recorded. Similar corrections were made for SUV_{mean}. When SUV_{max} corrected and SUV_{mean} corrected were zero on the post-treatment scans, then MTV and TLA were also zero. Percent change in ^{18}F-Fluciclovine SUVmax following therapy was calculated as: (Pre-treatment $SUV_{max\ corrected}$ – Post-treatment $SUV_{max\ corrected}$) / Pre-treatment SUV_{max} corrected x 100%. Similar measurements were made for SUV_{mean}, MTV, and TLA.

Calculation of Tumor Response on Surgical Specimens

All twenty-four patients proceeded to definitive surgical management of their primary breast malignancy. The entire tumor bed was marked and submitted to a pathologist specializing in breast malignancy and with 7 years experience in measurements in estimating percent of residual tumor according to published methods (*23*). In brief, volume of the tumor bed with post-therapy changes was measured, as

well as volume of residual invasive and in situ tumor and percent cellularity of the tumor in the tumor bed. From these measurements, percent tumor volume reduction was calculated as in 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 change in ^{18}F-Fluciclovine-avidity following therapy and percent tumor response on surgical specimens was assessed using Spearman's Rank correlation, along with asymptotic 95% confidence limits, and visualized with in a scatter plot with a regression line.

The proportion of patients in which ^{18}F-Fluciclovine avidity reduced to background following therapy was calculated based on histology (IDC vs. ILC), receptor status (ER+/HER2- vs. HER2+ vs. triple negative), and tumor grade (1/2 vs. 3) were described. Due to limited sample size and pilot nature of this prospective study, no formal hypothesis tests for these group differences were conducted.

Pathologic response of the primary breast malignancy was dichotomized into complete pathologic response (no residual invasive or in situ malignancy) and partial pathologic response (any residual invasive or in situ malignancy). To evaluate the accuracy of change in ^{18}F-Fluciclovine $SUV_{max\ corrected}$ for complete pathologic response,

we drew an ROC curve and estimated the area under the curve (AUC) with 95% confidence intervals.

P-values less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (The SAS Institute, Cary, NC).

RESULTS

Twenty-four female patients were prospectively accrued to the IRB-approved protocol and underwent baseline and post-neoadjuvant therapy ^{18}F-fluciclovine PET-CT. The median age of the cohort was 53 years (range 37-79 years). 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 minute scan, ^{18}F-Fluciclovine uptake was rapid, peaking at 5-10 minutes, then plateaued or slowly decreased until 30 minutes. 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, ranging from SUV_{max} 0.5 to 1.5. ^{18}F-fluciclovine-avid lesions, with avidity greater than breast background, were observed in the breast (all 24 patients), axillary nodes (in 19 of 24 patients), and extra-axillary nodes (in 3 of 24 patients) on the baseline ^{18}F-Fluciclovine scans. On post-neoadjuvant therapy scans, breast lesions in 12 of 24 patients decreased to background, while breast lesions in the other 12 patients decreased but remained appreciable above background. In the 19

patients with ^{18}F-fluciclovine-avid axillary nodes at baseline, 14 decreased to background on post-neoadjuvant therapy scans, while in the other 5 patients axillary nodes remained appreciable above background. In the 3 patients with ^{18}F-fluciclovine-avid extra-axillary nodes at baseline, 2 decreased to background on post-neoadjuvant therapy scans, while one remained appreciable above background. The number of patients with ^{18}F-fluciclovine-avid breast, axillary nodal, and extra-axillary nodal lesions, as well as their median and range for measures of ^{18}F-fluciclovine avidity, are reported in Table 2. An example of a patient with a primary breast cancer and axillary nodal metastases that all decreased to background following neoadjuvant therapy is demonstrated in Figure 2.

The reduction in ^{18}F-fluciclovine $SUV_{max\ corrected}$ of the 24 primary malignancies was correlated against the percent change in tumor response on pathology following neoadjuvant therapy. The median decrease in ^{18}F-fluciclovine $SUV_{max\ corrected}$ was 99% (range 33-100%). The median reduction in tumor on pathology was 92% (range 10-100%). The calculated Spearman's Rho was 0.79 (95% CI: 0.56-0.90), $p < .001$ (Table 3). A scatterplot of ^{18}F-fluciclovine $SUV_{max\ corrected}$ by tumor response on pathology is demonstrated in Figure 3.

The reductions in ^{18}F-fluciclovine $SUV_{max\ corrected}$ in the primary malignancy following neoadjuvant therapy were further analyzed by histology, receptor status, and tumor grade (Table 4). By histology, 10 of 18 primary IDC tumors reduced to background (median reduction 100%, range 39-100%), while only 2 of 6 primary ILC tumors reduced to background (median reduction 70%, range 33-100%). Analogous comparisons by receptor status and tumor grade are reported in Table 4.

Only five patients had a complete pathologic response (no residual invasive or in situ malignancy), compared with a partial pathologic response (any residual invasive or in situ malignancy). The small number of patients with complete pathologic response prevented analysis of cutoffs to predict complete pathologic response.

DISCUSSION

^{18}F-Fluciclovine is a promising tumor marker recently approved by the US Food and Drug Administration for the detection of recurrent prostate cancer. Recent studies also suggest promise for patients with breast malignancies. However, detection of malignancy and evaluation of tumor response are separate tasks. Changes in ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) avidity have been extensively proven to correlate with tumor response in breast cancer and many other malignancies (*24-27*). This prospective clinical trial provides evidence that changes in ^{18}F-Fluciclovine avidity also correlates well with tumor response in patients with breast cancer (Spearman's Rho 0.79, $p < 0.001$).

This prospective trial evaluated treatment response in primary breast malignancies following neoadjuvant therapy. As the entire primary breast malignancy normally undergoes surgical resection, and there are established criteria for measuring tumor response in the tumor bed on the surgical specimen (*23*), baseline and post-therapy/pre-surgery ^{18}F-Fluciclovine PET/CT provides an excellent opportunity to correlate changes in ^{18}F-Fluciclovine avidity with tumor response on pathology. The

usefulness of evaluating changes in ^{18}F-Fluciclovine avidity as a measure of tumor response may be most substantial for metastatic disease; however as metastases are not normally resected, the resected primary malignancy serves as a proxy for analysis. This prospective trial evaluated ^{18}F-Fluciclovine as a non-invasive biomarker of tumor response following therapy, but not as an early predictor of tumor response.

ILC, a subtype of breast cancer which 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 FDG-avid (*7,8*). This study included six patients with ILC which were all Fluciclovine-avid. Changes in ^{18}F-Fluciclovine $SUV_{max\ corrected}$ appeared to correlate with ILC tumor response, although numbers were low. Only 2 of 6 primary ILC malignancies demonstrated a 100% reduction in ^{18}F-Fluciclovine avidity, and both demonstrated complete pathologic response. ILC is known to have a lower rate of pathologic complete response following neoadjuvant therapy than IDC, although this may be secondary to ILC tumors more commonly expressing a ER+/HER2- receptor status, a phenotype that has a lower rate of pathologic complete response (*29,30*). This pattern appears in our small dataset.

^{18}F-Fluciclovine demonstrated a rapid tumor uptake and gradual decrease in avidity over time. The cause for the gradual decrease in avidity over time in not clear, but may be due to clearance of the tracer from the tumor cells, as ^{18}F-Fluciclovine is not modified intracellularly like FDG.

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 detection of liver metastases challenging, although lung, brain, and bone lesions may be readily visible.

The strength of this study is 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 strongly correlate with tumor response on pathology in this pilot study. Thus, ^{18}F-Fluciclovine PET/CT shows promise for monitoring response to therapy.

ACKNOWLEDGMENTS

We acknowledge financial support from the Susan G. Komen for the Cure Research Grant KG110441 (GAU) and GE Healthcare. We acknowledge support from the MSKCC Biostatistics Core and Radiochemistry & Molecular Imaging Probe Core (P30 CA008748) and the MSKCC Breast Cancer Research Fund.

REFERENCES

1. Huang C, McConathy J. Radiolabeled amino acids for oncologic imaging. *J Nucl Med.* 2013;54:1007-1010.

2. Shoup TM, Olson J, Hoffman JM, et al. Synthesis and evaluation of [18F]1-amino-3-fluorocyclobutane-1-carboxylic acid to image brain tumors. *J Nucl Med.* 1999;40:331-338.

3. Amzat R, Taleghani P, Miller DL, et al. Pilot study of the utility of the synthetic PET amino-acid radiotracer anti-1-amino-3-[(18)F]fluorocyclobutane-1-carboxylic acid for the noninvasive imaging of pulmonary lesions. *Mol Imaging Biol.* 2013;15:633-643.

4. Schuster DM, Nieh PT, Jani AB, et al. Anti-3-[(18)F]FACBC positron emission tomography-computerized tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. *J Urol.* 2014;191:1446-1453.

5. Schuster DM, Nanni C, Fanti S, et al. Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid: physiologic uptake patterns, incidental findings, and variants that may simulate disease. *J Nucl Med.* 2014;55:1986-1992.

6. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with 18F FACBC PET/CT: comparison with MR imaging and histopathologic analysis. *Radiology.* 2014;270:849-856.

7. Ulaner GA, Goldman D, Gonen M, et al. Initial results of a prospective clinical trial of 18F-Fluciclovine PET/CT in newly diagnosed invasive ductal and invasive lobular breast cancers. *J Nucl Med.* 2016; 57:1350-1356.

8. Tade FI, Cohen MA, Styblo TM, et al. Anti-3-[18F] FACBC (Fluciclovine) PET-CT of breast cancer an exploratory study. *J Nucl Med.* 2016;57:1357-1363.

9. Kondo A, Ishii H, Aoki S, et al. Phase IIa clinical study of [18F]fluciclovine: efficacy and safety of a new PET tracer for brain tumors. *Ann Nucl Med.* 2016;30:608-618.

10. Nanni C, Zanoni L, Pultrone C, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. *Eur J Nucl Med Mol Imaging.* 2016;43:1601-1610.

11. Odewole OA, Tade FI, Nieh PT, et al. Recurrent prostate cancer detection with anti-3-[18F]FACBC PET/CT: comparison with CT. *Eur J Nucl Med Mol Imaging.* 2016; 43:1773-1783.

12. Ren J, Yuan L, Wen G, Yang J. The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: a meta-analysis. *Acta Radiol.* 2016;57:487-493.

13. Ulaner GA, Riedl CC, Dickler MN, Jhaveri K, Pandit-Taskar N, Weber W. Molecular imaging of biomarkers in breast cancer. *J Nucl Med.* 2016;57 Suppl 1:53S-59S.

14. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. *Radiology.* 2004;233:830-849.

15. Lopez JK, Bassett LW. Invasive lobular carcinoma of the breast: spectrum of mammographic, US, and MR imaging findings. *Radiographics.* 2009;29:165-176.

16. Avril N, Menzel M, Dose J, et al. Glucose metabolism of breast cancer assessed by 18F-FDG PET: histologic and immunohistochemical tissue analysis. *J Nucl Med.* 2001;42:9-16.

17. 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.

18. Bos R, van Der Hoeven JJ, van Der Wall E, et al. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. *J Clin Oncol.* 2002;20:379-387.

19. 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.

20. Dashevsky BZ, Goldman DA, Parsons M, et al. Appearance of untreated bone metastases from breast cancer on FDG PET/CT: importance of histologic subtype. *Eur J Nucl Med Mol Imaging.* 2015;42:1666-1673.

21. Hogan MP, Goldman DA, Dashevsky B, et al. Comparison of 18F-FDG PET/CT for systemic staging of newly diagnosed invasive lobular carcinoma versus invasive ductal carcinoma. *J Nucl Med.* 2015;56:1674-1680.

22. Svadberg A, Wickstrom T, Hjelstuen O. Degradation of acetonitrile in eluent solutions for [18F]fluoride PET chemistry: impact on radiosynthesis of [18F]FACBC and [18F]FDG. *J Labelled Comp Radiopharm.* 2012;55:97-102.

23. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007;25:4414-4422.

24. Avril S, Muzic RF, Jr., Plecha D, Traughber BJ, Vinayak S, Avril N. (1)(8)F-FDG PET/CT for Monitoring of Treatment Response in Breast Cancer. *J Nucl Med.* 2016;57 Suppl 1:34S-39S.

25. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32:3059-3068.

26. Jones M, Hruby G, Solomon M, Rutherford N, Martin J. The Role of FDG-PET in the Initial Staging and Response Assessment of Anal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol.* 2015;22:3574-3581.

27. Kwee RM, Marcus C, Sheikhbahaei S, Subramaniam RM. PET with Fluorodeoxyglucose F 18/Computed Tomography in the Clinical Management and Patient Outcomes of Esophageal Cancer. *PET Clin.* 2015;10:197-205.

28. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer.* 2005;93:1046-1052.

29. Lips EH, Mukhtar RA, Yau C, et al. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Cancer Res Treat.* 2012;136:35-43.

30. Mamtani A, Barrio AV, King TA, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. *Ann Surg Oncol.* 2016.

31. Edge S, Byrd D, Compton C. AJCC Cancer Staging Manual. 7th Edition. New York, NY: Springer; 2010.

FIGURES

FIGURE 1. Time activity curve for the primary breast malignancy of a representative patient. ^{18}F-Fluciclovine uptake was rapid, peaking at 5-10 minutes, then slowly decreased until 30 minutes.

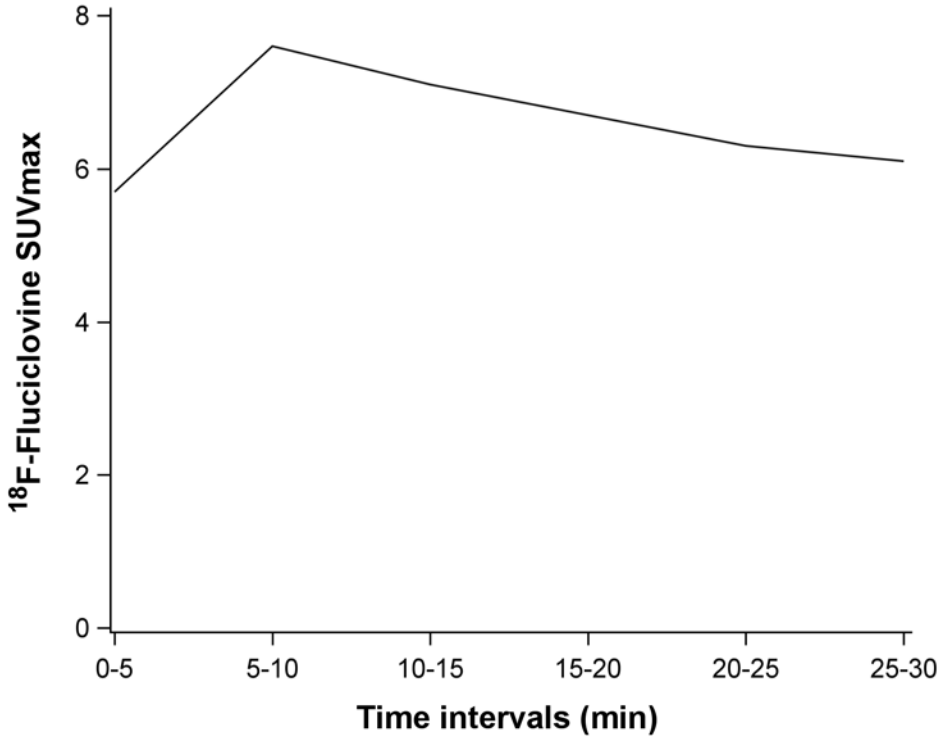

FIGURE 2. Reduction in ^{18}F-Fluciclovine avidity following neoadjuvant therapy in a 52 year old woman with grade 2 ER- /HER2+ IDC. (A) Axial ^{18}F-Fluciclovine PET, (B) axial CT, and (C) axial fused images at baseline demonstrate the ^{18}F-Fluciclovine avid primary breast mass (arrow) and ^{18}F-Fluciclovine avid axillary nodal metastases (dashed arrows). (D) Axial ^{18}F-Fluciclovine PET, (E) axial CT, and (F) axial fused images following neoadjuvant therapy demonstrate decrease of ^{18}F-Fluciclovine avidity of all lesions to background. On pathology, there was a complete pathologic response, with no residual tumor.

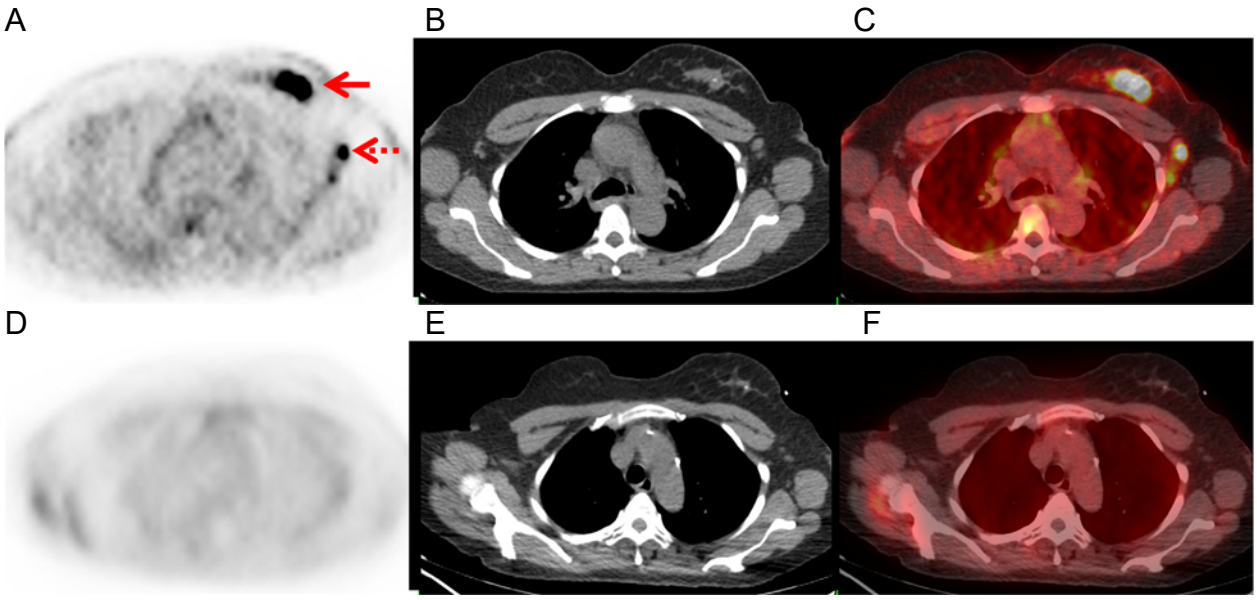

FIGURE 3. Scatterplot of percent change in ^{18}F-Fluciclovine $SUV_{max\ corrected}$ versus percent tumor volume reduction on pathology following neoadjuvant therapy. ρ = Spearman's rho.

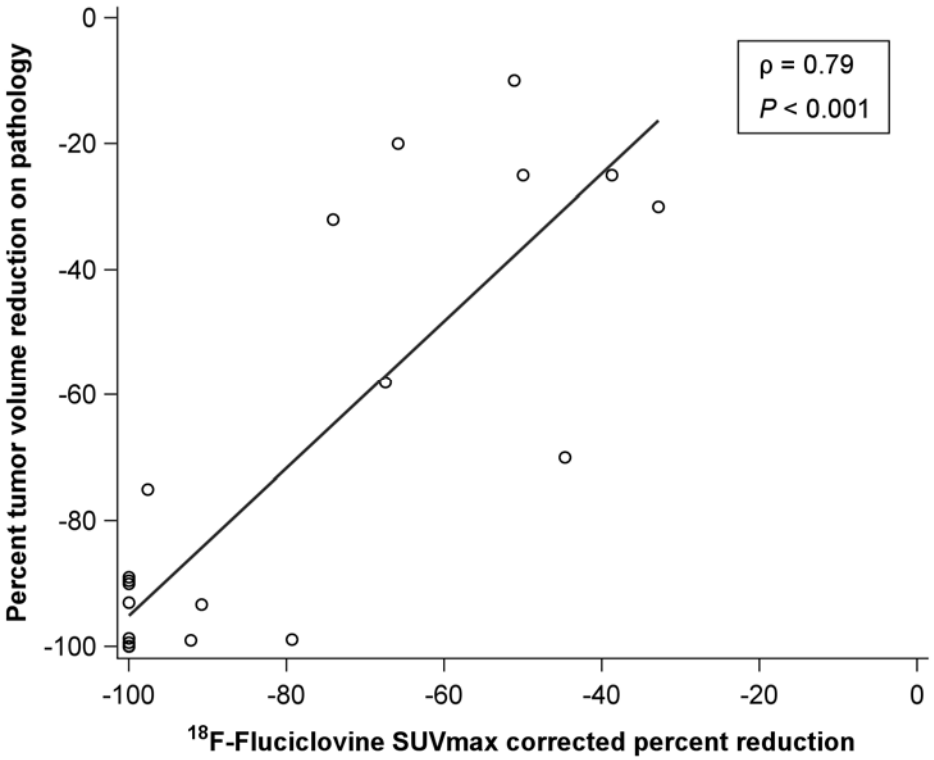

Table 1. Patient and Tumor Characteristics

		N (%)
Gender	Female	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)

AJCC = American Joint Committee on Cancer; IDC = invasive ductal cancer; ILC = invasive lobular cancer; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2. * Clinical classification according to the seventh edition of the AJCC Staging Manual (*31*).

Table 2. Number of patients with ^{18}F-fluciclovine-avid breast, axillary nodal and extra-axillary nodal lesions, as well as their median and range for measures of ^{18}F-fluciclovine avidity. On post-neoadjuvant therapy scans, breast lesions in 12 of 24 patients, axillary nodes in 14 of 19 patients, and extra-axillary nodes in 2 of 3 patients decreased to background. Lesions that decreased to background have corrected SUV_{max} (as well as SUV_{mean}, MTV, and TLG) of zero.

	Pre	**Post**
	Median (Range)	**Median (Range)**
Primary Lesion (N=24)		
$SUV_{max\ corrected}$	5.5 (1.4-15.5)	0.1 (0.0-4.3)
$SUV_{mean\ corrected}$	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 LN (N=19)		
$SUV_{max\ corrected}$	4.9 (0.6-13.2)	0.0 (0.0-2.6)
$SUV_{mean\ corrected}$	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)
Extra-axillary LN (N=3)		
$SUV_{max\ corrected}$	2.0 (1.4-3.2)	0.0 (0.0-0.4)
$SUV_{mean\ corrected}$	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)

MTV = mean tumor volume (in cubic centimeter), TLA = total lesion avidity

Table 3. Correlation between percent changes in ^{18}F-fluciclovine $SUV_{max\ corrected}$ of the primary malignancy and percent reduction in tumor burden on pathology following neoadjuvant therapy.

	SUV_{max}	**Pathology**		
	Median (Range)	**Median (Range)**	**Rho**	**p-value**
Percent Change	-99% (-33% to -100%)	-92% (-10% to -100%)	0.79	<.001

Table 4. Reductions in Fluciclovine $SUV_{max\ corrected}$ of the primary malignancy following neoadjuvant therapy based on histology, receptor status, and tumor grade.

Tumor Characteristic	N	N BG (%)	Median % Reduction (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			
1-2	9	3 (33.3)	-74.1% (-100.0% - -32.8%)
3	15	9 (60)	-100.0% (-100.0% - -38.7%)

BG = Number of patients reduced to background